Mavacamten for Hypertrophic Cardiomyopathy

Revised Scope Background and Scope

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Background

Hypertrophic cardiomyopathy (HCM) is a disorder of the heart due to dysfunction of the sarcomeres in cardiac muscle cells (myocytes).[1] Sarcomeres are cellular structures that are critical in myocyte contraction. The sarcomere dysfunction in HCM can lead to hypertrophy (thickening) of the heart. HCM can be due to a number of heritable genetic defects affecting sarcomere proteins. Hypertrophy related to sarcomere dysfunction distinguishes HCM from other forms of cardiac hypertrophy, such as hypertrophy caused by chronic high blood pressure, infiltrative disorders such as cardiac amyloidosis (a different disorder caused by deposition of proteins in heart muscle cells), or healthy, adaptive hypertrophy from athletic training. As such, doctors often need to perform tests to distinguish HCM and other forms of hypertrophy. In some cases, it can be difficult to differentiate HCM from other types of hypertrophy.

Specific single-gene mutations in 15 genes have been identified as associated with HCM,[2] although patients can have the clinical appearance of HCM (phenotypic HCM) without an identified gene mutation. The exact prevalence of HCM is uncertain and asymptomatic patients may only be diagnosed with HCM when an imaging test is performed for a different reason. An estimate using echocardiographic screening suggested a prevalence of HCM of 0.2%,[3] but screening with cardiac magnetic-resonance imaging, which is more sensitive and specific for cardiac hypertrophy, found a prevalence of 1.4%.[4] Not all patients with HCM mutations develop hypertrophy.[5]

Because of the thickening of the heart that can occur, a subset of patients with HCM can have narrowing and obstruction of the left ventricular outflow tract (LVOT), the path that blood takes when it exits the heart to the body. Of those with LVOT obstruction, some patients only have LVOT obstruction when they exert themselves and others have LVOT obstruction at rest. When blood is obstructed leaving the heart, patients can feel short of breath particularly with exertion. This syndrome of HCM with LVOT obstruction is called hypertrophic obstructive cardiomyopathy (HOCM or OHCM).

Although obstruction of the LVOT is a cause of exertional symptoms, including shortness of breath, patients with both HCM and HOCM can have these symptoms for other reasons. The mechanisms of exertional symptoms are diverse and can include diastolic dysfunction (difficulty filling the heart

with blood) and microvascular angina (chest discomfort from not enough blood supplying the thickened heart), in addition to LVOT obstruction.[6] Although many patients with HCM and HOCM have a normal life expectancy without symptoms, even asymptomatic patients are at risk of sudden cardiac death (SCD) and atrial fibrillation with risk of cardioembolic stroke.[6] With appropriate selection of higher-risk patients for implantable cardioverter-defibrillators (ICDs), the risk of SCD has decreased to about 0.5% per year.[7] When patients with HCM also develop atrial fibrillation, the risk of cardioembolic stroke is high,[8] and guidelines recommend anticoagulation regardless of other risk factors.[9]

For HOCM patients with exertional symptoms thought to be related to the LVOT gradient, principles of therapy involve reducing the magnitude of the LVOT gradient, which generally improves symptoms. Pharmacological approaches involve therapies that reduce cardiac contractility (negative inotropic agents) including beta blockers and calcium channel blockers.[10] For patients who still have symptoms or who are unable to tolerate these agents, invasive strategies such as septal myectomy (open heart surgery to remove a portion of heart muscle) or alcohol septal ablation (a catheter-based controlled heart attack to reduce the heart muscle tissue in the obstructed area) are considered.[10] No randomized trial has compared surgical myectomy to alcohol septal ablation, but guidelines favor surgical myectomy in most patients.[6]

A novel agent, mavacamten (Bristol Myers Squibb), has been tested in clinical trials. Mavacamten is an oral medication administered once per day that directly reduces adenosine triphosphatase activity in cardiac myosin heavy chain, one of the proteins in heart muscle cells.[11] This is a key step in how heart muscle cells make energy for contracting the heart. Unlike other therapies that reduce symptoms for HOCM patients, mavacamten more directly addresses the underlying disease process of HOCM by inhibiting sarcomeric contraction.[11] Mavacamten is under FDA review with an expected decision date in early 2022.

Stakeholder Input

The Revised Scope was developed with input from diverse stakeholders, including patients and patient groups, clinical experts, researchers, and the manufacturer of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders. All stakeholders emphasized the need for new therapies for patients with HOCM. We received extensive input from individual patients and patient groups highlighting the impact of HOCM on quality of life and the importance of individual decision-making. Patient groups emphasized the variability in patient experiences and outcomes, including those highlighted in "The Voice of the Patient Report for Hypertrophic Cardiomyopathy."[12] Clinicians reiterated the need for shared decision-making between patients and providers but had divergent opinions about mavacamten's place in therapy relative to existing treatment options, including surgery. ICER looks forward to continued engagement with additional stakeholders throughout its review

and encourages comments to refine our understanding of the clinical effectiveness and value of treatments.

Report Aim

This project will evaluate the health and economic outcomes of mavacamten for HOCM. The ICER Value Framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms—including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs—are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient groups, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the Revised Scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults with symptomatic HOCM. As data allow, we plan to review any available data in children with symptomatic HOCM. We may also separately review available evidence for the intervention in patients with symptomatic HCM without obstruction.

Interventions

The intervention of interest is mavacamten in addition to usual care.

Comparators

Mavacamten will be compared with usual care. This will include comparisons with adding mavacamten to existing therapy as would be estimated by the placebo arms of clinical trials, but may also involve comparisons with alternative therapies including medications typically used later than first line (e.g., disopyramide) and septal reduction procedures (e.g., myectomy and alcohol septal ablation).

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Symptoms of HOCM such as exertional intolerance, fatigue, shortness of breath, dizziness, arrhythmia, chest discomfort, mental acuity (with particular attentiveness to patient-reported outcomes)
    - Requirement for exercise restriction
    - Anxiety and depression
    - Overall mortality
    - SCD
    - Need for implantation of ICD
    - Heart failure
    - Rate of septal reduction therapy (septal ablation or myectomy)
    - Atrial fibrillation and stroke
    - Adverse events including:
        - Treatment-emergent adverse events and serious adverse events
- Other Outcomes
    - Peak oxygen consumption (pVO2 exercise capacity)
    - Post-exercise LVOT gradient and resting LVOT gradient
    - Left ventricular ejection fraction
    - New York Heart Association (NYHA) functional class
    - Cardiac biomarkers such as N-terminal pro B-type natriuretic peptide and high-sensitivity cardiac troponin I

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on the severity of the condition being treated
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)
Potential Other Benefit or Disadvantage†
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Health inequities
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape—to some extent—how the value of any effective treatments for a particular condition will be judged.

†Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a *de novo* economic model to assess the lifetime cost effectiveness of mavacamten in addition to usual care compared with usual care alone. We may also consider the lifetime cost effectiveness of mavacamten relative to surgical options (e.g., myectomy). The model structure will be based in part on a literature review of prior published models of cardiomyopathy as well as related conditions such as heart failure. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per quality-adjusted life year (QALY), and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The target population will consist of adults in the United States with symptomatic HOCM; we will not be modeling mavacamten in patients with HCM without obstruction. The model will consist of health states including heart failure as represented by different NYHA classes. A cohort of patients will transition among states during predetermined annual cycles over a lifetime time

horizon, modeling patients from treatment initiation until death. In addition, cost effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality-of-life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness among interventions. Treatment effectiveness will be estimated based on best available evidence, which may also involve a meta-analysis if evidence allows.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events, and direct medical costs. The health outcome of each intervention will be evaluated in terms of procedures or surgeries avoided, life years gained, QALYs gained, and equal value of life years gained (evLYG). Quality-of-life weights will be applied to each health state, including quality-of-life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life year gained, and cost per procedure or surgery avoided.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment price and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such intervention. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by mavacamten (e.g., need for septal myectomy or ablation), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of HOCM beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

1. Toepfer CN, Garfinkel AC, Venturini G, et al. Myosin Sequestration Regulates Sarcomere Function, Cardiomyocyte Energetics, and Metabolism, Informing the Pathogenesis of Hypertrophic Cardiomyopathy. *Circulation.* 2020;141(10):828-842.
2. Ingles J, Burns C, Barratt A, Semsarian C. Application of Genetic Testing in Hypertrophic Cardiomyopathy for Preclinical Disease Detection. *Circulation: Cardiovascular Genetics.* 2015;8(6):852-859.
3. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation.* 1995;92(4):785-789.
4. Massera D, McClelland RL, Ambale-Venkatesh B, et al. Prevalence of Unexplained Left Ventricular Hypertrophy by Cardiac Magnetic Resonance Imaging in MESA. *Journal of the American Heart Association.* 2019;8(8):e012250.
5. Maurizi N, Michels M, Rowin EJ, et al. Clinical Course and Significance of Hypertrophic Cardiomyopathy Without Left Ventricular Hypertrophy. *Circulation.* 2019;139(6):830-833.
6. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary. *Circulation.* 2020;142(25):e533-e557.
7. Maron BJ, Rowin EJ, Maron MS. Paradigm of Sudden Death Prevention in Hypertrophic Cardiomyopathy. *Circulation Research.* 2019;125(4):370-378.
8. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation.* 2001;104(21):2517-2524.
9. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Circulation.* 2014;130(23):e199-e267.
10. Fifer MA, Vlahakes GJ. Management of Symptoms in Hypertrophic Cardiomyopathy. *Circulation.* 2008;117(3):429-439.
11. Green EM, Wakimoto H, Anderson RL, et al. A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. *Science.* 2016;351(6273):617-621.
12. Hypertrophic Cardiomyopathy Association (HCMA). The Voice of the Patient Report for Hypertrophic Cardiomyopathy (HCM). https://www.4hcm.org/finalreportpfdd. Published 2021. Accessed 05/02/2021, 2021.