


# Migraine Patients With Cardiovascular Disease and Contraindications: An Analysis of Real-World Claims Data

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## Abstract

**Introduction:** Triptans, the most commonly prescribed acute treatments for migraine attacks are, per FDA labeling, contraindicated in cardiovascular (CV) disease patients and have warnings and precautions for those with CV risk factors. **Methods:** Headache specialists, cardiologists, and health economics and outcomes researchers convened to identify diagnostic codes for: (1) CV diseases contraindicating triptans based on FDA labeling; (2) conditions comprising “other significant underlying CV disease”; and (3) CV risk factors included as warnings and precautions for triptans. A retrospective, cross-sectional analysis of commercially insured adult US migraine patients in the 2017 Optum<sup>®</sup> Clinformatics<sup>®</sup> Data Mart (CDM) and the 2017 IBM<sup>®</sup> Watson Health MarketScan<sup>®</sup> Commercial Claims database was used to estimate the proportion of migraine patients with CV contraindications and warnings and precautions to triptans. **Results:** Of the 56,662 migraine patients analyzed from Optum CDM, 13.5% had  $\geq 1$  CV disease as specified in triptan labeling and an additional 8.5% had  $\geq 1$  “other CV disease” judged by the panel to constitute a “significant underlying CV disease” (total: 22.0% migraine patients). Of 176 724 migraine patients analyzed from MarketScan, 12.2% had  $\geq 1$  CV disease as specified in the labeling and an additional 8.0% had  $\geq 1$  “other significant underlying CV disease” (total: 20.2% of migraine patients). An additional 25.4% and 25.1% of migraine patients had  $\geq 2$  CV risk factors in Optum CDM and MarketScan. In total, 47.4% and 45.3% of migraine patients in both databases had a CV disease specified as a contraindication, an “other CV disease” endorsed as significant, or  $\geq 2$  CV risk factors identified as warnings and precautions to triptans. **Conclusions:** Analyses of more than 230,000 people with migraine showed that  $\geq 20\%$  of commercially insured US migraine patients have a CV condition that specifically contraindicates triptan treatment, and an additional 25% have  $\geq 2$  CV risk factors identified as warnings and precautions to triptans.

## Keywords

migraine, acute treatment, triptan, cardiovascular disease, risk factors

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## Introduction

Migraine is a chronic disease that is characterized by recurrent attacks of headache pain and associated neurological symptoms.<sup>1</sup> The incapacitating nature of migraine can lead to marked individual disability and can exert a substantial impact on many aspects of life, including social and emotional well-being, family, career, and finances.<sup>2–6</sup> For these reasons, migraine was identified as one of the leading causes of years lived with disability in the 2017 Global Burden of Diseases, Injuries, and Risk Factors Study.<sup>7</sup>

Acute treatments for migraine are taken at the time of a migraine attack, with the goals of rapidly treating pain

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and associated symptoms, restoring functional ability, and minimizing the need for repeat dosing or rescue medications.<sup>8,9</sup> Acute treatments for migraine include migraine-specific medications, such as triptans, ergots, gepants, and lasmiditan, and nonspecific medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioid analgesics.<sup>9,10</sup> The American Academy of Neurology<sup>8</sup> and the American Headache Society recommend triptans as first-line acute treatment for moderate or severe migraine attacks.<sup>9</sup> Triptans are the most commonly prescribed acute treatments for migraine.<sup>11-13</sup> A claims analysis of commercially insured patients in the United States from 2007 to 2013 revealed that 63% of patients who were prescribed any acute treatment for migraine had received a prescription for a triptan.<sup>11</sup> Population-based studies in the US, including the American Migraine Prevalence and Prevention (AMPP) and Chronic Migraine Epidemiology and Outcomes (CaMEO) studies, have shown that approximately 22% of people with migraine reported current use of a triptan to treat their migraine attacks.<sup>14,15</sup> Claims studies include only medically diagnosed migraine; lower rates of triptan use in population studies reflect the inclusion of people with migraine not being treated by health care professionals.

Triptans are selective serotonin (5-HT)<sub>1B/1D/1F</sub> receptor agonists.<sup>16</sup> Designed specifically to constrict cerebral blood vessels, their mechanism of action was initially attributed to vasoconstriction mediated by agonism of the 5-HT<sub>1B</sub> receptors on intracranial blood vessels.<sup>16</sup> However, triptan therapeutic efficacy is currently believed to be mediated, at least in part, by its agonism of 5-HT<sub>1F</sub> receptors located on sensory nerves of the trigeminal system, which innervate the face and oral and nasal cavities.<sup>16</sup> Nevertheless, triptans are vasoconstrictors and these effects may increase the risk of serious ischemic events in patients who have underlying cardiovascular (CV) diseases or risk factors for CV disease.<sup>17</sup> Indeed, migraine with aura is a significant and independent risk factor for ischemic stroke, and there is growing evidence of an association between migraine with aura and other CV disorders, including myocardial infarction, perioperative stroke, hypertension, venous thromboembolism, and atrial fibrillation.<sup>18-23</sup>

All triptans, as specified in the US Food and Drug Administration (FDA) labeling for the class, are contraindicated in patients with certain CV diseases (eg, coronary artery disease [CAD], coronary artery vasospasm, peripheral artery disease, stroke, uncontrolled hypertension, and ischemic bowel disease).<sup>24-30</sup> However, there are ambiguities and differences in the labeling of various triptans regarding certain CV contraindications. Some triptan labels include nonspecific language stating that the triptan is contraindicated in patients with “other significant underlying CV disease.”<sup>24,26,29</sup> The Warning and Precautions section of the labels advises an evaluation to identify underlying CV

disease in patients with multiple risk factors, but does not provide clear insights into the specific CV risk factors that are deemed to be relevant in this context.<sup>24-30</sup> Additionally, the lists of CV risk factors in the labels do not align with current clinical guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA).<sup>31</sup> Given the ambiguities and inconsistencies, it is difficult to estimate the proportion of people with migraine who have contraindications and precautions for triptan use. There are no clear published guidelines for interpreting and operationalizing the triptan labeling.

The objectives of this study were to operationalize the Contraindications and the Warnings and Precautions regarding CV diseases and CV risk factors in the triptan labels, and apply these operations to real-world insurance claims data to estimate the proportions of people with migraine who have contraindications and precautions for triptan use.

## Methods

### Data Sources

We conducted parallel analyses in 2 large administrative claims data sets to assess the consistency of results across 2 commercially insured populations. Data were extracted from the Optum<sup>®</sup> Clinformatics<sup>®</sup> Data Mart [CDM] (Eden Prairie, MN) and the IBM<sup>®</sup> Watson Health MarketScan<sup>®</sup> Commercial Claims and Encounters database (Somers, NY). Optum CDM contains administrative health claims data from members of a large national insurer in the United States. Administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and de-identified prior to inclusion in the database. For this study, data on commercially insured patients only were included. The MarketScan database contains cost, utilization, and clinical information associated with inpatient, outpatient, and prescription drug claims for employees and dependents covered by employer-sponsored private health insurance in the United States. All analyses were conducted in both databases.

### Study Sample

This was a retrospective cross-sectional analysis of administrative claims among commercially insured US patients with at least 1 inpatient or at least 2 outpatient medical claims with a migraine diagnosis (International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] code G43.XX) between January 1, 2017, and December 31, 2017. Patients were required to be aged 18 years or older on January 1, 2017, and have continuous 12-month medical and prescription benefits between January 1, 2017, and December 31, 2017.

## Identification and Operationalization of CV Disease

**Contraindications Specifically Listed in the Triptan Labels.** To address ambiguity in triptan labeling, we convened an expert panel composed of 5 neurologist-headache specialists, 1 family practitioner-headache specialist, 2 cardiologists, and 4 health economics and outcomes researchers to review the CV disease contraindications listed in triptan labels. The labels reviewed were those for almotriptan malate tablets,<sup>29</sup> naratriptan hydrochloride tablets,<sup>30</sup> frovatriptan succinate tablets,<sup>28</sup> sumatriptan succinate tablets,<sup>27</sup> rizatriptan benzoate tablets,<sup>26</sup> eletriptan hydrobromide tablets,<sup>25</sup> and zolmitriptan orally disintegrating tablets.<sup>24</sup> Upon careful review, the panel agreed on 5 broad categories of CV disease listed as contraindications in the triptan labels, which included ischemic heart disease, cerebrovascular disease, peripheral artery disease, uncontrolled hypertension, and gastrointestinal ischemia. Diseases included within each of these 5 broad CV disease groups were identified by ICD-10-CM codes on medical claims (Supplemental Table S1).

**“Other Significant Underlying CV Disease.”** Some of the triptan labels include nonspecific language stating that the triptan is contraindicated in patients with “other significant underlying CV disease.”<sup>24,26,29</sup> The cardiologist members of the expert panel generated a list of conditions that were not expressly listed in the triptan labels but were considered to be diseases that met the clinical definition of “other significant underlying CV disease.” This resulted in the identification of 4 additional conditions that potentially contraindicate triptans, including potentially life-threatening arrhythmias, structural heart disease, the presence of cardiac implants (eg, coronary grafts), and other serious cardiac conditions (eg, cardiac arrest). The panel reviewed ICD-10-CM codes by disease condition to identify relevant codes for the purpose of appropriately identifying these conditions. The conditions and their corresponding ICD-10-CM codes and criteria for claims identification are listed in Supplemental Table S2 in the supplementary data.

## Identification and Operationalization of CV Risk Factors

In addition to contraindications, the Warnings and Precautions in the triptan labels advise that “triptan-naive patients who have multiple CV risk factors (eg, increased age, diabetes, hypertension, smoking, obesity, and strong family history of CAD)” should have a CV evaluation performed prior to receiving the triptan.<sup>24-26,28-30</sup> One of the triptan labels (almotriptan malate) “strongly recommends that [almotriptan] not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors.”<sup>29</sup> The panel identified CV risk factors for evaluation in the

claims databases based on the following criteria: (1) generally accepted definition of CV risk per the ACC/AHA guidelines<sup>31</sup>; (2) generally available in claims data; and (3) consistent with the label caution regarding unrecognized CAD. Laboratory data (eg, fasting lipid profiles, fasting blood sugar, and blood pressure) and historical data on family history were unavailable in the claims databases. Accordingly, the identification of CV risk factors was limited to a non-laboratory-based set of criteria available in administrative claims data that could be specifically identified by diagnosis codes and medication fills. Based on these criteria, the panel identified the following 6 CV risk factors: hypertension, hyperlipidemia, diabetes mellitus, obesity, increased age, and smoking. The criteria and corresponding ICD-10-CM and medication codes used to identify these risk factors are provided in Supplemental Table S3 in the supplementary data.

Elixhauser comorbidity counts, the total of the numbers of comorbidity categories from an established set of 30 comorbidities,<sup>32</sup> were determined from ICD-10-CM codes.

## Statistical Analyses

The proportion of patients with migraine and CV disease and/or risk factors was estimated for 2017 in the Optum CDM and MarketScan commercial claims databases. Data were summarized using descriptive statistics. Sensitivity analysis was conducted for the definition of CV disease by including and excluding the criteria for essential hypertension, and for the definition of CV risk factors by varying the specific risk factors that were included as well as the number of risk factors required to identify a patient with CV risk (data not shown).

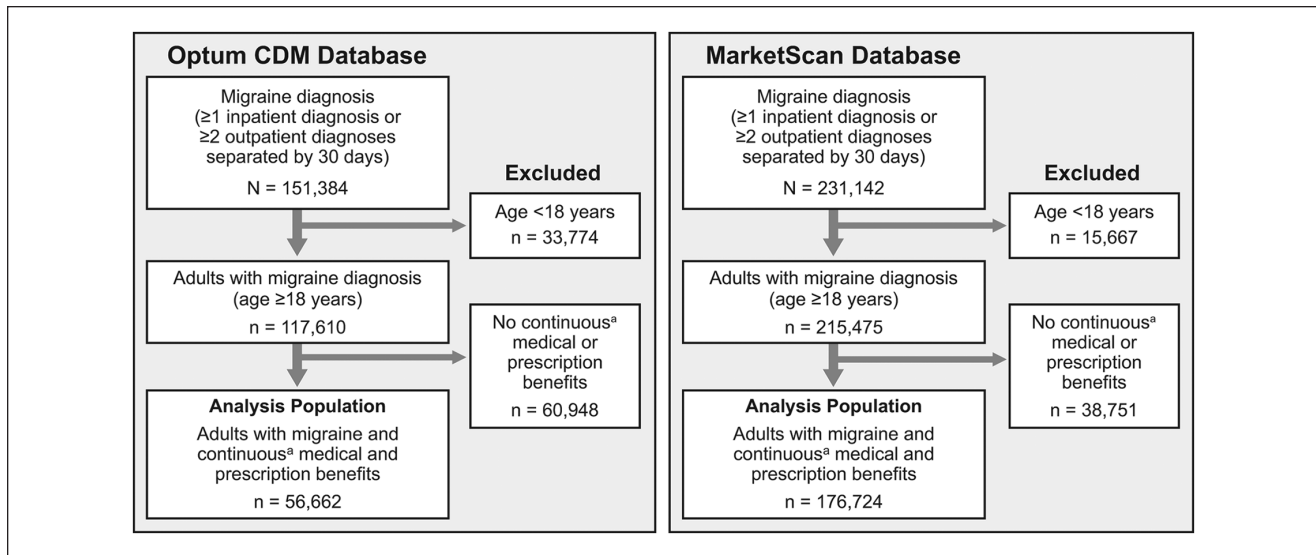
## Results

### Patient Characteristics

In the Optum CDM database, 151 384 migraine patients were identified in 2017. Of these, 56 662 were adults with continuous medical and prescription coverage for 12 months and were included in the analyses (Figure 1). In the MarketScan database, 231 142 migraine patients were identified in 2017, of whom 176 724 were adults with continuous medical and prescription coverage and were included in the analyses (Figure 1). Demographics and clinical characteristics are summarized by database in Table 1. Both populations were predominantly female, aged 35 to 64 years, and in both populations, approximately one fourth had received a diagnosis of chronic migraine.

### Prevalence of CV Disease

**Optum CDM Dataset.** Of the 56 662 migraine patients identified in the Optum CDM database, 13.5% had at least 1 CV



**Figure 1.** Sample selection.

Abbreviation: CDM, Clinformatics Data Mart.

<sup>a</sup>Continuous enrollment was defined as 12 months.

**Table 1.** Demographics and Clinical Characteristics of the Migraine Population.

	Optum CDM N= 56 662	MarketScan N= 176,724
Age group, years		
18–24	4843 (8.5)	16 806 (9.5)
25–34	10 004 (17.7)	28 474 (16.1)
35–44	15 500 (27.4)	46 320 (26.2)
45–64	26 315 (46.4)	85 124 (48.2)
Sex		
Female	47 731 (84.2)	150 256 (85.0)
Male	8 927 (15.8)	26 468 (15.0)
Insurance plan type		
Preferred provider organization	722 (1.3)	97 435 (55.1)
Point of service	42 845 (75.6)	14 287 (8.1)
Exclusive provider organization	6 445 (11.4)	34 886 (19.7)
Health maintenance organization	6 334 (11.2)	18 710 (10.6)
Other or unknown	316 (0.6)	11 406 (6.5)
Presence of chronic migraine diagnosis	14 203 (25.1)	47 669 (27.0)
Elixhauser comorbidity count		
0	12 974 (22.9)	43 100 (24.4)
1	14,359 (25.3)	47 288 (26.8)
2–3	17 968 (31.7)	57 004 (32.3)
4–5	7 273 (12.8)	20 328 (11.5)
≥6	4 088 (7.2)	9 004 (5.1)
Migraine-related comorbidities		
Mood disorder	16 974 (30.0)	46 609 (26.4)
Sleep disturbances	13 838 (24.4)	39 163 (22.2)
Rhinitis	10 744 (19.0)	31 614 (17.9)
Pain	6 640 (11.7)	17 173 (9.7)
Inflammatory bowel syndrome	3 443 (6.1)	8 853 (5.0)
Epilepsy	2 135 (3.8)	6 267 (3.5)

Abbreviations: CDM, Clinformatics Data Mart; CV, cardiovascular.  
All data are n (%).



**Table 2.** One-Year Rates of Cardiovascular Diseases Contraindicating Use of Triptans in Migraine Patients (2017 Data).

	Optum CDM N = 56 662	MarketScan N = 176 724
≥ 1 contraindication listed in triptan label	7653 (13.5)	21 495 (12.2)
Cerebrovascular/cardiovascular disease	3830 (6.8)	10 495 (5.9)
Ischemic cerebrovascular disease	3085 (5.4)	8482 (4.8)
Other cerebrovascular disease	1369 (2.4)	3683 (2.1)
Uncontrolled hypertension	2324 (4.1)	6154 (3.5)
Ischemic heart disease	2136 (3.8)	5751 (3.3)
Peripheral artery disease	1409 (2.5)	3885 (2.2)
Gastrointestinal ischemia	51 (0.1)	128 (0.1)
≥ 1 contraindication considered as “other significant cardiovascular disease” in triptan label	4833 (8.5)	14 180 (8.0%)
Structural heart disease	3113 (5.5)	8737 (4.9)
Arrhythmias	2582 (4.6)	7369 (4.2)
Cardiac surgery	484 (0.9)	1031 (0.6)
Other cardiac condition	4244 (7.5)	11 037 (6.2)
≥ 1 contraindication listed in triptan label or considered as “other significant cardiovascular disease” in triptan label	12 486 (22.0)	35 675 (20.2)

Abbreviations: CDM: Clinformatics Data Mart.

All data are n (%). Diagnosis codes included within each disease category are listed in Supplemental Tables S1 and S2 in the supplementary material.

disease specified as a contraindication in the triptan label (Table 2). The most common of these individual CV disease groups were cerebrovascular disease (6.8%), uncontrolled hypertension (4.1%), and ischemic heart disease (3.8%). An additional 8.5% of patients had at least 1 “other CV disease” endorsed as significant by the panel of experts (eg, structural heart disease [5.5%] and arrhythmias [4.6%]). Overall, 22.0% of migraine patients had at least 1 of these CV diseases listed as a contraindication or referenced as “other significant CV disease” in the triptan label. Rates of the specific CV diseases within each disease group are in Table 3.

**MarketScan Dataset.** Of the 176 724 patients with migraine identified in the MarketScan database, 12.2% had at least 1 CV disease specified as a contraindication in the triptan labels (eg, cerebrovascular disease [5.9%], uncontrolled hypertension [3.5%], and ischemic heart disease [3.3%]; Table 2). An additional 8.0% of patients had at least 1 “other CV disease” endorsed as significant by cardiologists (eg, structural heart disease [4.9%] and arrhythmias [4.2%]). Overall, 20.2% of migraine patients had at least 1 of these CV diseases listed as a contraindication or referenced as “other significant CV disease” in the triptan label. Rates of the specific CV diseases within each disease group are listed in Table 3.

### Prevalence of CV Risk Factors

**Optum CDM dataset.** Estimates of the prevalence of CV risk factors in the 2017 Optum CDM dataset are presented in Table 4. More than 20% of all migraine patients had

individual CV risk factors of hyperlipidemia (30.1%), hypertension (29.5%), and obesity (24.8%). Overall, 31.6% of migraine patients had at least 2 CV risk factors, 14.6% had at least 3 CV risk factors, and 5.3% had at least 4 CV risk factors. Among migraine patients without any claims-based evidence of a CV disease (n = 44,176), the rates of individual CV risk factors ranged from 6.5% for diabetes mellitus to 25.1% for hyperlipidemia (Table 4). In total, 25.4% of the patients without CV disease had at least 2 CV risk factors, 10.0% had at least 3 CV risk factors, and 3.1% had at least 4 CV risk factors.

**MarketScan dataset.** More than 20% of migraine patients in the 2017 MarketScan dataset had risk factors of hypertension (29.6%), hyperlipidemia (29.2%), and obesity (23.5%) (Table 4). Overall, 30.5% had at least 2 CV risk factors, 13.3% had at least 3 CV risk factors, and 4.3% of patients had at least 4 CV risk factors. Among patients without claims-based evidence of CV disease (n = 141 049), the rates of individual CV risk factors ranged from 6.6% for diabetes mellitus to 24.8% for hyperlipidemia (Table 4). In total, 25.1% of patients without CV disease had at least 2 CV risk factors, 9.6% had at least 3 CV risk factors, and 2.7% had at least 4 CV risk factors.

### Discussion

This retrospective analysis of 2 insurance claims databases estimated the prevalence of contraindications and warnings and precautions for the use of triptans. In the 2 independent samples, at least 12% had a contraindication to triptans specifically mentioned in the labeling, and an additional 8%

**Table 3.** One-Year Rates of Specific Cardiovascular Diseases in Patients With Migraine (2017 Data).

	Optum CDM N = 56 662	MarketScan N = 176 724
Contraindications specifically listed in triptan label <sup>a</sup>		
All cerebrovascular/cardiovascular diseases	3830 (6.8)	10 495 (5.9)
Ischemic cerebrovascular disease	3085 (5.4)	8482 (4.8)
Transient ischemic attack	2000 (3.5)	4800 (2.7)
Cerebral infarction	1287 (2.3)	3736 (2.1)
Cerebral occlusion	874 (1.5)	2634 (1.5)
Cerebral ischemia	178 (0.3)	519 (0.3)
Cerebrovascular syndrome	43 (0.1)	164 (0.1)
Other cerebrovascular disease	1369 (2.4)	3683 (2.1)
Sequelae of cerebrovascular disease	203 (0.4)	445 (0.3)
Intracerebral hemorrhage	50 (0.1)	102 (0.1)
Intracranial hemorrhage	50 (0.1)	106 (0.1)
Subarachnoid hemorrhage	30 (0.1)	71 (<0.1)
Other cerebrovascular disease	979 (1.7)	2908 (1.6)
Familial hypercholesterolemia	187 (0.3)	249 (0.1)
Wolff-Parkinson-White syndrome	46 (0.1)	128 (0.1)
Uncontrolled hypertension code	2324 (4.1)	6154 (3.5)
End organ hypertension	1317 (2.3)	3298 (1.9)
Uncontrolled essential hypertension	873 (1.5)	2517 (1.4)
Emergent hypertension	345 (0.6)	359 (0.2)
Secondary hypertension	218 (0.4)	711 (0.4)
Ischemic heart disease	2136 (3.8)	5751 (3.3)
Chronic ischemic heart disease	1408 (2.5)	3899 (2.2)
Angina pectoris	733 (1.3)	1933 (1.1)
Myocardial infarction	576 (1.0)	1171 (0.7)
Angioplasty or grafts for ischemic heart disease	395 (0.7)	560 (0.3)
Prinzmetal's angina	183 (0.3)	500 (0.3)
Acute ischemic heart disease	122 (0.2)	231 (0.1)
≥1 Peripheral artery disease	1409 (2.5)	3885 (2.2)
Peripheral atherosclerosis native vessels	429 (0.8)	1072 (0.6)
Atherosclerosis	102 (0.2)	250 (0.1)
Diabetic peripheral artery disease	82 (0.1)	185 (0.1)
Angioplasty or grafts for peripheral artery disease	26 (<0.1)	24 (<0.1)
Peripheral atherosclerosis graft	9 (<0.1)	10 (<0.1)
Other peripheral artery disease	973 (1.7)	2681 (1.5)
Other arterial disease	4 (<0.1)	8 (<0.1)
Gastrointestinal ischemia	51 (0.1)	128 (0.1)
Contraindications considered as "other significant cardiovascular disease" in triptan label <sup>a</sup>		
Structural heart disease	3113 (5.5)	8737 (4.9)
Valvular heart disease	2349 (4.1)	6687 (3.8)
Heart failure	609 (1.1)	1532 (0.9)
Congenital heart disease	581 (1.0)	1538 (0.9)
Hypertrophic cardiomyopathy	36 (0.1)	111 (0.1)
Arrhythmias	2582 (4.6)	7369 (4.2)
Other arrhythmia	1240 (2.2)	3572 (2.0)
Ventricular arrhythmia	805 (1.4)	2453 (1.4)
Atrial arrhythmia	709 (1.3)	1957 (1.1)
Channelopathy	202 (0.4)	418 (0.2)
Heart block	145 (0.3)	333 (0.2)
Cardiac surgery/implant	484 (0.9)	1031 (0.6)
Other cardiac condition	4244 (7.5)	11 037 (6.2)
Syncope	2939 (5.2)	8408 (4.8)
Personal history of embolism or sudden cardiac arrest	1001 (1.8)	1503 (0.9)
Abnormal result cardiac testing	272 (0.5)	814 (0.5)
Aneurysm	182 (0.3)	514 (0.3)
Embolic disease	103 (0.2)	215 (0.1)
Cardiac arrest	45 (0.1)	118 (0.1)
Family history of sudden cardiac death	28 (<0.1)	48 (<0.1)
Aortic dissection	26 (<0.1)	57 (<0.1)

Abbreviation: CDM, Clinformatics Data Mart.

<sup>a</sup>Category totals represent the proportion of people with at least 1 condition in the category and are not the sum of all subcategories. Some people may have more than 1 condition (ie, transient ischemic attack and cerebral infarction).

**Table 4.** One-Year Rates of Cardiovascular Risk Factors in Migraine Patients (2017 Data).

	Optum CDM	MarketScan		
	All N = 56,662	Without CV Disease <sup>a</sup> n = 44,176	All N = 176724	Without CV disease <sup>a</sup> n = 141049
<b>Cardiovascular risk factors</b>				
Hypertension	16742 (29.5)	10222 (23.1)	52231 (29.6)	33943 (24.1)
Hyperlipidemia	17076 (30.1)	11106 (25.1)	51544 (29.2)	34953 (24.8)
Diabetes mellitus	4926 (8.7)	2866 (6.5)	14959 (8.5)	9351 (6.6)
Obesity	14025 (24.8)	9966 (22.6)	41496 (23.5)	30788 (21.8)
Increased age <sup>b</sup>	5107 (9.0)	3131 (7.1)	17978 (10.2)	11830 (8.4)
Smoking	5236 (9.2)	3453 (7.8)	11722 (6.6)	8064 (5.7)
<b>No. of risk factors</b>				
≥ 1 risk factor	33253 (58.7)	23536 (53.3)	103385 (58.5)	75787 (53.7)
≥ 2 risk factors	17923 (31.6)	11214 (25.4)	53978 (30.5)	35366 (25.1)
≥ 3 risk factors	8263 (14.6)	4422 (10.0)	23580 (13.3)	13476 (9.6)
≥ 4 risk factors	3006 (5.3)	1353 (3.1)	7605 (4.3)	3753 (2.7)

Abbreviations: CDM, Clinformatics Data Mart; CV, cardiovascular.

All data are n (%).

<sup>a</sup>Patients without a CV disease specified as a contraindication in the triptan labels or referenced as “other significant CV disease” in the triptan labels.

<sup>b</sup>Men aged 55 years or older and women aged 60 years or older.

had an “other CV disease” classified as significant by an expert panel. In total, at least 20% of migraine patients had at least 1 of these CV contraindications. Rates of CV diseases in these commercially insured populations generally align with those reported in US population-based surveys of people with migraine.<sup>33,34</sup> An analysis of the 2009 AMPP Study data in respondents with episodic migraine (headache frequency of less than 15 days per month) found that 11.8% of respondents in the 40 to 59 year age group and 25.2% in the 60 years and older age group had a history of CV events, conditions, or procedures.

This study also shows that even among migraine patients without any claims-based evidence of CV disease as defined in triptan labels, approximately 25% had at least 2 CV risk factors. Our rates in all migraine patients are lower than those found in a 2009 population survey (the AMPP Study), which showed that 38.9% of women with episodic migraine and 41.6% of men with episodic migraine had at least 2 CV risk factors (among high cholesterol, hypertension, diabetes mellitus, obesity, and smoking).<sup>35</sup> The higher rate of CV risk factors in the AMPP Study may be partially attributable to the older age of the AMPP population (78% at least 40 years of age)<sup>33</sup> compared with the claims populations (46%–48% at least 45 years of age). Additionally, participants in the AMPP Study self-reported CV risk factors (eg, smoking, obesity),<sup>35</sup> which may be underreported in claims data. Nevertheless, our study still found that a substantial proportion of people with migraine have multiple CV risk factors.

The triptan labels<sup>24-30</sup> advise that a CV evaluation should be performed in triptan-naïve patients who have multiple CV risk factors (eg, increased age, diabetes

mellitus, hypertension, smoking, obesity, strong family history of CAD). The nature of the recommended CV evaluation is not specified. If the evaluation reveals evidence of CV disease or coronary artery vasospasm, the patient should not be treated with a triptan. For patients who have multiple CV risk factors but a negative CV evaluation, the triptan labels recommend that the health care provider should consider administering the first dose of the triptan in a medically supervised setting and performing an electrocardiogram (ECG) immediately following triptan administration. Depending upon the CV evaluation and the clinician’s confidence that the evaluation was adequate, an alternative is to refer the patient to a cardiologist for CV evaluation.

Acute treatment options are limited by FDA warnings for migraine patients with underlying CV disease or multiple CV risk factors. Historically, these patients have been limited to migraine nonspecific treatments, such as NSAIDs, non-opioid analgesics, acetaminophen, and caffeine analgesic combinations. However, all NSAIDs (eg, ibuprofen, diclofenac, and naproxen) carry an FDA boxed warning because of their association with increased risks of heart attack and stroke, if taken chronically.<sup>36</sup> An analysis of data from the CaMEO Study showed that respondents with both migraine and at least 1 CV comorbidity were 56% more likely than those without a CV comorbidity to be using an opioid to treat headache (odds ratio [OR], 1.56; 95% CI, 1.28-1.90).<sup>37</sup> These findings suggest that in the past, persons unable to take triptans were more likely to be treated with opioids, which authoritative guidelines and headache specialists recommend against for patients with migraine because of a lack of evidence

and the potential for medication overuse headache, as well as the potential for habituation, dependency, and addiction.<sup>38,39</sup> The recent availability of novel migraine-specific agents approved for the acute treatment of migraine, including gepants (ie, ubrogepant and rimegepant) and lasmiditan, could help to address the unmet needs of some of these patients.<sup>9</sup> Unlike triptans, gepants and lasmiditan are not vasoconstrictors and do not have CV contraindications and precautions in labeling.<sup>9,40-42</sup> Therefore, gepants and lasmiditan may fill a treatment gap in the substantial proportion of patients identified in the current study who should not take triptans.

Our data showed that approximately 84% to 85% of migraine patients were women, a result that aligns with epidemiological reports that the prevalence of migraine is two- to three-fold higher in women than in men.<sup>3,43</sup>

### Strengths and Limitations

This retrospective analysis of 2017 data from 2 comprehensive insurance claims databases allowed for the estimation of CV disease rates and CV risk factors in a large population of more than 230 000 patients with migraine overall. A sensitivity analysis of 2016 data in both databases yielded similar results, lending support to the consistency of the results over multiple years (data not shown). An additional strength of this study is that the criteria for clinically significant CV disease and CV risk factors were operationalized based on the consensus of an expert panel of headache specialists, a family practitioner, cardiologists, and health economics and outcomes researchers.

There are several limitations of our analysis. First, as with all retrospective claims analyses, administrative claims data are subject to coding errors, which may have resulted in misclassification of CV disease, CV risk factors, and/or study outcomes. Laboratory data (eg, fasting blood sugar, fasting lipid profile, or blood pressure values) were not available to confirm the presence of risk factors, although it is likely that the clinicians who assigned the diagnostic codes had access to this information. In addition, the prevalence of CV risk factors may be underestimated because of under-coding of some conditions in claims data, particularly smoking. Another limitation is that CV disease and CV risk factors were evaluated only over a 1-year time frame; as such, patients with CV disease or CV risk factors who had not consulted with their health care provider within the 1-year period were not included, potentially underestimating the true prevalence of CV disease and/or CV risk factors. However, results were similar in a separate analysis of MarketScan and Optum CDM claims from 2016 and a 2-year analysis of data from 2016 and 2017 (data not shown). Last, the sample was limited to patients with migraine enrolled in commercial insurance in the US; therefore, the results may not be generalizable to patients with

other types of insurance (eg, Medicare or Medicaid) or those without health insurance. Migraine is likely under-ascertained in these commercial databases. On the other hand, the sample is likely to be representative of migraine patients who carry a diagnosis and are eligible for prescription treatment.

### Conclusion

Real-world claims data indicate that at least 20% of commercially insured US patients with migraine have a CV condition that specifically contraindicates treatment with triptans, and that 25% of those without claims-based evidence of a CV condition have multiple risk factors identified as warnings and precautions for triptans. Clinicians should exercise caution in continuing to prescribe triptans to these patients. Although acute treatment options are limited for migraine patients with underlying CV disease or multiple CV risk factors, the recent approval of novel migraine-specific agents that are not contraindicated in patients with CV disease may help address the unmet acute treatment needs for these patients.

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## Supplemental Material

Supplemental material for this article is available online.

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