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SHORT REPORT

Real-world candidacy to mavacamten in a contemporary hypertrophic obstructive cardiomyopathy population

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Aims In the EXPLORER-HCM trial, mavacamten reduced left ventricular outflow tract obstruction (LVOTO) and improved functional capacity of symptomatic hypertrophic obstructive cardiomyopathy (HOCM) patients. We sought to define the potential use of mavacamten by comparing real-world HOCM patients with those enrolled in EXPLORER-HCM and assessing their eligibility to treatment.

Methods and results We collected information on HOCM patients followed up at 25 Italian HCM outpatient clinics and with significant LVOTO (i.e. gradient ≥30 mmHg at rest or ≥50 mmHg after Valsalva manoeuvre or exercise) despite pharmacological or non-pharmacological therapy. Pharmacological or non-pharmacological therapy resolved LVOTO in 1044 (61.2%) of the 1706 HOCM patients under active follow-up, whereas 662 patients (38.8%) had persistent LVOTO. Compared to the EXPLORER-HCM trial population, these real-world HOCM patients were older (62.1 ± 14.3 vs. 58.5 ± 12.2 years, $p = 0.02$), had a lower body mass index (26.8 ± 5.3 vs. 29.7 ± 4.9 kg/m^2, $p < 0.0001$) and a more frequent history of atrial fibrillation (21.5% vs. 9.8%, $p = 0.027$). At echocardiography, they had lower left ventricular ejection fraction (LVEF, 66 ± 7% vs. 74 ± 6%, $p < 0.0001$), higher left ventricular outflow tract gradients at rest (60 ± 27 vs. 52 ± 29 mmHg, $p = 0.003$), and larger left atrial volume index (49 ± 16 vs. 40 ± 12 ml/m^2, $p < 0.0001$). Overall, 324 (48.9%) would have been eligible for enrolment in the EXPLORER-HCM trial and 339 (51.2%) for treatment with mavacamten according to European guidelines.

Conclusions Real-world HOCM patients differ from the EXPLORER-HCM population for their older age, lower LVEF and larger atrial volume, potentially reflecting a more advanced stage of the disease. About half of real-world HOCM patients were found eligible to mavacamten.

Keywords Hypertrophic obstructive cardiomyopathy • Myosin inhibitors • Mavacamten • EXPLORER-HCM trial

Introduction

Two-thirds of patients with hypertrophic cardiomyopathy (HCM) present an obstructive phenotype (HOCM) defined as left ventricular outflow tract obstruction (LVOTO) at rest or during provocative manoeuvres.[1] If LVOTO and severe symptoms persist despite optimized medical therapy, septal reduction therapy (SRT) should be offered as treatment.[2,3] In the EXPLORER-HCM trial, cardiac myosin ATPase inhibition with mavacamten ameliorated LVOTO and improved functional capacity of symptomatic HOCM patients.[4] Furthermore, in the VALOR-HCM trial, mavacamten markedly reduced the proportion of HOCM patients amenable to SRT according to guideline criteria.[5] On these grounds, the European Society of Cardiology (ESC) guidelines for the management of cardiomyopathies recommend the addition of mavacamten if treatment with a β-blocker or a non-dihydropyridine calcium channel blocker (CCB) does not relieve symptoms in patients with resting or provoked LVOTO.[3]

To better define the potential impact of mavacamten use in clinical practice, we compared the cross-sectional features of real-world (RW) HOCM patients with those enrolled in EXPLORER-HCM and assessed their eligibility to mavacamten according to the trial inclusion criteria and ESC guideline recommendations.

Methods

We included patients with sarcomeric HOCM who performed at least one visit in the 12 months between 1 February 2022 and 1 February 2023 at 25 Italian HCM outpatient clinics. Diagnosis of HCM was defined as unexplained left ventricular hypertrophy with maximal left ventricular wall thickness of ≥15 mm (or ≥13 mm if familial HCM) as assessed by echocardiography or cardiac magnetic resonance. Patients with a known infiltrative or storage disorder causing cardiac hypertrophy that mimics HOCM were excluded. All included patients had significant LVOTO, defined as a peak left ventricular outflow tract (LVOT) gradient ≥30 mmHg at rest or ≥50 mmHg after Valsalva manoeuvre or exercise at the last clinical evaluation. We collected information on medical and family history, echocardiography, and medical therapy at the last clinical evaluation. If ever performed, we also collected information on cardiopulmonary exercise and genetic testing. In addition, participating centres provided information on the number of HCM patients under active follow-up who had LVOTO at HCM diagnosis and the number of patients who resolved LVOTO with medical or surgical therapy.

We evaluated the proportion of patients potentially eligible to mavacamten according to EXPLORER-HCM trial entry criteria (i.e. at least 18 years old, New York Heart Association [NYHA] functional class II or III, HOCM defined as resting or provocable LVOT gradient ≥50 mmHg, left ventricular ejection fraction [LVEF] ≥55%; excluded if paroxysmal atrial fibrillation [AF] present at screening) and ESC guidelines (i.e. symptomatic patients with resting or provocable LVOT gradient ≥50 mmHg already treated with or intolerant to β-blockers/CCB).

The investigation conforms with the principles outlined in the Declaration of Helsinki.[6]

Categorical data are presented as numbers and percentages; normally distributed continuous data as mean ± standard deviation. Two-tailed Student's *t*-test or Chi-squared test were used to compare normally distributed data and non-continuous variables expressed as proportions, respectively. Statistical analysis was performed using R Studio (version 2023.06.1 + 524 [2023.06.1 + 524]).

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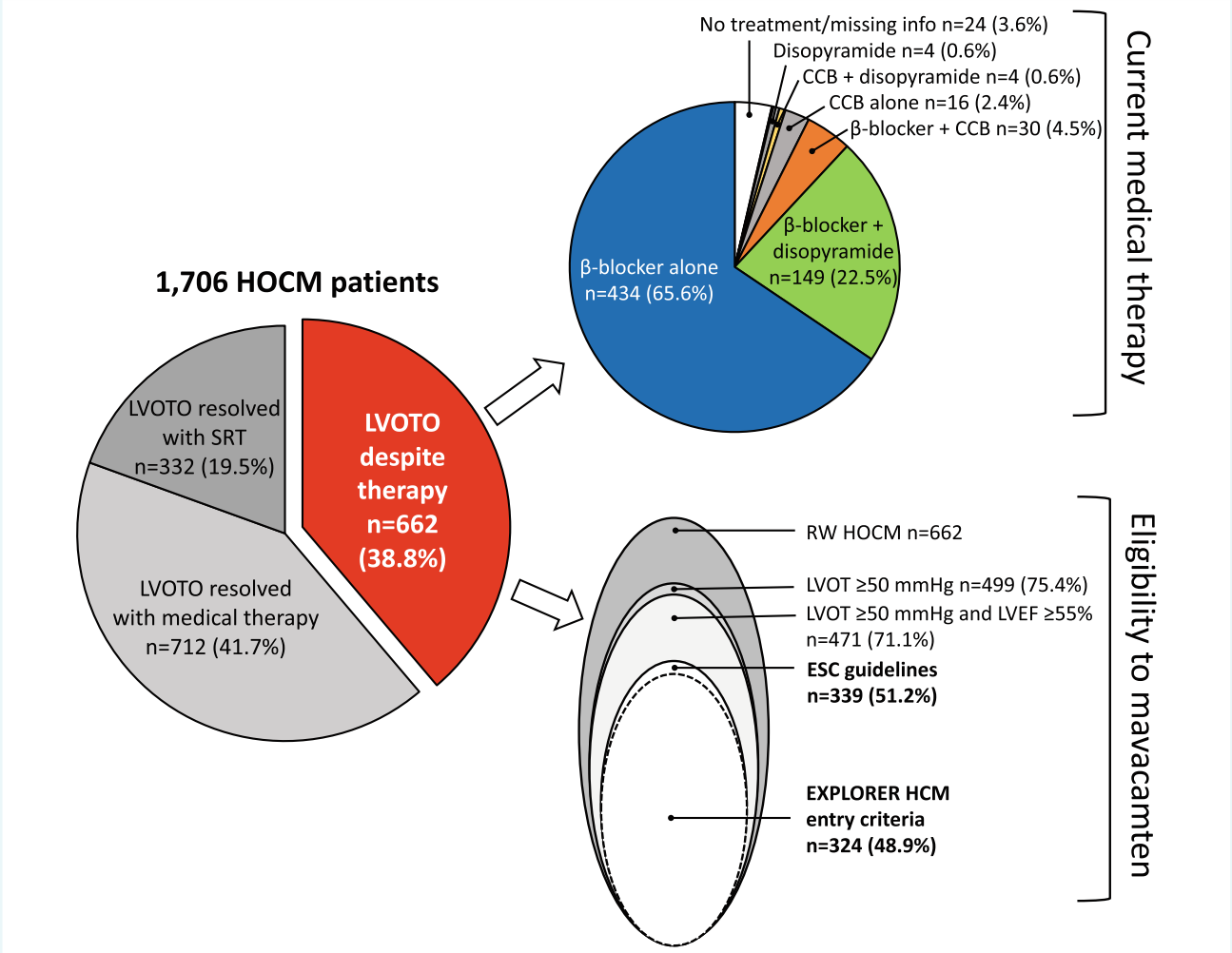

Figure 1 Treatment of left ventricular outflow tract obstruction in real-world (RW) hypertrophic obstructive cardiomyopathy (HOCM) patients and eligibility to mavacamten according to the 2023 European Society of Cardiology (ESC) guidelines and EXPLORER-HCM entry criteria. CCB, calcium channel blocker; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; SRT, septal reduction therapy.

Results

The 25 HCM referral centres participating in this survey followed up 1706 active patients with a history of LVOTO (HOCM). During a median time of 5.9 years from HCM diagnosis to the last clinical evaluation, resolution of LVOTO was observed in 1044 (61.2%) of these patients, of whom 332 (19.5%) underwent SRT, whereas 662 patients (38.8%) had residual LVOTO despite treatment (*Figure 1*).

At the last clinical evaluation, the mean age of this RW HOCM cohort was 62.1 ± 14.3 years, and 56.3% (373) of patients were male (*Table 1*). The mean body mass index (BMI) was 26.8 ± 5.3 kg/m^2 and there were 123 (18.6%) obese patients. A family history of HCM was reported by 147 (22.2%) patients. Most patients had NYHA class II symptoms ($n = 373$, 56.3%), 82 (12.4%) were NYHA class III, and the remaining 190 (28.7%) were asymptomatic (NYHA class I). A LVOT gradient ≥30 mmHg was detected at rest in 409 patients (61.7%), with a mean gradient of 60 ± 27 mmHg, and only with Valsalva or during exercise in 194 (29.3%) and 59 (8.9%) patients, with mean gradients of 69 ± 19 and 76 ± 30 mmHg, respectively. A history of AF was reported for 142 (21.5%) patients. Moderate or severe mitral regurgitation was observed in 196 patients (29.6%) and was secondary to systolic anterior motion in 169 (86.2%) of cases. Severe atrial dilatation defined as a left atrial volume index (LAVI) >48 ml/m^2 was reported for 229 patients (50.1% of those for whom information on LAVI was available).

Thirty-eight (5.7%) patients had already undergone SRT, 34 (5.1%) with myectomy and 4 with alcohol septal ablation (0.6%). All patients were receiving medical treatment for HOCM. The vast majority were treated with β-blockers alone ($n = 434$, 65.6%) or in combination with disopyramide ($n = 149$, 22.5%) or CCB ($n = 30$, 4.5%). Most used β-blockers were bisoprolol ($n = 188$, 30.6% of all β-blockers), metoprolol ($n = 186$, 30.3%) and nadolol ($n = 149$, 24.3%). There were 16 patients (2.4%) receiving CCB alone,

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Table 1 Characteristics of real-world hypertrophic obstructive cardiomyopathy patients versus EXPLORER-HCM trial patients

	RW HOCM patients ($n = 662$)	EXPLORER-HCM ($n = 123$)	*p*-value	RW EXPLORER-HCM-like ($n = 324$)	*p*-value
Clinical characteristics					
Age (years)	62.1 ± 14.3	58.5 ± 12.2	**0.02**	63.1 ± 13.7	**0.001**
Male sex, *n* (%)	373 (56.3)	66 (53.7)	0.6	158 (48.8)	0.4
BMI (kg/m^2)	26.8 ± 5.3	29.7 ± 4.9	**<0.0001**	26.4 ± 4.1	**<0.0001**
Obesity, *n* (%)	123 (18.6)			65 (20.1)	
Ethnicity, *n* (%)			**0.008**		**0.02**
Caucasian	648 (97.8)	115 (93.5)		318 (97.8)	
Asian	3 (0.4)	4 (3.3)		2 (0.6)	
Black, African, or African American	1 (0.1)	1 (0.8)		1 (0.3)	
Other	9 (1.4)	3 (2.4)		1 (0.3)	
Family history, *n* (%)					
Family history of HCM	147 (22.2)	33 (26.8)	0.22	71 (21.9)	0.27
Family history of SCD	94 (14.2)			45 (13.9)	
Medical history, *n* (%)					
Syncope	118 (17.8)			59 (18.2)	
Resuscitated SCD	7 (1.1)			3 (0.9)	
Atrial fibrillation	142 (21.5)	12 (9.8)	**0.027**	54 (16.7)	0.06
Paroxysmal/persistent	107 (16.1)				
Permanent	35 (5.3)				
Myocardial infarction	32 (4.8)			14 (4.3)	
CAD	44 (6.6)	12 (9.8)	0.2	21 (6.5)	0.24
History of LVEF <50%	16 (2.4)			5 (1.5)	
ICD	111 (16.7)			45 (13.9)	
Appropriate ICD discharge	14 (2.1)			6 (1.9)	
Prior septal reduction therapy					
Myectomy	34 (5.1)	11 (8.9)	0.09	19 (5.9)	0.25
ASA (%)	4 (0.6)			2 (0.6)	
Cardiovascular risk factors, *n* (%)					
Hypertension	356 (53.7)	57 (46.3)	0.13	184 (56.8)	0.05
Smoking	263 (39.7)			134 (41.4)	
Current	97 (14.7)			61 (18.8)	
Former	166 (25.1)			73 (22.5)	
Dyslipidaemia	313 (47.3)	27 (22.0)	**<0.0001**	153 (47.2)	**<0.0001**
Diabetes mellitus	74 (11.2)	6 (4.9)	**0.034**	37 (11.4)	**0.036**
COPD	41 (6.2)	2 (1.6)	**0.039**	25 (7.7)	**0.016**
NYHA functional class, *n* (%)			**0.01**		**0.01**
I	190 (28.7)	Excluded		Excluded	
II	373 (56.3)	88 (71.5)		266 (82.1)	
III	82 (12.4)	35 (28.5)		58 (17.9)	
Echocardiography					
LVEF (%)	66 ± 7	74 ± 6	**<0.0001**	68 ± 6	**<0.0001**
MWT (mm)	20 ± 4	20 ± 4	1.0	20 ± 4	1.0
LVOT gradient at rest (mmHg)	60 ± 27 ($n = 409$)[b]	52 ± 29	**0.003**	65 ± 24	**<0.0001**
LVOT gradient after Valsalva (mmHg)	69 ± 19 ($n = 194$)[b]	72 ± 32		70 ± 20	
LVOT gradient during exercise (mmHg)	76 ± 30 ($n = 59$)[b]	86 ± 34		75 ± 29	
LAVI (ml/m^2)	49 ± 16 ($n = 457$)[a]	40 ± 12	**<0.0001**	43 ± 25	0.22
Moderate or severe MR, *n* (%)	196 (29.6)			115 (35.5)	

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Table 1 (Continued)

	RW HOCM patients ($n = 662$)	EXPLORER-HCM ($n = 123$)	p-value	RW EXPLORER-HCM-like ($n = 324$)	p-value
SAM-related, *n* (%)	169 (25.5)			103 (31.8)	
Non SAM-related, *n* (%)	27 (4.1)			12 (3.7)	
Cardiopulmonary exercise testing					
Ever performed, *n* (%)	115 (17.4)	Required		63 (19.4)	
Peak oxygen consumption (ml/kg/min)	19.0 ± 4.5	18.9 ± 4.9	0.82	17 ± 5.3	
Background HCM therapy, *n* (%)					
β-blocker alone	434 (65.6)	94 (76.4)	0.08	211 (65.1)	**0.02**
β-blocker + disopyramide	149 (22.5)			86 (26.5)	
β-blocker + CCB	30 (4.5)				
CCB alone	16 (2.4)	25 (20.3)	**<0.0001**	7 (2.2)	**0.0007**
Disopyramide alone	4 (0.6)			3 (0.9)	
CCB + disopyramide (%)	4 (0.6)			1 (0.3)	
β-blocker + CCB + disopyramide	1 (0.2)			1 (0.3)	
Loop diuretics	98 (14.8)			41 (12.7)	
Anticoagulants	146 (22.1)			58 (17.9)	
DOACs	130 (19.6)			52 (16.0)	
VKA	16 (2.4)			6 (1.9)	
Genetic testing					
Performed, *n* (%)	393 (59.4)	90 (73.2)	**0.003**	187 (57.7)	**0.003**
P/LP variant identified (% of test with results)	124/393 (31.6)	28/90 (31.1)	0.92	54/187 (28.9)	0.78

ASA, alcohol septal ablation; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; ICD, implantable cardioverter defibrillator; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MWT, maximal wall thickness; MR, mitral regurgitation; NYHA, New York Heart Association; P/LP, pathogenic/likely pathogenic; RW, real-world; SAM, systolic anterior motion; SCD, sudden cardiac death; VKA, vitamin K antagonist.
[a]Number of available values.
[b]Number of patients with LVOT gradient detected at rest, with Valsalva or during exercise, respectively.

4 patients (0.6%) receiving CCB and disopyramide, and 4 patients receiving disopyramide alone (0.6%) (*Figure 1*).

Compared to the EXPLORER-HCM trial population, RW HOCM patients were older (62.1 ± 14.3 vs. 58.5 ± 12.2 years, $p = 0.02$) and had a lower BMI (26.8 ± 5.3 vs. 29.7 ± 4.9 kg/m^2, $p < 0.0001$). A history of AF was more common among RW patients (21.5% vs. 9.8%, $p = 0.027$). At echocardiography, LVEF was on average 8% lower (66 ± 7% vs. 74 ± 6%, $p < 0.0001$), LVOTO gradients at rest were higher (60 ± 27 vs. 52 ± 29 mmHg, $p = 0.003$), and left atrial dimensions were larger in RW patients versus the EXPLORER-HCM cohort (LAVI 49 ± 16 vs. 40 ± 12 ml/m^2, $p < 0.0001$). Only 115 (17.4%) RW patients performed cardiopulmonary exercise testing at least once; in these patients, peak oxygen consumption was similar to the EXPLORER-HCM population (19.0 ± 4.5 vs. 18.9 ± 4.9 ml/kg/min, $p = 0.82$).

Of the 662 RW HOCM patients included in this study, 339 (51.2%) would have been eligible for treatment with mavacamten according to ESC guideline recommendations.[3] The most common potential reasons for exclusion were NYHA class I ($n = 190$) and LVOT gradient <50 mmHg ($n = 163$). A smaller proportion of patients would be excluded because of LVEF <55% ($n = 22$, 3.3%). If EXPLORER-HCM trial entry criteria were applied, the number of patients potentially eligible to mavacamten treatment would decrease only slightly to 324 (48.9%) (*Figure 1*). These EXPLORER-HCM-like patients were representative of the entire RW HOCM population and exhibited the same differences from the EXPLORER-HCM trial cohort, with the exception of LAVI, which was comparable to the trial cohort (43 ± 25 vs. 40 ± 12 ml/m^2, $p = 0.22$; *Table 1*).

Discussion

The EXPLORER-HCM trial has opened a new chapter in the treatment of HOCM. The trial included symptomatic HOCM patients with a peak LVOT gradient (at rest or with provocation) ≥50 mmHg and LVEF ≥55%.[7] After 30 weeks, mavacamten improved exercise capacity, LVOT gradients, and symptoms,[4] and had a favourable impact on cardiac remodelling.[8] The EXPLORER-HCM trial population had clinical and echocardiographic characteristics comparable to the RW HOCM patients included in this survey, with few notable exceptions. First, RW patients had a lower BMI compared with the trial population, which might have contributed to the higher burden of symptoms in the EXPLORER-HCM cohort.[9] Second, a history of AF was twice as common in RW HOCM patients compared with the trial population. This might be explained, at least in part, by the exclusion from the trial of patients with a history of paroxysmal AF and AF present at the time of screening.[7]

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Another possibility is that, despite being on average less symptomatic, RW HOCM patients were in a more advanced stage of the natural history of the disease, a hypothesis that is also substantiated by the larger left atrial volume of RW patients, which becomes comparable to that of the trial cohort when RW patients are selected according to trial entry criteria (*Table 1*). Importantly, older age, history of AF, and left atrial dilatation portend poor long-term survival after surgical myectomy.[10] The considerable duration of follow-up also suggests that RW HOCM patients might have been subjected to a 'therapeutic inertia' due to their low burden of symptoms and/or the absence of further pharmacological therapeutic options. In this respect, although virtually all patients were receiving either a β-blocker or a CCB, it is worth noting that bisoprolol was the most used β-blocker, and only 158 patients (23.9%) were on disopyramide, which suggests that pharmacological therapy could also be further potentiated.

Among RW HOCM patients with LVOTO refractory to medical or surgical therapy, 51.2% were eligible to mavacamten according to ESC guideline recommendations.[3] The remaining patients would be excluded primarily based on the absence of symptoms or a LVOT gradient <50 mmHg. However, a high resting gradient portends an increased risk of mortality even in patients with mild or no symptoms.[11] Furthermore, a LVOT gradient ≥30 mmHg detected at rest is an independent predictor of HCM-related mortality, progression to heart failure, or stroke,[12] and its prognostic power is especially relevant in patients with NYHA functional class I or II symptoms.[13] Therefore, these patients might potentially benefit from treatment with myosin inhibitors. It must be noted that only 8.9% of patients in our RW HOCM cohort had a LVOT gradient ≥50 mmHg detected during exercise testing but no gradient at rest, suggesting that this test might be underused in our RW population. Therefore, because Valsalva manoeuvre underestimates the magnitude of exercise-induced obstruction,[1] the proportion of patients eligible to mavacamten might be larger than estimated in this study. This important issue might soon be overcome should the ongoing ODYSSEY trial demonstrate clinical benefit in symptomatic patients with no or only mild LVOTO (NCT05582395). We must also acknowledge that the strict application of other EXPLORER-HCM enrolment criteria that were not considered in this study (e.g. oxygen saturation at rest ≥90%, respiratory exchange ratio at screening >1.0) might decrease the proportion of RW patients eligible to mavacamten. However, we deem it unlikely that these criteria will guide clinical utilization of the drug.

In conclusion, the results of this survey indicate that RW HOCM patients with LVOTO resistant to medical or surgical therapy differ from those enrolled in the EXPLORER-HCM trial for their older age, lower LVEF, and larger atrial dimensions, potentially reflecting a more advanced stage of the disease. About half of RW HOCM patients might benefit from treatment with myosin inhibitors, which makes the identification of labile LVOTO and the use of exercise testing especially important in this patient population.

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