An economic systematic literature review for hypertrophic obstructive cardiomyopathy

Poster code: EE200

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Background

- Hypertrophic cardiomyopathy (HCM) is a chronic, complex, and multifactorial myocardial disorder characterized by left ventricular hypertrophy[1–4]
- Obstructive HCM can lead to debilitating symptoms (such as shortness of breath, fatigue, arrhythmias, chest pain, and syncope) and is associated with an increased risk of sudden cardiac death and adverse cardiovascular events[1]
- The objective of this systematic literature review (SLR) was to identify economic evaluations (EEs), health state utility values (HSUVs), and healthcare cost and resource use (HCRU) data associated with obstructive HCM and its treatments

Methods

- A systematic search of electronic databases including MEDLINE, Embase, EconLit, PsycINFO, and the International Health Technology Assessment (HTA) Database was conducted in December 2021 and updated in July 2023, in compliance with Preferred Reporting Items for Systematic reviews and Meta-Analyses and Cochrane Collaboration guidance
- Supplementary searches were conducted of conference proceedings since 2019, gray literature (PubMed/Google Scholar, HTA, and health economics websites), and bibliographies of all SLRs, HTAs, and EEs identified as part of database searches
- Full inclusion criteria are presented in **Table 1**
- In brief, studies were included if they reported:
  — adults (≥18 years) with diagnosed obstructive HCM
  — incremental costs and/or benefits associated with pharmacological therapies and/or septal reduction therapy (SRT) for the treatment of obstructive HCM, or HSUVs or HCRU data associated with obstructive HCM
- Record screening was performed by 2 independent researchers using the predefined eligibility criteria, with any disagreements resolved by a third reviewer
- The quality of EEs was assessed using the Drummond checklist

Results

- The December 2021 and updated July 2023 searches yielded 954 and 403 unique records, respectively, following deduplication
- The title/abstracts of the records were screened against predetermined eligibility criteria; 181 unique records were reviewed at full-text stage
- After factoring in results from the supplementary searches, 7 unique EEs, 2 HSUV studies, and 55 HCRU studies were included in total across the SLR and the update[a]

Economic evaluations

- The methodologies of the EEs, conducted from the perspective of 5 different countries (Australia, Canada, England, the Netherlands, and US), are summarized in **Table 2**. These included submissions to 3 HTA bodies: National Institute for Health and Care Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC), and Canadian Agency for Drugs and Technologies in Health (CADTH)
- Five of the studies included cost-effectiveness analyses, 1 was a cost-minimization analysis, and 1 was a net health benefit model. All studies used a Markov approach for modeling, with 6 analyses using a Markov model and 1 study, Institute for Clinical and Economic Review (ICER) 2021, using a semi-Markov model
- The majority of analyses (57%, 4/7) were conducted from a healthcare-payer perspective
- All models used health states based on New York Heart Association (NYHA) functional class, and 6/7 specifically modeled the pathways of patients with symptomatic obstructive HCM (the remaining was a conference abstract that did not specify severity)
- All of the analyses included mavacamten as the intervention, with 6/7 studies reporting that mavacamten, a myosin inhibitor, was used with standard of care (SoC; beta-blockers [BBs]/calcium channel blockers [CCBs]). Six studies compared mavacamten with SoC (BBs/CCBs), 2 studies with alcohol septal ablation (ASA) and myectomy, and 1 study with disopyramide
- Six analyses used a lifetime horizon, and 1 used a 25-year time horizon
- All but 1 of the analyses used data from EXPLORER-HCM (NCT03470545) to inform mavacamten efficacy, while the remaining study reported that data were sourced from the Tufts Medical Center. Three studies used additional data from the EXPLORER cohort of MAVA-LTE, the long-term extension study of EXPLORER-HCM
- Clinical data for comparator arms were sourced from a range of published literature and expert opinion
- Six models used utility data from EXPLORER-HCM. Resource use and cost inputs were taken from a variety of sources, dependent on the geographical focus

Table 1. PICOS inclusion criteria

Category	Economic evaluations	Utilities	Healthcare cost and resource use
Population	Adults (≥ 18 years) with diagnosed obstructive HCM		
Interventions/ comparators	• Non-vasodilating BBs (atenolol, bisoprolol, metoprolol, nadolol, pindolol, propranolol, sotalol) • Non-dihydropyridine CCBs (verapamil, diltiazem) • Class IA anti-arrhythmics (disopyramide, cibenzoline) • Angiotensin receptor neprilysin inhibitors (sacubitril valsartan) • Cardiac myosin inhibitors (mavacamten, aficamten) • SRT (ventricular septal myectomy, ASA)	• Any or none	• Any or none
Outcomes	• ICERs • Cost per clinical outcome • Total QALYs • Total LYG • Total costs • Incremental costs and QALYs	• HSUVs measured using a validated, published tool including (but not limited to): direct elicitation methods (e.g. standard gamble or time trade-off); indirect elicitation methods (e.g. EQ-5D, SF-6D, HUI, HUI2, or HUI3); and mapping from generic or disease-specific HRQoL measures (e.g. SF-36)	• Direct HCRU, including (but not limited to): treatments, administration, and hospitalization (inpatient/outpatient/ICU) • Indirect HCRU, including (but not limited to): productivity loss, home adaptation, and travel costs
Study type	• Cost-utility • Cost-effectiveness • Cost-consequence • Cost-benefit • Cost-minimization	• Any study design	• Any study design
Other considerations	• Peer-reviewed literature • Congress abstracts published in or after 2020 • Studies on human participants	• Peer-reviewed literature • Congress abstracts published in or after 2020 • Studies on human participants	• HCRU studies published in the last 10 years (2013 onwards) • Congress abstracts published in or after 2020 • Studies on human participants

ASA, alcohol septal ablation; BB, beta-blocker; CCB, calcium channel blocker; HCM, hypertrophic cardiomyopathy; HCRU healthcare cost and resource use; HRQoL, health-related quality of life; HSUV, health state utility value; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LYG, life-years gained; PICOS, Population, Intervention, Comparison, Outcomes, and Study type; QALY, quality-adjusted life-year; SF-6D, short-form 6-dimension; SF-36, 36-item short-form; SRT, septal reduction therapy.

Table 2. Summary of economic evaluations

Study, country, and perspective	Type of analysis and model	Model health states	Interventions, comparators, and sequencing	Time horizon and cycle lengths	Discounting	Currency and cost year
Buisman 2023, *Value Health* The Netherlands, societal perspective	Cost-effectiveness, Markov	NYHA classes I, II, III, and IV, and death	Mavacamten plus SoC (defined as BBs/CCBs) vs SoC alone	Lifetime horizon Cycle length NR	1.5% for benefits, 4% for costs	EUR Cost year NR
CADTH 2023 Canada, healthcare decision-makers	Cost-effectiveness, Markov	NYHA classes I, II, III, and IV, and death	Mavacamten with BBs/CCBs vs BBs/CCBs alone	Lifetime horizon Variable cycle length (2 or 4 weeks) for the first 30 weeks consistent with EXPLORER-HCM; 4-week cycle length after 30 weeks	1.5% for costs and benefits	CAD Cost year NR
Daaboul 2022, *J Am Coll Cardiol* US, healthcare payer	Cost-minimization, Markov	NYHA classes I, II, and III/IV, and death	Mavacamten vs SRTs	Lifetime horizon Cycle length NR	3% for costs	USD Cost year NR
Desai 2022, *Clin Ther* US, perspective NR	Net health benefit, Markov	NYHA classes I, II, and III/IV, and death	Mavacamten plus SoC (defined as BBs/CCBs) vs SoC alone	Lifetime horizon Variable cycle length (2 or 4 weeks) for the first 30 weeks consistent with EXPLORER-HCM; 4-week cycle length after 30 weeks	3% for benefits, NR for costs	USD Cost year NR
ICER 2021 (Sarker 2022) US, healthcare sector	Cost-effectiveness, semi-Markov	NYHA classes I, II, and III/IV, and death	Mavacamten with BBs/CCBs vs BBs/CCBs alone, disopyramide, or SRTs	Lifetime horizon, 4-week cycle length, based on available clinical data	3% for costs and benefits	USD Cost year 2021
NICE 2023 England, NHS and personal social services perspective	Cost-effectiveness, Markov	NYHA classes I, II, III, and IV, and death	Mavacamten plus SoC (defined as BBs/CCBs) vs SoC alone Following discontinuation from mavacamten the following treatment sequence was used: BB/CCB monotherapy, disopyramide combined with BB/CCB, SRT combined with BB/CCB	Lifetime horizon Variable cycle length (2 or 4 weeks) for the first 30 weeks consistent with EXPLORER-HCM; 4-week cycle length after 30 weeks	3.5% for costs and benefits	GBP Cost year 2021
PBAC 2022 Australia, healthcare system perspective (not explicitly stated, but assumed to be as a PBAC submission)	Cost-effectiveness, Markov	NYHA classes I, II, and III/IV, and death	Mavacamten plus SoC (defined as BBs/CCBs) vs SoC alone Following discontinuation from mavacamten the following treatment sequence was used: BB/CCB monotherapy, disopyramide combined with BB/CCB, SRT combined with BB/CCB	25 years Variable cycle length (2 or 4 weeks) for the first 30 weeks consistent with EXPLORER-HCM; 4-week cycle length after 30 weeks	5% for costs and benefits	AUD Cost year 2018/19

AUD, Australian Dollar; BB, beta-blocker; CAD, Canadian Dollar; CADTH, Canadian Agency for Drugs and Technologies in Health; CCB, calcium channel blocker; GBP, British pound sterling; ICER, Institute for Clinical and Economic Review; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; NYHA, New York Heart Association; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; SoC, standard of care; SRT, septal reduction therapy; USD, US Dollar.

Health state utility values

- HSUVs were available from 2 studies: EXPLORER-HCM, a randomized controlled trial in symptomatic obstructive HCM assessing mavacamten versus placebo that reported EQ-5D-5L utility data with US valuation; and SPIRIT-HCM (NCT03092843), a prospective observational study in patients with symptomatic obstructive HCM undergoing a septal myectomy
- In the US value set analysis of EXPLORER-HCM, the mean (standard deviation) change from baseline utility score at week 30 for mavacamten and placebo was 0.084 (0.163) and 0.009 (0.163), respectively. The unadjusted difference in mean change from baseline to week 30 between mavacamten and placebo was 0.075 (p = 0.002). The difference between mavacamten and placebo at 30 weeks using median scores and an Australian value set was 0.060[5]
- EXPLORER-HCM stratified utility scores by NYHA class, demonstrating significant decreases in utility scores as patients' symptoms worsen (i.e. as they move to a higher NYHA class)
- SPIRIT-HCM reported EQ-5D (-3L or -5L was not specified) utility scores for patients with symptomatic obstructive HCM undergoing septal myectomy. Utility scores significantly improved after surgical myectomy with a mean (95% confidence interval) change in baseline score of 0.18 (0.09–0.27; $p < 0.001$)
- The mean utility score at baseline of patients in SPIRIT-HCM was noted as being lower than the mavacamten arm of EXPLORER-HCM using a US value set (0.62 vs 0.814)

Healthcare cost and resource use

- The majority of data identified by the SLR were HCRU data and were heterogenous in nature. In total, 25 studies reported cost data alone or in addition to resource use data. Cost years spanned from 2011 to 2021, although most studies (15/25) did not report a cost year
- Studies were conducted in 12 different countries, with the majority from the US (36 studies), followed by the UK (5 studies), Germany (3 studies), and Japan (2 studies), with the remaining countries only being reported by 1 study each (Belgium, Brazil, Canada, China, France, Italy, Spain, and Sweden)
- The characteristics of populations included general patients with obstructive HCM, symptomatic patients, patients undergoing surgery (e.g. ASA, septal myectomy, or mitral valve procedures), patients with and without atrial fibrillation, patients older and younger than 65 years, and hospitalized patients
- Twenty-three studies reported baseline data by NYHA class. In general it was found that as NYHA class increased (i.e. a patient's symptoms worsened), healthcare costs also increased
- Cost data covered a range of domains, but most commonly reported inpatient/hospitalization costs (20 studies) or aggregated total costs (10 studies)
- Resource use was similarly diverse, most commonly covering hospital length of stay (38 studies), surgery (29 studies), hospitalization (15 studies), or rehospitalization (12 studies)
- Inpatient visits were more numerous among patients undergoing SRT; no definitive trends were noted among mean emergency and outpatient visits, with the latter varying widely: as low as 0.5 visits per patient per year among nonsurgically managed, asymptomatic patients, to 50.2 visits per patient per year among patients at 12-month follow-up after septal myectomy
- While no indirect cost data were noted, 2 studies published in 2023 reported indirect resource use. Charron 2023[6] reported increasing sick leave days per year as obstructive HCM symptoms worsened for French patients with NYHA classes I, II, III, and IV, respectively. Lowe 2023[7] reported that patients with obstructive HCM required a mean 33.9 and 51.5 support hours per week for patients in Italy and Spain, respectively. In addition, 46.9% and 85.7% required carer support in Italy for patients in NYHA classes III and IV, respectively. Similarly, 38.7% and 100% of patients with obstructive HCM in NYHA classes III and IV, respectively, required support in Spain

Conclusions

- A variety of heterogeneous cost and resource use data were identified, together with substantially fewer EEs and health state utility data. Changes in HSUVs and HCRU were found to be associated with changes in NYHA class, with increased cost and resource use burden and reduced utility for patients with worse symptoms, indicating the substantial burden that obstructive HCM places on healthcare systems and individuals
- All of the EEs included mavacamten as an intervention, with the majority using SoC (BBs/CCBs) as a comparator. This reflects the positioning of mavacamten within the treatment pathway as recommended by the 2023 European Society of Cardiology guidelines. There was similarity across the model types, health states, and assumptions
- The majority of HCRU data were from the US, revealing gaps in the literature for other healthcare systems
- Several studies failed to report disaggregated costs and were opaque in their reporting, making comparisons between studies difficult and limiting the ability to assess whether these data are reflective of clinical practice
- Indirect resource use data suggest the burden associated with care needs was substantial and increased as obstructive HCM symptoms worsened. Further research is needed to fully quantify the societal impacts of this condition

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Disclosures

- David Slater, Ellie Boulton, Hannah Luedke, and Alex Pashley are employees of Costello Medical.
- Taryn Krause, Michael Hurst, and Ervant J Maksabedian Hernandez are employees of Bristol Myers Squibb and may own stock options.

[a]Note: the number of included studies reported in the abstract has been updated in the poster owing to additional linking of study publications

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