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RESEARCH ARTICLE

Effect of beta-blocker therapy on the response to mavacamten in patients with symptomatic obstructive hypertrophic cardiomyopathy

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Aims

In the EXPLORER-HCM trial, mavacamten improved exercise capacity and symptoms in patients with obstructive hypertrophic cardiomyopathy (oHCM). Mavacamten effects on the primary endpoint, a composite of peak oxygen consumption (VO_2) and New York Heart Association (NYHA) class, were greater in patients not receiving background beta-blockers than in those receiving beta-blockers. We sought to determine if the effect of background treatment was consistent across other clinically meaningful parameters.

Methods and results

Subgroup analyses by beta-blocker use were performed in patients with oHCM from the EXPLORER-HCM and mavacamten long-term extension (MAVA-LTE) studies. In EXPLORER-HCM, 189 patients (75.3%) were receiving beta-blockers, and 62 (24.7%) were receiving non-dihydropyridine calcium channel blockers or no background HCM medication; 170 patients (90.4%) receiving beta-blockers had chronotropic incompetence. Improvements in peak VO_2 at week 30 with mavacamten versus placebo were lower with beta-blockers (mean difference [95% confidence interval (CI)]: 1.04 [0.12, 1.95] ml/kg/min) than without beta-blockers (mean difference [95% CI]: 2.69 [1.29, 4.09] ml/kg/min); improvements in non-heart rate-dependent parameters (V_E/VCO_2 slope) appeared unaffected by beta-blockers. Improvements in functional capacity parameters at week 30 with mavacamten versus placebo were independent of beta-blockade for post-exercise left ventricular outflow tract gradient (mean difference [95% CI]: −37.9 [−48.0, −27.9] mmHg with beta-blockers; −33.5 [−53.6, −13.3] mmHg without beta-blockers), proportion of patients with reduction of ≥1 NYHA class, Kansas City Cardiomyopathy Questionnaire clinical summary scores and N-terminal pro-B-type natriuretic peptide. Mavacamten benefits were reproduced and maintained in MAVA-LTE regardless of beta-blockade.

Conclusion

Mavacamten improved measures of functional capacity, left ventricular outflow tract obstruction, symptom burden and biomarkers in patients with HCM regardless of beta-blocker use. Beta-blocker use was often associated with chronotropic incompetence, affecting peak VO_2 and other heart rate-dependent measures, but had minimal impact on heart rate-independent measures.

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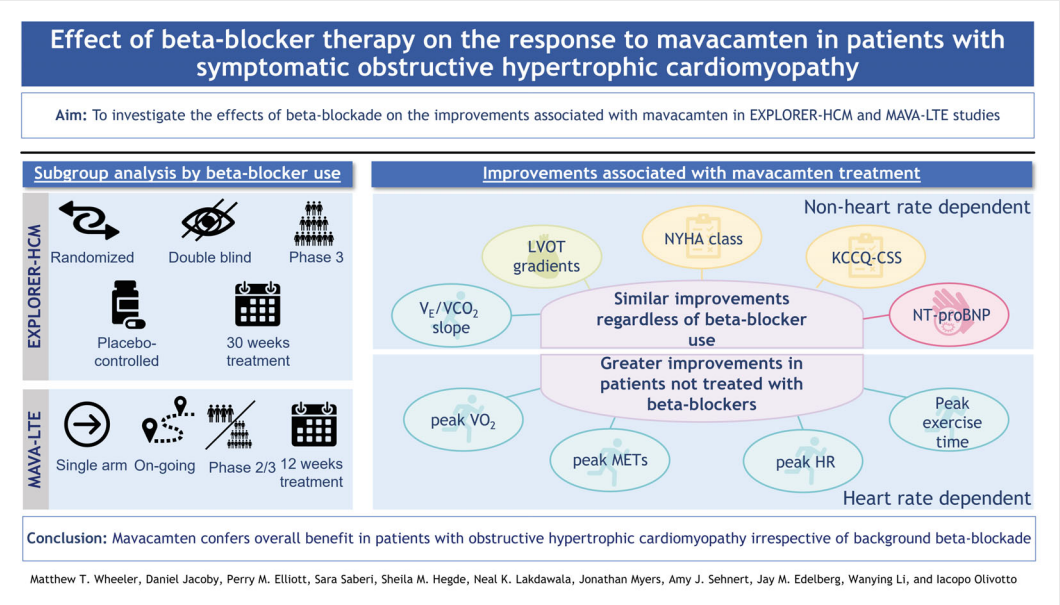
Graphical Abstract



Summary of the effect of beta-blocker therapy on the response to mavacamten in patients with symptomatic obstructive hypertrophic cardiomyopathy in the EXPLORER-HCM and MAVA-LTE studies. Mavacamten confers overall benefit in patients with obstructive hypertrophic cardiomyopathy irrespective of background beta-blockade. HR, heart rate; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LVOT, left ventricular outflow tract; MET, metabolic equivalent; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; V_E/VCO_2, minute ventilation to carbon dioxide production; VO_2, oxygen consumption.

Keywords Beta-blockers • Exercise capacity • Mavacamten • Obstructive hypertrophic cardiomyopathy • Symptoms

Introduction

Hypertrophic cardiomyopathy (HCM) is associated with excessive cardiac myosin–actin cross-bridging, with core pathophysiological features that include left ventricular (LV) hypertrophy, hypercontractility and poor LV compliance.[1,2] Dynamic LV outflow tract (LVOT) obstruction is present in approximately 65–70% of patients[2,3] and is a major determinant of heart failure symptoms and adverse outcomes.[3] Pharmacological therapy is recommended in patients with obstructive HCM (oHCM) to mitigate symptoms.[1,2] Therapies include beta-blockers, non-dihydropyridine calcium channel blockers and disopyramide.[1,2] Beta-blockers titrated to effectiveness or maximum tolerated dose and to resting heart rates of 60–65 bpm are recommended as first-line therapy, with substitution of non-dihydropyridine calcium channel blockers (e.g. verapamil) in patients for whom beta-blockers are ineffective or not tolerated.[1,2] Data supporting these recommendations are largely empiric because well-controlled clinical trials in patients with HCM are limited.[4] However, recent results from a randomized controlled trial in patients with oHCM indicated that the use of metoprolol reduces LVOT obstruction and improves symptoms and quality of life, but has no effect on measures of exercise capacity, peak oxygen consumption (VO_2) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) serum concentration.[5]

Mavacamten is a first-in-class, small-molecule, selective inhibitor of cardiac myosin[6,7] that targets the underlying pathophysiology of HCM. In the phase III EXPLORER-HCM study, mavacamten significantly improved the primary endpoint, a composite of peak VO_2 and New York Heart Association (NYHA) functional class, in patients with oHCM at week 30 compared with placebo.[8] Stable background therapy with beta-blockers or calcium channel blockers for HCM was allowed in the EXPLORER-HCM study.[8] In a pre-specified subgroup analysis, the effect of mavacamten compared with placebo on the primary endpoint was greater in patients without background beta-blocker use (difference [95% confidence interval (CI)]: 52.6% [32.9%, 72.2%] of patients) than in those with beta-blockade (difference [95% CI]: 8.7% [−3.6%, 21.1%] of patients).[8] Beta-blockers are known to blunt the heart rate response to exercise, thus affecting maximal

exercise capacity.[9] This is supported by recent evidence showing that beta-blockers impair exercise tolerance and peak VO_2 in patients with heart failure with preserved ejection fraction,[10] largely owing to chronotropic incompetence.[11]

Because of the marked and multidimensional benefit associated with mavacamten treatment in EXPLORER-HCM, we hypothesized that beta-blockers may have selectively affected its benefits in terms of peak VO_2 increase, which is strictly dependent on heart rate, but not across other clinically important, non-heart rate-dependent study endpoints. In the present study, we sought to evaluate this hypothesis based on functional and echocardiographic parameters, as well as serum cardiac biomarkers and measures of symptom burden. Data from both EXPLORER-HCM and an interim analysis of the mavacamten long-term extension study (MAVA-LTE) were included in our analyses.

Methods

Study design and patients

Subgroup analyses by beta-blocker use at baseline were performed using data from EXPLORER-HCM (pre-specified) and MAVA-LTE (*post hoc*). Both studies are registered on ClinicalTrials.gov (EXPLORER-HCM, NCT03470545; MAVA-LTE, NCT03723655).

EXPLORER-HCM was a randomized, double-blind, placebo-controlled, phase III study of mavacamten in patients with symptomatic oHCM conducted in 13 countries, the methodology of which has been described previously.[12] In brief, randomization was stratified by current beta-blocker use (yes or no), NYHA functional class (II or III), ergometer type (treadmill or bicycle) and cardiovascular magnetic resonance imaging sub-study (yes or no). Patients eligible for EXPLORER-HCM had: a diagnosis of HCM (unexplained LV hypertrophy with maximal LV wall thickness of ≥15 mm [or ≥13 mm with family history of HCM])[2,13]; peak LVOT gradient ≥50 mmHg at rest, after Valsalva manoeuvre or exercise; LV ejection fraction (LVEF) ≥55%; and NYHA functional classes II or III. Single-agent pharmacological therapy recommended by current guidelines for HCM was permitted, except disopyramide. Beta-blocker use at baseline and throughout the studies was based on information captured in the electronic case report form. According to the protocols, background HCM treatment was to remain unchanged (i.e. at a stable dose) unless there was a medically indicated need for adjustment.

The study included a 30-week treatment period followed by an 8-week post-treatment washout period. At week 38, patients returned for key assessments, after which they could consent to continue in MAVA-LTE, an ongoing multicentre, phase II/III study evaluating long-term administration of mavacamten for 252 weeks in patients who had completed either EXPLORER-HCM or the Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (MAVERICK-HCM) study.[14] All patients in MAVA-LTE received mavacamten irrespective of treatment received in the parent study. Patients and investigators were blinded to mavacamten dose and prior assigned treatment. In the present analyses, only patients who enrolled into MAVA-LTE from the EXPLORER-HCM study, referred to as the EXPLORER-LTE cohort, were included. EXPLORER-HCM and MAVA-LTE were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before enrolment.

Treatment

In EXPLORER-HCM, patients were randomized (1:1) to receive oral mavacamten at a starting dose of 5 mg or matching placebo once daily. Scheduled blinded dose titration steps occurred at week 8 and week 14 with dose adjustments to individualize doses (2.5, 5, 10, or 15 mg), so that target reductions in LVOT gradient (<30 mmHg) and mavacamten plasma concentrations (350–700 ng/ml) were achieved.[8]

Patients in the EXPLORER-LTE cohort received mavacamten at a starting dosage of 5 mg once daily. Scheduled dose titration steps were performed at weeks 4, 8 and 12 with dose adjustments to individualize doses (2.5, 5, 10, or 15 mg), based on target Valsalva LVOT gradient (≤30 mmHg) and resting LVEF (≥50%). Dose adjustment was performed at week 24 in patients who did not meet target post-exercise LVOT gradient (target <50 mmHg) on exercise stress echocardiography.

Assessments

In EXPLORER-HCM, cardiopulmonary exercise testing (CPET), using a standardized treadmill or bicycle ergometer, and post-exercise transthoracic echocardiography for gradients assessment were performed only at baseline and week 30. Other assessments, including resting echocardiography, NYHA functional class, patient reported outcomes, and serum concentrations of NT-proBNP and high-sensitivity cardiac troponin I (cTnI), were measured at baseline and week 30, and serially throughout the study. Health-related quality of life and symptom burden were assessed using two patient-reported outcomes at baseline, week 30 and serially throughout the study: the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and the Hypertrophic Cardiomyopathy Symptom Questionnaire shortness of breath (HCMSQ-SoB) subscore.[12,15,16] The prevalence of chronotropic incompetence at baseline, defined as inability to achieve 80% of predicted peak heart rate during maximal exercise testing, was assessed in patients from EXPLORER-HCM.[17] Post-exercise LVOT gradient, peak VO_2, NYHA functional class improvement and the patient-reported outcomes were pre-defined secondary endpoints; serum concentration of NT-proBNP was an exploratory endpoint.

In the EXPLORER-LTE cohort, results from resting transthoracic echocardiography, NYHA class assessment and serum concentrations of NT-proBNP were analysed at baseline and week 12.

Statistical analysis

Analyses were performed in subgroups according to beta-blocker usage at baseline (yes or no). Data were analysed with descriptive statistics, and no formal statistical comparisons were performed because neither study was designed or powered for subgroup analyses. Analyses for EXPLORER-HCM were performed at week 30 (primary analysis timepoint). For the ongoing MAVA-LTE study, interim data from week 12 were used (data cut-off, 30 October 2020) to ensure that enough patients were included in the analyses.

Owing to the high retention during the study and because the discontinuation rate was balanced between beta-blocker subgroups, imputation for missing data was not conducted. 95% CIs of response differences between mavacamten and placebo were based on normal approximation. SAS version 9.4 or higher was used for statistical analyses.

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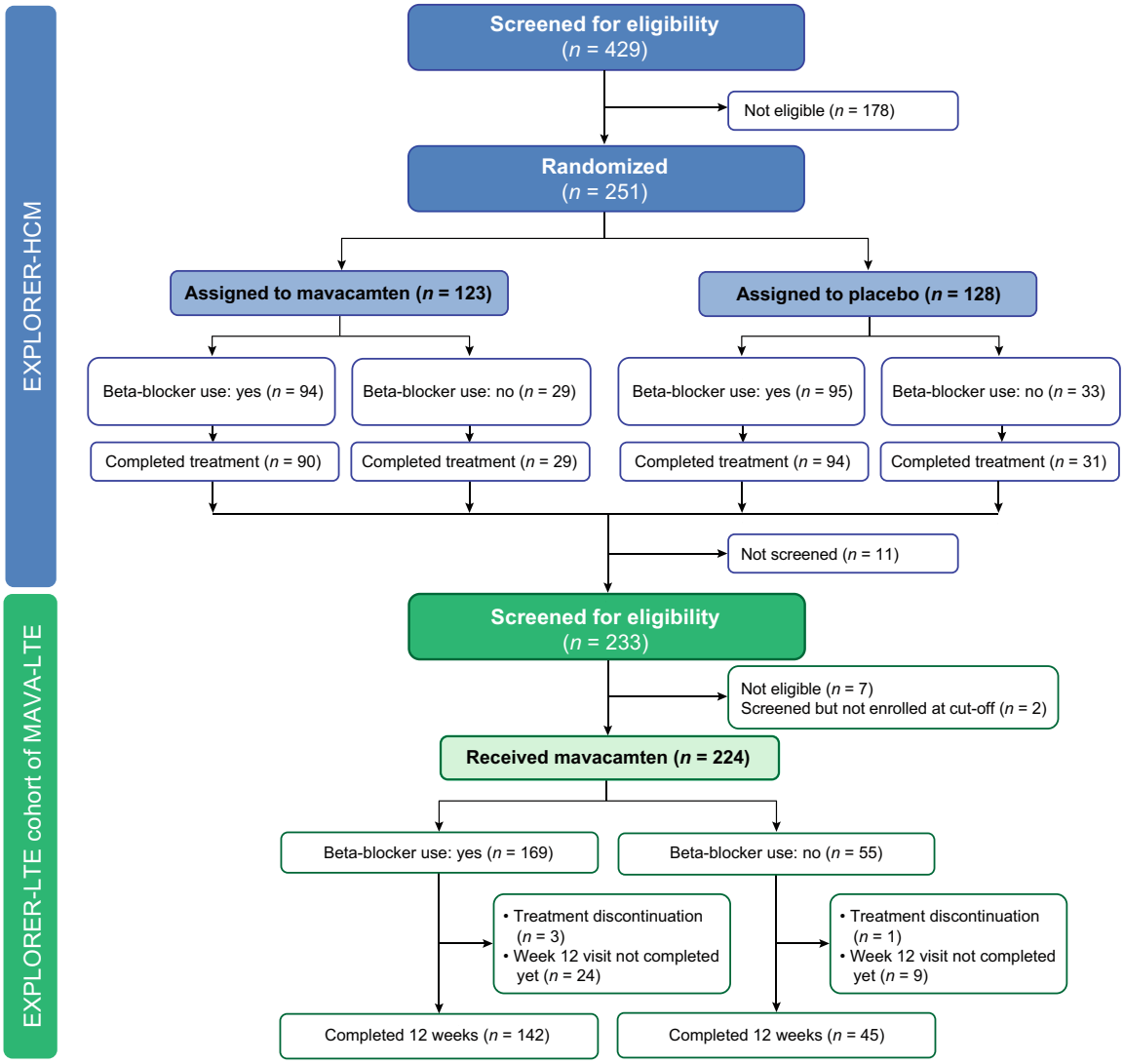

Figure 1 Study profiles.

Results

Patients

A total of 251 patients were enrolled in EXPLORER-HCM and randomly assigned to study treatment stratified by beta-blocker usage (mavacamten, $n = 123$; placebo, $n = 128$) (*Figure 1*). Overall, 189 patients (75.3%) were receiving concomitant beta-blockers (mavacamten, $n = 94$; placebo, $n = 95$); the remaining 62 patients (24.7%) were receiving calcium channel blockers (mavacamten, $n = 25$; placebo, $n = 17$) or no background medication (mavacamten, $n = 4$; placebo, $n = 16$). In total, 123 patients in the mavacamten group were included in this analysis, of whom 119 completed treatment up to week 30 (*Figure 1*). In the mavacamten group, mean (standard deviation [SD]) heart rate at baseline was 60 (8) bpm in patients receiving beta-blockers and 72 (11) bpm in patients not receiving beta-blockers. In the placebo group, mean (SD) heart rate at baseline was 62 (11) bpm in patients receiving beta-blockers and 65 (11) bpm in patients not receiving beta-blockers. Beta-blocker dose was adjusted during the study in 26 patients (10.4%; mavacamten, $n = 16$; placebo, $n = 10$).

From April 2019 onwards, 224 patients from EXPLORER-HCM (112 of whom previously received placebo) were enrolled in the EXPLORER-LTE cohort of the MAVA-LTE study and received mavacamten (*Figure 1*). Overall, 169 patients (75.4%) were receiving concomitant beta-blockers; the remaining patients were prescribed calcium channel blockers ($n = 37$) or neither background medication ($n = 18$). Mean (SD) heart rate at baseline was 63 (11) bpm in patients receiving beta-blockers and 68 (10) bpm in patients not receiving beta-blockers. At the time of this interim data cut, 187 patients had reached the week 12 visit and were included in this analysis (142 patients receiving beta-blockers and 45 not receiving beta-blockers). At the time of data analysis,

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Table 1 Baseline characteristics according to beta-blocker usage in EXPLORER-HCM and in the EXPLORER-LTE cohort of MAVA-LTE

	EXPLORER-HCM				EXPLORER-LTE cohort	
	Beta-blocker use: yes		Beta-blocker use: no		Beta-blocker use: yes	Beta-blocker use: no
	Mavacamten (*n* = 94)	Placebo (*n* = 95)	Mavacamten (*n* = 29)	Placebo (*n* = 33)	Mavacamten (*n* = 169)	Mavacamten (*n* = 55)
Age, years, median (range)	61 (26–82)	60 (18–78)	58 (33–80)	61 (19–81)	62 (19–83)	61 (21–82)
Sex, *n* (%)						
Male	51 (54.3)	64 (67.4)	15 (51.7)	19 (57.6)	105 (62.1)	30 (54.5)
Female	43 (45.7)	31 (32.6)	14 (48.3)	14 (42.4)	64 (37.9)	25 (45.5)
Ethnicity, *n* (%)						
White	88 (93.6)	83 (87.4)	27 (93.1)	31 (93.9)	158 (93.5)	52 (94.5)
Asian	3 (3.2)	2 (2.1)	1 (3.4)	0 (0)	3 (1.8)	0 (0)
Black, African American	1 (1.1)	5 (5.3)	0 (0)	0 (0)	5 (3.0)	2 (3.6)
American Indian, Alaskan Native	0 (0)	1 (1.1)	0 (0)	0 (0)	1 (0.6)	0 (0)
Unknown	2 (2.1)	4 (4.2)	1 (3.4)	2 (6.1)	2 (1.2)	1 (1.8)
Background HCM therapy, *n* (%)						
Beta-blocker	94 (100.0)	95 (100.0)	0 (0)	0 (0)	169 (100.0)	0 (0)
Calcium channel blocker	0 (0)	0 (0)	25 (86.2)	17 (51.5)	0 (0)	37 (67.3)
Neither	0 (0)	0 (0)	4 (13.8)	16 (48.5)	0 (0)	18 (32.7)
Heart rate, bpm	60 (8)	62 (11)	72 (11)	65 (11)	63 (11)	68 (10)
History of atrial fibrillation, *n* (%)	12 (12.8)	17 (17.9)	0 (0)	6 (18.2)	31 (18.3)	6 (10.9)
Blood pressure, mmHg						
Systolic	127.8 (16.5)	127.9 (13.8)	130.2 (15.2)	129.9 (16.7)	128.3 (16.1)	126.3 (12.9)
Diastolic	74.5 (10.7)	76.2 (9.7)	78.8 (10.6)	75.9 (10.5)	75.7 (10.3)	55 (9.6)
NYHA functional class, *n* (%)						
I[a]	0	0	0	0	9 (5.3)	5 (9.1)
II	69 (73.4)	72 (75.8)	19 (65.5)	23 (69.7)	112 (66.3)	34 (61.8)
III	25 (26.6)	23 (24.2)	10 (34.5)	10 (30.3)	48 (28.4)	16 (29.1)
Symptom scores						
KCCQ-CSS	71 (17)	72 (19)	71 (12)	67 (20)	–	–
HCMSQ-SoB	4.8 (2.6)	4.3 (3.0)	4.9 (2.1)	5.0 (3.8)	–	–
CPET parameters						
Peak VO_2, ml/kg/min	18.5 (4.8)	19.6 (4.7)	20.3 (5.0)	20.7 (5.5)	–	–
V_E/VCO_2 slope	33.3 (6.2)	31.9 (5.9)	34.5 (6.4)	33.9 (6.9)	–	–
Peak METs	5.3 (1.4)	5.6 (1.3)	5.8 (1.4)	5.9 (1.6)	–	–
Peak heart rate, bpm	118 (22)	119 (20)	137 (16)	139 (23)	–	–
Heart rate percent predicted	73.2 (12.3)	73.1 (10.3)	84.0 (9.0)	86.6 (12.8)	–	–
Peak exercise time, min	9.9 (4.0)	10.4 (4.2)	10.8 (4.3)	10.9 (4.2)	–	–
Echocardiographic parameters						
LVEF, %	74.5 (5.3)	74.1 (5.9)	72.8 (7.2)	74.3 (6.0)	74.6 (5.4)	72.1 (6.8)
LVOT gradient, resting, mmHg	51.2 (29.6)	51.6 (30.8)	53.2 (29.5)	49.7 (35.4)	49.8 (30.7)	45.5 (34.6)
LVOT gradient, Valsalva, mmHg	74.1 (32.2)	73.2 (30.9)	66.8 (29.9)	75.9 (35.5)	72.2 (32.5)[b]	62.5 (32.3)
Cardiac biomarkers						
NT-proBNP, ng/L, geometric mean (%CV)	888.4 (132.6)	706.0 (106.1)	501.4 (139.1)	418.6 (106.9)	804.3 (166.9)	450.4 (175.5)
High-sensitivity cTnI, ng/L, geometric mean (%CV)	11.7 (167.9)	12.1 (344.6)	15.9 (225.2)	13.5 (376.2)	–	–

Data are presented as mean (standard deviation), unless otherwise stated.

CPET, cardiopulmonary exercise testing; cTnI, cardiac troponin I; CV, coefficient of variation; HCM, hypertrophic cardiomyopathy; HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire shortness of breath subscore; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LTE, long-term extension; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MAVA-LTE, mavacamten long-term extension; MET, metabolic equivalent; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; V_E/VCO_2, minute ventilation to carbon dioxide production; VO_2, oxygen consumption.

[a]Patients with NYHA class I in the EXPLORER-LTE cohort were patients with NYHA class II or III at screening for EXPLORER-HCM and who had improved to NYHA class I at screening for MAVA-LTE.

[b]Data missing for three patients.

Table 2 Change from baseline at week 30 in EXPLORER-HCM according to beta-blocker usage

	Beta-blocker use: yes					Beta-blocker use: no				
	n	Mavacamten (*n* = 94)	*n*	Placebo (*n* = 95)	Difference (95% CI)	*n*	Mavacamten (*n* = 29)	*n*	Placebo (*n* = 33)	Difference (95% CI)
Symptoms										
NYHA functional class improvement,[a] %	94	64.9	95	34.7	30.2 (16.6, 43.8)	29	65.5	33	21.2	44.3 (22.1, 66.5)
KCCQ-CSS[b]	73	14.2 (14.3)	62	3.3 (13.7)	11.0 (6.2, 15.7)	19	11.0 (15.0)	26	6.3 (13.8)	4.7 (−4.0, 13.4)
HCMSQ-SoB[c]	67	−2.9 (2.8)	64	−0.7 (2.2)	−2.3 (−3.1, −1.4)	18	−2.5 (2.0)	22	−1.4 (2.9)	−1.1 (−2.7, 0.6)
CPET parameters										
Peak VO_2, ml/kg/min	91	1.13 (3.1)	94	0.09 (3.2)	1.04 (0.12, 1.95)	29	2.23 (3.0)	31	−0.46 (2.4)	2.69 (1.29, 4.09)
V_E/VCO_2 slope	91	−2.4 (4.5)	94	0.6 (4.1)	−2.9 (−4.1, −1.7)	29	−2.7 (4.9)	31	−0.1 (4.4)	−2.6 (−5.0, −0.2)
Peak METs	91	0.32 (0.89)	94	0.02 (0.91)	0.30 (0.04, 0.56)	29	0.64 (0.87)	31	−0.13 (0.67)	0.77 (0.38, 1.17)
Peak heart rate, bpm	91	13 (17)	94	3 (16)	10 (5.4, 14.8)	29	7 (15)	31	1 (12)	6 (−1.4, 12.6)
Heart rate percent predicted	91	8.5 (10.5)	94	2.3 (9.6)	6.2 (3.3, 9.1)	29	6.7 (14.6)	31	1.0 (7.4)	5.8 (−0.2, 11.7)
Peak exercise time, min	91	0.53 (2.21)	94	0.19 (2.08)	0.34 (−0.28, 0.96)	29	1.84 (2.88)	31	−0.04 (1.57)	1.9 (0.7, 3.1)
Echocardiographic parameters										
LVEF, %	88	−3.6 (7.7)	89	0.5 (7.1)	−4.0 (−6.2, −1.8)	26	−5.0 (7.6)	30	−1.3 (5.8)	−3.7 (−7.3, 0.0)
LVOT gradient, resting, mmHg	89	−37.5 (30.1)	92	−5.1 (27.5)	−32.5 (−40.9, −24.0)	28	−42.2 (27.9)	31	−6.8 (29.7)	−35.4 (−50.4, −20.3)
LVOT gradient, Valsalva, mmHg	89	−50.0 (36.8)	93	−10.4 (30.3)	−39.6 (−49.4, −29.7)	28	−46.3 (25.6)	31	−17.3 (32.8)	−29.0 (−44.4, −13.5)
LVOT gradient, after exercise, mmHg	89	−47.1 (37.9)	92	−9.1 (30.6)	−37.9 (−48.0, −27.9)	28	−47.9 (47.9)	30	−14.4 (26.4)	−33.5 (−53.6, −13.3)
Serum biomarkers										
NT-proBNP, ng/L	89	−1267 (1961)	90	64 (577)	—	27	−846 (1383)	31	−22 (445)	—
Ratio to baseline[d]	89	0.2 (283.6)	90	1.0 (50.4)	0.2 (0.2, 0.2)	27	0.2 (115.2)	31	1.0 (69.8)	0.2 (0.1, 0.3)[e]
cTnI, ng/L	89	−10 (21)	84	−17 (137)	—	25	−23 (43)	27	1 (21)	—
Ratio to baseline[d]	89	0.6 (46.9)	84	1.0 (161.3)	0.6 (0.5, 0.8)[e]	25	0.5 (57.5)	27	1.1 (60.8)	0.4 (0.3, 0.6)[e]

Data expressed as mean (standard deviation) for all parameters, unless otherwise stated.
CI, confidence interval; CPET, cardiopulmonary exercise testing; cTnI, cardiac troponin I; HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire shortness of breath subscore; HCM, hypertrophic cardiomyopathy; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MET, metabolic equivalent; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; V_E/VCO_2, minute ventilation to carbon dioxide production; VO_2, oxygen consumption.
[a]Defined as the proportion of patients with at least one NYHA functional class reduction.
[b]Scores range from 0 to 100, with higher scores reflecting better health status.
[c]Scores range from 0 to 18, with lower scores indicating a lower shortness of breath.
[d]Expressed as geometric mean (coefficient of variation %).
[e]Defined as the ratio between mavacamten and placebo.

the numbers of patients with missing data varied by outcome. The median duration of follow-up in the MAVA-LTE study at the cut-off date was 32.3 (range, 1.4–80.3) weeks. Baseline characteristics in EXPLORER-HCM and the EXPLORER-LTE cohort of MAVA-LTE by beta-blocker usage are presented in *Table 1*.

Chronotropic incompetence

In the EXPLORER-HCM population, 204 of 250 patients (81.6%) had chronotropic incompetence[17] at baseline as assessed during maximal exercise testing. When stratified by beta-blocker usage, chronotropic incompetence was present in 170 of 188 patients (90.4%) receiving beta-blockers and 34 of 62 patients (54.8%) without beta-blockers. One patient receiving beta-blocker was excluded from the analysis because their peak heart rate was lower than their resting heart rate.

Effects of beta-blocker versus non-beta-blocker use

Changes from baseline in functional, echocardiographic, symptom and biomarker parameters by beta-blocker usage in the EXPLORER-HCM study are presented in *Table 2* and *Figures 2* and *3A,B*, and those in the EXPLORER-LTE cohort are presented in *Table 3* and *Figure 3C*. Data were reported using descriptive statistics; while no formal statistical comparisons were performed, some differences were observed between subgroups.

Functional capacity

At week 30, in the EXPLORER-HCM study, mean (SD) change in peak VO_2 from baseline with mavacamten was 1.13 (3.1) ml/kg/min compared with 0.09 (3.2) ml/kg/min with placebo in patients using beta-blockers (mean difference [95% CI]: 1.04 [0.12, 1.95] ml/kg/min), and 2.23 (3.0) ml/kg/min compared with −0.46 (2.4) ml/kg/min, respectively, without beta-blockers (mean difference [95% CI]: 2.69 [1.29, 4.09] ml/kg/min) (*Table 2* and *Figure 2A*). Furthermore, mean peak metabolic equivalents (METs) at week 30 in the EXPLORER-HCM study were improved with mavacamten compared with placebo, and these improvements were greater in those without beta-blocker use (*Figure 2B*). The effect of mavacamten compared with placebo on mean peak exercise time was lower in patients using beta-blockers than in those who were not using beta-blockers (*Figure 2C*). Mean peak heart rate with maximal exercise at baseline and at week

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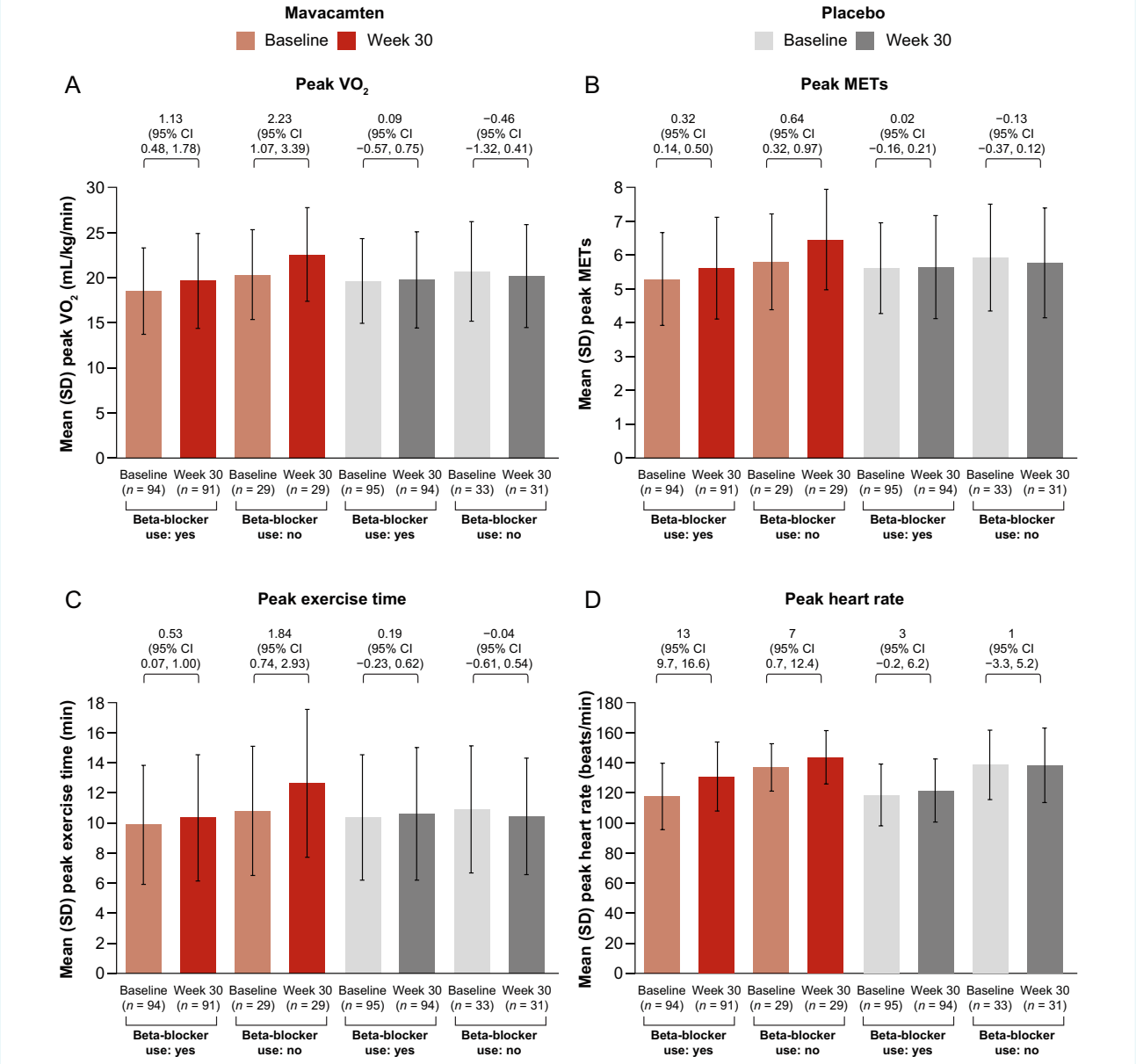

Figure 2 Mean (standard deviation [SD]) peak oxygen consumption (VO_2) (*A*), peak metabolic equivalents (METs) (*B*), peak exercise time (*C*), and peak heart rate (*D*) at baseline and week 30 in EXPLORER-HCM according to beta-blocker usage. CI, confidence interval.

30 was also lower in patients using beta-blockers than in those not using beta-blockers (*Figure 2D*). In contrast, at week 30, mavacamten improved the heart rate-independent parameter, ventilatory efficiency (minute ventilation to carbon dioxide production [V_E/VCO_2] slope), regardless of beta-blocker use compared with placebo (mavacamten, −2.4 [SD 4.5], placebo, 0.6 [SD 4.1] in patients using beta-blockers; mavacamten, −2.7 [SD 4.9], placebo, −0.1 [SD 4.4] in those not using beta-blockers) (*Table 2*).

Imaging parameters

In addition, mavacamten showed consistent benefits compared with placebo in LVOT gradient reduction at rest, after Valsalva manoeuvre or exercise at week 30 irrespective of beta-blocker use (*Table 2*). Furthermore, the effects of mavacamten on LVEF were independent of beta-blocker use. Indeed, mavacamten decreased mean (SD) LVEF at week 30 in EXPLORER-HCM by 3.6% (7.7%) compared with 0.5% (7.1%) with placebo in patients with beta-blockers (mean difference [95% CI]: −4.0% [−6.2%, −1.8%]), and by 5.0% (7.6%) compared with 1.3% (5.8%), respectively, without beta-blockers (mean difference [95% CI]: −3.7% [−7.3%, 0.0%]) (*Table 2*).

The beneficial effects of mavacamten on LVOT gradients and LVEF were similarly achieved and maintained after 12 weeks of

Table 3 Change from baseline with mavacamten at week 12 in the EXPLORER-LTE cohort of MAVA-LTE according to beta-blocker usage

	Beta-blocker use: yes			Beta-blocker use: no		
	n	Mean (SD) at week 12	Mean (SD) change from baseline	*n*	Mean (SD) at week 12	Mean (SD) change from baseline
Symptoms						
NYHA functional class improvement,[a] %	119	62		40	51	
Echocardiographic parameters						
LVOT resting, mmHg	121	18.4 (15.2)	−29.1 (30.3)	41	17.9 (14.6)	−32.6 (39.4)
LVOT Valsalva, mmHg	121	34.6 (23.5)	−35.5 (34.4)	41	29.9 (17.3)	−37.9 (36.0)
LVEF, %	121	70.6 (7.4)	−4.5 (7.5)	38	68.7 (7.7)	−3.1 (7.6)
Serum biomarkers						
NT-proBNP, ng/ml	122	532 (1052)	−1038 (1824)	40	228 (166)	−559 (706)
Ratio to baseline[b]	122	0.3 (112.3)	–	40	0.3 (91.6)	–

Interim analysis (data cut-off date 30 October 2020). Baseline was defined as the previous non-missing result on or before the first dose date and time, when applicable. Although 142 patients and 45 patients in the beta-blocker and non-beta-blocker groups, respectively, had completed the week 12 visit, there were missing data at the time of data analysis.

LTE, long-term extension; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MAVA-LTE, mavacamten long-term extension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

[a]Expressed as the proportion of patients with at least one NYHA functional class reduction.

[b]Expressed as geometric mean (coefficient of variation %).

treatment in the interim analysis of the EXPLORER-LTE cohort irrespective of beta-blocker usage (*Table 3*).

Symptoms

At 30 weeks, in the EXPLORER-HCM study, the proportion of patients with at least one NYHA functional class improvement was 64.9% with mavacamten and 34.7% with placebo in patients with beta-blockers, and 65.5% with mavacamten and 21.2% with placebo in patients without beta-blockers (*Table 2* and *Figure 3A,B*). Mavacamten was also associated with improvements in patient-reported quality of life and symptom burden at 30 weeks in the EXPLORER-HCM study. Mean (SD) change in KCCQ-CSS, in which higher scores indicate improved health status, was 14.2 (14.3) with mavacamten compared with 3.3 (13.7) with placebo in patients with beta-blockers, and 11.0 (15.0) compared with 6.3 (13.8), respectively, in patients without beta-blockers. Mean (SD) change in HCMSQ-SoB score at 30 weeks, in which lower scores indicate fewer symptoms, was −2.9 (2.8) with mavacamten compared with −0.7 (2.2) with placebo in patients with beta-blockers, and −2.5 (2.0) compared with −1.4 (2.9), respectively, in patients without beta-blockers.

In the EXPLORER-LTE cohort, improvements in NYHA functional class with mavacamten were maintained at 12 weeks regardless of beta-blocker usage (*Figure 3C*).

Serum biomarkers

At week 30, in the EXPLORER-HCM study, reductions in cTnI concentration with mavacamten were 40% and 60% greater than those with placebo at 30 weeks in patients with and without concomitant beta-blockers, respectively (*Table 2*). Reductions in NT-proBNP concentration with mavacamten were 80% greater than that with placebo irrespective of beta-blocker usage (*Table 2*), and were maintained compared with baseline at 12 weeks in the EXPLORER-LTE cohort regardless of beta-blocker usage (*Table 3*).

Discussion

Following the report of the effects of beta-blocker therapy on the primary endpoint of the EXPLORER-HCM study,[8] analyses using descriptive statistics of the EXPLORER-HCM study and the EXPLORER-LTE cohort of the MAVA-LTE study were conducted to understand the impact of concomitant beta-blocker therapy on the effects of mavacamten in patients with oHCM. Although beta-blocker treatment blunted the effect of mavacamten on VO_2 at peak exercise, its beneficial effects on clinically important endpoints of LVOT gradients, symptomatic burden and cardiac biomarkers were unaffected (*Graphical Abstract*). Thus, the present study supports the concept that patients with oHCM receiving beta-blockers may benefit from mavacamten and raises the hypothesis that its use as monotherapy may be a reasonable option to eliminate the side effects of beta-blockers, including chronotropic incompetence. While beta-blockade expectedly blunts peak exercise capacity in patients with oHCM, mavacamten may improve heart failure symptoms without affecting the heart rate response to exercise. Thus, in patients with a favourable response to mavacamten and who do not require beta-blocker treatment for other conditions, dose reduction or withdrawal of beta-blockers might result in a further incremental gain in exercise capacity. Importantly, beta-blockers may have other indications in patients with oHCM beyond treatment of obstruction. Beta-blocker use may be indicated in HCM in the absence of obstruction: for example, in patients with a history of syncope or symptomatic ventricular tachyarrhythmia, or in those with a history of persistent or permanent atrial fibrillation. Beta-blockers may

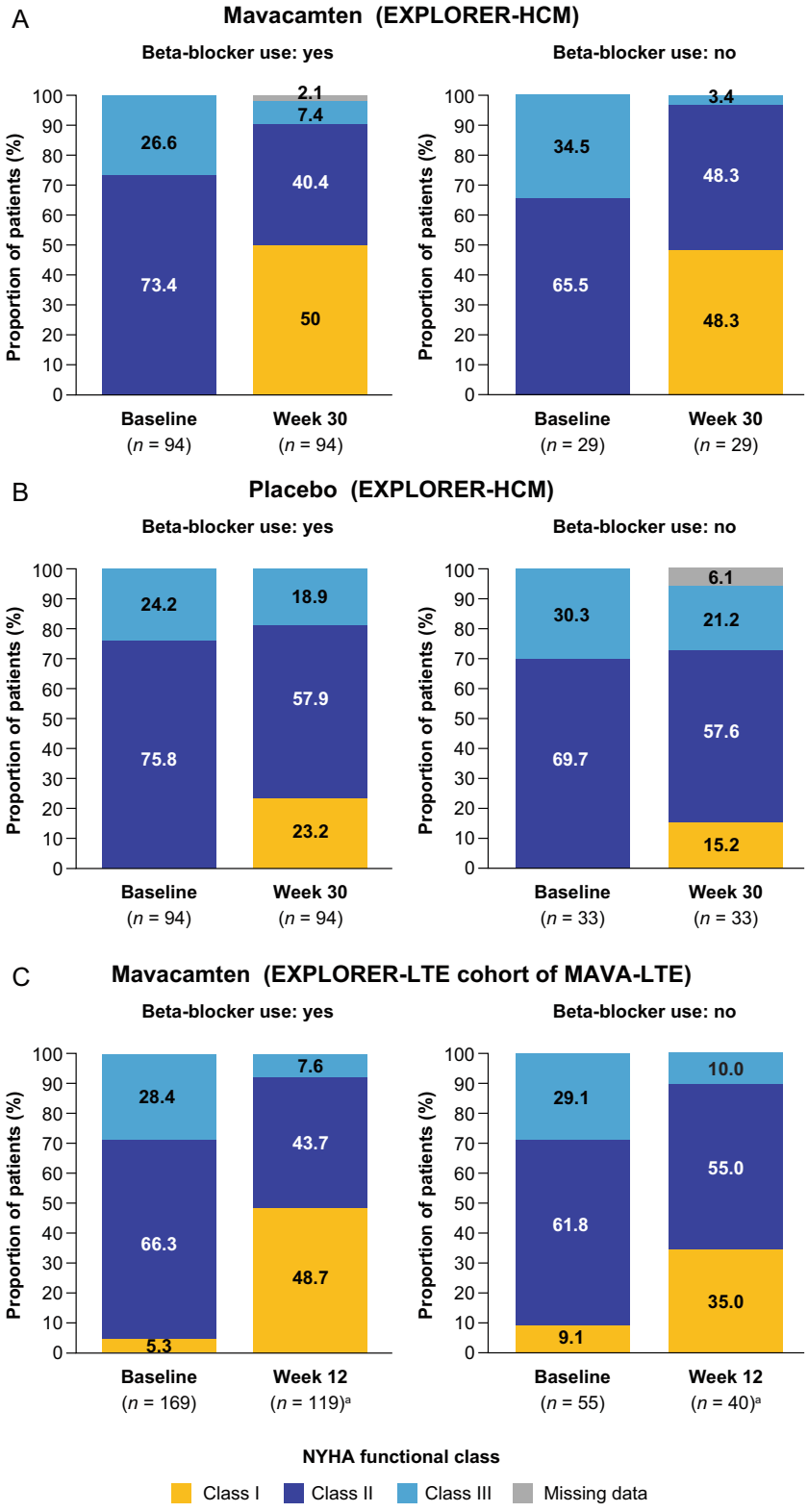

Figure 3 Distribution of New York Heart Association (NYHA) functional class at week 30 in EXPLORER-HCM for mavacamten (*A*) and placebo (*B*) and at week 12 in the EXPLORER-LTE cohort of MAVA-LTE for mavacamten (*C*). [a]Patients who did not complete the week 12 visit at the cut-off date and patients who completed the week 12 visit at the cut-off date with missing NYHA functional class data at week 12 were excluded.

also be used in patients with concomitant coronary artery disease, hypertension, or anxiety. Further studies are needed to address the safety and efficacy of beta-blocker withdrawal in patients with oHCM receiving mavacamten, and to establish the benefits of mavacamten as monotherapy. Beta-blocker withdrawal or dose reduction would have to be considered carefully and would be dependent on the individual's medical history and comorbidities.

Beta-blockers have been associated with reduced mortality in patients with myocardial infarction and coronary artery disease with heart failure and a reduced ejection fraction.[18,19] Treatment with beta-blockers has also been associated with reduction in chest pain symptoms and in arrhythmia.[20–22] However, there are important dose-dependent limitations and intolerance related to their use. Furthermore, beta-blockers are frequently associated with reduced exercise capacity through attenuation of chronotropic reserve.[11,23] Notably, in the EXPLORER-HCM population, over 90% of patients receiving beta-blockers had evidence of chronotropic incompetence at baseline. Thus, parameters affected by heart rate were affected by beta-blocker use (e.g. peak VO_2, METs, exercise time and peak heart rate). Nevertheless, a comparable degree of improvement with and without background beta-blockade on the important non-heart rate-dependent CPET metric of V_E/VCO_2 slope was observed. V_E/VCO_2 slope is derived by plotting minute ventilation versus CO_2 continuously throughout exercise. A more rapid rise in this slope (higher V_E/VCO_2) may reflect more severe diastolic dysfunction or an end-stage phase of HCM,[24] and has been correlated with adverse prognosis in multiple subtypes of heart failure and in patients with HCM.[25–30] Divergence of heart rate-dependent and -independent variables between beta-blocker and non-beta-blocker subgroups is therefore more likely to be the result of heart rate attenuation than because of reduced mavacamten efficacy.

Our results should be interpreted in the context of several limitations. While beta-blocker use was not controlled for dose, type or adherence in either study, the difference in peak heart rate at baseline between subgroups provides support that, on average, patients were adherent to beta-blockers and were dosed appropriately. Subgroup analyses by beta-blocker use were prospectively defined in the EXPLORER-HCM study, but performed on an *ad hoc* basis in the EXPLORER-LTE cohort. Additionally, neither study was designed or powered for subgroup analyses. For this reason, a formal statistical analysis of the data was not performed, and the findings should be considered exploratory and hypothesis-generating only. Study treatment and patient follow-up in the EXPLORER-LTE cohort continue and some data presented here are preliminary as data collection is still ongoing.

Conclusion

Mavacamten improved measures of functional capacity, LVOT obstruction, symptom burden (e.g. NYHA functional class) and biomarkers in patients with HCM regardless of beta-blocker use. Beta-blocker use was often associated with chronotropic incompetence, affecting peak VO_2 and other heart rate-dependent measures. However, non-heart rate-dependent CPET parameters were not affected. This indicates that although peak VO_2 assessment is clinically relevant, it does not reflect the full extent of mavacamten's beneficial effects. The potential adverse effects of chronotropic incompetence related to beta-blocker use in oHCM requires critical reappraisal in clinical practice.

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