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Running title: Betablockers or verapamil in hypertrophic cardiomyopathy

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Highlights

- Prognostic impact of beta blockers and verapamil in HCM is unknown
- Verapamil appears comparable to betablockers in terms of cardiovascular outcomes
- Verapamil is effective and safe as betablockers for low risk HCM patients

Abstract

Guidelines recommend betablockers as first line therapy in symptomatic patients with hypertrophic cardiomyopathy and non-dihydropyridine calcium channel blockers, particularly verapamil, as the second line therapy, despite absence of comparison trials between those two drugs. Since deleterious effects of verapamil have been reported in this setting, the present analysis aimed to evaluate the prognostic impact of betablockers and verapamil in a cohort of patients with hypertrophic cardiomyopathy.

From a nation-wide cohort of 1434 patients with a diagnosis of hypertrophic cardiomyopathy included in the French prospective observational REgistry of hypertrophic cardioMYopathy (REMY), we retrospectively analysed individuals with sarcomeric hypertrophic cardiomyopathy included in the three largest centers and treated either with betablockers or verapamil. Patients with a cardiac defibrillator or a pacemaker or who underwent a procedure of atrial fibrillation or septal ablation were excluded. The primary endpoint was the composite of cardiovascular death, hospitalization for heart failure and hospitalization for atrial fibrillation.

Out of 600 hypertrophic cardiomyopathy patients, 544 (91%) were treated with betablockers and 56 (9%) with verapamil. At inclusion, the two groups were comparable concerning presence/amplitude of obstruction and sudden cardiac death risk factors. At up to 8-year follow-up (median 3.9 years, IQR 2.1-5.8) no significant

differences were observed in the primary endpoint (132 [24%] vs. 10 [18%] under betablockers or verapamil respectively, HR=1.84, 95% CI=0.94–3.63).

In conclusion, in a real-world cohort of low risk patients with hypertrophic cardiomyopathy, verapamil therapy was not associated with a higher incidence of adverse events compared to betablocker therapy.

Keywords. Hypertrophic cardiomyopathy; prognosis; betablockers; verapamil.

Introduction

Hypertrophic cardiomyopathy (HCM) is among the most common inherited cardiac disease, with an estimated prevalence of at least 1:500 [1] and transmitted by an autosomal dominant pattern, but with a variable penetrance and phenotype expression. So far, medical therapy is recommended to reduce the symptomatic burden of obstruction in left ventricular outflow tract (LVOT) and impaired left ventricular filling due to cardiac muscle stiffness [2, 3]. Data supporting these recommendations derive from old observational studies on first generation betablockers (BB) and non-dihydropyridine calcium channel blockers (ND-CCB) resulting in reducing the LVOT gradient and improving symptoms and exercise tolerance [4-11]. The first small, randomized study on BB in obstructive HCM was only recently published, demonstrating a superiority of metoprolol over placebo in reducing LVOT obstruction (LVOTO), symptoms burden and improving quality of life, but without improvement in maximum exercise capacity [12]. Other observational studies showed a further functional improvement along with a reduction in LVOTO when adding disopyramide in severely symptomatic patients considered resistant to first-line therapy with betablockers or verapamil [13, 14].

European and American guidelines recommend the use of BB as first line drugs in symptomatic patients with HCM [2, 3]. ND-CCB, on the other hand, either verapamil

or diltiazem (rarely used in Europe), are recommended in patients intolerant or presenting contraindications to BB. However, nor BB or ND-CCB have provided so far any evidence of improving prognosis in HCM patients, either with an obstructive phenotype or not. Of note, numerous studies have highlighted the possibility of severe adverse effects with verapamil [15-17], leading to limit its use in patients with severe obstruction or elevated ventricular filling pressure [3], both conditions difficult to appreciate in clinical practice.

Since no comparison has been made between BB and ND-CCB as regard symptoms improvement and prognosis, the aim of the present retrospective analysis is to evaluate and compare the incidence of cardiovascular events in patients diagnosed with HCM, either obstructive or not, treated with BB or verapamil.

Methods

This study was part of the REMY (REgistry of hypertrophic cardioMYopathy) French research project (ClinicalTrials.gov Identifier: NCT01091480). REMY, initiated in 2010, is a nationwide observational prospective multicenter ongoing study on diagnosis, management and prognosis of sarcomeric and non-sarcomeric HCM that currently includes around 2000 patients, age >16 years, who provided written informed consent, in 26 academic or non-academic institutions. The study population has been previously reported [18]. Inclusion criteria were based on left ventricular (LV) hypertrophy ≥15mm in sporadic cases, and ≥13mm in the presence of a family

history of HCM, using any imaging technique (echocardiography, cardiac magnetic resonance imaging or computed tomography). Patients with abnormal LV loading conditions (i.e., severe systemic hypertension or significant aortic stenosis < $1cm^2$) were excluded. The relevant government institution, the National Commission of Informatics and Liberty, provided ethical clearance (CNIL agreement #909378). Only patients with proven (identified mutation) or presumed (no other identified cause of hypertrophy and strong clinical suspicion) sarcomeric HCM were included in the study.

The current substudy was confined to the three centers that included the largest number of patients (Hôpital Européen Georges-Pompidou, Paris, Hôpital Pointchaillou, Rennes, and Hôpital Haut Lévêque, Bordeaux), as these centers reported a complete systematic follow-up. All clinical and echocardiographic data from patients either on BB therapy or on verapamil therapy were collected. At enrolment, none of the patients had an ejection fraction below 50%. Patients taking both negative inotropic drugs at inclusion or taking none of them were excluded. The initiation of negative inotropic therapy was decided by the referring cardiologist, starting with a betablocker in case of ventricular outflow obstruction in the absence of contra-indication or intolerance, and verapamil in the other cases, in accordance with regular clinical practice. Of note, diltiazem is not used in France in patients with HCM. We excluded patients who had an implantable cardioverter defibrillator (ICD) or a pacemaker (PM) implanted at inclusion and patients who had previously undergone a procedure of atrial fibrillation (AF) ablation or a procedure of septal reduction therapy

(SRT), either percutaneous or surgical, as we considered these events as secondary outcomes **(Figure 1)**.

Active follow-up was performed by dedicated personnel by means of telephone interviews or mail and review of electronic medical records. The institutional clinical database was used to retrieve missing information related to the patient's outcome. In case of missing data, the patient's cardiologist or general practitioner was contacted by phone or, if necessary, patients or family were contacted themselves. At inclusion, personal and family history, symptoms (New York Heart Association (NYHA) functional class, syncope, chest pain), complete clinical examination, 12-lead surface ECG and resting echocardiography were collected. Other exams (e.g., stress echo, magnetic resonance imaging (MRI), genotyping) were not mandatory. Outpatient visits were scheduled at 18 months, 3 years and 5 years. During follow-up, intercurrent pre-defined events – death, hospitalization for heart failure, stroke or other thrombo-embolic events, sustained atrial (atrial fibrillation, atrial flutter and atrial tachycardia) or ventricular tachyarrhythmias, pacemaker or ICD implantation, septal reduction procedure – were notified and recorded in the database. Sustained ventricular tachycardia (VT) was defined as a VT with duration >30 sec. Follow-up duration was determined using the date of the most recent evaluation or the patient's date of death or heart transplant.

The primary outcome was a clinical composite of death for cardiovascular (CV) causes, hospitalizations for heart failure (HF) and hospitalization for AF. The

secondary outcomes included the single components of the primary outcome, and the need for ICD implantation (either in primary or secondary prevention) and for SRT. Symptomatic burden with NYHA class was evaluated at long term follow-up.

Categorical variables are reported as numbers (percentage) and compared with the Pearson's chi-squared or the Fisher exact test as appropriate. Continuous variables, given their non-normal distribution (tested by Shapiro–Wilk W test for normality), were reported as median (IQR) and compared with the two-sample Wilcoxon rank-sum (Mann–Whitney) test. Clinical follow-up was censored at the date of death or latest available follow-up. Data for patients lost to follow-up were censored at the time of the last contact. Adverse events are reported as observed number of events and as Kaplan-Meier estimated rates. Cumulative incidence of the primary outcome and its single components were assessed using the Kaplan-Meier method and compared between groups using the log-rank test for time to the first event. Estimated risks are expressed as unadjusted hazard ratios (HR) and 95% confidence intervals (CIs), calculated using Cox regression analysis. Two-sided P values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using Stata version 16.0 (Stata Corp, College Station, TX, USA).

Results

From a total of 1434 HCM patients followed-up at the three academic hospitals, we enrolled a cohort of 600 patients. Of these, 544 (91%) were taking BB as the only

inotropic negative therapy at the moment of register inclusion and 56 (9%) were taking verapamil. Baseline clinical, echocardiographic, ECG features and medical therapy are reported in **Table 1**. Baseline characteristics were largely similar among the groups, with the exception of arterial hypertension, as patients taking BB had higher prevalence of arterial hypertension than patients taking verapamil. Echocardiographic features were comparable as well, with a median interventricular septum thickness of 19 mm (IQR 17-21), a similar LV ejection fraction (EF) and approximately a third of the patients presenting resting LVOTO. Only one half of the cohort had an exercise stress test for the evaluation of the peak LVOT gradient.

Inclusion data are reported in **Table 2**. The results are largely comparable between the two groups. Approximately 70% of the entire enrolled population had a genetic testing, and, of these, almost 50% had a pathogenic or likely pathogenic variant identified.

Clinical events at up to 8 years of follow-up (median: 3.9, IQR 2.1-5.8) are listed in **Table 3**. No significant differences were observed in terms of incidence of the primary endpoint (132 [24%] vs 10 [18%] for patients taking BB or verapamil respectively, p = 0.283), nor in the incidences of all the secondary endpoints (104 [19%] vs 10 [18%] for hospitalization due to AF, p = 0.490; 40 [7%] vs 3 [5%] for hospitalization due to HF, p = 0.439; 33 [6%] vs 2 [4%] for CV death, p = 0.308). Cumulative event rates for the primary endpoint according to 8-year follow-up of the two groups and of the single components of the primary outcome are displayed in

Figure 2. No significant difference in the risk of the primary composite outcome were detected (HR 1.84, 95% CI 0.94 – 3.63).

During follow-up, 3% of patients on BB and 19% of patients taking verapamil had either discontinued or modified the negative inotropic drug. Patients treated with BB were more commonly symptomatic for dyspnoea (NYHA >1) than those receiving verapamil at long-term follow-up (238 [54.7%] vs 17 [38.6%] of patients taking BB and verapamil, respectively, p = 0.042) **(Figure 3)**.

Discussion

The aim of this study was to compare the use and prognostic impact of BB and verapamil in a population of HCM patients included in a large registry, representative of the real-life management of HCM in France. We also aimed at evaluating the safety of verapamil in this large cohort of patients, as previous complications (pulmonary oedema, syncope, atrioventricular block and death) have been scarcely reported with its use in these patients [15-17].

In our cohort, the use of BB is markedly more frequent than the use of verapamil (a 9 to 1 ratio), independently of obstruction or other clinical or imaging parameters, which means that the prescription is probably essentially guided by the intolerance or contra-indication to betablockade therapy. Baseline characteristics of the two groups are similar to those reported in previous cohorts: almost half of patients with HCM do not test positive for a pathogenic or likely pathogenic variant

[19, 20]. The phenotype of our cohort reflects the general epidemiology of HCM phenotype as well, showing a third of the entire population having significative LVOT obstruction (> 30 mmHg) at rest [21].

In HCM patients with LVOTO, either at rest or provocable, BB and verapamil, eventually associated with disopyramide, have been shown to reduce LVOT gradient and symptomatic burden [4-10, 12-14].

There is paucity of comparison among available drugs used for HCM patients and no medical therapy has shown so far prognostic impact in HCM patients. One single retrospective study compared long-term effects of propranolol versus verapamil in preventing sudden death in "low-risk" patients and showed that verapamil administration was associated with the occurrence of non-sudden cardiac deaths and a high incidence of side effects [22]. Natural history of HCM patients is characterized by events such as AF occurrence, hospitalizations for HF and sudden cardiac death [23]. For this purpose, our analysis aimed at evaluating the impact of these two drugs on the occurrence of CV events in HCM patients, such as AF, hospitalization for HF or CV death. In our analysis, verapamil therapy was not associated with an increase of cardiovascular events, including hospitalization for AF or HF, and cardiovascular death as compared to BB. However, patients taking verapamil were more likely to change or interrupt the negative inotropic drug (19%) than patients taking BB (3%) at long-term follow-up, mostly for unsatisfactory control of symptoms and/or LVOTO.

ND-CCB are associated with a number of side effects that could limit patients' compliance, especially in case of limited symptomatic burden, where the efficacy of negative inotropic drugs is still debated. A randomized trial comparing nadolol and verapamil indicated that there are no significative differences in terms of symptom burden reduction (in patients in NYHA class I-II) and compliance [24]. Similarly, a recent systematic review concludes that metoprolol has demonstrated efficacy in reducing LVOT gradient, while verapamil, especially, in improving patients' functional capacity. Moreover, both drugs exhibit a favourable risk profile [25].

While no differences were found between the BB group and the verapamil group in the number of symptomatic patients at baseline (NYHA > 1), a higher percentage of patients taking BB than those taking verapamil was symptomatic at long term follow-up. This subtle difference, however, partially contrasts with the 19% of the patients who were on verapamil at baseline who subsequently discontinued or modified the medication, primarily due to poor tolerance of mild side effects or persistence of symptoms. Unfortunately, precise data on the NYHA classification grading are not available, making it impossible to estimate the degree of dyspnoea. Of note, these low-risk patients, potentially with a low degree of LVOT obstruction, often present challenges in symptom assessment when using the NYHA classification as the sole parameter. The NYHA class assessment represents a symptomatic burden derived from different phenotypes of HCM, with the LVOTO as the main cause in the obstructive phenotype and the impaired diastolic filling as the main cause of the non-

obstructive one. Moreover, a reduction of functional capacity may occur with the occurrence of atrial arrhythmias, further limiting the filling of the typically stiff ventricle, coupled with reduced LVEF, determining further reduction in cardiac output. This classification system provides a rapid assessment of the functional status during physical exertion. However, as shown by Raphael et al., the NYHA classification system is subjective and poorly reproducible [26], as there is no widespread agreement on how to assign a patient to a class in clinical practice. Therefore, for all these reasons, we assume that NYHA functional class is not an accurate parameter to evaluate these patients, unless used in a larger rating scale [27].

Recent years have seen the rise of new drugs with promising characteristics that could change the quality of life of HCM patients and could have an impact on prognosis as well [28, 29]. Since data on efficacy and safety of these drugs in the real world for a longer follow-up are not yet available, BB and ND-CCB remain the mainstay of treatment in this setting. As a matter of fact, contemporary treatments for HCM remarkably reduced the mortality due to HCM, conferring a normal or near-normal life expectancy without significant adverse events to HCM patients. However, as we found that treatment of HCM patients with ND-CCB is not associated with more adverse outcomes when compared to patients treated with BB, a change of current clinical practice in therapeutic algorithm might be evaluated in large scale randomized trials.

Our study provides a snapshot of a cohort of low-risk patients with hypertrophic cardiomyopathy in France and our findings should be viewed as hypothesis-generating rather than a definitive assessment of treatment outcomes. We offer preliminary insights into the relative safety and efficacy of verapamil and BB, mainly showing how the use of both drugs is associated with low rate of adverse events in a low-risk population and how verapamil is relatively poorly tolerated in this setting, but its limitations necessitate cautious interpretation.

The present study has the important limit of being based on retrospective data analysis, with a relatively short follow-up. Moreover, the generalisability of the results is limited considering the characteristics of patients included in the main analysis, as the cohort of patients taking verapamil was much smaller than the one taking BB and as we excluded both patients with probably milder (e.g., those not requiring any therapy) and more severe disease (patients who already had interventions such as ICD implantation, AF ablation and SRT), explaining the low rate of events, especially sudden cardiac death and CV deaths (6% at 8-year follow-up compared with the rate of all-cause mortality of 25% reported in a large cohort at 10 years) [30]. Indeed, one of the main limitation of the present analysis is related to its limited statistical power in the detection of differences between the two treatment groups. Given the small sample size, this finding must be interpreted as hypothesis generating. Another limitation is the absence of baseline data on echocardiographic stress test and late gadolinium enhancement in a relevant quote of patients, maybe reflecting the

proportion of HCM patients have not access to the full spectrum of diagnostic tests necessary for the diagnostic and prognostic assessment. Finally, the enrolment in the study and the initiation of pharmacological therapy do not coincide, thereby creating a potential risk of bias since, for instance, data about the duration for which patients had been taking the medication are lacking. Lastly, we could not specify the type of beta-blocker used due to the lack of this information during data collection in the registry, the dosage of each drug and if this dosage changed over time during the observation period.

The findings underscore the need for larger, prospective studies that could more comprehensively evaluate the therapeutic impact of these drugs. Future research should aim to incorporate a broader range of parameters, including electrocardiographic, echocardiographic, and cardiac magnetic resonance imaging measures, to better identify the patient subsets most likely to benefit from either therapy.

Conclusions

In a real-world cohort of low risk patients with HCM, either obstructive or not, verapamil therapy was not associated with a higher incidence of CV events compared to BB therapy. In light of these results, verapamil appears to be an effective and safe alternative to BB in the therapeutic algorithm of HCM, at least until promising effective results of more specific molecules will be available.

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All authors have substantially contributed to the manuscript, they have read and approved the text.

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Figure legends.

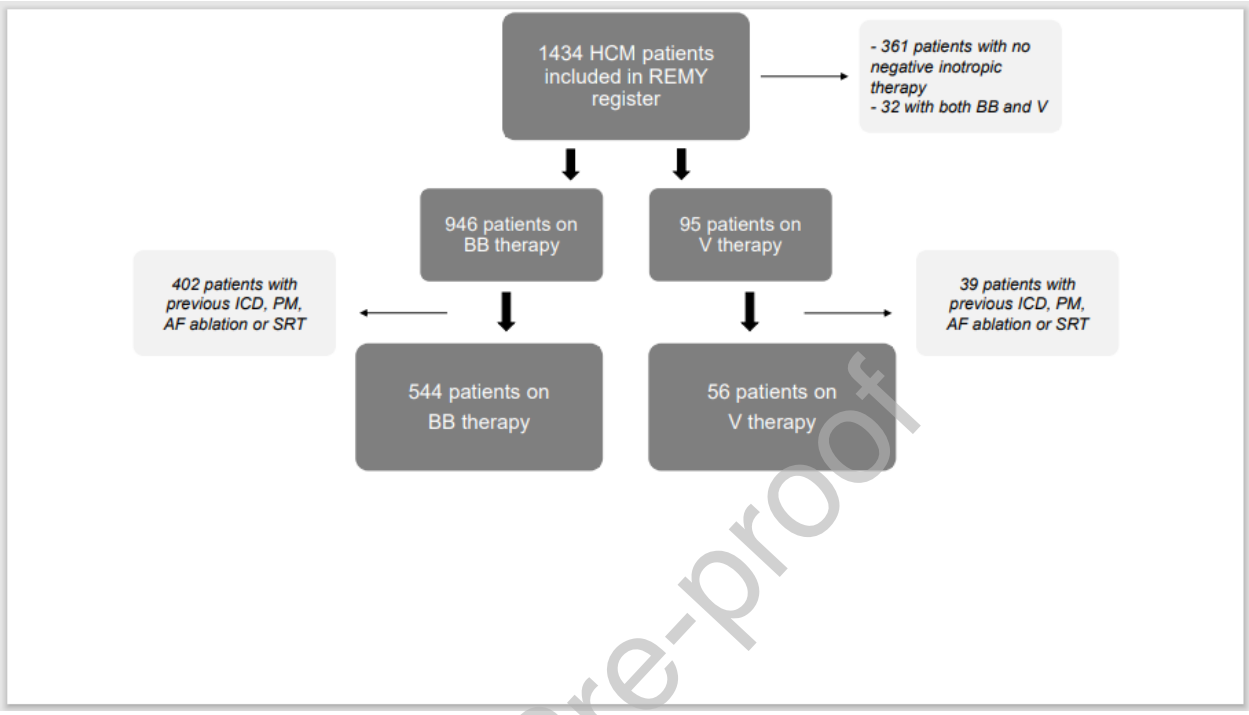

Figure 1. Study flowchart.

Abbreviations. AF, atrial fibrillation; BB, betablockers; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; PM, pacemaker; SRT, septal reduction therapy; V, verapamil.

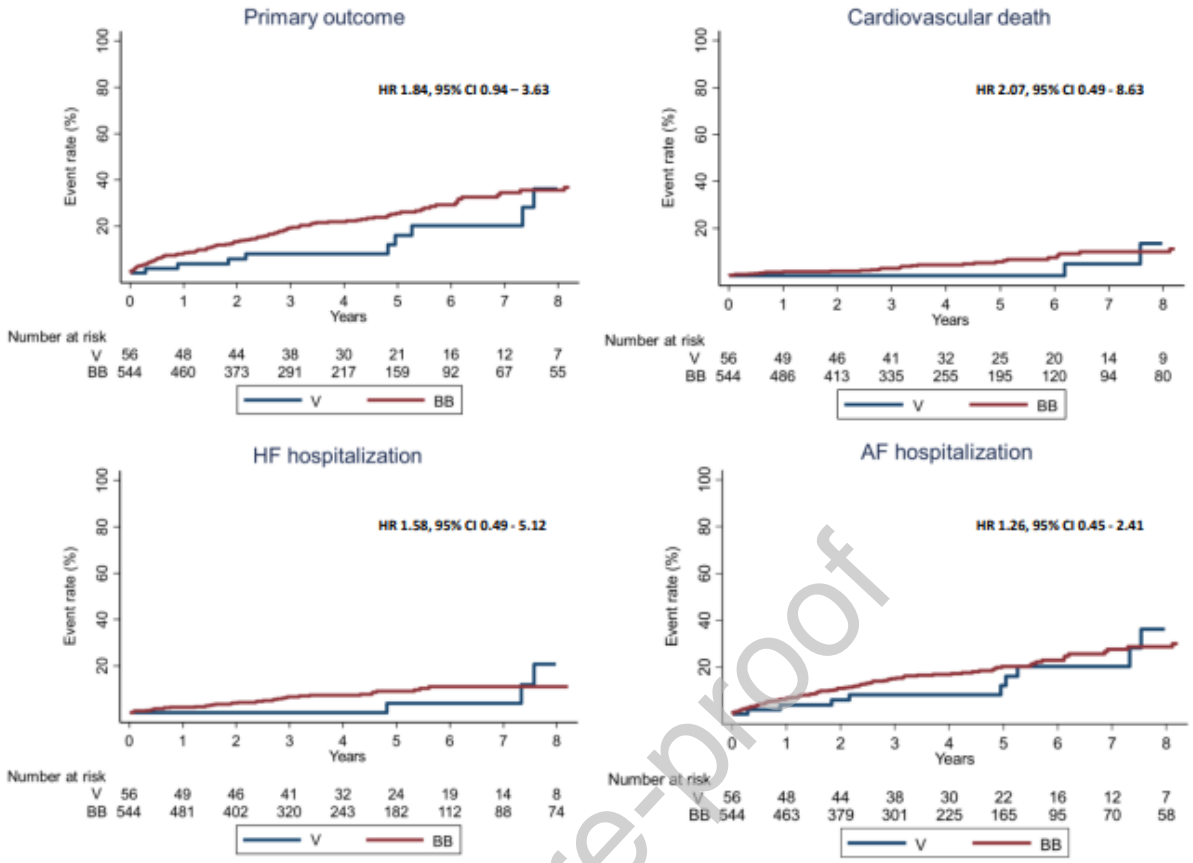

Figure 2. Kaplan Meier curves between the two groups for the primary endpoint and for the single components of the primary outcome at 8 years follow-up.

Abbreviations. AF, atrial fibrillation; BB, betablockers; HF, heart failure V, verapamil.

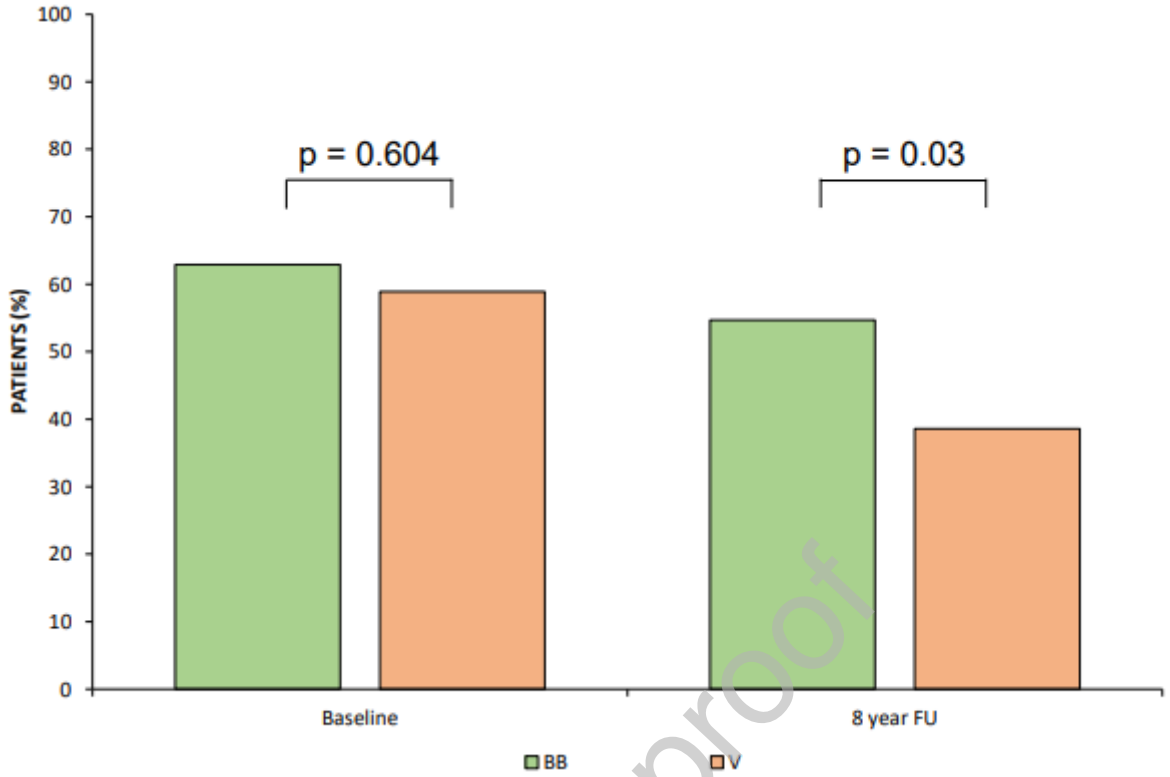

Figure 3. Percentage of symptomatic patients (NYHA >1) at baseline and at long-term follow-up between the two groups.

Abbreviations. BB, betablockers; V, verapamil.

Graphical abstract.

Abbreviations. AF, atrial fibrillation; CV, cardiovascular; HCM, hypertrophic cardiomyopathy; HF, heart failure.

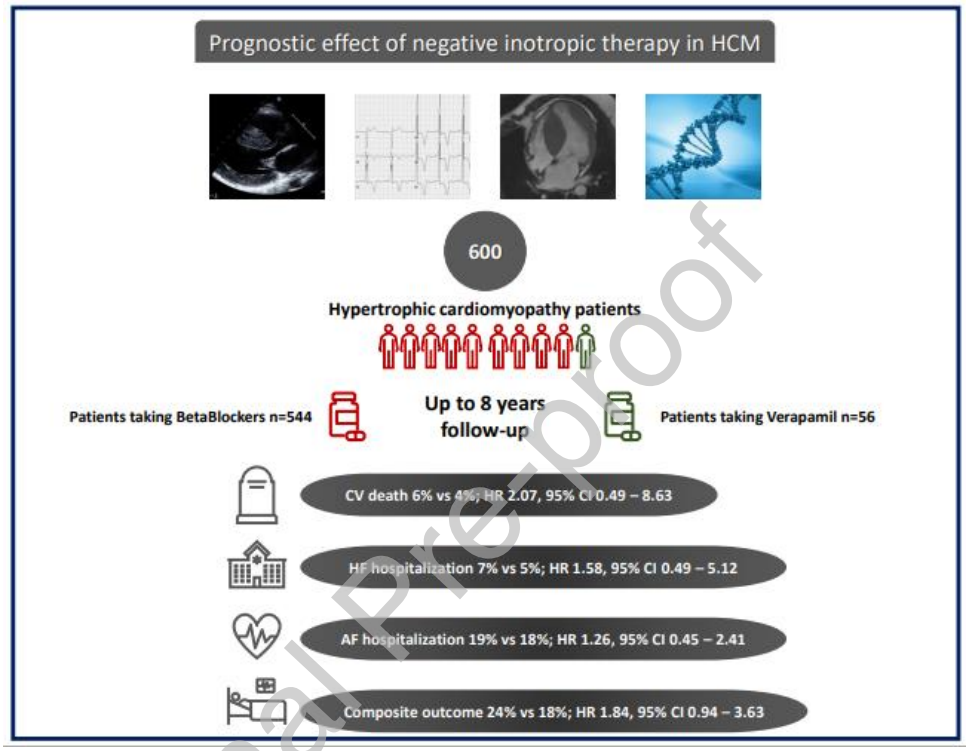

Table 1. Baseline clinical and echocardiographic characteristics of the whole population stratified by medical therapy for hypertrophic cardiomyopathy.

	BB (544)	V (56)	P Value
SEX (M)	377 (69.3)	42 (75)	0.229
AGE	57 (47-66)	58 (47.5-63)	0.797
AGE DIAGNOSIS	50 (35-61)	49 (34-57)	0.534
NYHA >1	343 (63)	33 (58.9)	0.604

EXERCISE ANGINA	179 (32.9)	17 (30.4)	0.415
HISTORY OF SYNCOPE	120 (22)	16 (28.6)	0.171
HISTORY OF AF	125 (23)	8 (14.3)	0.090
HISTORY OF VA*	75 (13.8)	7 (12.5)	0.493
ARTERIAL HYPERTENSION	243 (44.7)	17 (30.4)	**0.027**
PREVIOUS EMBOLIC STROKE	28 (5.1)	1 (1.8)	0.091
PREVIOUS PREGNANCY	85 (15.6)	5 (8.9)	0.125
ACTIVE SPORT†	87 (16)	11 (19.6)	0.293
PREVIOUS CV HOSPITALIZATION	238 (43.7)	21 (37.5)	0.229
CKD‡	19 (3.5)	1 (1.8)	0.428
BASAL ECHO PARAMETERS			
IVS (mm)	19 (17-22)	19 (17-21)	0.935
TDD LA (mm)	42 (36-48)	40 (37-44)	0.212
LVEF	68 (62-71)	70 (64-71)	0.366
PASP > 30 mmHg	72 (13.2)	7 (12.5)	0.540
MR > 2+	24 (4.4)	0	0.091
MITRAL VALVE SAM	192 (35.2)	22 (39.3)	0.321
RESTING LVOTO > 30 mmHg	172 (31.6)	17 (30.4)	0.493

MEDICAL THERAPY			
DISOPYRAMIDE	29 (5.3)	0	0.055
AMIODARONE	35 (6.4)	0	**0.029**

Abbreviations. AF, atrial fibrillation; BB, betablockers; CKD, chronic kidney disease; CV, cardiovascular; IVS, interventricular septum; LA, left atrium; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; M, male; MR, mitral regurgitation; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SAM, systolic anterior motion; TDD, telediastolic diameter; V, verapamil; VA, ventricular arrhythmias.

* History of VA is intended as previous evidence of non-sustained ventricular arrhythmias.

† Active sport is intended as number of patients doing sports regularly more than ordinary activities.

‡ Chronic kidney disease defined as eGFR < 60 ml/min/1.74m^2

Table 2. Diagnostic examinations at inclusion.

	BB (544)	V (56)	P Value
EXERCISE ECG	380 (69.9)	43 (76.8)	0.172
ABPR DROP	*32 (8.4)*	*4 (9.3)*	*0.506*
ISCHEMIC SIGNS	*8 (2.1)*	*2 (4.6)*	*0.268*
VA	*8 (2.1)*	*0*	*0.423*
CARDIAC MRI	408 (75)	40 (71.4)	0.338
LGE +	*228 (55.9)*	*26 (65)*	*0.173*
DOCUMENTED CAD	30 (5.5)	3 (5.4)	0.630
GENETIC TESTING	376 (69)	39 (69.6)	0.527
MUTATION*	*154 (41)*	*14 (46.1)*	*0.322*

Abbreviations. ABPR, abnormal blood pressure response at exercise; BB, betablockers; CAD, coronary artery disease; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; V, verapamil; VA, ventricular arrhythmias.

*Sarcomeric pathogenic or likely pathogenic variant

Table 3. Clinical outcomes at 8 year follow-up.

	BB (544)	V (56)	HR (95% CI)	P Value
COMPOSITE OUTCOME	132 (24%)	10 (18%)	1.84 (0.94-3.63)	0.283
HF HOSPITALIZATION	40 (7%)	3 (5%)	1.58 (0.49-5.12)	0.439
CV DEATH	33 (6%)	2 (4%)	2.07 (0.49-8.63)	0.308
AF	104 (19%)	10 (18%)	1.26 (0.45-2.41)	0.490
ICD IMPLANTATION	48 (9%)	5 (9%)	1.15 (0.46-2.89)	0.769
SRT	12 (2%)	0	/	/
SCD/APPROPRIATE ICD DISCHARGE	21 (4%)	0	/	/

Abbreviations. AF, atrial fibrillation; BB, betablockers; CV, cardiovascular; HF, heart failure; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death; SRT, septal reduction therapy; V, verapamil.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: