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Research Submission

Rates of Vascular Events in Patients With Migraine: A MarketScan® Database Retrospective Cohort Study

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Objective.—To estimate the baseline rates of vascular events among people with migraine.

Background.—Several novel medications that target the calcitonin gene-related peptide (CGRP) pathway are approved to treat people with migraine. Given that the CGRP pathway also plays a role in maintaining cardiovascular homeostasis, determining the baseline rates of vascular events among people with migraine will help inform the safety of these novel medications.

Methods.—In this retrospective cohort study, patients 18- to 64-year-old patients with migraine were identified from the MarketScan® database (January 2013-December 2017) and were categorized into 4 vascular risk categories: migraine with aura; and high, medium, and low vascular risk. Event rates (per 1000 person-years [PY]) for 19 vascular events were estimated overall, by risk category, and by baseline characteristics.

Results.—Among 1,195,696 patients with migraine, 4.8% (57,853/1,195,696) had migraine with aura, and 2.8% (33,949/1,195,696), 15.5% (184,782/1,195,696), and 77.9% (931,059/1,195,696) were at high, medium, and low risk of vascular events, respectively. Rates of ischemic stroke (per 1000 PY) were 5.1 (95% confidence interval [CI]: 5.0, 5.2) overall, 8.6 (95% CI: 8.1, 9.1) for patients with migraine aura, 47.2 (95% CI: 45.3, 49.0) in the high-risk group, 9.4 (95% CI: 9.1, 9.7) in the medium-risk group, and 2.9 (95% CI: 2.9, 3.0) in the low-risk group. Rates of acute myocardial infarction (per 1000 PY) were 1.8 (95% CI: 1.8, 1.9) overall, 1.9 (95% CI: 1.7, 2.2) for patients with migraine aura, 14.0 (95% CI: 13.0, 14.9) in the high-risk group, 3.9 (95% CI: 3.7, 4.1) in the medium-risk group, and 1.1 (95% CI: 1.0, 1.1) in the low-risk group. High-risk patients had the highest rates of each of 19 evaluated vascular events, and rates were higher for men, older age groups, and those with higher comorbidity scores, medication usage, and medical utilization.

Conclusion.—Our findings provide recent rates of vascular disease in patients with migraine. In the future, this information will be useful to help inform clinical risk:benefit decision making when assessing the use of therapies such as CGRP antagonists for migraine.

Key words: cardiovascular events, cerebrovascular events, headache, migraine, migraine aura, vascular events

Abbreviations: CGRP calcitonin gene-related peptide, CI confidence interval, IR incidence rate, PY person-years, SD standard deviation

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INTRODUCTION

There is growing evidence of an association between migraine and the risk of vascular events. The risk of hemorrhagic stroke, transient ischemic stroke, myocardial infarction, and unstable angina has been shown to be higher among people with migraine compared with those without migraine.[1] In addition, several systematic reviews and meta-analyses suggest that migraine with aura, which is experienced by approximately one-third of people with migraine,[2] may be a risk factor for ischemic stroke.[3-6] Associations between migraine and mortality due to cardiovascular and cerebrovascular events have also been observed.[7,8]

Although stroke and acute coronary events, especially in older patients, remain a concern for clinicians, few studies have examined the risk of other significant vascular events, such as venous thromboembolism, peripheral artery disease, and congestive heart failure, in patients with migraine. In addition, some drugs used to treat migraine, such as triptans, may have vascular effects and appear to be avoided where possible in patients with cardiovascular risk.[9,10] Furthermore, newer preventive medications have a role in the calcitonin gene-related peptide (CGRP) pathway which maintains cardiovascular homeostasis.[11] Understanding the baseline rates of vascular events will provide valuable information against which to compare the safety of established migraine medications (such as triptans), as well as the safety of novel medications that target the CGRP pathway.

We used data from a large US administrative claims database to descriptively provide more recent estimates of the burden of 19 vascular events among adults with migraine. The objective of our study was to estimate the rates of vascular events overall and in 4 different categories of patients with migraine, to give context to event rates observed with the real-world use of migraine medications.

METHODS

Study Design and Data Source.—In this retrospective cohort study, we identified a cohort of patients with migraine from the IBM MarketScan® Commercial Claims and Encounters database (date range: January 01, 2013 to December 31, 2017). The MarketScan® medical claims database represents the medical experience of insured employees and their dependents, early retirees, COBRA continues, and Medicare-eligible retirees with employer-sponsored Medical Supplemental plans. There are approximately 25 million annual patients in the database from 1996 to 2017. The underlying insured population from which the data are drawn was geographically diverse across the United States (47% – South, 18% – North, 17% – West, and 20% – North Central), 52% of plan participants were male, and 89% were enrolled in fee-for-service plans. The MarketScan® database contains fully adjudicated eligibility, pharmacy, procedure, and medical claims data for patients enrolled in large US health plans. These databases provide physician, hospital, and prescription drug services data and capture medical claims or encounter data from all available healthcare sites, including inpatient hospitals, outpatient hospitals, emergency rooms, physicians' offices, and surgery centers. The MarketScan® database is Health Insurance Portability and Accountability Act compliant, and all patient data are de-identified. Because identifying information cannot be linked back to the patients from whom the data were originally collected, the subsequent use of the data does not constitute human subject research requiring informed consent and does not require approval from an institutional review board.

This study is based on an analysis of automated medical and prescription claims, in individuals with a confirmed age and gender categorization. Because claims are collected for the purpose of payment, we assume that diagnoses and prescriptions reported in claims data are a true and accurate reflection of the health status and medication and health service usage for an individual. For the serious migraine and vascular diagnoses and related medication usage considered here, the presence of an associated claim was interpreted as indicating that the procedure was conducted, the disease was present, or the drug was consumed; the absence of a claim indicated the opposite. Consequently, there were no missing data.

Conflict of Interest: Karminder Gill, Victoria M. Chia, Rohini K. Hernandez, and Marco Navetta are employees and stockholders of Amgen Inc.
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Study Population.—The study sample was based on the available data in the MarketScan® claims database. Patients (18-64 years) were included in the migraine cohort if they met any of the following definitions during the study period: ≥1 migraine diagnosis claim for a "non-emergency" inpatient visit; ≥1 migraine diagnosis claim from an emergency room visit; ≥1 outpatient migraine diagnosis claim plus ≥1 acute migraine drug (triptan or ergot derivative) prescription claim within 180 days of each other; ≥2 outpatient migraine diagnoses between 7 and 180 days apart; or ≥2 acute migraine drug (triptan or ergot derivative) prescription claims between 7 and 180 days apart. The index date for inclusion in the cohort was the first date the patient met any of the migraine definitions. For definitions requiring 2 or more claims or 2 or more medication prescriptions, the index date was the first claims date or the first date for a prescription. In addition to meeting a migraine definition, patients were required to have 12 months of continuous medical and pharmacy eligibility prior to the index date for assessing medical history.

Patients with migraine were further categorized into 4 vascular risk categories (categories were not mutually exclusive) based on the presence of conditions prior to the index date: (1) migraine with aura (history of an aura diagnosis, irrespective of previous vascular events or risk factors for vascular events); (2) high risk of vascular events (history of any of the following 19 vascular events: ischemic stroke, hemorrhagic stroke, unspecified stroke, transient ischemic attack, subarachnoid hemorrhage, intracerebral hemorrhage, other acute cerebrovascular events, other ischemic cerebrovascular events, acute myocardial infarction, myocardial ischemia, congestive heart failure, acute ventricular tachycardia, acute atrial fibrillation, Prinzmetal angina, unstable angina pectoris, other and unspecified angina pectoris, coronary revascularization, peripheral artery disease, or venous thromboembolism); (3) medium risk of vascular events (history of hypertension, type I diabetes, type II diabetes, or hypercholesterolemia, but no history of the 19 previously specified vascular events); and (4) low risk of vascular events (no history of migraine aura, hypertension, diabetes, hypercholesterolemia, or any of the 19 previously specified vascular events). These categories were chosen because they had either clinical relevance to migraine (eg, migraine with aura) or are known risk factors for cardiovascular disease.

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to code baseline comorbidities and vascular outcomes from January 2013 to September 2015; ICD-10-CM codes were used from October 2015 to December 2017. To obtain equivalent ICD-10-CM codes for our study covariates, we used simple forward mapping from the ICD-9-CM definitions by referencing the 2017 General Equivalence Mappings. The ICD-9-CM and ICD-10-CM codes used to identify all vascular outcomes are presented in Supporting Table S1.

Outcome Assessments.—We evaluated each of the 19 vascular events during the follow-up period, overall, by vascular risk category, and by baseline patient characteristics. Person-time at risk was evaluated separately for each vascular outcome starting from the index date and ending at the date of the first occurrence of a vascular outcome of interest, death, termination of enrollment in the health plan submitting information to the MarketScan® database, or the administrative end of the study on December 31, 2017.

Covariates.—Patient characteristics were assessed during the baseline period and included demographics (gender and age [categories: 18-24, 25-34, 35-44, 45-54, 55-64]), use of acute migraine medications (analgesics, ergotamines, nonsteroidal anti-inflammatory drugs, opioids, and triptans), use of other medications of interest (antidepressants, antiepileptics, antihypertensives, anxiolytics, gastrointestinal medications, hormonal contraceptives, lipid-lowering agents, migraine-preventive treatments, and nonmigraine monoclonal antibodies), medical utilization (inpatient visits, emergency room visits, ambulatory visits), drug utilization (number of prescriptions), and medical history (anxiety, asthma, cancer [excluding nonmelanoma skin cancer], chronic kidney disease, constipation, Crohn's disease, depression, rheumatoid arthritis, and comorbidity score). Comorbidity score was based on the Deyo adaptation of the Charlson Comorbidity Index for administrative claims data.[12]

Statistical Analysis.—To examine patient characteristics overall and within vascular risk categories,

we used number (N) and percentages (%) to describe baseline patient characteristics such as nominal gender categories, dichotomous variables denoting the use of medications or presence of comorbidities, and ordinal variables such as categories of age, medical and drug utilization groupings, and comorbidity score groupings. Overall event rates as well as event rates stratified by vascular risk categories, demographic characteristics, medical history, and medication usage, were calculated as the number of incident events during the follow-up period divided by the total person-time at risk. All event rates, presented per 1000 person-years (PY), were estimated using a generalized linear model based on the Poisson distribution, and were unadjusted for any baseline patient characteristics.

We used propensity score analyses to match patients at medium risk of vascular events with those at low risk of vascular events. Alternative matching strategies, such as matching patients at high vascular risk to patients at low vascular risk, were not undertaken due to sample size considerations and low expected match rates between the sicker patients in the high vascular risk group and the relatively healthier patients in the low vascular risk group. The propensity scores were generated by a multivariable logistic regression model with group assignment as the dependent variable. The independent variables included in the propensity score model were demographics (age and gender), medication usage, medical and drug utilization metrics, and nonvascular medical history (anxiety, asthma, cancer [excluding nonmelanoma skin cancer], chronic kidney disease, constipation, depression, rheumatoid arthritis, and comorbidity score). Vascular events during the baseline period were excluded from the propensity score model because they are not relevant for migraine patients at medium or low risk of vascular events. Similarly, risk factors for vascular disease (diabetes, hypertension, and hyperlipidemia) were excluded from the propensity score model because they are only relevant for migraine patients who are at medium risk for vascular events. Caliper matching, in which patients from both study groups were ordered by their propensity score and randomly matched to individuals in the alternate study group, was employed for matching. The caliper, which specifies the maximum distance in the propensity score that should be used to create matched sets, was set to 0.01. We used a 1:1 matching ratio for these analyses. Ischemic stroke rates were then estimated in the matched migraine population. All analyses were conducted using SAS v9.2 (Cary, NC).

RESULTS

Patient Characteristics.—Out of 82,612,939 individuals enrolled in the MarketScan® claims database between January 01, 2013 and December 31, 2017, a total of 1,195,696 (1.4%) met the study criteria for inclusion in the migraine cohort. Of these, 57,853 (4.8%) had migraine with aura, 33,949 (2.8%) were at high risk of vascular events, 184,782 (15.5%) were at medium risk of vascular events, and 931,059 (77.9%) were at low risk of vascular events (Table 1). Overall, 82.5% of patients were female, and 17.7% were 55-64 years of age. Compared with other groups, patients at high risk of vascular events were more likely to be men (25.9% of the overall population), older (38.1% were at least 55 years old), sicker (51.2% with a comorbidity score of 1 or greater), and hospitalized (54.5% with at least 1 inpatient visit in the prior calendar year). In addition, 51.3% of patients at high risk of vascular events were hypertensive, 17.9% were diabetic, and 9.4% had a diagnosis of hyperlipidemia during the baseline period (data not presented). The characteristics of patients with migraine with aura were similar to patients at low risk of vascular events, but with a few notable differences: patients with migraine with aura were (1) more likely to be hospitalized (11.5% vs 7.4%) or visit emergency rooms (30.8% vs 14.5%); and (2) were sicker (comorbidity score >1 in 28.3% vs 19.6% of patients) (Table 1).

Ischemic Stroke Rates.—Overall, 11,175 patients experienced an ischemic stroke during the follow-up period (incidence rate [IR] = 5.1 [95% confidence interval [CI]: 5.0, 5.2] per 1000 PY; Table 2). Rates of ischemic stroke were 2.9 (95% CI: 2.9, 3.0) in the low-risk group, 9.4 (95% CI: 9.1, 9.7) in the medium-risk group, and 47.2 (95% CI: 45.3, 49.0) in the high-risk group. The rate of ischemic stroke for patients with migraine with aura was 8.6 (95% CI: 8.1, 9.1). Rates of ischemic stroke were higher in men (IR = 7.5 [95% CI: 7.2, 7.8]) than in women (IR = 4.7 [95% CI: 4.6, 4.8]) and increased with age, from 1.4 (95% CI: 1.2, 1.5) in the 18- to 24-year age group, 2.5 (95% CI: 2.3, 2.7) in the 25- to 34-year age group, 4.1 (95% CI: 3.9, 4.2) in the 35- to 44-year age

Table 1.—Baseline Characteristics of Patients With Migraine, Overall, and by Vascular Risk Categories†

Characteristic, n (%)	Overall (N = 1,195,696)	Migraine With Aura (N = 57,853)	High Vascular Risk (N = 33,949)	Medium Vascular Risk (N = 184,782)	Low Vascular Risk (N = 931,059)
Female	986,115 (82.5)	48,252 (83.4)	25,142 (74.1)	144,230 (78.1)	777,870 (83.5)
Age (years)					
18-24	139,843 (11.7)	6407 (11.1)	917 (2.7)	3321 (1.8)	129,415 (13.9)
25-34	218,127 (18.2)	11,454 (19.8)	2581 (7.6)	13,904 (7.5)	191,181 (20.5)
35-44	310,195 (25.9)	15,757 (27.2)	6372 (18.8)	40,222 (21.8)	250,537 (26.9)
45-54	315,657 (26.4)	14,813 (25.6)	11,139 (32.8)	64,961 (35.2)	228,883 (24.6)
55-64	211,874 (17.7)	9422 (16.3)	12,940 (38.1)	62,374 (33.8)	131,043 (14.1)
Acute migraine medications					
Analgesics	111,565 (9.3)	7343 (12.7)	4871 (14.3)	22,807 (12.3)	78,480 (8.4)
Ergots	5417 (0.5)	774 (1.3)	175 (0.5)	950 (0.5)	3693 (0.4)
Nonsteroidal anti-inflammatory drugs	341,372 (28.6)	16,364 (28.3)	11,394 (33.6)	67,702 (36.6)	249,990 (26.9)
Opioids	527,004 (44.1)	25,907 (44.8)	22,736 (67.0)	107,259 (58.0)	377,859 (40.6)
Triptans	354,965 (29.7)	15,149 (26.2)	6131 (18.1)	47,729 (25.8)	288,586 (31.0)
Other medications					
Antidepressants	434,712 (36.4)	20,270 (35.0)	15,813 (46.6)	83,600 (45.2)	319,452 (34.3)
Antiepileptics	298,552 (25.0)	17,177 (29.7)	14,252 (42.0)	61,152 (33.1)	209,764 (22.5)
Antihypertensives	321,253 (26.9)	15,647 (27.0)	18,899 (55.7)	127,754 (69.1)	165,743 (17.8)
Anxiolytics	334,771 (28.0)	16,239 (28.1)	14,370 (42.3)	69,261 (37.5)	238,928 (25.7)
Gastrointestinal medications	532,853 (44.6)	24,729 (42.7)	21,003 (61.9)	107,656 (58.3)	385,660 (41.4)
Hormonal contraceptives	228,910 (19.1)	9825 (17.0)	2338 (6.9)	15,927 (8.6)	201,400 (21.6)
Lipid-lowering agents	149,241 (12.5)	6438 (11.1)	12,399 (36.5)	62,096 (33.6)	71,716 (7.7)
Migraine-preventive treatments‡	560,241 (46.9)	27,440 (47.4)	22,568 (66.5)	122,371 (66.2)	394,140 (42.3)
Nonmigraine monoclonal antibodies	62,095 (5.2)	3120 (5.4)	3329 (9.8)	16,010 (8.7)	40,648 (4.4)
Medical utilization					
Inpatient visits					
0	1,073,598 (89.8)	51,189 (88.5)	15,450 (45.5)	153,939 (83.3)	862,141 (92.6)
1-2	100,238 (8.4)	5417 (9.4)	12,859 (37.9)	24,514 (13.3)	59,556 (6.4)
3+	21,860 (1.8)	1247 (2.2)	5640 (16.6)	6329 (3.4)	9362 (1.0)

Table 1.—(Continued)

Characteristic, n (%)	Overall (N = 1,195,696)	Migraine With Aura (N = 57,853)	High Vascular Risk (N = 33,949)	Medium Vascular Risk (N = 184,782)	Low Vascular Risk (N = 931,059)
Emergency room visits					
0	1,000,480 (83.7)	40,077 (69.3)	20,842 (61.4)	145,525 (78.8)	795,909 (85.5)
1-2	167,503 (14.0)	13,927 (24.1)	9958 (29.3)	32,517 (17.6)	118,439 (12.7)
3+	27,713 (2.3)	3849 (6.7)	3149 (9.3)	6740 (3.6)	16,711 (1.8)
Drug utilization					
Number of prescriptions					
0	178,458 (14.9)	13,520 (23.4)	5169 (15.2)	24,715 (13.4)	137,599 (14.8)
1-2	67,388 (5.6)	2612 (4.5)	591 (1.7)	2362 (1.3)	61,991 (6.7)
3+	949,850 (79.4)	41,721 (72.1)	28,189 (83.0)	157,705 (85.3)	731,469 (78.6)
Medical history					
Comorbidity score					
≤0	943,462 (78.9)	41,479 (71.7)	16,546 (48.7)	144,439 (78.2)	748,915 (80.4)
1	179,411 (15.0)	11,356 (19.6)	6184 (18.2)	23,329 (12.6)	140,590 (15.1)
2-3	60,016 (5.0)	4227 (7.3)	6964 (20.5)	13,426 (7.3)	36,868 (4.0)
4+	12,807 (1.1)	791 (1.4)	4255 (12.5)	3588 (1.9)	4686 (0.5)
Anxiety	119,604 (10.0)	7706 (13.3)	5860 (17.3)	25,080 (13.6)	83,781 (9.0)
Asthma	47,352 (4.0)	3578 (6.2)	3714 (10.9)	12,791 (6.9)	28,989 (3.1)
Cancer, excluding nonmelanoma skin cancer	22,663 (1.9)	1076 (1.9)	1985 (5.8)	6126 (3.3)	13,881 (1.5)
Chronic kidney disease	16,082 (1.3)	817 (1.4)	3333 (9.8)	7513 (4.1)	4989 (0.5)
Constipation	16,196 (1.4)	1399 (2.4)	1200 (3.5)	3789 (2.1)	10,549 (1.1)
Crohn's disease	5298 (0.4)	280 (0.5)	326 (1.0)	1043 (0.6)	3730 (0.4)
Depression	90,689 (7.6)	5052 (8.7)	4837 (14.2)	19,955 (10.8)	62,444 (6.7)
Rheumatoid arthritis	11,368 (1.0)	621 (1.1)	850 (2.5)	3339 (1.8)	6801 (0.7)

†The 4 vascular risk categories are not mutually exclusive.
‡Carisoprodol, cyproheptadine, guanfacine, memantine, methysergide, milnacipran, tizanidine.

Table 2.—Event Rates (Per 1000 Person-Years) for Selected Outcomes in Patients With Migraine, Overall, and by Vascular Risk Categories†

	Overall			Migraine With Aura			High Vascular Risk			Medium Vascular Risk			Low Vascular Risk		
Vascular Event	No. of Events	PYs at Risk	Rate (95% CI)	No. of Events	PYs at Risk	Rate (95% CI)	No. of Events	PYs at Risk	Rate (95% CI)	No. of Events	PYs at Risk	Rate (95% CI)	No. of Events	PYs at Risk	Rate (95% CI)
Cerebrovascular events															
Ischemic stroke	11,175	2,177,777	5.1 (5.0, 5.2)	994	115,553	8.6 (8.1, 9.1)	2603	55,209	47.2 (45.3, 49.0)	3113	331,667	9.4 (9.1, 9.7)	4982	1,698,849	2.9 (2.9, 3.0)
Hemorrhagic stroke	2181	2,190,500	1.0 (1.0, 1.0)	95	116,573	0.8 (0.7, 1.0)	467	58,094	8.0 (7.3, 8.8)	482	335,301	1.4 (1.3, 1.6)	1183	1,704,571	0.7 (0.7, 0.7)
Unspecified stroke	13,341	2,174,405	6.1 (6.0, 6.2)	1160	115,202	10.1 (9.5, 10.7)	3673	53,490	68.7 (66.5, 70.9)	3503	331,066	10.6 (10.2, 10.9)	5646	1,697,893	3.3 (3.2, 3.4)
Transient ischemic attack	10,292	2,177,482	4.7 (4.6, 4.8)	973	115,470	8.4 (7.9, 9.0)	2249	55,299	40.7 (39.0, 42.4)	2842	331,702	8.6 (8.3, 8.9)	4738	1,698,446	2.8 (2.7, 2.9)
Subarachnoid hemorrhage	1407	2,191,448	0.6 (0.6, 0.7)	64	116,582	0.6 (0.4, 0.7)	398	58,141	6.9 (6.2, 7.5)	300	335,489	0.9 (0.8, 1.0)	679	1,705,267	0.4 (0.4, 0.4)
Intracerebral hemorrhage	1772	2,191,108	0.8 (0.8, 0.9)	87	116,571	0.8 (0.6, 0.9)	466	58,076	8.0 (7.3, 8.8)	381	335,443	1.1 (1.0, 1.3)	881	1,705,054	0.5 (0.5, 0.6)
Other acute cerebrovascular	5573	2,184,277	2.6 (2.5, 2.6)	429	116,041	3.7 (3.4, 4.1)	1,689	55,994	30.2 (28.7, 31.6)	1419	333,673	4.3 (4.0, 4.5)	2312	1,702,261	1.4 (1.3, 1.4)
Other ischemic cerebrovascular	3080	2,189,643	1.4 (1.4, 1.5)	312	116,325	2.7 (2.4, 3.0)	843	57,726	14.6 (13.6, 15.6)	946	334,721	2.8 (2.7, 3.0)	1175	1,704,746	0.7 (0.7, 0.7)
Cardiovascular events															
Acute myocardial infarction	4011	2,188,322	1.8 (1.8, 1.9)	226	116,380	1.9 (1.7, 2.2)	807	57,777	14.0 (13.0, 14.9)	1296	334,302	3.9 (3.7, 4.1)	1813	1,703,780	1.1 (1.0, 1.1)
Myocardial ischemia	2397	2,189,981	1.1 (1.1, 1.1)	143	116,465	1.2 (1.0, 1.4)	997	57,229	17.4 (16.3, 18.5)	678	334,968	2.0 (1.9, 2.2)	678	1,705,246	0.4 (0.4, 0.4)
Congestive heart failure	9604	2,180,436	4.4 (4.3, 4.5)	542	115,915	4.7 (4.3, 5.1)	3627	53,571	67.7 (65.5, 69.9)	2915	332,110	8.8 (8.5, 9.1)	2878	1,702,397	1.7 (1.6, 1.8)
Acute ventricular tachycardia	2205	2,190,369	1.0 (1.0, 1.1)	123	116,510	1.1 (0.9, 1.2)	761	57,627	13.2 (12.3, 14.1)	500	335,206	1.5 (1.4, 1.6)	886	1,705,020	0.5 (0.5, 0.6)
Acute atrial fibrillation	8751	2,179,711	4.0 (3.9, 4.1)	504	115,887	4.4 (4.0, 4.7)	3841	52,237	73.5 (71.2, 75.9)	1859	333,251	5.6 (5.3, 5.8)	2876	1,701,909	1.7 (1.6, 1.8)
Prinzmetal angina	567	2,192,626	0.3 (0.2, 0.3)	58	116,575	0.5 (0.4, 0.6)	162	58,454	2.8 (2.3, 3.2)	130	335,725	0.4 (0.3, 0.5)	253	1,705,899	0.2 (0.1, 0.2)
Unstable angina pectoris	4546	2,187,203	2.1 (2.0, 2.1)	273	116,278	2.4 (2.1, 2.6)	1040	57,284	18.2 (17.1, 19.3)	1665	333,678	5.0 (4.8, 5.2)	1757	1,703,772	1.0 (1.0, 1.1)
Other and unspecified angina pectoris	5400	2,185,566	2.5 (2.4, 2.5)	395	116,063	3.4 (3.1, 3.7)	1023	57,201	17.9 (16.8, 19.0)	1957	333,049	5.9 (5.6, 6.1)	2261	1,702,978	1.3 (1.3, 1.4)

Table 2.— (Continued)

Vascular Event	Overall			Migraine With Aura			High Vascular Risk			Medium Vascular Risk			Low Vascular Risk		
	No. of Events	PYs at Risk	Rate (95% CI)	No. of Events	PYs at Risk	Rate (95% CI)	No. of Events	PYs at Risk	Rate (95% CI)	No. of Events	PYs at Risk	Rate (95% CI)	No. of Events	PYs at Risk	Rate (95% CI)
Coronary revascularization	2163	2,189,403	1.0 (1.0, 1.0)	117	116,433	1.0 (0.8, 1.2)	379	58,117	6.5 (5.9, 7.2)	615	334,824	1.8 (1.7, 2.0)	1101	1,704,010	0.7 (0.6, 0.7)
Peripheral artery disease	21,277	2,163,137	9.8 (9.7, 10.0)	1284	114,741	11.2 (10.6, 11.8)	3934	53,069	74.1 (71.8, 76.5)	7103	326,117	21.8 (21.3, 22.3)	9624	1,692,291	5.7 (5.6, 5.8)
Venous thromboembolism	9921	2,179,949	4.6 (4.5, 4.6)	640	115,769	5.5 (5.1, 6.0)	2237	55,604	40.2 (38.6, 41.9)	2347	332,893	7.1 (6.8, 7.3)	5030	1,699,282	3.0 (2.9, 3.0)

Rate is defined as the number of events divided by the number of PYs at risk.
†The 4 vascular risk categories are not mutually exclusive.
CI = confidence interval; PY = person-years.

group, and 6.1 (95% CI: 5.9, 6.3) in the 45- to 54-year age group, to 9.5 (95% CI: 9.2, 9.8) in the 55- to 64-year age group (Fig. 1A and Supporting Table S2). These patterns held true across all risk categories.

For medication usage, rates of ischemic stroke were highest among patients taking lipid-lowering agents (IR = 10.4 [95% CI: 10.0, 10.7]). For patients taking acute migraine medications, rates ranged from 1.8 (95% CI: 1.7, 1.9) for triptans to 6.3 (95% CI: 6.2, 6.5) for opioids (Supporting Table S2). High rates of ischemic stroke were also evident among patients with high medical utilization, that is, those with at least 3 inpatient visits (IR = 28.2 [95% CI: 26.5, 29.9]) or at least 3 emergency room visits (IR = 18.9 [95% CI: 17.6, 20.2]) during the baseline period. In addition, rates of ischemic stroke were higher among those with a comorbidity score of at least 4 (IR = 30.9 [95% CI: 28.6, 33.2]) than those with a comorbidity score of 0 or less (IR = 4.4 [95% CI: 4.3, 4.5]). When considering all comorbidities, the highest rates were among patients with chronic kidney disease (IR = 25.3 [95% CI: 23.4, 27.2]) (Supporting Table S2).

Acute Myocardial Infarction Rates.—The overall rate of acute myocardial infarction was 1.8 per 1000 PY (95% CI: 1.8, 1.9) (Table 2). Rates of acute myocardial infarction were 1.1 (95% CI: 1.0, 1.1) in the low vascular risk group, 3.9 (95% CI: 3.7, 4.1) in the medium vascular risk group, and 14.0 (95% CI: 13.0, 14.9) in the high vascular risk group. The rate for patients with migraine with aura was 1.9 (95% CI: 1.7, 2.2), which is similar to that in the overall migraine population. Rates of acute myocardial infarction were higher among men (IR = 3.5 [95% CI: 3.3, 3.7]) than in women (IR = 1.5 [95% CI: 1.4, 1.6]) and increased with age, from 0.3 (95% CI: 0.2, 0.4) in the 18- to 24-year age group to 4.3 (95% CI: 4.1, 4.5) in the 55- to 64-year age group (Fig. 1B and Supporting Table S3). Similar patterns were seen across all vascular risk categories.

As with ischemic stroke event rates, rates of acute myocardial infarction were highest among patients taking lipid-lowering agents (IR = 4.6 [95% CI: 4.3, 4.8]). For patients taking acute migraine medications, rates ranged from 1.1 (95% CI: 1.1, 1.2) for triptans to 2.5 (95% CI: 2.4, 2.6) for opioids (Supporting Table S3). Patients with high medication usage and high medical utilization had relatively high rates of acute myocardial

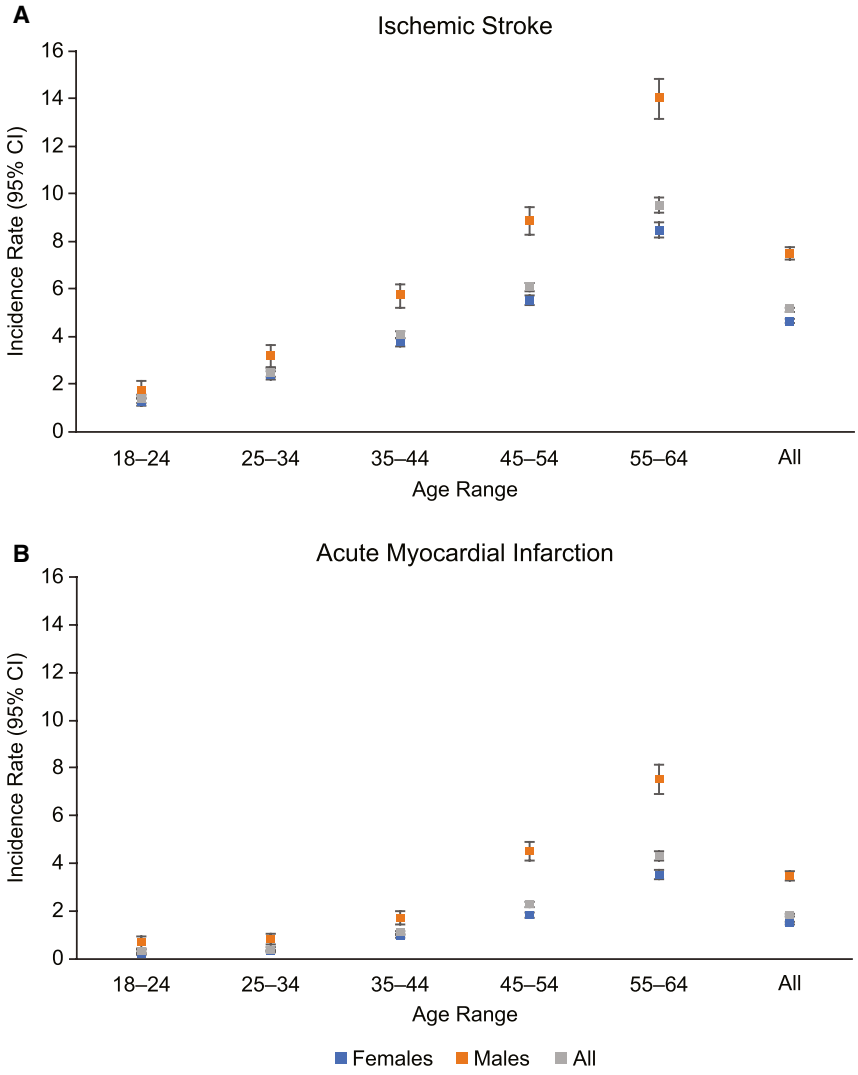

Fig. 1.—Incidence rates of (A) ischemic stroke and (B) acute myocardial infarction by gender and age group. CI = confidence interval.

infarction. Furthermore, patients with a comorbidity score of at least 4 had a higher rate of acute myocardial infarction (IR = 12.7 [95% CI: 11.3, 14.2]) than patients with a comorbidity score of 0 or less (IR = 1.5 [95% CI: 1.4, 1.6]) (Supporting Table S3).

Other Vascular Event Rates.—We evaluated the burden of 17 additional vascular events (Table 2). Overall rates of cerebrovascular events (per 1000 PY) ranged from 0.6 (95% CI: 0.6, 0.7) for subarachnoid hemorrhage to 6.1 (95% CI: 6.0, 6.2) for unspecified stroke, and overall rates of cardiovascular events ranged from 0.3 (95% CI: 0.2, 0.3) for Prinzmetal angina to 9.8 (95% CI: 9.7, 10.0) for peripheral artery disease.

Again, patients at high risk of vascular events had the highest rates of each cerebrovascular or cardiovascular event. Rates of hemorrhagic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage were lower among migraine patients with aura than patients at medium risk of vascular events, but rates for the remaining cerebrovascular events were similar between the 2 groups. In contrast, rates of each cardiovascular event, except for Prinzmetal angina, were lower among migraine patients with aura than patients at medium risk of vascular events (Table 2).

Similar to rates of ischemic stroke and acute myocardial infarction, rates of other vascular events

were higher for men compared with women and for older age groups compared with younger age groups (Supporting Table S4). For example, when comparing men and women in the oldest age group (55-64 years), respectively, the rates of cardiovascular events per 1000 PY (95% CI) were 15.6 (14.7, 16.5) and 9.6 (9.2, 9.9) for congestive heart failure, 30.8 (29.6, 32.1) and 22.6 (22.0, 23.1) for peripheral artery disease, 4.7 (4.2, 5.2) and 1.4 (1.2, 1.5) for coronary revascularization, and 9.3 (8.6, 9.9) and 6.3 (6.0, 6.6) for venous thromboembolism.

Matched Analyses.—In the overall migraine cohort, 184,782 patients were identified as having medium risk of vascular events and 931,059 were identified as having low risk of vascular events. Propensity score overlap before matching is shown in Figure 2A. A total of 148,588 patients in each group were successfully matched based on baseline demographic characteristics, medication usage, healthcare utilization, and medical history items. In matched patients, the standardized difference for all variables included in the propensity score model was less than 0.10 (Table 3), and there was a good overlap in the propensity score (Fig. 2B). The rate of ischemic stroke was 13.6 per 1000 PY (95% CI: 12.9, 14.2) in the medium-risk group and 7.4 per 1000 PY (95% CI: 7.0, 7.9) in the corresponding matched low-risk group (data not presented).

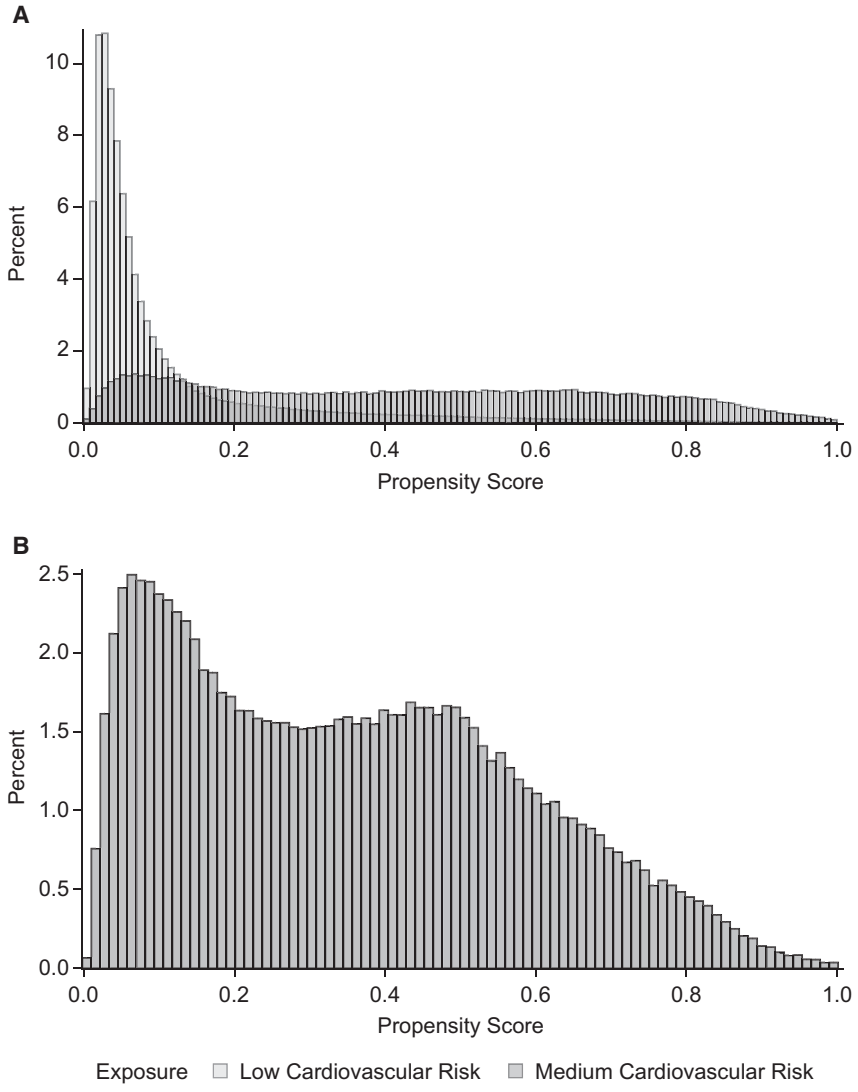

Fig. 2.—Propensity score* overlap before (A) and after (B) matching in patients with migraine at medium risk of cardiovascular events vs those at low risk of cardiovascular events. *The propensity score is the probability of group assignment, conditional on measured baseline covariates.

Table 3.—Distribution of Baseline Covariates Among Migraine Patients With Medium vs Low Vascular Risk, by Matching Status

Covariate	Before Propensity Score Matching			After Propensity Score Matching		
	Medium Vascular Risk Group (N = 184,782)	Low Vascular Risk Group (N = 931,059)	Standardized Difference	Medium Vascular Risk Group (N = 148,588)	Low Vascular Risk Group (N = 148,588)	Standardized Difference
Demographics, n (%)						
Gender						
Female	144,230 (78.1)	777,870 (83.6)	44.119 pt	118,316 (79.6)	118,784 (79.9)	−0.008
Male	40,552 (22.0)	153,189 (16.5)	0.14	30,272 (20.4)	29,804 (20.1)	0.008
Age (years)						
18-24	3321 (1.8)	129,415 (13.9)	−0.462	3215 (2.2)	5203 (3.5)	−0.081
25-34	13,904 (7.5)	191,181 (20.5)	−0.381	13,335 (9.0)	12,877 (8.7)	0.011
35-44	40,222 (21.8)	250,537 (26.9)	−0.120	36,613 (24.6)	31,362 (21.1)	0.084
45-54	64,961 (35.2)	228,883 (24.6)	0.233	52,800 (35.5)	50,779 (34.2)	0.029
55-64	62,374 (33.8)	131,043 (14.1)	0.474	42,625 (28.7)	48,367 (32.6)	−0.084
Time period						
2013	61,917 (33.5)	332,099 (35.7)	−0.045	51,684 (34.8)	53,103 (35.7)	−0.02
2014	43,023 (23.3)	210,389 (22.6)	0.016	34,380 (23.1)	34,610 (23.3)	−0.004
2015	29,726 (16.1)	141,637 (15.2)	0.024	23,089 (15.5)	22,282 (15.0)	0.015
2016	27,566 (14.9)	134,212 (14.4)	0.014	21,436 (14.4)	21,081 (14.2)	0.007
2017	22,550 (12.2)	112,722 (12.1)	0.003	17,999 (12.1)	17,512 (11.8)	0.010
Medication usage, n (%)						
Antihypertensives	128,783 (69.7)	162,107 (17.4)	1.241	93,140 (62.7)	94,159 (63.4)	−0.014
Gastrointestinal medications	106,843 (57.8)	382,470 (41.1)	0.340	81,011 (54.5)	80,751 (54.4)	0.004
Hormonal contraceptives	14,983 (8.1)	192,971 (20.7)	−0.365	14,137 (9.5)	13,833 (9.3)	0.007
Lipid-lowering agents	61,293 (33.2)	69,822 (7.5)	0.673	37,516 (25.3)	36,933 (24.9)	0.009
Nonsteroidal anti-inflammatory drugs	66,394 (35.9)	246,531 (26.5)	0.205	50,481 (34.0)	49,767 (33.5)	0.010
Nonmigraine monoclonal antibodies	15,979 (8.7)	40,534 (4.4)	0.175	11,261 (7.6)	11,490 (7.7)	−0.006
Opioids	106,897 (57.9)	376,832 (40.5)	0.353	80,880 (54.4)	80,530 (54.2)	0.005
Triptans	47,139 (25.5)	285,879 (30.7)	−0.116	41,281 (27.8)	42,412 (28.5)	−0.017
Medical utilization, mean (SD)						
Number of ambulatory visits	21.4 (18.4)	13.2 (14.3)	0.501	19.6 (16.3)	19.9 (20.7)	−0.016
Number of emergency room visits	0.4 (1.3)	0.2 (0.9)	0.153	0.4 (1.1)	0.4 (1.4)	0.006
Number of inpatient hospital stays	0.4 (1.8)	0.1 (1.0)	0.166	0.3 (1.5)	0.3 (2.1)	0.012

Table 3.—(Continued)

Covariate	Before Propensity Score Matching			After Propensity Score Matching		
	Medium Vascular Risk Group (N = 184,782)	Low Vascular Risk Group (N = 931,059)	Standardized Difference	Medium Vascular Risk Group (N = 148,588)	Low Vascular Risk Group (N = 148,588)	Standardized Difference
Drug utilization, mean (SD)						
Number of unique generic medications dispensed	10.7 (8.0)	6.5 (5.8)	0.602	9.7 (7.6)	9.7 (7.0)	0.012
Number of unique drug classes dispensed	9.6 (6.8)	6.0 (5.1)	0.605	8.7 (6.6)	8.7 (6.0)	−0.002
Number of outpatient pharmacy dispensings	36.1 (33.8)	19.0 (22.1)	0.599	32.1 (31.6)	31.8 (29.6)	0.008
Medical history, mean (SD)						
Comorbidity score	0.1 (1.2)	0.2 (0.7)	−0.168	0.1 (1.2)	0.2 (0.8)	−0.038
Anxiety	28,130 (15.2)	90,392 (9.7)	0.168	20,932 (14.1)	21,206 (14.3)	−0.005
Asthma	16,375 (8.9)	38,245 (4.1)	0.194	11,061 (7.4)	11,001 (7.4)	0.002
Chronic kidney disease	7590 (4.1)	5085 (0.6)	0.238	3788 (2.6)	3301 (2.2)	0.022
Cancer (excluding nonmelanoma skin cancer)	6528 (3.5)	14,840 (1.6)	0.123	4513 (3.0)	4719 (3.2)	−0.008
Constipation	5065 (2.7)	13,296 (1.4)	0.092	3590 (2.4)	3630 (2.4)	−0.002
Depression	20,653 (11.2)	64,199 (6.9)	0.150	15,303 (10.3)	15,562 (10.5)	−0.006
Rheumatoid arthritis	3354 (1.8)	6840 (0.7)	0.096	2261 (1.5)	2286 (1.5)	−0.001

SD = standard deviation.

DISCUSSION

In this study, 1,195,696 adult patients with migraine enrolled in the MarketScan® database were followed for more than 2 million PY for the occurrence of 19 vascular events. This real-world assessment of vascular events in insured patients with migraine provides a baseline risk assessment against which the risks of newer agents, such as inhibitors of the CGRP pathway, can be compared in future analyses. The highest rates for all vascular outcomes were observed among patients identified as being at high risk of vascular events during the baseline period. Rates of vascular events also increased with age and were higher for men than for women.

In the overall US population, the IR of acute myocardial infarction was ~2.5 per 1000 PY[13] and the IR of ischemic stroke was ~1.6 per 1000 PY.[14] In contrast, the IR of acute myocardial infarction observed in this large, diverse migraine population was 1.8 per 1000 PY. Previous studies in more narrowly defined migraine populations receiving prophylactic treatment showed lower rates of acute myocardial infarction. In a study that matched people with migraine to people without migraine, the estimated overall myocardial infarction rate was 1.45 per 1000 PY in patients with migraine, with rates ranging from 1.2 per 1000 PY for current users of triptan medications to 2.2 per 1000 PY for current users of ergot alkaloids.[15] In a more recent propensity-score matched analysis of people who initiated topiramate vs other prophylactic migraine medications, the myocardial infarction rates ranged from 0.8 per 1000 PY to 1.1 per 1000 PY, depending on the matched comparator. Myocardial infarction rates in patients initiating other preventive migraine medications were higher: antidepressants (1.4 per 1000 PY); anticonvulsants (1.4 per 1000 PY); cardiovascular treatments (1.8 per 1000 PY); and other prophylactic treatments (2.0 per 1000 PY).[16] Likewise, we observed a higher overall ischemic stroke rate (5.1 per 1000 PY) in our broad migraine population when compared with previous findings in more restricted migraine populations.[15,16]

Differences in rates may also be explained by changes in coding over time. Although we used the 2017 General Equivalence Mappings to map ICD-9-CM definitions to ICD-10-CM definitions, an approach that has demonstrated good performance for 3 cardiovascular outcomes (ischemic stroke, acute myocardial infarction, and angioedema),[17,18] more specific identification of outcomes in the ICD-10-CM era may result in differences in detection rates when compared with the ICD-9-CM era.

Migraine with aura compared with migraine without aura has been shown to be associated with an increased risk of ischemic stroke,[3,5,6,19] although the literature is inconsistent. The IR of ischemic stroke was higher in migraine patients with aura than the overall migraine population (8.6 vs 5.1 per 1000 PY, respectively). In contrast, we found that the IR of acute myocardial infarction in migraine patients with aura was similar to the rate in the overall migraine population (1.8 vs 1.9 per 1000 PY, respectively). For events overall, migraine patients with aura had a vascular disease burden similar to those at medium risk of cerebrovascular events, but a lower disease burden for selected cardiovascular events (including acute myocardial infarction, congestive heart failure, unstable angina pectoris, and peripheral artery disease). These findings are likely partially explained by the fact that the migraine aura group comprised all patients diagnosed with aura, including those with a history of vascular events or a history of risk factors for vascular events.

Prior to propensity score matching, the ischemic stroke rate was 9.4 per 1000 PY in migraine patients at medium risk of vascular events and 2.9 per 1000 PY in those at low risk of vascular events. After matching based on baseline demographic characteristics, medication usage, healthcare utilization, and medical history, the ischemic stroke rate was 13.6 per 1000 PY and 7.4 per 1000 PY in the matched medium-risk and low-risk vascular groups, respectively. Except for diagnoses of diabetes, hypertension, and hypercholesterolemia, baseline characteristics were well balanced between the medium and low vascular risk groups. As in the general population, migraine patients with risk factors for vascular disease (ie, diabetes, hypertension, and hypercholesterolemia) experience higher ischemic stroke rates when compared with migraine patients with no risk factors for vascular disease but who are otherwise similar with respect to baseline characteristics.[20,21]

This study has important limitations. First, we used the MarketScan® Commercial Claims and Encounters database for these analyses because most migraine patients are younger than 65 years. The

drawback of using a claims database for the study of migraine is that individuals who are uninsured, institutionalized, 65 years of age or older, or covered by Medicaid insurance are under-represented in claims data. Second, a previously validated algorithm used to identify migraine patients in administrative claims data had a relatively high specificity but low sensitivity, meaning that a high proportion of people with migraine was missed.[22] Assuming our migraine algorithm has similar performance statistics, the population analyzed in our study most likely represented patients seeking medical care for their headache and may not have included those who did not receive medications or diagnostic coding for migraine during their medical visit. Indeed, the medically insured population in this study is likely skewed toward individuals with migraine of sufficient severity to warrant medical intervention, but this is the most relevant population for physicians who are deciding to treat patients with novel medications such as monoclonal antibodies that target the CGRP pathway. Also, importantly, it is unknown whether the severity of migraine symptoms prompting more healthcare utilization would be expected to have any impact on cardiovascular risk. Third, our population had a higher percentage of females (82.5%) than reported for populations in large epidemiological studies of migraine (74.4-79.9%),[23] which may have had an effect on the baseline rate of ischemic stroke and myocardial infarction in our study. Fourth, we used a broad categorization for medications of interest (eg, the nonsteroidal anti-inflammatory drug category included medications with and without antiplatelet characteristics), which prevented us from evaluating the potential effects of other groupings on vascular event rates. Fifth, we note that the results presented here are descriptive only, and are not intended for causal interpretation. Finally, we employed an intention-to-treat approach when estimating event rates, such that patients remained in the same vascular risk category assigned on the index date during the entirety of their follow-up. An alternative approach, the per-protocol analysis, would have censored individuals when they moved to a higher vascular risk category. The impact of using the intention-to-treat approach to estimate event rates is likely small, with rates slightly higher in the medium and low vascular risk categories than those that would have occurred with the per-protocol approach.

CONCLUSION

In summary, our data provide updated evidence of the burden of vascular disease in patients with migraine, overall, by risk categories, and by baseline demographic and clinical characteristics. Understanding the baseline rates of cardiovascular and cerebrovascular events is particularly important among patients with migraine, as comorbid conditions and polypharmacy are common in this population. These baseline rates can help contextualize postmarketing data that arise after new classes of medications for the treatment of migraine are initiated in this population. In particular, our findings may be used to inform future assessments of the clinical risk:benefit of using newer therapies for migraine such as CGRP antagonists.

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Data Availability Statement*: Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.*

REFERENCES

1. Sacco S, Kurth T. Migraine and the risk for stroke and cardiovascular disease. *Curr Cardiol Rep*. 2014;16:524.
2. Goadsby PJ, Lipton RB, Ferrari MD. Migraine – Current understanding and treatment. *N Engl J Med*. 2002;346:257-270.
3. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: Systematic review and meta-analysis of observational studies. *BMJ*. 2005;330:63.
4. Hu X, Zhou Y, Zhao H, Peng C. Migraine and the risk of stroke: An updated meta-analysis of prospective cohort studies. *Neurol Sci*. 2017;38:33-40.
5. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: Systematic review and meta-analysis. *BMJ*. 2009;339:b3914.
6. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S. Migraine headache and ischemic stroke risk: An updated meta-analysis. *Am J Med*. 2010;123:612-624.
7. Schürks M, Rist PM, Shapiro RE, Kurth T. Migraine and mortality: A systematic review and meta-analysis. *Cephalalgia*. 2011;31:1301-1314.
8. Gudmundsson LS, Scher AI, Aspelund T, et al. Migraine with aura and risk of cardiovascular and all cause mortality in men and women: Prospective cohort study. *BMJ*. 2010;341:c3966.
9. Bigal ME, Golden W, Buse D, Chen YT, Lipton RB. Triptan use as a function of cardiovascular risk. A population-based study. *Headache*. 2010;50:256-263.
10. Roberto G, Raschi E, Piccinni C, et al. Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: Systematic review of observational studies. *Cephalalgia*. 2015;35:118-131.
11. MaassenVanDenBrink A, Meijer J, Villalon CM, Ferrari MD. Wiping out CGRP: Potential cardiovascular risks. *Trends Pharmacol Sci*. 2016;37:779-788.
12. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613-619.
13. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155-2165.
14. G. B. D. Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:459-480.
15. Velentgas P, Cole JA, Mo J, Sikes CR, Walker AM. Severe vascular events in migraine patients. *Headache*. 2004;44:642-651.
16. Hoffman V, Xue F, Ezzy SM, et al. Risk of cardiovascular and cerebrovascular events and mortality in patients with migraine receiving prophylactic treatments: An observational cohort study. *Cephalalgia*. 2019;39:1544-1559.
17. Panozzo CA, Welch EC, Woodworth TS, et al. Assessing the impact of the new ICD-10-CM coding system on pharmacoepidemiologic studies – An application to the known association between angiotensin-converting enzyme inhibitors and angioedema. *Pharmacoepidemiol Drug Saf*. 2018;27:829-838.
18. Panozzo CA, Woodworth TS, Welch EC, et al. Early impact of the ICD-10-CM transition on selected health outcomes in 13 electronic health care databases in the United States. *Pharmacoepidemiol Drug Saf*. 2018;27:839-847.
19. Seckinger A, Delgado JA, Moser S, et al. Target expression, generation, preclinical activity, and pharmacokinetics of the BCMA-T cell bispecific antibody EM801 for multiple myeloma treatment. *Cancer Cell*. 2017;31:396-410.
20. Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: A population-based study. *Neurology*. 2010;74:628-635.
21. Kurth T, Winter AC, Eliassen AH, et al. Migraine and risk of cardiovascular disease in women: Prospective cohort study. *BMJ*. 2016;353:i2610.
22. Kolodner K, Lipton RB, Lafata JE, et al. Pharmacy and medical claims data identified migraine sufferers with high specificity but modest sensitivity. *J Clin Epidemiol*. 2004;57:962-972.
23. Lipton RB, Manack Adams A, Buse DC, Fanning KM, Reed ML. A Comparison of the Chronic

Migraine Epidemiology and Outcomes (CaMEO) study and American Migraine Prevalence and Prevention (AMPP) study: Demographics and headache-related disability. *Headache*. 2016;56:1280-1289.

SUPPORTING INFORMATION

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