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The clinical challenge of managing a patient with HCM

### Dr. Olivatto:

Hello, in the previous talks we have heard about the challenges of diagnosing HCM and the new therapeutic options on the horizon.

These are my disclosures.

So in the next few minutes, what I would like to do is to talk about the challenges of treating patients with novel options.

Well, as we saw, the first question that you have to ask yourself when you see a patient with HCM is whether that is real HCM, whether it's not a phenocopy, whether it's not amyloid, whether you are looking at the proper classic disease. But the second question you have to ask yourself is, at what stage am I intercepting the patient? Is this a patient that has an initial conversion from genotype-positive status to phenotype, to full phenotype? So very early on in the disease, usually very young, is this a patient that has a full-fledged disease that's still in the hypercontractile phase, classic asymmetric hypertrophy? Maybe obstructive, maybe has arrhythmias. Maybe you have to protect from sudden death, but there's still not a lot of fibrosis, not a lot of regression.

Then there's a further stage that usually occurs over many years, and sometimes decades from the diagnosis, which is the adversary modeling stage, or stage 3 as we like to call it, where fibrosis sets in and begins to produce greater degrees of diastolic dysfunction. And then there's a fourth stage, which is only reached, fortunately, by a small minority of the patients, but it is really challenging to treat, which is the overt dysfunction where fibrosis is extensive and dysfunction becomes really hard to treat.

Well, in HCM history, now dating back now 50 years, the fairy tale has been a little grim for many years. And so it's like Cinderella wondering what she can wear for the ball but having virtually nothing to wear at all except for old clothes. And we have had old drugs to use for our patients which have never given us real satisfactory results and have never sort of targeted the core mechanisms of disease. This has really changed very dramatically and still is evolving very rapidly in the last few years. And now we are more like in the better scenario of Prince Charming looking at the wardrobe full of clothes and wondering, before going on Instagram, what kind of clothes he should wear for the ball. Because there are, as we've heard from the previous docs, many options on the horizon, some of which particularly myosin inhibitors, are already part of our current practice. And this is mirrored by the exploding number of molecules, as well as trials that are ongoing, which would have been unthinkable just 10 years ago.

So let's start with the treatment of obstruction because this is really where we have the most stringent, the most coded advances today. Of course, obstruction, as we have heard from Professor Elliott, is a frequent feature and a major determinant of symptoms and outcome. And again, as we also previously heard, in the recent guidelines released from the European Society of Cardiology just one year ago, we have a new entry after many, many years of algorithms which really never changed. You can see how mavacamten has now entered practice. It is the first and now the only registered and approved myosin inhibitor, and this is now considered a Class 2A indication for second-stage treatment of obstruction in patients who have failed to respond to beta-blockers before or instead of moving to surgery.

This has already changed in the last few months, since May, when the American revised guidelines had been released. And as you can see here, we now talk about myosin inhibitors and not mavacamten. So this is a class now because SEQUOIA came out in the

meantime. So the phase 3 aficamten trial, so we have 2 agents. We have a class of agents and the recommendation from Class 2 becomes now Class 1 level of evidence B.

Also, what changed dramatically is the staging of the algorithm. As you can see here, once the beta-blockers fail to produce the relief of the gradients and symptoms, now beta myosin inhibitors are on par with septal reduction therapy. So the discussion with the patient becomes, what do I do? You don't respond to beta-blockers. You still have symptoms. You still have a gradient. Well, you have an option for surgery, which is well established. Alcohol ablation, very nice results in experienced hands, but at the same time, ethically and medically, I need to inform the patient that there is an option which is medical, which may be equally effective and, to some extent, address the molecular mechanism of disease more in depth. So pills are now sort of on par with the scalpel.

This is because we have data. We have data from phase 3 trials. This is EXPLORER, which is now 4 years old. You can see mavacamten randomized to placebo, which showed in 251 patients over 32 weeks of treatment, very convincing reduction in resting gradients, Valsalva gradients, ProBNP, troponin release, marked improvement in quality of life and symptoms, and at the same time, very small reduction in systolic function and very nice safety profile.

In the VALOR trial, patients who were already listed for surgery because of symptoms and high gradients in 82% of the cases, as you can see on the left, were taken off the list because of response to treatment. And if you treat patients longer, over 90% of the patients, you can see, are not eligible anymore for surgery given the continuous efficacy of mavacamten in these patients.

And again, as we heard recently, SEQUOIA was released, phase 3 trial enrolling over 250 patients randomized to placebo or aficamten, again, symptomatic obstructive patients. And you can see, again, very marked efficacy on resting gradients, Valsalva gradients, improvement in symptoms, quality of life, biomarkers. Very, overall, I would say, very similar results. Very convincing results with a nice safety profile as well. And again, candidacy to surgery or alcohol ablation drops very significantly and actually very quickly because aficamten has a shorter half-life than mavacamten, and as long as the treatment is continued, patients largely remain non-eligible for surgery, whereas their gradients and symptoms go up during washout.

What about long term, because we know that trials are only limited in duration. Well, we now are following all these patients in long-term extensions of the two phase 3 trials I've mentioned. This is data from the EXPLORER-LTE, long-term extension. As you can see, there is continuing efficacy in terms of gradient reduction, symptomatic improvement, biomarkers, and continuing sort of good tolerability profile with preserved systolic function over time.

So, what about real life? What about the real world? We know that, to some extent, trials are fairy tales, but if you move to the real world, it's quite encouraging to see that the safety profile remains very favorable. Only less in this first series from the US of almost 1,900 patients, only less than 3% of patients had a duration decrease in left ventricular ejection fraction, which is the main concern in this sort of kind of treatments. And only 1% required hospitalization due to heart failure, which is actually low for the kind of population that was enrolled. So, very conforming safety and efficacy profile.

At the same time, with this treatment we know we are triggering something deeper. We're triggering remodeling of the ventricles, remodeling of the atria. What has been seen in a subset of the EXPLORER trial of patients undergoing CMR magnetic resonance at the beginning and end of this study, is that there is a limited but significant improvement in terms of cavity remodeling, increased cavity size, reduced LV mass, as well as remodeling of the left atrium, so reduced left atrial volumes. This is of course short term. It would be very interesting to see what happens in longer term and what happens to fibrosis, what happens to several of the other features of disease, but this will take longer time.

In the meantime, we are sufficiently convinced that we are not only acting on the gradients on the obstruction, but also on the substrate, on the structural substrate of the disease, that of course, the next effort is to demonstrate a clinical efficacy in patients with nonobstructive HCM which remains a major unmet need. And cardiac myosin inhibitors have a very good rationale for a number of reasons to improve diastolic function. For example, in this experience in vitro, you can see that the exposure to mavacamten prolongs sarcomere length. You can see, increases sarcomere length.

So think about hypercontractile hearts like HCM as Titanic hearts. These are hearts that with myosin inhibitors, can finally relax, find their real end diastolic sort of dimension, and this is extremely promising for improvement in nonobstructive disease. And in fact, there are two pilot studies, two phase 2 studies, one with mavacamten called MAVERICK-HCM, one with aficamten called REDWOOD-HCM.

This is data from REDWOOD. You can see how nicely there is a symptomatic improvement in these patients and biomarker improvement as well. And this is the biomarker. So based on these encouraging results, there are 2 large trials on the way. One is ODESSEY-HCM enrolling symptomatic nonobstructive patients and treated with mavacamten. And the other one is the ACACIA-HCM trial, which is, again, a large study on nonobstructive disease treated with aficamten. These data will be available probably in the next

several of years and hopefully will change the way we manage nonobstructive disease as well.

So if we want to finish where we began, I think it is quite encouraging to think that we now have a class of agents that are safe and well tolerated and extremely active and effective in patients who have symptoms related to obstruction but, at the same time, target very deep, very core mechanisms of HCM in general and, therefore, have a potential indication for each of the stages of disease, except possibly the end stage where nothing really seems to work. We can probably, in the next 10 years, think of this class of treatments and, in general, of other molecules in terms of sarcomere modulators, which are really a whole pipeline that's coming up as a sort of potential standard which we can give to patients irrespective of their phenotype, as far as they do have a diagnosis of HCM. Pretty much, like, in a patient with heart failure, you would block the renin-angiotensin system irrespective of the underlying diagnosis, and only then, once you've sort of addressed this sort of issue of hypercontractility, you can then address the individual phenotypic features such as arrhythmias, residual obstruction, fibrosis, and whatnot.

If this is the case, I think we will have a real important new tool for the treatment of our patients and hopefully in the next maybe 5 to 10 years also show that we are making a prognostic impact on our patients.

Thank you very much.