Journal of Pain Research

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ORIGINAL RESEARCH

A Pharmacovigilance Study from 2004 to 2024 Utilizing the FDA Adverse Event Reporting System (FAERS) Examines Ischemic Adverse Events Linked to Triptan Use in Migraine Therapy

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Background: Triptans are commonly employed for acute migraine relief, yet concerns remain regarding their potential association with ischemic adverse events (IAEs). This study aimed to evaluate the association between triptan use and IAEs using real-world data from the FDA Adverse Event Reporting System (FAERS).

Methods: We performed a retrospective pharmacovigilance analysis utilizing FAERS data spanning from Q1 2004 to Q3 2024. Reports of IAEs (stroke, including myocardial infarction, and other ischemic events) in patients using triptans were analyzed. The signal strength of triptan-associated IAEs was evaluated using disproportionality analysis with the reporting odds ratio (ROR) and Bayesian confidence propagation neural network (BCPNN).

Results: Analysis of the FAERS database (2004–2024) identified 1305 ischemic adverse events (AEs) linked to triptans, accounting for 6.60% of all triptan-related AEs. The report proportion varied among triptans, with naratriptan (12.23%) and almotriptan (12.15%) showing the highest rates, while sumatriptan (4.74%) had the lowest. Females comprised 69.4% of cases, and 20.4% of reports involved life-threatening outcomes or death. Disproportionality analysis revealed significant signals for almotriptan (ROR=3.34), naratriptan (ROR=2.96), and rizatriptan (ROR=2.41), with almotriptan exhibiting the strongest association. The most frequent ischemic AEs included arteriospasm coronary (ROR=33.59), reversible cerebral vasoconstriction syndrome (ROR=63.92), and coronary artery dissection (ROR=93.17). Mortality rates exceeded 6% for ischemic stroke and acute myocardial infarction. Time-to-onset analysis showed frovatriptan had the earliest median onset (3.5 days), while almotriptan had the longest (284 days). Serious AEs were more frequently reported for cerebral vasoconstriction, cerebral ischemia, and coronary artery disease ($p<0.05$). These findings suggest notable ischemic safety signals associated with triptans, particularly specific drug subtypes.

Conclusion: This pharmacovigilance study suggests a potential association between triptan use and ischemic adverse events, particularly in high-risk patients. Clinicians should carefully evaluate cardiovascular risk factors before prescribing triptans and consider alternative treatments for susceptible individuals. Additional prospective studies are required to validate these findings.

Keywords: triptans, migraine, ischemic adverse events, pharmacovigilance, FAERS, cardiovascular risk

Introduction

Migraine is a common neurological disorder impacting about 14% of people worldwide, with a higher reporting frequency in women.[1] Triptans, as selective serotonin 5-HT(1B/1D) receptor agonists, are commonly prescribed as the primary acute treatment for their effectiveness in alleviating migraine pain and related symptoms.[2] However, their vasoconstrictive properties raise concerns about ischemic adverse events (AEs), particularly in the cardiovascular, nervous, and gastrointestinal systems, where serotonin receptor activation may lead to vasospasm and tissue hypoxia.[3] It should be explicitly acknowledged that a significant subset of migraine patients cannot use triptans due to

Received: 4 July 2025
Accepted: 6 October 2025
Published: 11 October 2025

cardiovascular contraindications, poor tolerability, or lack of efficacy. Gepants offer effective and well-tolerated alternatives, featuring negligible cardiovascular risk and a minimal likelihood of medication-overuse headaches.[4] Beyond gepants, other emerging pharmacological therapies targeting the trigeminovascular system, along with cannabis-based therapies, hormonal and metabolic interventions, and other innovative treatment modalities, may prove to be valuable for the treatment of migraine.[5]

Triptans exert their therapeutic effects by constricting intracranial blood vessels via 5-HT1B receptors, but this mechanism may also affect coronary arteries, increasing the risk of ischemic coronary artery disease.[6] Although clinical trials suggest a low absolute risk, post-marketing reports and pharmacovigilance studies have documented cases of acute coronary syndrome even in patients without prior cardiovascular disease. The real-world patient population is far more heterogeneous. Post-marketing pharmacovigilance has been crucial in identifying rare but severe adverse events that were not fully captured in pre-approval studies due to limited sample size and duration.[7]

The FDA contraindicates triptans in patients with ischemic heart disease, yet concerns remain regarding their safety in individuals with undiagnosed vascular risk factors.[8] Cerebral vasoconstriction associated with triptans may precipitate ischemic stroke or reversible cerebral vasoconstriction syndrome (RCVS), particularly in susceptible individuals.[9] Previous studies have suggested an association between the use of triptans and cerebrovascular events; however, the causality assessment is complicated by confounding factors, such as the stroke risk associated with migraine.[10] Emerging evidence indicates that triptans may also contribute to mesenteric ischemia and colonic ischemia due to vasoconstriction of splanchnic vessels.[11] Although rare, these events can be life-threatening, with symptoms including severe abdominal pain, often leading to delayed diagnosis.

Given the widespread use of triptans and the potential severity of multi-system ischemic events, further investigation using real-world pharmacovigilance data remains warranted. This study analyzes reports from the FDA Adverse Event Reporting System (FAERS) to evaluate associations between triptan use and ischemic adverse events across cardiac, neurological, and gastrointestinal systems, with the aim of informing clinical risk assessment and patient management. FAERS is a large-scale, publicly available database consisting of spontaneous adverse event reports.[7] Its primary utility lies in its ability to detect rare yet serious adverse drug reactions—such as ischemic complications—that are often undetected in pre-marketing clinical trials due to limited sample sizes and follow-up durations. Thus, FAERS serves as a critical resource for post-marketing safety surveillance and characterizing real-world risk profiles.

Data and Methods

Data Sources

Utilizing the FAERS database, we conducted a pharmacovigilance analysis of ischemic adverse events associated with seven triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) used in migraine treatment. The FDA-managed FAERS database is essential for collecting reports on adverse events and medication errors related to approved drugs.[12] This study employed OpenVigil 2.1 software to extract adverse event data for seven triptans from FAERS, covering the period from Q1 2004 to Q3 2024. This study involves a secondary analysis of anonymized, publicly accessible data from the FAERS.[13] The study did not require ethical review and approval for human participants, as it complied with local laws and institutional guidelines.

Data Extraction

This study examined triptan-class drugs: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Adverse events (AEs) were categorized using the Medical Dictionary for Regulatory Activities (MedDRA; version 25.1), with preferred terms (PTs) grouped by system organ classes (SOCs). Reports were included only if one of the seven triptans was designated as the "primary suspect" (PS) in the therapy file, consistent with FDA standards. Duplicate reports were removed following FDA-recommended practices by comparing PRIMARYID, CASEID, and FDA_DT from the DEMO file.[14] MedDRA's structure includes five levels: lowest-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and system organ class (SOC). For this analysis, PTs associated with ischemic events (eg, myocardial infarction, cerebral ischemia, ischemic colitis) within relevant SOCs (eg, "Cardiac

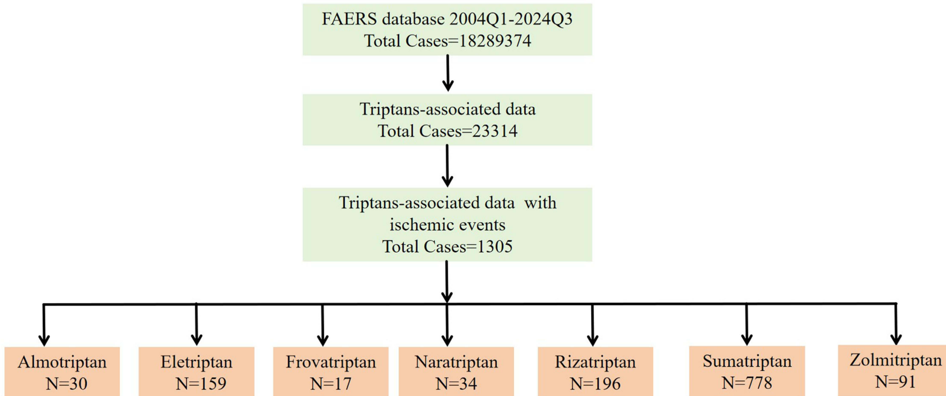

Figure 1 The FAERS database's pipeline flowchart for screening triptan-associated ischemic adverse events. 2004Q1 refers to the data for the first quarter of 2004, 2024Q3 refers to the data for the third quarter of 2024.

disorders", "Nervous system disorders", "Gastrointestinal disorders") were extracted. We incorporated all reports from the FDA Adverse Event Reporting System (FAERS) spanning Q1 2004 to Q3 2024 to maintain current data.

Data Screening Process

The complete screening procedure is illustrated in Figure 1. Reports were deemed duplicates if they aligned in terms of adverse events (related to ischemia), ISR number, submission date, medication (triptan drug), indication (such as migraine), gender, reporting country, and age. Reports where ischemic events could be attributed to concomitant medications (eg, vasoconstrictors, antihypertensives) or underlying conditions (eg, cardiovascular disease) were excluded. Only reports where a triptan was designated as the primary suspect drug were retained for further evaluation. After deduplication and filtering, the remaining reports were analyzed to assess the association between triptan use and ischemic events.[13]

Data Analysis

We conducted a comprehensive pharmacovigilance analysis using disproportionality and Bayesian methods to evaluate the potential link between triptan medications (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and ischemic events. Disproportionality assessments were conducted by calculating the proportional reporting ratio (PRR) and the reporting odds ratio (ROR) to compare the reporting rates of ischemic events, such as myocardial infarction, cerebral ischemia, and ischemic colitis, between triptans and other drugs within the FAERS database. Supplementary Table S1 details the formulas and signal thresholds used in our disproportionality analyses. To enhance signal detection robustness, we employed two Bayesian algorithms: the Bayesian Confidence Propagation Neural Network (BCPNN) and the Multi-item Gamma Poisson Shrinker (MGPS). We systematically evaluated potential safety signals using four methods: PRR, ROR, BCPNN, and MGPS. Their computational formulas and decision criteria are provided in standard contingency tables (Supplementary Table S1), where higher values suggest stronger drug-event associations. Furthermore, we assessed the temporal relationship between triptan exposure and ischemic events by calculating the time-to-onset, defined as the interval between medication initiation and adverse event reporting, excluding cases with inconsistent temporal data. The median time-to-event was determined to characterize the typical latency period. Finally, we assessed mortality outcomes associated with triptan-related ischemic events to evaluate the clinical severity of these adverse drug reactions. This multi-analytical approach provided a rigorous evaluation of ischemic risks potentially associated with triptan therapy.

Statistical Analysis

Statistical analyses were conducted using R software (v4.1.2) and Microsoft Excel 2019. A chi-square test was used to compare ischemic adverse events associated with triptans between serious and non-serious cases. Disproportionality

 https://doi.org/10.2147/JPR.S551333

analyses were conducted using four algorithms (PRR, ROR, BCPNN, and MGPS), with detailed formulas and thresholds provided in Supplementary Table S1. A two-tailed p-value <0.05 was considered statistically significant. Sensitivity analyses accounted for age, sex, and concurrent medication use. Data visualization was performed using ggplot2 in R.

Result

Baseline Characteristics of Ischemic Event Reports Associated with Triptans

Using the FAERS database, we analyzed ischemic adverse events in patients treated with triptans from Q1 2004 to Q3 2024, reviewing 18,289,374 adverse event reports. After removing duplicates, we identified 23,314 adverse events associated with triptans, including 1305 ischemic events. Ischemic adverse events constituted a minor portion of the total reported adverse reactions for all triptans, accounting for 6.60% (1305 out of 23,314) as shown in Table 1.

The analysis indicates an increase in the reported number of ischemic adverse events associated with triptans over the past decade. The reporting frequency of these events varied among triptans, with cases reported for almotriptan (30), eletriptan (159), frovatriptan (17), naratriptan (34), rizatriptan (196), sumatriptan (778), and zolmitriptan (91). Naratriptan and almotriptan exhibited the highest rates of ischemic AEs, at 12.23% (34 out of 244) and 12.15% (30 out of 217), respectively. The occurrence of ischemic adverse events for sumatriptan, eletriptan, frovatriptan, rizatriptan, and zolmitriptan was relatively low, with rates of 4.74% (778 out of 15,628), 4.89% (159 out of 3092), 7.46% (17 out of 211), 9.57% (196 out of 1852), and 10.63% (91 out of 765), respectively (Figure 2). In general, ischemic adverse events make up a significant portion of potential adverse events in various triptan treatments.

From the FAERS database, we collected 1305 cases of ischemic adverse events where triptans were the "primary suspect". Table 2 outlines the clinical characteristics of these patients. Ischemic adverse events (AEs) associated with triptans were more prevalent in females (69.4%) than males (18.0%), with 12.6% of cases lacking sex data (164/1305). The female proportion among AEs varied by triptan: almotriptan (80.0%, 24/30), eletriptan (73.6%, 117/159), frovatriptan (88.2%, 15/17), naratriptan (88.2%, 30/34), rizatriptan (69.9%, 137/196), sumatriptan (66.7%, 519/778), and zolmitriptan (70.3%, 64/91). In contrast, ischemic AEs in males were less frequent: almotriptan (16.7%, 5/30), eletriptan (16.4%, 26/159), frovatriptan (11.8%, 2/17), naratriptan (2.9%, 1/34), rizatriptan (17.9%, 35/196), sumatriptan (19.3%, 150/778), and zolmitriptan (17.6%, 16/91). Of the 1305 AE reports analyzed, most cases occurred in patients aged 18–65 years (66.4%, 867 cases), followed by those aged 66–85 (7.3%, 95 cases) and under 18 (0.6%, 8 cases). Life-threatening outcomes or death were reported in 20.4% (266/1305) of cases. Geographically, the US accounted for the highest proportion of reports (45.1%, 589 cases). Physicians submitted the majority of reports (34.2%, 446 cases), ahead of consumers (23.9%, 312 cases), other healthcare professionals (13.6%, 177 cases), and pharmacists (10.3%, 135 cases).

Table 1 Safety Adverse Events Among Different Triptans

Drug	Triptans-Associated AEs n	Triptans-Associated Ischemic AEs n	Triptans-Associated Ischemic AEs as PSn	ROR (95% CI)	PRR (X2)	EBGM (EBGM05)	IC (IC025)
Almotriptan	756	47	30	3.34 (2.49–4.49)	3.19 (72.27)	3.19 (2.5)	1.68 (0.01)
Eletriptan	8419	201	159	1.23 (1.07–1.41)	1.22 (8.2)	1.22 (1.09)	0.29 (0.08)
Frovatriptan	647	21	17	1.69 (1.09–2.61)	1.67 (5.73)	1.67 (1.16)	0.74 (−0.93)
Naratriptan	756	42	34	2.96 (2.17–4.05)	2.85 (51.62)	2.85 (2.2)	1.51 (−0.16)
Rizatriptan	5688	260	196	2.41 (2.13–2.73)	2.35 (205.44)	2.35 (2.12)	1.23 (−0.43)
Sumatriptan	45349	1069	778	1.22 (1.15–1.29)	1.21 (40.24)	1.21 (1.15)	0.28 (−1.39)
Zolmitriptan	2921	113	91	2.03 (1.68–2.45)	1.99 (56.59)	1.99 (1.7)	0.99 (−0.68)

Abbreviations: PS, primary suspect; ROR, reporting odds ratio; PRR, proportional reporting ratio; $\chi 2$, chi-squared; IC, information component; IC025, the lower limit of 95% CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

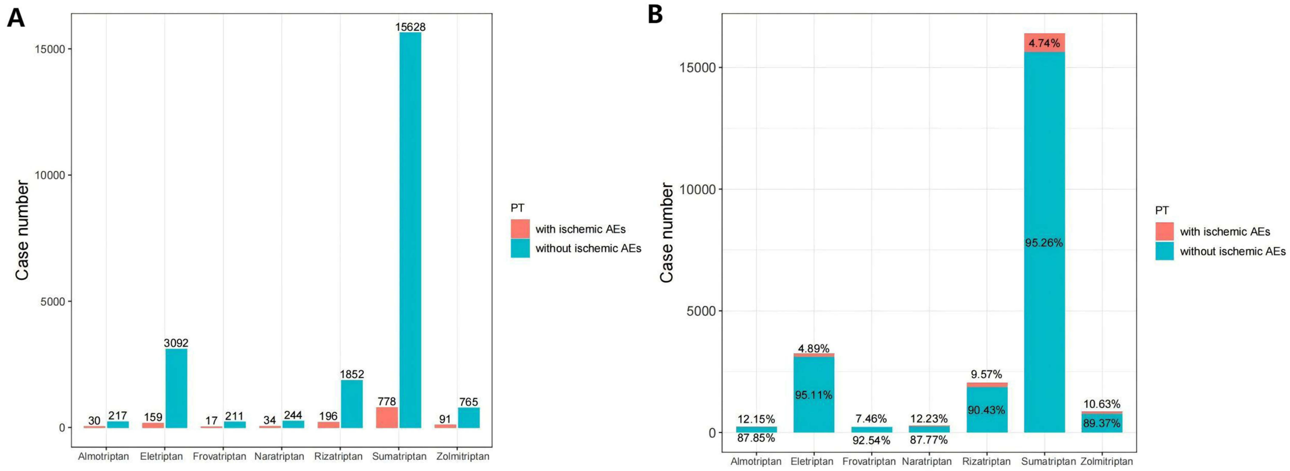

Figure 2 The bar chart above shows the number of reported ischemic adverse events and without ischemic adverse events of different triptans in the FAERS database from 2004 Q1 to 2024 Q3. (**B**) The proportional bar chart below shows the percentage of different triptans ischemic adverse events and without ischemic adverse events in the FAERS database from 2004 Q1 to 2024 Q3.

Disproportionality Analysis for Triptansrelated Ischemic AEs

Table 1 presents the signal values and correlations between triptans and ischemic adverse events. Almotriptan (N =30, ROR = 3.34, 95% CI[2.49~4.49], PRR = 3.19, X2 = 72.27), naratriptan (N = 34, ROR = 2.96, 95% CI [2.17~4.05], PRR = 2.85, X2 = 2.2), rizatriptan (N = 195, ROR =2.41, 95% CI [2.13~2.73], PRR = 2.35, X2 = 205.44), had significant signal values. Almotriptan showed the highest correlation with ischemic events among the triptans. Sumatriptan (N = 778, ROR = 1.22, 95% CI [1.15, 1.29], PRR = 1.21, X2 = 40.24) demonstrated reduced safety concerns regarding ischemic events.

A total of 1062 positive PT-level signals were identified (see Supplementary Table S2). The PT signals of cardiac disorders, gastrointestinal disorders, and nervous system disorders involved 557 signals (ROR range: 1.95~93.17), 165 signals (ROR range: 2.84~17.2), and 340 signals (ROR range: 1.64~63.92), respectively.

To gain deeper insights into the clinical features of ischemic adverse events (AEs) associated with triptan therapy, we investigated the ten most commonly reported ischemic AEs. The ten most common triptan-related ischemic AE signals are myocardial Infarction [N = 172, ROR = 0.86, 95% CI (0.74~1), PRR = 0.86, X2 = 3.77], arteriospasm Coronary [N = 132, ROR = 33.59, 95% CI (28.22~39.98), PRR = 33.52, X2 = 4002.76], cerebrovascular accident [N = 131, ROR =0.7,95% CI (0.59~0.83), PRR = 0.7, X2 = 17.07], colitis ischaemic [N = 119, ROR = 17.2, 95% CI (14.34~20.62), PRR = 17.17, X2 = 1775.15], reversible cerebral vasoconstriction syndrome [N = 107, ROR = 63.92, 95% CI (52.5~77.82), PRR = 63.82, X2 = 6141.94], acute myocardial infarction [N = 97, ROR = 2.93, 95% CI (2.4~3.58), PRR = 2.93, X2 = 122.89], angina pectoris [N = 82, ROR = 2.56, 95% CI (2.06~3.17), PRR = 2.55, X2 = 77.31], coronary artery dissection [N = 77, ROR = 93.17, 95% CI (73.6~117.93), PRR = 93.05, X2 = 6302.65], stress cardiomyopathy [N = 56, ROR = 9.76, 95% CI (7.49~12.7), PRR = 9.75, X2 = 434.52], acute coronary syndrome[N = 49, ROR = 5.25, 95% CI (3.96~6.95), PRR = 5.25, X2 = 167.36] (Figure 3 and Table 3).

To assist clinicians in identifying highly ischemic adverse events (AEs), we calculated the mortality rates for various AEs following triptan therapy, defined as the ratio of reported deaths to reported AEs (Figure 4). The findings indicated that mortality rates for ischemic stroke and acute myocardial infarction exceeded 6%. The mortality rates of triptans with concomitant ischemic events signals were 4.67% for reversible cerebral vasoconstriction syndrome, 4.65% for myocardial infarction, and 3.05% for cerebrovascular accident. There were no mortality rates of triptans with concomitant ischemic events signals for stress cardiomyopathy, coronary artery dissection, arteriospasm coronary, angina pectoris, and acute coronary syndrome.

https://doi.org/10.2147/JPR.S551333

Table 2 Baseline Characteristics of Ischemic Event Reports Associated with Triptans

Characteristics		Report Number, N (%)							
		Triptans	**Almotriptan**	**Eletriptan**	**Frovatriptan**	**Naratriptan**	**Rizatriptan**	**Sumatriptan**	**Zolmitriptan**
Number of reports		1305	30	159	17	34	196	778	91
Gender	Female	906 (69.4%)	24 (80.0%)	117 (73.6%)	15 (88.2%)	30 (88.2%)	137 (69.9%)	519 (66.7%)	64 (70.3%)
	Male	235 (18.0%)	5 (16.7%)	26 (16.4%)	2 (11.8%)	1 (2.9%)	35 (17.9%)	150 (19.3%)	16 (17.6%)
	Unknown or missing	164 (12.6%)	1 (3.3%)	16 (10.1%)	0 (0%)	3 (8.8%)	24 (12.2%)	109 (14.0%)	11 (12.1%)
Age (years)	<18	8 (0.6%)	1 (3.3%)	1 (0.6%)	0 (0%)	0 (0%)	2 (1.0%)	3 (0.4%)	1 (1.1%)
	18-65	867 (66.4%)	26 (86.7%)	0 (0%)	16 (94.1%)	21 (61.8%)	133 (67.9%)	518 (66.6%)	50 (54.9%)
	65-85	95 (7.3%)	1 (3.3%)	103 (64.8%)	0 (0%)	3 (8.8%)	13 (6.6%)	56 (7.2%)	12 (13.2%)
	Unknown or missing	330 (25.3%)	2 (6.7%)	45 (28.3%)	1 (5.9%)	10 (29.4%)	48 (24.5%)	198 (25.4%)	26 (28.6%)
Serious outcome	Death	51 (3.9%)	4 (13.3%)	3 (1.9%)	1 (5.9%)	0 (0%)	2 (1.0%)	40 (5.1%)	1 (1.1%)
	Life-threatening	215 (16.5%)	1 (3.3%)	12 (7.5%)	2 (11.8%)	3 (8.8%)	51 (26.0%)	130 (16.7%)	16 (17.6%)
	Hospitalization	556 (42.6%)	14 (46.7%)	67 (42.1%)	9 (52.9%)	20 (58.8%)	78 (39.8%)	317 (40.7%)	51 (56.0%)
	Disability	22 (1.7%)	0 (0%)	6 (3.8%)	1 (5.9%)	0 (0%)	4 (2.0%)	8 (1.0%)	3 (3.3%)
	Others	395 (30.3%)	9 (30.0%)	67 (42.1%)	4 (23.5%)	11 (32.4%)	49 (25.0%)	238 (30.6%)	17 (18.7%)
Reported Countries (Top five)	United States	589 (45.1%)	11 (36.7%)	72 (45.3%)	7 (41.2%)	6 (17.6%)	99 (50.5%)	371 (47.7%)	23 (25.3%)
	United Kingdom	145 (11.1%)	2 (6.7%)	1 (0.6%)	3 (17.6%)	4 (11.8%)	9 (4.6%)	122 (15.7%)	4 (4.4%)
	France	101 (7.7%)	4 (13.3%)	32 (20.1%)	2 (11.8%)	3 (8.8%)	4 (2.0%)	28 (3.6%)	28 (30.8%)
	Germany	85 (6.5%)	1 (3.3%)	2 (1.3%)	2 (11.8%)	4 (11.8%)	8 (4.1%)	66 (8.5%)	2 (2.2%)
	Japan	63 (4.8%)	N/A	10 (6.3%)	N/A	3 (8.8%)	4 (2.0%)	40 (5.1%)	6 (6.6%)
Reported Person	Physician	446 (34.2%)	5 (16.7%)	65 (40.9%)	10 (58.8%)	14 (41.2%)	80 (40.8%)	233 (29.9%)	39 (42.9%)
	Consumer	312 (23.9%)	4 (13.3%)	44 (27.7%)	4 (23.5%)	4 (11.8%)	50 (25.5%)	199 (25.6%)	7 (7.7%)
	Pharmacist	135 (10.3%)	4 (13.3%)	18 (11.3%)	0 (0%)	3 (8.8%)	12 (6.1%)	85 (10.9%)	13 (14.3%)
	Other health-professional	177 (13.6%)	6 (20.0%)	20 (12.6%)	1 (5.9%)	6 (17.6%)	25 (12.8%)	105 (13.5%)	14 (15.4%)
	Unknown	65 (5.0%)	7 (23.3%)	4 (2.5%)	2 (11.8%)	5 (14.7%)	11 (5.6%)	24 (3.1%)	12 (13.2%)
Reporting year	2004	38 (2.9%)	1 (3.3%)	17 (10.7%)	1 (5.9%)	N/A	5 (2.6%)	11 (1.4%)	3 (3.3%)
	2005	46 (3.5%)	8 (26.7%)	11 (6.9%)	2 (11.8%)	0 (0%)	12 (6.1%)	13 (1.7%)	0 (0%)
	2006	29 (2.2%)	3 (10.0%)	10 (6.3%)	1 (5.9%)	0 (0%)	10 (5.1%)	4 (0.5%)	1 (1.1%)
	2007	38 (2.9%)	1 (3.3%)	11 (6.9%)	3 (17.6%)	0 (0%)	12 (6.1%)	9 (1.2%)	2 (2.2%)
	2008	27 (2.1%)	0 (0%)	7 (4.4%)	0 (0%)	0 (0%)	8 (4.1%)	10 (1.3%)	2 (2.2%)
	2009	31 (2.4%)	0 (0%)	0 (0%)	1 (5.9%)	1 (2.9%)	11 (5.6%)	15 (1.9%)	3 (3.3%)
	2010	32 (2.5%)	0 (0%)	9 (5.7%)	0 (0%)	1 (2.9%)	12 (6.1%)	9 (1.2%)	1 (1.1%)
	2011	19 (1.5%)	0 (0%)	4 (2.5%)	0 (0%)	0 (0%)	4 (2.0%)	10 (1.3%)	1 (1.1%)
	2012	31 (2.4%)	0 (0%)	5 (3.1%)	0 (0%)	10 (29.4%)	2 (1.0%)	14 (1.8%)	0 (0%)
	2013	41 (3.1%)	0 (0%)	7 (4.4%)	2 (11.8%)	0 (0%)	6 (3.1%)	24 (3.1%)	2 (2.2%)

	2014	86 (6.6%)	3 (10.0%)	7 (4.4%)	1 (5.9%)	0 (0%)	10 (5.1%)	61 (7.8%)	4 (4.4%)
	2015	71 (5.4%)	4 (13.3%)	3 (1.9%)	2 (11.8%)	3 (8.8%)	12 (6.1%)	38 (4.9%)	9 (9.9%)
	2016	75 (5.7%)	1 (3.3%)	14 (8.8%)	3 (17.6%)	5 (14.7%)	6 (3.1%)	39 (5.0%)	7 (7.7%)
	2017	82 (6.3%)	2 (6.7%)	5 (3.1%)	0 (0%)	2 (5.9%)	4 (2.0%)	57 (7.3%)	12 (13.2%)
	2018	75 (5.7%)	3 (10.0%)	4 (2.5%)	1 (5.9%)	0 (0%)	8 (4.1%)	52 (6.7%)	7 (7.7%)
	2019	95 (7.3%)	0 (0%)	8 (5.0%)	0 (0%)	0 (0%)	26 (13.3%)	56 (7.2%)	5 (5.5%)
	2020	106 (8.1%)	0 (0%)	10 (6.3%)	0 (0%)	0 (0%)	10 (5.1%)	77 (9.9%)	9 (9.9%)
	2021	77 (5.9%)	0 (0%)	2 (1.3%)	0 (0%)	9 (26.5%)	8 (4.1%)	51 (6.6%)	7 (7.7%)
	2022	94 (7.2%)	0 (0%)	17 (10.7%)	0 (0%)	1 (2.9%)	9 (4.6%)	58 (7.5%)	9 (9.9%)
	2023	165 (12.6%)	1 (3.3%)	4 (2.5%)	0 (0%)	0 (0%)	16 (8.2%)	142 (18.3%)	2 (2.2%)
	2024	47 (3.6%)	3 (10.0%)	4 (2.5%)	0 (0%)	2 (5.9%)	5 (2.6%)	28 (3.6%)	5 (5.5%)

Abbreviation: N/A, Not Applicable.

https://doi.org/10.2147/JPR.S551333

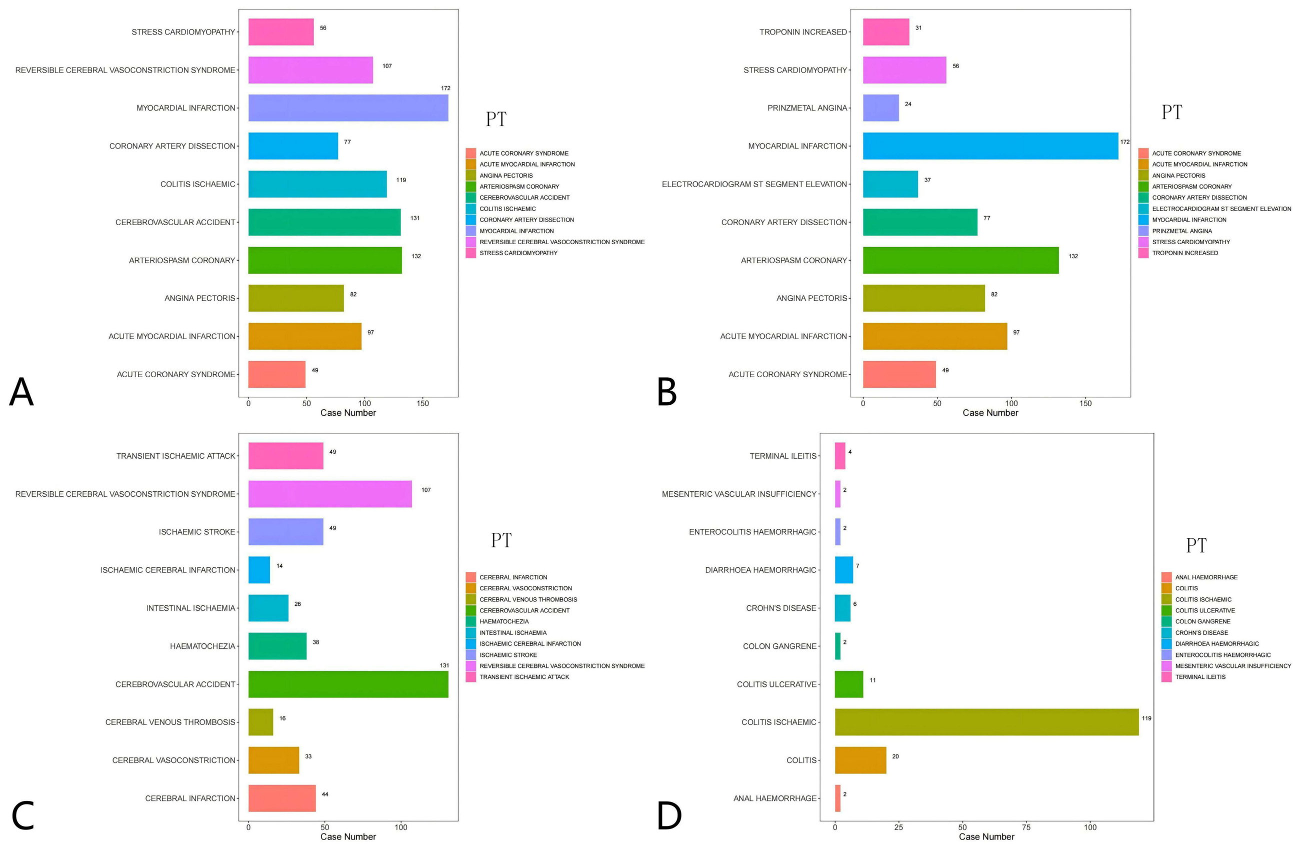

Figure 3 The number of reported cases of the first ten types of Triptans related ischemic AEs under different System Organ Class types. (**A**) Cardiac Disorders, Gastrointestinal Disorders And Nervous System Disorders; (**B**) Cardiac Disorders; (**C**) Nervous System Disorders; (**D**) Gastrointestinal Disorders.
Abbreviation: PT, preferred term.

Time to Onset of Ischemic Adverse Event

Figure 5 illustrates the onset time of ischemic adverse events for different triptans. Frovatriptan had a median onset time of 3.5 days, with an interquartile range of 2.25 to 23.5 days. Almotriptan exhibited the longest onset time, averaging 284

Table 3 The Signal Values of the First Ten Types of Triptans Related Ischemic AEs

Preferred Term (PTs)	Report Number	ROR (95% CI)	PRR (X2)	EBGM (EBGM05)	IC (IC025)
Cardiac Disorders, Gastrointestinal Disorders And Nervous System Disorders					
Myocardial Infarction	172	0.86 (0.74–1)	0.86 (3.77)	0.86 (0.76)	−0.21 (−0.43)
Arteriospasm Coronary	132	33.59 (28.22–39.98)	33.52 (4002.76)	32.25 (27.88)	5.01 (4.76)
Cerebrovascular Accident	131	0.7 (0.59–0.83)	0.7 (17.07)	0.7 (0.61)	−0.52 (−0.77)
Colitis Ischaemic	119	17.2 (14.34–20.62)	17.17 (1775.15)	16.84 (14.46)	4.07 (3.81)
Reversible Cerebral Vasoconstriction Syndrome	107	63.92 (52.5–77.82)	63.82 (6141.94)	59.31 (50.31)	5.89 (5.6)
Acute Myocardial Infarction	97	2.93 (2.4–3.58)	2.93 (122.89)	2.92 (2.47)	1.55 (1.26)
Angina Pectoris	82	2.56 (2.06–3.17)	2.55 (77.31)	2.55 (2.13)	1.35 (1.03)
Coronary Artery Dissection	77	93.17 (73.6–117.93)	93.05 (6302.65)	83.74 (68.75)	6.39 (6.04)
Stress Cardiomyopathy	56	9.76 (7.49–12.7)	9.75 (434.52)	9.65 (7.74)	3.27 (2.89)
Acute Coronary Syndrome	49	5.25 (3.96–6.95)	5.25 (167.36)	5.22 (4.13)	2.38 (1.97)

(*Continued*)

Table 3 (Continued).

Preferred Term (PTs)	Report Number	ROR (95% CI)	PRR (X2)	EBGM (EBGM05)	IC (IC025)
Cardiac Disorders					
Myocardial Infarction	172	0.86 (0.74–1)	0.86 (3.77)	0.86 (0.76)	−0.21 (−0.43)
Arteriospasm Coronary	132	33.59 (28.22–39.98)	33.52 (4002.76)	32.25 (27.88)	5.01 (4.76)
Acute Myocardial Infarction	97	2.93 (2.4–3.58)	2.93 (122.89)	2.92 (2.47)	1.55 (1.26)
Angina Pectoris	82	2.56 (2.06–3.17)	2.55 (77.31)	2.55 (2.13)	1.35 (1.03)
Coronary Artery Dissection	77	93.17 (73.6–117.93)	93.05 (6302.65)	83.74 (68.75)	6.39 (6.04)
Stress Cardiomyopathy	56	9.76 (7.49–12.7)	9.75 (434.52)	9.65 (7.74)	3.27 (2.89)
Acute Coronary Syndrome	49	5.25 (3.96–6.95)	5.25 (167.36)	5.22 (4.13)	2.38 (1.97)
Electrocardiogram St Segment Elevation	37	10.11 (7.31–13.99)	10.11 (299.98)	10 (7.62)	3.32 (2.85)
Troponin Increased	31	4.17 (2.93–5.93)	4.17 (74.22)	4.15 (3.09)	2.05 (1.54)
Prinzmetal Angina	24	23.05 (15.36–34.58)	23.04 (492.33)	22.44 (15.98)	4.49 (3.9)
Gastrointestinal Disorders					
Colitis Ischaemic	119	17.2 (14.34–20.62)	17.17 (1775.15)	16.84 (14.46)	4.07 (3.81)
Colitis	20	0.52 (0.34–0.81)	0.52 (8.63)	0.52 (0.36)	−0.93 (−1.56)
Colitis Ulcerative	11	0.25 (0.14–0.46)	0.25 (24.13)	0.25 (0.15)	−1.98 (−2.81)
Diarrhoea Haemorrhagic	7	0.69 (0.33–1.45)	0.69 (0.95)	0.69 (0.37)	−0.53 (−1.55)
Crohn'S Disease	6	0.09 (0.04–0.2)	0.09 (56.02)	0.09 (0.05)	−3.49 (−4.58)
Terminal Ileitis	4	8.14 (3.04–21.81)	8.14 (24.82)	8.07 (3.54)	3.01 (1.72)
Colon Gangrene	2	21.47 (5.27–87.4)	21.47 (38.05)	20.95 (6.47)	4.39 (2.69)
Mesenteric Vascular Insufficiency	2	15.45 (3.81–62.59)	15.45 (26.54)	15.19 (4.71)	3.92 (2.24)
Anal Haemorrhage	2	0.68 (0.17–2.7)	0.68 (0.31)	0.68 (0.21)	−0.57 (−2.23)
Enterocolitis Haemorrhagic	2	1.2 (0.3–4.8)	1.2 (0.07)	1.2 (0.38)	0.26 (−1.41)
Nervous System Disorders					
Cerebrovascular Accident	131	0.7 (0.59–0.83)	0.7 (17.07)	0.7 (0.61)	−0.52 (−0.77)
Reversible Cerebral Vasoconstriction Syndrome	107	63.92 (52.5–77.82)	63.82 (6141.94)	59.31 (50.31)	5.89 (5.6)
Transient Ischaemic Attack	49	1.31 (0.99–1.73)	1.31 (3.53)	1.31 (1.03)	0.39 (−0.02)
Ischaemic Stroke	49	2.53 (1.91–3.35)	2.53 (45.14)	2.52 (2)	1.34 (0.93)
Cerebral Infarction	44	1.64 (1.22–2.21)	1.64 (11.09)	1.64 (1.28)	0.72 (0.29)
Haematochezia	38	0.66 (0.48–0.91)	0.66 (6.68)	0.66 (0.51)	−0.6 (−1.06)
Cerebral Vasoconstriction	33	41.92 (29.55–59.48)	41.9 (1254.01)	39.93 (29.8)	5.32 (4.81)
Intestinal Ischaemia	26	4.49 (3.05–6.6)	4.48 (70.03)	4.47 (3.23)	2.16 (1.6)
Cerebral Venous Thrombosis	16	8.12 (4.96–13.29)	8.12 (98.91)	8.05 (5.33)	3.01 (2.31)
Ischaemic Cerebral Infarction	14	11.16 (6.59–18.91)	11.16 (127.77)	11.02 (7.09)	3.46 (2.71)

Abbreviations: PTs, preferred terms; ROR, reporting odds ratio; PRR, proportional reporting ratio; $\chi 2$: chi-squared; IC: information component; IC025: the lower limit of 95% CI, of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI, of EBGM.

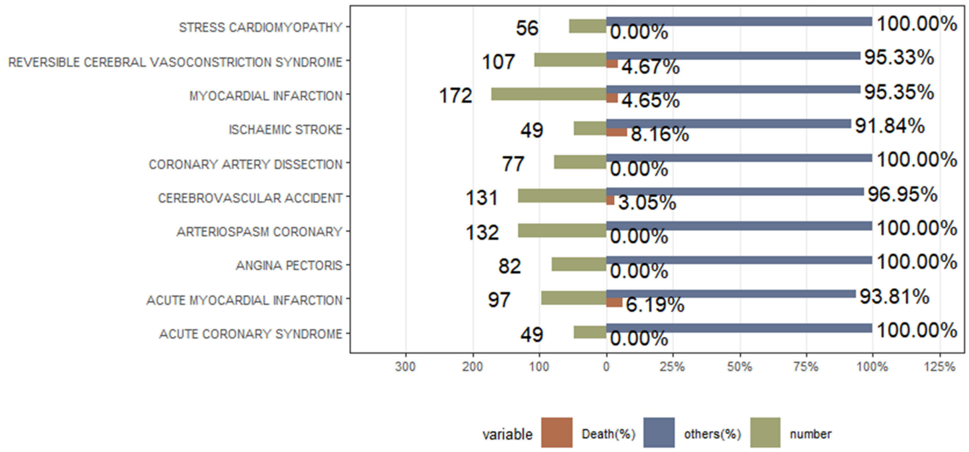

Figure 4 Death cases and their proportion in triptans concomitantly with ischemic AEs.

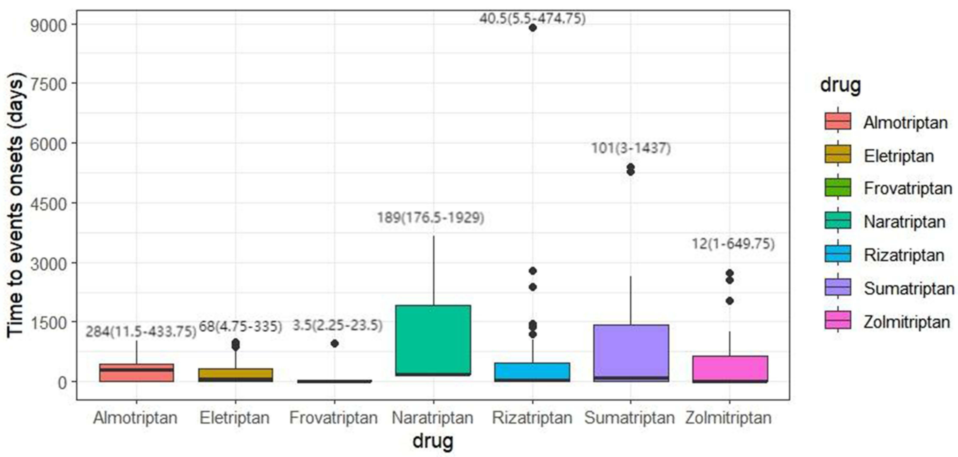

Figure 5 Time to onset of ischemic adverse events for different triptans.

days (IQR 11.5–433.75 days). Naratriptan exhibited the broadest range, with a median duration of 189 days (IQR 176.5–1929 days). The median time for eletriptan, rizatriptan, sumatriptan, and zolmitriptan were 68 days (IQR: 4.75~335 days), 40.5 days (IQR:5.5~474.75 days), 101 days (IQR: 3~1437 days), 12 days (IQR: 1~649.75 days), respectively. This study characterizes the temporal profile of ischemic adverse events associated with triptan use, providing valuable data on the timing of onset and strengthening the potential signal for this safety concern.

Comparison Between Serious and Nonserious Groups for Triptans-Related Ischemic AEs

Table 4 indicates a statistically significant difference in PTs between severe and non-severe ischemic AEs in patients receiving triptans. Six adverse events (AEs) were significantly more likely to be reported as serious ($p < 0.05$), including cerebral vasoconstriction ($p < 0.001$), cerebral ischemia ($p = 0.004$), gastrointestinal hemorrhage ($p = 0.001$), coronary artery disease ($p = 0.01$), increased blood creatine phosphokinase ($p = 0.021$), and coronary artery occlusion ($p = 0.021$). Other adverse events, including acute myocardial infarction ($p = 0.348$), cerebral thrombosis ($p = 0.511$), cerebrovascular accident ($p = 0.722$), intestinal infarction ($p = 0.690$), and thalamic infarction ($p = 0.606$), were more frequently reported as non-serious ($p > 0.05$).

Table 4 Comparison Between the Serious and Non-Serious Groups for Ischemic Adverse Events

Types of PTs	Serious Case	Non-Serious Cases	P-value
Acute Myocardial Infarction	6(0.097)	85(0.059)	0.348
Blood Creatine Phosphokinase Increased	3(0.048)	13(0.0091)	0.021
Cerebellar Infarction	2(0.032)	8(0.0056)	0.084
Cerebral Ischaemia	3(0.048)	9(0.0063)	0.004
Cerebral Thrombosis	1(0.016)	4(0.0028)	0.511
Cerebral Vasoconstriction	8(0.13)	25(0.017)	0.000
Cerebrovascular Accident	4(0.065)	123(0.086)	0.722
Coronary Artery Disease	2(0.032)	4(0.0028)	0.010
Coronary Artery Occlusion	3(0.048)	13(0.0091)	0.021
Coronary Artery Thrombosis	1(0.016)	5(0.0035)	0.606
Gastrointestinal Haemorrhage	2(0.032)	2(0.0014)	0.001
Haematochezia	1(0.016)	33(0.023)	1.000
Infarction	2(0.032)	4(0.0028)	0.010
Intestinal Infarction	1(0.016)	6(0.0042)	0.690
Ischaemic Stroke	4(0.065)	45(0.031)	0.284
Myocardial Infarction	8(0.13)	163(0.11)	0.866
Myocardial Ischaemia	1(0.016)	14(0.0098)	1.000
Rectal Haemorrhage	1(0.016)	11(0.0077)	0.997
Reversible Cerebral Vasoconstriction Syndrome	5(0.081)	94(0.066)	0.836
Thalamic Infarction	1(0.016)	5(0.0035)	0.606
Troponin Increased	2(0.032)	29(0.02)	0.845

Abbreviations: PTs, preferred terms.

Discussion

Triptans are first-line treatments for acute migraine due to their selective agonism of 5-HT(1B/1D) receptors, which are associated with cranial vasoconstriction and pain relief.[15] However, their vasoactive properties raise concerns regarding ischemic adverse events (AEs), particularly in patients with cardiovascular or cerebrovascular risk factors. Real-world evidence indicates a small but significant increase in the risk of ischemic events such as acute myocardial infarction and ischemic stroke, contrasting with the low incidence (<0.01%) reported in clinical trials that excluded high-risk individuals.[16] Similarly, gastrointestinal complications—including ischemic colitis—are frequently and strongly associated with triptan use, a finding supported by both previous and present pharmacovigilance studies.[7] The baseline demographic of triptan users is predominantly female (3:1 ratio), consistent with the higher prevalence of migraine among women, leading to a greater absolute number of AEs reported in female patients.[7]

Our disproportionality analysis identified significant variability in ischemic risk among triptans. Almotriptan showed the strongest association (ROR = 3.34, 95% CI, 2.49–4.49), followed by naratriptan (ROR = 2.96) and rizatriptan (ROR = 2.41). Although sumatriptan had the highest number of reported ischemic AEs (N = 778), it exhibited the most favorable safety profile (ROR = 1.22). These differences may be attributable to pharmacological variations, including half-life, bioavailability, and receptor affinity. Sumatriptan's shorter half-life (~2 hours) and lower bioavailability (~14%) likely result in less sustained vasoconstriction compared to agents such as almotriptan (half-life ~3 hours) and eletriptan (half-life ~4 hours), which demonstrate prolonged vascular activity.[17–19] Additionally, second-generation triptans like almotriptan and eletriptan exhibit higher affinity for vascular 5-HT(1B/1D) receptors, potentially increasing cerebral vasoconstriction, whereas sumatriptan shows more balanced receptor activation.[20,21] Dosing frequency and cumulative exposure may further modulate risk.[22] These findings align with previous evidence suggesting that second-generation triptans may carry higher cardiovascular risks despite improved tolerability, underscoring the need for individualized risk assessment when selecting triptan therapy.[23]

We identified 1062 positive signals for ischemic AEs, primarily affecting the cardiac (N = 557), nervous (N = 340), and gastrointestinal (N = 165) systems. The most notable cardiac AEs included coronary artery dissection (ROR = 93.17), acute myocardial infarction (ROR = 2.93; mortality >6%), stress cardiomyopathy (ROR = 9.76), and acute coronary syndrome (ROR = 5.25). The high ROR for coronary artery dissection suggests a drug-induced vascular injury mechanism, consistent with prior case reports.[24] The significant association with AMI reinforces concerns about triptan use and coronary vasospasm, particularly in patients with atherosclerosis.[25,26] Among neurological AEs, reversible cerebral vasoconstriction syndrome (RCVS) demonstrated the strongest signal (ROR = 63.92), supporting previous associations between vasoactive medications and this syndrome.[27] Triptans may exacerbate cerebrovascular dysregulation, especially in individuals with endothelial dysfunction.[28] The considerable mortality associated with ischemic stroke emphasizes the need for careful patient selection.[29] A significant association was also observed for ischemic colitis (ROR = 17.2), likely resulting from splanchnic vasoconstriction, consistent with earlier studies.[30,31]

Analysis of the top ten most frequently reported triptan-related ischemic adverse events (AEs) reveals a distinct clinical profile dominated by vasospastic disorders, including coronary artery dissection (ROR = 93.17), reversible cerebral vasoconstriction syndrome (RCVS; ROR = 63.92), and coronary arteriospasm (ROR = 33.59). These findings suggest that triptans may precipitate ischemic events primarily via excessive 5-HT1B-mediated vasoconstriction, endothelial dysfunction, or vascular hyperreactivity, particularly in susceptible individuals.[32] The strong signal for coronary artery dissection underscores a potential interaction with underlying vascular fragility, such as fibromuscular dysplasia—a condition prevalent in women that merits further investigation.[33] Paradoxically, myocardial infarction (MI), despite having the highest case count (N = 172), yielded a negative disproportionality signal (ROR = 0.86). Triptans' potential ischemic risk may be masked in overall data due to channeling bias, as they are preferentially prescribed to healthier patients with lower baseline cardiovascular risk. This may reflect under-reporting due to misattribution to pre-existing conditions, masking by migraine symptoms, or presentation outside the drug's pharmacokinetic window. Alternatively, the observed signal may be influenced by indication bias, as triptans are typically prescribed to younger migraine patients—especially premenopausal women—who have lower baseline cardiovascular risk.[34] Some studies suggest that migraine relief itself might confer protective effects, though this may represent methodological artifact rather than true cardioprotection.[35] Given their known vasoconstrictive risks, triptans remain contraindicated in patients with cardiovascular disease per FDA labeling.[36] Future studies should account for indication bias and validate these findings through rigorous epidemiological designs.

The substantial mortality (>6%) associated with ischemic stroke and AMI highlights the importance of pre-treatment cardiovascular risk assessment, including screening for hypertension, smoking, and coronary artery disease.[37] High-risk patients should avoid triptan use, and early recognition of ischemic symptoms is essential.[38]

Significant variations in time-to-onset were observed among triptans. Frovatriptan had the shortest median onset (3.5 days), while almotriptan had the longest (284 days). Naratriptan showed a wide interquartile range (176.5–1929 days), suggesting considerable variability in individual susceptibility, possibly due to differences in pharmacokinetics, receptor affinity, or dosing patterns.[39–41] These findings underscore the importance of personalized treatment approaches.[42]

Serious adverse event (AE) reporting varied, with cerebral vasoconstriction, cerebral ischemia, gastrointestinal hemorrhage, coronary artery disease, elevated creatine phosphokinase levels, and coronary artery occlusion being more frequently reported as serious conditions. This highlights the acute vasoconstrictive complications associated with these events.[43] In contrast, myocardial infarction, cerebral thrombosis, and cerebrovascular accident showed no significant association with serious reporting, likely as they often arise from chronic atherosclerotic processes rather than acute vasospasm.[44] Triptans'short half-life and restricted use in cardiovascular disease may attenuate observable associations, and attribution bias may further influence reporting patterns.[45–47] The absence of a significant association with serious reporting does not indicate safety but may reflect methodological limitations or heterogeneous AE mechanisms.

This study has several limitations inherent to pharmacovigilance analyses. A key constraint is that the number of adverse event reports is influenced by a drug's market prevalence and reporting practices, rather than reflecting inherent risk alone. Therefore, direct comparisons of raw report counts between triptans are not appropriate; disproportionality analysis serves as the primary method for detecting potential safety signals. For instance, sumatriptan's high number of reports coupled with a low ROR is consistent with its widespread use and does not indicate greater safety. Furthermore, spontaneous reporting systems might underreport events such as myocardial infarction, often linked to pre-existing cardiovascular conditions, while possibly overestimating acute vasospastic incidents like RCVS due to reporting bias.[48,49] The analysis could not fully account for important confounders such as migraine-related vascular risk or underlying cardiovascular comorbidities, nor did it examine dose-response relationships or drug interactions that may modify ischemic risk.[50–52] Additionally, the exclusion of high-risk patients from triptan use in clinical practice may limit the generalizability of these safety signals to real-world populations.[53,54] These limitations highlight the need for adjusted observational studies and mechanistic research to better characterize triptans' vascular safety profile.

Conclusion

This comprehensive pharmacovigilance study, leveraging the FAERS database, identifies a detectable association between triptans and ischemic adverse events, contributing valuable insights into their safety profile. Although ischemic events represented a relatively small proportion of total triptan-related adverse events, their rising report proportion in recent years warrants heightened clinical awareness. Disproportionality analysis linked specific triptans to ischemic events; however, clinical relevance depends not only on ROR magnitude but also on case seriousness, frequency, and affected patient characteristics. Furthermore, serious cases frequently involved cerebral vasoconstriction, cerebral ischemia, and coronary artery occlusion, whereas non-serious cases were more often associated with acute myocardial infarction and cerebrovascular accidents. These findings suggest that clinicians should exercise caution when prescribing triptans, especially for patients with underlying cardiovascular risk factors, and remain vigilant for potential delayed ischemic complications. While triptans continue to be a foundational treatment for migraine, the possibility of ischemic adverse events should be carefully considered. Further studies, particularly well-controlled observational investigations and mechanistic research, are needed to better characterize risk profiles, validate these signals, and establish strategies for long-term monitoring to improve patient safety.

Ethic Statement

According to item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China, research projects meeting one of the following conditions may apply for exemption from ethical review: research conducted using legally obtained publicly available data, or research using anonymized data that cannot identify specific individuals and does not involve personal privacy or commercial interests.

Disclosure

The authors declare that they have no competing interests.

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