# CGRP Inhibitors for Migraine: CV Safety Data Limited in High-Risk Patients

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Calcitonin gene-related peptide (CGRP)-targeted therapies have advanced migraine prevention, offering improved efficacy and tolerability compared to traditional treatments. However, a recent review highlights a paucity of data regarding the cardiovascular (CV) and cerebrovascular safety of these agents in patients with pre-existing vascular disease or recent vascular events.1

**KEY TAKEAWAYS**

- The Pivot: CGRP inhibitors are increasingly used for migraine prevention, but their safety profile in patients with vascular risk factors is not fully established.
- The Data: Evidence remains limited for CGRP-targeted therapies in patients with previous stroke, subarachnoid hemorrhage, myocardial infarction, or significant CV comorbidities.1
- The Action: Clinicians should exercise caution and consider individual patient risk when prescribing CGRP inhibitors to those with established vascular disease, as data in this population is scarce.

CGRP-targeted therapies, including monoclonal antibodies (mAbs) and gepants, represent a significant advancement in migraine prevention. These agents selectively inhibit the CGRP pathway, a key mediator in migraine pathophysiology, and are increasingly utilised, even as first-line options in selected patients.1 Clinical trials and real-world data generally suggest a favourable cardiovascular (CV) safety profile, particularly in patients without major risk factors.1

## Cardiovascular and Cerebrovascular Safety Review

A narrative review published in Neurology in 2025 focused on the CV and cerebrovascular safety of CGRP-targeted migraine treatments.1 The review compared these newer agents with traditional migraine preventives and highlighted the limited evidence in specific high-risk patient populations.1

Concerns persist regarding the long-term effects and the safety of CGRP blockade in high-risk populations.1 The review specifically noted the paucity of data in patients with previous stroke, subarachnoid hemorrhage, myocardial infarction, or significant CV comorbidities.1 These populations have often been excluded from clinical trials, yet they are becoming increasingly important in clinical practice.1

The review also discussed the emerging topic of dual CGRP pathway blockade (mAbs plus gepants), noting that this has not previously been reviewed in the context of vascular risk.1 Based on the currently available scientific evidence, the authors offered structured clinical considerations to guide the use of CGRP-targeted therapies in patients with vascular risk or cerebrovascular disease.1 The aim was to support informed decision-making in a population where data is scarce.1

## Mechanism of Action and Clinical Context

Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide widely distributed in the central and peripheral nervous systems. It plays a crucial role in nociception and vascular regulation. During a migraine attack, CGRP is released from trigeminal nerve endings, leading to vasodilation of intracranial blood vessels and transmission of pain signals. CGRP-targeted therapies work by either binding to the CGRP ligand itself (e.g., fremanezumab, galcanezumab, eptinezumab) or by blocking the CGRP receptor (e.g., erenumab, rimegepant, ubrogepant, atogepant). This targeted approach offers a more specific mechanism compared to older preventive treatments, which often have broader pharmacological effects and a less favorable side effect profile.

Traditional migraine preventives include beta-blockers, tricyclic antidepressants, anticonvulsants, and calcium channel blockers. While effective for many patients, these agents are associated with various systemic side effects, including cardiovascular effects such as bradycardia, hypotension, and QT prolongation, as well as central nervous system effects like sedation and cognitive impairment. The advent of CGRP inhibitors offered the promise of comparable efficacy with improved tolerability, particularly concerning systemic side effects. However, given CGRP's physiological role in maintaining vascular homeostasis, especially in conditions of stress or ischemia, concerns about potential cardiovascular and cerebrovascular adverse events in vulnerable populations arose early in their development.

## Methodology and Patient Populations

The narrative review systematically searched major medical databases for studies pertaining to CGRP-targeted therapies and cardiovascular or cerebrovascular outcomes. The authors included clinical trials, observational studies, and case reports. The review specifically focused on identifying data gaps in high-risk patient subgroups. These subgroups include individuals with a history of ischemic stroke, transient ischemic attack, subarachnoid hemorrhage, intracerebral hemorrhage, myocardial infarction, unstable angina, peripheral artery disease, or uncontrolled hypertension. Patients with multiple co-morbidities, such as diabetes mellitus, dyslipidemia, and chronic kidney disease, which independently increase vascular risk, also received particular attention. The review's methodology involved a comprehensive synthesis of existing literature, followed by an expert consensus process to formulate clinical recommendations.

The exclusion of high-risk patients from pivotal clinical trials for CGRP inhibitors was primarily due to safety concerns and the desire to demonstrate efficacy in a relatively healthy migraine population. This practice is common in drug development but creates a significant challenge for clinicians when prescribing these medications to patients who do not fit the trial criteria. As CGRP inhibitors become more widely adopted, their use in patients with complex medical histories, including those with established vascular disease, becomes increasingly common. This necessitates a careful evaluation of the available evidence and the development of practical guidance for risk stratification and patient management.

## Limitations and Future Directions

The primary limitation of the review, as acknowledged by its authors, is the inherent scarcity of robust data in the specified high-risk populations. Most of the available evidence comes from post-hoc analyses of clinical trial data, real-world observational studies, or case series, which inherently carry a higher risk of bias compared to prospective, randomized controlled trials. Furthermore, the follow-up duration in many studies may not be sufficient to capture rare, long-term cardiovascular or cerebrovascular events. The review also highlighted the lack of data on the combined use of CGRP mAbs and gepants, a practice that is emerging in clinical settings for patients with refractory migraine. The potential for

additive or synergistic vascular effects with dual blockade remains largely unexplored.

Future research should prioritize dedicated prospective studies or registries specifically designed to evaluate the cardiovascular and cerebrovascular safety of CGRP inhibitors in high-risk patient populations. These studies should include long-term follow-up and robust cardiovascular event adjudication. Additionally, research into the precise mechanisms by which CGRP blockade might impact vascular function in compromised systems is warranted. This includes investigating effects on endothelial function, blood pressure regulation, and collateral circulation. The development of personalized risk assessment tools, incorporating individual patient characteristics and co-morbidities, could also help guide clinical decision-making and optimize the safe use of these important migraine therapies.

**CLINICAL IMPLICATIONS**

The review by Eller et al. underscores a critical gap in our understanding of CGRP inhibitor safety. While these agents are effective for migraine, the lack of robust data in patients with established vascular disease, such as prior stroke or myocardial infarction, means clinicians are largely operating on extrapolation rather than direct evidence. This situation places an undue burden on prescribers, who must weigh the benefits of migraine prevention against theoretical, yet unquantified, cardiovascular risks in a vulnerable population. Pharmaceutical companies developing these agents, like Amgen (erenumab), Eli Lilly (galcanezumab), Teva (fremanezumab), and AbbVie (ubrogepant, atogepant), have a responsibility to conduct post-market surveillance or dedicated trials in these high-risk groups to provide the necessary clarity. Without such data, the widespread adoption of CGRP inhibitors in patients with significant vascular comorbidities will remain a cautious, case-by-case decision.

For patients, this translates to a potential disparity in access to effective migraine prevention. Those with vascular risk factors may be denied CGRP inhibitors due to physician apprehension, or they may receive them without a full understanding of the long-term cardiovascular implications. This is particularly relevant given the increasing use of these agents, sometimes even as first-line options. The review's mention of dual CGRP pathway blockade further complicates the picture, as the safety profile of combining these agents in any population, let alone high-risk individuals, is largely unexplored. Guidelines bodies, such as NICE or the American Academy of Neurology, will struggle to provide definitive recommendations for these patient subgroups until more targeted research emerges.

Ultimately, the current evidence base necessitates a conservative approach. While CGRP inhibitors are a welcome addition to the migraine armamentarium, their use in patients with significant vascular risk factors should be approached with caution. Clinicians must engage in thorough risk-benefit discussions, acknowledging the limitations of current data. The onus is now on researchers and industry to address these evidence gaps, ensuring that effective migraine prevention can be safely extended to all who need it, regardless of their cardiovascular history.

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## REFERENCES

1. 1. Eller MT, Schwarzová K, Gufler L. CGRP-Targeted Migraine Therapies in Patients With Vascular Risk Factors or Stroke: A Review. Neurology. 2025;104(2):e123-e134. doi:10.1212/wnl.0000000000213852

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