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Target population for a selective cardiac myosin inhibitor in hypertrophic obstructive cardiomyopathy: Real-life estimation from the French REgister of hypertrophic cardioMYopathy (REMY)

Abbreviated title: Target population for a selective cardiac myosin inhibitor in HoCM

Tweet: In a cohort of 1059 adult patients with hypertrophic cardiomyopathy selected from a French registry, almost one third were eligible for a cardiac myosin inhibitor therapy at baseline, and 8.9% more became eligible during follow-up.

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Highlights

- We aimed to identify the real-life target population for a selective cMI in HCM
- We studied 1059 adult patients with HCM enrolled in REMY (a French HCM registry)
- 325 (30.7%) of these patients were potential candidates for a cMI
- 9% more became eligible for a cMI during follow-up

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Abstract

Background: The efficacy of current pharmacological therapies in hypertrophic cardiomyopathy is limited. A cardiac myosin inhibitor, mavacamten, has recently been approved as a first-in-class treatment for symptomatic hypertrophic obstructive cardiomyopathy.

Aims: To assess the profile and burden of cardiac myosin inhibitor candidates in the hypertrophic cardiomyopathy prospective REgister of hypertrophic cardioMYopathy (REMY) held by the French Society of Cardiology.

Methods: Data were collected at baseline and during follow-up from patients with hypertrophic cardiomyopathy enrolled in REMY by the three largest participating centres.

Results: Among 1059 adults with hypertrophic cardiomyopathy, 461 (43.5%) had obstruction; 325 (30.7%) of these were also symptomatic, forming the “cardiac myosin inhibitor candidates” group. Baseline features of this group were: age 58 ± 15 years; male sex ($n = 196$; 60.3%); diagnosis-to-inclusion delay 5 (1–12) years; maximum wall thickness 20 ± 6 mm; left ventricular ejection fraction $69 \pm 6\%$; family history of hypertrophic cardiomyopathy or sudden cardiac death ($n = 133$; 40.9%); presence of a pathogenic sarcomere gene mutation ($n = 101$; 31.1%); beta-blocker or verapamil treatment ($n = 304$; 93.8%), combined with disopyramide ($n = 28$; 8.7%); and eligibility for septal reduction therapy ($n = 96$; 29%). At the end of a median follow-up of 66 (34–106) months, 319 (98.2%) were treated for obstruction ($n = 43$ [13.2%] received disopyramide), 46 (14.2%) underwent septal reduction therapy and the all-cause mortality rate was 1.9/100 person-years (95% confidence interval 1.4–2.6) (46 deaths). Moreover, 41 (8.9%) patients from the initial hypertrophic obstructive cardiomyopathy group became eligible for a cardiac myosin inhibitor.

Conclusions: In this cohort of patients with hypertrophic cardiomyopathy selected from the REMY registry, one third were eligible for a cardiac myosin inhibitor.

Keywords:

Hypertrophic cardiomyopathy

Obstruction

Registry

Cardiac myosin inhibitor

1. Abbreviations

cMI	cardiac myosin inhibitor
HCM	hypertrophic cardiomyopathy
HoCM	hypertrophic obstructive cardiomyopathy
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOTO	left ventricular outflow tract obstruction
NYHA	New York Heart Association
REMY	REgister of hypertrophic cardioMYopathy
SRT	septal reduction therapy

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2. Background

Hypertrophic cardiomyopathy (HCM) is the most frequent cardiomyopathy, affecting 1/200 to 1/500 of the adult population [1, 2]. Obstructive HCM (HoCM) is defined as the presence of a peak left ventricular (LV) outflow tract obstruction (LVOTO) ≥ 30 mmHg, either at rest or provoked. About two thirds of all patients with HCM have obstruction, together with a higher prevalence of symptoms, heart failure and sudden cardiac death [3]. Non-vasodilating beta-blockers or non-dihydropyridine calcium channel blockers are first-line treatments [4, 5], and disopyramide may be combined with either of them in case of failure [4-6]. However, the efficacy of these drugs has not been tested thoroughly [7], whereas septal reduction therapy (SRT) is a validated [4, 5, 8, 9], but invasive, option [10, 11]. These perfectible results paved the way for innovative specific non-invasive approaches, such as the new cardiac myosin inhibitors (cMIs).

In HCM, mutations affecting cardiac sarcomere proteins reduce the normal percentage of beta-myosin in a super-relaxed configuration (OFF state), potentially leading to higher adenosine triphosphatase activity and a higher actin-myosin interaction rate, with reduced myocardial compliance and increased contractility [12-14]. Mavacamten is an allosteric reversible selective cMI that reduces sarcomeric contractility [15] and decreases cardiac myosin heavy chain adenosine triphosphatase activity, with a reduction in the number of myosin heads accessible for interaction with actin [16], thus shifting the myosin population towards an energy-sparing super-relaxed state [17]. Reductions in LV hypertrophy, cardiomyocyte disarray and myocardial fibrosis have been demonstrated in mavacamten-treated HCM transgenic mice expressing cardiac myosin mutations [16].

In symptomatic patients with HoCM, the phase 2 open-label PIONEER-HCM trial [18] and the phase 3 EXPLORER-HCM [19] and VALOR-HCM [20] trials demonstrated that mavacamten markedly reduces exercise LVOTO and symptoms and improves peak oxygen consumption (pVO_2). These results led to the approval of this first cMI in June 2023, defining cMI candidates as patients with HCM with obstruction ≥ 30 mmHg, New York Heart Association (NYHA) class II/III, left ventricular ejection fraction (LVEF) $\geq 55\%$ and no history of SRT [19-21].

To assess the profile, management and burden of real-world patients with HCM who are cMI candidates, we retrospectively analysed the French multicentre REgister of hypertrophic cardioMYopathy (REMY), which is held by the French Society of Cardiology.

3. Methods

3.1. Description of REMY

REMY was initiated in 2010, is ongoing and is endorsed by the French Society of Cardiology; it prospectively includes patients with a diagnosis of HCM in 26 centres in France, with a systematic follow-up. Inclusion criteria are age ≥ 16 years and LV hypertrophy ≥ 15 mm in sporadic cases or ≥ 13 mm in the presence of a family history of HCM. Patients with LV hypertrophy as a result of abnormal loading conditions, such as aortic stenosis or hypertension, are excluded by medical history and echocardiographic evaluation. For data collection, we use an anonymized electronic case report form hosted by the French Society of Cardiology. At inclusion, sociodemographic data, imaging features, investigations, genetic testing information, history of predefined cardiovascular events, current medications and invasive treatments are collected. The National Commission for Informatics and Liberty provided ethical clearance (agreement n°909378, 02 December 2009) and a consent form is signed at inclusion.

3.2. Study group

In our study, we first excluded the following patients from the analysis: patients aged < 18 years; patients with non-sarcomeric HCM (genetic or infiltrative diseases, such as Fabry disease or amyloidosis, were ruled out by medical history, systematic biological and genetic tests and multimodality imaging); patients without at least one follow-up visit within 2 years; patients with LVEF $< 55\%$ (using the echocardiographic biplane Simpson method or magnetic resonance imaging); and those with a lack of main data (unknown LVEF, obstruction or NYHA class at inclusion). Thereafter, the analysis was restricted to adult patients with HCM (HCM group) from the three largest HCM university centres (Georges Pompidou European Hospital in Paris, Haut Lévêque Hospital in Bordeaux and Pontchaillou Hospital in Rennes) with minimal ($< 10\%$) or no missing data. In that cohort, we selected patients with obstruction ≥ 30 mmHg (HoCM group) based on echocardiography and, among those, patients in NYHA class II or III and thus potentially eligible for cMI therapy (cMI candidates group) (Fig. 1)

3.3. Statistical analysis

Continuous data are expressed as mean \pm standard deviation when following a normal distribution and otherwise as median (interquartile range). Categorical data are displayed as counts

and percentages. Survival analyses were conducted using the Kaplan-Meier method, and all-cause mortality rates were computed for 100 person-years.

4. Results

Among 1829 patients included in REMY, we selected 1059 adult patients with HCM included in the three main university centres mentioned above. Among them, 461 (43.5%) presented with obstruction ≥ 30 mmHg (HoCM group), the majority (338; 73.3%) having an obstruction ≥ 50 mmHg. In the HoCM group, 325 (30.7%) were in NYHA class II or III at baseline (cMI candidates group), and thus were potentially eligible for cMI therapy (Fig. 1). The cMI candidates group characteristics at baseline were the following: 196 (60.3%) were male; the mean age was 58 ± 15 years; the median delay from diagnosis to inclusion was 5 (1–12) years; the mean maximum LV wall thickness reached 20 ± 6 mm; the mean LVEF was $69 \pm 6\%$; a family history of HCM or sudden cardiac death was present in 133 (40.9%); and 101 (31.1%) had a confirmed pathogenic sarcomere gene mutation. Moreover, 304 (93.8%) patients received drug therapy for obstruction relief (either a beta-blocker or verapamil; combined with disopyramide in 28 [8.7%] cases) and 96 (29.5%) were eligible for SRT (Fig. 2).

At the end of 66 (34–106) months of follow-up, 319 (98.2%) patients received a negative inotropic treatment compared with 93.8% at baseline, a difference essentially caused by the increasing number of patients receiving disopyramide in combination ($n = 43$; 13.2%). Despite optimized drug therapy, there were 65 (20.0%) patients still eligible for SRT at follow-up. Nevertheless, SRT was performed in only 46 patients (14.2% of the cMI candidates group) during about 6 years of follow-up (septal alcoholization, $n = 31$; surgical myectomy, $n = 15$). In addition, the all-cause mortality rate was 1.9 per 100 person-years (95% confidence interval 1.4–2.6), with a total of 46 deaths.

Finally, in the cMI candidates group, 77 (23.7%) patients became asymptomatic with optimization of drug therapy (and no longer eligible for a cMI), and 57 (17.5%) worsened from NYHA class II to III. Conversely, 41 (8.9% of the HoCM group and 3.9% of the total HCM cohort) asymptomatic patients (NYHA class I) became symptomatic (NYHA class II or III), and thus potentially eligible for a cMI.

5. Discussion

Systolic anterior motion of the mitral valve, the hallmark of HoCM, is a consequence of the combination of ante-position and elongation of the mitral valve, together with subaortic flow

acceleration in a narrowed LV outflow tract, as a result of myocardial hypertrophy and hypercontractility. Obstruction has deleterious effects, such as mitral regurgitation of variable severity, impaired LV relaxation, atrial dilatation (with increased risk of atrial fibrillation) and decreased LV stroke volume [22]. Patients with HoCM are more often and severely symptomatic during exercise, particularly after a frugal meal and/or ingestion of alcohol, and the presence of obstruction predicts the evolution towards severe functional limitation. The magnitude of the LV outflow tract gradient is also part of a specific HCM sudden cardiac death score proposed in the European guidelines for the management of HCM [3, 5, 23].

5.1. Limitations of current therapies for obstruction in symptomatic HoCM

Non-specific negative inotropic drugs currently used to decrease obstruction, such as beta-blockers, verapamil and disopyramide, have often shown disappointing or incomplete results, and the high doses required to reach gradient reduction are poorly tolerated in general [24]. Furthermore, large randomized studies with these drugs are lacking. Only one randomized controlled trial compared metoprolol to placebo in 29 patients with HoCM during a 2-week follow-up, and it failed to demonstrate any improvement in objective functional capacity [7]. Invasive procedures, such as surgical myectomy and transcatheter alcohol septal ablation, although very effective at abolishing obstruction and improving symptoms [8, 9], are not free from severe complications, particularly in low-volume procedure centres [10]; moreover, residual obstruction requiring reintervention still raises concerns [10]. In addition, our study highlights the low volume of SRT performed in France, with only 46 procedures performed in about 6 years of follow-up.

5.2. Efficacy of cMIs in HoCM

cMIs are small molecules that modulate multiple steps of the myosin chemomechanical cycle. Specifically, mavacamten reduces steady-state adenosine triphosphatase activity by inhibiting the rate of phosphate release of cardiac myosin, and reduces the number of myosin heads that can interact with the actin thin filament during transition from the weakly to the strongly bound state [16, 25], thus promoting the myosin super-relaxed state [17]. These drugs (mavacamten and aficamten) constitute a new therapeutic class that saves myocardial energy, attenuates hypercontractility and LV relaxation disorders and dramatically reduces LVOTO. In the EXPLORER-HCM trial [19], the largest ever conducted in this disease, 50% of patients with HoCM – still symptomatic despite optimal medical

treatment with a beta-blocker or a calcium channel blocker – became asymptomatic with mavacamten as add-on therapy, 65% of them improved by at least one NYHA class and sustained abolition of obstruction at exercise was reached in 57%, with 74% < 50 mmHg. In the VALOR-HCM trial [20], 82% of patients with HoCM in NYHA class III who were referred for SRT were no longer eligible for the procedure (guideline eligibility criteria for SRT not fulfilled or patient refusal to proceed with SRT) after 16 weeks of treatment with mavacamten as add-on therapy; furthermore, 27% become completely asymptomatic. Long-term efficacy of mavacamten has been recently demonstrated in the MAVA-LTE trial, which showed persistent reduction of LVOTO at week 84 and sustained functional performance amelioration at week 42 [26]. Based on those pivotal results, the 2023 European Society of Cardiology guidelines on cardiomyopathies considered mavacamten a second-line therapy, like disopyramide, for the management of patients with HoCM remaining symptomatic despite beta-blocker or calcium channel blocker treatment (class IIa, level of evidence A), whereas monotherapy may be considered if the previous treatments are contraindicated or poorly tolerated (class IIa, level of evidence B) [21]. Nevertheless, the burden of real-world patients with HCM who are cMI candidates remains unknown.

5.3. Potential target population for a cMI

From the 1059 selected adult patients with HCM (HCM group) enrolled in the three main REMY university centres (total $n = 1829$ patients), about 40% presented with obstruction – a lower-than-expected proportion, as it has been suggested that about two thirds of patients with HCM have an obstruction at initial evaluation at rest or after provocation [27, 28]. In the large international SHaRe registry conducted in tertiary reference centres in the USA and the European Union [29], the prevalence of patients with obstruction was even lower (28%), but the systematic use of provocative manoeuvres was not reported. The smaller proportion of patients with obstruction in these large cohorts may have multiple explanations, such as the well-known variability in obstruction over time, underutilization (or non-optimal use) of the Valsalva manoeuvre and exercise echocardiography to demask obstruction and the effects of drug therapy. In our adult HoCM group, patients were diagnosed at least 1 year earlier than inclusion in REMY, and they were therefore already receiving drug therapy for obstruction; this was confirmed by similar frequencies of use of beta-blockers and calcium channel blockers at inclusion and at the end of follow-up (85.1%). This proportion may be even higher in real-life, as HCM reference centres are more inclined to optimize drug therapy for obstruction relief, and particularly to combine a beta-blocker or verapamil with disopyramide. Furthermore, about one fourth

of the cMI candidates group became asymptomatic during follow-up, which might reflect the greater use of disopyramide and the favourable results of invasive procedures. Conversely, almost 10% of patients with HoCM became symptomatic at follow-up, thus becoming potentially eligible for cMI treatment. Taking all these numbers into account, the current study suggests that the potential target population for a cMI represents at least one third of all adults with HCM.

It may be argued that only patients with HoCM with obstruction > 50 mmHg were included in the EXPLORER-HCM and VALOR-HCM trials, whereas our cMI-eligible REMY patients were selected by a gradient > 30 mmHg. Even if we had applied this more stringent criterion to our adult population with HoCM, 252 (24%) patients would still have been eligible for cMI treatment. Finally, the similarity of the HoCM cohorts included in the EXPLORER-HCM trial and REMY are underlined (Table 1), reinforcing the main conclusion.

5.4. Potential limitations of cMI use in HoCM

Some uncertainties remain concerning cMI therapy for HoCM: (1) there is no available comparison with standard therapy for obstruction (the ongoing MAPLE trial comparing mavacamten with metoprolol might answer that question) [30]; (2) whether standard medications for obstruction may be tapered during a cMI treatment remains to be demonstrated [26]; (3) there is some uncertainty about the efficacy and tolerance of cMIs in young patients (in the two pivotal studies the average age was relatively high); (4) the efficacy of mavacamten has been demonstrated in HCM with LVOTO, whereas patients with mid-cavitary obstruction were not included in the main studies; (5) substantial structural changes in cardiac structure have been suggested in mavacamten-treated patients [31], and are currently being studied in the ongoing MEMENTO trial (ClinicalTrials.gov Identifier: NCT06112743); and (6) there is no demonstration of the efficacy of mavacamten on morbidity and mortality (as for all the current drugs used in HCM treatment).

More importantly, long-term cMI therapy safety remains to be established in real-life prescription. Because of their negative inotropic effect, cMIs decrease LVEF in HoCM. The reduction is usually moderate, although sometimes it may be more severe, but nevertheless was always reversible after drug cessation in the pivotal studies [19, 20]. Thus, in the EXPLORER-HCM trial, the absolute reduction in LVEF was 4% in the mavacamten group, whereas 6% of the treated patients experienced a reduction of LVEF below 50%. The MAVA-LTE interim results [26] reported a mean decrease in LVEF of $7 \pm 8.3\%$ at week 84, without significant reduction after week 16, confirming the EXPLORER

data [19]; among the 12 (5%) patients in whom the drug was temporarily suspended because of LVEF < 50%, no sustained LVEF impairment was observed, and seven of them rejoined the trial. Finally, the possibility of increased toxicity (with reduced LVEF heart failure) as a result of unexpected concomitant prescriptions acting on cytochrome CYP2C19, particularly in patients who are low metabolizers, might represent a concern in real-life prescription.

5.5. Limitations of the current work

More than 40% of patients with HCM enrolled in REMY were excluded from our analysis. Although some of these patients were excluded because of non-sarcomeric causes, young age and low LVEF, 23 inclusion centres were excluded as a result of the large proportion of patients lacking data at inclusion or at the end of follow-up. The inclusion restriction to the three largest university centres might reduce the yield of our findings, and may represent a source of selection bias.

6. Conclusions

In this cohort of patients with HCM enrolled in a national prospective registry, at least one-third were potentially eligible for a cMI at baseline, whereas nearly 10% more became eligible during follow-up.

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Disclosure of interest

A. H. has served as an advisor to Alnylam, Amicus, Bristol Myers Squibb, Cytokinetics, Gilead, Myokardia, Pfizer and Sanofi Genzyme.

The other authors declare that they have no competing interest.

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Figure legends

Fig. 1. Study scheme. cMI: cardiac myosin inhibitor; EU: European Union; HCM: hypertrophic cardiomyopathy; HoCM: obstructive hypertrophic cardiomyopathy; LVEF: left ventricular ejection fraction; LVOTO: left ventricular outflow tract obstruction; NYHA: New York Heart Association; REMY: Register of hypertrophic cardioMYopathy; SRT: septal reduction therapy.

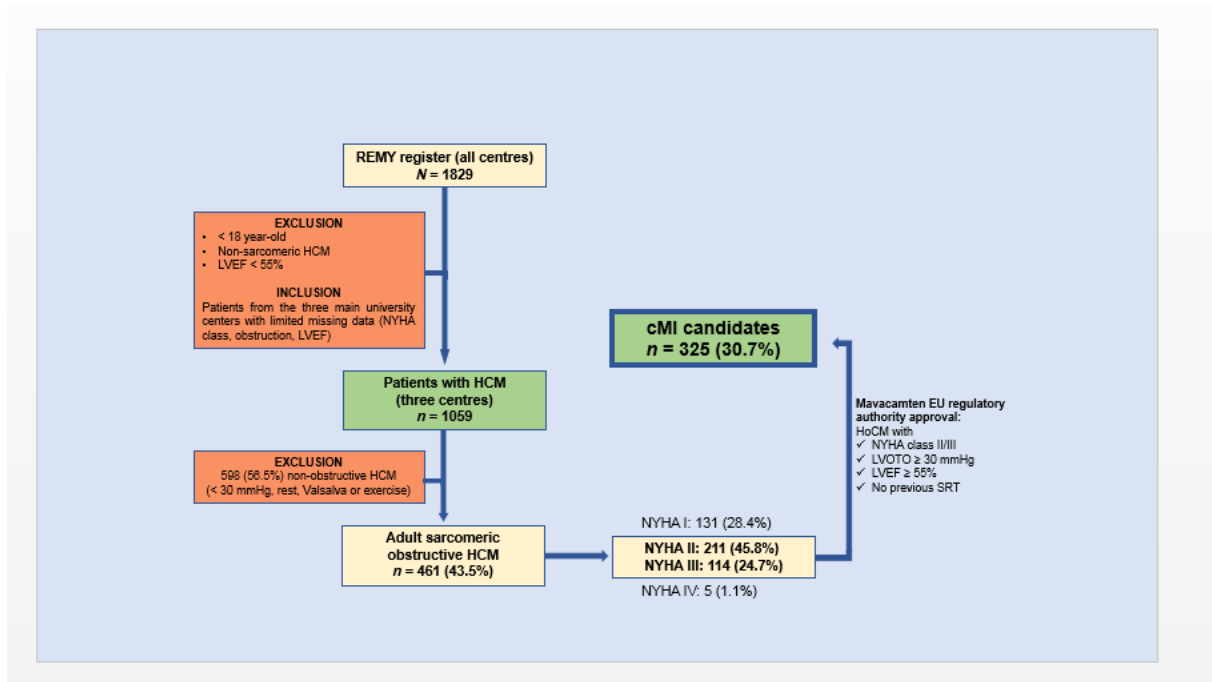
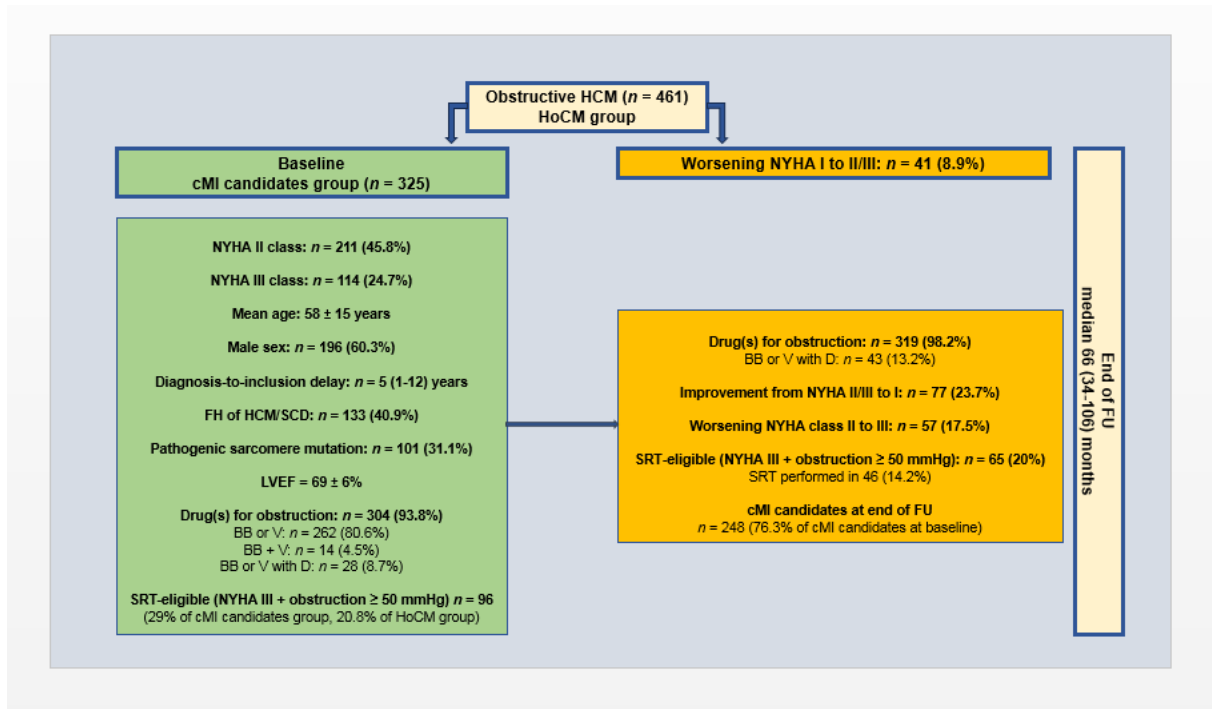


Fig. 2. Baseline and follow-up features. BB: beta-blocker; cMI: cardiac myosin inhibitor; D: disopyramide; FH: family history; FU: follow-up; HCM: hypertrophic cardiomyopathy; HoCM: obstructive hypertrophic cardiomyopathy; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SCD: sudden cardiac death; V: verapamil.



Central illustration. Proportion of patients with a potential indication for a cardiac myosin inhibitor in hypertrophic cardiomyopathy. cMI: cardiac myosin inhibitor; FU: follow-up; HCM: hypertrophic cardiomyopathy; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SRT: septal reduction therapy

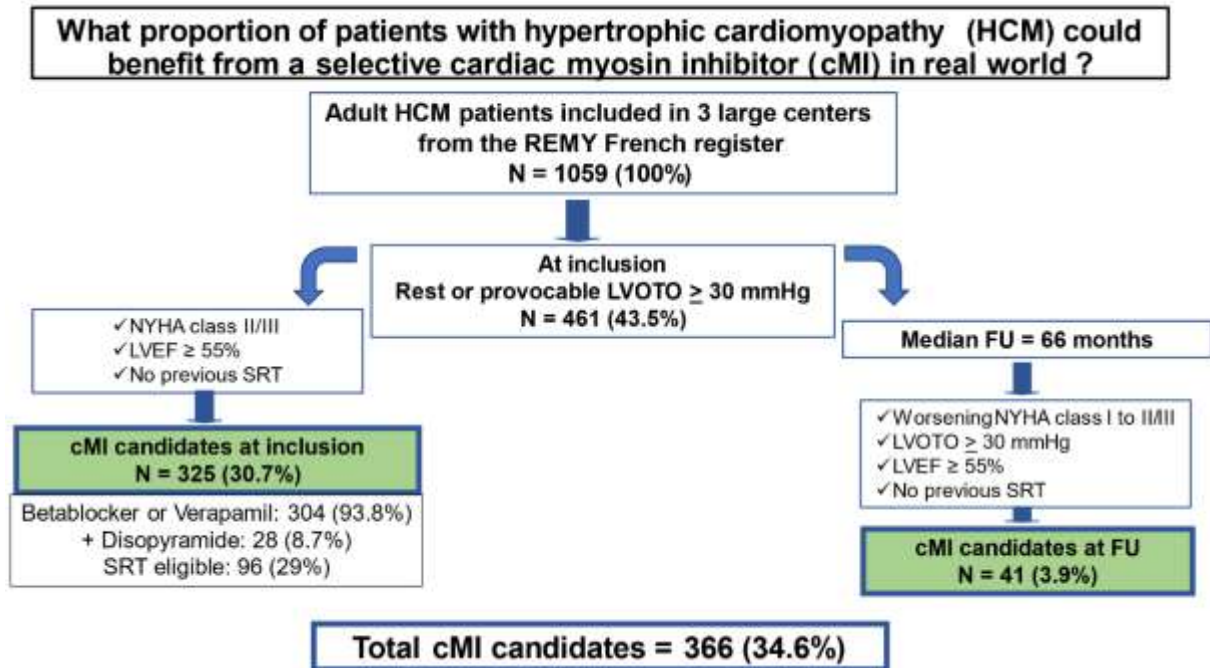


Table 1

Baseline clinical data: A comparison of three hypertrophic obstructive cardiomyopathy cohorts.

	REMY-HCM ^a	REMY-HCM cMI candidates group ^b	EXPLORER-HCM
	(n = 1059; 100%)	(n = 325; 30.6%)	(n = 123; 100%)
Age (years)	54 ± 16	54 ± 16	58 ± 12
Male sex	715 (67.5)	196 (60.3)	66 (54)
Obstruction ≥ 30 mmHg	461 (43.5)	325 (100)	0 (0)
Obstruction ≥ 50 mmHg	338 (31.9)	252 (77.5)	123 (100)
NYHA class I	406 (38.3)	0 (0)	0 (0)
NYHA class II	456 (43.1)	211 (64.9)	88 (72)
NYHA class III	197 (18.6)	114 (35.1)	35 (28)
HCM family history	374 (35.3)	84 (25.8)	33 (27)
Identified sarcomere gene mutation ^c	275/794 (34.6)	101/325 (31.1)	28/90 (31)
LVEF (%)	67 ± 7	69 ± 6	74 ± 6
BB and/or CCB use	965 (91.1)	304 (93.8)	119 (96.7)
ICD carriers	222 (20.9)	73 (22.4)	27 (22)

Data are expressed as mean ± standard deviation or number (%). BB: beta-blocker; CCB: calcium channel blockers; cMI: cardiac myosin inhibitor; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; REMY: REgister of hypertrophic cardioMYopathy.

^a Restricted to three main centres participating in REMY.

^b NYHA class II/III, left ventricular outflow tract obstruction ≥ 30 mmHg, LVEF ≥ 55%, no previous septal reduction therapy.

^c Positive/total tested (%).