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ORIGINAL RESEARCH ARTICLE

Differences in Healthcare Resource Use and Cost by Pharmacotherapy Among Patients with Symptomatic Obstructive Hypertrophic Cardiomyopathy: Real-World Analysis of Claims Data

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Abstract

Background For symptomatic obstructive hypertrophic cardiomyopathy (oHCM), limited evidence exists on healthcare resource utilization (HRU) and cost for patients with symptomatic oHCM by treatment categories. We evaluated whether HRU and costs vary by initial treatment in symptomatic oHCM.

Methods This is a retrospective study of medical and pharmacy claims from 2016 to 2021 to identify (per International Classification of Disease Tenth Revision diagnosis codes) adult patients in the USA with symptomatic oHCM. Patients included in the study cohort were required to be treatment naïve (≥ 12 months' activity before first treatment) and symptomatic (fatigue, chest pain, syncope, dyspnea, heart failure, or palpitations within 3 months of index date). Patients were grouped by first index treatment [beta blocker (BB), calcium channel blockers (CCB), disopyramide, combination therapy], and HRU and costs [per person per year (PPPY), in USD] by initial treatment were reported.

Results Among 7334 patients with symptomatic oHCM, initial treatment included BB (65.8%), CCB (21.1%), disopyramide (1.2%), or BB + CCB (11.9%). Overall, 87.2% were prescribed monotherapy. Outpatient visits were the main driver of all-cause HRU (mean 11.5 PPPY), and varied by initial treatment (BB: 11.0, CCB: 10.5, disopyramide: 7.2, combination therapy: 12.1). All-cause urgent care visits were more frequent than inpatient visits (means: 5.4 and 0.83 PPPY, respectively). All-cause incurred costs were $46,628 PPPY overall and varied by treatment (BB: $47,029, CCB: $42,124, disopyramide: $27,007, combination therapy: $54,024).

Conclusions In this large, US-based cohort of patients with symptomatic oHCM, initial therapy was most commonly BB and CCB monotherapy. Costs and HRU were high for most patients, but greater for those treated initially with combination therapy.

1 Introduction

Hypertrophic cardiomyopathy (HCM) is a chronic, progressive myocardial disorder defined by left ventricular (LV) hypertrophy with a reported disease prevalence of one case per 1250 people in the general population [1, 2]. Approximately two-thirds of diagnosed HCM cases are obstructive HCM (oHCM) [3], with an estimated 50% of patients being symptomatic [4]. For symptomatic oHCM, standard treatment traditionally consists of pharmacotherapy with beta-blockers (BB) or calcium channel blockers (CCB) as first-line, combination therapy (BB + CCB, disopyramide + BB, disopyramide + CCB, or disopyramide + BB + CCB) as second-line, and invasive procedures such as septal reduction therapy for patients refractory to pharmacotherapy. However, BB have notable limitations in patients with symptomatic oHCM, and patients do not uniformly experience relief from symptoms [6], and real-world studies have reported that a low percentage of oHCM patients are receiving disopyramide [7, 8].

A novel class of agents, cardiac myosin inhibitors, is being studied to modify disease expression and outcomes for patients with symptomatic oHCM [9–11]. Most recently, aficamten significantly improved exercise capacity compared with placebo and was consistent across all prespecified subgroups reflective of patient baseline characteristics and treatment strategies, including patients receiving or not receiving background BB therapy [12]. Regarding these new

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Key Points

For symptomatic obstructive hypertrophic cardiomyopathy (oHCM), limited evidence exists on healthcare resource utilization (HRU) and cost for patients with symptomatic oHCM by treatment categories.

Among 7334 patients with symptomatic oHCM, all-cause HRU and costs were high for most patients, but greater for those treated initially with combination therapy.

These findings show significant differences exist for HCM-related HRU [outpatient visits, urgent care (UC) visits, pharmacy] and costs [total cost, outpatient costs, emergency room (ER) cost, pharmacy cost], describing the economic burden endured by patients as a result of their HCM.

treatments emerging for patients with symptomatic oHCM, it is timely to assess the economic burden of current first- and second-line therapy for this disease. Previous studies have outlined the economic burden for patients with symptomatic oHCM [13, 14], but there is limited evidence on healthcare resource utilization (HRU) and cost for patients with symptomatic oHCM by pharmacotherapy. Therefore, we sought to determine whether HRU and costs vary by initial treatment in symptomatic oHCM, and whether combination therapy is associated with higher HRU and costs than monotherapy.

2 Methods

2.1 Data Source and Study Design

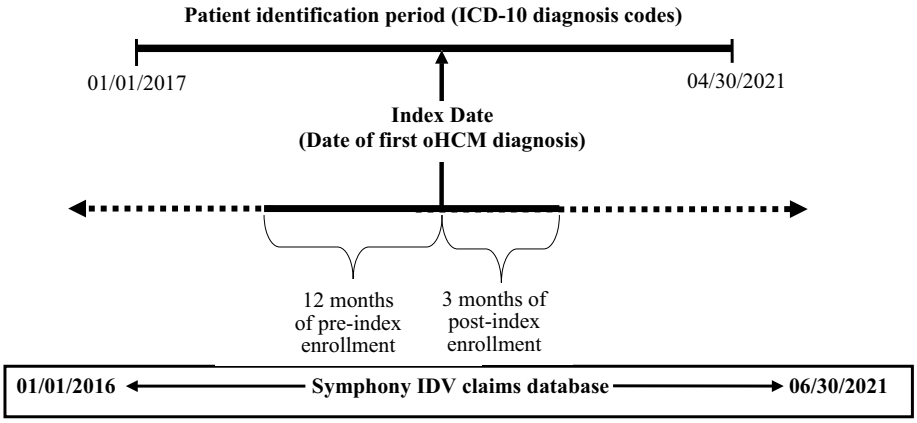
This is a retrospective analysis of longitudinal medical and pharmacy claims data from the Symphony Integrated Dataverse (IDV) database. The IDV contains prescription, medical, and hospital claims across the USA for all healthcare insurance types, including over 10 billion deidentified prescriptions claims linked to over 280 million unique patients. These prescription drug claims are linked to hospital and physician practices claims with medical procedure [i.e., current procedural terminology (CPT) and International Classification of Disease Tenth Revision (ICD-10)] for nearly 180 million patients. The study was carried out from 1 January 2016 to 30 June 2021, including the baseline period (for demographic and clinical information), the index period (to identify eligible patients), and the follow-up period (for study outcomes). Patients were identified during the identification period from 1 January 2017 to 30 April 2021, with the first HCM diagnosis being considered the index diagnosis date, and a pre-index period of 12 months (Fig. 1). Index treatment date was defined as the first treatment with a BB, CCB, or disopyramide after diagnosis date. The claims data in this study were de-identified in compliance with the Health Insurance Portability and Accountability Act, and thus this study did not require approval from an institutional review board. The data underlying this article are available in the article in its entirety.

2.2 Patient Selection, Characteristics, and Study Outcomes

The patient population for this study consisted of adult (age ≥ 18 years at index treatment date) patients with symptomatic oHCM identified from the Symphony IDV database. To focus on the differences in economic burden by initial therapy, only patients receiving a pharmacotherapy were included. Patients with oHCM who met the following criteria were included in this study (1) ≥ two claims of oHCM (ICD-10 diagnosis code: I42.1) at least 30 days apart, or (2) one diagnosis of HCM (ICD-10 diagnosis code: I42.2) along with either a diagnosis of oHCM (ICD-10 diagnosis code: I42.1) at least 30 days apart or a septal reduction therapy procedure any time after HCM diagnosis. The full patient selection criteria are summarized in Fig. 2. Patients with Fabry disease and/or amyloidosis were excluded from this analysis. Previous studies have used similar selection criteria based on ICD-10 codes to identify patients with oHCM in real-world data [4, 7, 8, 13–17].

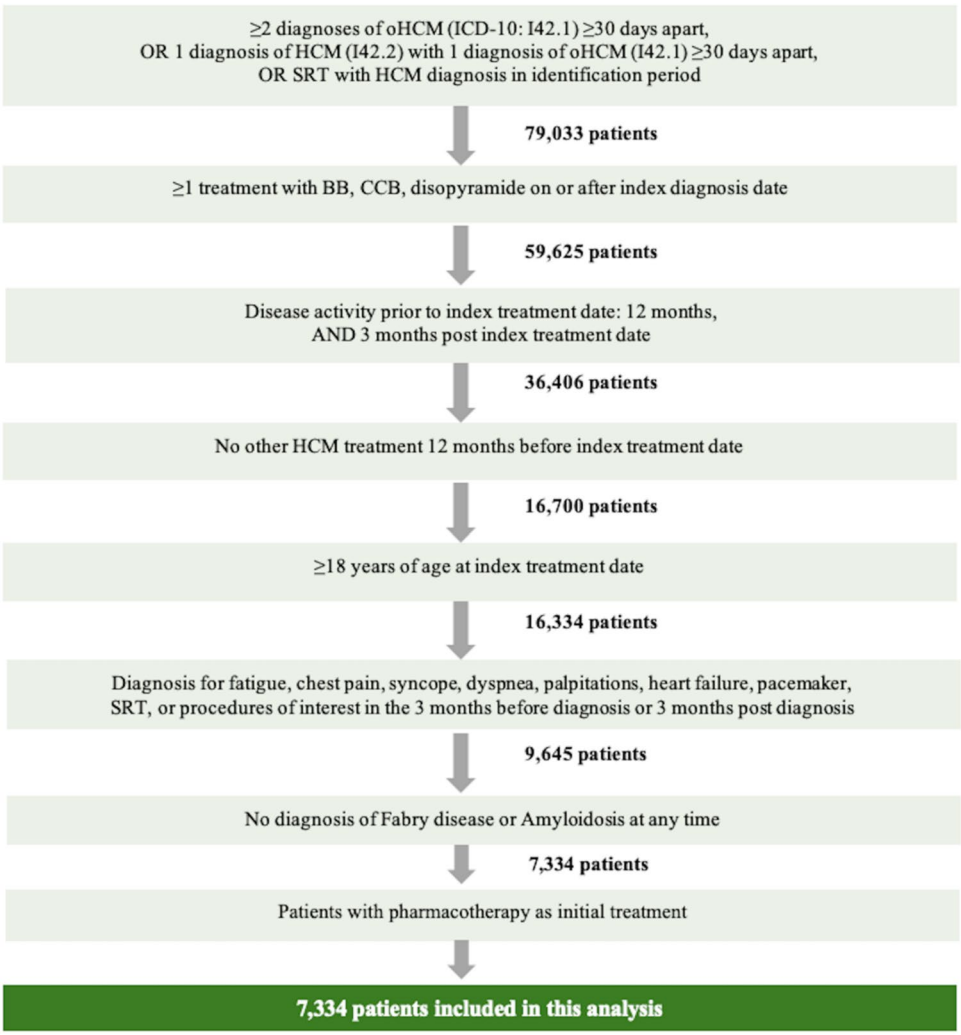
Patients were followed from their index treatment date until the end of index treatment due to either (1) discontinuation, (2) treatment switch, (3) treatment augmentation, or (4) end of activity in the database. Treatment discontinuation was defined as a gap of at least 60 days between the end of the days' supply of a prescription and the next prescription. The discontinuation date is the last prescription date plus its days' supply. If the treatment comprises a monotherapy drug class, the treatment will be considered to have been discontinued if the drug class is discontinued. If the treatment comprises a combination of drug classes, the treatment will be considered to have been discontinued if either of the drug classes is discontinued. A patient is considered to have switched if (a) they start treatment with a new treatment drug class between 30 days prior to end of the days' supply of the prior drug class with a 60-day gap with the current treatment and 60 days post discontinuation. The earlier of (a) the date prior to the start of the new treatment and (b) end of the days' supply with a 60-day gap will be considered the date of treatment discontinuation with the previous treatment. A patient is considered to have their treatment augmented if they start treatment with a new drug class more

Fig. 1 Observation period



than 30 days prior to treatment discontinuation with current treatment. The date prior to the start of the new treatment will be considered the date of treatment discontinuation with the previous treatment. Death status is not available in the Symphony IDV database and could not be specifically considered in the follow-up duration. However, if the patient died without meeting any of the other above criteria first, they would be followed up with until their last active record date.

Fig. 2 Patient selection criteria



Patient demographics and comorbidities were calculated 12 months prior to index date (excluding index date). All-cause and HCM-related HRU and costs were evaluated by initial treatment categories including BB, CCB, and disopyramide. Combination treatments were defined by the addition of a different treatment category occurring within 30 days of the index treatment category. Healthcare resource utilization and costs were evaluated for each healthcare setting, defined as inpatient admissions, outpatient visits, emergency room (ER) visits, urgent care (UC) visits, other visits, and pharmacy costs (HCM-related prescriptions and non-HCM related prescriptions). Emergency room and UC visits were identified by their respective CPT codes. HCM-related outcome variables included in this analysis were identified by an HCM claim on the ICD-10 code in any position, with predefined procedures and treatments based on the AHA/ACC treatment guidelines for patients with HCM [5]. Cost categories are reported as the charged amount billed by the payer, except for prescriptions, which were defined as final adjudicated costs.

2.3 Statistical Analysis

Descriptive statistics were presented as means and standard deviation (SD), median, and interquartile range (IQR) for continuous variables, and frequencies and proportions for categorical and dichotomous variables. Baseline characteristics were compared with chi-squared test for categorical variables or Kruskal–Wallis test for continuous variables. Differences between initial treatment categories were evaluated by Kruskal–Wallis for continuous variables and chi-squared tests for categorical variables. Generalized linear models with a gamma distribution and log link clustered on the patient were used to estimate per-person-per-year (PPPY) costs, and generalized estimating equations with a negative binomial distribution clustered on the patient were used to estimation PPPY visits. The mean difference in PPPY costs/visits, 95% confidence intervals (CIs), and *p*-values were estimated for the patient cohort and stratified by initial treatment. These estimates were evaluated for each healthcare setting; missing or unavailable data were not included.

3 Results

Among 7334 patients with symptomatic oHCM, 57.8% were female with a mean age of 62.1 (14.0) years. Initial treatment included BB (65.8%), CCB (21.1%), BB + CCB (11.9%), or disopyramide (1.2%). Patients receiving BB as initial therapy were younger (BB: 60.9 ± 14.5 years; CCB: 65.0 ± 12.6 years; BB + CCB: 63.0 ± 13.0 years; disopyramide: 63.3 ± 12.9 years) and less were female (BB: 55.8%; CCB: 61.7%; BB + CCB: 60.2%; disopyramide: 68.5%; Table 1). Additionally, 87.2% were prescribed monotherapy and 11.8% combination therapy. Regardless of treatment, the majority of patients resided in the South (35.1%; $p = 0.0018$) and had Medicare coverage (43.0%; $p < 0.0001$). There were significant differences in comorbidities across the initial treatment groups, most notably stroke, diabetes, renal failure, hypertension, and chronic pulmonary disease (all $p < 0.0001$).

There were no significant differences in total all-cause incurred healthcare costs across treatment groups, but the greatest costs were contributed to BB + CCB combination therapy ($p = 0.0719$; Fig. 3a): BB: $47,029; CCB: $42,142; disopyramide: $27,007; and BB + CCB: $54,024. Irrespective of treatment, outpatient visits contributed the most to overall costs. Outpatient visits were the main driver of HRU and varied by initial treatment: BB: 11.0; CCB: 10.5; BB + CCB: 12.1; and disopyramide: 7.2 ($p = 0.0196$; Fig. 3b). Urgent care visits were more frequent than inpatient visits (mean: 5.4 and 0.83 PPPY, respectively). Overall, there were significant differences in all-cause HRU for hospitalizations, ER visits, outpatient visits, and all-cause costs including ER and UC costs (Table 2).

For HCM-related costs, there were significant differences in total costs among the total cohort ($p = 0.0156$), with the greatest cost contributed to patients receiving disopyramide: $16,646 ($7213–$38,413). Disopyramide also had the greatest pharmacy cost ($1846, $p < 0.0001$), followed by BB + CCB ($606), BB ($350), and CCB alone ($346). Significant differences were also seen in HCM-related OP and ER cost (Table 3). Across initial treatment groups, there were significant differences in HCM-related HRU for outpatient ($p = 0.0233$) and UC visits, and prescription fills ($p < 0.0001$).

4 Discussion

This is the first study, to our knowledge, to utilize a national database of medical and pharmacy claims to evaluate whether HRU and costs vary by initial treatment in symptomatic oHCM, and to assess the total cost of care for patients with symptomatic oHCM across utilization categories, beyond the scope of the price of a pharmacotherapy. We report several benchmark findings on the burden of current medical therapy for symptomatic oHCM. The majority of patients were prescribed monotherapy, with older patients and more female patients receiving combination therapy. Combination therapy also was associated with greater all-cause HRU and costs for patients with symptomatic oHCM, which were driven by outpatient utilization and costs. Across treatment categories, there were significant differences in all-cause HRU including ER, UC, and pharmacy utilization, and costs for hospitalization, outpatient, ER, and

Table 1 Patient baseline characteristics

	Total ($n = 7334$)	BB alone ($n = 4826$)	CCB alone ($n = 1544$)	BB + CCB ($n = 875$)	Disopyramide ($n = 89$)	p-value
Female, *n* (%)	4236 (57.8)	2695 (55.8)	953 (61.7)	527 (60.2)	61 (68.5)	< 0.0001
Age in years, mean (SD)	62.1 (14.0)	60.9 (14.5)	65.0 (12.6)	63.0 (13.0)	63.3 (12.9)	< 0.0001
18–34	401 (5.5)	318 (6.6)	50 (3.2)	30 (3.4)	3 (3.4)	
35–44	498 (6.8)	365 (7.6)	67 (4.3)	61 (7.0)	5 (5.6)	
45–54	989 (13.5)	708 (14.7)	159 (10.3)	111 (12.7)	11 (12.4)	
55–64	1762 (24.0)	1162 (24.1)	351 (22.7)	231 (26.4)	18 (20.2)	
65+	684 (50.2)	2273 (47.1)	917 (59.4)	442 (50.5)	52 (58.4)	
Index treatment year, *n* (%)						0.3287
2017	1439 (19.6)	937 (19.4)	322 (20.9)	160 (18.3)	20 (22.5)	
2018	1707 (23.3)	1156 (24.0)	345 (22.3)	189 (21.6)	17 (19.1)	
2019	1806 (24.6)	1189 (24.6)	382 (24.7)	219 (25.0)	16 (18.0)	
2020	1516 (20.7)	970 (20.1)	317 (20.5)	206 (23.5)	23 (25.8)	
2021	866 (11.8)	1688 (19.6)	513 (18.6)	423 (19.2)	34 (24.2)	
Region, *n* (%)						0.0018
Northeast	1805 (24.6)	1193 (24.7)	344 (22.3)	241 (27.5)	27 (30.3)	
Central	1925 (26.2)	1323 (27.4)	378 (24.5)	206 (23.5)	18 (20.2)	
South	2577 (35.1)	1659 (34.4)	578 (37.4)	313 (35.8)	27 (30.3)	
West	1007 (13.7)	635 (13.2)	242 (15.7)	114 (13.0)	16 (18.0)	
Unknown	20 (0.3)	16 (0.3)	2 (0.1)	1 (0.1)	1 (1.1)	
Insurance, *n* (%)						< 0.0001
Cash	430 (5.9)	266 (5.5)	104 (6.7)	46 (5.3)	14 (15.7)	
Commercial	418 (5.7)	286 (5.9)	80 (5.2)	45 (5.1)	7 (7.9)	
Employer group	680 (9.3)	477 (9.9)	130 (8.4)	62 (7.1)	11 (12.4)	
Medicaid	1005 (13.7)	662 (13.7)	196 (12.7)	139 (15.9)	8 (9.0)	
Medicare	3157 (43.0)	1988 (41.2)	721 (46.7)	424 (48.5)	24 (27.0)	
Pharmacy benefit manager	664 (9.1)	460 (9.5)	129 (8.4)	69 (7.9)	6 (6.7)	
Unspecified	929 (12.7)	652 (13.5)	180 (11.7)	80 (9.1)	17 (19.1)	
Other*	51 (0.7)	35 (0.8)	4 (0.2)	10 (1.1)	2 (2.2)	
Time from first diagnosis to index treatment, days						< 0.0001
Mean (SD)	448.1 (466.1)	419.7 (462.4)	510.8 (471.4)	489.1 (465.6)	500.2 (443.3)	
Median (IQR)	323.5 (698.0)	272.5 (663.0)	405.5 (733.5)	389.0 (698.0)	407.0 (559.0)	
Follow-up period, days						< 0.0001
Mean (SD)	296.3 (349.1)	316.0 (358.5)	258.9 (332.0)	270.0 (328.5)	132.2 (152.3)	
Median (IQR)	147.0 (341.0)	168.0 (381.0)	113.0 (279.5)	126 (294)	70.0 (143.0)	
Comorbidities, *n* (%)						
Atrial fibrillation	1747 (23.8)	1098 (22.8)	397 (25.7)	225 (25.7)	27 (30.3)	0.0195
Atrial flutter	323 (4.4)	206 (4.3)	81 (5.2)	32 (3.7)	4 (4.5)	0.2645
Ventricular fibrillation	52 (0.7)	38 (0.8)	6 (0.4)	7 (0.8)	1 (1.1)	0.3927
Ventricular tachycardia	544 (7.4)	384 (8.0)	91 (5.9)	62 (7.1)	7 (7.9)	0.0594
Supraventricular tachycardia	367 (5.0)	245 (5.1)	79 (5.1)	38 (4.3)	5 (5.6)	0.8085
Chronic pulmonary disease	1891 (25.8)	1130 (23.4)	488 (31.6)	254 (29.0)	19 (21.3)	< 0.0001
Hypertension	4959 (67.6)	1804 (37.4)	723 (46.8)	432 (49.4)	30 (33.7)	< 0.0001
Congestive heart failure	2777 (37.9)	1778 (36.8)	588 (38.1)	370 (42.3)	41 (46.1)	0.0074

Table 1 (continued)

	Total ($n = 7334$)	BB alone ($n = 4826$)	CCB alone ($n = 1544$)	BB + CCB ($n = 875$)	Disopyramide ($n = 89$)	p-value
Renal failure	1034 (14.1)	573 (11.9)	264 (17.1)	187 (21.4)	10 (11.2)	< 0.0001
Obesity	1595 (21.7)	1029 (21.3)	332 (21.5)	215 (24.6)	19 (21.3)	0.1971
Diabetes	1788 (24.4)	1086 (22.5)	406 (26.3)	281 (32.1)	15 (16.9)	< 0.0001
Valvular disease	2728 (37.2)	1845 (38.2)	541 (35.0)	300 (34.3)	42 (47.2)	0.0065
Stroke	366 (5.0)	203 (4.2)	101 (6.5)	60 (6.9)	2 (2.2)	< 0.0001
Dyslipidemia	3707 (50.5)	2374 (49.2)	830 (53.8)	465 (53.1)	38 (42.7)	0.0023
Coronary artery disease	2169 (29.6)	1401 (29.0)	448 (29.0)	302 (34.5)	18 (20.2)	0.0019

*Other insurance includes processors, third-party, and workers compensation

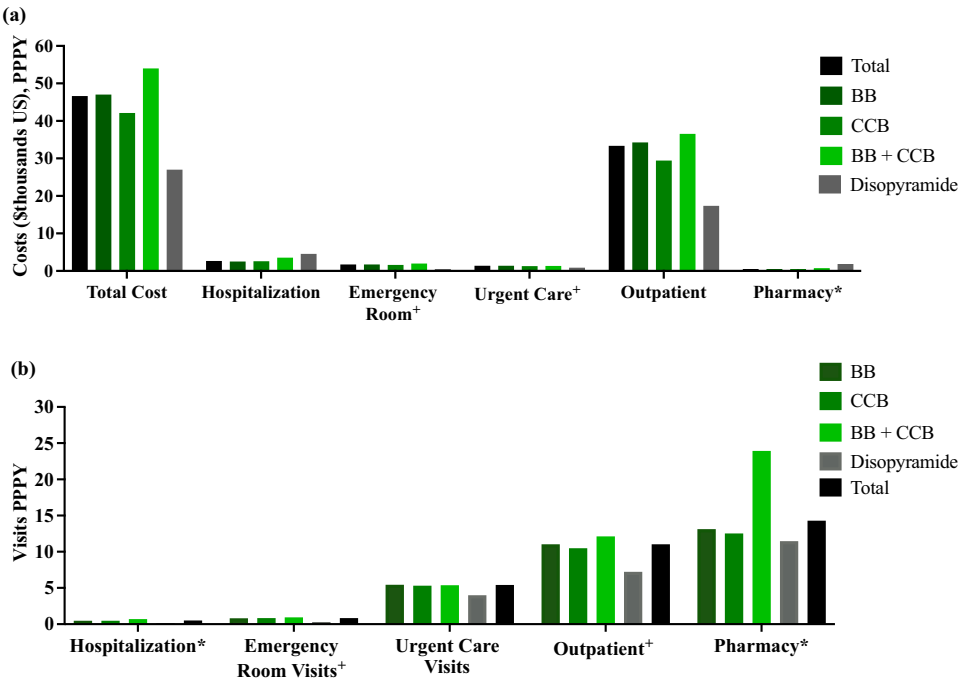


Fig. 3 All-cause **a** healthcare costs and **b** HRU by index treatment choice. Pharmacy visits are defined as the total number of prescriptions per person per year. *PPPY* per person per year. $^{*}p < 0.0001$. $^{+}p < 0.05$

pharmacy—which increase with combination BB + CCB therapy. Significant differences also exist for disease-specific HCM-related HRU (outpatient visits, UC visits, and pharmacy) and costs (total cost, outpatient costs, ER cost, and pharmacy cost).

While there are no recent studies to directly compare with the present study, we expand upon recent real-world evidence studies that report on the economic burden of symptomatic oHCM [4, 15, 16]. Previous studies have shown the frequent use of first- and second-line therapy for symptomatic oHCM [7, 8, 13], suggesting the escalation of treatment contributes to an increased economic burden for patients [17]. Desai et al. (2023) reported that, among oHCM patients who are symptomatic, they present with a high comorbidity burden and resource utilization due to frequent echocardiograms, ER visits, and hospitalizations [17]. Similarly, the present study reported a significant burden of comorbidities at initial treatment, and high resource utilization and costs over the disease course, but they were driven by outpatient utilization. We expand upon this previous study [17] to show that there are significant differences in HRU, and costs based on initial treatment, with greater economic burden for those treated initially with BB + CCB combination therapy.

Furthermore, for patient's refractory to pharmacotherapy, septal reduction therapy is utilized in ~ 20% of symptomatic patients with New York Heart Association Functional Class III through IV patients [5, 18]. While septal reduction therapy has demonstrated efficacy in providing symptom relief and long-term survival similar to that in the general

Table 2 All-cause HRU and costs by index treatment choice

	Total ($n = 7334$)	BB alone ($n = 4826$)	CCB alone ($n = 1544$)	BB + CCB ($n = 875$)	Disopyramide ($n = 89$)	p-Value
All-cause total cost*, $ PPPY (95% CI)	$46,628 ($43,172–50,362)	$47,029 ($42,673–51,830)	$42,142 ($35,906–49,461)	$54,024 ($44,104–66,176)	$27,007 ($15,166–48,095)	0.0719
All-cause related hospitalizations						
Patients with hospitalizations, *n* (%)	1526 (20.8%)	1032 (21.4%)	277 (17.9%)	213 (24.3%)	4 (4.5%)	
Number of hospitalizations, PPPY (95% CI)	0.5 (0.47–0.53)	0.47 (0.44–0.5)	0.48 (0.42–0.55)	0.7 (0.58–0.84)	0.12 (0.05–0.32)	< 0.0001
Hospitalization cost, $ PPPY (95% CI)	$2700 ($2409–3026)	$2545 ($2219–2918)	$2614 ($2003–3411)	$3558 ($2612–4847)	$4591 ($670–$31,455)	0.2496
Length of stay, mean per hospitalization (95% CI)	4.80 (4.46–5.17)	4.69 (4.32–5.09)	5.11 (4.01–6.51)	4.96 (4.30–5.72)	3.00 (1.79–5.03)	0.2784
All-cause outpatient visits						
Patients with outpatient visits, *n* (%)	5690 (77.6%)	3842 (79.6%)	1122 (72.7%)	672 (76.8%)	54 (60.7%)	
Number of outpatient visits, PPPY (95% CI)	11.01 (10.6–11.44)	11.04 (10.53–11.58)	10.48 (9.7–11.31)	12.14 (10.8–13.64)	7.23 (5.11–10.22)	0.0196
Outpatient cost, $ PPPY (95% CI)	$33,375 ($30,12–36,972)	$34,289 ($30,185–38,951)	$29,469 ($23,764–36,543)	$36,548 ($27,562–48,462)	$17,348 ($8,728–34,478)	0.1525
All-cause emergency room visits						
Patients with ER visits, *n* (%)	1709 (23.3%)	1163 (24.1%)	317 (20.5%)	224 (25.6%)	5 (5.6%)	
Number of ER visits, PPPY (95% CI)	0.83 (0.77–0.9)	0.82 (0.74–0.9)	0.84 (0.71–1)	0.94 (0.79–1.12)	0.17 (0.07–0.4)	0.0018
ER cost, $ PPPY (95% CI)	$1749 ($1598–1914)	$1757 ($1565–1974)	$1627 ($1363–1942)	$1980 ($1588–2468)	$503 ($198–1276)	0.0332
All-cause urgent care visits						
Patients with UC visits, *n* (%)	4,848 (66.1%)	3306 (68.5%)	950 (61.5%)	549 (62.7%)	43 (48.3%)	
Number of UC visits, PPPY (95% CI)	5.40 (5.25–5.55)	5.44 (5.26–5.63)	5.33 (5–5.68)	5.38 (4.95–5.85)	4.0 (2.89–5.54)	0.3060
UC cost, $ PPPY (95% CI)	$1376 ($1329–1424)	$1398 ($1342–1456)	$1332 ($1217–1458)	$1364 ($1237–1503)	$832 ($598–1157)	0.0182

CI confidence interval, *ER* emergency room, *HCM* hypertrophic cardiomyopathy, *PPPY* per person per year, *UC* urgent care

*Total cost does not equal the sum of the components, because each component was modeled separately, and the cost that could not be classified into a setting are not listed in the table

population, recent studies show that patients experience an array of complications post septal reduction therapy, including atrial fibrillation, heart failure, and cardiovascular hospitalization [19–21]. A recent analysis also reported that the utilization of septal reduction therapy leads to increased economic burden for patients with symptomatic oHCM [14], along with requiring the subsequent need for first-line pharmacotherapy post-procedure as well [8, 22]. However, the rationale for continued medication use post septal myectomy is unclear and requires further investigation [22].

The progression of the disease course of symptomatic patients and the escalation of these recommended pharmacotherapies may suggest the lack of effectiveness of these treatments. In the recent update to HCM guidelines, recommendation was made for discouragement of combination BB + CCB therapy as it is unsupported by current clinical

Table 3 HCM-related HRU and costs by index treatment choice

	Total ($n = 7334$)	BB alone ($n = 4826$)	CCB alone ($n = 1544$)	BB + CCB ($n = 875$)	Disopyramide ($n = 89$)	p-Value
HCM-related total cost*, $ PPPY (95% CI)	$14,153 ($13,089–15,303)	$14,881 ($13,552–16,341)	$10,792 ($9054–12,865)	$14,665 ($11,624–$18,503)	$16,646 ($7213–$38,413)	0.0156
HCM-related hospitalizations						
Patients with hospitalizations, *n* (%)	599 (8.2%)	415 (8.6%)	102 (6.6%)	80 (9.1%)	2 (2.2%)	–
Number of hospitalizations, PPPY (95% CI)	0.15 (0.14–0.17)	0.15 (0.13–0.16)	0.14 (0.11–0.17)	0.20 (0.15–0.25)	0.06 (0.01–0.22)	0.0810
Hospitalization cost, $ PPPY (95% CI)	$1421 ($1215–1661)	$1430 ($1191–1718)	$1299 ($864–1952)	$1411 ($970–2053)	$4521 ($646–31,624)	0.6702
Length of stay, mean per hospitalization (95% CI)	4.91 (4.29–5.63)	5.11 (4.27–6.12)	4.89 (3.93–6.10)	4.00 (3.43–4.67)	3.00 (1.19–7.56)	0.1398
HCM-related outpatient visits						
Patients with outpatient visits, *n* (%)	3503 (47.8%)	2478 (51.3%)	607 (39.3%)	386 (44.1%)	32 (36.0%)	–
Number of outpatient visits, PPPY (95% CI)	3.65 (3.49–3.83)	3.87 (3.65–4.1)	2.99 (2.7–3.32)	3.59 (3.19–4.04)	2.64 (1.83–3.8)	< 0.0001
Outpatient cost, $ PPPY (95% CI)	$10,536 ($9572–11,597)	$11,238 ($10,028–12,594)	$7688 ($6209–9519)	$10,495 ($7765–14,185)	$9438 ($4216–21,126)	0.0233
HCM-related emergency room visits						
Patients with ER visits, *n* (%)	558 (7.6%)	384 (8.0%)	92 (6.0%)	81 (9.3%)	1 (1.1%)	–
Number of ER visits, PPPY (95% CI)	0.22 (0.19–0.25)	0.22 (0.19–0.26)	0.19 (0.14–0.25)	0.25 (0.19–0.34)	0.03 (0–0.23)	0.1219
ER cost, $ PPPY (95% CI)	$466 ($400–542)	$482 ($400–581)	$339 ($241–478)	$616 ($419–907)	$100 ($14–699)	0.0501
HCM-related urgent care visits						
Patients with UC visits, *n* (%)	3247 (44.3%)	2298 (47.6%)	565 (36.6%)	357 (40.8%)	27 (30.3%)	–
Number of UC visits, PPPY (95% CI)	2.25 (2.17–2.34)	2.35 (2.24–2.46)	1.92 (1.75–2.11)	2.30 (2.05–2.59)	1.59 (1.12–2.27)	0.0005
UC cost, $ PPPY (95% CI)	$633 ($605–662)	$671 ($634–709)	$514 ($465–568)	$627 ($551–714)	$369 ($254–537)	< 0.0001
HCM-related pharmacy						
Patients with at least one pharmacy record, *n* (%)	7334 (100%)	4,826 (100.0%)	1544 (100.0%)	875 (100.0%)	89 (100.0%)	–
Number of pharmacy record, PPPY (95% CI)	14.28 (14.04–14.52)	13.12 (12.86–13.39)	12.53 (12.13–12.94)	23.92 (23.02–24.85)	11.46 (10.02–13.1)	< 0.0001
Pharmacy cost, $ PPPY (95% CI)	$394 ($369–420)	$350 ($322–382)	$346 ($309–387)	$606 ($510–719)	$1846 ($1460–2335)	< 0.0001

CI confidence interval, *ER* emergency room, *HCM* hypertrophic cardiomyopathy, *PPPY* per person per year, *UC* urgent care

*Total cost does not equal the sum of the components, because each component was modeled separately, and the cost that could not be classified into a setting are not listed in the table

evidence [23]. In this present analysis, we found that ~12% of patients with symptomatic oHCM received combination BB + CCB therapy as index treatment. While the use of combination therapy as index treatment is most likely due to patients being treated for other cardiovascular comorbidities, it is noteworthy to mention, as the combination group incurred the highest total cost and number of pharmacy visits. These increased costs and HRU may be offset for patients with symptomatic oHCM due to novel therapies being evaluated in patients with symptomatic oHCM, including cardiac myosin inhibitors mavacamten and aficamten. The 2023 European guidelines recommend cardiac myosin inhibitors (mavacamten) as a second-line therapy when BBs, CCBs, and/or disopyramide are poorly tolerated or ineffective [24]. Notably, for patients receiving combination therapy, reduction in utilization may be most impacted by earlier use of cardiac myosin inhibitors, which is being evaluated in the MAPLE-HCM trial, an ongoing randomized controlled trial assessing aficamten compared with metoprolol as first-line therapy for patients with oHCM.

This study provides real-world evidence on the HRU, and costs associated current standard of care pharmacotherapy in a large cohort of patients with symptomatic oHCM from a nationwide all-payer database. These findings highlight the need for novel treatments, such as cardiac myosin inhibitors, to reduce the economic burden of and need for combination therapy for patients with symptomatic oHCM. Considering the majority of patients with symptomatic oHCM in this study had Medicare healthcare coverage, future research is warranted to evaluate the economic impact of these emerging pharmacotherapies on the resource utilization and cost of care for patients with symptomatic oHCM.

5 Limitations

This study is subject to several limitations, which are common across claims database analyses. The diagnoses, comorbidities, HRU, and costs of patients with HCM were identified on the basis of ICD-10-CM diagnosis codes. The presence of a diagnosis code on a medical claim does not necessarily indicate a positive presence of disease because the medical record may have been incorrectly coded or included as a rule-out criterion rather than the actual disease. Also, diagnosis codes only signify the presence of the disease and do not detail the characteristics or the nature of the disease as you would find in electronic medical record data. This limitation was overcome by requiring eligible patients to have at least two claims with diagnosis codes for HCM. It was also ensured that generic codes, such as codes for "other cardiomyopathy" and "unspecified cardiomyopathy," which could be used for HCM, were not included in the identification of HCM patients for the study.

Diagnosis codes were used to identify patients with symptomatic oHCM, and a combination of symptoms, comorbidities, and procedures was used to identify symptomatic oHCM in this study. Since the claims database does not have a record of all symptoms of a patient, and some of the symptoms could be attributed to comorbidities, there is the possibility of difference in actual proportion of patients with symptomatic oHCM and the estimates in this study. The Symphony IDV database does not include death status, patient demographic data such as race/ethnicity, socioeconomic status, annual household income, rural versus urban geography, education level, and other socioeconomic factors. Future research should focus on these social determinants of health and evaluate whether disparities in HRU and cost exist based on index treatment strategies in patients with HCM. Additionally, access to pharmacy data in the database was limited to HCM-related pharmacotherapies; thus, all-cause pharmacy includes the same medications as HCM-related, and evaluating additional pharmacotherapies [such as auriculoventricular (AV) nodal blocking agents] discussed in the most recent HCM guidelines was not possible. This analysis was not adjusted for any baseline or patient characteristics, and the results should be interpreted as such. Lastly, the definition of costs in this analysis was costs meaning the amount billed by the payer. This may not be reflective of what a patient pays for their cost of care, but what the charged amount is by payer in the US healthcare system.

6 Conclusion

In this large, US-based cohort of treatment-naïve patients with symptomatic oHCM, initial therapy was most commonly BB and CCB monotherapy, but a substantial minority received combination medical therapy. All-cause HRU and costs were high for most patients, but greater for those treated initially with combination therapy. These findings show significant differences exist for HCM-related HRU (outpatient visits, UC visits, and pharmacy) and costs (total cost, outpatient costs, ER cost, and pharmacy cost), describing the economic burden endured by patients as a result of their HCM. Further research is needed to understand the impact of emerging pharmacotherapies on the cost of care for patients with symptomatic oHCM.

Declarations

Disclosures M. Butzner and S. Shreay are full-time employees and hold stock of Cytokinetics Incorporated. E. Papademetriou, R. Potluri, and X. Liu have no disclosures to report.

Statement of Authorship This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Author Contributions M. Butzner: conceptualization, methodology, investigation, supervision, validation, visualization, project administration, writing—original draft preparation, and reviewing and editing. E. Papademetriou and X. Liu: conceptualization, methodology, data curation, data analysis, validation, visualization, and writing—reviewing and editing. R. Potluri: investigation, data curation, data analysis, project administration, and writing—reviewing and editing. Sanatan Shreay: conceptualization, methodology, investigation, validation, and writing—reviewing and editing.

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Conflict of Interest M. Butzner and S. Shreay are full-time employees and hold stock of Cytokinetics Incorporated. E. Papademetriou, R. Potluri, and X. Liu are employees of Putnam Associates, which was contracted to perform the analyses.

Data Availability Statement All data generated or analyzed during this study are included in this published article.

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Code Availability Not applicable.

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References

1. Elliott PM, Anastasakis A, Authors/Task Force members, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733–79. https://doi.org/10.1093/eurheartj/ehu284.
2. Butzner M, Maron M, Sarocco P, et al. Clinical diagnosis of hypertrophic cardiomyopathy over time in the United States (A Population-Based Claims Analysis). Am J Cardiol. 2021;159:107–12. https://doi.org/10.1016/j.amjcard.2021.08.024.
3. Lu DY, Pozios I, Haileselassie B, et al. Clinical outcomes in patients with nonobstructive, labile, and obstructive hypertrophic cardiomyopathy. J Am Heart Assoc. 2018;7(5): e006657. https://doi.org/10.1161/JAHA.117.006657.
4. Jain SS, Li SS, Xie J, et al. Clinical and economic burden of obstructive hypertrophic cardiomyopathy in the United States. J Med Econ. 2021;24(1):1115–23. https://doi.org/10.1080/13696998.2021.1978242.
5. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2020 Dec 22;142(25):e633]. Circulation. 2020;142(25):e558–631. https://doi.org/10.1161/CIR.0000000000000937.
6. Nistri S, Olivotto I, Maron MS, et al. β Blockers for prevention of exercise-induced left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2012;110(5):715–9. https://doi.org/10.1016/j.amjcard.2012.04.051.
7. Butzner M, Sarocco P, Maron MS, et al. Characteristics of patients with obstructive hypertrophic cardiomyopathy in real-world community-based cardiovascular practices. Am J Cardiol. 2022;174:120–5. https://doi.org/10.1016/j.amjcard.2022.03.023.
8. Butzner M, Rowin E, Yakubu A, et al. Clinical characteristics and healthcare resource utilization among patients with obstructive hypertrophic cardiomyopathy treated in a range of settings in the United States. J Clin Med. 2022;11(13):3898. https://doi.org/10.3390/jcm11133898.
9. Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet. 2020 Sep 12;396(10253):758]. Lancet. 2020;396(10253):759–69. https://doi.org/10.1016/S0140-6736(20)31792-X.
10. Maron MS, Masri A, Choudhury L, et al. Phase 2 Study of Aficamten in Patients With Obstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2023;81(1):34–45. https://doi.org/10.1016/j.jacc.2022.10.020.
11. CY 6031 Study Will Evaluate the Effects of Treatment With Aficamten (CK-3773274) Over a 24-week Period on Cardiopulmonary Exercise Capacity and Health Status in Patients With Symptomatic oHCM (SEQUOIA-HCM)
12. Cytokinetics. Cytokinetics Announces Positive Results From SEQUOIA-HCM, the Pivotal Phase 3 Clinical Trial of Aficamten in Patients With Obstructive Hypertrophic Cardiomyopathy. December 27, 2023, https://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-announces-positive-results-sequoia-hcm-pivotal. Accessed 18 Jan 2024
13. Butzner M, Maron MS, Sarocco P, et al. Healthcare resource utilization and cost of obstructive hypertrophic cardiomyopathy in a US population. Am Heart J ournal Plus Cardiol Res Pract. 2022;13: 100089. https://doi.org/10.1016/j.ahjo.2022.100089.
14. Butzner M, Maron MS, Sarocco P, et al. Costs and healthcare resource utilization for obstructive hypertrophic cardiomyopathy with septal reduction therapy. J Invasive Cardiol. 2022;34(12):E866–72.
15. Owens AT, Sutton MB, Gao W, et al. Treatment changes, healthcare resource utilization, and costs among patients with symptomatic obstructive hypertrophic cardiomyopathy: a claims database study. Cardiol Ther. 2022;11(2):249–67. https://doi.org/10.1007/s40119-022-00257-7.
16. Naidu SS, Sutton MB, Gao W, et al. Frequency and clinicoeconomic impact of delays to definitive diagnosis of obstructive hypertrophic cardiomyopathy in the United States. J Med Econ. 2023;26(1):682–90. https://doi.org/10.1080/13696998.2023.2208966.
17. Desai NR, Sutton MB, Xie J, et al. Clinical outcomes, resource utilization, and treatment over the disease course of symptomatic obstructive hypertrophic cardiomyopathy in the United States.

Am J Cardiol. 2023;192:16–23. https://doi.org/10.1016/j.amjcard.2022.12.030.
18. Marstrand P, Han L, Day SM, et al. Hypertrophic cardiomyopathy with left ventricular systolic dysfunction: insights from the SHaRe Registry. Circulation. 2020;141(17):1371–83. https://doi.org/10.1161/CIRCULATIONAHA.119.044366.
19. Hoss, et al. JACC. 2021;77:534.
20. Bytyçi I, Nistri S, Mörner S, Henein MY. Alcohol septal ablation versus septal myectomy treatment of obstructive hypertrophic cardiomyopathy: a systematic review and meta-analysis. J Clin Med. 2020;9(10):3062. https://doi.org/10.3390/jcm9103062.
21. Altibi AM, Elman M, Zhao Y, et al. Cardiovascular hospitalizations post septal myectomy for obstructive hypertrophic cardiomyopathy: a 3-year analysis of 5,101 patients. J Cardiac Fail. 2024;30(1):199–200. https://doi.org/10.1016/j.cardfail.2023.10.201.
22. Post T, Elman M, Kim M, et al. Standard of care medication patterns of use before and after septal myectomy in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2024;83(13_Supplement):552. https://doi.org/10.1016/S0735-1097(24)02542-7.
23. Ommen SR, Ho CY, Asif IM, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: a Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149(23):e1239–311. https://doi.org/10.1161/CIR.0000000000001250.
24. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 2023;44(37):3503–626. https://doi.org/10.1093/eurheartj/ehad194.