Risk of Cardiovascular Outcomes Among Patients with Migraine Using Contemporary Agents

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INTRODUCTION

- Triptans, first-line treatment for acute migraine, are contraindicated in over 20% of migraine patients due to their cardiovascular conditions, significantly limiting treatment options for this substantial population[1]
- Since 2020, FDA has approved non-vasoconstrictive alternatives (CGRP antagonists, 5-HT1F receptor agonist) that theoretically offer safer options for patients with cardiovascular risk factor
- Limited real-world evidence comparing cardiovascular risks exists, as clinical trials typically excluded patients with cardiovascular disease

OBJECTIVES

- Our study aimed to compare the risk of cardiovascular outcomes among patients treated with ubrogepant, rimegepant, and lasmiditan versus those treated with sumatriptan

METHODS

Data Source

- Utilized a large comprehensive administrative health claims database from 2016 to 2023

Study Design

- Retrospective cohort study design
- Three separate pairwise comparisons: sumatriptan vs. ubrogepant, sumatriptan vs. rimegepant, and sumatriptan vs. lasmiditan

Study Population

Inclusions

- Adults (≥18 years) with first-time use of migraine medications between 2016-2023
- At least 1 inpatient or 2 outpatient claims with migraine diagnosis (ICD-10-CM code G43.XX)
- 12 months of continuous enrollment before the index date

Exclusion

- Prior use of study medications in the year before index date
- Prior use of other acute migraine-specific medications (triptans, ergots, atogepant) in the year before index date
- Diagnosis of abdominal migraine and Pregnancy in the year before index date

METHODS

- Concurrent use of use of CGRP monoclonal antibodies for migraine prevention (erenumab, galcanezumab, fremanezumab, eptinezumab) on index date

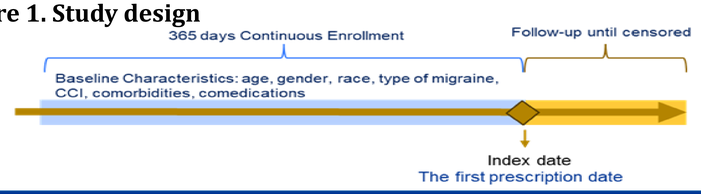
Outcomes

- Three-point major adverse cardiovascular events (MACE), defined as a composite of acute myocardial infarction, stroke, and cardiovascular death

Statistical Analysis

- Created propensity scores using baseline characteristics (patient demographics, index year, migraine type, comorbidities, concomitant medications) and assessed cohort balance using SMD
- Performed propensity score matching (nearest neighbor, 0.1 SD caliper): 1:1 ratio for ubrogepant-sumatriptan and rimegepant-sumatriptan; 1:2 for lasmiditan-sumatriptan
- Assessed time to event using Cox proportional hazards models

Figure 1. Study design



RESULTS

- After propensity score matching, the analysis included three relatively well-balanced cohorts: ubrogepant vs. sumatriptan (2,834 patients each), rimegepant vs. sumatriptan (2,710 patients each), and lasmiditan vs. sumatriptan (165/330 patients)

Table 1. Baseline Characteristic

Main Analysis	Cohort 1			Cohort 2			Cohort 3		
	Ubrogepant (n=2,834)	Sumatriptan (n=2,834)	SMD	Rimegepant (n=2,710)	Sumatriptan (n=2,710)	SMD	Lasmiditan (n=165)	Sumatriptan (n=330)	SMD
Age	50	49.9	0.001	51	51.4	-0.02	49.2	50.6	-0.09
Gender(female)%	88.1	89.7	0.05	86.7	87.1	0.01	84.9	87	0.06
Migraine with aura	14.9	15	0	15.7	16.4	0	10.3	12.7	0.13
Charlson Comorbidity Index(mean/std)	1.3/1.9	1.2/1.8	0.05	1.5/2	1.5/2	0.01	1.6/1.9	1.7/1.8	-0.05
Selected Comorbid Conditions, n(%)									
Dyslipidemia	42.6	40.4	0.05	45.8	44.1	0.03	43.6	44.6	-0.02
Obesity	33	31.6	0.03	35.7	34.1	0.03	32.7	40.3	-0.15
Hypertension	41	38.6	0.05	44.5	44.2	0.01	39.4	45.2	-0.11
Ischemic heart disease	12.3	11.3	0.03	14	14.3	-0.01	20.6	21.8	-0.03
Other CGRP antagonists	22	19.7	0.06	23	20	0.07	43	41.8	0.02

RESULTS

- Patients receiving rimegepant had a 47% higher risk of composite MACE endpoint compared to those receiving sumatriptan (Table 2)
- Ubrogepant users demonstrated a trend toward increased MACE risk compared to sumatriptan recipients, though these associations did not reach statistical significance

Table 2. Main Analysis

Main Analysis	Cohort 1		Cohort 2		Cohort 3	
	Ubrogepant (n=2,834)	Sumatriptan (n=2,834)	Rimegepant (n=2,710)	Sumatriptan (n=2,710)	Lasmiditan (n=165)	Sumatriptan (n=330)
MACE composite						
No. of events	121	139	142	160	14	22
Incidence (1000ppy)	32.89	24.91	50.93	31.12	55.06	37.01
HR (95% CI)	1.27 (0.99-1.64)	Ref	1.46 (1.15-1.86)	Ref	1.52 (0.76-3.05)	Ref

CONCLUSIONS

- To the best of our knowledge, this is the first large-scale study comparing cardiovascular outcomes of contemporary migraine agents versus sumatriptan in a real-world setting
- Contrary to the assumption that non-vasoconstrictive CGRP antagonists would have better cardiovascular safety than triptans, our study observed a higher MACE risk with rimegepant compared to sumatriptan

Strengths

- Our study included patients with cardiovascular risk factors who are typically excluded from clinical trials, providing real-world evidence on safety in populations of greatest clinical interest.

Limitations

- Despite thorough matching procedures, residual confounding may persist due to channeling bias, as second-line medications are often prescribed to patients with contraindications to first-line therapy
- Reliance on claims data omits key clinical parameters that may influence treatment selection and outcomes
- Prescription records cannot verify actual medication adherence, potentially misclassifying exposure

References:
1. Oswald JC, et al. J Pain Res. 2018;11:2221-2227