


RESEARCH SUBMISSION

Cardiovascular risk and triptan usage among patients with migraine

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Abstract

Background: Migraine, a neurovascular disorder evident by recurrent headaches, is associated with increased risk of ischemic vascular events, including ischemic stroke and myocardial infarction. Triptans, acute migraine-specific treatment, cause vasoconstriction, complicating treatment decisions, especially for patients with migraine with cardiovascular risk factors. This study examined associations between triptan usage and cardiovascular (CV) events in patients with migraine.

Methods: This retrospective, population-based cohort study conducted in southern Israel utilized data from Clalit Health Services. Electronic medical records from January 2000 to January 2022 were analyzed to assess triptan usage and CV events within 90 days post-purchase among patients aged ≥ 18 years with a diagnosis of migraine based on International Classification of Diseases, Ninth Revision codes or triptan claims. Sensitivity analyses accounted for varying timeframes and usage patterns.

Results: Among 26,054 patients with migraine, 12,560 (48.2%) initiated triptan therapy. The prevalence of CV risk factors including dyslipidemia, diabetes mellitus, hypertension, smoking, atrial fibrillation, and obesity was higher in the non-triptan group (standardized mean difference [SMD] = 0.028–0.289). The mean (standard deviation) number of triptan pills used per month was 1.9 (1.5), with most patients (89.5%) using 1–4 pills/month. CV events within 90 days occurred slightly more in the triptan group (5.1%) compared to the non-triptan group (4.1%, SMD = 0.047). Multivariable analysis revealed no significant association between triptan use and increased CV events (adjusted hazard ratio 0.96, 95% confidence interval 0.77–1.23), controlling for demographic variables and CV risk factors. Sensitivity analyses also showed no significant risk with triptan use across different timeframes and usage patterns, reinforcing these findings. In the triptan group, patients with CV events were more likely to use triptans frequently, with a higher average number of pills per month.

Abbreviations: CHS, Clalit Health Services; CI, confidence interval; CV, cardiovascular; DAG, directed acyclic graph; (a)HR, (adjusted) hazard ratio; ICD, International Classification of Diseases; IPTW, inverse probability of treatment weighting; NMC, Negev Migraine Cohort; SEI, socioeconomic index; SMD, standardized mean difference.

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Conclusions: This retrospective, population-based study found that triptan usage did not increase CV risk among patients with migraine, even in those with existing CV risk factors, where no formal contraindication exists. The study highlights the importance of considering individual risk factors when prescribing triptans, as certain subgroups may still be at higher risk.

Plain Language Summary

Migraine is a common condition that is sometimes treated with medications called triptans, which can cause narrowing of blood vessels. This study looked at whether using triptans is linked to a higher risk of cardiovascular events, such as heart attacks or strokes, in patients with and without cardiovascular risk factors. The results showed no significant increase in cardiovascular risk for triptan users, suggesting that these medications can be safely prescribed to most patients as long as frequent and uninterrupted use are carefully monitored.

KEYWORDS

cardiovascular risk factors, ischemic stroke, ischemic vascular events, migraine, myocardial infarction, triptans

INTRODUCTION

Migraine is a neurovascular disorder evident by recurrent headaches and significant disability.¹ Beyond its burden on quality of life, several studies demonstrate an association between migraine, particularly migraine with aura in younger women, and increased risk of ischemic vascular events, including ischemic stroke and myocardial infarction.²⁻⁷ However, the absolute risk remains low, and the underlying mechanisms remain under investigation.

While cardiovascular (CV) risk factors such as hypertension and dyslipidemia are common with migraine,⁸⁻¹² causal associations remain unclear. A recent study suggest that these vascular disorders might be a consequence of migraine,¹³ while others suggest they are contributory factors.¹⁴ Several embolic factors are also implicated in migraine pathophysiology, including atrial fibrillation and patent foramen ovale.^{15,16} In addition, sociodemographic factors such as low socioeconomic status predict increased vascular risk with migraine. Given well-documented associations between socioeconomic status and CV health, it is critical to investigate its role in relation to migraine.¹⁷

A further complication that may affect vascular health is the role of specific anti-migraine medications. To date, few pharmacological options specifically target acute migraine attacks, with triptans being the most prescribed migraine-specific medication. Triptans, selective serotonin receptor agonists, effectively treat acute migraine attacks by targeting meningeal blood vessels and the trigeminovascular system receptors. Triptans inhibit the release of vasoactive peptides, including calcitonin gene-related peptide, into the synaptic cleft, suppress neurogenic inflammation, and block pain transmission along the trigeminal nerve.

The association between triptans and CV events has been a subject of investigation due to their vasoconstrictive properties.¹⁸ Triptans' receptor specificity, with minimal effects on intracerebral vasculature, underpins their CV safety despite concerns about vasoconstriction. On the other hand, research has shown that triptans can cause vasoconstriction in coronary arteries.¹⁹ This complicates risk-benefit analyses as reflected in treatment guidelines for patients with migraine, particularly those with established CV disease.

The emergence of gepants; calcitonin gene-related peptide receptor antagonists, which may impair compensatory vasodilation, with evidence from animal models suggesting potential vascular risks²⁰, reinforces the need for robust data on triptans' safety to guide treatment decisions even in the age of gepants.

Evidence addressing the real-world CV safety of triptan use remains limited. Existing studies have predominantly focused on highly selected populations or have lacked comprehensive data on confounding factors. Furthermore, the association between triptan usage and short-term CV events has not been adequately explored in population-based cohorts, leaving a critical gap in understanding the safety of triptans for patients with migraine, particularly those with pre-existing CV risk factors.

We hypothesized that triptan usage, a common acute treatment for migraine, would be associated with an increased incidence of CV events, such as myocardial infarction and ischemic stroke, among patients with migraine, particularly within a short timeframe (90 days) following drug purchase. This study aimed to examine this interplay between triptan usage and CV events in patients with migraine. Further understanding could lead to more effective prevention strategies and treatment options.

METHODS

Study setting

The healthcare system in Israel is universal, funded by monthly member premiums, user fees, and progressive income taxation up to 44%. The National Health Insurance Law mandates that all residents belong to one of four health service networks, which are legally prohibited from denying membership or canceling coverage. Clalit Health Services (CHS) is the largest of the four networks, serving most Israelis.

The CHS divided Israel into geographic regions to ensure that residents within each have similar access to health services. This study focuses on patients in the southern Negev region. The Negev, with Be'er Sheva as its capital, is home to 8.2% of Israelis; the majority are Jewish and 33% are Arab-Bedouin. Most municipalities in the south are ethnically homogenous. Soroka University Medical Center, a tertiary 1191-bed medical center, part of the CHS hospital network, is the largest regional hospital in southern Israel, providing comprehensive acute care and follow-up treatment. This unique setup in a large geographic area facilitates comprehensive and population-based assessment, with minimal referral bias, such that few patients are lost to follow-up, except for mortality.

Study design

This retrospective population-based cohort study was conducted to examine associations between triptan usage and CV events in patients with migraine. The study included all adults diagnosed with migraine within the southern district of the Clalit network. Eligible participants with migraine were identified based on recorded diagnoses according to the International Classification of Diseases, Ninth Revision (ICD-9, 1975), and/or claims for specific anti-migraine medication (triptans) between 2000 and 2022. The included ICD-9 codes were 346.x for migraine, encompassing classic migraine (346.0), common migraine (346.1), and other specified or unspecified migraine (346.8, 346.9). Triptans are migraine-specific²¹ and are only approved in Israel for the acute treatment of migraine. Triptans are prescription medications in Israel and cannot be purchased over the counter.

Participants

Patients with migraine examined for this study were derived from the Negev Migraine Cohort (NMC), a previous population-based, retrospective, observational cohort study within CHS, consisting of 26,054 adult (aged ≥ 18 years) patients with migraine, compared to 55,083 1:2 matched non-migraine controls, identified by sex, age and primary clinic from 2000 to 2022. The methodology, as well as patient characteristics, are described thoroughly elsewhere.²²

Data sources and variables

Anonymized electronic medical records include demographic information, clinical diagnoses, and medication purchases. Patients who purchased triptans between January 2000 and January 2022 were followed for 90 days post-purchase. Triptan usage was operationalized as the number of different types of triptans used and the frequency of purchases within the study period. Primary outcomes, occurrence of CV events (i.e., myocardial infarction or ischemic stroke) within 90 days post-triptan purchase, and CV risk factors, were identified using ICD codes and patient records. CV risk factors included hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking, as well as absolute contraindications to triptan use (i.e., prior myocardial infarction, prior ischemic stroke, coronary artery disease, atrial fibrillation/flutter, peripheral vascular disease). The Israel Central Bureau of Statistics socioeconomic index (SEI) was used as a proxy for socioeconomic status.

There were no missing data for the primary variables of interest, including triptan purchase, CV events, and demographic or clinical covariates used in the analyses. Patient records from the electronic medical records system were complete due to the comprehensive nature of the CHS database, which minimizes data loss. Additionally, no patients were excluded from the analysis based on missing data. Patients with <90 days of follow-up after triptan initiation were excluded.

Study sample size

The sample size was determined by the total number of eligible participants identified from the NMC database within the study period consisting of 26,054 participants: 12,560 in the triptan group and 13,494 in the non-triptan group. This population-based approach ensured that all available data were included for analysis, maximizing the study's ability to identify associations despite the relatively low prevalence of CV events in specific subgroups.

Quantitative variables

The following quantitative variables were assessed: age at migraine diagnosis, body mass index, SEI, hemoglobin A_{1c} levels (analyzed only for patients with diabetes mellitus), low-density lipoprotein cholesterol levels, triptan initiation age, time to triptan initiation post-diagnosis, triptan usage (categorized based on frequency and monthly pill consumption), CV risk factor diagnosis age, follow-up duration, and time from triptan purchase to CV event.

Statistical analyses

To describe demographics, clinical characteristics, and triptan usage, the distributions of continuous variables were assessed using

the Shapiro–Wilk test, then we computed means \pm standard deviations (SDs) for normally distributed quantitative variables, medians and interquartile ranges (IQRs) for non-normally distributed quantitative variables, and percentages for categorical variables. Continuous variables were evaluated using either independent samples *t*-tests for normally distributed data or Mann–Whitney *U* tests for non-normally distributed data. For categorical variables, Pearson's chi-squared test or Fisher's exact test was applied, depending on the expected cell counts. We compared the prevalence of CV risk factors, along with the usage of related medications and laboratory values, documented over the entire follow-up period, and CV events between the triptan versus non-triptan groups. All hypothesis testing was two-tailed, and a $p < 0.05$ was considered statistically significant. Scatter plots were generated to depict temporal associations between migraine diagnosis, triptan purchase, and CV events over time.

A multivariable mixed-effects regression model was computed to evaluate associations between triptan use and CV events, adjusting for demographic variables and CV risk factors. Cox proportional hazards models were computed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for CV events. We also undertook between-group analyses, patients with migraine with and without CV risk factors including hypertension, diabetes mellitus, dyslipidemia, obesity and smoking at treatment initiation compared to those with prior CV events.

In the triptan group, the categorization into subgroups with and without CV risk factors was made according to the time point of starting triptan therapy. For the non-triptan group, this categorization was based on a time point of 4 years after the migraine diagnosis, representing the median time to initiate triptan therapy in the triptan group.

Assumptions underlying statistical models were thoroughly evaluated. For the Cox proportional hazards model, the proportional hazards assumption was tested using Schoenfeld residuals. Multicollinearity among covariates was assessed using the variance inflation factor, and model fit was evaluated using Akaike information criterion values and log-likelihood ratios.

Bias

To reduce selection bias, the inverse probability of treatment weighting (IPTW) methodology was used. We included variables in the IPTW based on the results of a univariable analysis, as well as clinical or epidemiological significance using a directed acyclic graph (DAG) to represent hypothesized associations between variables. The DAG connecting triptan exposure with CV events, considering potential confounders and mediators such as demographic characteristics and CV risk factors is depicted in Figure 1. In the DAG, arrows between variables indicate associations; unconnected variables have no direct association. All statistical analyses were performed with consideration of the DAG framework

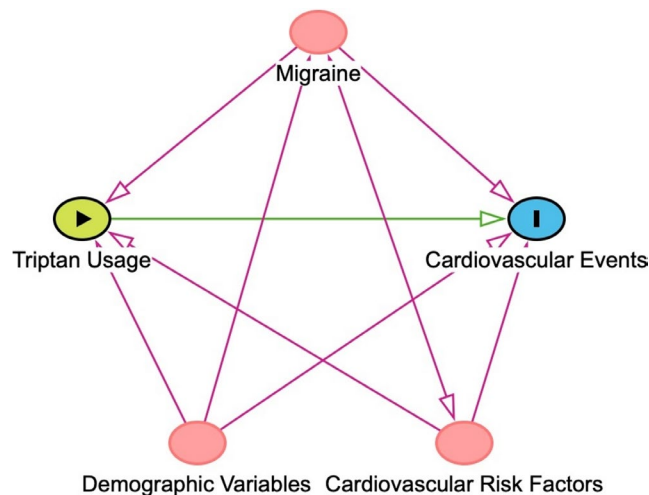


FIGURE 1 Directed acyclic graphs of the assumptions on relationship between variables. Demographics variables: sex, ethnicity, social status, migraine diagnosis age. cardiovascular risk factors: hypertension, diabetes mellitus, smoking, dyslipidemia, obesity. [Colour figure can be viewed at wileyonlinelibrary.com]

and included covariates to minimize the bias of the estimands of triptan exposure on study outcomes. The baseline covariates included in the IPTW model were sex, ethnicity, SEI, age at migraine diagnosis, and CV risk factors (i.e., hypertension, diabetes mellitus, smoking, dyslipidemia, obesity).

For the IPTW methodology, conditional exchangeability was evaluated, assuming no unmeasured confounders between the treatment and control groups. Consistency, which assumes that the treatment effect is well-defined, was ensured by clearly defining triptan exposure as the purchase of the medication and using stabilized weights to account for differences in treatment probabilities. Balance between the groups was assessed using standardized mean differences (SMDs) before and after weighting. SMDs < 0.1 were considered indicative of adequate balance. The positivity assumption was verified by ensuring overlap in the distribution of propensity scores across treatment groups, and no extreme or unstable weights were observed.

Sensitivity analyses were conducted to account for the time from triptan purchase to the CV event, considering both 1 month and 6 months post-purchases. This approach was necessary because our data reflects the purchases of the drug rather than their actual consumption. In addition, we performed sensitivity analyses based on whether patients took triptans only once or more than once, according to the specific type of triptan used, and the monthly mean number of triptans taken to see if there was a dose–response association between triptan usage and CV events.

All analyses were performed using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) in the RStudio 2024.04.2 environment (Posit PBC, Boston, MA, USA). R Packages: “ggplot2” (version 3.5.1), “lme4” (version 1.1–35.4) for mixed-effects models and “WeightIt” (version 1.3.1) for IPTW.

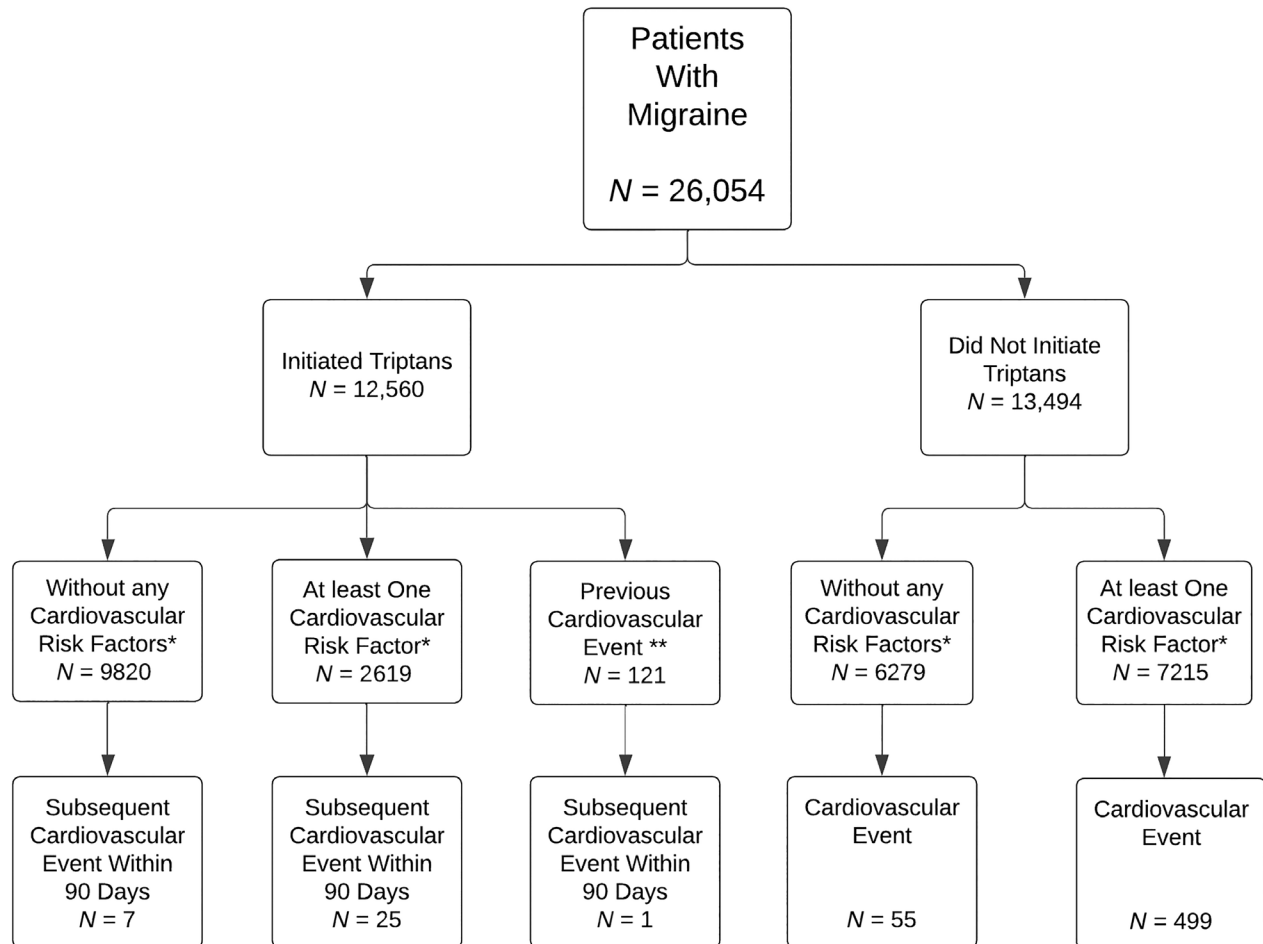
Ethical considerations

This study received ethical approval from the Soroka University Medical Center Institutional Helsinki Committee, reference number 0322-23. Patient records were anonymized and de-identified prior to analysis. As this research was retrospective in nature, utilizing previously collected data, and due to the complete de-identification process, the requirement for informed consent was formally waived by the Institutional Review Board.

RESULTS

Study population and baseline characteristics

In this retrospective, population-based study, the total sample comprised 26,054 patients with migraine, categorized into those who initiated triptan therapy (12,560 [48.2%]) and those who did not (13,494 [51.8%]). Patients categorized into the non-triptan group had no recorded triptan purchase during the study period. [Figure 2](#)



* Cardiovascular Risk Factors include hypertension, diabetes, dyslipidemia, obesity, and smoking.

** Cardiovascular Events include myocardial infarction and ischemic stroke.

For the non-triptan group, this categorization into subgroups with and without cardiovascular risk factors was based on a time point of 4 years after the migraine diagnosis, representing the median time to initiate triptan therapy in the triptan group.

The absence of a subgroup for migraine patients who did not initiate triptans and had a previous cardiovascular event is due to the fact that, at the reference time point (4 years after the migraine diagnosis), no recorded cardiovascular events were observed.

FIGURE 2 Study flowchart.

provides a detailed flowchart of the study sample. The flowchart further divides each group based on the presence of CV risk factors, distinguishing between patients with no risk factors, those with at least one risk factor, and those with a previous CV event. The flowchart also details the subsequent incidence of CV events within 90 days, showing how the study tracks CV outcomes in relation to triptan usage and existing risk factors.

The sex distribution is similar across groups, with 74.4% female in the triptan group and 74.6% female in the non-triptan group (SMD=0.006). The mean age at migraine diagnosis was slightly higher in the triptan group (mean [SD] 39.8 [14.2] years) compared

to the non-triptan group (mean [SD] 36.3 [14.4] years, SMD=0.244). The prevalence of CV risk factors including dyslipidemia, diabetes mellitus, hypertension, smoking, atrial fibrillation, and obesity were higher in the non-triptan group (SMD=0.028–0.289). Medication usage, including acetylsalicylic acid, anticoagulants, antiplatelets, statins, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, was also higher in the non-triptan group (SMD=0.023–0.105). Additionally, the mean low-density lipoprotein cholesterol and hemoglobin A_{1c} levels, analyzed only for patients with diabetes mellitus to represent the glycemic control, were higher in the non-triptan group (SMD=0.061–0.065) (Table 1).

TABLE 1 Demographic and clinical characteristics of the study population.

Characteristic	Patients with migraine			SMD
	Triptan group (N = 12,560)	Non-triptan group (N = 13,494)	Overall (N = 26,054)	
Demographic data				
Female sex, n (%)	9339 (74.42)	10,069 (74.6)	19,408 (74.5)	0.006
Ethnicity, n (%)				0.080
Jewish	10,036 (79.9)	11,201 (83.0)	21,237 (81.5)	
Arab/Bedouin	2444 (19.5)	2220 (16.5)	4664 (17.9)	
Other	80 (0.6)	73 (0.5)	153 (0.6)	
Socioeconomic index				
Mean (SD)	8.7 (3.9)	8.9 (3.7)	8.86 (3.8)	0.061
Median (IQR)	9.0 (2.0–7.0)	9.0 (2.0–7.0)	9.0 (2.0–7.0)	
Migraine diagnosis age, years				
Mean (SD)	39.8 (14.2)	36.3 (14.4)	38.0 (14.4)	0.244
Median (IQR)	38.4 (23.0–47.9)	32.5 (23.0–42.0)	35.5 (23.0–42.0)	
CV risk factor data				
Dyslipidemia, n (%)	3340 (26.6)	3981 (29.5)	7321 (28.1)	0.093
Diabetes mellitus, n (%)	1067 (8.5)	1590 (11.8)	2657 (10.2)	0.102
Hypertension, n (%)	2223 (17.7)	3040 (22.5)	5263 (20.2)	0.137
Smoking, n (%)	3680 (29.3)	4103 (30.4)	7783 (29.9)	0.028
Obesity, n (%)	3855 (30.7)	4326 (32.1)	8181 (31.4)	0.035
Atrial fibrillation, n (%)	176 (1.4)	345 (2.5)	521 (2.0)	0.289
Patent foramen ovale, n (%)	50 (0.4)	54 (0.4)	104 (0.4)	0.025
At least one CV risk factor, n (%)	6019 (47.9)	7215 (53.4)	13,234 (50.8)	0.113
CV risk factor diagnosis age, years				
Mean (SD)	47.6 (14.5)	43.3 (15.0)	45.5 (14.9)	0.296
Median (IQR)	47.8 (22.2–58.6)	42.4 (19.0–58.5)	45.4 (19.0–58.6)	
Acetylsalicylic acid, n (%)	2650 (21.1)	3160 (23.4)	5810 (22.3)	0.046
Anticoagulants, n (%)	665 (5.3)	1028 (7.6)	1693 (6.5)	0.023
Antiplatelets, n (%)	3893 (31.0)	4835 (35.8)	8728 (33.5)	0.105
Statins, n (%)	3227 (25.7)	4094 (30.3)	7321 (28.1)	0.066
ACE inhibitors and ARBs, n (%)	2486 (19.8)	3089 (22.9)	5575 (21.4)	0.049
LDL, mg/dL, mean (SD)	104.0 (26.1)	110.6 (23.3)	106.7 (25.8)	
HbA _{1c} , %, mean (SD)	5.4 (0.7)	5.8 (1.0)	5.5 (0.8)	

Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; CV, cardiovascular; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range, first quartile–third quartile; LDL, low-density lipoprotein; SD, standard deviation; SMD, standardized mean difference.

Triptan usage patterns

Table 2 provides an overview of triptan usage among patients with migraine. The table shows that among 48.2% of patients with migraine who initiated triptan therapy, 23.8% used triptans once. The mean (SD) age at triptan initiation is 40.5(14.2)years. Among those who used triptans, sumatriptan was purchased most often (36.3%), followed by rizatriptan (30.4%) and eletriptan (28.2%). The mean (SD) number of triptan pills used per month was 1.9(1.5)pills/month, and most patients (89.5%) used 1–4pills/month. The mean (SD) maximum number of triptan pills per month was 3.6(2.8)pills/month, with 14.0% of patients using 5–9pills/month, suggesting the need for prophylactic therapy, and 9.2% using ≥ 10 pills, indicative of medication overuse.

TABLE 2 Triptan usage among patients with migraine.

Variable	Patients with migraine (N=26,054)
Triptan status, n (%)	
Did not initiate	13,494 (51.8)
Used once	6202 (23.8)
Used more than once	6358 (24.4)
Triptan initiation age, years	
Mean (SD)	40.5 (14.2)
Median (IQR)	39.2 (28.0–47.9)
Time to triptan initiation post-diagnosis, years	
Mean (SD)	2.5 (1.2)
Median (IQR)	3.7 (1.5–5.9)
Triptan type, n (%)	
Sumatriptan	4554 (36.3)
Rizatriptan	3818 (30.4)
Eletriptan	3542 (28.2)
Zolmitriptan	568 (4.5)
Naratriptan	78 (0.6)
Mean triptan pills/month	
Mean (SD)	1.9 (1.5)
Groups, n (%)	
1–4	5850 (89.5)
5–9	541 (8.3)
≥ 10	143 (2.2)
Maximum triptan pills/month	
Mean (SD)	3.6 (2.8)
Groups, n (%)	
1–4	5020 (76.8)
5–9	917 (14.0)
≥ 10	597 (9.2)

Abbreviations: IQR, interquartile range, first quartile–third quartile; SD, standard deviation.

Cardiovascular outcomes

Table 3 shows the study outcomes. The median (IQR) follow-up period was 10.4(5.0–13.0)years for both the triptan and non-triptan groups. The prevalence of CV events, including myocardial infarction and ischemic stroke, was slightly higher in the triptan group (5.1%) compared to the non-triptan group (4.1%, SMD=0.047). A small subset (0.3%) of triptan users experienced a subsequent CV event within 90days of triptan use.

Figure 3 depicts the individual timelines for the 33 patients who experienced a CV event within 90days of a triptan purchase. The graph illustrates the varied temporal associations between the diagnosis of migraine, subsequent triptan treatment, and the occurrence of CV events. Some patients exhibit dense clustering of triptan purchase, suggesting frequent usage, while others show sporadic usage, which may indicate episodic treatment (as needed).

Table S1 contrasts the demographic and clinical characteristics and triptan usage between patients with migraine who experienced a subsequent CV event within 90days of triptan use (N=33) and those who did not (N=12,527). The table highlights that the patients with migraine with subsequent CV events had a higher prevalence of CV risk factors (SMD=2.624). Additionally, patients with migraine with subsequent CV events were more likely to have used triptans more frequently, with 81.8% using triptans more than once compared to 51.0% in the non-CV group (SMD=1.366). The mean number of triptan pills per month was significantly higher in the CV event group (2.8 vs. 1.9 pills/month, SMD=0.328).

Exposure-outcome associations

The results of the exposure–outcome association analysis are summarized in Figure 4. This shows the results of a multivariable weighted mixed-effects survival regression model computed to evaluate associations between triptan use and CV events, adjusting for demographic variables (age, sex, ethnicity, SEI) and CV risk factors (hypertension, diabetes mellitus, smoking, dyslipidemia, obesity). Variables included in the IPTW model were based on univariable analysis results and their clinical or epidemiological significance.

The use of triptans in the 3months prior to the CV event was not significantly associated with an increased hazard for these events (adjusted HR [aHR] 0.96, 95% CI 0.77–1.23). Sensitivity analyses considering: (a) both 1month (aHR 0.84, 95% CI 0.68–1.06) and 6months (aHR 0.83, 95% CI 0.67–1.05) post-triptan purchase, (b) whether the patients took triptans only once (aHR 0.99, 95% CI 0.69–1.15) or more than once (aHR 1.02, 95% CI 0.83–1.29), (c) specific type of triptan (aHR 0.79–1.07), and (d) the monthly mean number of triptans taken; none of these sensitivity analyses demonstrated a statistically significant risk of taking triptans on CV events, reinforcing our primary findings.

In addition, another sensitivity analysis excluding certain CV risk factors from the multivariable model showed consistent results,

TABLE 3 Cardiovascular outcomes and follow-up characteristics among patients with migraine by triptan usage status.

Variable	Patients with migraine			SMD
	Triptan group (N = 12,560)	Non-triptan group (N = 13,494)	Overall (N = 26,054)	
Follow-up, years				0.184
Mean (SD)	10.0 (5.0)	9.8 (4.5)	9.9 (4.9)	
Median (IQR)	10.4 (5.0–13.0)	10.4 (5.0–13.0)	10.4 (5.0–13.0)	
Myocardial infarction, n (%)	389 (3.1)	308 (2.3)	697 (2.7)	0.050
Ischemic stroke, n (%)	300 (2.4)	295 (2.2)	595 (2.3)	0.014
CV event, n (%)	638 (5.1)	554 (4.1)	1192 (4.6)	0.047
CV event age, years				0.121
Mean (SD)	63.2 (12.5)	61.7 (12.5)	62.5 (12.5)	
Median (IQR)	63.0 (34.7–64.5)	61.2 (38.9–65.8)	61.7 (38.9–65.8)	
Subsequent CV event within 90 days from triptans, n (%)	33 (0.3)	NA	NA	NA

Abbreviations: CV, cardiovascular; IQR, interquartile range, first quartile–third quartile; SD, standard deviation; SMD, standardized mean difference.

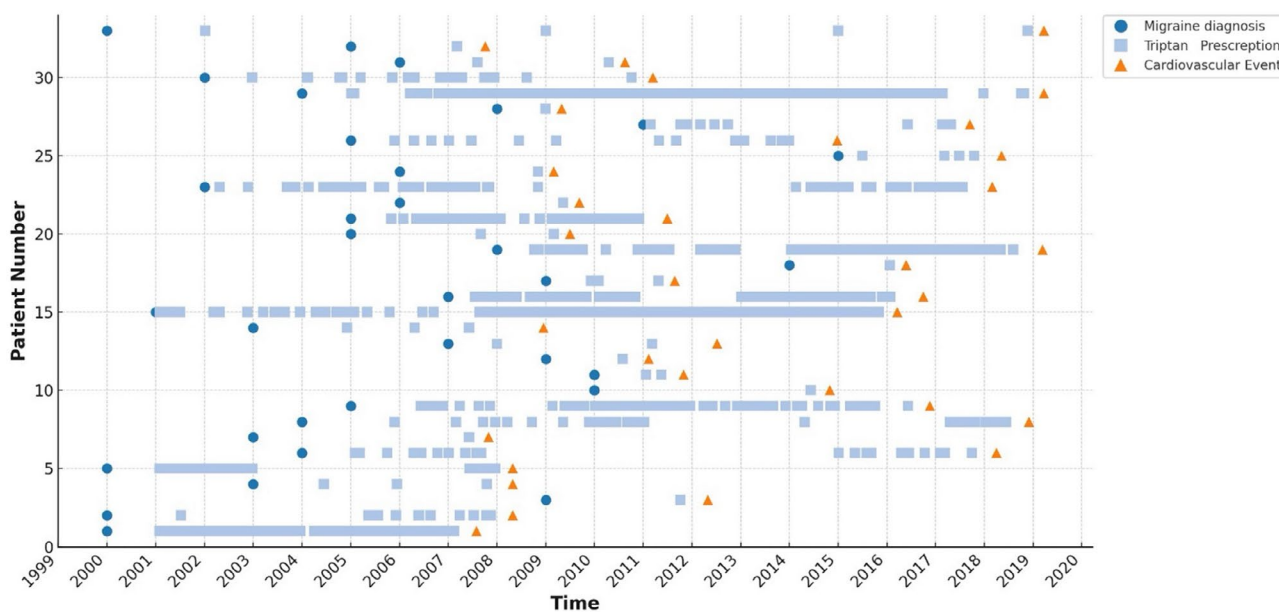


FIGURE 3 Temporal patterns of migraine diagnoses, triptan purchase, and cardiovascular events. [Colour figure can be viewed at wileyonlinelibrary.com]

with no significant association between triptan use and CV events. These findings suggest that the observed lack of association was not driven by over-adjustment for baseline CV risk factors.

DISCUSSION

In this retrospective, population-based study, we analyzed associations between triptan usage and CV events in patients with migraine. The main finding was that triptan use did not increase the risk of CV events among patients with migraine, even among those with existing CV risk factors. In this sample, 12,560 patients with migraine initiated triptan treatment with no CV risk factors: only seven had a

CV event within a 90-day period after triptan purchases. In contrast, 2619 patients with migraine with at least one CV risk factor had 25 CV events. Notably, in the subgroup with a previous CV event, which comprised 121 patients, only one had a CV event within 90 days. This finding is notable given the widespread use of triptans as one of the few effective acute migraine-specific treatments.²³

Migraine has a well-documented association with an increased risk of CV events compared to the general population, particularly in younger women (aged <45 years) with aura.^{24–26} Within the NMC, patients with migraine had a higher prevalence of CV events, including myocardial infarction and ischemic stroke. This increased prevalence can be partially explained by the higher occurrence of vascular and cardioembolic risk factors among patients with migraine. These

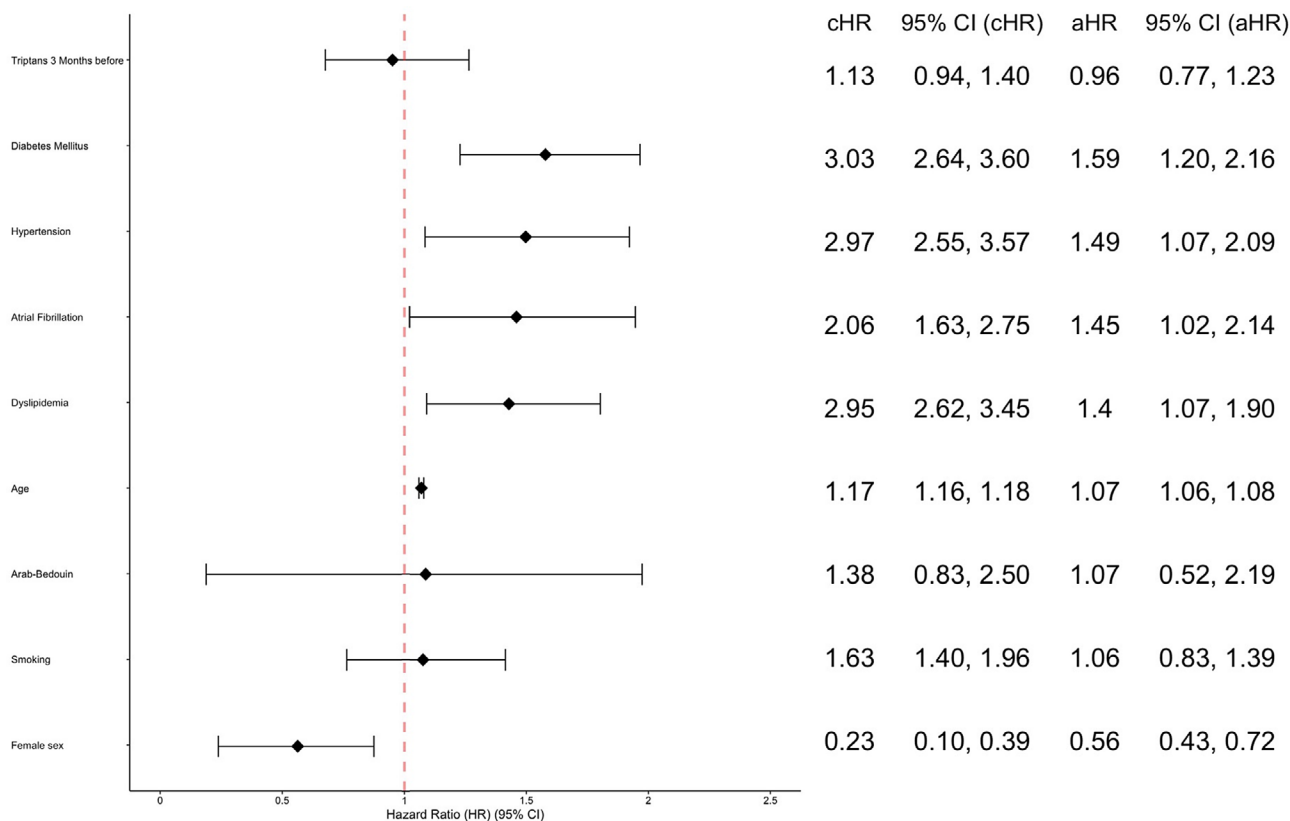


FIGURE 4 Exposure–outcome association analysis; survival analysis for cardiovascular events by triptan usage. A multivariable weighted mixed-effects regression model to evaluate associations between triptan use and cardiovascular events, adjusting for demographic variables and cardiovascular risk factors. Variables included in the inverse probability of treatment weighting modeling were sex, ethnicity, social status, migraine diagnosis age, and cardiovascular risk factors (i.e., hypertension, diabetes mellitus, smoking, dyslipidemia, obesity). aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

findings are congruent with a growing body of research using different methodologies and cohorts.^{9,27–31} However, our study did not distinguish between migraine with and without aura, which is a critical factor in assessing stroke risk.

Triptans are a cornerstone in acute migraine-specific treatment due to their efficacy in alleviating headache symptoms. However, their vasoconstrictive properties have raised concerns about their safety in patients with CV risk factors, leading some clinicians to avoid prescribing triptans to such patients.³² These concerns are also reflected in treatment guidelines, which contraindicate the use of triptans in patients with coronary or cerebrovascular disease.³³ In our study population, the non-triptan group exhibited a higher prevalence of CV risk factors, as well as increased usage of related medications and elevated laboratory values. This pattern likely reflects the caution exercised by doctors in prescribing triptans to patients with existing CV risk factors. The clinical hesitation to prescribe triptans in patients with CV risk factors, such as diabetes, dyslipidemia, and controlled hypertension, has persisted despite no formal contraindication in current treatment guidelines.³³ A recent survey by Robblee et al.³⁴ highlighted that headache specialists exhibit varying levels of comfort when prescribing triptans to patients with these risk factors, reflecting ongoing uncertainties in clinical practice.

Our findings suggest that such caution may not be warranted, as an association between triptan use and increased risk of CV events within 90 days of drug purchases was not found. Triptans remain contraindicated in patients with prior myocardial infarction, stroke, or uncontrolled hypertension, and our study does not suggest that triptans are safe in those specific populations. The distinction between contraindications and general CV risk factors is critical, as overestimating risk could lead to unnecessary avoidance of triptans in patients who might otherwise benefit from effective migraine treatment.

The higher CV event rate in the non-triptan subgroup without CV risk factors may reflect differences in healthcare interaction patterns. Patients who initiated triptans likely had more frequent healthcare visits, enabling earlier identification and management of CV risks. This might contrast with the non-triptan subgroup, where subclinical or undiagnosed CV risks could contribute to the elevated CV event rates. Moreover, the higher CV event rates in the non-triptan subgroup with CV risk factors likely reflect the greater severity of CV risk factors in this group, and may indicate unmanaged CV conditions, as these patients may have been excluded from triptan use due to safety concerns.

Current evidence on CV risk associated with triptans is mixed. A recently published case-crossover study reported an increased risk of

ischemic stroke and myocardial infarction following first-time triptan use, particularly in patients with a high-risk CV profile.³⁵ Conversely, other studies have not demonstrated a similar association. A retrospective propensity-matched cohort study found no significant increase in the risk of acute myocardial infarction, heart failure or, all-cause death among triptan users.¹⁸ Similarly, Hall et al.³⁶ also reported no elevated risk of stroke or myocardial infarction in triptan users compared to non-users. The American Headache Society has also reviewed the CV safety of triptans and concluded that chest symptoms during triptan use are typically non-serious and not ischemic. While CV events have occurred, their incidence is extremely low and that the CV risk-benefit profile of triptans favors their use in the absence of contraindications.^{37,38}

The presumed vascular risk is attributed to the direct activity of the triptan on blood vessels, and as the half-life of most triptans is 2–6h,³⁹ we expect triptan-induced events to occur within 24h post-exposure. Migraine's dynamic nature means that a patient's triptan exposure varies over time. Attempting to compare patients with migraine who ever purchased triptans to other patients with migraine will include triptan-exposed patients who took it only once in their lives (nearly 50% of the patients).⁴⁰ Petersen et al.³⁵ attempted to overcome this complexity by evaluating the risk of vascular events within 14 days following the first initial triptan exposure against other 14-day intervals for the same patients. Our findings align with the selective action of triptans on meningeal blood vessels and the trigeminovascular system receptors, minimizing intracerebral vasoconstriction. These results provide reassurance about their CV safety in appropriately selected patients.

It is important to note that certain subgroups of patients with migraine may be at higher risk of CV events, highlighting the need for careful consideration of individual risk factors when prescribing triptans to patients with migraine.⁴¹ In our study, patients with CV events were more likely to have used triptans multiple times and had a higher average number of pills taken per month. [Figure 3](#) illustrates the varied temporal associations between the diagnosis of migraine, subsequent triptan treatment, and the occurrence of CV events. The graph suggests that patients with frequent triptan purchase, especially those without significant breaks in treatment, are at elevated risk of CV events. This observation suggests that duration of uninterrupted triptan treatment might play a role in CV risk. Conversely, patients with few triptan purchases do not show a clear temporal association with CV events, which could imply that episodic triptan use may carry a different level of risk. This observation is a novel finding with limited prior discussion in the literature. These results highlight the potential importance of considering both the frequency and continuity of triptan use when evaluating CV safety. Further studies are warranted to explore this association and its implications for clinical practice.

This study has several limitations. First, the assumption that the time of triptan purchase aligns with the actual time of consumption. This may affect the analysis of usage patterns and their immediate effects. To address this limitation, we conducted sensitivity analyses examining CV event risks within 30 days and 6 months after

purchases. These analyses also did not show any increased risk associated with triptan use, supporting our results from the 90-day period analysis. As prescriptions in Israel must be filled within 3 months, we considered patients with CV events to be exposed only if they purchased triptans in the 90 days before the event. Another limitation is the relatively small number of CV events in the triptan-user group, which may limit the ability to detect subtle differences in risk (i.e., small effect sizes). Furthermore, as the cohort was derived from a single healthcare system in southern Israel, the findings may not be fully generalizable to populations with different demographic or clinical characteristics. Additionally, our study lacks data on alternative acute migraine treatments, such as ergots, in the non-triptan cohort. This is a limitation, as these medications could confound the observed CV outcomes. Lastly, despite adjusting for demographic and CV risk factors, residual confounding from unmeasured variables, such as migraine severity and frequency, access to healthcare, smoking intensity (e.g., pack-years) and type of tobacco use, and blood pressure measurements over time to distinguish between controlled and uncontrolled hypertension may still influence the results.

CONCLUSIONS

Among patients with migraine, even those with multiple CV risk factors, such as hypertension, diabetes, and dyslipidemia, triptan use did not increase the risk of CV events. These findings may provide reassurance to clinicians and ease concerns regarding the CV safety of triptans for patients with CV risk factors, where no formal contraindication exists. Nevertheless, it is essential for clinicians to carefully evaluate individualized patient profiles when prescribing triptans to patients with migraine, including monitoring of high-frequency users, particularly for patients with underlying or emerging CV risks.

AUTHOR CONTRIBUTIONS

Ido Peles: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Ruth Smadar Shneyour:** Formal analysis; investigation; software; visualization. **Eran Levanon:** Conceptualization; writing – original draft; writing – review and editing. **Yana Mechnik Steen:** Conceptualization; writing – original draft; writing – review and editing. **Ibraheem Abu Salameh:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Michal Gordon:** Conceptualization; formal analysis; methodology; software; writing – original draft; writing – review and editing. **Ran Abuhasira:** Conceptualization; formal analysis; methodology; supervision; writing – original draft; writing – review and editing. **Victor Novack:** Conceptualization; formal analysis; investigation; methodology; supervision; writing – original draft; writing – review and editing. **Gal Ifergane:** Conceptualization; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Gal Ifergane received consulting fees and honorariums from Teva, Novartis, Eli Lilly, Pfizer, and Abbvie. Gal Ifergane received research support from Teva and Pfizer. Ido Peles, Ruth Smadar Shneyour, Eran Levanon, Yana Mechnik Steen, Ibraheem Abu Salameh, Michal Gordon, Ran Abuhasira, and Victor Novack have no conflicts to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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