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When ß-Blockers Fall Short in oHCM: Time for a New Approach?

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Dr. Masri:
Hello. This is CE on ReachMD, and I'm Dr. Ahmad Masri. Here with me today is Dr. Anjali Owens.

So, Dr. Owens, despite the optimized guideline-directed medical therapy, what residual risks and patient impacts remain in obstructive hypertrophic cardiomyopathy?

Dr. Owens:
Thank you, Ahmad. It's a pleasure to be here today. And as you know, our first-line therapy, according to our 2024 guidelines for HCM, are really non-vasodilating beta-blockers and calcium channel blockers. And these drugs were not designed specifically for hypertrophic cardiomyopathy, but at least in the case of beta-blockers, can blunt adrenergic response and tone, and in some patients, that makes them feel a bit better.

However, we frequently run into side effects with these AV nodal blocker medications. In the case of beta-blockers, at higher doses, we certainly see fatigue. We can see erectile dysfunction. And at high doses, they can cause chronotropic incompetence that actually make patients feel worse in terms of their effort tolerance. With regard to calcium channel blockers, although better tolerated from a fatigue standpoint, we often run into problems like constipation that can be bothersome at higher doses.

And despite the use of these medicines, we frequently see that LVOT obstruction persists on follow-up echoes and that effort intolerance persists on stress echocardiogram. And we know that as long as that LVOT obstruction is present, that those patients are at risk for long-term adverse remodeling from the mitral regurgitation that's SAM mediated, as you know. We see progressive dilation of the left atrium that can lead to AFib, and, of course, long term, the development of pulmonary hypertension.

So despite use of first-line AV nodal blockers, we see that the disease itself progresses because these drugs were not developed to target HCM.

Dr. Masri:
Yeah, great. And you've alluded to this already. Treating symptoms is an important goal, for sure, but I think the evolving evidence is showing us that if you don't treat the underlying condition as well, the underlying hemodynamics and the pathophysiology, it's not very clear that you're actually achieving what you want to achieve.

This is where these cardiac myosin inhibitors came into play, because these are the only class of medications that affect the sarcomere, which is largely the underlying culprit in hypertrophic cardiomyopathy, by inducing or introducing hypercontractility. And you want to modulate that hypercontractility to improve symptoms, improve hemodynamics, and reduce the risk of progression to potentially heart failure and other things.

And I think, from an earlier introduction, compared with beta-blockers, we have the recent results of the MAPLE-HCM trial, which the natural progression of studying these drugs is that first you layer them on top of standard of care, but then MAPLE came and tested the idea that aficamten can be a frontline monotherapy, first-line monotherapy for these patients. And what we have seen is that really targeting this underlying pathophysiology was more beneficial in terms of improved exercise capacity, improved symptoms, reducing biomarkers and measures of wall stress, while our first-line therapy, metoprolol, as a reflection of beta-blockers, really led to a reduction in exercise capacity, slight improvement in symptoms. If you look at cross-trial comparison, it is within the magnitude of what is expected for placebo response and then worsened measures of wall stress without affecting LVOT gradients.

So I think this is, in a way, coming full circle back to this concept of do you really only rely on symptoms, or should you have other objective findings and markers that allow you to really confidently say, I think I am changing this natural history of the disease, and I think I am benefiting my patients beyond what is expected for some minor symptom improvement.

Dr. Owens:
I totally agree. I mean, it's very eye-opening to look at the MAPLE results in the context of what we've been doing for decades to patients, which is high-dose beta blockade. And as you highlighted in MAPLE, we finally had a trial of aficamten head-to-head against metoprolol, with the standard sort of up-titration of metoprolol to high doses at 200 mg a day, and what that really does to your heart. And so although you might have a slight improvement in KCCQ or symptomatology from the patient, you really are able to see objectively in this trial that exercise tolerance worsened, biomarkers worsened, left atrial size enlarged in the metoprolol group compared with stark improvements in the aficamten group. And I think that really brings us to a new era of what we should consider for first-line therapy in obstructive HCM.

So thank you for that, and that's all the time we have today. Join us for the next episode and thanks again.

Announcer:
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