RESEARCH ARTICLE

Calcitonin Gene–Related Peptide Inhibitors and Cardiovascular Events in Patients With Migraine

A Retrospective, Observational Cohort Study

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Neurology® 2026;106:e214479. doi:10.1212/WNL.0000000000214479

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Abstract

Background and Objectives

Calcitonin gene–related peptide (CGRP) inhibitors have entered widespread use in the United States for treatment of migraine, but data on their cardiovascular risk profile are lacking. The objective of this study was to determine whether exposure to a CGRP inhibitor is associated with cardiovascular events in patients with migraine.

Methods

A retrospective, observational, cohort study was conducted using computerized claims data from a proprietary, insurance-based registry, MarketScan (by Merative). Beneficiaries with at least one claim related to a migraine diagnosis and continuous coverage for at least 12 months before migraine diagnosis were included. Using a sequential trial framework, the rate of cardiovascular events was computed in those who did and did not initiate a CGRP inhibitor, using both crude estimates and those derived in propensity score overlap-weighted cohorts. Adjusted hazard ratios (HR) and corresponding 95% CI were computed. The principal exposure was initiation of any CGRP inhibitor. The primary end point was a composite of myocardial infarction (MI), cerebral ischemic stroke, revascularization, peripheral arterial disease, or central retinal artery occlusion (CRAO). Secondary end points included each component individually. A falsification end point (humeral fracture) was included.

Results

In total, 900,370 beneficiaries (median age 41 [Q1, Q3: 31, 51] years; 77.8% female) were included, of whom 58,679 initiated a CGRP inhibitor and 841,691 did not initiate a CGRP inhibitor during the study period. Beneficiaries initiating a CGRP inhibitor exhibited a greater degree of cardiovascular morbidity at baseline than noninitiators. In the overlap-weighted analysis, there was a higher rate of the primary end point among beneficiaries who initiated a CGRP inhibitor (8.77 events/1,000 person-years vs 6.76 events/1,000 person-years; aHR 1.26 [95% CI 1.10–1.45]). Initiation of a CGRP inhibitor was associated with a significantly higher rate of one secondary end point (ischemic stroke [aHR 1.26 (95% CI 1.07–1.49)]) but not 4 other secondary end points: MI, revascularization, CRAO, and intracranial hemorrhage.

Discussion

In a nationwide cohort study, initiation of a CGRP inhibitor was associated with an increased risk of a composite of cardiovascular events; however, the magnitude of the increased risk was low.

Classification of Evidence

This study provides Class II evidence that in patients with migraine, initiation of a CGRP inhibitor was associated with a modestly increased risk of a composite of cardiovascular events.

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Supplementary Material

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Glossary

CGRP = calcitonin gene–related peptide; **CRAO** = central retinal artery occlusion; **HR** = hazard ratio; **ICH** = intracranial hemorrhage; **MI** = myocardial infarction; **PAD** = peripheral arterial disease; **SMD** = standardized mean difference.

Introduction

Migraine is a common condition that causes acute, disabling attacks of craniofacial pain and is a risk factor of cardiovascular events.[1] Calcitonin gene–related peptide (CGRP) inhibitors comprise an emerging class of migraine abortive and preventive agents that have become increasingly widespread since 2018. This medication class includes 4 small-molecule CGRP receptor antagonists, one monoclonal antibody to the CGRP receptor, and 3 monoclonal antibodies to soluble CGRP. These medications are well tolerated.[2] However, because of their relative novelty, their cardiovascular risk profile is supported by fewer data.

In theory, CGRP inhibitors may have an adverse cardiovascular risk profile, because CGRP—under normal physiology—may confer benefits with respect to blood pressure reduction and the adaptive response to vascular injury.[3] Several analyses that pooled short-term data from randomized, controlled, clinical trials have been published, which did not show an elevated risk of cardiovascular events among patients treated with a CGRP inhibitor.[4-6] Similarly, postmarketing surveillance studies from the United States[7,8] and Europe[9] have not raised concerns about elevated cardiovascular risk. A previous population-based study[10] of fee-for-service Medicare beneficiaries in the United States found that there was no elevated risk of cardiovascular events in those who initiated a CGRP monoclonal antibody when compared with those who received an onabotulinum toxin injection. However, this study primarily included those older than 65 years and did not consider small-molecule CGRP receptor antagonists.[10]

The objective of this study was to determine whether CGRP inhibitor initiation was associated with major adverse cardiovascular and cerebrovascular events in a nationally representative cohort of adults aged 18–64 years with migraine in the context of real-world practice.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Because this study used deidentified data, the requirement for informed consent was waived by the Institutional Review Board of the Duke University School of Medicine, Durham, NC (919-668-5111).

Study Design

This is a retrospective, observational, cohort study. The primary objective was to determine whether exposure to a CGRP inhibitor was associated with an increased risk of cardiovascular events. A complete "Statistical Analysis Plan" and the completed Reporting of Studies Conducted Using Observational Routinely-Collected Data (RECORD)[11] checklist are included in the Supplementary Material (eSAP).

Study Setting

Data were derived from the computerized files of MarketScan by Merative, a proprietary health insurance program that includes deidentified, longitudinal, patient-level claims and specialty data for more than 270 million unique patients.[12] Data on inpatient stays, outpatient care, and pharmacy claims were used for this study.

Study Population

Adults aged 18–64 years (inclusive) with a claim corresponding to migraine at any point during their period of coverage, who were enrolled in private health insurance captured in the MarketScan Commercial Database, were included. The study period was 2018–2023, chosen to correspond with the period during which CGRP inhibitors became available in the United States.

This study included beneficiaries with 12 months of continuous medical and prescription coverage before the first diagnosis of migraine. Beneficiaries without continuous coverage; those with incomplete medical history/prescription data; and those with a history of cerebral ischemic stroke, myocardial infarction (MI), central retinal artery occlusion (CRAO), peripheral arterial disease (PAD), revascularization, or intracranial hemorrhage (ICH) before the index date were excluded.

Exposures

The exposure in this study was initiation of a member of the CGRP inhibitor medication class. This was defined as ≥1 prescription fill for small-molecule CGRP receptor antagonists (rimegepant, ubrogepant, zavegepant, or atogepant) or a monoclonal antibody to the CGRP receptor (erenumab) or soluble CGRP (eptinezumab, fremanezumab, or galcanezumab). Once a beneficiary had a prescription fill for a member of this class, they were removed from the pool of beneficiaries to initiate a CGRP inhibitor (and so repeat prescription fills were not reflected in our primary analysis). International Classification of Diseases coding strategies used to identify individual medications are included within the eSAP.

End Points

The primary study end point was time to development of a major adverse cardiovascular or cerebrovascular event, which included (1) MI, (2) cerebral ischemic stroke,[13] (3)

PAD, (4) revascularization, or (5) retinal stroke (CRAO).[14] Secondary end points included each component of the composite end point considered individually and time to ICH. A falsification end point (humeral fracture) was included to examine for the possibility of residual confounding across groups.

Statistical Analyses

The study cohort was disaggregated into CGRP inhibitor–initiating and noninitiating patients. Descriptive statistics were computed using counts and percentages for categorical variables and medians with first (Q1) and third (Q3) quartiles for continuous variables. Between-group differences were outlined by means of standardized mean differences (SMDs).

A series of propensity score overlap-weighted[15-17] Cox models were fit to examine the association between CGRP inhibitor initiation and each study end point. In overlap weighting, individual beneficiaries are weighted in proportion to their propensity to be in the opposite group, thereby giving more weight to those beneficiaries with the closest overlap in baseline characteristics. First, propensity scores were derived from a multiple logistic regression model, with CGRP inhibitor initiation vs noninitiation as the dependent variable. Covariates included age, biological sex, time from migraine diagnosis to index date, migraine with aura, comorbidities (including cardiovascular risk factors), state, geographic region, and metrics of overall health care utilization (number of inpatient days in preceding year, number of emergency department visits, and number of outpatient visits). Given the impact that concomitant triptan exposure could have on any observed results, several parameters reflecting baseline migraine medication use were included (including number of unique prescription medications in the year before index date, an indicator variable reporting triptan exposure [or not], total days of triptan coverage in the year before, and number of other migraine medications in the year before index date). Self-reported race and ethnicity are not available in MarketScan and thus could not be included in this analysis.

To partially mitigate the impact of selection bias and immortal time bias on observed results, a sequential trial design was adopted. In this design, the study period is divided into epochs of 1 week in length. Each 1-week period corresponds to the period after which a subsequent trial data set is created and is hereafter referred to as a "trial replicate." The anchor data for each trial include the date of CGRP fill (in the case of CGRP inhibitor initiation) or a randomly selected date in the same week (in the case of no CGRP inhibitor initiation). Once a beneficiary initiates a CGRP inhibitor, they are not included in subsequent trial replicates but remain enrolled in all previous trials until censoring or the end of the study period. Propensity scores were re-derived for each individual trial replicate to ensure that the most up-to-date metrics of health care utilization were accounted for. Censoring occurred after development of an end point, at loss of coverage, or at the end of the study period. This approach was replicated for each secondary end point and for the falsification end point.

All trial data sets were pooled into a single data set with indicators for the trial group. A standard Cox model was fit with stratification by trial group using the jackknife method for standard error estimation to account for the inclusion of individuals multiple times. This was repeated in a propensity score overlap-weighted cohort. A hazard ratio (HR) with its corresponding 95% CI was derived for each end point in both unweighted and weighted cohorts. The minimum strength of association that an unmeasured confounder would need to exhibit to negate the observed results (the E value[18]) was computed for our primary end point.

To assess the sensitivity of the observed results to the mode of CGRP inhibitor use, CGRP inhibitors were divided into those that are primarily used for abortive therapy (rimegepant, ubrogepant, zavegepant) and those that are primarily used for preventive therapy (atogepant, erenumab, eptinezumab, fremanezumab, and galcanezumab) and the analysis was repeated. In a further supplemental analysis, we excluded beneficiaries who did not exhibit ongoing claims for their originally assigned therapy (an approximate analog of a per-protocol framework). In this supplemental analysis, (1) within each individual synthetic trial, if a beneficiary was assigned no CGRP treatment at index, they were censored at the date of CGRP initiation and (2) within each synthetic trial, if a patient was assigned CGRP treatment at trial index, they were censored 30 days after the end of their days supply of the last CGRP prescription received, provided that occurred within the study period (calculated from date of last prescription + days supply + 30 days).

A two-sided alpha of 0.05 was considered indicative of statistical significance for all statistical tests. Because the width of the presented 95% CIs was not adjusted for multiplicity, all point estimates and their corresponding 95% CIs for each secondary end point should be treated as hypothesis-generating only. Analyses were performed using Python software (version 3.12.0; in a proprietary Snowflake-based environment) and in R (version 4.4.2).

Data Availability

This study used data from MarketScan by Merative. Use of this data set requires a data usage agreement with Merative; thus, individual deidentified beneficiary data cannot be shared. The statistical analysis plan (SAP) for this study is available in the eSAP. Exploratory data analysis was performed before finalizing the SAP, and thus, this analysis cannot be considered as prespecified. Data sharing agreements require an application process to Merative for other researchers to access the data. Analytic code is available on request to the corresponding author.

Results

Baseline Characteristics

Figure 1 presents the flowchart of the study cohort derivation. In total, 900,370 beneficiaries (median age 41 [Q1, Q3: 31,

51] years; 77.8% female) were included, of whom 58,679 initiated a CGRP inhibitor and 841,691 did not initiate a CGRP inhibitor. Among those who initiated a CGRP inhibitor, 41,871 initiated a small-molecule CGRP (rimegepant, ubrogepant, zavegepant, or atogepant) and 16,808 initiated a monoclonal antibody (erenumab, eptinezumab, fremanezumab, or galcanezumab). Baseline characteristics of the study cohort are presented in Table 1. In general, those initiating a CGRP inhibitor were more likely to be female (84.2% vs 77.4% [SMD 0.741]) and a greater proportion exhibited vascular risk factors including hypertension (23.9% vs 21.2% [SMD 0.065]), hyperlipidemia (24.3% vs 20.9% [SMD 0.081]), and diabetes mellitus (7.4% vs 6.4% [SMD 0.041]). There was also a greater preponderance of migraine with aura among CGRP inhibitor initiators (19.6% vs 9.2% [SMD 0.297]). Those initiating a CGRP inhibitor exhibited higher overall metrics of health care utilization, including a higher total prescription count in the year before the index date (10.0 [Q1, Q3: 6.0, 16.0]) vs 5.0 [Q1, Q3: 2.0, 9.0]) and a higher number of outpatient visits (15.0 [Q1, Q3: 7.0, 27.0] vs8.0 [Q1, Q3: 3.0, 18.0]). Standardized mean differences in the unweighted and overlap-weighted cohorts are depicted in eFigure 1.

Primary End Point

Table 2 and Figure 2 present the crude and overlap-weighted estimates for the primary analysis comparing initiation of any CGRP inhibitor with no CGRP inhibitor initiation. In the crude analysis, initiation of a CGRP inhibitor was associated with a higher rate of the primary composite end point (8.78 events/1,000 person-years vs 5.73 events/1,000 person-years; HR 1.44 [95% CI 1.31–1.59]). In the overlap-weighted analysis, there remained a higher rate of the primary end point (8.77 events/1,000 person-years vs 6.76 events/1,000 person-years; aHR 1.26 [95% CI 1.10–1.45]). The E-value for the point estimate in the primary analysis was 1.83.

Secondary End Points

There was a higher adjusted rate of ischemic stroke among CGRP inhibitor initiators (aHR 1.26 [95% CI 1.07–1.49]). There was a nominally but not significantly increased hazard of the other secondary end points including MI (aHR 1.27 [95% CI 0.99–1.64]), revascularization (aHR 1.23 [95% CI 0.82–1.84]), CRAO (aHR 1.52 [95% CI 0.28–8.15]), and ICH (aHR 1.48 [95% CI 0.85–2.55]).

Falsification End Point

CGRP inhibitor initiation was not associated with a higher rate of humeral fracture (1.54/1,000 person-years vs 1.44/1,000 person-years; aHR 1.04 [95% CI 0.76–1.42]).

Supplemental/Sensitivity Analyses

Initiation of an abortive small-molecule CGRP inhibitor was associated with a higher rate of the primary end point (9.15/1,000 person-years vs 6.63/1,000 person-years; aHR 1.31 [95% CI 1.12–1.53]; Table 3). Similarly, abortive small-molecule CGRP inhibitor initiation was associated with a higher hazard of ischemic stroke (aHR 1.36 [95% CI 1.12–1.64]) and ICH (aHR 1.86 [95% CI 1.03–3.38]), but not MI (aHR 1.16 [95% CI 0.85–1.57]), revascularization (aHR 1.26 [95% CI 0.79–2.02]), or CRAO (aHR 3.02 [95% CI 0.51–17.96]). Initiation of a preventive CGRP inhibitor was associated with a higher rate of the primary end point (aHR 1.33 [95% CI 1.10–1.61]; Table 4), MI (aHR 1.50 [95% CI 1.08–2.10]), and ischemic stroke (aHR 1.29 [95% CI 1.02–1.64]), but not revascularization (aHR 1.30 [95% CI 0.74–2.28]) or ICH (aHR 0.92 [95% CI 0.37–2.30]). When we censored beneficiaries who deviated from their originally assigned treatment strategy, the results were largely unchanged for our primary end point (aHR 1.35 [95% CI 1.16–1.57]).

Figure 1 Flowchart of Cohort Derivation

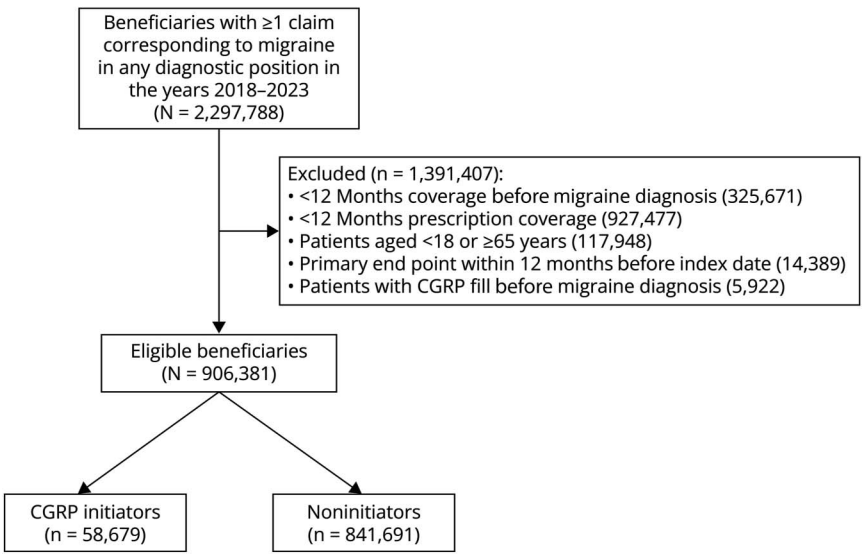


Table 1 Baseline Characteristics of the Study Population (Unweighted)

	Overall (N = 900,370)	CGRP user (n = 58,679)	Non-CGRP user (n = 841,691)	SMD
Age (y, median, [Q1, Q3])	41.0 (31.0, 51.0)	41.0 (32.0, 50.0)	41.0 (30.0, 51.0)	−0.006
Biological sex, n (%)				0.174
Female	700,777 (77.8)	49,422 (84.2)	651,355 (77.4)	
Male	199,593 (22.2)	9,257 (15.8)	190,336 (22.6)	
Year of migraine diagnosis, n (%)				0.176
2018	216,344 (24.0)	11,725 (20.0)	204,619 (24.3)	
2019	177,636 (19.7)	10,519 (17.9)	167,117 (19.9)	
2020	136,613 (15.2)	10,422 (17.8)	126,191 (15.0)	
2021	134,433 (14.9)	10,709 (18.3)	123,724 (14.7)	
2022	115,556 (12.8)	8,769 (14.9)	106,787 (12.7)	
2023	119,788 (13.3	6,535 (11.1)	113,253 (13.5)	
Region, n (%)				0.213
South	410,971 (45.6)	32,276 (55.0)	378,695 (45.0)	
North Central	192,065 (21.3)	11,329 (19.3)	180,736 (21.5)	
West	148,671 (16.5)	7,074 (12.1)	141,597 (16.8)	
Northeast	146,729 (16.3)	7,938 (13.5)	138,791 (16.5)	
Unknown	1,934 (0.2)	62 (0.1)	1,872 (0.2)	
Medical history, n (%)				
Hypertension	192,303 (21.4)	14,012 (23.9)	178,291 (21.2)	0.065
Depression	190,970 (21.2)	17,061 (29.1)	173,909 (20.7)	0.196
Hyperlipidemia	190,166 (21.1)	14,260 (24.3)	175,906 (20.9)	0.081
Migraine with aura	89,291 (9.9)	11,477 (19.6)	77,814 (9.2)	0.297
COPD	63,156 (7.0)	5,484 (9.3)	57,672 (6.9)	0.092
Diabetes mellitus	58,076 (6.5)	4,350 (7.4)	53,726 (6.4)	0.041
Liver disease (mild)	34,705 (3.9)	2,693 (4.6)	32,012 (3.8)	0.039
Cerebrovascular disease	26,357 (2.9)	2,922 (5.0)	23,435 (2.8)	0.114
Connective tissue disease	23,855 (2.6)	2,518 (4.3)	21,337 (2.5)	0.097
Valvular heart disease	23,479 (2.6)	1,975 (3.4)	21,504 (2.6)	0.048
Illicit drug use	20,124 (2.2)	1,490 (2.5)	18,634 (2.2)	0.021
Peripheral vascular disease	16,818 (1.9)	1,562 (2.7)	15,256 (1.8)	0.057
Diabetes mellitus (complicated)	15,694 (1.7)	1,247 (2.1)	14,447 (1.7)	0.03
Renal disease	12,125 (1.3)	959 (1.6)	11,166 (1.3)	0.025
Cancer (nonmetastatic)	10,865 (1.2)	669 (1.1)	10,196 (1.2)	0.007
Psychiatric disease	10,436 (1.2)	868 (1.5)	9,568 (1.1)	0.03
Congestive heart failure	8,533 (0.9)	7,915 (0.9)	618 (1.1)	0.011
Peptic ulcer disease	6,138 (0.7)	577 (1.0)	5,561 (0.7)	0.036
Cancer (metastatic)	5,240 (0.6)	198 (0.3)	5,042 (0.6)	0.038
Hemiplegia/paraplegia	3,378 (0.4)	335 (0.6)	3,043 (0.4)	0.031

Continued

Table 1 Baseline Characteristics of the Study Population (Unweighted) *(continued)*

	Overall (N = 900,370)	CGRP user (n = 58,679)	Non-CGRP user (n = 841,691)	SMD
HIV	1,708 (0.2)	104 (0.2)	1,604 (0.2)	0.003
Liver disease (moderate-severe)	984 (0.1)	43 (0.1)	941 (0.1)	0.013
Dementia	879 (0.1)	94 (0.2)	785 (0.1)	0.019
Overall health care utilization[a]				
Prescription count, n (%)	5.0 [2.0, 10.0]	10.0 [6.0, 16.0]	5.0 [2.0, 9.0]	0.713
Triptan prescription count, n (%)	193, 385 (21.5)	26, 422 (45.0)	166, 963 (19.8)	0.559
Other migraine prescription count, n (%)[b]	1, 048 (0.1)	446 (0.8)	602 (0.1)	0.107
Inpatient admission count (median [Q1, Q3])	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.001
Outpatient visits (median [Q1, Q3])	9.0 [4.0, 18.0]	15.0 [7.0, 27.0]	8.0 [3.0, 18.0]	0.393
ED visits (median [Q1, Q3])	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.105

Abbreviations: COPD = chronic obstructive pulmonary disease; ED = emergency department; CGRP = calcitonin gene–related peptide; HIV = human immunodeficiency virus; n = number; Q1 = first quartile; Q3 = third quartile; SMD = standardized mean difference.
[a] In the 12 mo preceding study index date.
[b] Other than triptans and CGRP inhibitors.

Classification of Evidence

This study provides Class II evidence that in patients with migraine, initiation of a calcitonin gene–related peptide (CGRP) inhibitor was associated with a modestly increased risk of a composite of cardiovascular events.

Discussion

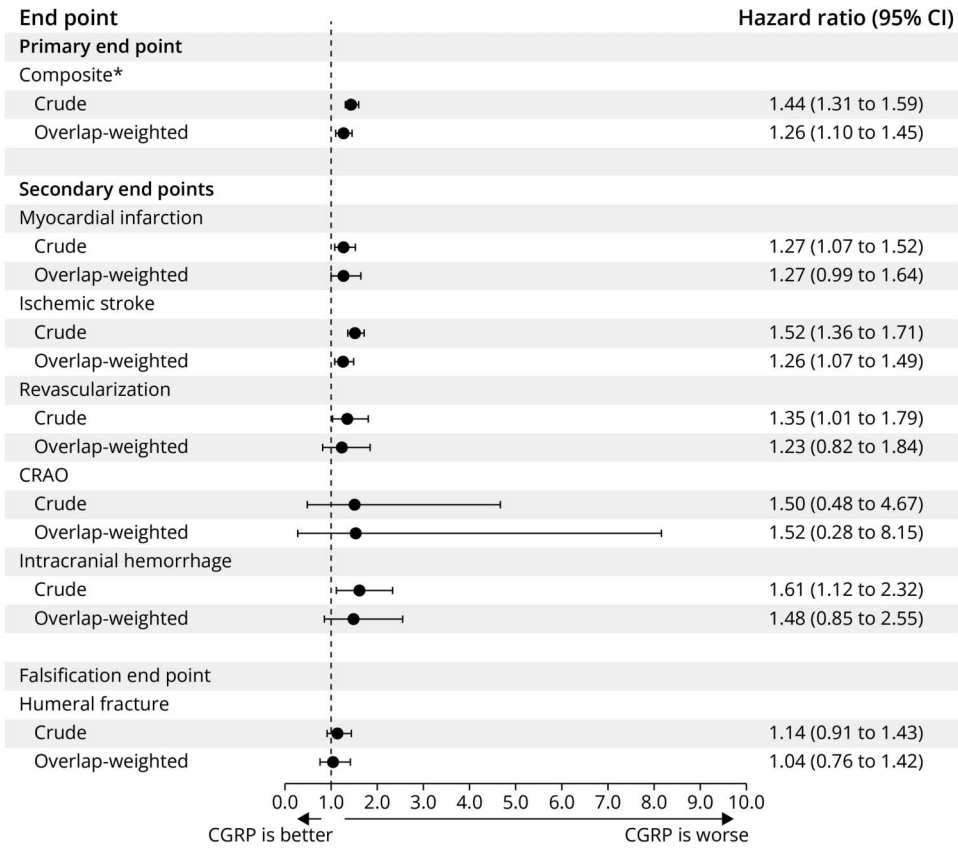
In this nationwide study of MarketScan beneficiaries aged 18–64 years with a diagnosis of migraine and almost 50,000 person-years of combined CGRP inhibitor exposure,

Table 2 Primary and Secondary Study End Points

	Unweighted cohort[a]			Weighted cohort[b]		
	CGRP initiation	No CGRP initiation		CGRP initiation	No CGRP initiation	
	Count (%)	Count (%)	HR (95% CI)	Count (%)	Count (%)	HR (95% CI)
Primary end point						
Composite of **MI** **Ischemic stroke** **Revascularization** **PAD** **CRAO**	8.78	5.73	1.44 (1.31–1.59)	8.77	6.76	1.26 (1.10–1.45)
Secondary end points						
MI	2.42	1.89	1.27 (1.07–1.52)	2.42	1.91	1.27 (0.99–1.64)
Ischemic stroke	5.81	3.48	1.52 (1.36–1.71)	5.81	4.43	1.26 (1.07–1.49)
Revascularization	0.94	0.72	1.35 (1.01–1.79)	0.93	0.77	1.23 (0.82–1.84)
CRAO	0.06	0.04	1.50 (0.48–4.67)	0.06	0.04	1.52 (0.28–8.15)
ICH	0.58	0.31	1.61 (1.12–2.32)	0.58	0.37	1.48 (0.85–2.55)
Falsification end point						
Humeral Fracture	1.54	1.36	1.14 (0.91–1.43)	1.54	1.44	1.04 (0.76–1.42)

Abbreviations: CRAO = central retinal artery occlusion; CGRP = calcitonin gene–related peptide; HR = hazard ratio; ICH = intracranial hemorrhage; MI = myocardial infarction; RAO = retinal artery occlusion.
[a] The unweighted cohort comprised 36,544,503 person-trials with an aggregate CGRP exposure of 49,680.9 person-years and non-CGRP exposure of 69,022,657.4 person-years.
[b] The weighted cohort comprised 65,554.6 person-trials with an aggregate CGRP exposure of 49,497.5 person-years and non-CGRP exposure of 65,990.5 person-years.

Figure 2 Study End Points in Patients Exposed to CGRP Inhibitors (Versus Not Exposed to CGRP Inhibitors)



CGRP = calcitonin gene–related peptide.

there was a modestly increased risk of major adverse cardiovascular events among those who initiated a CGRP inhibitor. Those initiating a CGRP inhibitor had a substantially higher burden of cardiovascular risk factors (including hypertension, hypercholesterolemia, and diabetes mellitus), a higher likelihood of having migraine with aura, and a higher tendency to overall health care utilization. Thus, it is strongly likely that, in real-world practice, clinicians are correctly selecting out participants at higher cardiovascular risk for CGRP inhibitor therapy and, although these parameters were included in deriving propensity scores, it remains probable that unmeasured elements of cardiovascular risk may explain the observed association. Our primary study result was durable when stratified by abortive vs preventive CGRP inhibitors and when results were analyzed under a per protocol-type framework. The low absolute magnitude of this association adds to the body of literature, suggesting that CGRP inhibitors can be deployed safely in people with migraine, even when there are preexisting vascular risk factors.

These findings occur in the context of several previous studies. Small, retrospective, observational cohort studies[19-21] and a phase 4, randomized, controlled trial[22] did not indicate an elevated risk of cardiovascular events among patients initiating a CGRP inhibitor. Pooled analyses of late-stage clinical trials of fremanezumab,[4] galcanezumab,[5] and erenumab[6] did not detect evidence of increased cardiovascular risk across increasing dosage or when compared with placebo-allocated trial participants. In each study, cardiovascular events occurred in less than 1% of enrolled participants. Strengths of secondary clinical trial analyses include the use of standardized case record forms, uniform selection criteria, and the ability to track physiologic data. For instance, 2 pooled analyses[5,6] examined temporal trajectories of blood pressure while one pooled analysis[6] further examined pulse and QT interval during exposure to CGRP inhibitors. Neither demonstrated any significant difference between those exposed to CGRP inhibitors and placebo participants. However, even pooled analyses of large trials remain underpowered to detect important but rare safety events especially among populations that are at low cardiovascular risk at trial entry. It is important to note that it is challenging to directly compare our study with these previous studies because administrative claims databases confer different population attributes than regional observational cohort studies or clinical trial cohorts.

Several postmarketing surveillance studies have examined safety reports of patients exposed to CGRP monoclonal antibodies. A study drawing data from the European Spontaneous Adverse Event Reporting System[9] identified a low overall risk of cardiovascular events. However, those event reports included new hypertension, venous thromboembolism, atrial

Table 3 Primary and Secondary Study End Points Stratified by CGRP Subtype: Abortive Small-Molecule CGRP Inhibitors[a] vs No Initiations

	Unweighted cohort[b]			Weighted cohort[c]		
	CGRP initiation	No CGRP initiation		CGRP initiation	No CGRP initiation	
	Rate per 1,000 person-years	Rate per 1,000 person-years	HR (95% CI)	Rate per 1,000 person-years	Rate per 1,000 person-years	HR (95% CI)
Primary end point						
Composite	9.15	5.68	1.51 (1.34–1	9.15	6.63	1.31 (1.12–1.53)
Secondary end points						
MI	2.21	1.90	1.17 (0.92–1.48)	2.21	1.91	1.16 (0.85–1.57)
Ischemic stroke	6.28	3.41	1.64 (1.43–1.89)	6.27	4.31	1.36 (1.12–1.64)
Revascularization	0.96	0.72	1.39 (0.97–1.99)	0.96	0.77	1.26 (0.79–2.02)
CRAO	0.10	0.04	2.46 (0.79–7.64)	0.10	0.04	3.02 (0.51–17.96)
ICH	0.70	0.31	1.93 (1.27–1.93)	0.70	0.36	1.86 (1.03–3.38)
Falsification end point						
Humeral fracture	1.28	1.35	0.96 (0.71–1.31)	1.28	1.43	0.90 (0.61–1.33)

Abbreviations: CRAO = central retinal artery occlusion; CGRP = calcitonin gene–related peptide; HR = hazard ratio; ICH = intracranial hemorrhage; MI = myocardial infarction; RAO = retinal artery occlusion.
[a] Rimegepant, ubrogepant, or zavegepant.
[b] The unweighted cohort comprised 35,954,205 person-trials with an aggregate CGRP exposure of 30,932.4 person-years and non-CGRP exposure of 67,399,909.4 person-years.
[c] The weighted cohort comprised 53,196.2 person-trials with an aggregate CGRP exposure of 30,807.8 person-years and non-CGRP exposure of 63,176.7 person-years.

fibrillation, and MI. The proportion of reported safety events that were associated with cardiovascular risk ranged from 11.7% (galcanezumab) to 14.1% (fremanezumab). In a study drawn from the US FDA Adverse Events Reporting System,[8] the risks of major adverse cardiovascular events were quantified among those exposed to CGRP monoclonal antibodies. The reporting rate for MI per 1,000 exposed patients was 0.04 for erenumab, 0.08 for galcanezumab, and 0 for fremanezumab. The reporting rate for ischemic stroke was 0.02 for erenumab and 0 for both fremanezumab and galcanezumab. The reporting rate for "cerebrovascular accident" (reported separately to "ischemic stroke") was 0.11 for erenumab, 0.08 for fremanezumab, and 0.05 for galcanezumab. A second postmarketing surveillance study from the FDA Adverse Events Reporting System[7] reported signals for hypertension and palpitations that were shared across constituents of the CGRP monoclonal antibody class.

There are several potential explanations for the observed results. First, CGRP is an endogenous neuropeptide that is secreted by perivascular sensory nerves with pleiotropic effects. Thus, it is biologically plausible that inhibition of CGRP activity increases vascular risk by inducing vasospasm and opposing other beneficial effects. Although exhibiting a distinct mechanism of action, vasospasm is posited as the mechanism that associates triptans with cardiovascular events[23,24] (although this proposed mechanism remains subject to debate because it is not clear that triptans exhibit a vasoconstrictive effect on the intracranial vasculature in humans).[25] Second, use of a CGRP inhibitor may act as a proxy for heightened migraine severity.[26] Migraine severity is associated with cardiovascular risk but likely increases the likelihood of filling a prescription for a CGRP inhibitor. Third, because CGRP inhibitors are believed to confer lower cardiovascular risk than other drug classes, it may be that physicians are preferentially prescribing them to patients with elevated cardiovascular risk for treatment. Fourth, it is plausible that CGRP inhibitors increase the propensity to develop hypertension. Published studies have yielded conflicting conclusions on the impact of CGRP inhibitors on hypertension.[27-29] However, postmarketing surveillance has suggested a signal with respect to development of hypertension for erenumab,[30] which now carries a boxed warning concerning the development of hypertension from FDA.

There are several methodological attributes of this study. First, it includes a representative population of adults younger than 65 years from a nationwide, proprietary, insurance-based registry. Second, this study actively identified beneficiaries who were exposed to CGRP inhibitors. This contrasts with postmarketing surveillance studies based on adverse events reporting systems, which rely on passive reporting by clinicians in real-world practice and do not contain information on the untreated general population. Third, we ascertained end points across multiple venues of care including inpatient admissions, outpatient clinic visits, and emergency

Table 4 Primary and Secondary Study End Points Stratified by CGRP Subtype: Preventive CGRP Inhibitors[a] vs No Initiation

	Unweighted cohort[b]			Weighted cohort[c]		
	CGRP initiation	No CGRP initiation		CGRP initiation	No CGRP initiation	
	Rate per 1,000 person-years	Rate per 1,000 person-years	HR (95% CI)	Rate per 1,000 person-years	Rate per 1,000 person-years	HR (95% CI)
Primary end point						
Composite	8.16	5.51	1.42 (1.21–1.67)	8.15	6.33	1.33 (1.10–1.61)
Secondary end points						
MI	2.75	1.87	1.46 (1.11–1.92)	2.75	1.88	1.50 (1.08–2.10)
Ischemic stroke	5.04	3.27	1.44 (1.18–1.77)	5.04	4.04	1.29 (1.02–1.64)
Revascularization	0.90	0.71	1.28 (0.80–2.07)	0.89	0.75	1.30 (0.74–2.28)
CRAO	<0.01	0.04	—	<0.01	0.04	—
ICH	0.37	0.29	1.14 (0.50–2.40)	0.37	0.35	0.92 (0.37–2.30)
Falsification end point						
Humeral fracture	1.96	1.36	1.45 (1.05–2.00)	1.96	1.42	1.34 (0.90–1.99)

Abbreviations: CRAO = central retinal artery occlusion; CGRP = calcitonin gene–related peptide; HR = hazard ratio; ICH = intracranial hemorrhage; MI = myocardial infarction; RAO = retinal artery occlusion.
[a] Atogepant, erenumab, eptinezumab, fremanezumab, or galcanezumab
[b] The unweighted cohort comprised 35,366,556 person-trials with an aggregate CGRP exposure of 18,748.4 person-years and non-CGRP exposure of 65,663,806.8 person-years.
[c] The weighted cohort comprised 41,700.2 person-trials with an aggregate CGRP exposure of 18,689.6 person-years and non-CGRP exposure of 60,459.3 person-years.

department presentations. Fourth, we used propensity score overlap weighting—a technique that emulates some aspects of a randomized controlled trial—in which those beneficiaries with the highest overlap in baseline characteristics were preferentially weighted. The overlap-weighting procedure was repeated for each individual trial replicate, which accounts for the possibility of changing vascular risk over time. Fifth, given the risks of immortal time bias and selection bias in observational studies that include actively treated beneficiaries and untreated controls, we adopted a sequential trial framework in which beneficiaries can contribute risk both before and during treatment initiation. Sixth, to assay for residual confounding, we included a falsification end point (humeral fracture), which indicated minimal residual difference across groups with respect to unmeasured confounders that might affect general medical risk or frailty. Finally, while migraine activity is an association of cardiovascular events,[31-36] we included time from migraine diagnosis to index data in propensity score derivation so as to harmonize this time interval between treated and untreated groups in our overlap-weighted population.

This study carries several limitations. First, in general, migraine is not well captured in administrative claims data because the most commonly used algorithms exhibit high specificity but low sensitivity.[37] However, in this study, we found that over 90% of those beneficiaries who initiated a CGRP inhibitor had a billing claim related to migraine before that prescription fill, likely a function of insurance reimbursement practices for this newer drug class. Second, MarketScan lacks key data including mortality, race, and ethnicity and only captures data on those participants who are actively enrolled in a participating insurance plan. Thus, we are unable to distinguish those who die from those who lose continuous insurance coverage, a property with could introduce bias in to the study if mortality is distributed systematically differently across CGRP inhibiting beneficiaries and non-CGRP inhibiting beneficiaries. In addition, in some cases, migraine index may be a function of the time of insurance enrollment as opposed to the true index date (although we suspect that this misclassification is nondifferential with respect to our principal exposure groups). These findings may not generalize to those participants who have an alternative mode of health care coverage, leave employment, or participate in a state-sponsored health care plan. Third, the principal exposure in this study is the first prescription fill for a CGRP inhibitor. The rationale for this design choice was that we wished to understand whether a strategy of clinician assignment to CGRP inhibitor therapy (and subsequent medication exposures that may or may not occur downstream of that) was associated with an increased risk of cardiovascular events. We performed a supplemental analysis in which beneficiaries were censored on deviating from their assigned exposure group, and results were largely unchanged. However, complex adherence patterns and the cadence of subsequent fills are not captured in this study design and may represent an important mediator of observed associations. Future work analyzing CGRP inhibitor therapy as a time-

varying exposure will be necessary to overcome this strong caveat. Fourth, the use of only a single falsification end point is a limitation. Residual, unmeasured confounding may exist across multiple dimensions (residual vascular risk, residual propensity to interact with the health care system, or residual frailty), and further falsification end points would have given context to the single presented falsification end point. Fifth, the individual elements of the composite primary end point may have distinct underlying causes (including ones that are independent of CGRP inhibitor exposure), and this important aspect cannot be disentangled with administrative claims data. Sixth, in our subgroup analysis, we clustered medications according to those primarily used for abortive therapy and those primarily used as preventive therapy, and an analysis clustering medications by pharmacologic category (small-molecule CGRP inhibitor vs monoclonal antibody) was not performed. Seventh, to assess study feasibility, we performed exploratory data analysis before locking our SAP. Based on this exploratory analysis, we purchased 2 additional years of data (2022 and 2023) from the vendor to increase the number of CGRP inhibitor–initiating beneficiaries in our data set to (a) improve the precision of our derived estimates and (b) better represent contemporary practice. Thus, this analysis cannot be considered prespecified. Finally, this observational study does not allow definitive causal inference to be made because the possibility of residual, unmeasured confounding remains. Indeed, the E-value corresponding to the point estimate for our primary analysis was 1.83—meaning that the observed aHR could be negated by an unmeasured confounder that is associated with both CGRP inhibitor initiation and our end point by a hazard ratio of at least 1.83 each. The CGRP inhibitor–initiating and noninitiating groups likely differ regarding unmeasured factors, which are not fully captured in our propensity score models.

In a nationwide cohort study, the initiation of a CGRP inhibitor was associated with an increased risk of a composite of cardiovascular events; however, the magnitude of the increased risk was low.

Author Contributions

J.B. Lusk: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. L.E. Wilson: drafting/revision of the manuscript for content, including medical writing for content. C. Moore: study concept or design; analysis or interpretation of data. S. Yarnell: study concept or design; analysis or interpretation of data. C. Kalapura: study concept or design; analysis or interpretation of data. A. Choudhury: study concept or design; analysis or interpretation of data. M. Schrag: study concept or design; analysis or interpretation of data. S. Poli: study concept or design; analysis or interpretation of data. F. Li: study concept or design; analysis or interpretation of data. B. Mac Grory: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

This study was funded by grant 23MRFSCD1077188 from the American Heart Association and by the Duke University Office of the Provost.

Disclosure

J.B. Lusk is supported by grants 23MRFSCD1077188 and 25GLP1450119 from the American Heart Association and by Duke Bass Connections. L.E. Wilson reports no disclosures relevant to the manuscript. C. Moore is supported by grants from NIH-NINDS (K01-NS121195), International Headache Society, Lily USA LLC, Duke Headache and Pain Dept Research, and Duke Office of Research & Innovation and is supported by and serves as a consultant for AbbVie Inc. S. Yarnell reports compensation from Sanofi Pasteur Inc. C. Kalapura and A. Choudhury report no disclosures relevant to the manuscript. M. Schrag reports compensation from the REVISION trial for data and safety monitoring services; compensation from Raymond James for consultant services; grants from the NIH; and compensation from Labaton Sucharow for consultant services. S. Poli reports acting as coordinating investigator of the REVISION trial (NCT04965038) and receiving research support from BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, German Federal Joint Committee Innovation Fund, German Federal Ministry of Education and Research, Helena Laboratories, and Werfen, as well as speakers' honoraria/consulting fees from Alexion, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Daiichi Sankyo, Portola, and Werfen. F. Li is supported by Duke Bass Connections and reports employment by Duke University. B. Mac Grory is supported by grants K23HL161426, UG3NS138219, and R03HL178686 from the NIH, grants 23MRFSCD1077188 and 25GLP1450119 from the American Heart Association, and grant 2835124 from the Duke Office of Physician Scientist Development; by Duke Bass Connections; and by the Duke University Office of the Provost. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® May 20, 2025. Accepted in final form October 30, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Rebecca Burch, MD.

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