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EFFECTIVENESS AND SAFETY OF ANTI-CGRP MONOCLONAL ANTIBODIES FOR MIGRAINE PREVENTION IN REAL-WORLD PRACTICE: A SYSTEMATIC REVIEW

Dawid Studziński *(Corresponding Author, Email: dawid.studzinski99@gmail.com)*
Municipal Hospital in Zabrze, Zabrze, Poland
ORCID ID: 0009-0005-3834-716X

Marcin Schulz
II Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Zabrze, Poland
ORCID ID: 0009-0006-4466-5794

Karolina Osińska
Municipal Hospital in Kędzierzyn-Koźle, Kędzierzyn-Koźle, Poland
ORCID ID: 0009-0003-9731-0629

Agnieszka Morawa
Municipal Hospital in Zabrze, Zabrze, Poland
ORCID ID: 0009-0001-2325-7998

Anna Kołcz
School of Medicine, Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0006-1446-2865

Michał Kulczak
Silesian Center for Heart Diseases, Zabrze, Poland
ORCID ID: 0009-0006-4968-3318

Konrad Turczynowski
University Hospital in Krakow, Kraków, Poland
ORCID ID: 0009-0007-2331-5928

Kamil Turczynowski
University Hospital in Krakow, Kraków, Poland
ORCID ID: 0009-0009-7573-4029

Grzegorz Machelski
Municipal Hospital in Zabrze, Zabrze, Poland
ORCID ID: 0009-0003-5341-8208

Jan Gajewski
Municipal Hospital in Zabrze, Zabrze, Poland
ORCID ID: 0009-0002-4761-0300

ABSTRACT

The transition from Phase III trials to real-world evidence (RWE) is critical for understanding monoclonal antibody (mAb) performance in complex, comorbid populations. This review evaluates the real-world effectiveness and safety of calcitonin gene-related peptide (CGRP) pathway inhibitors in routine clinical practice.

A systematic search of PubMed (2021–2026) identified observational studies, including prospective registries (e.g., PEARL, GARLIT, MAB-MIG) and large-scale claims analyses, regarding erenumab, fremanezumab, galcanezumab, and eptinezumab.

Synthesis of 32 studies (n > 1 million patients) demonstrates robust effectiveness across diverse populations. Real-world data confirm sustained ≥ 50% responder rates (ranging from 40%–75% in most cohorts) and significant reductions in acute medication use. Benefits were maintained over 12–36 months, even in patients with chronic migraine and medication overuse headaches. Large-scale analyses (MarketScan, Medicare) indicate that CGRP inhibitors are not associated with an increased risk of myocardial infarction or stroke compared to onabotulinumtoxinA, even in older adults. Switching between ligand and receptor targets remains an effective strategy for initial non-responders.

RWE establishes that anti-CGRP mAbs provide durable effectiveness and high adherence in difficult-to-treat populations. The data confirm a favorable cardiovascular safety profile, supporting their role as a cornerstone of modern migraine prevention.

KEYWORDS

Anti-CGRP Monoclonal Antibodies, Cardiovascular Safety, Prophylaxis, Medication Overuse Headache, Migraine, Real-World Evidence

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1. Introduction

Migraine is a debilitating neurological disorder and a leading cause of years lived with disability worldwide [1-2]. For decades, preventive management relied on non-specific oral medications, such as beta-blockers, antiepileptics, and antidepressants, which were originally developed for other indications [3-4]. While these traditional therapies can reduce attack frequency, they are often associated with modest efficacy and poor tolerability, leading to low adherence and high discontinuation rates in clinical practice [5]. Consequently, many patients cycle through multiple ineffective treatments, resulting in disease progression and a reliance on acute medications that may lead to medication overuse [6-7].

The therapeutic landscape shifted significantly with the development of monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway, the first class of drugs specifically designed for migraine pathophysiology [8]. Currently, four agents are available: erenumab, which targets the CGRP receptor, fremanezumab, galcanezumab, and eptinezumab, which target the CGRP ligand. Unlike traditional oral preventives, these biologics offer high specificity, favorable tolerability profiles, and convenient administration schedules ranging from monthly subcutaneous injections to quarterly intravenous infusions [8-9]. Randomized controlled trials (RCTs) have consistently demonstrated their efficacy in reducing monthly migraine days (MMD) and improving quality of life across episodic and chronic migraine populations.

However, the strict inclusion criteria of pivotal trials often limit the generalizability of these findings to routine clinical practice [8]. RCTs frequently exclude complex patient populations, such as those with significant cardiovascular comorbidities, medication overuse headache (MOH), or histories of multiple preventive treatment failures [10-11]. Real-world evidence (RWE) is therefore essential to bridge the gap between controlled efficacy and effectiveness in unselected populations. Specifically, robust data are needed to assess the safety of CGRP blockade in patients with cardiovascular risk factors—such as hypertension and

older age—given the neuropeptide's physiological role in vasodilation [9], [12]. Furthermore, understanding the performance of these mAbs in "difficult-to-treat" cohorts, including whether they are effective in patients with MOH without prior detoxification, remains a critical clinical priority [7]. This systematic review synthesizes current observational data to evaluate the real-world effectiveness and safety of anti-CGRP mAbs in these diverse and complex populations.

2. Aim

The primary objective of this systematic review is to evaluate the real-world effectiveness and safety of the four currently available anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies—erenumab, fremanezumab, galcanezumab, and eptinezumab—for migraine prevention. Utilizing observational data published from 2021 to 2026, this study seeks to determine the longitudinal impact (up to 36 months) of these therapies on migraine frequency and acute medication consumption within refractory and medication-overuse populations. Furthermore, this review aims to characterize the cardiovascular safety profile of CGRP blockade in unselected patient cohorts, including older adults and those with vascular comorbidities, while assessing the clinical utility of antibody class-switching as a management strategy.

3 Methods

3.1 Search strategy

This review follows the PRISMA guidelines for systematic reviews. It is based on scientific articles found through a search in PubMed databases using the following MeSH terms: ("Migraine Disorders"[MeSH] OR migraine[Title/Abstract]) AND ("Calcitonin Gene-Related Peptide"[MeSH] OR CGRP[Title/Abstract] OR "anti-CGRP"[Title/Abstract] OR erenumab[Title/Abstract] OR fremanezumab[Title/Abstract] OR galcanezumab[Title/Abstract] OR eptinezumab[Title/Abstract]) AND ("real-world"[Title/Abstract] OR "real life"[Title/Abstract] OR observational[Title/Abstract] OR registry[Title/Abstract] OR retrospective[Title/Abstract] OR prospective[Title/Abstract]). The aim was to collect the most recent available studies; therefore, the following filters were applied: “in the last 5 years” and “free full text availability”. A total of 157 publications in English were selected.

3.2 Eligibility Criteria

To ensure a high-level synthesis of real-world evidence, we established the following inclusion and exclusion criteria for the retrieved studies:

Inclusion Criteria:

- **Population:** Adults over the age of 18 with a clinical diagnosis of episodic or chronic migraine.
- **Interventions:** Patients initiated on one of the four anti-CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, or eptinezumab) as a preventive therapy.
- **Study Design:** Original research using real-world observational designs, including prospective or retrospective cohorts and national registry analyses.
- **Outcome:** Studies reporting on clinical effectiveness (e.g., reduction in monthly migraine days or responder rates), safety and tolerability (specifically cardiovascular events and adverse effect profiles), and clinical utility (e.g., switching strategies or medication overuse management).
- **Timeframe:** Publications between January 2021 and February 2026.
- **Language:** Publications written in English.
- **Text Availability:** Articles with free full-text available.

Exclusion Criteria:

- Studies involving a pediatric population (under 18 years of age).
- Narrative reviews, systematic reviews, or literature reviews.
- Expert opinions, editorials, letters to the editor, or conference abstracts.
- Case reports with small sample sizes ($n < 10$).
- Publications without free full-text access.
- Post-hoc analyses of randomized controlled trials (RCTs) that do not represent routine clinical practice.

3.3 Data Collection

An independent literature review was conducted by each author. Initially, the titles and abstracts of the 157 identified articles were screened to determine their relevance to the effectiveness and safety of anti-CGRP monoclonal antibodies in clinical practice. Articles that fulfilled the inclusion criteria were subjected to full-text analysis to confirm their eligibility. These articles were systematically evaluated based on various parameters, including Demographic groups addressed, Clinical outcomes reported, Management strategies described. To ensure reliability and precision, the collected data were cross-verified during the selection process. The finalized dataset was meticulously organized and synthesized to present a comprehensive analysis of the current landscape of anti-CGRP therapy, emphasizing recent progress in long-term persistence and real-world safety. Overall, a total of 32 studies from PubMed have been chosen for conducting this systematic review on the effectiveness and safety of anti-CGRP monoclonal antibodies.

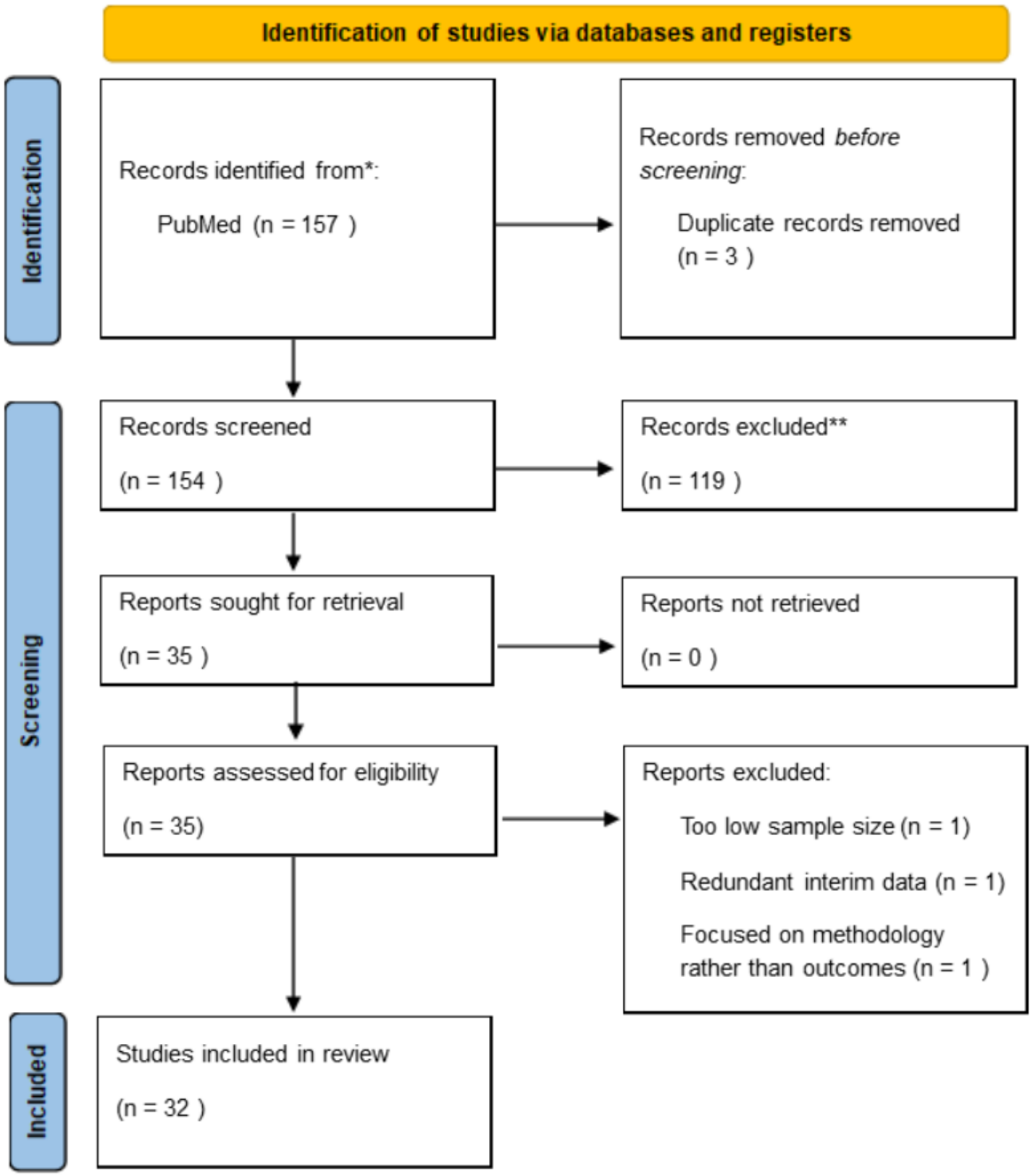

Fig. 1. *PRISMA flowchart for conducting the literature search.*

4 Results

4.1. Study Selection and Characteristics

Narrative of the PRISMA Flow

The systematic search yielded a robust volume of literature regarding the real-world application of anti-CGRP monoclonal antibodies. After removing duplicates and screening for relevance based on the inclusion criteria—specifically observational studies, prospective registries, and large-scale retrospective claims analyses published between 2021 and 2026—a total of 32 articles were selected for final synthesis. These studies encompass a wide range of methodologies, including single-center prospective observations, multicenter prospective registries, and large administrative database analyses.

Summary of Evidence Base

The reviewed studies represent a diverse global population, ensuring high external validity. The evidence base includes data from major European nations, specifically Italy [5], [13-14], [9], [32], Spain [15-16], France [17], Germany [4], the United Kingdom [18] and Denmark [2]. Furthermore, significant data were synthesized from North American cohorts utilizing US insurance claims databases [12], [19] and Medicare data [20], as well as observational studies from Canada [21] and multi-site clinical investigations [31]. The review also incorporates data from the Asia–Pacific region, including Japan [11], Thailand [3] and Australia [22].

Study Heterogeneity

The included studies exhibit heterogeneity in design, ranging from the prospective Pan-European PEARL registry [6], [10], including specific national sub-analyses [9], and the Italian I-GRAINE registry [14] to retrospective audits of hospital records [23]. The synthesis also contrasts prospective clinical data, which allows for granular assessment of headache phenotypes and patient-reported outcomes (PROs), with large-scale retrospective administrative claims analyses [19], [21] that provide statistical power for rare safety events but lack detailed clinical resolution.

4.2. Effectiveness in Large-Scale Prospective Registries

The PEARL Program

The Pan-European Real Life (PEARL) study provides extensive data on the effectiveness of fremanezumab. In the third interim analysis involving 1,140 participants, 58.5% of patients achieved a ≥ 50% reduction in monthly migraine days (MMD) during the six-month period following initiation [6]. These results were sustained, with consistent reductions in acute medication use and disability scores observed through 12 months [6]. Updated evidence from the Italian cohort of the PEARL study (n=343) corroborated these findings, reporting that 61.2% of participants reached the ≥50% MMD reduction threshold at month 6 [9]. A specific sub-analysis of the PEARL cohort focused on "difficult-to-treat" patients—those with at least three prior preventive treatment failures—demonstrated a 53.8% response rate (≥50% reduction in MMD) over the first six months, confirming that efficacy translates to complex real-world populations [10].

The GARLIT and MAB-MIG Data

Data from the Italian GARLIT study on galcanezumab (*n*=163) demonstrated rapid effectiveness, with a ≥50% responder rate of 64.7% at month 1, increasing to 76.5% at month 6 for high-frequency episodic migraine patients [5]. In the chronic migraine (CM) cohort, MMDs decreased significantly from a baseline of 21 to 7 days at month 6 [5]. Similarly, the Spanish MAB-MIG registry (*n*=210), which evaluated erenumab in a refractory cohort (mean of 7.8 prior failures), reported a responder rate of 37.1% at 12 weeks, with a mean MMD reduction of 6.28 days [16]. Predictors of good response in this cohort included simultaneous onabotulinumtoxinA treatment and the absence of medication overuse [16].

Primary Outcomes

Across these major registries, the real-world effectiveness of anti-CGRP mAbs is consistent. In a Danish single-center study of erenumab (*n*=300), 71.4% of patients achieved a ≥30% reduction in MMDs by week 12, and 34% maintained a sustained ≥30% reduction throughout 52 weeks [2]. Japanese real-world data (*n*=150) covering erenumab, galcanezumab, and fremanezumab reported a ≥50% responder rate of 53.7% at 6 months [11]. In the United States, the multi-site REVIEW study on intravenous eptinezumab (N=94) demonstrated a doubling of patient-reported "good days" per month (from 8 to 18) and a two-thirds reduction in patients requiring ≥10 days of acute medication [31]. Collectively, these studies confirm that significant reductions in migraine frequency and acute medication intake are achievable in routine practice, often exceeding the magnitude of benefit observed in pivotal clinical trials for refractory patients [5].

4.3. Long-term Outcomes and Disease Modification

Persistence Rates

Long-term follow-up data suggest high persistence rates, though some attrition occurs over time. In a French registry study of erenumab, 58.8% of patients remained ≥50% responders at 12 months [17]. In the Italian I-GRAINE registry, which followed patients for up to three years, the proportion of ≥50% responders progressively increased during treatment retention, reaching 77.8% during the discontinuation phase after the third year [14]. However, discontinuation is notable; a US claims analysis indicated that 13.5% of patients discontinued CGRP inhibitors within the first year, with discontinuation probability rising to 29.3% by the second year [21].

Course Modification

Evidence suggests that prolonged anti-CGRP therapy may modify the disease course. The I-GRAINE study introduced the concept of cyclic treatment and discontinuation. It found that patients who completed three consecutive 12-month treatment cycles showed a significantly lower relapse rate to chronic migraine (2.3%) and medication overuse (1.3%) during the third discontinuation period compared to the first (67.7% and 34.2%, respectively) [14]. Conversely, a study analyzing three consecutive one-year cycles found that while MMDs decreased during treatment, they rebounded during mandatory suspension periods, suggesting that for many patients, the underlying disease activity persists without treatment [13]. Additionally, in the French registry, 57.3% of patients reverted from chronic to episodic migraine at month 3 [17].

4.4. Management of Medication Overuse and Treatment Resistance

MOH Outcomes

Real-world evidence strongly supports the efficacy of anti-CGRP mAbs in patients with medication overuse headache (MOH) without the need for traditional detoxification. Silvestro et al. compared outcomes in 200 patients stratified by MOH complexity and detoxification strategy, finding no significant difference in headache frequency reduction between those who underwent detoxification and those who did not [7]. Both groups achieved significant improvements, suggesting mAbs alone are sufficient. Scheffler et al. corroborated this in a retrospective analysis (n=291), reporting successful treatment without prior detoxification and a low relapse rate of 15.4% among responders [24]. Furthermore, the French FHU INOVPAIN registry reported a 46.5% transition rate from medication overuse to non-overuse after three months of erenumab treatment [17]. A randomized phase 4 trial of erenumab specifically in MOH patients confirmed sustained remission of MOH in over 60% of participants over one year [25].

Refractory Populations

Anti-CGRP mAbs demonstrate efficacy in "difficult-to-treat" populations. In the REFINE study, patients classified as "resistant" showed significant improvement over 6 months, whereas those classified as "refractory" (failure of all drug classes) had more stable but persistent disability [26]. However, real-world audits show effectiveness even in extreme resistance. For instance, in a UK audit of erenumab in resistant CM (mean 8.3 prior failures), 48% of patients were ≥30% responders at 6 months [27]. A monocentric cohort of 203 severe, resistant CM patients emphasized that while migraine frequency reduction is significant, disability improvements may be even more pronounced; 89.5% to 100% of these refractory patients achieved a ≥50% reduction in their MIDAS score [32]. Similarly, intravenous eptinezumab showed effectiveness in Australian patients who had previously failed onabotulinumtoxinA, fremanezumab, and galcanezumab, with significant reductions in MMDs and acute analgesic use [22].

4.5. Switching Strategies and Class-Specific Responses

Switching Efficacy

Switching between anti-CGRP mAbs is a viable strategy for non-responders. A controlled cohort study indicated that switching to a different antibody class (ligand to receptor or vice versa) resulted in a significantly greater reduction in MMDs (-3.9 days) compared to standard care (-0.03 days) [28]. A study by Lambru et al. found that 35.9% of patients who failed erenumab became responders when switched to fremanezumab [29]. Similarly, Triller et al. reported that approximately one-third of patients refractory to subcutaneous mAbs achieved a ≥30% reduction in MMDs after switching to intravenous eptinezumab [4]. However, Jaimes et al. found no statistically significant difference in response rates whether the switch involved a change in the mechanism of action (ligand vs. receptor) or maintained the same target [23].

Non-Responder Analysis

The concept of "False Nonresponders" has emerged to describe patients who do not meet strict frequency-based reimbursement criteria (e.g., ≥50% MMD reduction) but experience clinically meaningful benefits. Muñoz-Vendrell et al. identified 106 such patients who continued treatment despite missing efficacy targets; 91.5% showed improvements in other domains such as headache intensity, disability (MIDAS/HIT-6), or quality of life [30]. Conversely, "true nonresponders" who discontinued treatment had worse baseline profiles and higher rates of psychiatric comorbidity [30].

4.6. Safety and Cardiovascular (CV) Outcomes

Large-Scale CV Analysis

The cardiovascular safety profile of CGRP inhibitors remains a subject of investigation with somewhat conflicting real-world data. A large Medicare claims study (*n*=9,153) found that initiation of anti-CGRP mAbs was not associated with an increased risk of composite CV events (myocardial infarction or stroke) compared to onabotulinumtoxinA in older adults or those with disability [20]. Similarly, a US claims database analysis by Dodick et al. (*n*=108,019) found no difference in the risk of hypertension, acute MI, or stroke between new users of erenumab and users of other anti-CGRP mAbs or onabotulinumtoxinA [12]. In contrast, a separate analysis of the MarketScan database (*n*=900,370) by Lusk et al. reported that initiation of CGRP inhibitors was associated with a slightly higher rate of composite cardiovascular events (HR 1.26) in overlap-weighted analysis, although the authors noted this must be interpreted with caution given the observational nature and potential for residual confounding [19].

Older Populations

Safety in older adults appears favorable. A prospective study specifically monitoring blood pressure in patients over age 60 (*n*=155) treated with erenumab, fremanezumab, or galcanezumab found no significant changes in systolic or diastolic blood pressure over 12 months [1]. This supports the safety of these agents in aging populations with higher baseline cardiovascular risk.

General Tolerability

Anti-CGRP mAbs are generally well-tolerated in routine practice. The most frequently reported adverse events are constipation and injection site reactions. The PEARL study noted a constipation rate of 3.9% for fremanezumab, which is notably lower than rates reported for erenumab in other real-world studies (up to 20–40%) [6]. In the GARLIT study (galcanezumab), constipation and injection site reactions were the most common events, though they tended to resolve over time [5]. Discontinuation due to adverse events remains low across studies, generally under 10% [6].

5. Limitations

This systematic review is subject to several limitations inherent to the observational nature of the included studies and the heterogeneity of the available real-world evidence.

5.1. Heterogeneity of Study Designs and Populations

The synthesized evidence exhibits significant methodological heterogeneity, ranging from prospective multicenter registries [5], [10] to single-center retrospective chart reviews [11]. While prospective studies like PEARL and I-GRAINE offer robust longitudinal data, they are open-label, leaving patient-reported outcomes (PROs) susceptible to placebo effects and expectations of benefit [4], [18]. This is particularly relevant for intravenous formulations such as eptinezumab, where the mode of administration may enhance the placebo response [4]. Furthermore, the definition of "refractory" or "difficult-to-treat" migraine varied across geographic regions due to differing national reimbursement criteria. Studies from Italy, the UK, and Spain predominantly enrolled patients with highly resistant chronic migraine who had failed multiple prior preventives [5], [8], [29], whereas administrative claims analyses from the US included broader, less refractory populations [19], [12]. This selection bias limits the generalizability of effectiveness findings to the wider, unselected migraine population [5], [13].

5.2. Data Granularity and Ascertainment Bias

There is a distinct trade-off between sample size and clinical granularity in the included literature. Large-scale administrative claims studies provided statistical power to detect rare cardiovascular events [12], [19]. However, these datasets rely on billing codes (ICD-10) and prescription fills, which do not confirm medication consumption or capture critical clinical confounders such as body mass index (BMI), smoking status, family history, or specific headache phenotypes [12], [19], [20]. Conversely, clinical registries provided detailed phenotypic data but often suffered small sample sizes and missing data, particularly regarding PROs like HIT-6 and MIDAS scores [6], [23], [30]. Retrospective studies also faced challenges in reliably distinguishing between Monthly Migraine Days (MMD) and Monthly Headache Days (MHD) due to incomplete diary entries [23–24].

5.3. Confounding by Concomitant Medication and Management

In real-world practice, anti-CGRP mAbs are frequently added to existing therapeutic regimens rather than replacing them. Many participants in the reviewed cohorts were on concomitant oral preventives or onabotulinumtoxinA [17], [22], [29]. While some studies attempted to adjust for this, the concurrent use of multiple preventives makes it difficult to isolate the specific therapeutic effect of the CGRP inhibitor [22]. Additionally, management strategies for medication overuse varied significantly, with some centers employing detoxification programs and others not, introducing procedural heterogeneity that complicates the assessment of mAb efficacy in this subgroup [7].

5.4. Attrition Bias and Follow-up Duration

Long-term effectiveness data are potentially influenced by attrition bias. As noted in the I-GRAINE and REFINE studies, retention rates drop over time, and patients lost to follow-up often have different baseline characteristics or response profiles compared to completers [13], [26]. This "survivor bias" may lead to an overestimation of long-term effectiveness in per-protocol analyses, as non-responders are more likely to discontinue treatment early [13], [24]. hile some studies utilized intention-to-treat (ITT) analyses to mitigate this [12-13], many relied on completer cohorts. Furthermore, the mandatory treatment discontinuation rules enforced by some healthcare systems (e.g., in Italy) introduce artificial interruptions in therapy that may affect the natural trajectory of disease evolution and response durability [13].

6. Conclusions

This systematic review of real-world evidence confirms that the efficacy of anti-CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, and eptinezumab) established in clinical trials translates into robust effectiveness in routine clinical practice. Data synthesized from over 1 million patients indicate that these therapies provide rapid, clinically meaningful, and durable reductions in monthly migraine days and disability scores, particularly in "difficult-to-treat" populations with multiple prior preventive failures.

A pivotal finding is the capacity of these agents to manage medication overuse headache (MOH). Real-world data suggest a paradigm shift, demonstrating that CGRP inhibition significantly reduces acute medication intake and resolves overuse without the necessity of traditional withdrawal or detoxification strategies. Furthermore, clinical utility is enhanced by the viability of "switching" strategies; patients unresponsive to one antibody class (ligand or receptor) frequently achieve a beneficial response when switched to the alternative class.

Regarding safety, while large-scale claims analyses suggest a need for continued pharmacovigilance concerning a small potential signal for cardiovascular events, prospective studies in vulnerable populations—including the elderly—demonstrate a favorable vascular profile with no significant impact on blood pressure compared to standard care. Finally, the identification of "false non-responders" highlights the limitation of frequency-based reimbursement criteria, as many patients experience substantial improvements in quality of life and headache intensity despite missing standard reduction targets. Collectively, anti-CGRP mAbs represent a transformative therapeutic option, offering sustained disease modification for patients with high unmet needs.

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