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Optimal pharmacological management of HCM by clinical manifestations

Dr. Garica-Pavia:
Hello. So today I'm going to talk about optimal pharmacological management of HCM by clinical manifestations.

These are my conflicts of interest.

Hypertrophic myopathy is a very heterogeneous disease. We certainly have patients who have a number of complications, but we also have some patients who have a benign, unstable outcome. When we have any patient with hypertrophic myopathy in our clinic, we have to address four domains. One is family issues and genetics. The other is estimation of sudden cardiac death risk and whether we want to implant or not an ICD on these patients. And then we have addressing cardioembolic complications and how to treat heart failure symptoms. These last two domains are the ones that we usually address through pharmacological therapies.

If we focus into the first one, cardioembolic complications, atrial fibrillation, now we know it's a very common arrhythmia in patients with hypertrophic myopathy. You can see here in this meta-analysis that more than 20% of patients with hypertrophic myopathy had concomitant AFIB. If we look into thromboembolic complications of these patients, we realize that it's really high. You see that the prevalence of thromboembolic complications in patients with HCM is above 27% in this meta-analysis. And we look into the incidence of thromboembolic complications per year in these populations, is about 3.7% which isroughly more than a CHADS-VASc risk of 2 in the CHADS-VASc score that we usually use to address thromboembolic risk in in patients with non-valvular atrial fibrillation. Therefore, all patients with hypertropic myopathy should be anticoagulated regardless of the CHADS-VASc score, because this is a young population where the CHADS-VASc score does not appear to correlate well with the clinical outcomes of these patients.

In contrast, we have other markers that we can use in order to predict thromboembolic complication in this population, as the left atrium size. Here, you can see a study that was conducted in Europe, and you can see how the relationship between left atrial size and thromboembolic complications increases with a left atrium about 45-50 mm.

There are several studies who address in the past what was the of anticoagulants in this population. And you see here that they do work. They do prevent embolic complications in this population.

If we go into the type of anticoagulation that we might use in these patients, there are emerging data showing that we can use indistinctively direct oral anticoagulants and vitamin K antagonists; and therefore we lately have a preference on direct oral anticoagulants, because certainly the use of them is more simpler than with vitamin K antagonist. And the treatment satisfaction of the patients is higher with no difference in efficacy.

When addressing heart failure complications, we have in mind that we have two type of patients, those with nonobstructive HCM and those with obstructive HCM. For those with nonobstructive HCM, we can use diuretics, drugs to control rhythm, and also drugs to control rate. As beta blockersor digoxin. Regarding diuretics, we can use every diuretic that is available, but there is emerging data about SGLT2 inhibitors, showing that these might be particularly effective and beneficial in this population of patients. This is a very small study from India with 48 patients, 24 treated with SGLT2 inhibitors, and 24 not treated with this agent.

You can see here that there was a benefit in those treated with SGLT2 inhibitors on diastolic parameters on echo, but also clinical

benefit that says, through NYHA class, 6-minute walking test, and NT-proBNP levels. There is emerging data from in vitro, so in the rationale of using these drugs in this population. And this is a study that was published in April 2024 showing that both three different SGLT2 inhibitors when administrated to of hypertrophic myopathy patients with the mutations, they enhanced relaxation in these. Therefore, this could be particularly beneficial for patients with hypertrophic myopathy, nonobstructive. And I'm sure we will see several clinical trials with these agents applied to these patients in upcoming years.

If we move into obstructive HCM patients, we certainly have a variety of different alternatives in them, some of them that have been used during more than 60 years, and all of them have been captured and included in the recently published HCM guidelines. You can see here that it was recommended in these patients who have symptoms to start therapy with beta blockers. And if they remain symptomatic, then move into calcium channel blockers. And if, even with this drug, they still are symptomatic, then at the same level, you can try this disopyramide or mavacamten, the first of its kind, a, cardiac myosin inhibitor. But it is interesting to see that the evidence below that support the use of these drugs in hypertrophic myopathy patients with obstruction is pretty limited.

You see here, the only clinical trial comparing with placebo that has assessed the effects of a beta blocker in these patients, this is the TEMPEST study, where 29 patients were randomized to receive metoprolol or placebo during 2 weeks and their switch to the other therapy. In this trial, it was shown that metoprolol decreased left ventricular outflow tract gradients at rest and also during exercise, but also improved symptoms without changing maximum exercise capacity on the CPET test. Moreover, it was shown that treatment with metoprolol was associated with increased stroke volume without changing PCP values in the right cath.

When assessing what is the evidence behind the use of verapamil or diltiazem, the data are even poorer, and this is one of the studies that was conducted in showing the beneficial effect of verapamil in these type of patients. This was published in 1993, it would involve 16 patients, but it is worth noting that only 8 of them will have being classified as obstructive HCM according to the type of definition that we are using nowadays. Regarding disopyramide, we really like this drug, which helps our patients, but it's usually associated with several side effects that sometimes are difficult to handle in these patients.

Lastly, we have the cardiac myosin inhibitors, mavacamten and aficamten, that have been developed over the last 2-3 years, with an impressive setup of different trials in different situations, so obstructive phase 2 and phase 3, and nowadays phase 3 nonobstructive HCM trials that are being conducted. We will need to see if these drugs are effective in this new scenario. But we certainly know from the results of the EXPLORER-HCM trial, a phase 3 trial in obstructive HCM, which was published in 2020, were that this agent is very effective in patients with hypertrophy myopathy, with an astonishing improvement in quality of life and also based on the decrease of left ventricular outflow tract obstruction and improvement in other parameters, like biomarkers, 6-minute walking test, and so on.

So we have a bright future ahead of us. Currently, pharmacological therapies for HCM are used to prevent embolic complications and treat heart failure symptoms. For those with nonobstructive HCM, we have diuretics and also rate-limiting medications. And for those with obstructive HCM, we now see that the therapy will probably change progressively with the incorporation of these new type of drugs called cardiac myosin inhibitors.

Thank you very much for your attention.