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Recommendations on the management of HCM in guidelines: European vs. American views

Dr. Masri:
Hello, my name is Ahmed Masri. I'm a cardiologist and a hypertrophic cardiomyopathy specialist at Oregon Health and Science University in Portland, Oregon, United States.

Dr. Barriales-Villa:
Hello, I am Roberto Barriales-Villa, cardiologist from Unidad de Cardiopatías familiares Hospital Universitario, A Coruña, Spain.

Dr. Masri:
Thank you for joining us. We will be having a discussion today about precision medicine and focused recommendations in both the European Society of Cardiology HCM guidelines as well as the American guidelines as well. I'll hand it over to Roberto to start.

Dr. Barriales-Villa:
Thank you very much, Matt. These are my disclosures.

In 2023, the European guidelines for the management of cardiomyopathies was presented. In these guidelines, there was an update of the 2014 European hypertrophic cardiomyopathy guidelines. Regarding nonobstructive hypertrophic cardiomyopathy, there were no novelties. If the patient has no gradient and the left ventricular radiation fraction was preserved, the task force recommended medical treatment with beta-blockers, calcium antagonists and low-dose diuretics. All of this with a low level of evidence.

But regarding obstructive hypertrophic cardiomyopathy, there are many changes. If the patient has a gradient equal or superior to 50 mmHg and the patient is symptomatic, the task force recommended the use of beta-blockers. But if the beta-blockers are contraindicated or there is an intolerance to beta-blockers, you can use verapamil or diltiazem. But if the patient is still symptomatic, you can add disopyramide to the beta-blockers or to the calcium antagonist.

The level of evidence to these drugs is a recommendation Class 1 with a level of evidence B. That means that data derived from a single randomized clinical trial or large non-randomized studies. But in 2023, for the first time in a hypertrophic cardiomyopathy guidelines, a myosin inhibitor, a disease-modifying treatment, was included. The task force recommended mavacamten as a second-line therapy when prior treatment with beta-blockers, calcium antagonists, or disopyramide was not effective or was poorly tolerated by the patient. This indication for mavacamten is IIA; mavacamten must be titrated to maximum tolerated dose with echocardiographic surveillance of left ventricular ejection fraction, of course, and should be considered in addition to a beta-blocker or verapamil or diltiazem. That's because the studies, the EXPLORER and VALOR-HCM, considered to have beta-blocker calcium antagonist plus mavacamten.

The level of evidence of mavacamten was A. For the first time in the guidelines we have this level of evidence for the drug because the data derived from multiple randomized clinical trials, in this case from the VALOR-HCM and from the EXPLORER-HCM, of course, a multiple sub-analysis. But it's a second-line therapy because the task force considered that in the absence of direct head-to-head comparison between beta-blockers, calcium antagonists, and myosin inhibitors, it could not be recommended as first-line therapy.

If what happened is the patient has contradiction to beta-blockers, calcium antagonist, or disopyramide, can we use mavacamten as

monotherapy? Well, we have no experience, but in the EXPLORER there were patients just with mavacamten, because with the intolerance to beta-blockers we can use it, but with a low level of evidence.

And what happens if the patient is taking disopyramide? Can the patient take disopyramide and mavacamten? Well, in the EXPLORER disopyramide was not allowed. So safety, of course, has not been established. In the VALOR-HCM at least 20% of the patients were on with disopyramide and the efficacy and safety of the patients taking mavacamten alone or mavacamten and disopyramide were similar. So we can use this mavacamten with disopyramide, but patients should be closely monitored.

To conclude, in the 2023 European guidelines, a myosin inhibitor should be started as a second-line treatment and prior to septal reduction therapies.

And now, Ahmed is going to talk about the American just-released guidelines.

Dr. Masri:
As you can see here, the plan originally was to talk to you about the 2020 guidelines, but just a few days ago we got the 2024 multisociety guidelines for hypertrophic cardiomyopathy. And so we already reviewed the level of evidence as well as the classes of recommendation, but it's very interesting to keep that in mind because you could get a green box, which is a Class 1 indication, but your level of evidence can still be derived from either expert opinion or from observational studies. So something to keep in mind as we go.

These are from the 2020 guidelines showing you that despite the fact there are varying degrees of level of evidence, all of these recommendations for therapeutic interventions and management in hypertrophic cardiomyopathy are just derived from either non-randomized clinical data, observational data, or expert opinion and whatnot.

Here, we're showing you the management of obstructive hypertrophic cardiomyopathy in the new 2024 guidelines that were just recently published. And a lot of it resembles what the European guidelines show us, except when you come after having used beta-blockers or calcium channel blockers. So that's the first difference. But after you tried those, then you get a slew of options, which is myosin inhibitor, disopyramide, or considering septal reduction therapy. These were put at the same level so that you can have a discussion with the patient. But interestingly enough, this is not as simple because these therapies are not comparable in terms of their level of evidence. And it’s really putting them at the same level in a way that’s more reflective of practice rather than reflective of evidence.

And so you can see here, when you look at the actual text for the recommendation you get a Class 1 for patients getting beta-blockers or calcium channel blockers. But then you get a Class 1 with level of evidence randomized for the other recommendation of using a myosin inhibitor, disopyramide, or going to SRT. But the reality is the only one with randomized evidence is a myosin inhibitor. In this case, mavacamten in the guidelines. Disopyramide and SRT, septal reduction therapy, do not have randomized level of evidence. And so in the routine clinical practice, that's how we actually approach it. We approach it by recommending either a myosin inhibitor or septal reduction therapy to patients. But disopyramide is only, nowadays, recommended in really specific scenarios and situations.

And then, just the comparison to 2020 guidelines, which nothing changed except for the myosin inhibitors, you can see that the level of evidence is not randomized for disopyramide and septal reduction therapy.

How about management of nonobstructive HCM? As you have guessed it, there is actually nothing to manage nonobstructive HCM with. In the European guidelines, there is not much mentioned about this because, simply, there are no proven therapies. Here in the US guidelines, you get a level of evidence 1 for beta-blockers and calcium channel blockers, but those are not proven. And if you go and look at the citations from 1 to 5 for the guidelines, none of them actually provide strong evidence, even observational evidence, that this should be the case.

And so I just put this here, kind of just to give you a perspective. This is the recently published trial, open-label, that we've done in 41 patients with a myosin inhibitor aficamten. This is actually the most data that we have in this space and just gives you an idea how small the amount of data we have in this space. And we are very fortunate to have multiple phase 3 trials running in this space for myosin inhibitors, as well as other medications to try and generate more evidence for what we can use for these patients who typically have exercise limitations once they get symptomatic.

And touch briefly on this for evaluating genetics. The guideline recommendations are still somewhat restrictive, focusing on sarcomere, 8 genes in the sarcomere family. But we will be really missing a lot of the rare variants as well as a lot of the phenocopies. And so I would keep an open mind when evaluating genetics and go beyond the 8 genes mentioned here.

And then finally, to touch base on ICD use, this hasn't changed much. This looks like the typical guidelines where you have classic risk factors and then you could use non-sustained ventricular tachycardia and late gadolinium enhancement on CMR to guide you if you have intermediate risk there.

And so again, as I mentioned, in 2024, we are in a new era for hypertrophic cardiomyopathy. Before this era, you would have not have had any of these randomized clinical trials or open-label clinical trials. Here, we're talking about all these trials for mavacamten, aficamten, gene therapy, as well as many other drugs that are in development as well at this stage. And so that's what we want to strive for. We want to strive to move from the left-hand of this screen where we're looking at level of evidence that is mainly observational non-randomized expert consensus and 2A/2B to a level of evidence that is, A, randomized and Class 1 in hypertrophic cardiomyopathy. And I truly believe that we will get there in the next few years.

Thank you.

Dr. Barriales-Villa:
Thank you. Thank you very much, Ahmed, for this presentation. It's fantastic. A brief question. Do you think that in the future we're going to have just one guidelines, American and European together? I know, it's a tricky question, but what's your opinion?

Dr. Macri:
So that's an interesting question. I am not involved in the development of the American guidelines. I think there's still a lot of differences between the two at this stage in time. I don't think that the therapeutic interventions will be much different in the future. There's going to be so many clinical trials that you simply cannot ignore them in collective. And I think we're going to get to a stage where this Class 1 indication for beta-blocker is probably going to go away as well at some point in the future. I mean, you're competing against non-safety for a long time, you're competing against the prices of the beta-blockers being very cheap. But at the same time, you know, we have a head-to-head trial right now, MAPLE-HCM, running and if that shows that beta-blockers, essentially, are neutral or maybe even detrimental from a side effect and adverse event profile, then maybe this will change. But I think the divergence in the guidelines will continue to be in terms of risk of sudden death assessment and maybe as well as genetics. But mainly the risk of sudden death assessment, which you know, is very, very different between the two iterations. And I think that's one of the reasons why we might not be there anytime soon. But hopefully, because I think both European cardiologists as well as American cardiologists, they actually do use the guidelines interchangeably sometimes, and they do focus on which guidelines speak more to them. It's not necessarily that they focus on just one iteration or the other.

Dr. Barriales-Villa:
Okay. Thank you. Anyway, the future is bright for this disease. Thank you very much.