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Current Concepts in Diagnosis and Management of Hypertrophic Cardiomyopathy

Managing the care of patients with HCM is challenging, primarily because of a lack of treatment options. Lifestyle factors remain important for improving left ventricular outflow tract (LVOT) gradient and — in effect — reducing

symptoms. The lifestyle management conversation includes specific recommendations relating to avoidance: avoidance of competitive sports, volume depletion, and intense isometric exertion, as well as staying away from certain therapies, such as angiotensin-converting enzyme inhibitors or amlodipine, to name two.

Sleep apnea can also be a contributing factor to HCM, suggesting that patients, especially patients with obesity, talk to their general practitioner about better managing their sleep apnea.

Once lifestyle has been addressed, the issue becomes medical therapy. So far there is not a lot to offer. Beta-blockers are considered first-line therapy because they reduce heart rate and

dynamic outflow tract obstruction. If beta-blockers are not tolerated, then calcium-channel blockers, like verapamil, become the next line of therapy.

Disopyramide is a class IA antiarrhythmic drug and a sodium-channel blocker that effectively reduces LVOT tract gradients in adults with HCM. The problem with this agent is its

side effects, which many patients may not tolerate.

For outflow tract obstruction, interventional options include alcohol septal ablation to reduce hypertrophied myocardium and surgical reduction, mostly via myectomy, which is strongly recommended to be performed in experienced centers with experienced surgeons.

With medical care largely limited to lifestyle factors, mostly managed with avoidance, and limited medical therapy available.

Fast-Moving Field

The management of patients with HCM may be one of the fastest-maturing realms of contemporary cardiovascular care. First via a National Institutes of Health-funded registry that is using

advanced imaging to improve risk stratification, and second, through the development of novel medical treatments that might avoid the need for septal reduction therapy.

The HCMR (Hypertrophic Cardiomyopathy Registry), funded by the National Heart, Lung, and Blood Institute, is a prospective database of 2,755 patients with HCM recruited from

44 sites in six countries. The case population is representative of "real-world" HCM practice. Based on their European Society of Cardiology risk scores, the patient population is of low risk at the start of this 5-year effort.

The primary goal of the registry is to improve risk prediction to better estimate an individual patient's

likelihood of developing heart failure or experiencing sudden cardiac death.

The plan is to integrate CMR imaging, biomarker, and genetic data with standard clinical and echocardiographic findings; more specifically, data gathered include high-sensitivity troponin T, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and genotype analysis to assess

whether these novel biomarkers provide additional risk stratification. Then data mining techniques will be used to develop better predictive measures.

Why CMR? Myocardial fibrosis, measured by CMR, has gained interest as a potential determinant of risk in patients with HCM. The presence of substantial late gadolinium enhancement, a marker of replacement

fibrosis, has been associated with a 2-fold increase in sudden cardiac death risk and a 3-fold increase in composite events if present in >15% of left ventricular mass.

It is expected that insights gained from HCMR will directly impact patient care by providing a systematic evidence base to inform and advance

management guidelines and develop predictive models.

Early Lessons

Recently, the baseline characteristics of the HCMR were published in *JACC (***Ref 1),** Two relatively distinct populations were identified. One, sarcomere mutation positive, is more likely to demonstrate reverse septal curvature

morphology and have more extensive late gadolinium enhancement (LGE). This group likely has less resting LVOT obstruction. The second group, sarcomere mutation negative, is more likely to demonstrate isolated basal septal hypertrophy, with less LGE but more LVOT obstruction.

As the investigators explained, the first of these groups represents the

Mendelian form of familial HCM. The second group more likely has multifactorial disease, as evidenced by the higher burden of causes of secondary left ventricular (LV) hypertrophy due to factors such as hypertension, high body mass index, male sex, older age, etc. The key feature in many HCM patients is dynamic LVOT; it is not fixed

obstruction, like aortic stenosis, but rather dynamic depending on the loading and physiologic conditions. This explains why the lifestyle conversation is so important; it is possible to impact outflow tract gradient and, in effect, symptoms with lifestyle changes.) And the second group (more likely to have multifactorial disease) has more LVOT obstruction.

The finding that significant resting outflow obstruction indicates a lower likelihood of the familial form of HCM was not suspected. The authors added that it was also notable that apical HCM is less likely to reflect sarcomeric HCM.

An Alternative to Septal Reduction?

The newest clinical study of mavacamten, relates to a first-in-class reversible inhibitor of cardiac-specific myosin.

A myosin inhibitor reduces myocyte contractility and, in numerous small studies, mavacamten has been shown to reduce outflow tract obstruction. Indeed, it can take a patient with a severe gradient and take outflow tract

obstruction down close to zero without having an impact on ejection fraction (EF).

The results of the MAVERICK-HCM trial were recently reported in *JACC* and suggest that the drug improves myocardial wall stress.(**Ref 2**) Specifically, in the double-blind, placebo-controlled, dose-ranging phase II study, mavacamten was generally

well tolerated and associated with significant dose-dependent reductions in NT-proBNP (reduced by 53% in the pooled mavacamten group versus 1% in the placebo group; p = 0.0005) and cardiac troponin I plasma levels (decreased by 34% in the pooled mavacamten group versus a 4% increase in the placebo group; p = 0.0009).

Dr. Desai is heading up VALOR-HCM, a blinded, placebo-controlled phase III trial trying to determine whether mavacamten can be an effective alternative to septal reduction therapy. Patients are being randomized to mavacamten or placebo and then evaluated at 16 and 32 weeks to determine whether to proceed with septal reduction therapy.

One pressing question to be addressed is the long-term effect of reducing contractility. Dr. Desai said, "We don't know whether it will lower ejection fraction and cause heart failure, although that hasn't been seen in preliminary studies."

In MAVERICK-HCM, 12.5% of patients (n = 5) had a drop in their LVEF to ≤45%, which led to stopping the drug

per pre-specified protocol. All five patients had recovery of LVEF and experienced no long-term negative effects.

In commenting on MAVERICK-HCM, commentators wrote, "In the future, we may see targeted pharmacological approaches in genetically at-risk family members of all forms of HCM patients in addition to gene-therapy

treatments."(**Ref 3**) They added, MAVERICK-HCM "has offered a glimmer of hope in a high-risk nonobstructive HCM population with limited available therapies."

Take-home Messages:

- The Hypertrophic Cardiomyopathy Registry (HCMR) is the largest systematic, prospective natural

history study of patients with hypertrophic cardiomyopathy (HCM). It includes comprehensive cardiac magnetic resonance (CMR) imaging data in addition to other clinical metrics, genotyping, and biomarker analysis.

- HCMR should facilitate patient-specific risk profiling to identify those at risk of heart failure,

arrhythmias, and other adverse outcomes, including mortality.

- In patients with nonobstructive HCM, the myosin inhibitor mavacamten was generally well tolerated and associated with a reduction in key biomarkers, suggesting that active therapy improves myocardial wall stress and

might be an effective alternative to septal reduction therapy.

References:

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