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eISSN 2450-3118 · Open Access · Peer-reviewed

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SOLECKA, Katarzyna, FENGLER, Karolina, URBANIK, Agata, JAKUBOWSKA, Olga, KOMINIAK, Dominika, OĆWIEJA, Zuzanna, WYBORSKA, Agata, PIETRZAK, Kamila, MIŃKOWSKI, Mikołaj, and GASCON, Marcel. Gepants in Migraine Treatment: Cardiovascular Safety and Clinical Implications. *Quality in Sport*. 2026;74:74997. <https://doi.org/10.12775/QS.2026.74.74997>

ARTICLE TIMELINE

Received: 04.08.2026. Revised: 24.08.2026. Accepted: 07.09.2026. Published: 18.09.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2026.

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Gepants in Migraine Treatment: Cardiovascular Safety and Clinical Implications

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Abstract

Background. Migraine is a chronic neurological disorder of significant clinical and social importance, affecting approximately 15% of the global population. The last decade has seen a breakthrough in migraine pharmacotherapy due to the introduction of gepants—small-molecule CGRP (calcitonin gene-related peptide) receptor antagonists, which are effective in both the treatment of acute migraine phases and the prophylaxis of attacks. CGRP is one of the most potent vasodilators in the body, playing a key role in the regulation of vascular tone and exhibiting cardioprotective properties. Consequently, the pharmacological blockade of the CGRP pathway raises legitimate concerns regarding its potential impact on the cardiovascular system.

Aim. The objective of this study is to provide a comprehensive assessment of the cardiovascular risk associated with gepant therapy in patients suffering from migraine.

Material and Methods. The objective of this narrative review is to conduct a systematic assessment of the cardiovascular risk associated with the administration of gepants in patients with migraine, based on available data from clinical trials, meta-analyses, and observational studies. A systematic search was conducted in the following electronic databases:

- PubMed
- Embase
- Web of Science

The search covered publications from March 2004 to April 2026.

Summary. Available data from short-term studies suggest a favorable safety profile for gepants; however, their long-term impact on the cardiovascular system, particularly in patients with pre-existing cardiovascular diseases, necessitates further, well-designed prospective studies. It is concluded that they constitute a significant therapeutic alternative for patients with contraindications to triptans, while simultaneously highlighting the requirement for continued long-term research.

Keywords: migraine, CGRP, gepants, cardiovascular safety, pharmacotherapy

Introduction

Migraine is one of the most prevalent chronic neurological disorders, characterized by recurrent episodes of headache of moderate to high intensity, often accompanied by autonomic symptoms such as nausea, vomiting, or hypersensitivity to light and sound stimuli. This condition represents a significant public health challenge—affecting approximately 15% of the global population [1], with over 3.5 million people suffering from it in Poland. Migraine not only diminishes patients' quality of life but is also associated with substantial social and economic consequences resulting from workplace absenteeism and reduced productivity.

Given these data, it is noteworthy to emphasize the association between migraine (particularly migraine with aura) and an elevated risk of cardiovascular diseases. Epidemiological studies indicate that migraine patients are more susceptible to ischemic stroke, myocardial infarction, and cardiovascular mortality. This relationship is especially prominent in younger women and persists independently of classical risk factors, such as hypertension or dyslipidemia [2]. Consequently, migraine is increasingly perceived not merely as an isolated neurological entity, but as an element of a broader spectrum of systemic disorders.

Advances in understanding the pathophysiology of migraine have led to the identification of the crucial role of calcitonin gene-related peptide (CGRP), which is involved in pain transmission mechanisms and the regulation of vascular tone. CGRP is one of the most potent

endogenous vasodilators and exhibits cardioprotective properties, including through its influence on the vascular system and modulation of the inflammatory response. These discoveries formed the basis for the development of new targeted therapies[3-6].

One of the most significant therapeutic innovations of the last decade is the introduction of gepants—small-molecule CGRP receptor antagonists. These drugs demonstrate efficacy in both the treatment of acute migraine attacks and in disease prophylaxis, providing an alternative to traditional therapies such as triptans [7]. Unlike triptans, gepants do not exhibit vasoconstrictive activity [8-9], which makes them a particularly attractive therapeutic option for patients with contraindications to serotonergic medications.

Despite a favorable efficacy profile, the mechanism of action of gepants—involving the blockade of the CGRP pathway—raises certain concerns regarding their impact on the cardiovascular system. Due to the physiological role of CGRP in maintaining vascular homeostasis and protecting the circulatory system, its long-term inhibition could potentially be associated with adverse consequences, especially in patients burdened with cardiovascular diseases. In light of the increasing use of gepants in clinical practice and the significant number of migraine patients with additional cardiovascular risk factors, a thorough safety assessment of this drug class is essential. This paper focuses on analyzing available data regarding the cardiovascular risk associated with gepant administration, with particular emphasis on their use in patients with circulatory system diseases.

The Impact of Migraine on Cardiovascular Risk

Migraine, particularly migraine with aura, is currently recognized as an independent risk factor for cardiovascular diseases, including ischemic stroke, myocardial infarction, and cardiovascular mortality [10-12]. This association is notably robust in younger women and persists independently of traditional cardiovascular risk factors [11].

In the large-scale Women's Health Study cohort, which included 27,858 women followed for an average of 22.6 years, the adjusted incidence of major cardiovascular events was 3.36 per 1,000 person-years in women with migraine with aura, compared to 2.11 per 1,000 person-years in women without migraine or with migraine without aura ($p<0.001$). This risk was comparable to the risk associated with elevated systolic blood pressure or high total cholesterol, and higher than the risk associated with obesity or an unfavorable lipid profile [11].

A meta-analysis of 18 prospective cohort studies, encompassing 370,050 patients with migraine, demonstrated that migraine is linked to an increased risk of myocardial infarction,

ischemic stroke, and hemorrhagic stroke. In subgroup analyses, migraine with aura was associated with an even higher risk of all these events, as well as an increased risk of cardiovascular mortality [12].

The European Society of Cardiology currently recommends the inclusion of migraine with aura in cardiovascular risk assessments [13]. Furthermore, the 2024 American Heart Association/American Stroke Association guidelines recognize migraine, especially with aura, as a stroke risk factor, emphasizing a stronger association with ischemic rather than hemorrhagic stroke and a higher risk profile among young women [5].

Mechanism of Action of Gepants

Gepants are small-molecule CGRP receptor antagonists that block the binding of CGRP to its receptor, thereby interrupting the signaling cascade responsible for migraine pain [14-16]. In contrast to triptans, which act as agonists of the 5-HT_{1B} and 5-HT_{1D} serotonin receptors and exhibit vasoconstrictive effects, gepants appear to lack such activity [8-9].

The CGRP receptor is a complex consisting of the calcitonin receptor-like receptor (CLR) and the receptor activity-modifying protein 1 (RAMP1) [6][17]. Gepants bind selectively and with high affinity to the human calcitonin gene-related peptide (CGRP) receptor, exerting an antagonistic effect. Consequently, they prevent the actions of CGRP at three key levels:

1. **Prevention of cerebral vasodilation** – the blockade of CGRP receptors on vascular smooth muscle cells prevents CGRP-induced dilation of intracranial arteries [17][18].
2. **Inhibition of neurogenic inflammation** – gepants prevent the activation of mast cells and the subsequent release of inflammatory mediators within the perivascular space of the meninges [6][18].
3. **Blockade of pain signal transmission** – antagonism of CGRP receptors within the trigeminocervical complex prevents the transmission of nociceptive signals to higher pain centers [18].

The Role of CGRP in Cardiovascular Physiology

CGRP is one of the most potent vasodilators known in both cerebral and peripheral circulation. For this reason, among others, it is essential to analyze its potential impact on cardiovascular risk [6][9]. These peptides play a vital role in cardiovascular physiology through the following mechanisms:

Vasodilation and blood pressure reduction – CGRP is released from sensory fibers and induces potent vasodilation by activating adenylate and guanylate cyclase, leading to the production of cAMP and cGMP. This process ultimately results in the opening of K-ATP channels and the relaxation of vascular smooth muscles [6][19].

Cardioprotective effects – CGRP protects against the development and progression of hypertensive states, potentially counteracting pro-hypertensive systems such as the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system [17][20]. In models of heart failure and ischemia, CGRP mitigates various aspects of their pathophysiology, including cardiac hypertrophy, reperfusion injury, cardiac inflammation, and apoptosis [17][20-21].

Interactions with Medications Used in Patients with Cardiovascular Diseases

Gepants demonstrate a relatively favorable interaction profile with medications used in cardiovascular diseases, with the primary interactions concerning metabolism via CYP3A4 rather than direct pharmacodynamic interactions with cardiological drugs.

1. Beta-blockers and ACE inhibitors In the available literature, no clinically significant pharmacodynamic interactions have been identified between gepants and beta-blockers or angiotensin-converting enzyme (ACE) inhibitors [22-23]. Importantly, beta-blockers and ACE inhibitors/angiotensin II receptor antagonists can be administered concurrently as migraine prophylaxis in patients with cardiovascular diseases, offering a dual therapeutic benefit [23-24]. It should be emphasized that verapamil, a calcium channel blocker, is a moderate CYP3A4 inhibitor and increases ubrogepant exposure approximately 3.5-fold, which necessitates a dose reduction of ubrogepant to 50 mg (per FDA Drug Label).

2. Statins Gepants do not exhibit direct pharmacodynamic interactions with statins [22][25]. Statins metabolized by CYP3A4 (atorvastatin, lovastatin, simvastatin) could theoretically compete for the same metabolic pathway as gepants; however, there are no reports in the literature of clinically significant interactions.

3. Antiplatelet and Anticoagulant Agents Clinical trials have not demonstrated significant pharmacodynamic interactions between gepants and antiplatelet agents (acetylsalicylic acid, clopidogrel) or anticoagulants (warfarin, direct oral anticoagulants) [9][22][25][26]. Ubrogepant has shown no pharmacokinetic interactions with naproxen, suggesting the safety of co-administration with non-steroidal anti-inflammatory drugs (NSAIDs) that possess antiplatelet activity (per FDA Drug Label).

The Impact of Gepants on Electrocardiographic Parameters and Arterial Blood Pressure

A systematic review of available data regarding the impact of gepants on electrocardiographic parameters, arterial blood pressure, and heart rate is presented below.

1. Impact on Electrocardiographic Parameters Available data from clinical trials indicate that gepants do not exhibit a significant impact on electrocardiographic parameters, particularly the QT interval responsible for ventricular repolarization [27-30].

Ubrogepant was the subject of a dedicated study assessing its effect on cardiac repolarization (a so-called "thorough QT study"). It was demonstrated that both the therapeutic dose and a fourfold supratherapeutic dose do not cause clinically significant QT interval prolongation, remaining well below the safety thresholds defined by regulatory agencies [27]. Similarly, rimegepant, even at doses many times exceeding the therapeutic dose, shows no impact on cardiac repolarization. In phase 3 clinical trials, no significant changes in electrocardiographic recordings were observed compared to placebo [28][29].

In the ELEVATE and PROGRESS pivotal trials, atogepant did not show clinically significant changes in ECG recordings. A single case of ventricular arrhythmia reported in the ELEVATE trial was assessed by investigators as unrelated to the treatment [28]. According to current information, all available gepants are characterized by a favorable electrocardiographic safety profile, with no evidence of QT interval prolongation or other clinically significant conduction or repolarization disorders.

2. Impact on Arterial Blood Pressure Clinical trials of gepants have consistently demonstrated a lack of clinically significant changes in arterial blood pressure compared to placebo. In the ubrogepant pivotal trials (ACHIEVE I and II), no increased incidence of cardiovascular adverse events, including blood pressure changes, was found, regardless of the patients' baseline cardiovascular risk profile [31]. In the PROGRESS trial evaluating atogepant for chronic migraine prophylaxis, no clinically significant changes in blood pressure or pulse rate were observed relative to placebo [32]. Analogously, the ELEVATE study showed no clinically significant differences in the proportion of patients with potentially clinically significant blood pressure values between the atogepant and placebo groups [28].

Despite favorable clinical trial results, post-marketing surveillance data indicate a potential risk of arterial hypertension associated with CGRP blockers as a drug class. A systematic review by Croteau et al. (2026) identified 106 cases of hypertension related to CGRP blockers reported to the FAERS system and in medical literature, of which 28 cases (26%) were associated with

gepants [33]. Reports of *de novo* hypertension were slightly more frequent than exacerbations of existing hypertension, and the time from treatment initiation to the onset of hypertension was ≤ 30 days in two-thirds of the cases. In more than one-third of the cases, it was necessary to initiate new antihypertensive treatment or increase the dosage of existing medications [33].

Analysis of the Incidence of Cardiovascular Events in Patients Treated with Gepants

Data from cohort studies indicate a potentially increased risk of cardiovascular events in patients initiating CGRP inhibitor therapy (including gepants), although results vary depending on the study population and the specific type of cardiovascular incident.

A cohort study by Lusk et al. (2026) represents the largest study to date, encompassing 900,370 patients with migraine (median age 41 years; 77.8% women). This analysis was observational and retrospective in nature, based on a review of extensive medical databases. During the data observation period, a higher incidence of cardiovascular events was recorded in the group using CGRP inhibitors (8.77 events per 1,000 person-years) compared to the control group (6.76 events per 1,000 person-years). This corresponds to a relative risk increase of 26% (hazard ratio [HR] = 1.26) [34].

Further detailed analysis revealed a statistically significant increase in the risk of ischemic stroke, whereas no significant differences were found between patients using CGRP inhibitors and the control group for other cardiovascular events, such as myocardial infarction, revascularization procedures, intracranial hemorrhage, or retinal artery occlusion. However, it must be emphasized that the 26% figure includes both gepants and anti-CGRP monoclonal antibodies, which limits the possibility of directly attributing these results solely to the gepant class. Furthermore, it is noteworthy that patients initiating CGRP inhibitor therapy exhibited a poorer health profile at the time of study enrollment, which may indicate the presence of residual confounding, despite the application of advanced statistical methods [34].

Consideration should also be given to the analysis by Giacon et al. (2026), which provides a systematic review of the post-marketing safety of calcitonin gene-related peptide (CGRP) inhibitors, including both monoclonal antibodies (mAbs) directed against CGRP or its receptor and gepants [35]. The authors conducted a systematic literature review encompassing 30 publications based primarily on the analysis of spontaneous adverse event reporting databases, such as FAERS (Food and Drug Administration Adverse Event Reporting System), Vigibase (WHO), and EudraVigilance (European Medicines Agency). The analysis of post-marketing data revealed potential, rare, yet clinically significant adverse events associated with

monoclonal antibody therapy. These include reversible cerebral vasoconstriction syndrome (RCVS) and carotid artery dissection. To date, these phenomena have not been unequivocally confirmed in relation to gepants, which may suggest a differing vascular risk profile between these drug classes. However, it must be stressed that the absence of a signal is not equivalent to the absence of risk, and these data require further validation. Notably, certain adverse effects common to the entire class of CGRP inhibitors were recorded, including Raynaud's phenomenon [35].

Comparison of the Safety Profiles of Individual Gepants

All four approved gepants (rimegepant, ubrogepant, atogepant, and zavegepant) exhibit a comparable overall cardiovascular safety profile; however, significant differences exist in the frequency and types of reported adverse events among individual agents [4][35].

Rimegepant is the only gepant approved for both acute and prophylactic migraine treatment. Analyses of the VigAccess and FAERS databases have indicated that among the three oral gepants, rimegepant shows the strongest signal of disproportionate reporting for cardiac events, despite all three drugs having a comparable overall frequency of cardiological reports. Rimegepant is also characterized by the highest number of reports of Raynaud's phenomenon among the gepants. In long-term open-label studies, one case of first-degree atrioventricular block potentially related to rimegepant was recorded [4].

Ubrogepant is approved exclusively for the acute treatment of migraine. The ACHIEVE I and II trials, involving 3,358 participants, demonstrated that the safety and efficacy of ubrogepant did not vary according to the presence of cardiovascular risk factors—11% of participants were classified as having moderate-to-high CV risk, 32% as low CV risk, and 58% as having no CV risk factors. The proportion of participants reporting adverse events was comparable across all risk categories and similar to placebo [27][31][36]. In the ACHIEVE I trial, one case of pericardial effusion was recorded as a serious adverse event in the 50 mg ubrogepant group; however, it occurred 48 hours after dosing [31].

Atogepant is approved solely for migraine prophylaxis. In the ELEVATE (episodic migraine) and PROGRESS (chronic migraine) trials, atogepant demonstrated a favorable safety profile with no clinically significant differences in blood pressure or heart rate between groups. One case of ventricular tachycardia was reported as a serious adverse event, but it was deemed by the investigator to be unrelated to the treatment [28].

Zavegepant is the only gepant administered intranasally and is approved for the acute treatment of migraine. Its adverse event profile is dominated by respiratory symptoms related to the route of administration. A systematic review did not detect specific cardiovascular signals or signals of disproportionate reporting for serious cerebrovascular events for zavegepant [37].

Nevertheless, it is worth noting that FDA labels for all gepants contain shared warnings regarding the development or exacerbation of hypertension (most commonly within 7 days of treatment initiation) and Raynaud's phenomenon. Pharmacological studies on isolated human coronary arteries have also revealed differences in receptor affinity among gepants: atogepant and rimegepant exhibit greater potency in meningeal arteries than in coronary arteries, whereas ubrogepant and zavegepant show similar potency in both vessel types. Data suggest that such differences may have implications for cardiovascular safety, although their clinical significance requires further investigation [38].

Safety Assessment of Gepant Administration in Patients with a History of Cardiovascular Disease

The aforementioned data indicate that CGRP-targeted therapy constitutes an effective and well-tolerated method for migraine prophylaxis, as confirmed by both clinical trials and real-world evidence. The majority of available analyses suggest a lack of significant increase in the risk of major cardiovascular incidents compared to other treatment modalities, such as onabotulinumtoxinA [39]. However, attention should be drawn to the fact that recent observational studies suggest the possibility of a slight increase in the risk of composite cardiovascular events, particularly ischemic stroke [34]. It must be emphasized that the observed increase in risk has a small absolute value and may result from a higher burden of risk factors within the treated population.

Conclusions

Available data indicate that gepants represent an effective and well-tolerated therapeutic option for the treatment of acute migraine and its prophylaxis, especially in patients with contraindications to triptans. Clinical trials have not demonstrated a significant impact of this drug class on cardiovascular parameters, including arterial blood pressure and electrocardiographic indices; however, it should be noted that these observations primarily pertain to populations with relatively low to moderate cardiovascular risk and a limited observation period.

The results of observational studies and post-marketing data analyses suggest the potential occurrence of rare cardiovascular events, including arterial hypertension. Nevertheless, their interpretation is limited due to the potential influence of confounding factors and the nature of the data sources, which do not allow for the establishment of a causal relationship. Furthermore, it should be noted that some available analyses aggregate various classes of CGRP pathway inhibitors, which limits the ability to unequivocally define a safety profile specific to gepants.

In summary, gepants exhibit a favorable cardiovascular safety profile in available short-term studies; however, their long-term impact on the circulatory system, particularly in patients burdened with cardiovascular diseases, necessitates further, well-designed prospective studies.

Disclosure

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All authors have read and agreed to the published version of the manuscript.

Funding statement: The study did not receive special funding.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process.

During the preparation of this work, the authors used ChatGPT (OpenAI) for the purpose of language editing and stylistic improvement only. The authors reviewed and approved the final version of the manuscript and take full responsibility for its content.

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