Prognostic factors and surrogate endpoints in obstructive hypertrophic cardiomyopathy: A systematic literature review

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Background

- A previous review evaluated the relationship between prognostic factors and final clinical endpoints in hypertrophic cardiomyopathy (HCM) but not in the obstructive HCM population subgroup[1]
- Evidence of the relationship between potential prognostic factors, such as resting left ventricular outflow tract pressure gradient (LVOT-PG) or New York Heart Association (NYHA) class, and other final clinical endpoints in obstructive HCM may inform the appropriateness of using surrogate endpoints when the availability of long-term cardiovascular endpoints may be limited

Objectives

- To undertake a systematic literature review (SLR) of observational studies in obstructive HCM that reported:
  - Associations between prognostic factors (patient characteristics at study baseline) and final clinical endpoints (occurring at end of follow-up) and/or
  - Associations between potential surrogate endpoints (occurring after baseline) and final clinical endpoints

Methods

- A SLR was conducted according to a prespecified protocol
- Searches of MEDLINE, Embase, and Cochrane were conducted on December 16, 2022. Bibliographies of relevant SLRs were hand searched
- The Embase searches included indexed conference abstracts. In addition, abstracts from the 2021 and 2022 annual meetings of the American Heart Association, the European Society of Cardiology, the Heart Failure Society of America, and the American College of Cardiology were hand searched
- Titles and abstracts followed by full-text articles were screened according to predefined population, interventions, comparators, outcomes, and study types (PICOS; **Table 1**)
- Data from studies providing evidence for a relationship between prognostic factors and/or potential surrogate endpoints and final clinical endpoints in a population who had not undergone septal reduction therapy (SRT) were extracted by 1 reviewer and quality checked by a second
- Where a hazard ratio (HR) was not provided, but Kaplan-Meier curves for a final clinical endpoint were available, Cox proportional hazards were estimated by digitization of the Kaplan-Meier curves

Table 1. PICOS and time horizon defining the criteria for study inclusion

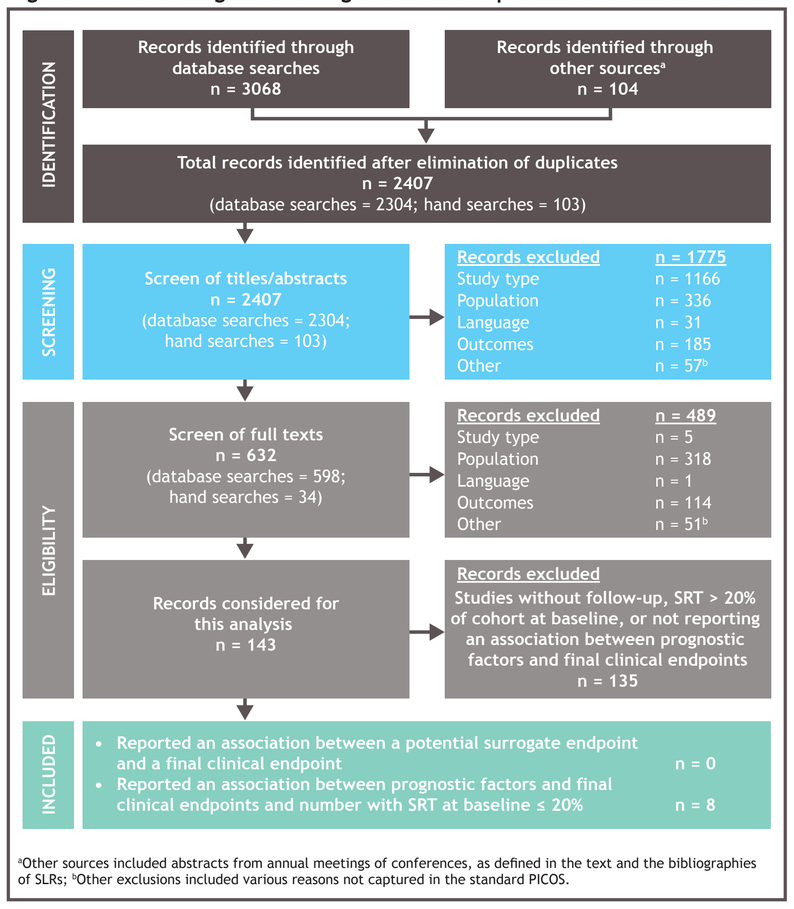
PICOS element	Inclusion criteria
Population	• Adults diagnosed with obstructive HCM • ≤ 20% of the study cohort previously received SRT including myectomy or ASA[a]
Interventions/ comparators	None or any
Outcomes	Analyses expressing the relationship between ≥ 1 prognostic factor and/or surrogate outcome and any of the final clinical endpoints (either as a composite outcome or individually) Prognostic factors and/or potential surrogate endpoints • NYHA class • pVO_2 • LVOT-PG • LVEF • NT-proBNP levels • KCCQ • HCMSQ • CPET parameters Final clinical endpoints • All-cause mortality • Cardiovascular mortality • Sudden cardiac death • Heart failure • Stroke • Atrial fibrillation • Acute myocardial infarction • Implantable device use (including ICDs and pacemakers) • Deep vein thrombosis (including embolism and pulmonary embolism) • Major adverse cardiovascular events • Hospitalization
Study type	Observational study with follow-up ≥ 1 year
Date restrictions	• Full-text publications: no date limit • Conference abstracts: published in 2021 or 2022

[a]This criterion is designed to reflect the population eligible for clinical trials of new pharmacological interventions for obstructive HCM.
ASA, alcohol septal ablation; CPET, cardiopulmonary exercise testing; HCMSQ, Hypertrophic Cardiomyopathy Symptom Questionnaire; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide ; pVO_2, peak oxygen consumption.

Results

- The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram is shown in **Figure 1**
- Of 2407 records identified, 8 studies were eligible for inclusion. All of these studies reported the results of an analysis which assessed the relationship between a prognostic factor and 1 or more final clinical endpoints of interest

Figure 1. PRISMA diagram showing the selection process of included studies



[a]Other sources included abstracts from annual meetings of conferences, as defined in the text and the bibliographies of SLRs; [b]Other exclusions included various reasons not captured in the standard PICOS.

Table 2. Population characteristics and definition of obstructive HCM in included studies

Reference	Geography	N (without/with baseline SRT)	Age, mean (SD),[a] years	Follow-up time, mean (SD),[a] years	Obstructive HCM definition
Desai et al. (2015)[2]	Single site, Cleveland, OH, US	1530 (1530/0)	50 (13)	8.1 (6)	LVOT-PG ≥ 30 mm Hg[b]
Lakdawala et al. (2022)[3]	Multi-site, US, Brazil, Italy, and the Netherlands	2495 (2269/226)	48 (17)	1 (NR)	At least 1 record of LVOT-PG > 30 mm Hg or SRT
Hutt et al. (2022)[4]	Single site, Cleveland, OH, US	2119 (2119/0)	56.1 (12) and 54.1 (13)[c]	Median, 5.4 (IQR, 2.8-9.2)[d]	LVOT-PG ≥ 30 mm Hg at rest or with provocation, including Valsalva maneuvers and amyl nitrite inhalation[b]
Hamada et al. (2021)[5]	Multi-site, Japan	129 (129/0)	55.9 (12.7) and 52.3 (13.7)[c]	15.8 (5.6) and 17.8 (7.2)[c]	LVOT-PG ≥ 30 mm Hg at rest
Sorajja et al. (2012)[6]	Single site, US	182 (182/0)	53 (15)	4.0 (3.2)	LVOT-PG of > 30 mm Hg at rest or > 50 mm Hg with provocation (Valsalva strain or amyl nitrite inhalation)
Wang et al. (2022)[7]	Multi-site, US	3322 (2870/452)	61.0 (14.8)	2.4 (NR)	One record of a diagnosis of obstructive HCM according to ICD-9, 425.1x or ICD-10, I42.1 or 1 record of LVOT-PG ≥ 30 mm Hg
Elliott et al. (2006)[8]	Single site, UK	288 (288/0)	46 (16)	Median, 4.3 (IQR, 2.2-7.3)	LVOT-PG ≥ 30 mm Hg; exercise during measurement of LVOT-PG is not mentioned
Maron et al. (2003)[9]	Multi-site, Italy and US	273 (273/0)	50 (21)	5.1 (5.3)	LVOT-PG ≥ 30 mm Hg under resting conditions

[a]Data are mean (SD) unless otherwise stated; [b]In Hutt et al. (2022)[4] and Desai et al. (2015),[2] maximal LVOT-PG was defined as the highest recorded gradient, resting or provoked (provocation was not used in patients with resting LVOT-PG > 50 mm Hg); [c]In groups with low and high NT-proBNP ratio reported in Hutt et al. (2022)[4] and in groups A and B, respectively, reported in Hamada et al. (2021);[5] [d]Over both low and high NT-proBNP ratio groups Hutt et al. (2022).[4]
ICD-9/10, International Classification of Diseases, Ninth/Tenth Revision; IQR, interquartile range; LV, left ventricle; NR, not reported; SD, standard deviation.

Table 3. Studies reporting the relationship between NYHA class and a final clinical endpoint

Reference	Statistical analysis	Prognostic factor	Final clinical endpoint	Direction of relationship between prognostic factor and final clinical endpoint	Reported relationship (point estimate [95% CI], *P* value)[a]
Desai et al. (2015)[2]	Multivariate HR (adjusted for age, sex, and SRT time updated)	NYHA class, assumed to be impact of changing from class I or II to class III or IV	Cardiovascular mortality and/or implantable defibrillator discharge	↑	1.46 (1.15-1.86), *P* = 0.002
Lakdawala et al. (2022)[3]	1-year probabilities (%) vs NYHA class I using chi-squared tests	NYHA class I	All-cause mortality	↑[c]	0.39 (0.14-1.1)
		NYHA class II vs I[b]			0.92 (0.50-1.86), *P* = 0.180
		NYHA class III/IV vs I[b]			3.64 (2.22-5.97), *P* < 0.001
Hutt et al. (2022)[4]	Univariate HR	NYHA class[d]	Death, ICD discharge, or heart transplant	—	0.99 (0.87-1.13); *P* = 0.9
Wang et al. (2022)[7]	Multivariate HR for time-varying NYHA class (adjusted for age at HCM diagnosis, gender, and race)	NYHA class II vs I	All-cause mortality	↑	1.51 (1.13-2.00)[e]
		NYHA class III vs I			2.77 (2.12-3.63)[e]
		NYHA class IV vs I			7.09 (5.22-9.61)[e]
		NYHA class II vs I	Atrial fibrillation or flutter	↑	1.75 (1.32-2.32)[e]
		NYHA class III vs I			2.47 (1.86-3.27)[e]
		NYHA class IV vs I			3.17 (1.97-5.12)[e]
		NYHA class II vs I	All-cause hospitalization	↑	1.48 (1.28-1.71)[e]
		NYHA class III vs I			2.10 (1.82-2.43)[e]
		NYHA class IV vs I			2.39 (1.93-2.97)[e]
		NYHA class II vs I	Cardiovascular-related hospitalization	↑	1.64 (1.40-1.92)[e]
		NYHA class III vs I			2.40 (2.06-2.81)[e]
		NYHA class IV vs I			2.72 (2.16-3.42)[e]
Maron et al. (2003)[9]	Univariate HR from Kaplan-Meier curves	NYHA class II vs I	Death from heart failure or stroke or progression to NYHA class III or IV	↑	2.652 (1.553-4.528), *P* = 0.0004

↑ An increase (i.e. worsening) in NYHA class is statistically significantly associated with an increased risk of the outcome — No statistically significant association between NYHA class and risk of the outcome

[a]Results of reported statistical analyses exploring the relationship between the prognostic factor and the listed follow-up outcome; [b]With reference to NYHA class I; [c]Applies to the relationship between NYHA class III/IV and I only; [d]It may be assumed that HR refers to a 1-step change in NYHA class (in line with reporting of baseline numbers in each NYHA class); [e]*P* < 0.05.

Table 4. Studies reporting the relationship between resting or maximal LVOT-PG at baseline and a final clinical endpoint

Reference	Statistical analysis	Prognostic factor (change for which HR is reported)	Final clinical endpoint	Direction of relationship between prognostic factor and final clinical endpoint	Reported relationship (point estimate [95% CI], *P* value)
Hutt et al. (2022)[4]	Univariate HR	Maximal LVOT-PG (increase by 1 mm Hg assumed)	Death, ICD discharge, or heart transplant	—	1.00 (0.99-1.01), *P* = 0.7
Hamada et al. (2021)[5]	Multivariate HR	Resting LVOT-PG (increase by 1 mm Hg assumed)	All-cause mortality	—	2.695 (0.662-9.958), *P* = 0.1606
	Multivariate HR	Resting LVOT-PG (increase by 1 mm Hg assumed)	Cardiac mortality	—	1.394 (0.125-12.174), *P* = 0.7754
Sorajja et al. (2012)[6]	Multivariate RR	Resting LVOT-PG (increase by 1 mm Hg)	Mortality or progression to NYHA class ≥ III or CCS angina class ≥ III	↑	1.01 (1.00-1.02), *P* = 0.01
Elliott et al. (2006)[8]	Univariate HR from Kaplan-Meier curves	Resting LVOT-PG (1 step increase through categories 30-50 mm Hg, 50-70 mm Hg, 70-90 mm Hg, ≥ 90 mm Hg)	All-cause mortality or transplantation	↑	1.402 (1.128-1.743), *P* = 0.002
Maron et al. (2003)[9]	Univariate HR from Kaplan-Meier curves	Resting LVOT-PG (1 step increase through categories 30-49 mm Hg, 50-69 mm Hg, ≥ 70 mm Hg)	Death from heart failure or stroke or progression to NYHA class ≥ III	—	1.174 (0.425-1.706), *P* = 0.65

↑ An increase in LVOT-PG is statistically significantly associated with an increased risk of the outcome — No statistically significant association between LVOT-PG and risk of the outcome

CCS, Canadian Cardiac Society; RR, relative risk.

- No studies were identified that assessed the relationship between a potential surrogate endpoint and a final clinical endpoint of interest
- The 8 included studies differed in their definition of obstructive HCM, age (46-61 years), and follow-up time (1-15.8 years) (**Table 2**)
- Although there were variations in the definitions of final clinical endpoints across studies, all studies included all-cause or cardiovascular mortality alone or composite with non-fatal cardiac outcomes
- Of the 5 studies identified that assessed NYHA as a prognostic factor for a final clinical endpoint of interest, 4 reported a statistically significant increase in final clinical endpoints, with increasing severity of symptoms based on NYHA class (**Table 3**)[2,3,7,9]
  - The single study that did not report a statistically significant relationship was a univariate analysis only[4]
- Of the 4 studies investigating the relationship between *resting* LVOT-PG and final clinical endpoints, 2 reported a statistically significant trend, showing that an increase in resting LVOT-PG is associated with an increased risk of final clinical endpoints (**Table 4**)
  - Of the studies reporting a statistically significant effect, 1 study reported a RR of 1.01 per mm Hg (95% CI, 1.00-1.02) (*P* = 0.01),[6] and the other contained a Kaplan-Meier curve from which a HR of 1.402 (95% CI, 1.128-1.743) (*P* = 0.002) was estimated,[8] for outcomes as shown in **Table 4**
  - For the 2 studies that found no statistically significant prognostic relationship, 1 indicated a numerical relationship for both all-cause and cardiac mortality with large uncertainty owing to the limited sample size (n = 129).[5] The inclusion of progression to NYHA class ≥ III in the composite endpoint for the other study may have impacted the relationship[9]
- Only 1 study reported a relationship between maximal LVOT-PG and final clinical endpoints, and this was neither numerically nor statistically significant (**Table 4**)[4]
- Only 1 study (Hutt et al. [2022][4]) considered the relationship between NT-proBNP ratio and any final clinical endpoint (composite of death, heart transplant, or ICD discharge). A significant association was observed with a multivariate HR of 1.24 (95% CI, 1.13-1.36) per log unit (*P* < 0.001)[4]
- Sorajja et al. (2012)[6] was the only study identified that considered the relationship between pVO_2 and any final clinical endpoint (composite of mortality or progression to NYHA class ≥ III or CCS angina class ≥ III). Results found a statistically significant reduction in the univariate RR of the final endpoint of 0.92 (95% CI, 0.89-0.96) per mL/min/kg (*P* = 0.002)[6]

Conclusions

- A relationship between increased disease severity as measured by NYHA class at baseline and increased risk of death at follow-up was reported across most identified studies
- An inconsistent relationship between LVOT-PG at baseline and mortality was seen, suggesting that this relationship is less certain
- Evidence for other possible prognostic factors (e.g. from CPET such as pVO_2, or echocardiography such as LVEF) associated with final clinical endpoints in obstructive HCM without SRT is lacking or limited. Research is needed to assess these relationships
- Further research is needed to determine whether it is feasible to quantitatively synthesize the available data

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Disclosures

- Taryn Krause and Michael Hurst are current employees of Bristol Myers Squibb and may own shares in Bristol Myers Squibb. Alan Fleming, Jessica Costello, Emma Hawe, and Caroline Ling are current employees of RTI Health Solutions. Carla Zema is a contractor for Bristol Myers Squibb.

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