Sex differences in clinical outcomes for obstructive hypertrophic cardiomyopathy in the USA: a retrospective observational study of administrative claims data

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ABSTRACT

Objectives To evaluate sex differences in demographic and clinical characteristics, treatments and outcomes for patients with diagnosed obstructive hypertrophic cardiomyopathy (oHCM) in the USA.

Setting Retrospective observational study of administrative claims data from MarketScan Commercial Claims and Encounters Database from IBM Watson Health.

Participants Of the 28 million covered employees and family members in MarketScan, 9306 patients with oHCM were included in this analysis.

Main outcome measures oHCM-related outcomes included heart failure, atrial fibrillation, ventricular tachycardia/fibrillation, sudden cardiac death, septal myectomy, alcohol septal ablation (ASA) and heart transplant.

Results Among 9306 patients with oHCM, the majority were male (60.5%, p<0.001) and women were of comparable age to men (50±15 vs 49±15 years, p<0.001). Women were less likely to be prescribed beta blockers (42.7% vs 45.2%, p=0.017) and undergo an implantable cardioverter-defibrillator (1.7% vs 2.6%, p=0.005). Septal reduction therapy was performed slightly more frequently in women (ASA: 0.08% vs 0.05%, p=0.600; SM: 0.35% vs 0.18%, p=0.096), although not statistically significant. Women were less likely to have atrial fibrillation (6.7% vs 9.9%, p<0.001).

Conclusion Women were less likely to be prescribed beta blockers, ACE inhibitors, anticoagulants, undergo implantable cardioverter-defibrillator and have ventricular tachycardia/fibrillation. Men were more likely to have atrial fibrillation. Future research using large, clinical real-world data are warranted to understand the root cause of these potential treatment disparities in women with oHCM.

INTRODUCTION

Patients with hypertrophic cardiomyopathy (HCM) are characterised by inherited left ventricular hypertrophy unexplained by secondary causes.1,2 Patients with HCM are at risk for stroke, atrial fibrillation, ventricular tachycardia and sudden cardiac and heart failure (HF)-related death, which increase with obstruction HCM (oHCM).3,4 Previous studies of sex differences in single-centre HCM cohorts have shown that women are typically older than men at diagnosis and present with more severe symptoms, greater obstruction and advanced HF, worse survival and are at increased need for septal reduction therapy.5,6,9,10,11 These studies have also shown that women more frequently had hypertension,9,12 but there were no differences in survival between men and women.5,11 Real-world sex differences in outcomes for patients with oHCM among multiple care settings across the USA are unknown. Characterising a larger group of oHCM patients is important for understanding whether these health disparities in women including greater HF extend to a larger population in the USA. Therefore, we used a large, commercial
Table 1  Patient demographics and clinical characteristics

|                                | Total cohort | Female       | Male          | P value   |
|--------------------------------|--------------|--------------|---------------|-----------|
| No of patients, n (%)          | 9306         | 3680 (39.54) | 5626 (60.46)  | <0.001    |
| Age, continuous, mean±SD       | 49.21±14.56  | 50.02±14.51  | 48.67±14.61   | <0.001    |
| Geographic region, n (%)       |              |              |               | 0.001     |
| Northeast                      | 2349 (25.24) | 882 (23.97)  | 1467 (26.08)  | –         |
| North central                  | 1891 (20.32) | 738 (20.05)  | 1153 (20.49)  | –         |
| South                          | 3826 (41.11) | 1593 (43.29) | 2233 (39.69)  | –         |
| West                           | 1224 (13.15) | 456 (12.39)  | 768 (13.65)   | –         |
| Unknown                        | 16 (0.17)    | 11 (0.3)     | 5 (0.09)      | –         |
| Health plan type, n (%)        |              |              |               | <0.001    |
| Comprehensive                  | 292 (3.21)   | 136 (3.7)    | 156 (2.77)    | –         |
| Exclusive provider organisation| 48 (0.53)    | 13 (0.35)    | 35 (0.62)     | –         |
| Health maintenance organisation| 1003 (11.04) | 396 (10.76)  | 607 (10.79)   | –         |
| Point of service plan          | 817 (8.99)   | 317 (8.61)   | 500 (8.89)    | –         |
| Preferred provider organisation| 5184 (57.04)| 2106 (57.23)| 3078 (54.71)  | –         |
| Point of service plan with capitation| 93 (1.02) | 37 (1.01) | 56 (1.00) | – |
| Consumer driven health plan    | 878 (9.66)   | 317 (8.61)   | 561 (9.97)    | –         |
| High deductible health plan    | 774 (8.52)   | 255 (6.93)   | 519 (9.23)    | –         |
| Missing                        | 217 (2.39)   | –            | –             | –         |
| Diagnostic tests, n (%)        |              |              |               |           |
| 12-lead ECG                    | 2817 (30.27) | 1132 (30.76) | 1685 (29.95)  | 0.405     |
| Holter                         | 597 (6.42)   | 237 (6.44)   | 360 (6.40)    | 0.937     |
| Cardiac stress test            | 727 (7.81)   | 251 (6.82)   | 476 (8.46)    | 0.004     |
| Coronary angiography           | 84 (0.90)    | 34 (0.92)    | 50 (0.89)     | 0.861     |
| Any myocardial imaging         |              |              |               |           |
| Echocardiogram                 | 1938 (20.83) | 806 (21.9)   | 1132 (20.12)  | 0.039     |
| CT                             | 48 (0.52)    | 17 (0.46)    | 31 (0.55)     | 0.558     |
| MRI                            | 334 (3.59)   | 125 (3.40)   | 209 (3.71)    | 0.420     |
| Nuclear or positron emission tomography| 214 (2.30) | 83 (2.26) | 131 (2.33) | 0.818 |
| Any HCM genetic test           | 158 (1.70)   | 65 (1.77)    | 93 (1.65)     | 0.679     |
| Comorbidities of Interest, n (%)|              |              |               |           |
| Ventricular tachycardia/ventricular fibrillation| 680 (7.31) | 223 (6.06) | 457 (8.12) | 0.001 |
| Coronary artery disease        | 968 (10.40)  | 337 (9.16)   | 631 (11.22)   | 0.002     |
| Diabetes                       | 1337 (14.37) | 575 (15.63)  | 762 (13.54)   | 0.005     |
| Dyslipidaemia                  | 1943 (20.88) | 687 (18.67)  | 1256 (22.32)  | <0.001    |
| Hypertension                   | 3979 (42.76) | 1632 (44.35) | 2347 (41.72)  | 0.012     |
| Stroke                         | 144 (1.55)   | 69 (1.88)    | 75 (1.33)     | 0.038     |
| Concomitant medication, n (%)  |              |              |               |           |
| ACEi                           | 1057 (11.36) | 364 (9.89)   | 693 (12.32)   | 0.001     |
| ARB                            | 806 (8.66)   | 331 (9.00)   | 475 (8.44)    | 0.355     |
| Antihypertensics               | 668 (7.18)   | 241 (6.55)   | 427 (7.59)    | 0.058     |
| Anticoagulants                 | 756 (8.12)   | 254 (6.9)    | 502 (8.92)    | 0.001     |
| Beta blockers                  | 4114 (44.21) | 1571 (42.69) | 2543 (45.20)  | 0.017     |
| Calcium channel blockers       | 1736 (18.65) | 699 (18.99)  | 1037 (18.43)  | 0.496     |
| Surgical procedures, n (%)     |              |              |               |           |
| Coronary revascularisation     |              |              |               |           |

Continued
medical and pharmacy claims database to evaluate sex differences in demographic and clinical characteristics, treatments and outcomes for patients with oHCM.

**METHODS**

**Study design and data source**

This retrospective observational study queried the MarketScan Commercial Claims and Encounters Database from IBM Watson Health (MarketScan) to identify patients with ≥1 claim with an International Statistical Classification of Diseases, Tenth Revision, Clinical Modification diagnosis code (ICD-10) of oHCM (I42.1) from 2016 to 2018 (see online supplemental figure 1) for a flowchart of oHCM cohort attrition). These methods and database have been reported previously. All diagnostic and surgical procedures, drug therapies, comorbidities, and clinical outcomes were captured by the presence of at least 1 claim of corresponding ICD-10 or Healthcare Common Procedure Coding System/Current Procedural Terminology codes after the initial diagnosis claim of oHCM. HCM-related outcomes included HF, atrial fibrillation, ventricular tachycardia/fibrillation, sudden cardiac death, septal myectomy, alcohol septal ablation (ASA) and heart transplant. MarketScan contains deidentified, patient-specific data on reimbursed healthcare claims for employees, retirees, and their dependents of over 250 medium and large employers and health plans. These data include approximately 28 million covered employees and family members per year under private insurance plans; no Medicaid or Medicare data are included.

**Patient and public involvement**

Patients and the general public were not involved in the development of this study.

**Data elements and statistical analysis**

Descriptive statistics were performed on patient demographic and clinical characteristics, treatments and outcomes. Data were expressed as mean±SD for continuous variables and proportions for categorical variables. Student’s t-test was used to compare continuous patient characteristics (age) between men and women with diagnosed oHCM. χ² tests were used to compare categorical patient demographics, clinical characteristics including diagnostic tests, comorbidities, medication use and surgical procedures, and HCM-related clinical outcomes (HF, atrial fibrillation and sudden cardiac death) between men and women with diagnosed oHCM. Tests were two sided and p<0.05 was considered statistically significant. Missing data were reported as missing or unavailable when reporting this information. Statistical analyses were performed with SAS, V.9.4 (SAS Institute).

**RESULTS**

A total of 9306 patients with oHCM were included in the study (table 1), with men making up the majority of the

| | Total cohort | Female | Male | P value |
|---|-------------|--------|------|--------|
| Coronary artery bypass graft | 3 (0.03) | 1 (0.03) | 2 (0.04) | 0.826 |
| Percutaneous coronary intervention | 6 (0.06) | 2 (0.05) | 4 (0.07) | 0.756 |
| Mitral valve surgery | 1 (0.01) | 0 (0.00) | 1 (0.02) | 0.419 |
| Implantable pacemaker | 43 (0.46) | 19 (0.52) | 24 (0.43) | 0.533 |
| Implantable cardioverter defibrillator | 206 (2.21) | 62 (1.69) | 144 (2.56) | 0.005 |

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; HCM, hypertrophic cardiomyopathy.

Figure 1 Proportion of patients in age group by sex categorial age in cohort by sex. oHCM, obstructive hypertrophic cardiomyopathy.

Figure 2 Comparison of sex differences in oHCM clinical characteristics differences in clinical characteristics for patients with oHCM by sex. CAD, coronary artery disease; Echo, echocardiogram; oHCM, obstructive hypertrophic cardiomyopathy.
sample (5626 males, 60.5%, p<0.001). Women were of comparable age to men (50±15 vs 49±15 years, p<0.001) and more likely to be 55–64 years of age (51.1% vs 45.3%, p<0.001) (figure 1). Patients primarily lived in the South (41.1%) and were insured by a preferred provider organisation (57%). Women were more likely to have an echo-cardiogram (21.9% vs 20.1%, p=0.039) but less likely to undergo cardiac stress testing (6.8% vs 8.5%, p=0.004). Other diagnostic procedures occurred at low rates in the total cohort, with 12-lead ECG performed most frequently (30.3%); all other diagnostic tests occurred at rates under 8%.

As seen in figure 2, women were more likely to have hypertension (44.4% vs 41.7%, p=0.012), diabetes (15.6% vs 13.5%, p=0.005), and stroke (1.9% vs 1.3%, p=0.038) but less likely to have dyslipidaemia (18.7% vs 22.3%, p<0.001), and coronary artery disease (9.2% vs 11.2%, p=0.002). Compared with men, women were less likely to be prescribed beta blockers, ACEi, anticoagulants and ICD (figure 3). Women were less likely to undergo an implantable cardioverter-defibrillator (1.7% vs 2.6%, p=0.005) (figure 3). Women were less likely to have hypertension, diabetes, and stroke and less likely to have ventricular tachycardia/fibrillation and atrial fibrillation. In regard to treatment, women were less likely to be prescribed beta blockers, ACEi, anticoagulants and undergo implantable cardioverter-defibrillator. Men were more likely to have atrial fibrillation.

Contrary to a previous study that women on average were 6 years older than men at time of diagnosis, women in our cohort were of comparable age to men and were also more likely to be 55–64 years of age compared with men. However, we did not exclude patients with a diagnosis of oHCM prior to 2016 and the initial claim of oHCM diagnosis in this study period should not be considered the original date of oHCM diagnosis. Low rates of diagnostic procedures in our study could be a result of the short period of observation time in relation to a disease that has low mortality overall.

We gained new insights into sex differences in patients with oHCM, which reflect the inherent nature of using medical and pharmacy claims that represent a nationwide population across commercial insurance plans. The majority of patients in our cohort resided in the South and women with oHCM were more likely to live and outcomes in a nationwide US population over a 3-year time period, using an updated reporting system of ICD-10 diagnosis codes. Women were more likely to have hypertension, diabetes, and stroke and less likely to have ventricular tachycardia/fibrillation and atrial fibrillation. In regard to treatment, women were less likely to be prescribed beta blockers, ACEi, anticoagulants and undergo implantable cardioverter-defibrillator. Men were more likely to have atrial fibrillation.

DISCUSSION
Prior to this investigation, medical and pharmacy claims data have not been used to evaluate sex differences in oHCM treatment and risk of severe HCM-related events. Using a large, commercial insurance database, our results revealed numerous sex differences in oHCM treatment and outcomes in a nationwide US population over a 3-year period, using an updated reporting system of ICD-10 diagnosis codes. Women were more likely to have hypertension, diabetes, and stroke and less likely to have ventricular tachycardia/fibrillation and atrial fibrillation. In regard to treatment, women were less likely to be prescribed beta blockers, ACEi, anticoagulants and undergo implantable cardioverter-defibrillator. Men were more likely to have atrial fibrillation.
in the South. This difference in US region may suggest greater clinical identification of familial HCM in southern states; however, there has been no meaningful association between better detection and clinical identification of oHCM by US region. Additionally, we saw significantly lower rates of treatment in women, including treatment with beta blockers, ACEi, anticoagulants and implantable cardioverter-defibrillators. Despite the greater prevalence of diabetes in women, ACEi usage was lower in females may reflect a true disparity in treatment management. Women being under treated with beta blockers could be explained by the higher prevalence of coronary artery disease in males, resulting in greater beta blocker use rather than this being a true disparity in the treatment of women. The marginally lower use of implantable cardioverter-defibrillators may not be clinically meaningful as women were less likely to have ventricular tachycardia/fibrillation and, subsequently, presented with lower rates of sudden cardiac death. However, sex differences in placement of implantable cardioverter-defibrillators have been reported in other cardiovascular diseases. Previous investigations in patients with ischaemic and non-ischaemic cardiomyopathy have also shown that use of implantable cardioverter-defibrillators for primary prevention of sudden cardiac death was significantly lower in women. Further exploration of beta blocker and implantable cardioverter-defibrillator use in patients with oHCM is needed to validate these findings and to potentially understand the root cause of this disparity in female patients.

The limited use of contemporary treatments such as septal reduction therapy in this oHCM cohort (regardless of sex) raise the question of whether this nationwide population was well managed or did not have persistent severe symptoms despite drug therapy, requiring the need for surgery over this 3-year observational period. Additionally, capturing patients undergoing septal resection therapy could be associated with patient health insurance. A recent study evaluating sex differences in outcomes from septal resection therapy in oHCM used the National Inpatient Sample and captured the largest cohort of oHCM patients (N=11 701) with septal resection therapies to date. The National Inpatient Sample is an all-payer database and their population older than ours (late fifth decade to mid sixth decade). Patients in the National Inpatient Sample undergoing these procedures at older ages may be covered by Medicare or Medicaid and not commercial insurance. Nevertheless, by accessing a large, medical and pharmacy claims database, we were able to observe and validate previously reported sex differences in oHCM treatment and outcomes and reflect on new insights from a nationwide commercially insured population. In our data, women experienced lower use of contemporary treatment than previously observed. While the magnitude of these sex differences in most cases was not large, lower rates of treatments in women with oHCM may lead to worse clinical outcomes and be a missed opportunity to improve the health and quality of life of women through appropriate treatment. It is important to characterise sex differences of oHCM patients in the general US population in order to validate diagnostic and treatment strategies for patients with this disease. Future research should investigate the impact of oHCM on women and identify approaches for increasing awareness, educating the public, and providing recommendations to providers for treating women with oHCM.

There are several limitations of this analysis that are common in claims data. MarketScan includes only individuals with private insurance (no Medicaid or Medicare) and these results may not be generalisable to patients with other types of health insurance or who are uninsured. Additionally, this analysis did not account for continuing enrollment of patients and patients may have disenrolled during this study period which could result in lower diagnostic, surgical and drug treatment rates. Due to the inherent nature of claims, we were unable to collect deep level clinical data and distinguish between specific diagnostic characteristics that you would in electronic medical records. Finally, we chose to focus on ICD-10 diagnosis codes, which are more specific and generally can be considered a more precise reporting of clinically diagnosed oHCM than previous ICD versions; however, this limits our ability to capture data prior to 2016 which may have also resulted in lower diagnostic, surgical and drug treatment rates. Nevertheless, our analysis reflects a contemporary 3-year period, and a major strength of this study is the ability to provide the first data on sex differences in treatment and outcomes in a large, national sample of patients diagnosed with oHCM in the USA.

CONCLUSION

In this large commercially insured population of oHCM patients in the USA, women were less likely to be prescribed beta blockers, ACEi, anticoagulants, undergo implantable cardioverter-defibrillator and have ventricular tachycardia/fibrillation. Men were more likely to have atrial fibrillation. The results of this analysis may aid providers in the treatment of women with oHCM and future studies using large, clinical real-world evidence are warranted to understand the root cause of these potential treatment disparities in women with oHCM.

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