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Systematic literature review of the efficacy and safety of pharmacological treatments and septal reduction therapies for obstructive hypertrophic cardiomyopathy

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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, in spite of maximally tolerated drug therapy, 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 (ASA).[1,2]

Objective

- The objective of the clinical systematic literature review (SLR) was to describe the efficacy and safety of interventions (eg, pharmacological treatments and SRT) used for the treatment of obstructive HCM.

Methods

- An SLR was performed using a prespecified protocol, to identify relevant studies evaluating pharmacological treatment and SRT for adults with obstructive HCM.
- Literature searches were conducted via electronic searches in Embase®, MEDLINE® and MEDLINE® In-Process (via ProQuest); the Cochrane Central Register of Controlled Trials (CENTRAL); and the Cochrane Database of Systematic Reviews (CDSR). The searches were run from database inception until August 2, 2021 and updated on December 3, 2021.
- Cardiovascular conference proceedings and health technology assessment (HTA) websites were also searched for relevant literature for the previous 3 years up to August 2, 2021, then updated on December 3, 2021.
- Inclusion criteria are presented in **Table 1**.
- Studies enrolling patients with concomitant malignancies, genetic syndromes, or other diagnoses that mimic obstructive HCM and non-English-language publications were excluded from the review.
- Record screening was performed by two independent researchers. If an agreement could not be reached about the eligibility of a study, discrepancies were resolved by a third reviewer.
- Risk of bias assessments were conducted for all included studies by means of the Center for Reviews and Dissemination[3] assessment criteria for randomized controlled trials (RCTs) and the Newcastle Ottawa Scale for observational studies.
- Data from the included studies were summarized using a narrative synthesis.

Table 1. Pre-specified inclusion criteria of the SLR

Population	Interventions and comparators	Outcomes	Study design
Inclusion criteria			
Adults (≥ 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 • Cardiac myosin inhibitor – Mavacamten – CH-274 • SRT – Ventricular septal myectomy – Alcohol septal ablation • Placebo • Standard of care • No comparator	Efficacy outcomes specifying the following • NYHA class • pVO_2 • V_E/VO_2 • LVOT gradient • NT-proBNP levels • LVEF • Dyspnea • KCCQ-CSS • HCMSQ-SoB • SF-36 • EQ-5D • HUI • Survival Safety outcomes • AEs • Discontinuation	• RCTs • Non-RCTs • Single-arm trials • Prospective studies • Retrospective studies • Interventional observational studies

AEs, adverse events; BB, beta blocker; CCB, calcium channel blocker; HCM, hypertrophic cardiomyopathy; HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath; HUI, Health Utility Index; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract obstruction; NT-proBNP, N-terminal-pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen consumption; RCT, randomized controlled trial; SF-36, 36-item Short-Form Health Survey; SLR, systematic literature review; SRT, septal reduction therapy; V_E/VO_2, ventilation – oxygen consumption.

Results

Search and study selection

- The results from the literature searches (August 2 and December 3, 2021) were combined.
- Following de-duplication, the titles and abstracts of 1742 unique records were screened for eligibility. From those, 603 were selected for full text screening. A further 227 records were identified for screening by gray literature searches.
- In total, 227 records, as identified by all searches, reported on 219 studies that met the inclusion criteria, consisting of 2 RCTs, 3 randomized crossover studies, and 214 observational studies.
- Of the 219 studies, 50 were conducted more than 20 years ago, 75 between 2002 and 2012 (more than 10 years ago), and 94 between 2012 and 2022. All of the crossover RCTs assessing pharmacological treatment were published before 1990.

Study characteristics

- The characteristics of the 219 studies included are presented in **Table 2**. The majority of the studies were conducted in single countries and often in single institutions. Most studies were conducted in Europe (95 studies spread across the continent, with the majority in Germany), followed by North America (55 studies, 46 of which were in the USA), and Asia (35 studies, 33 of which were in China). Only 3 studies took place across different continents.

Patient characteristics

- Across all 219 studies, the number of patients assessed per treatment varied greatly (**Figure 1**), from 4 patients to 2956 patients. Most of the studies had treatment arms with fewer than 50 patients.
- Similarly, mean age values ranged between 22.7 and 73.3 years for each intervention arm, with most studies reporting mean age values between 50 and 60 years.

Efficacy and safety

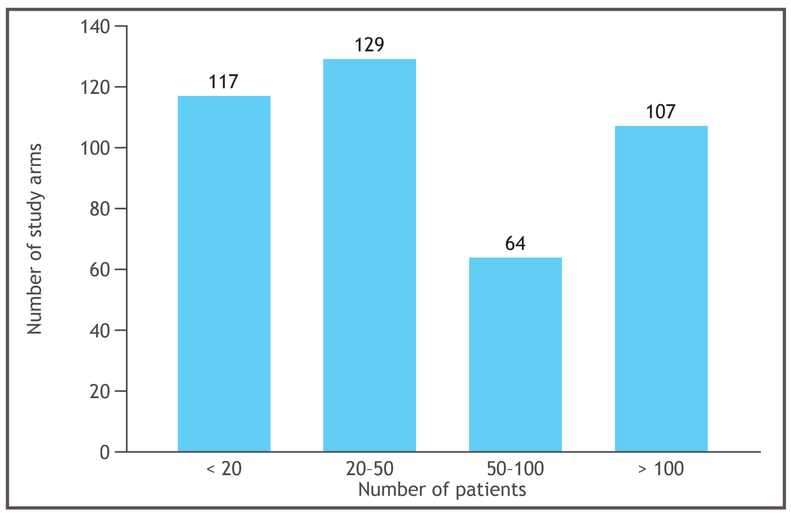
- New York Heart Association (NYHA) functional class was most commonly reported as mean score or percentages of patients in each NYHA class at different time points.
- Health-related quality of life (HRQoL) was assessed using EQ-5D, KCCQ, SF-12, Minnesota Living with Heart Failure Questionnaire, and HCMSQ-SoB scales.
- Additional outcomes were found but were infrequently reported across studies. These included peak oxygen uptake, left ventricular ejection fraction, biomarkers and survival.

Table 2. Characteristics of studies

Pharmacological treatments	RCT	4	Parallel	1
			Crossover	3
	Observational – comparative	10	Prospective	3
			Retrospective	7
	Observational – single arm	9	Prospective	4
			Retrospective	5
Pharmacological treatments + SRTs	RCT	0	Parallel	0
			Crossover	0
	Observational – comparative	10	Prospective	2
			Retrospective	8
	Observational – single arm	1	Prospective	1
			Retrospective	0
SRT	RCT	1	Parallel	1
			Crossover	0
	Observational – comparative	35	Prospective	4
			Retrospective	31
	Observational – single arm	149	Prospective	29
			Retrospective	120

RCT, randomized control trial; SRT, septal reduction therapy.

Figure 1. Distribution of number of study arms per number of patients assessed



NYHA functional class

- Two randomized studies (1 parallel and 1 crossover) and 150 observational studies reported NYHA functional class. Of these, 34 were comparative studies and 116 were single-arm studies.
- Two randomized studies (1 parallel RCT and 1 crossover RCT) reported changes in NYHA functional class in patients receiving pharmacological treatments (**Table 3**).
- There were no randomized studies evaluating the impact of SRTs on NYHA functional class.

Change in left ventricular outflow tract (LVOT) gradient

- Two parallel RCTs and 2 randomized crossover studies reported changes in LVOT gradient. Of these, 3 studies evaluated pharmaceutical treatments and one parallel RCT evaluated SRT (**Table 3**).
- In addition, 202 observational studies reported LVOT outcomes; of those, 43 were comparative studies and 159 were single-arm studies.
- Ten prospective observational comparative studies showed statistically significant improvements for LVOT at rest for mavacamten (PIONEER-HCM and PIONEER-OLE), verapamil (2 studies), disopyramide (1 study), pilsicainide (1 study), propranolol (1 study), and SRTs (7 studies).
- All of the observational studies reported LVOT outcomes (as score/score change/percentage change of resting, Valsalva, and post-exercise LVOT).
  - Across observational studies reporting mean changes from baseline in resting LVOT gradient, outcomes ranged from −92 mmHg for patients receiving surgical myectomy with mitral valve replacement to −0.1 mmHg for patients receiving conservative pharmacological treatment.
  - Across observational studies reporting mean changes from baseline in Valsalva LVOT gradient, outcomes ranged from −102 mmHg for patients receiving transcoronary ablation of septal hypertrophy (TASH) to −47.1 mmHg for patients receiving mavacamten 2 to 5 mg/day for 12 weeks.

HRQoL assessed by EQ-5D

- The EQ-5D instrument assessed HRQoL in 2 studies, 1 parallel RCT, and 1 retrospective, non-randomized study (**Table 4**).

Safety and tolerability

- Overall, 1 parallel RCT and 5 non-randomized studies reported safety and tolerability data. The evidence was heterogeneous with respect to intervention and the study types, and data were descriptive.
- Safety data for pharmacological treatments were reported in 1 parallel RCT (EXPLORER-HCM) (**Table 5**) and 1 non-randomized study (Korovina et al. 1998) (**Table 6**).

Table 3. Changes in NYHA functional class and in LVOT gradient reported in RCTs

Study type	Treatment(s)	Main outcomes
Change in NYHA functional class		
Olivotto et al. *Lancet* 2020 Parallel RCT	Mavacamten (n = 117) Placebo (n = 123)	At 30 weeks, 65% of patients receiving mavacamten experienced ≥ 1 NYHA class improvement compared with 31% in the placebo group, with a mean difference of 33.8% (95% CI, 22.2-45.4%; $P < 0.0001$).
Cosnay et al. *Arch Mal Coeur Vaiss* 1987 Crossover RCT	Verapamil Propranolol (n = 16 across both treatment arms)	Improvements of the mean score for the functional capacity were reported for verapamil (from 2.81 ± 0.58 to 0.81 ± 0.33, $P < 0.001$) and propranolol (from 2.81 ± 0.58 to 1.19 ± 0.43, $P < 0.001$) treatments, and for metoprolol versus placebo ($P < 0.01$).
Change in LVOT gradient		
Pharmacological treatments		
Olivotto et al. *Lancet* 2020 Parallel RCT	Mavacamten (n = 117) Placebo (n = 122)	At 30 weeks, patients in the mavacamten group experienced a mean decrease in post-exercise LVOT gradient of −47 (SD 40) mmHg versus −10 (SD 30) mmHg in the placebo arm (mean difference, −35.6, (95% CI, 43.2 to −28.1; $P < 0.0001$).
Pollick et al. *Am J Cardiol* 1988 Crossover RCT	Disopyramide (n = 10) Propranolol (n = 10) Placebo (n = 10)	At 4 days, the improvement in LVOT gradient at rest from baseline was greater for disopyramide (from 61 mmHg to 5 mmHg) than for propranolol (from 61 mmHg to 30 mmHg) ($P = 0.01$), and for propranolol versus placebo ($P < 0.01$).
Cosnay et al. *Arch Mal Coeur Vaiss* 1987 Crossover RCT	Verapamil (n = 16) Propranolol (n = 16)	Decreases of resting LVOT gradient were seen from 98.4 to 42 mmHg with verapamil and to 83.5 with propranolol ($P < 0.05$ versus baseline for both groups). There was no statistical comparison between the two groups.
Septal reduction therapies		
Naydenov et al. *J Am Coll Cardiol* 2017 Parallel RCT	Septal myectomy (n = 38) ASA (n = 38)	A significant decrease in the LVOT gradient at rest was observed after septal myectomy (89.2%) and ASA (60.4%) compared with baseline ($P < 0.001$ versus baseline for both groups).

ASA, alcohol septal ablation; CI, confidence interval; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; RCT, randomized controlled trial; SD, standard deviation.

Table 4. Change in EQ-5D-5L index scores

Publication	Treatment arm	Efficacy population	EQ-5D-5L, mean (SD)	Difference (95% CI)	*P* value
Xie et al. *Value Health* 2021	Mavacamten (n = 123)	n = 96	Change from baseline: 0.084 (0.163) Unadjusted	At 30 weeks, unadjusted 0.075 (0.028, 0.122) At week 30, adjusted: 0.073 (0.027, 0.118)	$P = 0.002$
	Placebo (n = 128)	n = 89	Change from baseline: 0.009 (0.163) Unadjusted		$P = 0.002$
Cooper et al. *EuroIntervention* 2017	Computed tomography-guided ASA	n = 20	Baseline = 0.51 (0.24) Post ASA = 0.78 (0.16)		Post-ASA versus pre-ASA $P < 0.0001$

ASA, alcohol septal ablation; CI, confidence interval; SD, standard deviation.

Table 5. Summary safety outcomes for treatment-emergent and serious adverse events reported in the EXPLORER-HCM trial

Study name	Publication	Treatment arm	Patients with ≥ 1 TEAE, n (%)	SAE, n	Patients with ≥ 1 SAE, n (%)[a]	Death, n (%)
Explorer-HCM, NCT03470545	Olivotto et al. *Lancet* 2020	Mavacamten (n = 123)	108 (88)	11	10 (8)	0
		Placebo (n = 128)	101 (79)	20	11 (9)	1 (1)

[a]Note that death is included in serious adverse events.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 6. Summary safety outcomes for TEAEs for verapamil, nifedipine, nitrendipine, propranolol, and penbutolol, for studies evaluating septal myectomy or ASA

Publication	Treatment arm	Safety definition	TEAE, n (%)
Korovina et al. *Klin Med* 1998	Long-term therapy with verapamil (n = 16)	Any drug-related side effects	3 (0.19)
	Long-term therapy with nifedipine (n = 24)	Any drug-related side effects	6 (0.25)
	3-month course of treatment of nitrendipine (n = 15)	Any drug-related side effects	12 (0.8)
	3-month course of treatment of diltiazem (n = 24)	Any drug-related side effects	9 (0.37)
	Long-term therapy with propranolol (n = 55)	Any drug-related side effects	18 (0.33)
	3-month course of treatment of penbutolol (n = 13)	Any drug-related side effects	6 (0.46)
Delahaye et al. *Arch Mal Coeur Vaiss* 1988	SM (n = 25)	Early post-operative complications (total)	7 (28)
Leonardi et al. *Catheter Cardiovasc Interv* 2013	ASA (n = 110)	Procedural complication rate (young)	10 (9.1)
	ASA (n = 159)	Procedural complication rate (middle-aged)	10 (6.3)
	ASA (n = 120)	Procedural complication rate (elderly)	25 (20.8)
Leal et al. *Rev Port Cardiol* 2011	ASA (n = 14)	Procedural complications	– (6.7)
Veselka et al. *Can J Cardiol* 2014	ASA (n = 75)	Procedure-related complications – complete heart block	– (8)
		Procedure-related complications – transient AV block II	– (2.7)
		Procedure-related complications – post-interventional sustained ventricular tachycardia/fibrillation requiring defibrillation	– (2.7)

ASA, alcohol septal ablation; AV, atrioventricular; SM, septal myectomy; TEAE, treatment-emergent adverse event.

- Four non-randomized studies reported safety data for SRTs.
- Procedural-related complications were reported in 3 studies associated with ASA treatment, including the study by Leonardi et al. reported higher events in elderly compared to young and middle-aged patients (**Table 6**). Procedural-related complications across these 3 studies ranged from 6.7% to 20.8%.
- Early-post operative complications were recorded for 28% of patients treated with septal myectomy (**Table 6**).

Limitations

- Given that only English-language publications were included in the SLR, relevant data may have been missed.
- The SLR aimed to identify a range of study types, many of which are prone to bias (eg, retrospective designs). As such, these results should be interpreted with caution.
- Apart from the mavacamten study (EXPLORER-HCM), the majority of studies were small and assessed as low or indeterminable quality.
- Although a larger body of evidence was available for SRTs, studies were of low or indeterminable quality and heterogeneous, varying by study design, intervention technique, and geographical location, and often evaluated procedures conducted many years ago.

Conclusions

- **There is a paucity of quality data investigating the absolute and relative efficacy, safety, and tolerability of pharmacological interventions and SRTs. Among all 219 studies, only 4 were randomized and 3 had a crossover design. Many of the data pertained to interventions conducted many years ago.**
- **Although there was positive evidence supporting the interventions for which there were data, the variable study quality together with the clinical and methodological heterogeneity across studies prevented firm conclusions from being drawn.**
- **More robust research evaluating current treatments for obstructive HCM is needed.**

References

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