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Safety of Triptans in Patients Who Have or Are at High Risk for Cardiovascular Disease: A Target Trial Emulation

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Abstract

Objective: To evaluate the safety of triptans in migraine patients with cardiovascular disease or elevated cardiovascular risk.

Patients and Methods: We retrieved data from a multistate US-based health system (January 2000 to August 2022) on adults with migraine and confirmed cardiovascular/cerebrovascular disease, or at least two cardiovascular risk factors. We compared the effect of triptans to nontriptan treatments on major adverse cardiovascular events (MACE) and its components at 60 days of starting treatments. We emulated a target trial and used propensity score matching for analysis.

Results: The 3518 patients in the triptan group were matched to the 3518 patients in the nontriptan group (median age, 55 years; 80.60% female). At 60 days, 52 patients (1.48%) in the triptan group had MACE, compared with 13 patients (0.37%) in the nontriptan group (relative risk [RR], 4.00; 95% CI, 2.24 to 7.14). Patients treated with triptans also had significantly higher risk of nonfatal myocardial infarction (15 patients (0.43%) vs 0 patients (0.00%)); heart failure (RR, 4.50; 95% CI, 1.91 to 10.61); and nonfatal stroke (RR, 8.00; 95% CI, 1.00 to 63.96). Five patients (0.14%) in each group died. The findings were consistent when analyses were restricted to sumatriptan, oral administration of triptan, patients with chronic migraine, history of cardiovascular disease, or history of cerebrovascular disease.

Conclusion: Triptans likely increase the risk of MACE; however, the incidence of MACE remains low in migraine patients with cardiovascular disease or elevated cardiovascular risk.

Trial Registration: Treatments of Migraine With Triptans in Individuals With Elevated Cardiovascular Risk and in Pregnant Women. ClinicalTrials.gov Identifier: NCT05854992 (https://classic.clinicaltrials.gov/ct2/show/NCT05854992)

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Migraine is the second leading cause of disability worldwide, affecting 14.4% of the global population. For the acute treatment of migraine attacks, the use of triptans, nonsteroidal anti-inflammatory drugs, acetaminophen, dihydroergotamine, calcitonin gene-related peptide antagonists, lasmiditan, and some nonpharmacologic treatments are associated with improved pain and function.[1] A systematic review conducted by the Agency for Healthcare Quality and Research evidence-based practice program has shown this effectiveness[2,3]; however, the systematic review also found that patients with established cardiovascular disease or at high risk of cardiovascular events were often excluded from clinical trials.

Triptans, the mainstay treatment for migraine attacks and the one supported by the highest quality evidence, are considered vasoactive and are contraindicated in individuals with cardiovascular disease or at high risk of cardiovascular events.[4-6] These individuals are usually excluded from randomized clinical trials. Yet, triptans are highly effective for migraine and remain frequently prescribed

for migraine in various clinical settings.[7,8] Consequently, clinicians appear to have varying levels of risk tolerance when considering triptan use in individuals with cardiovascular disease or who have one or more cardiovascular risk factors, and data are limited in these populations. Furthermore, a recent large retrospective cohort study found that 14% of patients who were prescribed triptans had a least one contraindication.[9]

When systematic review evidence is insufficient for decisionmaking, as in this case, it has been suggested to obtain supplemental evidence from health system data.[10] Therefore, we conducted a target trial emulation (ie, a hypothetical randomized trial) to evaluate the safety of triptans in migraine patients with cardiovascular disease or multiple cardiovascular risk factors using electronic health record (EHR) data from a large tristate health system.

PATIENTS AND METHODS

Study Design

In this target trial emulation, we emulated a randomized clinical trial that hypothetically assigned patients to triptans or nontriptan treatments. Data were retrieved from Mayo Clinic EHRs. Mayo Clinic is a large integrated health care system with three main campuses in Minnesota, Arizona, and Florida, as well as regional hospitals and clinics in southern Minnesota and Wisconsin. The EHR routinely collects and maintains medical records from all patients, including patient demographics, disease diagnosis, medication prescription and usage, and health care use (Supplemental Material 1, available online at http://www.mayoclinicproceedings.org).

The study was approved by the Mayo Clinic Institutional Review Board (IRB #22-005920). No patient-identifiable data were collected. The first and last authors vouch for the accuracy and completeness of the data presented in this manuscript.

Eligibility Criteria

We included all adult patients (≥18 years of age) with at least one visit (outpatient, inpatient, and emergency room visit) at any Mayo Clinic sites between January 1, 2000, and August 31, 2022. Eligible patients were those with (1) at least a 1-year history of migraine with or without aura; (2) confirmed cardiovascular or cerebrovascular disease (including myocardial infarction [MI], coronary artery disease, cerebrovascular disease, stroke), or at least two cardiovascular risk factors (including diabetes, hyperlipidemia, hypertension, obstructive sleep apnea, or peripheral vascular disease); and (3) at least 1 year of no prior triptan treatment or no previous triptan treatment. We excluded pregnant patients and patients who were prescribed ergot alkaloids or dihydroergotamine within 60 days before or after time zero, defined as the date of starting triptan (the recruitment date).

Interventions

The first group (triptan group) received acute migraine treatment with any prescribed triptan. The second group (nontriptan group) received standard-of-care management of acute migraine without triptan. To follow real-world clinical practices, upon prescribing physicians' discretion, the following triptan treatments were eligible for inclusion: sumatriptan, Treximet (sumatriptan/naproxen combination), zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan. We did not restrict dose, frequency, duration, or delivery routes.

Outcome

The primary outcome was a composite of major adverse cardiovascular events (MACE) at 60 days of starting treatments. Major adverse cardiovascular events were defined as all-cause death, nonfatal myocardial infarction, nonfatal stroke, heart failure, transient cerebral ischemia, or revascularization. Secondary outcomes included the individual components of the composite MACE outcome at 60 days.

Specification of the Target Trial

The key components of the target trial are summarized in Supplemental Material 2 (available online at http://www.mayoclinicproceedings.

org). Definitions and related International Classification of Disease, ninth and tenth revision (ICD-9 and ICD-10) codes are listed in the Supplemental Material 1. Briefly, cardiovascular disease was defined as any of the following: MI, revascularization, acute or chronic ischemic heart disease, heart failure, or angina pectoris. Cerebrovascular disease included stroke, any type of cerebral infarction (eg, stenosis, occlusion, embolism, or thrombosis), vascular syndromes of brain, and transient cerebral ischemic attacks and related syndromes. Vascular risk factors included diabetes, overweight/obesity, hyperlipidemia, hypercholesterolemia, alcohol-related disorders, nicotine dependence, sleep apnea, primary and secondary hypertension, and peripheral vascular disease/atherosclerosis. We collected these data at or closest to time zero.

To emulate the randomization process, patients in the triptan group were exactly matched with those in the nontriptan group in a 1:1 ratio. Propensity scores matching based on logistic regression were performed using nearest neighbor matching to minimize bias while maintaining sufficient power.[11] The matching factors were those clinical and demographic factors that are potentially associated with treatment assignment and outcomes, including age, race (White vs others), sex (female vs male), type of migraine (chronic vs episodic), aura (yes vs no), cardiovascular disease (yes vs no), cerebrovascular disease (yes vs no), transient cerebral ischemic attacks (yes vs no), and vascular risk factors (diabetes, overweight/obesity, hyperlipidemia, hypercholesterolemia, alcohol related disorders, nicotine dependence, sleep apnea, primary and secondary hypertension, and peripheral vascular disease/atherosclerosis). For the same outcome, we included the first event occurring within 60 days of time zero.

A manual review of randomly selected patients (20%) in the matched groups was performed to assure accuracy and integrity of data that were electronically extracted. The overall quality of the data was judged to be excellent. Most of the errors (less than 5% of the randomly selected data) were conflicting EHR entries from different clinical encounters and were corrected. All the outcome events were manually verified.

Statistical Analysis

Analyses were conducted according to patients' initial treatment assignment, similar to the "intention-to-treat" principle in a randomized controlled trial. Balance between the treatment groups was evaluated using estimated propensity score and a dot chart of standardized percentage bias for each variable.[12] A difference of equal or less than 10% was deemed optimal.[13,14] We calculated relative risk (RR) and absolute risk difference (RD) of the outcomes between the groups. Time to MACE and individual components were also evaluated using the Kaplan-Meier estimators. Subgroup analyses were conducted based on type of triptan, administration route, migraine with aura, chronic migraine, history of cardiovascular disease, and history of cerebrovascular disease. We conducted sensitivity analysis based on doubly robust estimation using inverse probability–weighted regression adjustment when the treatment model was wrong (ie, due to unobserved confounding).[15] Additional sensitivity analyses were performed to include patients who received triptan outside emergency departments, outpatients only, and patients who had regular visits at Mayo Clinic (defined as patients who had a designated primary care physician, family medicine physician, or more than five office visits within 3 years of time zero), or triptan prescriptions from neurologists only. A two-tailed $P<.05$ was considered statistically significant. All statistical analyses were conducted using Stata version 17.0 (StataCorp LLC).

RESULTS

Patient Characteristics

Between January 1, 2000, and August 31, 2022, 64,350 adult patients with migraine diagnosis and increased cardiovascular risks were identified from Mayo Clinic EHR. Of these, 3518 patients who received triptan were matched to 3518 patients who received treatments without triptans and were included

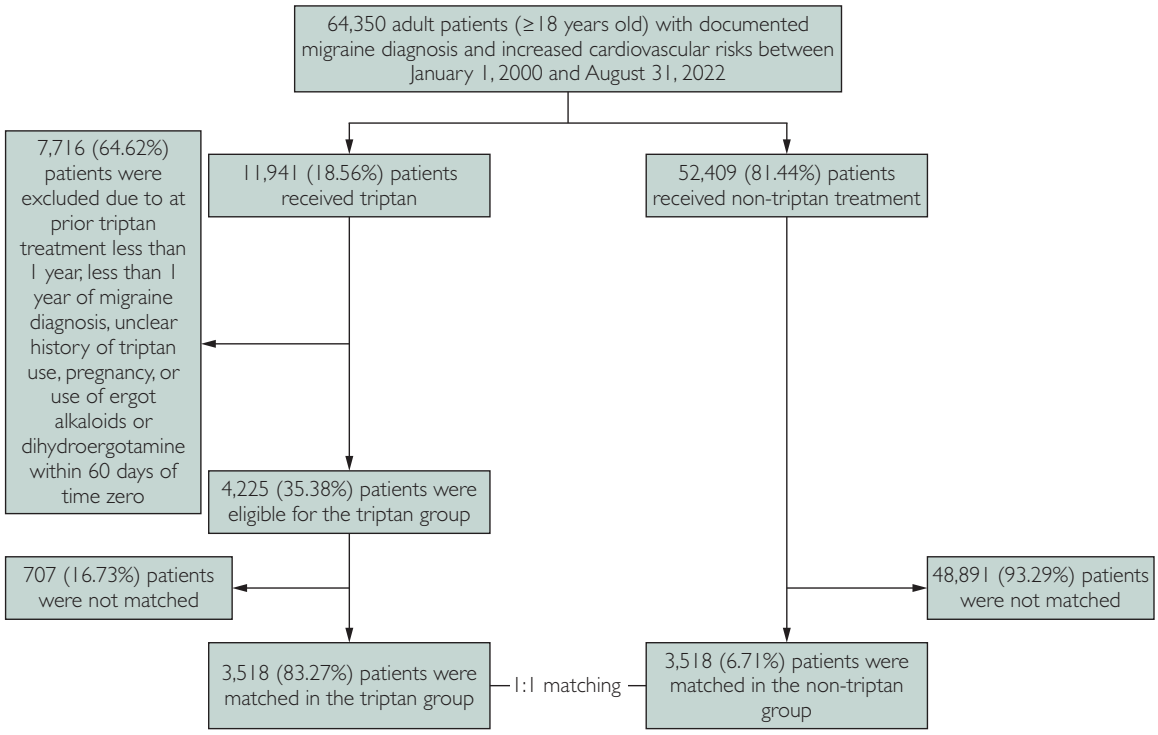

FIGURE 1. Patient enrollment and matching for the target trial emulation.

in the analyses (Figure 1). The median age of the study population was 55 years (Q1-Q3, 45-64 years); 80.60% were female; and 89.88% were White. Chronic migraine was reported in 32.63% whereas 26.56% reported aura. Table 1 shows the baseline characteristics of the matched patients. The study groups were well balanced in terms of demographic and clinical characteristics and estimated propensity score (Supplemental Material 3 and Supplemental Figures 1 and 2, available online at http://www.mayoclinicproceedings.org). In the triptan group, 707 (16.73%) eligible patients were not matched; however, the matched group was similar to the eligible group (Supplemental Material 3 and Supplemental Table 1, available online at http://www.mayoclinicproceedings.org).

Sumatriptan was the most prescribed triptan (2035 patients, 57.85%), followed by rizatriptan (1001 patients, 28.45%), naratriptan (182 patients, 5.17%), eletriptan (157 patients, 4.46%), zolmitriptan (125 patients, 3.55%), Treximet (64 patients, 1.82%), almotriptan (37 patients, 1.05%), and frovatriptan (31 patients, 0.88%). Route of administration included oral (3,228 patients, 92.10%), subcutaneous injection (158 patients, 4.51%), and nasal spray (119 patients, 3.39%).

Primary and Secondary Outcomes

Figure 2, Supplemental Material 3, and Supplemental Figures 3 through 6 (available online at http://www.mayoclinicproceedings.org) show the cumulative incidence curves for the composite and individual components of MACE. The median time to MACE was 5.5 days (Q1-Q3, 0-31 days) with triptan vs 15 days (Q1-Q3, 5-36 days) with nontriptan treatment. The absolute risk of primary and secondary outcomes was overall low (Table 2). At 60 days, 52 patients (1.48%) in the triptan group had MACE, compared with 13 patients (0.37%) in the nontriptan group (RR, 4.00; 95% CI, 2.24 to 7.14; RD per 1000 patients, 11.09; 95% CI, 6.54 to 15.63). Patients treated with

TABLE 1. Baseline and Clinical Characteristics of the Matched Patients Between Triptan Group and Standard Care Group[a]

Characteristics	Triptan (n=3518)	Nontriptan (n=3518)
Median age (Q1-Q3), y	55 (44-63)	55 (45-64)
Female	2840 (80.73)	2831 (80.47)
Race		
White	3154 (89.65)	3170 (90.11)
Other	364 (10.35)	348 (9.89)
Chronic migraine	1172 (33.31)	1124 (31.95)
With aura	967 (27.49)	902 (25.64)
History of cardiovascular disease	613 (17.43)	556 (15.80)
History of cerebrovascular disease	234 (6.65)	171 (4.86)
History of transient cerebral ischemic attacks	154 (4.38)	102 (2.90)
Vascular risk factors		
Diabetes	972 (27.63)	941 (26.75)
Overweight/obesity	2201 (62.56)	2219 (63.08)
Hyperlipidemia/ Hypercholesterolemia	2503 (71.15)	2518 (71.58)
Alcohol related disorders	448 (12.74)	428 (12.17)
Nicotine dependence	892 (25.36)	874 (24.84)
Sleep apnea	1472 (41.84)	1461 (41.53)
Primary and secondary hypertension	1669 (47.44)	1715 (48.75)
Peripheral vascular disease/ atherosclerosis	426 (12.11)	391 (11.11)

[a]Values are median (Q1-Q3) or n (%) as appropriate.

triptans also had significantly higher risk of nonfatal MI (15 patients (0.43%) vs 0 patients (0.00%); RD per 1000 patients, 4.26; 95% CI, 1.83 to 6.70); nonfatal stroke (RR, 8.00; 95% CI, 1.00 to 63.96; RD per 1000 patients, 1.99; 95% CI, 0.04 to 3.94); and heart failure (RR, 4.50; 95% CI, 1.91 to 10.61; RD per 1000 patients, 5.97; 95% CI, 2.59 to 9.35). Five patients (0.14%) in the triptan group died vs 5 (0.14%) in the nontriptan group (RR, 1.00; 95% CI, 0.29 to 3.45; RD per 1000 patients, 0.00; 95% CI, −2.05 to 2.05). Three patients (0.09%) in the triptan group had a revascularization procedure whereas no patient in the nontriptan group reported revascularization.

Type of Triptans

Supplemental Material 3 and Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org) list the findings by two most prescribed triptans, sumatriptan and rizatriptan. Compared with nontriptan, sumatriptan was associated with significantly higher risk of MACE (sumatriptan, 36 patients (1.77%) vs 9 patients (0.44%); RR, 4.00; 95% CI, 1.99 to 8.03; RD per 1000 patients, 13.27; 95% CI, 6.64 to 19.90). Because of the small number of patients who received rizatriptan, the difference between rizatriptan and nontriptan on MACE events was imprecise. There was no significant difference on all-cause death between the triptan group (sumatriptan or rizatriptan) and the nontriptan group. We were unable to analyze other types of triptan due to small sample size.

Route of Administration

Among patients who received oral triptan, triptans were associated with significantly higher risk of MACE compared with the nontriptan group (oral, 48 patients (1.49%) vs 10 patients (0.31%), respectively) (Supplemental Material 3 and Supplemental Table 3, available online at http://www.mayoclinicproceedings.org). Because of the small number of patients who received intranasal or subcutaneous injection triptans, the difference between triptan and nontriptan use on MACE events was highly imprecise.

Chronic Migraine and Aura

Among patients with chronic migraine, the triptan group had significantly higher risk of MACE (13 patients (1.21%) vs 1 patient (0.09%)) and heart failure (7 patients (0.66%) vs 0 patient (0.00%)) compared with the nontriptan group (Supplemental Material 3 and Supplemental Table 4, available online at http://www.mayoclinicproceedings.org). We found no significant difference between the two groups among patients with aura (Supplemental Material 3 and Supplemental Table 5, available online at http://www.mayoclinicproceedings.org).

History of Cardiovascular Disease or History of Cerebrovascular Disease

Among patients with history of cardiovascular disease or history of cerebrovascular disease, triptans were associated with significantly higher risk of MACE compared with the nontriptan group (Supplemental Material 3 and

TABLE 2. Major Adverse Cardiovascular Events by Treatment Groups[a]

Outcome	n (%)		Relative risk (95% CI)	Risk difference (95% CI)
	Triptan (n=3518)	Nontriptan (n=3,518)		Events/1000 patients
MACE	52 (1.48)	13 (0.37)	4.00 (2.24 - 7.14)	11.09 (6.54-15.63)
All-cause death	5 (0.14)	5 (0.14)	1.00 (0.29 - 3.45)	0.00 (−2.05 to 2.05)
Nonfatal myocardial infarction	15 (0.43)	0 (0.00)	N/A	4.26 (1.83-6.70)
Nonfatal stroke	8 (0.23)	1 (0.03)	8.00 (1.00 - 63.96)	1.99 (0.04-3.94)
Transient cerebral ischemia	5 (0.14)	1 (0.03)	5.00 (0.58 - 42.80)	1.14 (−0.51 to 2.79)
Heart failure	27 (0.77)	6 (0.17)	4.50 (1.91-10.61)	5.97 (2.59-9.35)
Revascularization	3 (0.09)	0 (0.00)	N/A	0.85 (−0.40 to 2.10)

[a]MACE, major adverse cardiovascular events; N/A, not applicable.

Supplemental Tables 6 and 7, available online at http://www.mayoclinicproceedings.org).

Sensitivity Analysis

The results of the main analysis were consistent with those of sensitivity analyses (based on receiving triptan outside emergency departments, outpatients only, patients who had regular visits, or triptan prescriptions from neurologists only). These results are summarized in Supplemental Material 3 and Supplemental Tables 8 through 11 (available online at http://www.mayoclinicproceedings.org). Based on doubly robust estimation using inverse probability weighted regression adjustment, the analysis found that triptan use was associated with significantly higher risk of MACE (RR, 3.41; 95% CI, 1.42 to 5.39).

DISCUSSION

This target trial emulation evaluated the safety of triptans in migraine patients with cardiovascular disease or multiple cardiovascular risk factors. Triptans were found to significantly increase risk of MACE compared with nontriptan treatments. However, the overall incidence of MACE remained low. The findings were consistent when we restricted to sumatriptan, oral administration, chronic migraine, history of cardiovascular disease, and history of cerebrovascular disease. This data suggest that the risk is inherent to triptan use in those with vascular conditions and risk factors given that it was present regardless of triptan type or route of administration.

Previous studies have estimated that more than 2 million adults with episodic migraine in the United States have one or more prior cardiovascular event, condition, or procedure and more than 900,000 have a high nonlaboratory Framingham cardiovascular disease risk score.[4,5] As such, there are more than 3 million adults with migraine in the United States who have contraindications or relative contraindications to the migraine-specific acute treatment of triptans. Identifying a proper treatment regimen in these individuals is challenging.

Historically, there has been concern with use of triptans in patients with cardiovascular disease and risk factors.[7,16-18] However, there has been lack of consensus in how to operationalize these concerns in practice. For example, one study found that just over half of headache specialists and only half of family practitioners would not use a triptan at any age for patients with more than three vascular risk factors.[19] Given this inconsistency, as seen in the current study and past studies, patients with cardiovascular disease and risk factors still end up with triptan prescriptions.[7,16-18,20] One study previously observed that triptan use in those with established cardiovascular disease increased with headache-related disability, suggesting that there was a

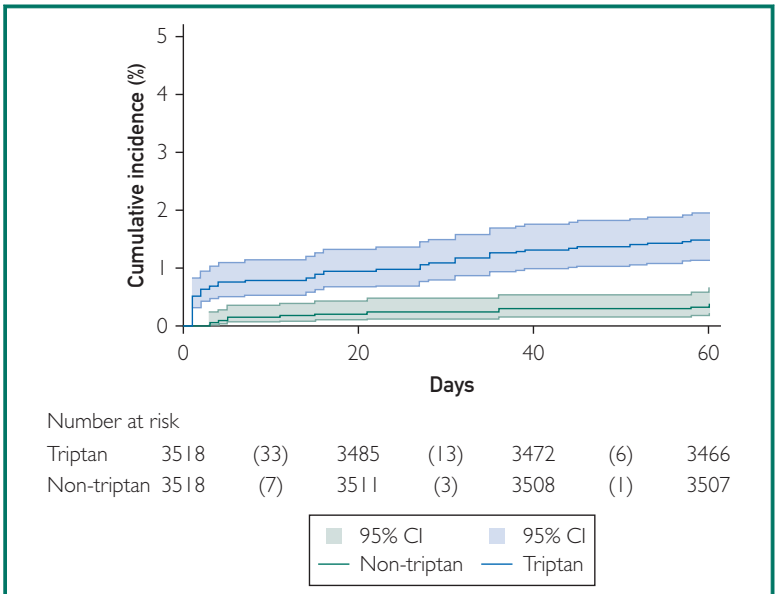

FIGURE 2. Cumulative incidence of major adverse cardiovascular events between triptan and nontriptan treatments at 60 days.

balance of risks and benefits.[18] In 2002, the American Headache Society assembled the Triptan Cardiovascular Safety Expert Panel to evaluate evidence on triptan-associated cardiovascular risk and formulate consensus recommendations for their use in patients with migraine.[21,22] The following observations/recommendations were made: (1) The majority of data on triptans were derived from patients without known coronary artery disease; (2) Chest symptoms with use of triptans was generally nonserious and not explained by ischemia; (3) The incidence of serious cardiovascular events with triptans in clinical trials and practice appeared to be extremely low; and (4) The cardiovascular risk-benefit profile of triptans favored their use in the absence of contraindications. The expert panel observed that most studies pertaining to this topic involved patients without cardiovascular disease; therefore, claims regarding safety of triptan use would thus be limited to that population. This has subsequently left a gap in knowledge which the current study helps to fill.

Some studies have suggested that triptans did not increase the risk of stroke, MI, cardiovascular death, ischemic heart disease, or mortality.[23-26] However, these studies evaluated patients with migraine in general, in whom triptans were prescribed to those at low risk. This contrasts with the current emulated trial which focused on people who have known cardiovascular disease or risk factors. In addition, a recent case-crossover study evaluated all people in nationwide Danish registries who were initiating triptans in terms of developing ischemic outcomes. The study suggested a statistically significant increase in the odds of MI, ischemic stroke, or any stroke.[27] Case patients had a high-risk cardiovascular profile. These results are consistent with our findings. Their overall event rate was also low, which is what we also found.[27]

Although the current study showed increased risk of vascular events with triptans in patients with migraine and cardiovascular disease or risk factors, the overall incidence of these events remained low. Hence, shared decision-making remains important to trade off benefits and harms. The current findings support the continued avoidance of use of triptans in patients with cardiovascular disease or multiple vascular risk factors. For these patients, there has historically been a lack of acute treatment options. In recent years, a number of new migraine-specific treatments have been developed, including 5-hydroxytryptamine1F receptor agonists (lasmiditan) and calcitonin gene-related peptide antagonists (rimegepant, ubrogepant, and zavegepant), that may be good options for patients with contraindications to triptans.[28,29] Although preclinical studies and post hoc analyses suggest that the newer drugs are safe for patients with cardiovascular disease and risk factors, long-term studies are needed to confirm cardiovascular safety. One network meta-analysis suggested that lasmiditan, rimegepant, and ubrogepant were less effective than most triptans for pain freedom or pain relief at 2 hours,[28] which is another factor to consider during shared decision making.

Study Limitations

Data from EHRs show that a patient was prescribed triptan; however, it cannot confirm

that they consumed it, at what time, in what manner, and at what exact dose. We were also unable to identify co-administration of over-the-counter pain medications, or loss to follow-up. Ascertaining loss to follow-up in studies based on EHR is not possible as opposed to a trial. However, we believe that the impact of loss to follow-up on our main findings was not large because our conclusions were robust in a sensitivity analysis based on patients who had regular visits to Mayo Clinic facilities (defined as patients who had a designated primary care physician, family medicine physician, or more than five office visits within 3 years of time zero). It is plausible that patients who were lost to follow-up were those whose headache had improved with the statin or with over-the-counter medications. It is also plausible that patients who did not return were those who had a cardiovascular event that prompted them to seek medical attention outside of our health system, but this is less likely. We chose a follow-up duration of 60 days, which is an arbitrary number that is likely appropriate because triptans are vasoactive drugs that may induce angina and ischemia after even a single use. Increasing the follow-up time may lead to co-interventions and other extraneous variables to be introduced and confound the observed association.

Despite multiple sensitivity analyses, confounding by severity of migraine, severity of cardiovascular disease, or concomitant medications remains possible. Thus, findings of the target trial emulation should be more aligned with those from pragmatic trials.[30] This study found that 32.67% of the patients had chronic migraine whereas 26.76% were reported with aura based on the ICD codes. The aura frequency is consistent with the prevalence of migraine with aura in the general population reported at approximately 25% to 30% of people with migraine.[31] However, the chronic migraine prevalence is higher than the general population (1% to 2%). This may be due to selection bias for patients with higher disease disability or that the population of interest simply has a higher rate of chronic migraine given that many cardiovascular risk factors (eg, obesity, sleep issues, etc) are also risk factors for chronic migraine.[32,33] Consistent with most migraine trials, the majority of our included participants were White and female, which may limit extrapolation to other individuals. For example, the MASALA (Mediators of Atherosclerosis in South Asians Living in America) study has shown that South Asians in the United States are at heightened risk of cardiovascular disease.[34,35] Additionally, the differential impact of triptans on the various cardiovascular risk factors remains uncertain — for instance, unanswered questions remain as to whether the risk is the same if a person has diabetes vs hyperlipidemia.

CONCLUSION

Triptans were found to significantly increase risk of MACE compared with nontriptan treatments. However, the overall incidence of MACE outcomes remained low. The findings suggest that the risk is inherent to triptan use in those with vascular conditions and risk factors given that it was present regardless of triptan type or route of administration.

POTENTIAL COMPETING INTERESTS

All authors report no potential competing interests.

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Drs. Wang, and Murad had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wang, VanderPluym, Halker Singh,

Murad. Acquisition, analysis or interpretation of the data: Wang, VanderPluym, Halker Singh, Alsibai, Roellinger, Firwana, Murad. Drafting of the manuscript: Wang, VanderPluym, Halker Singh, Murad. Critical revision of manuscript for important intellectual content: Wang, VanderPluym, Halker Singh, Alsibai, Roellinger, Firwana, Murad. Statistical analysis: Wang, Murad. Obtaining funding: Murad. Study supervision: Wang, Murad.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AHRQ,** Agency for Healthcare Research and Quality; **EHR,** electronic health records; **MACE,** major adverse cardiovascular events; **MI,** myocardial infarction; **RD,** absolute risk difference; **RR,** relative risk

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