



Real-World Effectiveness of Mavacamten in Canada: Insights from the MAVEN Study

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ABSTRACT

Introduction: Previous studies have demonstrated the efficacy and safety of mavacamten in patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM), primarily outside of Canada, with limited Canadian real-world data evidence. The MAVEN study aimed to describe the real-world effectiveness of mavacamten in Canadian patients with oHCM.

Methods: This multi-center, retrospective physician survey of patient charts included 115

patients with oHCM who initiated mavacamten between January 2023 and November 2024 across five Canadian sites. Effectiveness was assessed by changes in clinical characteristics and outcomes, including New York Heart Association (NYHA) functional class, resting and Valsalva left ventricular outflow tract (rLVOT and vLVOT, respectively) gradients, and left ventricular ejection fraction (LVEF), from treatment initiation to the most recent available assessment.

Results: Baseline demographic and clinical characteristics were consistent with previously

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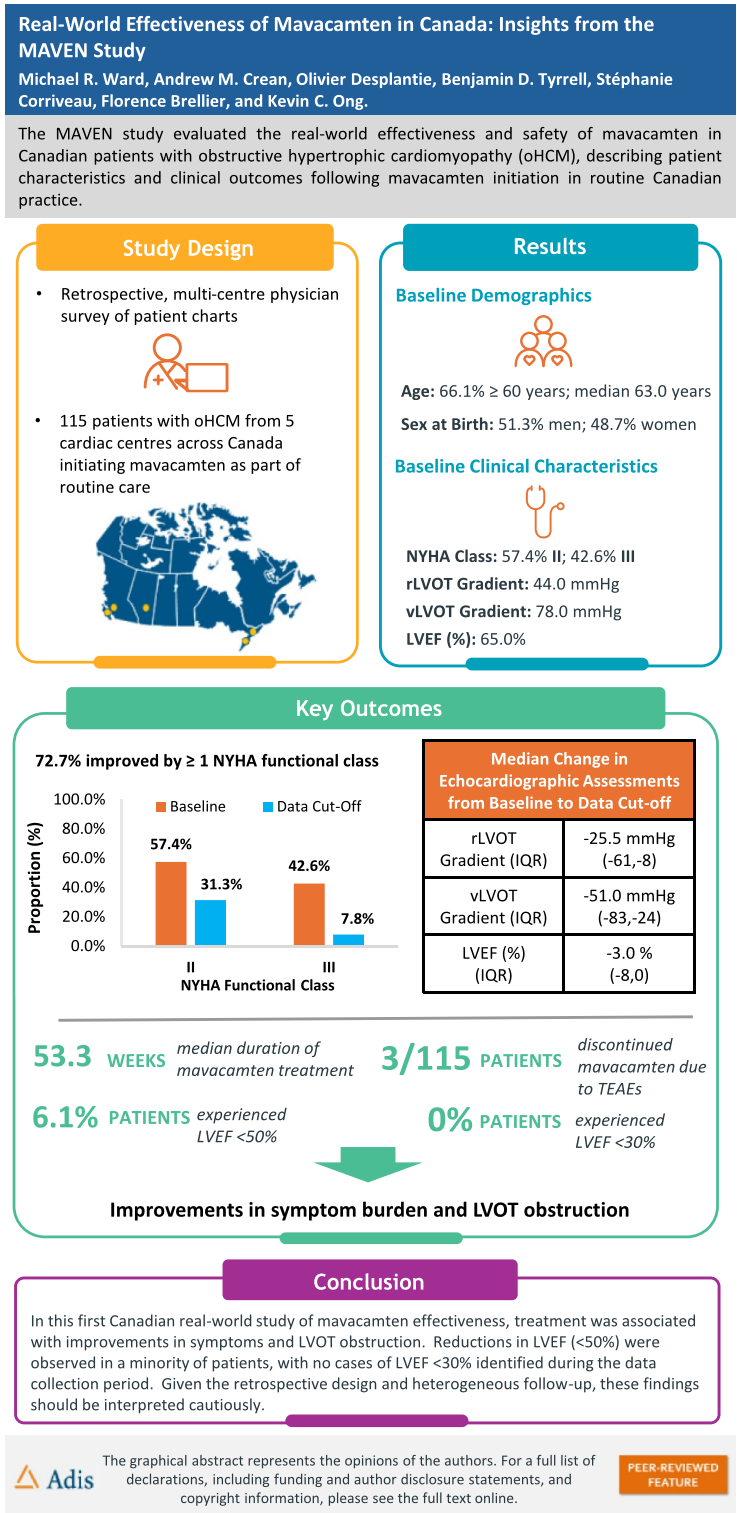
published data (median age 63.0 years; 66.1% aged ≥ 60 years; 51.3% male, 48.7% female patients; 57.4% NYHA class II, 42.6% NYHA class III). Median baseline rLVOT and vLVOT gradients were 44.0 and 78.0 mmHg, respectively, and median LVEF was 65.0%. Overall, 72.7% of patients improved by ≥ 1 NYHA functional class. Median reductions in rLVOT and vLVOT gradients were -25.5 (interquartile range [IQR]: -61 , -8) mmHg and -51.0 (IQR: -83 , -24) mmHg, respectively, while median LVEF changed by -3.0% (IQR: -8 , 0). Mavacamten was discontinued in 8.7% of patients, including 2.6% due

to treatment-emergent adverse events. Reductions in LVEF $< 50\%$ were observed in 6.1% of patients, and no patient experienced an LVEF $< 30\%$.

Conclusions: In this first Canadian real-world study of mavacamten effectiveness, treatment was associated with improvements in symptoms and LVOT obstruction. Reductions in LVEF $< 50\%$ were observed in a minority of patients, with no cases of LVEF $< 30\%$. Given the retrospective design and heterogeneous follow-up of this study, these findings should be interpreted cautiously.

Graphical abstract available for this article.

Graphical Abstract:



Keywords: Obstructive hypertrophic cardiomyopathy; Mavacamten; LVOT; LVEF; Real-world data

Key Summary Points

Why carry out this study?

Real-world evidence on mavacamten remains limited, particularly within Canada's risk-management framework where CYP2C19 genotyping and a Risk Evaluation and Mitigation Strategies (REMS) program are not required

The MAVEN study evaluated the real-world effectiveness, treatment patterns, and safety of mavacamten in Canadian patients with obstructive hypertrophic cardiomyopathy (oHCM) included in an early access program, both from academic and community centers

What was learned from the study?

In this multi-center retrospective cohort of 115 patients from five sites, mavacamten was associated with improvements in symptom burden (72.7% of evaluable patients experienced an improvement of at least one New York Heart Association [NYHA] functional class) and reductions in left ventricular outflow tract (LVOT) obstruction (resting [r]LVOT: – 25.5 mmHg, interquartile range [IQR]: – 61 to – 8; Valsalva [v]LVOT: – 51.0 mmHg, IQR: – 83 to – 24)

Mavacamten was well tolerated, with limited relevant reductions in LVEF and discontinuations

The study contributes important real-world evidence supporting the use of mavacamten in patients with oHCM and may help inform clinical decision-making, patient monitoring and future research evaluating long-term outcomes

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to DOI <https://doi.org/10.6084/m9.figshare.34021974>.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is predominantly characterized by left ventricular hypertrophy in the absence of another cardiac, systemic, or metabolic disease. HCM affects approximately one in 500 individuals worldwide [1]. Dynamic left ventricular outflow tract (LVOT) obstruction occurs in nearly 70% of patients, with roughly one-third exhibiting obstruction at rest and another one-third requiring provocation to reveal the obstruction. LVOT obstruction is associated with dyspnea, reduced exercise capacity, and other symptoms [2, 3]. Patients with symptomatic obstructive HCM (oHCM) often experience reduced quality of life and are at increased risk of atrial fibrillation, heart failure, and malignant ventricular arrhythmias [4, 5].

Conventional pharmacologic therapies of oHCM, including beta blockers (BBs), calcium channel blockers (CCBs), and disopyramide, primarily provide symptomatic relief but do not address the underlying molecular mechanisms of the disease and often are insufficient [6]. Septal reduction therapies (SRT), such as septal myectomy or alcohol septal ablation, are options for patients unresponsive to pharmacotherapy; however, these procedures are invasive and access in Canada is limited to specialized center [3].

Mavacamten is a selective, reversible cardiac myosin inhibitor that targets hypercontractility and normalizes the proportion of myosin heads that can bind with actin [7–9]. Randomized

controlled trials (EXPLORER-HCM and VALOR-HCM) have demonstrated mavacamten's efficacy (reduction in LVOT gradients and improvement in New York Heart Association (NYHA) functional class) and safety [10, 11]. Based on these clinical trial data, mavacamten was approved by Health Canada in November 2022 [12] for the treatment of symptomatic oHCM (NYHA functional class II–III). As part of the approval, a risk management plan was put into place, which includes the provision of healthcare professional education, a patient wallet card, and patient education materials. Mavacamten use in Canada does not require patients to be enrolled in a Risk Evaluation and Mitigation Strategy (REMS) program as mandated by the US Food and Drug Administration (FDA) [13], nor is CYP2C19 (cytochrome P450 2C19) genotyping required as stipulated by the European Medicines Agency (EMA) [14]. Despite these regulatory differences, it is important to note that the recommended dosage and administration schedule remain consistent between US [13] and Canadian [12] patients. To support access, a Patient Support Program (PSP) was established in Canada to assist patients and healthcare providers in navigating and facilitating treatment access [15, 16].

Since its approval across five continents, mavacamten's efficacy, safety, and real-world effectiveness has been demonstrated in multiple clinical trials, including long-term extension and real-world studies [10, 11, 17]. However, these studies were conducted outside of Canada. As such, MAVEN is the first real-world study to evaluate the effectiveness and safety of mavacamten in patients with oHCM within the context of the Canadian healthcare system and the PSP model.

METHODS

Study Design and Population

This observational, multi-center, retrospective physician survey of patient charts was designed to obtain real-world data on mavacamten use in patients with symptomatic

oHCM. A convenience sample of patients were recruited from five cardiology centers across three Canadian provinces (Alberta, Ontario, and British Columbia). To minimize selection bias, eligible patients were screened and included consecutively, beginning with the earliest eligible index date. Eligible patients included adults (age ≥ 18 years) with symptomatic oHCM (NYHA class II or III) who initiated mavacamten through the PSP between 4 January 2023 and 12 November 2024, as part of routine clinical care. Patients were excluded if they had received a cardiac myosin inhibitor within 6 weeks prior to the index date (date of first prescribed dose of mavacamten). Although not formally listed as an inclusion criterion, patients were not receiving contraindicated medications at time of treatment initiation since a pharmacist from the third-party provider reviewed their medications prior to PSP enrollment.

Ethics

The study protocol was reviewed and approved by the relevant Research Ethics Boards/Institutional Review Boards at each participating site, which granted a waiver of informed consent because the study involved the retrospective use of de-identified patient data.

The study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) [18] and applicable regulatory requirements. A waiver of consent was obtained from the research ethics board at each participating site prior to the abstraction and use of routinely collected, pseudo-anonymized, medical record data, in accordance with local requirements. All research procedures complied with the ethical principles of the Declaration of Helsinki. Ethics approval was provided by the Advarra Institutional Review Board (IRB00000971), the Western University Health Sciences Research Ethics Board (HSREB) (IRB00000940), the Ottawa Health Science Network Research Ethics Board (OHSN-REB) (IRB00002616), the Health Research Ethics Board of Alberta—Community Health

Committee (HREBA-CHC) (IRB1240005), and the University of British Columbia Providence Health Care Research Ethics Board (UBC-PHC REB) (IRB00000777).

Data Sources and Variables of Interest

Data were collected through a physician-completed survey, with participating physicians abstracting relevant clinical information from patient medical records. Baseline data were collected within 12 months prior to mavacamten initiation (index date) to accommodate variability in routine clinical practice and included demographics, medical history, clinical characteristics, and mavacamten treatment information. Demographic and clinical characteristics closest to the index date were reported as baseline data. When actual age data were not captured, age band categories were collected instead. Clinical characteristics included NYHA functional class, resting LVOT gradient (rLVOT), Valsalva LVOT gradient (vLVOT), and left ventricular ejection fraction (LVEF).

As this was a multi-center, retrospective chart review, echocardiographic assessments were performed according to each participating center's routine clinical practice, thus no standardized imaging acquisition protocols or core laboratory adjudication were used. Medical history data were collected from the date of confirmed oHCM diagnosis up to the index date, and included prior background oHCM treatments, SRT history, and age at oHCM diagnosis.

Follow-up assessments were collected from the index date until the site-specific chart survey date (date of first chart entered by the site), discontinuation of mavacamten, or date of last available clinical data, whichever occurred first. Data collected during follow-up included clinical and imaging data (NYHA, vLVOT, rLVOT, and LVEF), mavacamten treatment details (dose, age, modifications), concomitant oHCM pharmacological treatments, and adverse events. As assessments were performed as part of routine care, clinical variables (e.g., NYHA, vLVOT, rLVOT, and LVEF) were not available at all timepoints, therefore the most recent clinical

follow-up assessments were used for analysis (i.e., data cut-off).

In the EXPLORER-HCM and VALOR-HCM clinical trials, patients with a reduced LVEF of < 30% necessitated permanent discontinuation of mavacamten [10, 11]. Accordingly, for purposes of this retrospective study, adverse events were defined as any occurrence of LVEF < 30% following mavacamten initiation. In addition, clinically relevant incidents of LVEF < 50% were also collected, as this is the threshold for left ventricular systolic dysfunction [2, 3].

Study Outcomes

The effectiveness of mavacamten was assessed by changes in NYHA functional class, vLVOT gradient, and rLVOT following treatment initiation. Mavacamten discontinuation rates and changes to concomitant oHCM therapies were also evaluated. Lastly, safety was assessed by the incidence of LVEF < 30% and LVEF < 50%, the latter representing left ventricular systolic dysfunction [2, 3].

Statistical Analysis

Statistical analyses were descriptive. Continuous variables were summarized using mean, standard deviation (SD), median, and interquartile range (IQR), and categorical variables using counts and percentages. Proportions were calculated by dividing the number of patients satisfying a given endpoint criterion by the number of patients with available data for that endpoint (i.e., as observed analyses).

Two post-hoc subgroup analyses were completed to explore mavacamten's effect on LVEF and its real-world effectiveness. The first analysis examined patients on mavacamten monotherapy throughout the observation period (i.e., patients receiving mavacamten alone from treatment initiation to data cut-off). The second analysis examined mavacamten effectiveness and LVEF changes in patients who achieved a vLVOT gradient < 20 mmHg within the first 12 weeks of mavacamten initiation, a threshold at which the Canadian product monograph recommends dose reduction. This subgroup was

further stratified according to whether a mavacamten dose adjustment occurred (“Dose Change” subgroup) or did not occur (“No Dose Change” subgroup) to explore the impact of clinical decision-making on treatment outcomes.

Patients with missing values were omitted from the total prior to calculation of percentages. For change from baseline endpoints, analyses were restricted to patients that had both baseline and follow-up assessment data points available. All analyses were performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA).

RESULTS

Baseline Demographics and Patient Characteristics

A total of 115 eligible patients were included in the study. Baseline demographics and clinical characteristics are summarized in Table 1. The study cohort comprised 51.3% male and 48.7% female patients, with 66.1% aged ≥ 60 years. Among patients with an available oHCM diagnosis date (56.5%; 65/115), 60.0% had been diagnosed within 2.5 years of mavacamten initiation, 24.6% between 2.5 to 5 years, and 15.4% (10) more than 5 years prior. At treatment initiation, 57.4% (66/115) of patients were classified as NYHA functional class II and 42.6% as NYHA functional class III.

Mavacamten Dosing and Concomitant Medications

Nearly all patients (98.3%; 113/115) initiated mavacamten at 5 mg daily, while two patients (1.7%) initiated mavacamten at 2.5 mg, consistent with the Canadian product monograph [12]. At week 12, 73.9% of patients (82/111) remained on 5 mg daily. By week 52, 47.6% (30/63) were receiving 5 mg, 25.4% (16/63) 10 mg, 15.9% (10/63) 2.5 mg, and 4.8% (3/63) 15 mg; dosing data were not available for four patients (6.3%).

During follow-up, 47.8% of patients (55/115) required no dose modification, 37.4% (43/115) underwent one dose adjustment, and 14.8%

Table 1 Baseline demographic and clinical characteristics

Characteristics	Study population (N = 115)
<i>Age at index date (years), n (%)</i>	
≤ 49	14 (12.2)
50–59	25 (21.7)
60–69	39 (33.9)
70–79	29 (25.2)
≥ 80	8 (7.0)
<i>Age (years) (N = 65^a), median (range)</i>	63.0 (22, 87)
<i>Sex at birth, n (%)</i>	
Male	59 (51.3%)
Female	56 (48.7%)
<i>BMI (kg/m²), median (range)</i>	28.9 (19, 54)
<i>Race or ethnicity^b, n (%)</i>	
White, non-Hispanic	69 (60.0%)
Asian, non-Hispanic	10 (8.7%)
Hispanic	2 (1.7%)
Other ^c , non-Hispanic	7 (6.1%)
Unknown	27 (23.5%)
<i>SRT prior to mavacamten initiation, n (%)</i>	
Yes	11 (9.6%)
<i>Type of SRT, n (%)</i>	
Surgical myectomy	1 (9.1%)
Alcohol septal ablation	10 (90.9%)
<i>NYHA functional class, n (%)</i>	
NYHA class II	66 (57.4%)
NYHA class III	49 (42.6%)
<i>Valsalva-induced LVOT gradient (mmHg) (N = 95^e), median (IQR)</i>	78.0 (60, 100)
<i>Resting LVOT gradient (mmHg) (N = 106^d), median (IQR)</i>	44.0 (16, 75)
<i>LVEF (%) (N = 111^f), median (IQR)</i>	65.0 (60, 70)
<i>BMI Body mass index, IQR interquartile range, LVEF left ventricular ejection fraction, LVOT left ventricular outflow</i>	

Table 1 continued

tract, *NYHA* New York Heart Association, *SRT* septal reduction therapy

^aActual age data was missing for 50 patients

^bMultiple options could be selected per patient

^cAdditional details for the “Other” race or ethnicity category were not captured

^dBaseline Valsalva-induced LVOT gradient data was missing for 20 patients

^eBaseline resting LVOT gradient data was missing for 9 patients

^fBaseline LVEF data was missing for 4 patients

(17/115) required two or more modifications. At data cut-off, 48.7% of patients (56/115) were receiving 5 mg, 25.2% (29/115) 10 mg, 13.9% (16/115) 2.5 mg, and 3.5% (4/115) 15 mg, while 8.7% (10/115) had discontinued mavacamten.

During mavacamten treatment, 80.9% of patients (93/115) received concomitant background oHCM therapy, including BBs only (67.8%, 78/115) and non-dihydropyridine CCBs only (10.4%, 12/115). Two patients (1.7%, 2/115) received both BBs and/or CCBs either concurrently or sequentially and one patient (0.9%, 1/115) discontinued disopyramide at mavacamten initiation and subsequently switched to a BB (Electronic Supplementary Material [ESM] Fig. S1). There were no patients receiving a combination of mavacamten and

disopyramide following mavacamten initiation, as it is recommended to avoid this combination due to the potential risk for worsening LV systolic function [19]. By data cut-off, the number of patients on concomitant background therapies decreased to 70.4% (81/115), including BBs in 63.5% (73/115), and non-dihydropyridine CCBs in 6.1% (7/115). Correspondingly, the proportion of patients receiving mavacamten monotherapy increased from 19.1% (22/115) at treatment initiation to 29.5% (34/115) at data cut-off (ESM Fig. S1).

Mavacamten Effectiveness

Most patients (72.7%) demonstrated an improvement of ≥ 1 NYHA functional class at their most recent clinical assessment (median duration 38.7 weeks following mavacamten initiation) (Fig. 1). Changes in LVOT gradients since mavacamten initiation were determined by comparing each patient's LVOT gradient results during follow-up to their results at baseline (Figs. 2, 3). From baseline to data cut-off (i.e., most recent clinical assessment), a clinically meaningful reduction in rLVOT and vLVOT gradients was observed (median changes: -25.5 mmHg [IQR: $-61, -8$] and -51.0 mmHg [IQR: $-83, -24$], respectively). At data cut-off, 89.6% and 67.0% of patients achieved a rLVOT gradient (Fig. 2)

NYHA class distribution at baseline, n (%) (N=115)		NYHA class at data cut-off, n (%) (N=99)				Change in NYHA class from baseline to data cut-off:
		I	II	III	IV	
II	66 (57.4%)	36 (36.4%)	17 (17.2%)	3 (3.0%)	1 (1.0%)	Improvement
III	49 (42.6%)	17 (17.2%)	19 (19.2%)	6 (6.1%)	0 (0.0%)	No change
Distribution of data at cut-off, n (%) (N=99)		53 (53.5%)	36 (36.4%)	9 (9.1%)	1 (1.0%)	Worsening

Fig. 1 New York Heart Association (*NYHA*) functional class in the MAVEN cohort: summary of NYHA functional class from baseline to each patient's last recorded data cut-off, with a median duration of 38.7 (range: 5–95)

weeks after mavacamten initiation. Of 115 patients, 16 (13.9%) had unknown NYHA class post-mavacamten initiation; nine were baseline NYHA class II and seven were NYHA class III

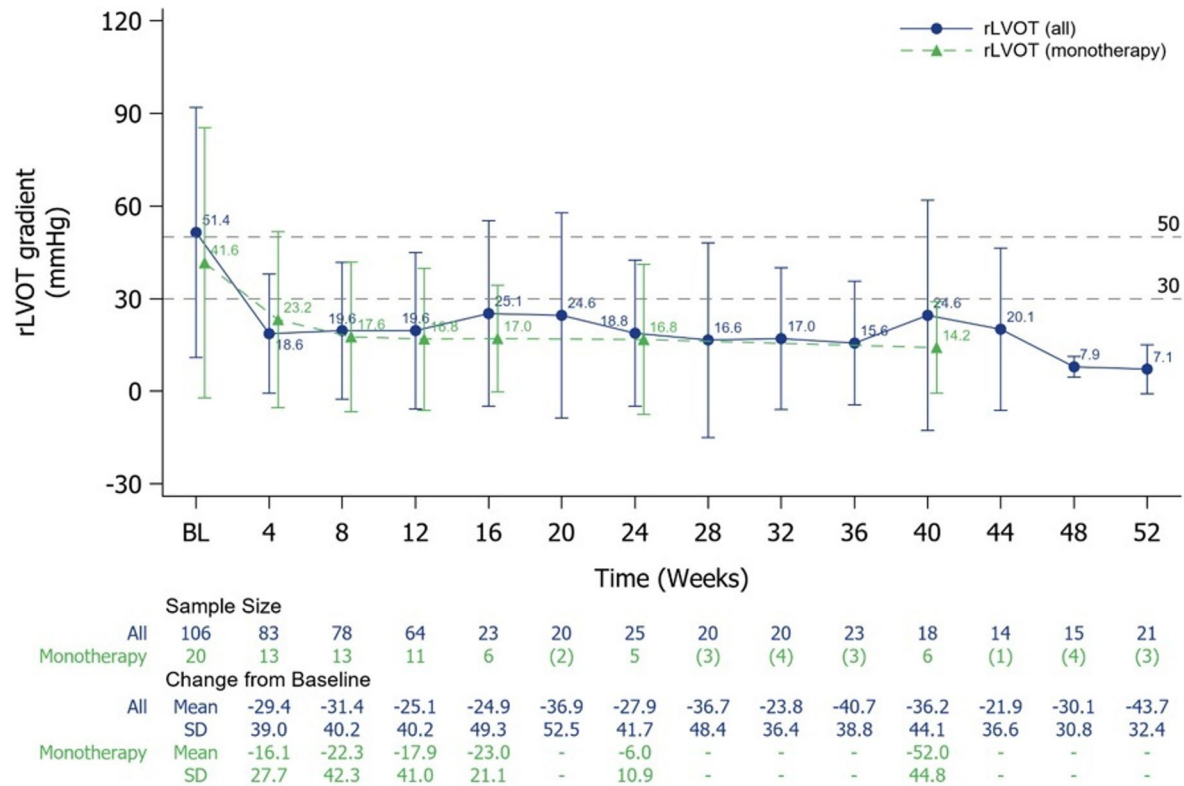


Fig. 2 Resting left ventricular outflow (*rLVOT*) gradients. Mean (standard deviations [SD]) resting LVOT (*rLVOT*) gradients are displayed at each timepoint up to 52 weeks after initiation of mavacamten for the overall cohort (solid line) and the monotherapy subgroup (dotted line). Dashed horizontal lines indicate the 30 mmHg obstruction threshold and the 50 mmHg septal reduction therapy threshold. Baseline was defined as the last measurement obtained

prior to mavacamten initiation, with changes assessed relative to baseline. In the sample size row, an 'N' in parentheses marks a visit with < 5 patients; at those visits the means are not plotted and the changes from baseline are shown as '-'. As this analysis was descriptive in nature, no statistical comparisons or *p*-values were calculated for changes from baseline or between groups

and vLVOT gradient of ≤ 30 mmHg (Fig. 3), respectively.

Safety and Tolerability of Mavacamten

During the data collection period, the median duration of mavacamten treatment was 53.3 (range 5–95) weeks, corresponding to 116.2 patient-years of treatment exposure. At the time of analysis, about half of patients (51.3%) had received mavacamten for ≥ 52 weeks. A mild reduction in LVEF was observed following mavacamten initiation, with a median change of -3.0% (IQR: $-8, 0$) at data cut-off (Fig. 4).

During follow-up, seven patients (6.1%) experienced an LVEF $< 50\%$, including four (3.5%) with LVEF 40–50% and three (2.6%) with LVEF 30–39%. There were no incidences of LVEF $< 30\%$. Among patients with LVEF $< 50\%$, four patients subsequently recovered to an LVEF $\geq 50\%$, two patients permanently discontinued treatment, and one restarted mavacamten at a reduced dose following treatment interruption. Mavacamten was permanently discontinued in 8.7% of patients (10/115), corresponding to a discontinuation rate of 8.6 per 100 patient-years. Permanent discontinuation due to treatment-emergent adverse events

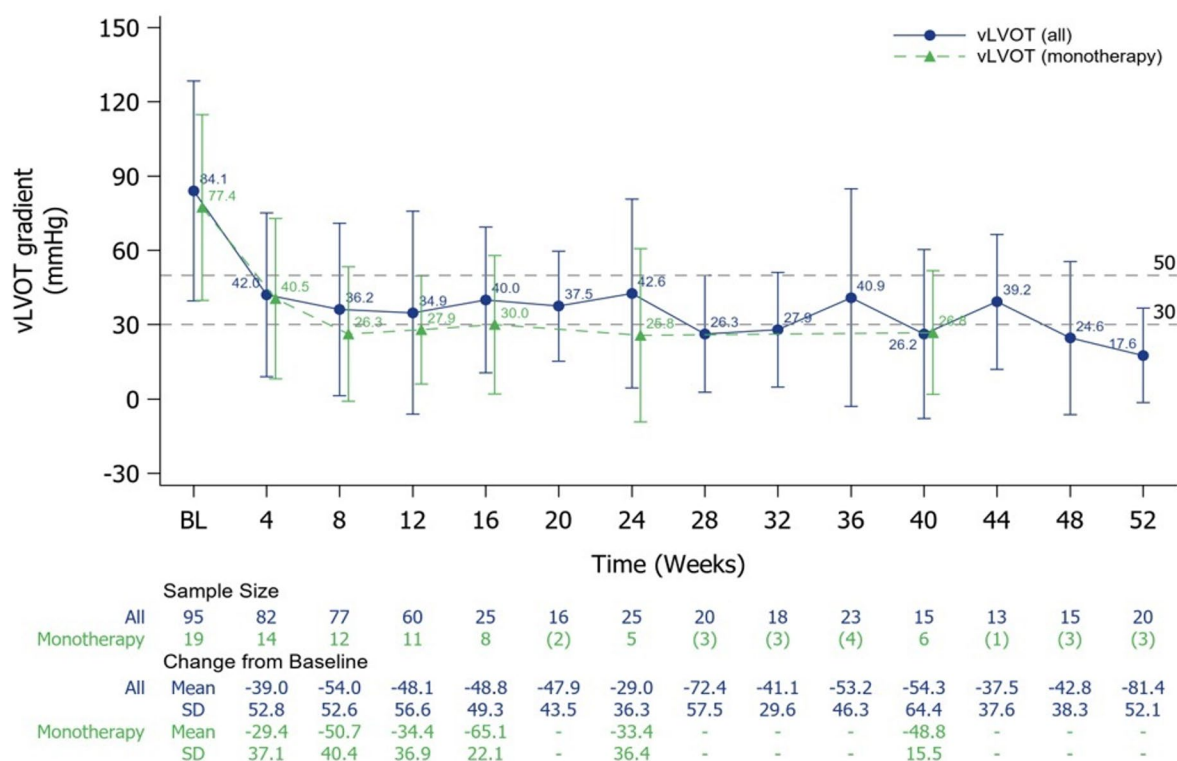


Fig. 3 Valsalva left ventricular outflow (*vLVOT*) gradients. Mean (standard deviation [SD]) values for Valsalva LVOT (*vLVOT*) gradients are displayed at each timepoint up to 52 weeks after starting mavacamten for the overall cohort (solid line) and the monotherapy subgroup (dotted line). Dashed horizontal lines indicate the 30 mmHg obstruction threshold and the 50 mmHg septal reduction therapy threshold. Baseline was defined as the last measurement

obtained prior to mavacamten initiation, with changes assessed relative to baseline. In the sample size row, an 'N' in parentheses marks a visit with fewer than 5 patients. At those visits the means are not plotted and the changes from baseline are shown as '-'. As this analysis was descriptive in nature, no statistical comparisons or *p*-values were calculated for changes from baseline or between groups

(TEAEs) occurred in 2.6% of patients (3/115), including two cases attributed to reduced LVEF (<50%).

Post-Hoc Analyses

Mavacamten Monotherapy

Baseline demographic and clinical characteristics were generally comparable between patients receiving mavacamten monotherapy (i.e., patients receiving mavacamten alone from treatment initiation to data cut-off) and those receiving combination therapy (mavacamten + BB or CCB), although patients in the monotherapy

subgroup were older (median age 70.4 years vs. 60.9 years). Following mavacamten initiation, all patients receiving mavacamten demonstrated meaningful reductions in rLVOT and vLVOT gradients (Figs. 2, 3). Additionally, most monotherapy patients (72.2%) demonstrated an improvement of ≥ 1 NYHA functional class at their most recent clinical assessment (ESM Fig. S2). In the monotherapy subgroup, the median rLVOT gradient at the most recent assessment was 7.0 (IQR 5–9) mmHg, with a mean change from baseline of -27.9 mmHg, and 95.2% of patients achieved an rLVOT gradient ≤ 30 mmHg at follow-up compared with 60.0% at baseline. Similarly, 81.0% of patients receiving mavacamten monotherapy achieved a vLVOT gradient ≤ 30 mmHg by data

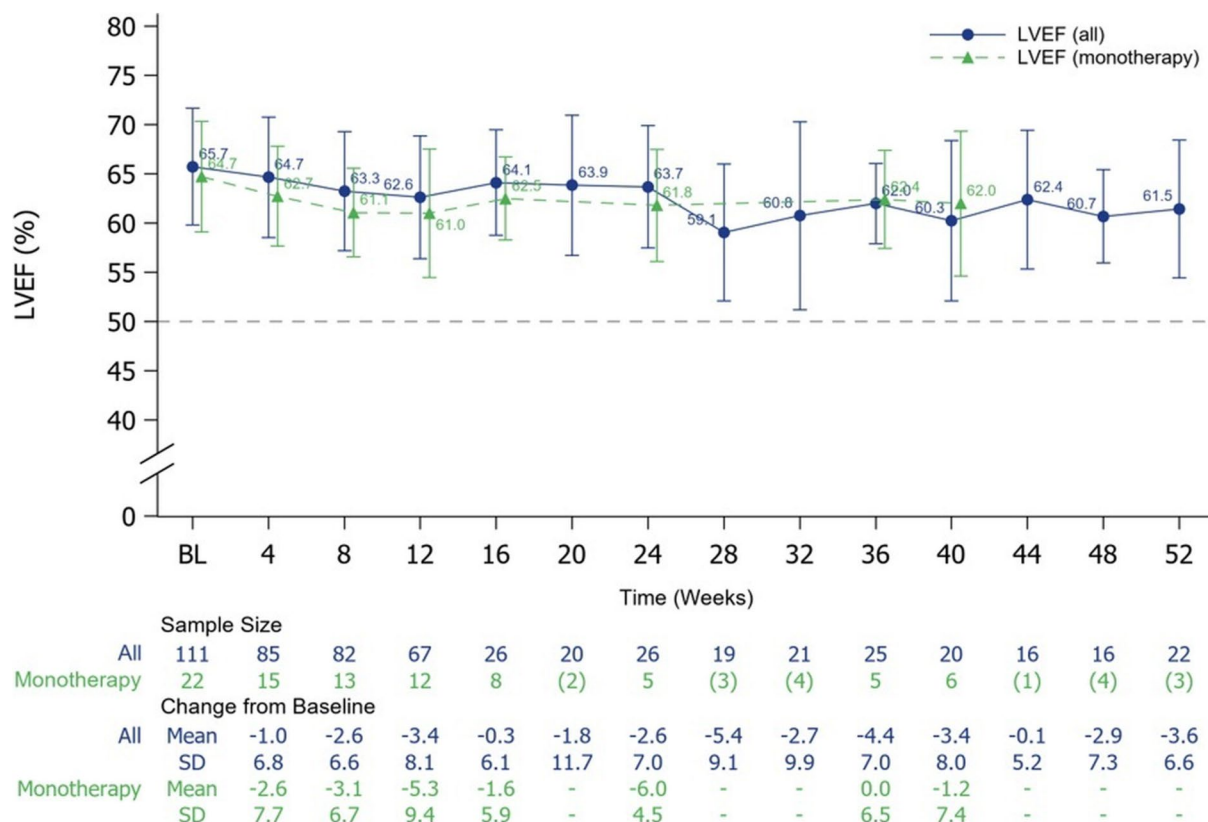


Fig. 4 Left ventricular ejection fraction (*LVEF*). Mean (standard deviations [SD]) *LVEF* values at each timepoint up to 52 weeks after starting mavacamten are displayed for the overall cohort (solid line) and the monotherapy subgroup (dotted line). The horizontal dashed line marks a *LVEF* of 50%, the threshold for LV systolic dysfunction. Baseline was defined as the last measurement obtained

prior to mavacamten initiation, with changes assessed relative to baseline. In the sample size row, an ‘N’ in parentheses marks a visit with < 5 patients. At those visits the means are not plotted and the changes from baseline are shown as ‘-’. As this analysis was descriptive in nature, no statistical comparisons or *p*-values were calculated for changes from baseline or between groups

cut-off, compared with 63.7% of those receiving combination therapy. No patients receiving monotherapy discontinued mavacamten because of TEAEs, whereas three patients (3.2%) receiving combination therapy discontinued mavacamten because of TEAEs (ESM Table S1).

Dose Change Status for Patients with LVOT Gradient < 20 mmHg During Treatment Initiation

Patients who achieved a vLVOT gradient < 20 mmHg during the first 12 weeks of treatment were stratified according to whether a mavacamten dose adjustment occurred (“Dose Change”) or those that did not have an

adjustment (“No Dose Change”). At baseline, patients in the “Dose Change” subgroup were generally less symptomatic, with a higher proportion of patients classified as NYHA class II but had a higher median vLVOT gradient than those in the “No Dose Change” subgroup (ESM Table S2).

All patients in the “Dose Change” subgroup initiated mavacamten at 5 mg daily (100%; 28/28), and most (60.7%; 17/28) subsequently underwent dose reduction to 2.5 mg. By data cut-off, 42.9% (12/28) were receiving 2.5 mg of mavacamten, while 25.0% (7/28) were on 5 mg, and 14.3% (4/28) were on 10 mg, while five patients (17.9%) discontinued treatment.

Following mavacamten initiation, an improvement of ≥ 1 NYHA functional class was observed in all evaluable patients in the “No Dose Change” subgroup (100%; 22/22) and in 65.4% of evaluable patients in the “Dose Change” subgroup (17/26). Both subgroups demonstrated reductions in rLVOT and vLVOT gradients relative to baseline. Median changes in the “Dose Change” subgroup were -30.5 (IQR: $-70, 0$) mmHg for rLVOT and -69.5 (IQR: $-114, -21$) mmHg for vLVOT, compared with -35.0 (IQR: $-66, -8$) mmHg and -50.0 (IQR: $-79, -32$) mmHg, respectively, in the “No Dose Change” subgroup. Two patients in the “Dose Change” subgroup discontinued mavacamten due to TEAEs, whereas no discontinuations occurred in the “No Dose Change” subgroup (ESM Table S2). Improvements in NYHA functional class were not uniformly aligned with reductions in LVOT gradients, suggesting that changes in symptoms and hemodynamic measures may not always occur in parallel.

DISCUSSION

This study provides the first Canadian real-world evidence describing mavacamten effectiveness and safety in patients with symptomatic oHCM. A key strength of this study is its inclusion of patients managed in three academic and two community-based centers, thereby providing a representative assessment of mavacamten use in routine Canadian clinical practice. Many Canadian patients treated with mavacamten in this study demonstrated improvements in NYHA functional class and LVOT gradients, with a low incidence of reduced LVEF.

Baseline demographics and clinical characteristics of participants in the MAVEN trial, including age, sex distribution, and NYHA functional class, closely mirrored those reported in the Canadian mavacamten PSP cohort [16], which represents the largest published Canadian mavacamten population to date ($N = 683$). These similarities support the representativeness of the MAVEN cohort and the applicability of its findings to contemporary Canadian patients with symptomatic oHCM. The baseline characteristics

of the MAVEN cohort were also broadly consistent with those of both clinical trial cohorts and real-world studies conducted outside of Canada [10, 11, 17, 20–25]. Among patients with a documented oHCM diagnosis date, 60% initiated mavacamten therapy within 2.5 years of their clinical diagnosis although disease onset likely preceded clinical recognition.

The median duration of mavacamten exposure was 53.3 weeks (range 5–95 weeks; 116.2 patient-years), which is comparable to interim VALOR-HCM trial findings [11], and longer in several other real-world studies [22, 24–26]. Exposure duration was limited by the timing of data cut-off and should not be interpreted as premature discontinuation. Nearly all patients 98.3% (113/115) initiated mavacamten at 5 mg daily, and approximately three-quarters remained on either 5 mg or 10 mg at data cut-off (48.7% and 25.2%, respectively), consistent with previous findings [17, 22, 23]. Dose modifications occurred primarily during initiation, with 11.1% and 9.5% of patients undergoing dose increases at weeks 12 and 16, respectively, reflecting individualized titration based on clinical response and safety monitoring [17]. Variability in the timing and frequency of echocardiographic assessments is an inherent feature of routine clinical practice. Unlike clinical trials, real-world imaging is guided by clinical need and local practice patterns rather than protocol-mandated timepoints. Exercise stress echocardiography was not routinely performed, precluding assessment for residual exercise LVOT gradients as a potential cause for persisting symptoms. Further research is warranted to better characterize treatment monitoring and dose optimization in Canadian practice.

At mavacamten treatment initiation, most patients (80.9%) were receiving background oHCM medication, predominantly BBs, consistent with previous clinical trials, real-world studies [22–28], and Canadian PSP data [15, 16]. However, by data cut-off, use of background oHCM medications had decreased to 70.4%, with 29.6% of patients receiving mavacamten monotherapy. This proportion is higher than the that reported in previous clinical trials and real-world cohorts [15, 17, 20, 22, 25]. Similar reductions in background oHCM therapy have

been reported in clinical and real-world studies. In VALOR-HCM, 18.5% of patients reduced background therapy by week 56 [11], while 7.4% of patients in the EXPLORER cohort of MAVA-LTE reduced BB or CCB doses by $\geq 50\%$ [29]. Similarly, Reza et al. reported that 14% of patients reduced their background oHCM therapy within 36 weeks of mavacamten initiation [22]. As mavacamten targets the pathophysiological mechanisms driving oHCM disease [7–9], reliance on traditional pharmacological treatments may decrease. Intolerance to first-line therapies and treatment burden may also prompt an increase in monotherapy use. While the reasons for these treatment changes were not systematically captured, the observed increase in mavacamten monotherapy may reflect evolving real-world treatment strategies. Additional real-world evidence is needed to better understand treatment decisions and mavacamten use in optimizing oHCM care.

The effectiveness observed in this MAVEN study aligns with findings from studies conducted outside of Canada. At the most recent NYHA assessment (median duration 39 weeks following mavacamten initiation), 46.1% of the patients enrolled in MAVEN achieved NYHA functional class I, and most patients (73%) improved by at least one NYHA functional class. Similarly, real-world studies have reported that 44–46% of patients achieved NYHA class I after 36 weeks of mavacamten treatment and that $> 60\%$ of patients showed improvement by at least one class [9, 22–25, 27, 28]. Collectively, these findings reinforce the therapeutic value of mavacamten in alleviating oHCM symptom burden. Reduction in LVOT gradients complemented the symptomatic improvement, with 89.6% and 67.0% of patients achieving rLVOT and vLVOT gradients ≤ 30 mmHg, respectively, at data cut-off. Similar reductions in LVOT gradients have been reported previously [23, 26], with a recent study observing that 70.6% of patients achieved a vLVOT gradient < 30 mmHg after 6 months of treatment [30].

Mavacamten was generally well-tolerated in this cohort, although comparisons with randomized clinical trials are limited by the retrospective design and descriptive methodology of the present study. Overall, 8.7% of patients

permanently discontinued mavacamten, including 2.6% due to TEAEs. TEAE-related discontinuation varies across real-world studies, ranging from no permanent discontinuations in several US cohorts [22, 23, 26, 30] to 6.7% reported in an European cohort [24]. This variation in discontinuations between regions may be attributed to implementation of the US REMS program, which facilitates closer monitoring and temporary treatment interruptions when LVEF falls below 50%, potentially reducing permanent discontinuation.

No patients in MAVEN experienced LVEF $< 30\%$; however, seven patients (6.1%) experienced an LVEF $< 50\%$ while on mavacamten, of whom four had an LVEF between 40% and 49% and three had an LVEF between 30% and 39%. Among these patients, two patients permanently discontinued treatment, four subsequently recovered to an LVEF $\geq 50\%$, and one restarted treatment at a lower dose without a subsequent LVEF assessment available. Although treatment interruptions and the clinical consequences of LVEF decline were not systematically captured, these findings highlight the importance of ongoing echographic LVEF monitoring during mavacamten therapy and suggest a resolution of LVEF reductions when mavacamten dose is reduced or discontinued. Overall, the discontinuation rate of mavacamten in a Canadian population was consistent with, or lower than, that observed in clinical trials and real-world settings, supporting the tolerability profile of this drug.

The effectiveness of mavacamten was further explored in two exploratory post-hoc subgroup analyses that were conducted to generate hypotheses to guide future patient management strategies. Given the small sample sizes, these findings should be interpreted descriptively and not as predictive of individual patient response. The first subgroup analysis evaluated patients who received mavacamten as a monotherapy from initiation to data cut-off and showed comparable symptom reductions to those receiving combination therapy (i.e., mavacamten + BB/non-dihydropyridine CCB). The second subgroup analysis examined patients who achieved vLVOT gradient < 20 mmHg during initiation, comparing those who underwent a dose adjustment (as per the treatment algorithm

recommended in the approved labeling [12]) to those who did not. Both subgroups demonstrated symptom improvements and reductions in rLVOT and vLVOT gradients. Patients in the “Dose Change” subgroup had higher baseline vLVOT gradient and greater absolute reductions in gradient; however, dose modification decisions could not be determined from the available data and likely reflect multiple clinical considerations beyond gradient measurements alone.

Overall, improvements in symptoms, NYHA functional status, and LVOT gradients were observed across both the overall study cohort and exploratory subgroups. Further investigation within the Canadian clinical setting is required to determine whether physiological improvements (e.g., decrease in septal thickness, improved diastolic functional parameters) accompany these positive clinical outcomes.

Limitations

This study has several limitations inherent to its retrospective, real-world design. Patient selection was based on a convenience sample from five high-volume center across three Canadian provinces, introducing the potential for selection bias and limiting generalizability to the broader Canadian oHCM population. Our study did not use a predefined responder definition. Instead, treatment effects were assessed using changes in established clinical (NYHA class) and echocardiographic measures parameters (LVOT gradient and LVEF), which are well-established outcomes in oHCM. Data were collected through a physician-completed chart survey and were thus limited to variables with routinely available data; for example, laboratory biomarkers and details on previous and concomitant treatments were not collected. More objective measurements, such as the Six-Minute Walk Distance (6MWD) test and Cardiopulmonary Exercise Testing (CPET), are not routinely performed and were not consistently available in patients’ charts. In addition, outcomes were assessed using the most

recent available clinical assessment, resulting in heterogeneous follow-up durations (range: 5–95 weeks) and variability in the timing of endpoint evaluation. Echocardiographic assessments were performed as part of routine clinical practice without standardized acquisition protocols or core laboratory adjudication, which may have introduced inter-site variability in LVOT gradient and LVEF measurements. However, this variability is inherent to real-world clinical care and reflects routine practice outside the structured setting of clinical trials. Safety assessments were limited to protocol-defined LVEF outcomes (<50% and <30%) and did not capture the full spectrum of all adverse events. Finally, all analyses, including subgroup analysis, were descriptive, without formal hypothesis testing or adjustment for potential confounding factors, including baseline differences between subgroups; therefore, causal inferences cannot be made, and the findings should be interpreted cautiously within the context of routine clinical practice.

CONCLUSIONS

In this multi-centre retrospective real-world study, mavacamten use in Canadian patients with symptomatic oHCM was associated with improvements in NYHA functional class and reductions in LVOT gradients during routine clinical care. Reductions in LVEF (<50%) were observed in a minority of patients, while no clinically relevant case of LVEF < 30% was identified during the data collection period. Given the retrospective design of the study and the descriptive nature of the analyses, these findings should be interpreted cautiously. Nevertheless, MAVEN provides the largest Canadian real-world dataset evaluating mavacamten’s effectiveness in routine clinical practices. Further prospective studies with standardized clinical and imaging assessments are needed to better characterize the long-term effectiveness and safety of mavacamten in patients with oHCM.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to information governance.

Declarations

Conflict of Interest. Stephanie Corriveau and Florence Brellier are employees of Bristol Myers Squibb Company. Michael R. Ward has received consulting and speaking fees from Bristol Myers Squibb Company. Andrew M. Crean has received research support from and serves on the Speakers Bureau for Bristol Myers Squibb Company. Olivier Desplantie, Benjamin D. Tyrrell, and Kevin C. Ong have nothing to disclose.

Ethical Approval. The study protocol was reviewed and approved by the relevant Research

Ethics Boards/Institutional Review Boards at each participating site, which granted a waiver of informed consent because the study involved the retrospective use of de-identified patient data. The study was conducted in accordance with the Guidelines for Good Pharmacological Practices (GPP) and applicable regulatory requirements. A waiver of consent was obtained from the research ethics board at each participating site prior to the abstraction and use of routinely collected, pseudo-anonymized, medical record data, in accordance with local requirements. All research procedures complied with the ethical principles of the Declaration of Helsinki. Ethics approval was provided by the Advarra Institutional Review Board (IRB00000971), the Western University Health Sciences Research Ethics Board (HSREB) (IRB00000940), the Ottawa Health Science Network Research Ethics Board (OHSN-REB) (IRB00002616), the Health Research Ethics Board of Alberta—Community Health Committee (HREBA-CHC) (IRB1240005), and the University of British Columbia Providence Health Care Research Ethics Board (UBC-PHC REB) (IRB00000777).

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