Received: 27 June 2024 | Accepted: 21 January 2025

DOI: 10.1111/head.14912

RESEARCH SUBMISSION

Effect of erenumab versus other migraine preventive medications on cardiovascular and cerebrovascular outcomes: A United States claims database-based observational cohort study

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Funding information
Novartis; Amgen Inc.

Abstract

Objective: To estimate the real-world risk of cardiovascular events among patients with migraine treated with erenumab and other migraine preventive medications.

Background: Migraine preventive treatment with calcitonin gene-related peptide (CGRP) pathway inhibitors, such as erenumab and others, may theoretically result in cardiovascular effects due to a lack of compensatory vasodilation with CGRP pathway inhibition.

Methods: In this retrospective observational cohort study, we estimated the unadjusted cumulative risk (CR) of new-onset hypertension, acute myocardial infarction (MI), or stroke among patients with migraine newly treated with erenumab, other anti-CGRP pathway monoclonal antibodies (mAbs), standard oral preventive medications, and onabotulinumtoxinA using data from the MarketScan® Commercial and Medicare Supplemental medical claims database. Comparative analyses to assess the relative risk (RR) of vascular events were gated on the comparability of treatment groups with respect to baseline demographics and clinical characteristics. Potential bias due to unmeasured confounding was evaluated via negative control outcome (NCO) analyses. Confounding based on measured covariates and differential informative censoring were addressed with inverse probability weights.

Results: A total of 108,019 new users of migraine preventive medications were included. Unadjusted CR (95% confidence interval [CI]) of hypertension at 12 months of treatment was: erenumab, 9.34% (8.79–9.89%); other anti-CGRP pathway mAbs, 9.42% (8.92–9.92%); standard oral preventive medications, 9.09% (8.77–9.41%); and onabotulinumtoxinA, 9.10% (8.39–9.81%). NCO analyses identified minimal concerns related to unmeasured confounding in erenumab versus other mAbs and erenumab versus onabotulinumtoxinA comparisons. Adjusted RRs (95% CIs) of acute MI and stroke, respectively, at 36 months of treatment were 1.02 (0.45–1.59) and 0.90

Abbreviations: BP, blood pressure; CGRP, calcitonin gene-related peptide; CI, confidence interval; CR, cumulative risk; CVD, cardiovascular disease; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; IP, inpatient; ITT, intention-to-treat; mAb, monoclonal antibody; MI, myocardial infarction; NCO, negative control outcome; OP, outpatient; OT, on-treatment; PS, propensity score; RR, relative risk; SMD, standardized mean difference.

(0.56–1.25) for erenumab versus other mAbs and 0.87 (0.19–1.55) and 0.97 (0.42–1.52) for erenumab versus onabotulinumtoxinA.

Conclusions: In this analysis of the MarketScan medical claims database, we found no difference in the risk of vascular events in patients treated with erenumab versus other anti-CGRP pathway mAbs or onabotulinumtoxinA.

Plain Language Summary

It has been suggested that erenumab, a preventive treatment for migraine, may pose a higher risk of events such as heart attack and stroke compared with other migraine preventive medications. In this study, we analyzed the MarketScan medical claims database of ~100,000 patients with migraine who were new users of erenumab and other migraine preventive medications and observed the occurrence of events such as high blood pressure, heart attack, or stroke in different treatment groups. We found no difference in the risk of vascular events in patients treated with erenumab versus those treated with other migraine preventive medications.

KEYWORDS
acute myocardial infarction, cardiovascular, erenumab, hypertension, stroke

INTRODUCTION

Migraine is a neurological disease that affects more than 10% of the global population.[1,2] Patients with migraine have a high risk of developing cardiovascular disease (CVD) and associated outcomes, including myocardial infarction (MI), stroke, and hypertension.[3–8] Calcitonin gene-related peptide (CGRP) is a neuropeptide and a potent vasodilator implicated in the pathophysiology of migraine.[9,10] As such, a theoretical risk of cardiovascular and cerebrovascular adverse events resulting from the use of migraine preventive medications inhibiting the CGRP pathway has been hypothesized.[11]

Erenumab (erenumab-aooe in the United States) is the first approved anti-CGRP pathway therapy for migraine. It is a human monoclonal antibody (mAb) against the canonical CGRP receptor and is indicated for the prevention of migraine in adults.[12,13] The potential for a higher risk of cardiovascular and cerebrovascular adverse events with erenumab treatment has been extensively examined in preclinical and clinical studies. In a preclinical study with cynomolgus monkeys and an in vitro study with isolated human coronary arteries, supratherapeutic exposure to erenumab had no clinically meaningful effects on heart rate or blood pressure (BP).[14] Clinical studies and dedicated cardiovascular-related safety studies of erenumab showed no increased risk of cardiovascular or cerebrovascular adverse events with erenumab compared with placebo.[15–17] It is important to highlight that patients were excluded from participating in these studies if they had certain preexisting cardiovascular conditions (e.g., acute MI and or stroke) during the 6–12 months preceding study enrollment. In the post-marketing setting using real-world data, there have been limited reports of hypertension or elevated BP among patients with migraine after treatment with erenumab.[18] In most of these published reports, relevant patient characteristics were missing; in cases when they were available, reports of hypertension were based on a single event of BP elevation or occurred in patients with a history of hypertension or in those who had risk factors for hypertension, which made association and causation very difficult to ascertain.[19]

In 2020, the United States Prescribing Information for erenumab was updated to include new-onset hypertension and worsening of existing hypertension following use of erenumab. To date, the product labels for other anti-CGRP pathway treatments, with respect to hypertension, have remained unchanged. The primary objective of this medical claims-based observational cohort study was to evaluate the risk of new-onset hypertension, acute MI, and stroke among patients with migraine newly treated with erenumab or other migraine preventive medications. Additionally, formal comparative analyses between erenumab and other migraine preventive medications for acute MI and stroke were conducted. In conducting comparative analyses, a principled approach was employed that included incorporating the use of negative control outcomes (NCO) to evaluate the potential impact of unmeasured confounding.[20]

METHODS

Study design

This observational cohort study estimated the risk of new-onset hypertension, acute MI, or stroke among new users of erenumab, other anti-CGRP pathway mAbs (galcanezumab-gnlm, fremanezumab-vfrm, and eptinezumab-jjmr), standard oral preventive medications (topiramate, valproic acid, divalproex sodium), and onabotulinumtoxinA by using data from the MarketScan®

Commercial and Medicare Supplemental medical claims database. The study period was from May 17, 2018 (date of Food and Drug Administration approval of erenumab in the United States) to June 30, 2021, and consisted of a 12-month baseline period that included the index date (earliest date for a prescription claim for one of four treatment groups) and a follow-up period (Figure 1). Follow-up was evaluated with an intention-to-treat (ITT) analysis and an on-treatment (OT) analysis. Under the ITT analysis, follow-up began the day after the index date and ended at the first occurrence of the outcome of interest, disenrollment from an eligible health plan, or administrative end of study. Under the OT analysis, follow-up was defined in a manner similar to the ITT analysis but also included discontinuation or switching of study medication as censoring events.

As this study did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board review or approval and patient consent were not required. All database records were de-identified and fully compliant with the United States patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996.

Participants

The study population included commercially insured patients across the United States (South [41.4%], Midwest [22.2%], West [12.3%], Northeast [11.9%], and Unknown [12.2%]). Full patient eligibility criteria are described in Table S1. Briefly, patients had to be 18–64 years of age on the index date, have >1 year of continuous medical and pharmacy coverage up to and including the index date (i.e., baseline period), and have a diagnosis of migraine during the baseline period. New user groups were based on the first use of a medication during the study period without any use of that medication during the 12-month baseline period. Some patients were counted more than once if they had switched to other preventive medications after initiating the index medication during the study period (i.e., drug switching).

Variables and definitions

Migraine was identified based on the following algorithm: one or more migraine diagnosis claim (identified using International Classification of Disease, 10th Revision, Clinical Modification [ICD-10-CM] diagnosis code of G43.xxx) from a non-emergency inpatient (IP) visit, an emergency room visit, an outpatient (OP) visit associated with a neurologist visit, or an OP visit regardless of provider specialty, with one or more prescription claim for an acute migraine-specific medication (triptans or ergot-derivatives) within 365 days of each other, two or more migraine diagnosis claims from an OP visit regardless of provider specialty that are 7 to 365 days apart, or two or more prescription claims for acute migraine-specific medications (triptans or ergot-derivatives) that are 7 to 365 days apart.

The study outcomes of new-onset hypertension, acute MI, or stroke were identified from claims data by using ICD-10-CM diagnosis codes during the follow-up period. New-onset hypertension was defined as occurrence of one IP, one emergency room, or one evaluation and management OP diagnosis (any position) of hypertension (definition 1 [ICD-10-CM: I10, I11.x, I12.x, I13.xx, and I16.x]). Patients with a history of hypertension during the baseline period were excluded from analyses estimating cumulative risk (CR) of hypertension. Sensitivity analyses using other algorithms for hypertension were also explored (Supplementary Appendix). Acute MI was defined as the occurrence of one IP diagnosis of acute MI (ICD-10-CM: I21.xx excluding I21.Ax).[21] Stroke (ICD-10-CM: I60.xx, I61.x, and I63.xxxx) was defined as the occurrence of one IP diagnosis of ischemic or hemorrhagic stroke.[22] Covariates included baseline demographics and clinical characteristics (e.g., comorbidities, concomitant medications, and risk factors for the study outcomes;

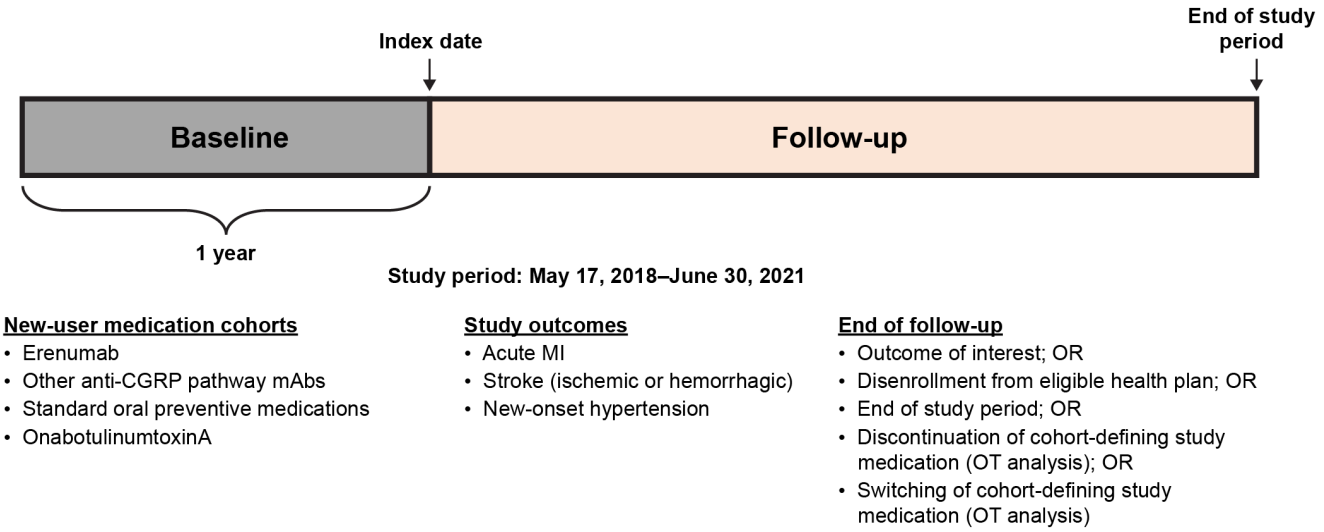

FIGURE 1 Study design. The index date is the date of the first claim for a study treatment medication. CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody; MI, myocardial infarction; OT, on-treatment. [Colour figure can be viewed at wileyonlinelibrary.com]

Supplementary Appendix). There were no missing data for demographics such as age and sex. Therefore, we did not employ techniques for addressing missing data.

Statistical analysis

Analytic methods

Patient baseline demographics, clinical characteristics, and estimates of the unadjusted CR of new-onset hypertension, acute MI, or stroke in the new-user treatment groups were evaluated with descriptive statistics. Mean and standard deviation or median and percentile estimates were used for continuous variables; frequency and percentages were used for categorical variables.

The decision to proceed with comparative analysis for acute MI and stroke outcome analyses between erenumab and a reference treatment group was based on a framework of three decision points (gates). In the first gate, comparability between new-user treatment cohorts was assessed by evaluating the balance in demographic and clinical characteristics using propensity scores (PSs) and standardized mean differences (SMDs). Separate linear-logistic models were used to estimate the probability of receiving erenumab (i.e., the PS) relative to each of the other migraine treatment groups based on a set of relevant demographic and clinical characteristics.[23] Patients who were not within the overlapped regions of the PS distributions across treatment comparisons were excluded. SMDs for all baseline variables used in the PS were assessed prior to and after the balancing of PS distributions to ensure comparability of exposure groups. Imbalance in a baseline variable was defined as an SMD >0.1.[24] The purpose of the second gate was to ensure that the observed number of outcome events in each treatment group would be sufficient to support the estimation of relative risk (RR). While the sample size was based on the available data, this study required at least 40 events (20 events/treatment arm) for each primary analysis comparison to proceed. The third gate evaluated the presence of unmeasured bias by using NCO analyses.[20] Valid NCOs theoretically share the same confounding structure as the treatment and outcome of interest but are not causally related to treatment. A statistically significant association between a treatment and an NCO would imply that confounding was not fully addressed in the study. The following NCOs were included in the analyses: accidents, anemia, asthma, electrocardiogram use, echocardiography use, fractures, herpes vaccine use, influenza vaccine use, mammography, osteoarthritis, and pelvic examination. NCOs with RRs <0.87 or >1.15 with 95% confidence intervals (CIs) excluding the null (1.0) were considered suggestive of bias in the treatment group comparison of interest.

If exposure groups were deemed comparable (gates 1 and 2) and there was minimal concern for unmeasured confounding bias based on the NCO analyses (gate 3), formal comparative analyses between erenumab and each of the other exposure groups were conducted for the outcomes of acute MI and stroke, where the effect measures of interest were adjusted CRs and the RR. Given the challenges of evaluating and avoiding misclassification for drug-induced hypertension when using administrative claims data, a decision was made a priori not to conduct a formal comparative analysis for this outcome. Confounding was handled by inverse probability of treatment weights, and informative censoring was handled by inverse probability of censoring weights.

The analyses of hypertension, acute MI, or stroke were stratified by prior history of the following covariates: CVD, migraine aura, and risk factors for CVD and analyses of acute MI or stroke were also stratified by prior history of hypertension. All descriptive and comparative analyses were undertaken in the R version 4.4.1 environment (R Foundation for Statistical Computing, Vienna, Austria) using the "causalRisk" package (version 0.39.03).[25]

RESULTS

Participants

A total of 616,421 new users of migraine preventive medications were screened and 98,470 unique patients met eligibility criteria (Figure S1). After accounting for drug switching, 108,019 were analyzed across the four treatment groups: erenumab ($n=19,220$), other anti-CGRP pathway mAbs ($n=23,244$), standard oral preventive medications ($n=53,842$), and onabotulinumtoxinA ($n=11,713$). Baseline demographics and clinical characteristics were observed to be generally similar across the treatment groups except for the standard oral preventive medications group, which had a younger population and lower proportion of patients with chronic migraine, those with migraine with aura, and those taking acute or preventive migraine medication (Table 1, Figure S2).

Unadjusted CR of hypertension, acute MI, or stroke in migraine preventive treatment groups

The unadjusted CR of hypertension (algorithm definition 1) was estimated after 12 months of migraine preventive treatment using an ITT analysis. The overall CR (95% CI) of hypertension across treatment groups was as follows: erenumab, 9.34% (8.79–9.89%); other anti-CGRP pathway mAbs, 9.42% (8.92–9.92%); standard oral preventive medications 9.09% (8.77–9.41%); and onabotulinumtoxinA 9.10% (8.39–9.81%) (Table 2). Results of stratified analyses indicated that the CR of hypertension was generally higher among patients with a history of CVD or a history of risk factors for CVD than among patients without these conditions. Assessment of additional hypertension algorithms indicated that the overall CR of hypertension was generally similar across the treatment groups (Table S2).

The overall unadjusted CR (95% CI) of acute MI after 36 months of follow-up was as follows: erenumab, 0.41% (0.22–0.59%); other anti-CGRP pathway mAbs, 0.39% (0.25–0.52%); standard oral preventive medications, 0.53% (0.38–0.67%); and onabotulinumtoxinA,

TABLE 1 Baseline demographics and clinical characteristics.

Characteristic	Erenumab *n* = 19,220	Other anti-CGRP pathway mAbs *n* = 23,244	Standard oral preventive medications *n* = 53,842	OnabotulinumtoxinA *n* = 11,713
Age, years, mean (SD)	44.1 (11.5)	43.7 (11.5)	40.4 (12.1)	43.7 (11.4)
Age, *n* (%)				
18–24 years	1510 (7.9)	1867 (8.0)	7004 (13.0)	828 (7.1)
25–34 years	2421 (12.6)	3243 (14.0)	10,523 (19.5)	1733 (14.8)
35–44 years	5179 (26.9)	6316 (27.2)	14,978 (27.8)	3254 (27.8)
45–54 years	6271 (32.6)	7227 (31.1)	13,690 (25.4)	3551 (30.3)
55–64 years	3839 (20.0)	4591 (19.8)	7647 (14.2)	2347 (20.0)
Sex, female, *n* (%)	16,603 (86.4)	20,142 (86.7)	45,704 (84.9)	10,449 (89.2)
Geographic region, *n* (%)				
Midwest	4183 (21.8)	4763 (20.5)	12,454 (23.1)	2600 (22.2)
Northeast	2513 (13.1)	2492 (10.7)	6035 (11.2)	1775 (15.2)
South	7833 (40.8)	10,298 (44.3)	22,681 (42.1)	3922 (33.5)
West	2369 (12.3)	2586 (11.1)	6174 (11.5)	2153 (18.4)
Unknown	2322 (12.1)	3105 (13.4)	6498 (12.1)	1263 (10.8)
Chronic migraine, *n* (%)	7687 (40.0)	7808 (33.6)	4140 (7.7)	4373 (37.3)
Migraine with aura, *n* (%)	3329 (17.3)	3960 (17.0)	5149 (9.6)	1891 (16.1)
Acute migraine medications, *n* (%)				
Triptans	13,264 (69.0)	15,707 (67.6)	27,032 (50.2)	7061 (60.3)
Opioids	8969 (46.7)	10,585 (45.5)	21,422 (39.8)	5770 (49.3)
NSAIDs	8557 (44.5)	10,042 (43.2)	20,791 (38.6)	5168 (44.1)
Non-NSAIDs non-opioids	3779 (19.7)	4452 (19.2)	7859 (14.6)	2548 (21.8)
Ergotamines	616 (3.2)	533 (2.3)	320 (0.6)	249 (2.1)
Migraine preventive medications, *n* (%)				
Any	16,796 (87.4)	20,124 (86.6)	32,475 (60.3)	10,026 (85.6)
Antiseizure	10,554 (54.9)	12,621 (54.3)	8107 (15.1)	6686 (57.1)
Antidepressants	10,523 (54.8)	12,604 (54.2)	22,701 (42.2)	6991 (59.7)
Antihypertensives	6937 (36.1)	8103 (34.9)	12,691 (23.6)	4275 (36.5)
Other medications, *n* (%)				
Antihypertensives	8823 (45.9)	10,370 (44.6)	18,517 (34.4)	5536 (47.3)
Beta-blockers	5261 (27.4)	6214 (26.7)	9865 (18.3)	3341 (28.5)
Lipid-lowering medications	3187 (16.6)	3790 (16.3)	6872 (12.8)	1816 (15.5)
Diuretics	2086 (10.9)	2547 (11.0)	5391 (10.0)	1369 (11.7)
Calcium-channel blockers	1960 (10.2)	2252 (9.7)	3548 (6.6)	1265 (10.8)
Antidiabetics	1582 (8.2)	1936 (8.3)	4423 (8.2)	962 (8.2)
Angiotensin receptor blockers	1225 (6.4)	1312 (5.6)	2803 (5.2)	702 (6.0)
Angiotensin-converting enzyme inhibitors	1214 (6.3)	1473 (6.3)	3610 (6.7)	729 (6.2)
Other antihypertensives	544 (2.8)	670 (2.9)	1373 (2.6)	363 (3.1)
Anticoagulants	402 (2.1)	426 (1.8)	961 (1.8)	262 (2.2)
Antiplatelet	176 (0.9)	192 (0.8)	506 (0.9)	144 (1.2)
Healthcare utilization, mean (SD)				
Outpatient visits	24.6 (21.3)	24.0 (20.7)	19.1 (18.2)	28.5 (24.1)
Inpatient visits	0.1 (0.5)	0.1 (0.5)	0.2 (0.6)	0.2 (0.5)
ER visits	0.8 (2.8)	0.7 (1.9)	0.9 (1.9)	0.9 (2.5)

(Continues)

TABLE 1 (Continued)

Characteristic	Erenumab $n = 19,220$	Other anti-CGRP pathway mAbs $n = 23,244$	Standard oral preventive medications $n = 53,842$	OnabotulinumtoxinA $n = 11,713$
Generic medications dispensed	12.9 (7.6)	12.7 (7.6)	9.8 (6.9)	13.2 (7.9)
Unique drug classes dispensed	11.6 (6.5)	11.5 (6.5)	8.9 (5.9)	11.9 (6.7)
Comorbidities, *n* (%)				
Anxiety	5447 (28.3)	6685 (28.8)	14,448 (26.8)	3826 (32.7)
Depression	4474 (23.3)	5413 (23.3)	10,967 (20.4)	3151 (26.9)
Hypertension	4066 (21.2)	4916 (21.1)	11,238 (20.9)	2534 (21.6)
Hypercholesterolemia	3427 (17.8)	4122 (17.7)	7896 (14.7)	1956 (16.7)
Tobacco-use disorder	2889 (15.0)	3724 (16.0)	8795 (16.3)	1909 (16.3)
Asthma	1807 (9.4)	2206 (9.5)	4782 (8.9)	1155 (9.9)
Diabetes mellitus	1283 (6.7)	1543 (6.6)	3622 (6.7)	791 (6.8)
Cardiac arrhythmias and conduction disorders	848 (4.4)	1007 (4.3)	2117 (3.9)	610 (5.2)
Ischemic/hemorrhagic stroke	204 (1.1)	241 (1.0)	892 (1.7)	192 (1.6)
Epilepsy/seizure/convulsions	722 (3.8)	870 (3.7)	1927 (3.6)	460 (3.9)
Renal disease	620 (3.2)	696 (3.0)	1069 (2.0)	350 (3.0)
Malignancy (nonmelanoma)	495 (2.6)	515 (2.2)	1062 (2.0)	357 (3.1)
Liver disease/cirrhosis	438 (2.3)	554 (2.4)	1177 (2.2)	321 (2.7)
Chronic obstructive pulmonary disease	433 (2.3)	529 (2.3)	1238 (2.3)	312 (2.7)

Abbreviations: CGRP, calcitonin gene-related peptide; ER, emergency room; mAb, monoclonal antibody; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

0.49% (0.24–0.73%) (Table 3). The overall unadjusted CR (95% CI) of stroke after 36 months of treatment was as follows: erenumab, 0.91% (0.61–1.22%); other anti-CGRP pathway mAbs, 0.93% (0.68–1.17%); standard oral preventive medications, 1.07% (0.93–1.22%); and onabotulinumtoxinA, 1.22% (0.77–1.67%) (Table 4). Overall, patients with a history of CVD, a history of risk factors for CVD, or a history of hypertension across all treatment groups had a higher CR of acute MI or stroke.

Assessment of comparability and residual bias

Before evaluating the RR of acute MI or stroke in the erenumab group compared with the other treatment groups, the extent of balance of baseline covariates and residual bias between the erenumab group and each of the other treatment groups was assessed to determine if the groups were comparable. When the erenumab group was assessed for comparability with the standard oral preventive medications group, there was a noticeable difference in the distribution and overlap of PSs for the two treatment groups, as well as an imbalance of covariates used in deriving the PSs based on SMDs between the groups (Figure S2A). These imbalances were reflected in some patients with extremely high PS weights in the weighted PS models. A 1% trim was therefore used to exclude extreme weights and improve PS overlap. However, the NCO analysis models for this comparison failed to converge. Thus, the comparison of the erenumab group with the standard oral preventive medications group did not proceed to comparative analyses that would estimate the RRs of acute MI or stroke. For the comparison of erenumab and other anti-CGRP pathway mAbs, there was sufficient overlap of unweighted PSs, thus no trimming of the PSs was required (Figure S2B). However, to make the erenumab versus onabotulinumtoxinA groups more comparable, patients with exposure to botulinum toxins in the year prior to initiation were excluded and a 1% PS trim was performed (Figure S2C). For the comparisons of erenumab versus other anti-CGRP pathway mAbs and erenumab versus onabotulinumtoxinA, the results of the NCO analyses suggested that the covariates included in our analyses sufficiently minimized residual bias (Figure S3).

Adjusted CR and RR of acute MI or stroke with erenumab compared with other migraine preventive treatments

The adjusted 36-month CR curves of acute MI or stroke for the erenumab and other anti-CGRP pathway mAbs groups were similar under an ITT follow-up model (Figure 2). No drug switching was observed within ±1 year of patients' index date in the comparative analyses. The adjusted CR (95% CI) of acute MI was 0.37% (0.24–0.59%) in the erenumab group and 0.37% (0.26–0.52%) in the other

TABLE 2 Unadjusted cumulative risk of hypertension at 12 months stratified by risk factors.

Variable	Erenumab	Other anti-CGRP pathway mAbs	Standard oral preventive medications	OnabotulinumtoxinA
Overall, *n*	15,154	18,328	42,604	9179
Number of events	1094	1355	3118	634
CR, % (95% CI)	9.34 (8.79–9.89)	9.42 (8.92–9.92)	9.09 (8.77–9.41)	9.10 (8.39–9.81)
History of CVD				
No history of CVD, *n*	14,855	17,951	41,560	8921
Number of events	1056	1319	2984	589
CR, % (95% CI)	9.17 (8.62–9.72)	9.38 (8.88–9.88)	8.92 (8.60–9.24)	8.70 (7.99–9.40)
Prior history of CVD, *n*	299	377	1044	258
Number of events	38	36	134	45
CR, % (95% CI)	18.69 (12.78–24.60)	11.19 (7.59–14.79)	15.88 (13.27–18.48)	22.56 (16.11–29.02)
History of migraine aura				
No history of migraine aura, *n*	12,592	15,308	38,699	7705
Number of events	908	1113	2853	528
CR, % (95% CI)	9.31 (8.71–9.92)	9.27 (8.72–9.81)	9.14 (8.81–9.48)	9.06 (8.29–9.84)
Prior history of migraine aura, *n*	2562	3020	3905	1474
Number of events	186	242	265	106
CR, % (95% CI)	9.46 (8.10–10.82)	10.19 (8.92–11.47)	8.56 (7.53–9.59)	9.30 (7.52–11.07)
History of risk factors for CVD				
No history of risk factors for CVD, *n*	13,082	15,929	38,125	8063
Number of events	808	1035	2503	477
CR, % (95% CI)	8.06 (7.51–8.62)	8.25 (7.74–8.75)	8.12 (7.80–8.44)	7.83 (7.12–8.54)
Prior history of risk factors for CVD, *n*	2072	2399	4479	1116
Number of events	286	320	615	157
CR, % (95% CI)	17.40 (15.42–19.38)	17.14 (15.30–18.97)	17.28 (15.99–18.59)	18.01 (15.21–20.80)

Note: Patients with a history of hypertension during the baseline period were excluded from this analysis.

Abbreviations: CGRP, calcitonin gene-related peptide; CI, confidence interval; CR, cumulative risk; CVD, cardiovascular disease; mAb, monoclonal antibody.

anti-CGRP pathway mAbs group; the RR (95% CI) of acute MI with erenumab versus other anti-CGRP pathway mAbs was 1.02 (0.45–1.59) (Table 5). The adjusted CR (95% CI) of stroke was 0.84% (0.64–1.10%) in the erenumab group and 0.94% (0.71–1.23%) in the other anti-CGRP pathway mAbs group; the RR (95% CI) of stroke with erenumab versus other anti-CGRP pathway mAbs was 0.90 (0.56–1.25). Results of stratified analyses generally showed a comparable risk of acute MI or stroke between erenumab and other anti-CGRP pathway mAbs for strata with a sufficient number of outcomes. However, for some strata the number of events was small and led to wide CIs (Tables S3 and S4, Figures S4–S9).

Similarly, for the erenumab and onabotulinumtoxinA groups, the overall and stratified results indicated that the risk of acute MI or stroke within 36 months after treatment was comparable (Figure 2, Table 3, Figures S4–S9). The adjusted CR (95% CI) of acute MI was 0.41% (0.24–0.67%) in the erenumab group and 0.47% (0.28–0.78%) in the onabotulinumtoxinA group; the RR (95% CI) of acute MI with erenumab versus onabotulinumtoxinA was 0.87 (0.19–1.55). The adjusted CR (95% CI) of stroke was 1.01% (0.69–1.49%) in the erenumab group and 1.05% (0.73–1.50%) in the onabotulinumtoxinA group; the RR (95% CI) of stroke with erenumab versus onabotulinumtoxinA was 0.97 (0.42–1.52).

The overall CR and the CR when outcomes were stratified by prior history of events obtained under the OT follow-up model for the outcome of acute MI or stroke were consistent with those under the ITT follow-up model (Tables S3–S7). Given that less follow-up time was included in the OT models, there were fewer outcomes observed in some strata compared with the ITT analysis.

DISCUSSION

Anti-CGRP pathway mAbs are effective treatments for migraine prevention.[12,26–29] However, there is a theoretical risk of cardiovascular and cerebrovascular events with inhibition of the CGRP pathway due to the role of CGRP in vascular tone regulation[30] and

TABLE 3 Unadjusted cumulative risk of acute myocardial infarction at 36 months stratified by risk factors.

Variable	Erenumab	Other anti-CGRP pathway mAbs	Standard oral preventive medications	OnabotulinumtoxinA
Overall, *n*	19,220	23,244	53,842	11,713
Number of events	33	42	111	24
CR, % (95% CI)	0.41 (0.22–0.59)	0.39 (0.25–0.52)	0.53 (0.38–0.67)	0.49 (0.24–0.73)
History of CVD				
No history of CVD, *n*	18,469	22,352	51,282	11,097
Number of events	26	27	78	18
CR, % (95% CI)	0.37 (0.18–0.55)	0.28 (0.16–0.40)	0.41 (0.27–0.54)	0.40 (0.16–0.64)
Prior history of CVD, *n*	751	892	2560	616
Number of events	7	15	33	6
CR, % (95% CI)	1.55 (0.37–2.74)	3.21 (1.37–5.05)	3.03 (1.64–4.42)	2.02 (0.18–3.86)
History of migraine aura				
No history of migraine aura, *n*	15,891	19,284	48,693	9822
Number of events	26	34	94	20
CR, % (95% CI)	0.42 (0.20–0.63)	0.41 (0.25–0.56)	0.49 (0.34–0.63)	0.47 (0.21–0.74)
Prior history of migraine aura, *n*	3329	3960	5149	1891
Number of events	7	8	17	4
CR, % (95% CI)	0.37 (0.08–0.66)	0.30 (0.07–0.53)	0.84 (0.29–1.40)	0.54 (0.00–1.17)
History of risk factors for CVD				
No history of risk factors for CVD, *n*	13,802	15,929	38,125	8063
Number of events	12	12	34	5
CR, % (95% CI)	0.18 (0.06–0.30)	0.15 (0.06–0.25)	0.28 (0.13–0.43)	0.22 (0.00–0.48)
Prior history of risk factors for CVD, *n*	6138	7315	15,717	3650
Number of events	21	30	77	19
CR, % (95% CI)	0.88 (0.37–1.39)	0.89 (0.53–1.26)	1.11 (0.79–1.43)	1.03 (0.51–1.56)
History of hypertension				
No history of hypertension, *n*	15,154	18,328	42,604	9179
Number of events	18	15	43	11
CR, % (95% CI)	0.30 (0.10–0.49)	0.18 (0.08–0.28)	0.29 (0.15–0.43)	0.38 (0.09–0.67)
Prior history of hypertension, *n*	4066	4916	11,238	2534
Number of events	15	27	68	13
CR, % (95% CI)	0.81 (0.35–1.27)	1.15 (0.65–1.66)	1.42 (0.98–1.86)	0.86 (0.37–1.34)

Abbreviations: CGRP, calcitonin gene-related peptide; CI, confidence interval; CR, cumulative risk; CVD, cardiovascular disease; mAb, monoclonal antibody.

potential function as a protective vasodilatory mechanism during episodes of cerebral and cardiac ischemia.[31] While clinical trials have made significant contributions to understanding the safety and efficacy of anti-CGRP pathway mAbs, the generalizability of the results to patients with histories of any recent or acute CVD and cerebrovascular disease is limited due to the common exclusion of such patients from clinical trials.[12,27,32,33] To address this gap in data, real-world evidence based on patients with a range of comorbidities, including histories of CVD and cerebrovascular disease, must be generated.

Although studies examining cardiovascular-related outcomes among users of anti-CGRP pathway mAbs have been conducted, they are limited in number and sample size[34–36] and may not have adequately controlled for confounders.[36] Additionally, accounting for the comparability of baseline demographics, clinical characteristics, and history of risk factors might not have been feasible. Selection of migraine-preventive treatment is likely affected by many factors associated with a patient's clinical presentation and medical history of comorbid and coexistent diseases that may bias comparison of treatment groups in non-interventional, non-randomized (i.e., real-world) settings. To address these limitations, this study examined the medical claims of ~100,000 new users of migraine preventive medications and employed the use of inverse probability weights and NCO analyses, along with a requirement

TABLE 4 Unadjusted cumulative risk of stroke at 36 months stratified by risk factors.

Variable	Erenumab	Other anti-CGRP pathway mAbs	Standard oral preventive medications	OnabotulinumtoxinA
Overall, *n*	19,220	23,244	53,842	11,713
Number of events	78	99	332	53
CR, % (95% CI)	0.91 (0.61–1.22)	0.93 (0.68–1.17)	1.07 (0.93–1.22)	1.22 (0.77–1.67)
History of CVD				
No history of CVD, *n*	18,469	22,352	51,282	11,097
Number of events	54	71	165	32
CR, % (95% CI)	0.74 (0.44–1.04)	0.66 (0.47–0.84)	0.66 (0.53–0.79)	0.67 (0.38–0.96)
Prior history of CVD, *n*	751	892	2560	616
Number of events	24	28	167	21
CR, % (95% CI)	5.60 (2.88–8.32)	7.99 (3.24–12.75)	9.60 (7.88–11.32)	11.74 (4.52–18.95)
History of migraine aura				
No history of migraine aura, *n*	15,891	19,284	48,693	9822
Number of events	59	77	258	36
CR, % (95% CI)	0.82 (0.54–1.11)	0.92 (0.64–1.20)	0.95 (0.81–1.09)	0.92 (0.51–1.33)
Prior history of migraine aura, *n*	3329	3960	5149	1891
Number of events	19	22	74	17
CR, % (95% CI)	1.36 (0.26–2.46)	0.95 (0.44–1.47)	2.23 (1.59–2.87)	2.76 (1.02–4.51)
History of risk factors for CVD				
No history of risk factors for CVD, *n*	13,802	15,929	38,125	8063
Number of events	31	36	99	18
CR, % (95% CI)	0.40 (0.25–0.55)	0.42 (0.26–0.58)	0.45 (0.33–0.56)	0.61 (0.21–1.01)
Prior history of risk factors for CVD, *n*	6138	7315	15,717	3650
Number of events	47	63	233	35
CR, % (95% CI)	1.98 (1.11–2.85)	2.01 (1.31–2.70)	2.58 (2.17–2.98)	2.45 (1.38–3.51)
History of hypertension				
No history of hypertension, *n*	15,154	18,328	42,604	9179
Number of events	39	48	123	22
CR, % (95% CI)	0.57 (0.31–0.83)	0.48 (0.32–0.64)	0.49 (0.38–0.60)	0.61 (0.25–0.96)
Prior history of hypertension, *n*	4066	4916	11,238	2534
Number of events	39	51	209	31
CR, % (95% CI)	2.18 (1.12–3.24)	2.52 (1.55–3.49)	3.27 (2.72–3.82)	3.31 (1.76–4.86)

Abbreviations: CGRP, calcitonin gene-related peptide; CI, confidence interval; CR, cumulative risk; CVD, cardiovascular disease; mAb, monoclonal antibody.

of a minimum number of events for comparative analysis, offering a robust approach to address the limitations of real-world data use for causal inference.

Baseline characteristics across all treatment groups were comparable, except for the standard oral preventive medications group. Hence, comparative analyses between the erenumab and standard oral preventive medications groups were not conducted. Nevertheless, the unadjusted CR of MI or stroke in the standard oral preventive medication group was comparable to that estimated in the erenumab group. Comparative analyses between erenumab and other peptide-targeting anti-CGRP pathway mAbs and between erenumab and onabotulinumtoxinA were undertaken, because they passed all the prespecified gates for determining comparability between exposure groups and had enough outcomes to support the estimation of RR. Analyses of these treatment groups indicated that the risk of acute MI or stroke under an ITT model was comparable between erenumab and other anti-CGRP pathway mAbs and between erenumab and onabotulinumtoxinA, as supported by adjusted RR estimates close to the null value (1.0). In addition, RRs for acute MI or stroke stratified by history of CVD, presence of a cardiovascular risk factor, history of migraine aura, or history of hypertension also did not suggest an increased risk of cardiovascular events in erenumab versus other anti-CGRP pathway mAbs or onabotulinumtoxinA.

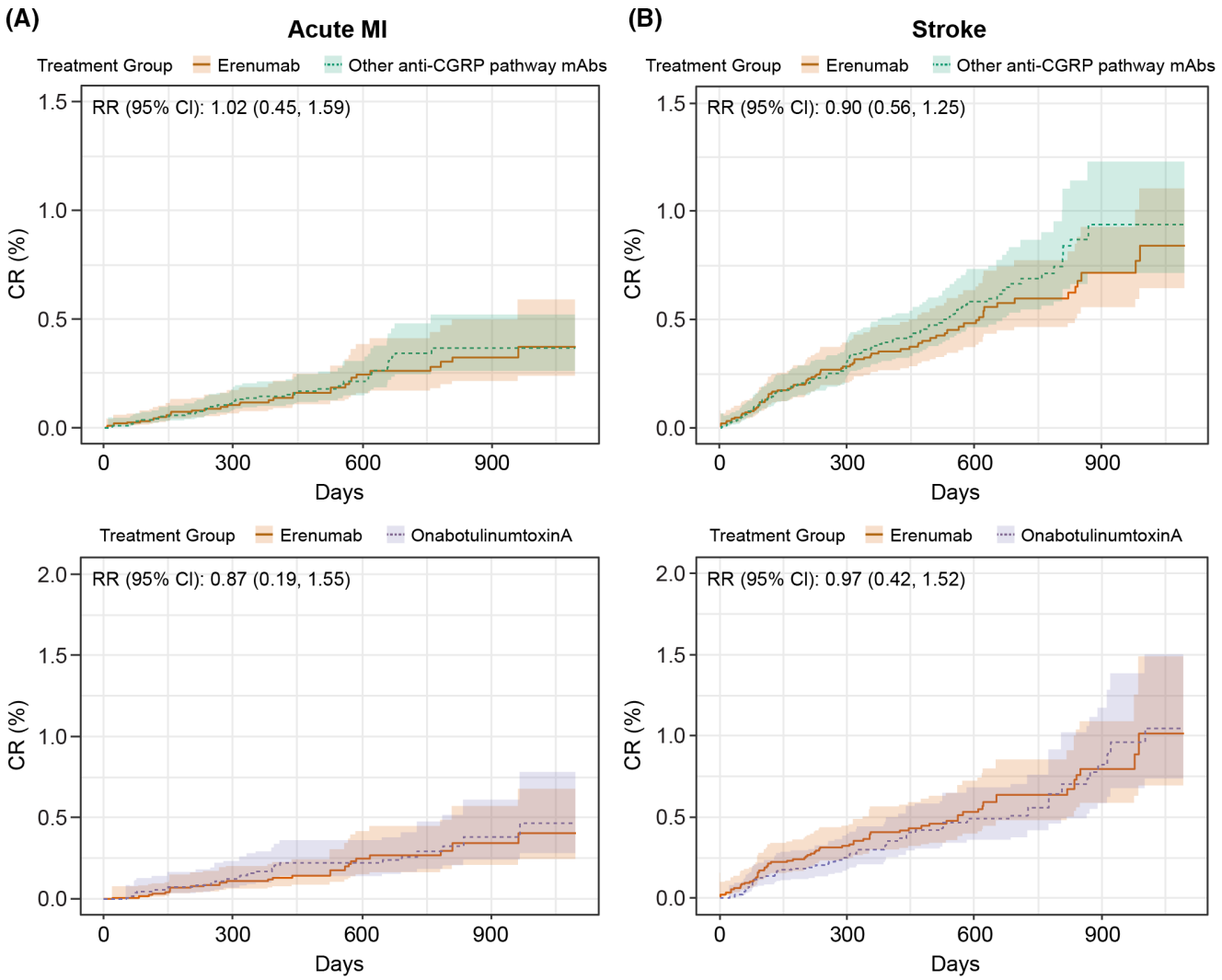

FIGURE 2 Adjusted CR plots of acute MI (A) and stroke (B) for 36 months under an ITT follow-up model. Other anti-CGRP pathway mAbs and onabotulinumtoxinA groups served as reference groups for RR estimates. The solid and dashed lines represent the CR, and the shaded areas represent the 95% CI. CGRP, calcitonin gene-related peptide; CI, confidence interval; CR, cumulative risk; ITT, intention-to-treat; mAb, monoclonal antibody; MI, myocardial infarction; RR, relative risk. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Adjusted cumulative risk and relative risk of acute myocardial infarction or stroke at 36 months.

Outcome	Effect measure	Erenumab ($n = 19,220$)	Other anti-CGRP pathway mAbs ($n = 23,244$)	Erenumab[a] ($n = 14,919$)	OnabotulinumtoxinA[a] ($n = 11,413$)
Acute MI	Number of events	33	42	23	23
	CR, % (95% CI)	0.37 (0.24–0.59)	0.37 (0.26–0.52)	0.41 (0.24–0.67)	0.47 (0.28–0.78)
	RR (95% CI)	1.02 (0.45–1.59)		0.87 (0.19–1.55)	
Stroke	Number of events	78	99	60	51
	CR, % (95% CI)	0.84 (0.64–1.10)	0.94 (0.71–1.23)	1.01 (0.69–1.49)	1.05 (0.73–1.50)
	RR (95% CI)	0.90 (0.56–1.25)		0.97 (0.42–1.52)	

Abbreviations: CGRP, calcitonin gene-related peptide; CI, confidence interval; CR, cumulative risk; mAb, monoclonal antibody; RR, relative risk; MI, myocardial infarction.

[a]Sample size reflects a 1% trim and exclusion of patients with exposure to botulinum toxins in the year prior to index.

None of the NCOs except for one were associated with exposure to erenumab in both comparisons, other anti-CGRP pathway mAbs and onabotulinumtoxinA. The erenumab group had a significantly lower risk of asthma compared with the onabotulinumtoxinA group (RR [95% CI] 0.85 [0.77–0.93]) (Figure S3). Literature suggests that CGRP affects allergic airway inflammation by modulating dendritic

cell function in vivo.[37] Treatment with anti-CGRP pathway medications such as erenumab may affect asthma, and although the effect of erenumab has not been studied in asthma, using asthma as an NCO may have been inappropriate.

Similar to the ITT follow-up model, the OT follow-up model also did not identify an increased risk of cardiovascular events associated with erenumab compared with other anti-CGRP pathway mAbs or onabotulinumtoxinA. However, estimated risks for the OT model had low precision, as treatment arms had fewer events and/or less follow-up time compared with the ITT models. Thus, RRs in the OT model estimates were correspondingly less precise, reducing our ability to make confident inferences from them.

Unlike stroke and acute MI for which the adjusted CR and RR were evaluated, no formal comparative analysis was conducted for hypertension due to inherent challenges when evaluating drug-induced hypertension using administrative claims data. Diagnosis of hypertension is based on an accurate assessment of BP measurements; however, in clinical practice BP measurements are often suboptimally performed, which may result in misdiagnosis of hypertension.[38,39] It can be difficult to distinguish between true hypertension from transient increases observed due to "white-coat" syndrome,[40] as well as hypertension caused by other medical conditions rather than the medication itself.[41] Despite these limitations, in this study the unadjusted CR of hypertension over 12 months was similar across treatment groups, as well as when the treatment groups were stratified using various risk factors. In addition, sensitivity analyses using four additional algorithms of hypertension also showed similar risk across the four treatment groups. It should be noted that although primary analyses were gated on a minimum number of events per treatment arm, subgroup analyses were not similarly gated, and some subgroup analyses may therefore be underpowered.

As the source of data for these analyses is medical and prescription billing claims, it is important to highlight certain inherent limitations. A prescription claim does not indicate that the medication was consumed or taken as prescribed. Medications obtained over the counter or provided as samples by the physician would not be included in claims data. A diagnosis code on a medical claim may not truly indicate the presence of the disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than the actual disease. While there may be instances where medications are not used as prescribed or diagnoses are not reported, in this study, we assumed that the diagnosis for a chronic and debilitating condition with the presence of an associated claim indicated the disease was present, the procedure was conducted, or the drug was consumed. Conversely, the absence of a claim indicates the opposite. Duration of follow-up can be limited in claims data due to individuals changing health insurance plans. Additionally, important confounding factors are not adequately captured in claims data (i.e., smoking), which may result in residual confounding. Lastly, this study was limited to individuals with employer-sponsored health coverage included in the MarketScan® Commercial and Medicare Supplemental Medical Claims database; thus, the results of this analysis may not be generalizable to individuals with other types of insurance coverage, those without health insurance, or those who first obtained their medication through free drug programs.

Switching was observed for a small proportion of patients (<10%) in the comparative analyses, reflecting real-world usage patterns. Given the nature of the ITT analysis, in which follow-up included person-time after patients may discontinue or switch study medications, overlaps in person-time was possible. However, no patients in a given new-user group had claims for the other medication within 1 year of their index date. For example, in the erenumab versus other anti-CGRP pathway mAbs comparative analysis, no new users of other anti-CGRP pathway mAbs had claims for erenumab ±1 year of their index date, and no new users of erenumab had claims for other anti-CGRP pathway mAbs within 1 year of their index date. The same was true in the erenumab versus onabotulinumtoxinA comparative analysis. The OT analyses (in which patient follow-up ceases once a patient discontinues or switches study medication) produced results similar to the ITT analyses; thus, we believe that the ITT estimates and their interpretations remain robust. However, it should be noted that due to the shorter follow-up time of the OT analyses, the number of events were fewer (<20 events) for some of the sub-analyses (adjusted CR and RR analyses of acute MI stratified by risk factors).

The potential effects of CGRP receptor blockade on the severity of these events were not assessed in the present study. Observations from a randomized, double-blind, placebo-controlled study suggest that CGRP receptor inhibition with erenumab does not negatively affect tolerance to myocardial ischemia or impede compensatory vasodilation among patients with known coronary artery disease.[42]

The strength of this study lies in utilizing real-world data from a large patient population of ~100,000 to provide a more direct and real-world comparison of risk of cardiovascular outcomes across different classes of migraine preventive medications. The benefits of this approach are two-fold; first, previous reports comparing the risk of vascular events mostly utilized data from clinical trials in which the patient population was smaller and less diverse, and second, the treatment risk was compared against placebo but not against other migraine preventive medications.[15,43,44] The unadjusted risks of hypertension among users of erenumab and other migraine preventive treatments were also consistent with the findings from trial data at a population level.[15] However, we acknowledge the limited inferences that can be made across treatment groups regarding new-onset hypertension based solely on unadjusted risk estimates. A major challenge in observational comparative analyses is the lack of exchangeability, with unbalanced baseline characteristics between treatment groups and potential differential drop-out across the different arms of the study. In this study, we utilized inverse probability of treatment weights to account for confounding and inverse probability of censoring weights to account for informative censoring. NCOs were used to evaluate exchangeability between treatment cohorts for comparative analyses.

CONCLUSIONS

This study employed rigorous methods to assess the risk of cardiovascular and cerebrovascular outcomes in a real-world setting. The unadjusted CR of hypertension was similar across the treatment groups, while the adjusted CR of acute MI or stroke in patients treated with erenumab was not increased relative to incidence in patients treated with other anti-CGRP pathway mAbs or with onabotulinumtoxinA. This comparability in CRs between treatment groups suggests that there is no increased risk of cardiovascular or cerebrovascular events among patients with migraine treated with erenumab compared with those treated with other standard oral migraine preventive medications, onabotulinumtoxinA, and other anti-CGRP pathway mAbs.

AUTHOR CONTRIBUTIONS

David W. Dodick: Methodology; writing – review and editing. **Stewart J. Tepper:** Writing – review and editing. **Jessica Ailani:** Writing – review and editing. **Ani C. Khodavirdi:** Writing – review and editing. **Nico Pannacciulli:** Writing – review and editing. **Alan Fu:** Formal analysis; methodology; software; writing – review and editing. **Shia T. Kent:** Formal analysis; methodology; software; writing – review and editing. **Karminder Gill:** Conceptualization; methodology; writing – review and editing. **Robert Urman:** Methodology; writing – review and editing. **Sam S. Oh:** Methodology; supervision; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

This study was sponsored by Amgen Inc. and Novartis. Medical writing and editorial assistance were provided by Qais Al-Hadid, PhD (Amgen Inc.), Lisa Humphries, PhD (Amgen Inc.), and Varsha Jain, PhD (Cactus Life Sciences, part of Cactus Communications) and was funded by Amgen Inc.

FUNDING INFORMATION

This study was funded by Amgen Inc. and Novartis.

CONFLICT OF INTEREST STATEMENT

David W. Dodick received consulting fees from Amgen, Atria, CapiThera Ltd., Cerecin, Ceruvia Lifesciences LLC, CoolTech, Ctrl M, Allergan, AbbVie, Biohaven, GlaxoSmithKline, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Genentech, Nocira, Perfood, Praxis, AYYA Biosciences, Revance, and Pfizer; received honoraria from American Academy of Neurology, Headache Cooperative of the Pacific, Canadian Headache Society, MF Med Ed Research, BioPharm Communications, CEA Group Holding Company (Clinical Education Alliance LLC), Teva (speaking), Amgen (speaking), Eli Lilly (speaking), Lundbeck (speaking), Pfizer (speaking), Vector Psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, MedLogix Communications, Medica Communications LLC, MJH Life Sciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, and Cambridge University Press. Non-profit board membership: American Brain Foundation, American Migraine Foundation, ONE Neurology, Precon Health Foundation, International Headache Society Global Patient Advocacy Coalition, Atria Health Collaborative, Arizona Brain Injury Alliance, and Domestic Violence HOPE Foundation/Panfila; received research support from Department of Defense, National Institutes of Health, Sperling Foundation, American Migraine Foundation, Henry Jackson Foundation, and Patient-Centered Outcomes Research Institute (PCORI). Stock options/shareholder/patents/board of directors: Ctrl M (options), Aural Analytics (options), Axon Therapeutics, ExSano (options), Palion (options), Man and Science, Healint (options), Theranica (options), Second Opinion/Mobile Health (options), Epien (options/board), Nocira (options), Matterhorn (shares/board), Ontologics (shares/board), King-Devick Technologies (options/board), Precon Health (options/board), AYYA Biosciences (options), Axon Therapeutics (options/board), Cephalgia Group (options/board), and Atria Health (options/employee). Patent 17189376.1-1466:v, Title: Onabotulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis (Non-royalty bearing). Patent application submitted: SynaQuell® (PreCon Health). **Stewart J. Tepper** received research funding from AbbVie, Eon, Amgen, Annovis, Axsome, Cassava, Cognition, Eli Lilly, Inhibikase, Ipsen, Lundbeck, Merz, Neurolief, Pfizer, PrecisionMed, Revance, Scilex, Suven, and UCB; served as consultant and/or on advisory boards (honoraria) of AbbVie, Eon, AlphaSights, Amgen, Aruene/eNeura, Atheneum, Axsome Therapeutics, Becker Pharmaceutical Consulting, ClearView Healthcare Partners, Click Therapeutics, CoolTech, CRG, Decision Resources, Defined Health, DRG, Eli Lilly, ExpertConnect, FCB Health, Fenix, GLG, Guidepoint Global, Health Advances, Health Science Communications, HMP Communications, Impel, Initiator Pharma, Interactive Forums, KeyQuest, Ki Health Partners, Krog and Partners, Lundbeck, M3 Global Research, Magellan Health, Magnolia Innovation, Miravo Healthcare, MJH Holdings, NeuroFront Therapeutics, Neurolief, Nocira, Novartis, P Value Communications, Pain Insights, Inc., Palion Medical, Perfood, Pfizer, Pulmatrix, Putnam Associates, Rehaler, SAI MedPartners, Satsuma, Scilex, Slingshot Insights, Spherix Global Insights, Strategy Inc., Synapse Medical Communication, System Analytic, Taylor and Francis, Tegus, Teva, Theranica, Tonix, Trinity Partners, Unity HA, Vial, and XOC; received salary from Dartmouth-Hitchcock Medical Center, Thomas Jefferson University, and Ki Health Partners; served on speakers bureau of AbbVie, Eli Lilly, Pfizer, Scilex, and Teva; received CME honoraria from American Academy of Neurology, American Headache Society, Annenberg Center for Health Sciences, Catamount Medical Education, Diamond Headache Clinic, Forefront Collaborative, Haymarket Medical Education, HMP Global, Medical Education Speakers Network, Medical Learning Institute PeerView, Migraine Association of Ireland, Miller Medical Education, National Association for Continuing Education, North American Center for CME, The Ohio State University, Physicians' Education Resource, PlatformQ Education, Primed, Vindico Medical Education, and WebMD/Medscape. **Jessica Ailani** received consulting (Honoraria) fees from AbbVie, Eon, Dr. Reddy's, Eli Lilly, GlaxoSmithKline,

Lundbeck, Linpharma, Ipsen, Merz, Miravo, Pfizer, Neurolief, Gore, Satsuma, Scilex, Theranica, and Tonix; received grant to institution for clinical trials from Parema and Ipsen; served on editorial boards/steering committee of Current Pain and Headache Reports, Medscape, and SELF magazine (medical editor). **Ani C. Khodavirdi, Nico Pannacciulli, Shia T. Kent, Karminder Gill, Robert Urman**, and **Sam S. Oh** are employees and stockholders of Amgen Inc. **Alan Fu** was an Amgen Inc. employee at the time of the study and holds Amgen Inc. stocks and is currently an employee of Astellas.

AUTHORSHIP

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Dodick DW, Tepper SJ, Ailani J, et al. Effect of erenumab versus other migraine preventive medications on cardiovascular and cerebrovascular outcomes: A United States claims database-based observational cohort study. *Headache*. 2025;65:919-932. doi:10.1111/head.14912