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Economic and humanistic burden in patients with obstructive hypertrophic cardiomyopathy – a systematic literature review

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Introduction

- Hypertrophic cardiomyopathy (HCM) is a rare, chronic, progressive disorder characterized by primary left ventricular hypertrophy that results in excessive contraction of the heart muscle, leading to cardiac dysfunction.
- Obstructive HCM is a subtype of HCM, characterized by obstruction to the left ventricular outflow tract.
- Standard of care pharmacological treatments for obstructive HCM provide symptomatic relief and may include beta blockers, calcium channel blockers and antiarrhythmics, such as disopyramide.[1,2]
- Invasive interventions for moderate to severe obstructive HCM, in spite of maximally tolerated drug therapy, include septal reduction therapies (SRTs) such as septal myectomy and alcohol septal ablation.[1,2]

Objective

- The objective of this systematic literature review (SLR) was to identify economic evidence relevant to obstructive HCM in adults, including economic evaluations, healthcare resource use (HCRU), costs, quality of life (QoL), and health-state utilities associated with treatments and the disease state.

Methods

- An SLR was performed using a prespecified protocol, to identify relevant economic evaluations, HCRU, costs, QoL, and utility studies.
- Literature searches were conducted with no language or geographical restrictions in Medline (In-Process), Embase, APA PsychINFO, and EconLit via the ProQuest platform, together with NHS EED, DARE, HTA databases via the Centre for Reviews and Dissemination platform.
  - Searches were run from database inception until August 2, 2021, then updated on December 3, 2021.
- Relevant gray literature sources including cardiovascular conference proceedings, and HTA websites were also searched for data available up to 3 years prior to August 2, 2021, with searches updated on December 3, 2021.
- The inclusion criteria are presented in **Table 1**, as defined using the PICOS framework.
- Record screening was performed by 2 independent researchers, using the predefined inclusion and exclusion criteria with any disagreements resolved by a third reviewer.

Results

Study selection

- The results from both literature searches (August 2, 2021 and December 3, 2021) were combined.
- In total, 41 records reporting on 36 studies and reports met the predefined inclusion criteria (**Table 1**).
- Of those included, there was 1 economic evaluation, 27 studies with HCRU, 10 with costs, 11 with health-related quality of life (QoL), and 1 with utilities, respectively. There were no studies providing disutilities.
- Just 1 study reported data associated with pharmacological treatment (mavacamten, EXPLORER-HCM). The majority of studies evaluated invasive interventions (n = 26) or pacing (n = 4), with the remainder reporting at a disease level (n = 4).
- While studies were conducted in several countries, the majority were conducted in the USA (**Table 2**).

Economic models

- A *de novo* semi-Markov cost-utility model comparing mavacamten with standard of care (beta blockers and/or calcium channel blockers), disopyramide, myectomy and septal ablation over a lifetime time-horizon from a US healthcare sector perspective was identified (ICER report 2021). Outcomes included cost per quality-adjusted life-year gained and cost per life-year gained. The model was developed using available clinical data and a placeholder price, given the analysis predated mavacamten launch in the USA. The report concluded that the results were inconclusive because the actual cost-effectiveness of mavacamten will depend on its (real) price.

Resource use

- Of the 27 studies that reported resource use, 23 studies reported data associated with invasive interventions: 1 on non-cardiac surgery, 11 studies on septal myectomy (with or without concomitant treatments), 4 studies on alcohol septal ablation, 1 study on both septal myectomy and alcohol septal ablation, 2 on mitral valve repair and plication, 2 on resection-plication-release repair, 1 on trans-atrial Alfieri repair, and 1 on short atrioventricular delay pacing.
  - The majority (n = 22) of studies reported the length of stay (LOS) in hospital, which ranged from 2 days to 19 days for the treatment of patients with obstructive HCM.
  - Among these, 5 studies reported on LOS in an intensive care unit setting for septal myectomy (n = 3, range 2.7 to 4 days), septal myectomy plus prophylactic amiodarone (n = 1, median 2 days), or myectomy with papillary muscle realignment (n = 1, mean 2.6 days).
- Four studies provided data related to obstructive HCM overall including number of annual hospitalizations, the numbers of ER visits and outpatient visits and the LOS in hospital.

Healthcare costs

- Only direct healthcare costs were identified by the SLR. From a total of 10 studies:
  - three studies compared septal myectomy with alcohol septal ablation, 1 focused on septal myectomy, 1 reported on alcohol septal ablation, and 1 on short AV delay pacing and myectomy. These studies reported on costs related to obstructive HCM, inpatient hospitalization, HCM-related medication, surgery, outpatient visits, and hospitalization in the event of complications.
  - four studies reported on disease-level costs such as summary hospitalization, outpatient and emergency department visits, and pharmacy costs.
- Nine studies reported direct costs for the USA in USD and 1 study reported direct hospitalization costs associated with SRT in Sweden (in SEK).
- The data demonstrated high costs associated with SRT. Total hospitalization costs ranged from 35,024 USD to 162,203 USD for septal myectomy and from 15,661 USD to 84,041 USD for alcohol septal ablation. Hospitalization costs were significantly lower for septal ablation (15,661 USD for males, 16,465 USD for females) than for septal myectomy (36,754 USD for males, 35,025 USD for females) (p = 0.001) when compared directly.
- No studies were identified reporting on cost data associated with pharmacological treatments for obstructive HCM.
- No information on indirect costs associated with obstructive HCM were identified.

QoL and health state utilities

- Twelve studies reporting on health-related QoL and utilities of patients with obstructive HCM were identified. Of those, 10 studies provided QoL data for patients who underwent SRT or pacing and 1 study provided QoL and utility data from a randomized controlled trial assessing the effectiveness of mavacamten versus placebo for the treatment of obstructive HCM.

Table 1. Prespecified inclusion criteria of the SLR

	Population	Intervention / Comparator		Outcomes	Study design
Economic evaluations	Adult (≥ 18 years) diagnosed with obstructive HCM	• Non-vasodilating BB - Atenolol - Bisoprolol - Metoprolol - Nadolol - Pindolol - Propranolol - Sotalol • Non-dihydropyridine CCB - Verapamil - Diltiazem • Class IA anti-arrhythmic - Disopyramide - Cibenzoline	• Angiotensin receptor neprilysin inhibitor - Sacubitril valsartan (Entresto) • Cardiac myosin inhibitor - Mavacamten - CK-274 • SRT - Ventricular septal myectomy - Alcohol septal ablation • Placebo • Standard of care • No comparator • Any of those listed compared with each other	• Incremental cost-effectiveness ratio • Incremental cost-utility ratio • Incremental costs • Quality adjusted life-years • Life-years gained	• Cost-effectiveness evaluations • Cost-utility evaluations • Cost-benefit evaluations • Cost minimization analyses • SLRs[a]
Healthcare resource use and costs	Adult (≥ 18 years) diagnosed with obstructive HCM	No restriction		• Direct and indirect resource use • Direct and indirect costs	• Randomized trials • Non-randomized trials • SLRs[a]
Health state utilities and health-related quality of life	Adult (≥ 18 years) diagnosed with obstructive HCM	No restriction		• Utility and disutility data derived by: - EQ-5D - Short-Form Health Survey 36 and 12 - Visual analog scale - Kansas City Cardiomyopathy Questionnaire - HCM Symptom Questionnaire Shortness of Breath	• Randomized trials[b] • Non-randomized trials[b] • Patient interviews • SLRs[a] • Patient surveys

[a]Data from the 3 most recent systematic reviews will be checked to ensure no relevant report was missed by the search strategy. Data from the systematic review will not be extracted.
[b]Clinical Trials will be screened to identify humanistic burden outcomes.
BB, beta blocker; CCB, calcium channel blocker; HCM, hypertrophic cardiomyopathy; SLR, systematic literature review; SRT, septal reduction therapy.

Table 2. Included studies with location and outcomes

Study	Study location	Economic model	Healthcare resource use	Costs	QoL	Utilities
Economic evaluation						
ICER, 2021	USA	✓[a]				
Pharmacological treatments						
EXPLORER-HCM	Multi-regional			✓	✓	✓
Olivotto et al. 2020						
Spertus et al. 2021						
Xie et al. 2021						
Naidu et al. 2021						
EXPLORER-HCM and MAVA-LTE						
Jacoby et al. 2021						
Invasive interventions						
Akita et al. 2018	Japan		✓		✓	
Balaram et al. 2012	USA		✓		✓	
Balaram et al. 2005	USA		✓			
Balaram et al. 2008	USA		✓			
Boekstegers, 2013	Germany				✓	
Butzner et al. 2021	USA		✓	✓		
Chothani et al. 2016	USA		✓	✓		
Collis et al. 2017	UK		✓			
Collis et al. 2018	UK		✓			
Holst et al. 2019	USA		✓			
Jain et al. 2019	USA		✓			
Javidgonbadi et al. 2021	Sweden		✓	✓		
Kim et al. 2016	USA		✓	✓		
Lin et al. 2019	USA				✓	
Panaich et al. 2014	USA		✓	✓		
Pruna-Guillen et al. 2021	Spain		✓			
Serber et al. 2007	USA				✓	
Shalen et al. 2019	USA		✓			
Shalen et al. 2021	USA		✓		✓	
Singh et al. 2017	USA		✓			
Song et al. 2018	USA		✓			
Van der Merwe et al. 2018	Belgium		✓			
Vassileva et al. 2011	USA		✓			
Verdugo et al. 2019	Chile		✓			
Wong et al. 2021	USA		✓			
Yatabe et al. 2019 (non-cardiac surgery)	Japan		✓			
Berruezo et al. 2011	Spain				✓	
Gadler et al. 1999	Sweden				✓	
Galve et al. 2010	Spain				✓	
Linde et al. 1999	EU				✓	
Population-based						
Akhtar et al. 2020	USA		✓	✓		
Desai et al. 2019	USA		✓	✓		
Jain et al. 2021	USA		✓	✓		
Rungatscher et al. 2016	USA		✓	✓		
TOTAL	**36**	**1**	**27**	**10**	**11**	**1**

[a]Mavacamten versus beta blockers/calcium channel blockers alone, disopyramide, myectomy, or septal ablation. Model inputs were not reported separately.
EU, European Union; QoL, quality of life; SRT, septal reduction therapy.

- No QoL or utility data relating to other pharmacological treatments were identified.
- No utility data associated with SRT were found.
- No disutilities associated with any treatments were found.
- QoL data were obtained using the Kansas City Cardiomyopathy Questionnaire (KCCQ), Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ), EQ-5D-5L, EQ-VAS, Short Form-36, Karolinska questionnaire, Karolinska QoL visual analog scale, Short Form-12, and Minnesota Living with Heart Failure Questionnaire scales.
- Data indicated that SRT for the treatment of obstructive HCM was associated with improvements in QoL 30 days after procedure and up to 1 year post-procedure. However, there was substantial clinical and methodological heterogeneity across studies.
- Treatment with mavacamten versus placebo was associated with statistically significant improvements in KCCQ-Clinical Summary Score, HCMSQ-Shortness of Breath and EQ-5D-5L (using a US value set) at 30 weeks.

Limitations

- It is possible that some QoL and utility data from other populations may be generalizable to obstructive HCM (e.g. non-obstructive HCM); however, they were excluded from the review.
- As health systems and treatment pathways vary by region, cost, and resource use, data may not be generalizable to other countries.
- This SLR did not include a formal assessment of study and outcome quality, so data should be interpreted with caution.

Conclusions

- **There is generally a paucity of economic evidence associated with obstructive HCM.**
- **No studies were found that reported on indirect costs, invasive intervention utilities or adverse event disutilities.**
- **While there were some exceptions, the majority of studies reporting on resource use, costs, QoL and utilities were conducted in the USA.**
- **The cost and resource use data were heterogeneous and, where available, pertained mostly to SRT. The data demonstrated a high economic burden associated with SRT.**
- **There is a lack of QoL and health state utility available for pharmacological treatments, except for mavacamten, which was shown to improve outcomes relative to placebo.**
- **Further research is needed to characterize fully the economic and humanistic burden of obstructive HCM.**

References

1. Elliot PM, et al. *Eur Heart J* 2014;35:2733–2779.
2. Ommen SR, et al. *Circulation* 2020;142:e558–e631.

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