The Journal of Prevention of Alzheimer's Disease 13 (2026) 100473

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Review

Safety profiles of lecanemab: A systematic review and meta-analysis of randomized controlled trials and real-world evidence

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ARTICLE INFO

Keywords:
Lecanemab
Alzheimer's disease
Real-world evidence
Amyloid-related imaging abnormalities
ApoE4

ABSTRACT

Background: Safety profiles of lecanemab, an anti-amyloid-β antibody for the treatment of early Alzheimer's disease (AD), remain uncertain and may vary between randomized controlled trials (RCTs) and real-world evidence (RWE) studies.
Objectives: This systematic review and meta-analysis aimed to evaluate the safety, tolerability, and acceptability of lecanemab based on findings from both RCTs and emerging RWE studies.
Methods: We systematically searched major databases and clinical trial registries from their inception to June 2025. Random-effects meta-analyses were performed to estimate the pooled incidence of key safety outcomes, including amyloid-related imaging abnormalities (ARIA), infusion-related reactions (IRRs), and treatment discontinuation (due to ARIA, adverse events [AEs], or any cause). The risk of ARIA according to the ApoE4 genotype was assessed via relative risk (RR). This study was registered with PROSPERO (No. CRD420251110679).
Results: A total of two RCTs and five RWE studies encompassing 1576 patients were included. The pooled ARIA incidence was 19% (95% CI: 16%-23%), which was significantly modulated by ApoE4 status (RR 1.45 for heterozygotes, 3.54 for homozygotes vs noncarriers) and the pooled symptomatic ARIA incidence was 3% (95% CI: 2%-4%). IRRs occurred in 26% (95% CI: 19%–34%), with heterogeneity reduced in patients receiving specific pre-infusion prophylaxis. The pooled rate of discontinuation due to AEs was 8% (95% CI: 5%-11%), with discontinuation due to ARIA occurring in 5% (95% CI: 3%-7%) of patients in RWE studies.
Conclusions: Lecanemab-related ARIA demonstrates a clear ApoE4 gene-dose effect, supporting routine ApoE4 genotyping before treatment. Standardizing pre-infusion prophylaxis may reduce variability in IRRs incidence, while prompt recognition and management of ARIA are critical for improving treatment tolerability. These findings provide important evidence to support the safe clinical use of lecanemab.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the leading cause of dementia in older adults. It represents one of the greatest economic and social burdens of the 21st century, with significant mortality and morbidity. According to the *World Alzheimer Report 2022*, over 55 million individuals worldwide are currently living with AD or related dementias. This number is projected to increase to 82 million by 2030 and to 138 million by 2050 [1]. AD typically begins with impairments in memory, language, and cognitive processing. As the disease progresses, patients may experience emotional instability, personality changes, and behavioral disturbances. Ultimately, neurons that regulate fundamental physiological functions such as ambulation, speech and swallowing are also affected [2]. Pathologically, AD is characterized by extracellular amyloid-β (Aβ) plaque deposition and intracellular neurofibrillary tangles (NFTs) composed of

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https://doi.org/10.1016/j.tjpad.2025.100473
Received 23 October 2025; Received in revised form 5 December 2025; Accepted 8 December 2025
Available online 1 January 2026

hyperphosphorylated tau protein. Soluble Aβ oligomers that diffuse into the synaptic cleft disrupt synaptic signaling [3,4], whereas NFTs induce potentially reversible impairments in synaptic function [5,6]. Furthermore, Aβ aggregation promotes tau hyperphosphorylation, tau propagation, and the formation of insoluble NFTs [7,8]. These mechanisms establish Aβ as a key therapeutic target in AD.

Lecanemab (BAN2401), a humanized monoclonal antibody targeting Aβ protofibrils, is a pioneering therapy approved by the U.S. Food and Drug Administration (FDA) for early AD [9]. However, its safety profiles remain a matter of considerable debate and have led to divergent regulatory decisions worldwide, including the FDA's issuance of a black box warning and the European Medicines Agency's (EMA) refusal to grant marketing authorization [10,11]. The primary safety concerns are amyloid-related imaging abnormalities (ARIA) and infusion - related reactions (IRRs). ARIA—which includes vasogenic edema or effusion (ARIA-E) as well as microhemorrhages or superficial siderosis (ARIA-H)—represents the most clinically significant risk, as it may lead to treatment discontinuation and therefore requires particular attention. Notably, the relationship between ApoE4 and the incidence of ARIA remains inconclusive, underscoring the need for further investigation. IRRs, while generally mild and transient, are the most frequently reported adverse events (AEs) and contribute to the overall treatment burden [12].

Evidence on lecanemab's safety profiles initially comes from randomized controlled trials (RCTs) conducted in highly selected patient populations under strict, standardized monitoring protocols. While these trials provide valuable insights, their idealized conditions raise important concerns regarding generalizability. In routine clinical practice, patient populations are more heterogeneous and monitoring less uniform, which may provide additional evidence of safety outcomes. Consequently, real-world evidence (RWE) from post-marketing studies is critical for a more comprehensive and pragmatic assessment of lecanemab's safety in broader clinical settings.

The recent emergence of RWE has enabled the synthesis and comparison of RCT data, a step that is both feasible and clinically necessary. Combining evidence from these complementary sources is essential to refine clinical guidelines and strengthen risk-benefit discussions with patients. However, direct integration of RCT and RWE data on lecanemab safety is lacking. Accordingly, we conducted this systematic review and meta-analysis to evaluate safety profiles of lecanemab across RCTs and real-world settings, with a particular focus on quantifying the risk of ARIA stratified by ApoE4 genotype.

2. Methods

This systematic review and meta-analysis was registered in PROSPERO (No. CRD420251110679). The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

2.1. Search strategy

We systematically searched the following databases and registers from inception to June 23, 2025 with no language restrictions: PubMed, Web of Science, Embase, the Cochrane Library, ClinicalTrials.gov, the EU Clinical Trials Registry (EUCTR), the Australian New Zealand Clinical Trials Registry (ANZCTR), and the World Health Organization's International Clinical Trials Registry Platform (ICTRP). The complete list of search terms is provided in Table S1.

2.2. Inclusion and exclusion criteria

The inclusion criteria for studies were as follows: (1) RCTs or RWE studies evaluating lecanemab in patients with AD; (2) reported safety as a primary or key secondary outcome, including ARIA, IRRs or both; and (3) administered lecanemab at the FDA-approved dosage of 10 mg/kg intravenously every two weeks [12].

Exclusion criteria: Studies were excluded if they met any of the following conditions: (1) long-term open-label extension (OLE) phases of RCTs (>18 months), with only core-phase data analyzed to ensure comparability with typically shorter RWE studies (<12 months); (2) RWE studies based solely on spontaneous reporting systems (e.g., the FDA Adverse Event Reporting System [FAERS]), due to limited patient-level data and substantial methodological heterogeneity; or (3) studies involving patients with mild cognitive impairment (MCI) attributable to causes other than AD.

Study selection: Two independent reviewers (Lin Qi and Fangxue Zheng) screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Discrepancies were resolved through discussion. The screening process was managed via EndNote 21.

2.3. Data extraction and quality assessment

The following information was extracted from the included studies: author, year of publication, study design, participant characteristics, intervention details, treatment duration, and summary outcomes for safety, tolerability, and acceptability.

Risk of bias in RCTs was assessed via the RoB 2.0 tool [14], which evaluates bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. The overall risk of bias is determined by the highest level of concern in any domain: studies are rated as low risk if all domains are low, as having some concerns if at least one domain raises some concerns, and as high risk if any domain is judged to have a high risk of bias. For RWE studies, the JBI critical appraisal checklist was applied, which evaluates methodological quality across ten domains related to the study's design, conduct, and analysis. Studies were considered high quality when most domains were clearly met, and lower quality when multiple items were unmet or unclear [15]. Each study was assessed by two independent reviewers (Lin Qi and Fangxue Zheng), with any discrepancies resolved through discussion and consensus. Publication bias was not assessed due to the small number of included studies (<10).

2.4. Outcomes

The primary outcomes were safety, tolerability, and acceptability. Safety was defined by the incidence of ARIA and IRRs. Tolerability was measured by the rate of study discontinuation due to AEs. Acceptability was assessed as the rate of study withdrawal for any reason. Furthermore, a subgroup meta-analysis using relative risk (RR) was conducted to evaluate the risk of ARIA across different ApoE4 genotypes.

2.5. Data analysis

We conducted meta-analyses via the "meta" package [16] in R version 4.5.1 [17] and assessed heterogeneity of effect sizes across studies using Cochran's Q test and the I^2 statistic, with I^2 values ≥ 50 % or a p value < 0.05 from the Q test indicating significant heterogeneity. Prior to the meta-analysis, we applied the Freeman-Tukey double arcsine transformation to stabilize the variance of proportional data and improve the validity of the pooled analysis. Given the expected heterogeneity in study settings and the limited number of included studies, we selected a random-effects model for the meta-analysis of all outcomes. Finally, we generated forest plots for each outcome to visually represent the results.

3. Results

A total of 1985 records were identified through database and registry searches. After removing 1061 duplicates, 901 records were excluded based on title and abstract screening due to irrelevance (n = 667),

publication type (abstracts or unpublished full texts, $n = 205$), or study protocols ($n = 29$). Full texts of 23 articles were assessed for eligibility, with 15 excluded for the following reasons: safety data solely from the FAERS database ($n = 7$), duplicate or overlapping data ($n = 2$), and lack of necessary outcome data ($n = 6$).

Ultimately, eight publications were included: four articles from two RCTs (NCT01767311 and NCT03887455) [18–21], and four articles representing five RWE studies [22–25]. Among the RWE studies, one publication reported on two distinct cohorts from the UW Medicine Memory and Brain Wellness Center (MBWC) and Abington Neurological Associates (ANA) [24]. The other three RWE studies were respectively from the Norton Neuroscience Institute Memory Center [25], the Washington University Memory Diagnostic Center [23], and the Cognitive Neurology Unit at Tel Aviv Medical Center [22] (Fig. 1). Moreover, the data from the RCTs were extracted from the latest publications.

3.1. Study characteristics

Study characteristics are summarized in Table 1. In total, 1576 participants were included across seven studies: 1020 individuals from RCTs and 556 from RWE studies.

3.2. Risk of bias assessment

The included RCTs presented some concerns regarding the overall risk of bias; nevertheless, the majority of individual domains were rated as low risk, indicating robust methodological quality (Fig. S1). The RWE studies were similarly appraised as high quality, with each study satisfying at least seven of the ten checklist criteria (Table S2). On the basis of these assessments, all studies were deemed methodologically sound and suitable for inclusion in the meta-analysis.

3.3. Safety outcomes

3.3.1. ARIA incidence

As shown in Fig. 2A, the pooled incidence of ARIA across all included studies ($N = 1459$) was 19 % (95 % CI:16 %–23 %), with moderate heterogeneity ($I^2 = 42.3$ %). When stratified by study type, the pooled incidence in RWE studies was 20 % (95 % CI:17 %–25 %) with no

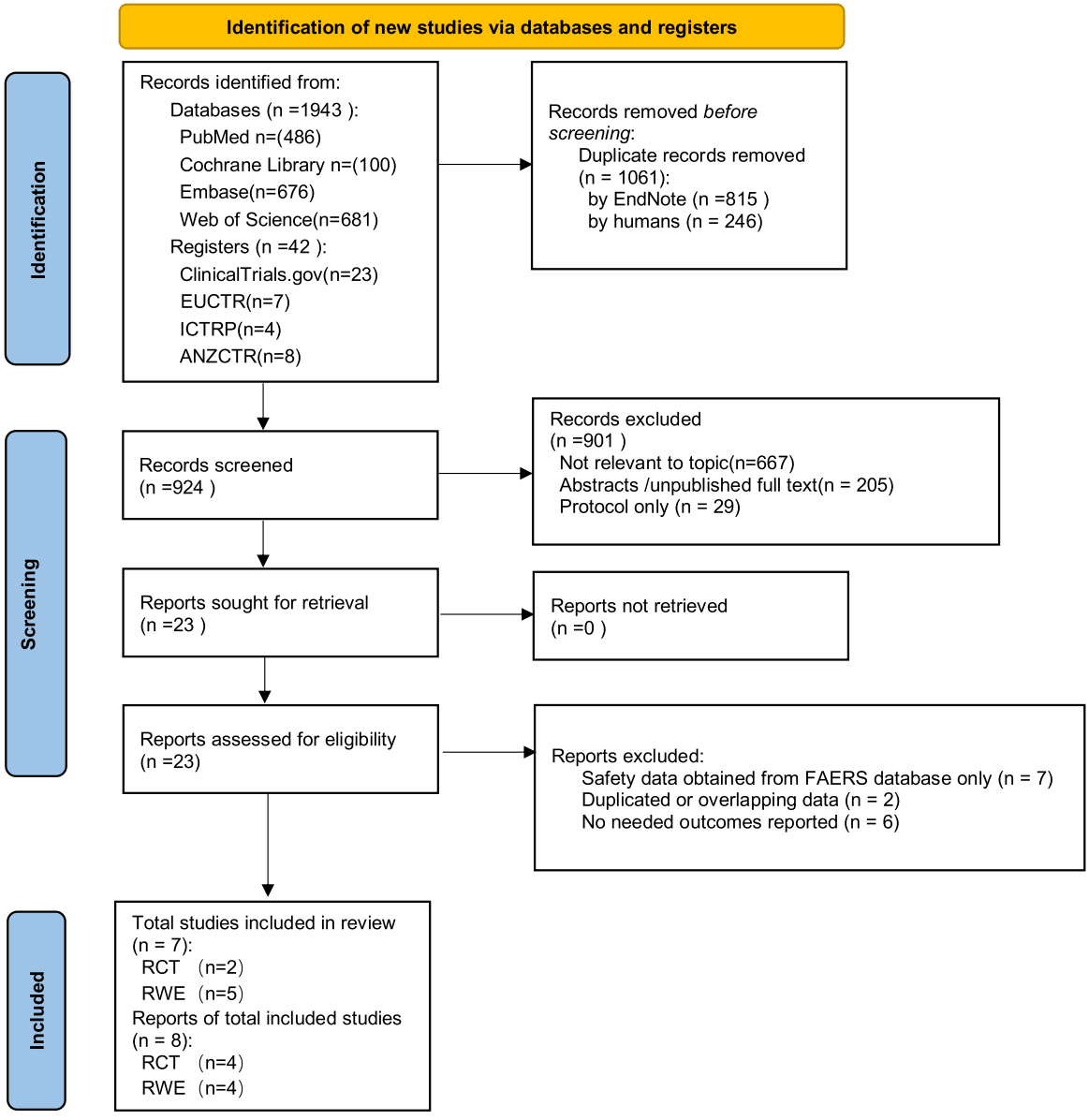

Fig. 1. PRISMA 2020 flow diagram of literature screening.

Table 1
Characteristics of included studies on the use of lecanemab for AD.

	TypeofStudy	Country	Population(n)	Age(Mean ± SD)	Follow − upMonths	Dosage	DiseaseSeverity	ARIAincidence	ARIA − Eincidence	ARIA − Hincidence	ConcurrentARIA − E/Hincidence	SympomaticARIAincidence	AsympomaticARIAincidence	ARIAincidenceofApoE4noncarriers	ARIAincidenceofApoE4heterozygotes	ARIAincidenceofApoE4homozygotes	IRRsincidence	DiscontinuationduetoARIA	DiscontinuationduetoAEs	All − causetreatmentdiscontinuation
Swanson et al. 2021 [19, 26]	Multicenter, double-blind, placebo-controlled, parallel-group randomized clinical trial	Multicountry	161	72.7 (8.7)	18 m	10 mg/kg/2 weeks	MCI or Mild AD (MMSE score ≥22)	20/161	16/161	10/161	6/161	5/161	15/161	11/112	4/39	5/10	32/161	/	24/161	71/161
Dyck et al. 2023 [20, 18]	Multicenter, double-blind, placebo-controlled, parallel-group randomized clinical trial	Multicountry	859	71.1 (8.9)	18 m	10 mg/kg/2 weeks	MCI or Mild AD (MMSE score 25.5 ± 2.2)	191/898	113/898	152/898	74/898	31/898	160/898	37/278	91/479	63/141	237/898	/	62/898	169/898
Shields et al. 2024 [25]	Retrospective Single Arm Cohort	USA	71	72 (49–90)	6 m	10 mg/kg/2 weeks	MCI or Mild AD (MMSE score25.0 (19–30) MoCA score20.2 (7–26))	12/50	7/50	9/50	4/50	3/50	9/50	2/26	6/36	4/9	(with pre-infusion prophylaxis 8/31)	5/71	/	13/71
Bregman et al. 2025 [27]	Prospective Single Arm Cohort	Israel	86	71.99 (8.2)	8.2 ± 2.9 m	10 mg/kg/2 weeks	MCI or Mild AD (MMSE score24.0 ± 2.7)	16/86	3/86	13/86	/	1/86	15/86	/	/	/	19/86	5/86	5/86	17/86
Paczynski et al. 2025 [23]	Retrospective Single Arm Cohort	USA	234	74.4 (6.7)	6.5 m (mean)	10 mg/kg/2 weeks	MCI or Mild AD (MMSE score24 ±4)	42/194	29/194	/	/	11/194	31/194	11/74	24/102	7/16	87/234(with pre-infusion prophylaxis 10/37)	10/234	18/234	23/234
Rosenbloom et al. 2025 (MBWC) [24]	Retrospective Single Arm Cohort	USA	70	71	30 ± 15 w	10 mg/kg/2 weeks	MCI or AD (MOCA mean score 21)	12/70	6/70	9/70	3/70	2/70	10/70	/	/	4/9	/	5/70	7/70	7/70
Rosenbloom et al. 2025 (ANA) [24]	Retrospective Single Arm Cohort	USA	95	73	54 ± 19 w	10 mg/kg/2 weeks	MCI orAD (MMSE mean score22)	/	7/95	2/95	/	1/95	/	/	/	/	/	3/95	3/95	5/95

MMSE: Mini-Mental State Examination; MoCA: Montreal cognitive assessment.

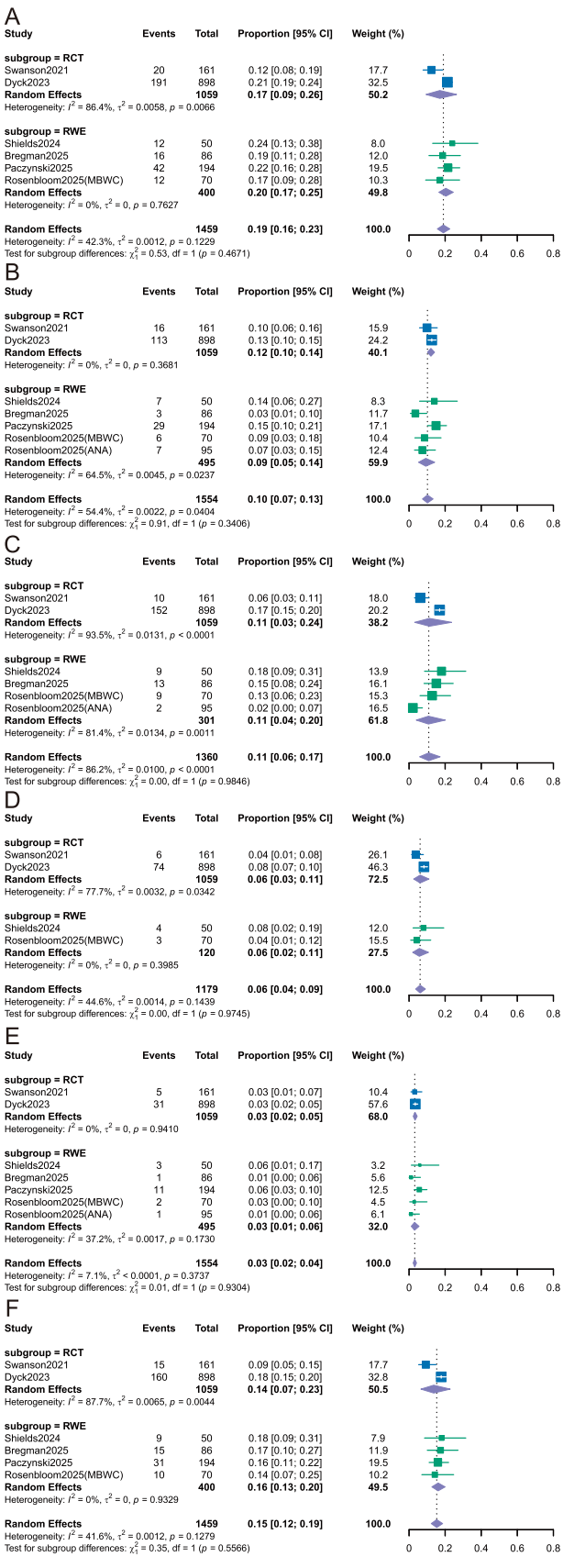

Fig. 2. Forest plot of ARIA incidence by subtype in RCTs and RWE studies. A. Overall ARIA; B. ARIA-E; C. ARIA-H; D. Concurrent ARIA–E and ARIA-H; E. Symptomatic ARIA; F. Asymptomatic ARIA.

heterogeneity (I^2= 0.0 %) (Fig. 2A). In contrast, substantial heterogeneity was observed between the two RCTs (I^2= 86.4 %), with reported incidences of 12 % and 21 %, respectively (Fig. 2A).

For ARIA-E, the pooled incidence was 10 % (95 % CI: 7 %−13 %), with moderate heterogeneity (I^2 = 54.4 %) (Fig. 2B). The pooled incidence in RCTs was 12 % (95 % CI: 10 %−14 %) with no heterogeneity (I^2 = 0.0 %), whereas estimates from RWE studies ranged from 3 % to 15 %, with higher heterogeneity (I^2 = 64.5 %) (Fig. 2B). The pooled incidence of ARIA-H was 11 % (95 % CI: 6 %−17 %), with high heterogeneity (I^2 = 86.2 %) (Fig. 2C). Heterogeneity remained high within both RCTs (11 %, 95 % CI: 3 %−24 %, I^2 = 93.5 %) and RWE studies (11 %, 95 % CI: 4 %−20 %, I^2 = 81.4 %) (Fig. 2B) (Fig. 2C). For concurrent ARIA-E and ARIA-H, the pooled incidence was 6 % (95 % CI: 4 %−9 %), with moderate heterogeneity (I^2 = 44.6 %) (Fig. 2D). Among RCTs, the incidence was 6 % (95 % CI: 3 %−11 %), with high heterogeneity (I^2 = 77.7 %) (Fig. 2D). RWE studies showed a similar incidence of 6 % (95 % CI: 2 %−11 %), with no heterogeneity (I^2 = 0 %) (Fig. 2D).

Symptomatic ARIA occurred in 3 % of patients with lecanemab (95 % CI: 2 %−4 %), with minimal heterogeneity (I^2 = 7.1 %). Incidence estimates were consistent in RCTs (3 %, 95 % CI: 2 %−5 %; I^2 = 0 %) and in RWE studies (3 %, 95 % CI: 1 %–6 %; I^2 = 37.2 %) (Fig. 2E). Asymptomatic ARIA was more common. Across all studies (N = 1459), the pooled incidence was 15 % (95 % CI: 12 %−19 %), with moderate heterogeneity (I^2 = 41.6 %) (Fig. 2F). In RCTs, the incidence was 14 % (95 % CI: 7 %−23 %) with substantial heterogeneity (I^2 = 87.7 %). In RWE studies, the pooled incidence was 16 % (95 % CI: 13 %−20 %), with no heterogeneity (I^2 = 0 %) (Fig. 2F).

3.3.2. *ARIA risk by ApoE4 genotype*

The incidence of ARIA substantially varied across different ApoE4 genotypes, demonstrating a clear gene-dose effect. Among ApoE4 noncarriers, the pooled incidence of ARIA was 12 % (95 % CI: 9 %−15 %) with no heterogeneity (I^2=0.0 %) between RCTs (12 %) and RWE studies (13 %) (Fig. 3A). The incidence increased to 19 % (95 % CI: 16 %−22 %) in heterozygotes, with low heterogeneity (I^2=10.0 %) and the incidence was 16 % in RCTs and 22 % in RWE studies (Fig. 3B). Among ApoE4 homozygotes, the incidence was the highest, reaching 45 % (95 % CI: 37 %−52 %) with no heterogeneity (I^2=0.0 %), an incidence observed consistently in both RCTs (45 %) and RWE studies (44 %) (Fig. 3C).

To further explore the effect of ApoE4 genotype on ARIA risk, we also estimated the pooled RR. Compared with noncarriers, the RR for ARIA was 1.45 (95 % CI: 1.15–1.82, I^2= 0.0 %) for ApoE4 heterozygotes (Fig. 3D). The RR increased to 3.54 (95 % CI: 2.55–4.92, I^2= 0.0 %) for ApoE4 homozygotes (Fig. 3E). Subgroup analyses by study type revealed similar point estimates, although the confidence intervals were wider (Fig. 3D) (Fig. 3E).

3.3.3. *IRRs incidence*

The analysis of all 1379 patients yielded an overall incidence of IRRs of 26 % (95 % CI: 19 %−34 %). Notably, substantial heterogeneity was observed across different study designs (RCT vs. RWE, I^2= 82.1 %), within RCTs (I^2= 67.9 %) and within RWE (I^2= 85.1 %). (Fig. 4A). In a subgroup analysis of RWE studies that utilized pre-infusion prophylaxis with acetaminophen and loratadine, the pooled incidence of IRRs was 26 % (95 % CI: 16 %−38 %), and heterogeneity was no longer present (I^2= 0.0 %) (Fig. 4B).

3.4. *Tolerability and acceptability outcomes*

3.4.1. *Discontinuation due to ARIA*

Data on discontinuation due to ARIA were only available from five RWE studies (N = 556). The pooled discontinuation rate was 5 % (95 % CI: 3 %−7 %), with no heterogeneity (I^2= 0.0 %) (Fig. 5A).

3.4.2. *Discontinuation due to any adverse event*

The pooled discontinuation rate due to any AE was 8 % (95 % CI: 5

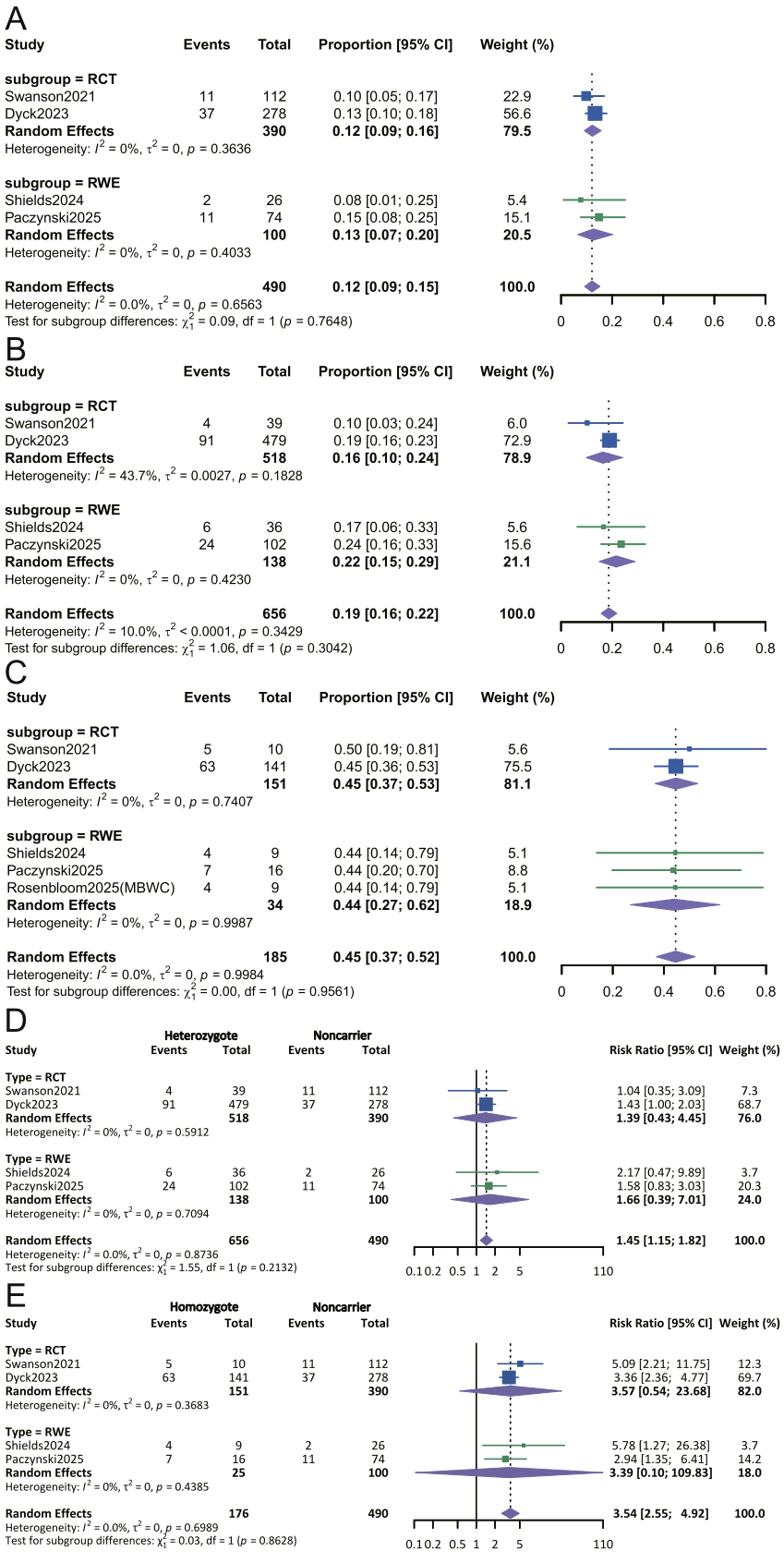

Fig. 3. Forest plot of ARIA incidence stratified by ApoE4 genotype in RCTs and RWE studies. A. ApoE4 noncarriers; B. ApoE4 heterozygotes; C. ApoE4 homozygotes; D. RR: Heterozygotes vs. noncarriers; E. RR: Homozygotes vs. noncarriers.

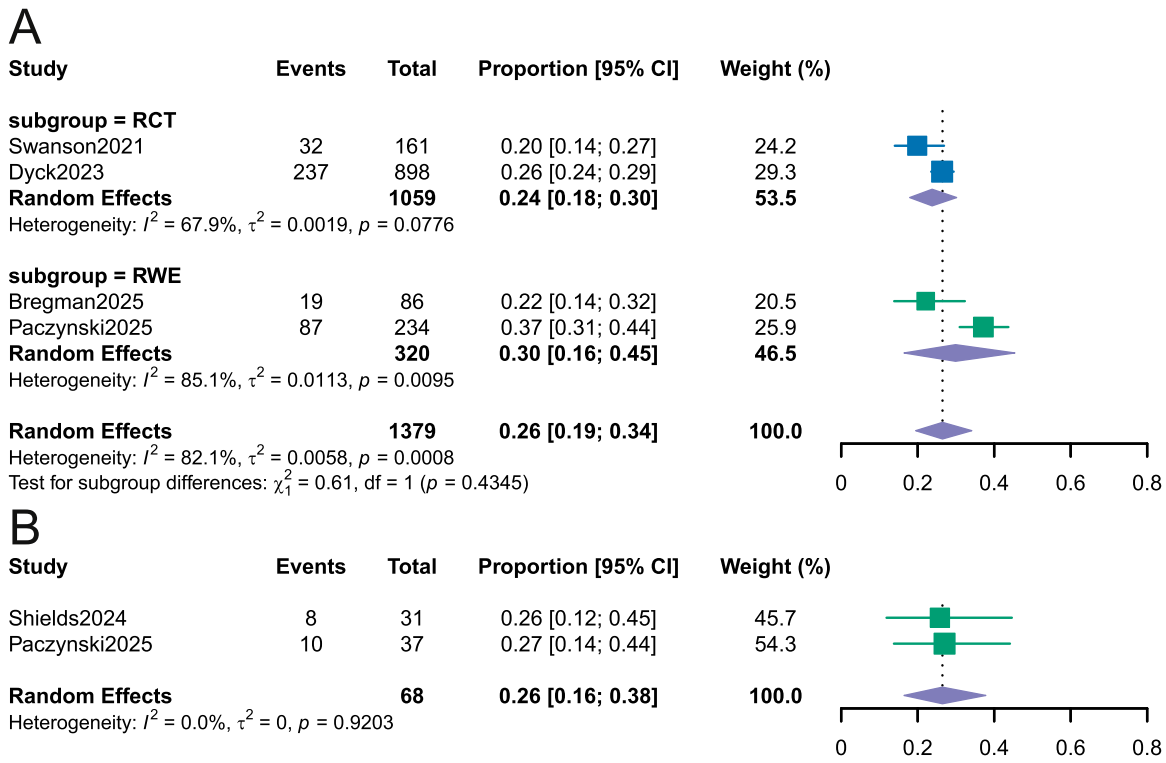

Fig. 4. Forest plot of IRRs incidence. A. IRRs incidence in RCTs and RWE studies; B. IRRs incidence with pre-infusion prophylaxis in RWE studies.

%−11 %), with heterogeneity (I^2= 63.8 %) across different studies (Fig. 5B). Heterogeneity was prominent between the two RCTs (15 % vs. 7 %). In contrast, the pooled rate within RWE studies was more consistent at 7 % (95 % CI: 4 %−9 %, I^2= 18.1 %).

3.4.3. *Discontinuation for any reason*

A pooled analysis of 1615 patients across both RCTs and RWE studies revealed that the discontinuation rate for any reason was 17 % (95 % CI: 9 %−27 %), with substantial heterogeneity across all studies (I^2= 93.0 %) (Fig. 5C). The heterogeneity was particularly high between the two RCTs (44 % vs. 19 %, I^2= 97.6 %).

4. Discussion

This systematic review and meta-analysis, which evaluated the safety profiles of lecanemab in RCTs and real-world settings, yielded three key observations. First, the risk of ARIA is considerable and exhibits a clear gene-dose-dependent association with the ApoE4 allele, a pattern consistently observed across both RCTs and RWE studies. Second, although the overall incidence of IRRs is elevated, the substantial heterogeneity across studies appears largely attributable to variations in management strategies, particularly the implementation of pre-infusion prophylaxis. Third, ARIA has emerged as the principal safety-related determinant of treatment discontinuation in clinical practice.

4.1. *The gene-dose effect of ApoE4 on ARIA risk*

Our analysis confirmed and quantified the pivotal role of ApoE4 in modulating ARIA risk. The incidence inscreases from 12 % in noncarriers to 19 % in heterozygotes and peaks at a striking 45 % in homozygotes. This clear gene-dose effect is further underscored by our RR analysis, which shows that compared with noncarriers, heterozygotes have a 1.5-fold increased risk (RR = 1.45) of developing ARIA, while homozygotes face a dramatic 3.5-fold increased risk (RR = 3.54). This strong association is consistent with the known pathophysiologic roles of ApoE4 in AD, which include promoting amyloid pathology [28,29], compromising blood-brain barrier integrity [30,31], and dysregulating neuroinflammatory responses[32], all of which are likely to increase ARIA susceptibility.

This finding has profound clinical implications. The unfavorable risk-benefit profile in ApoE4 homozygotes, especially when considering emerging evidence of diminished therapeutic benefit in this subgroup [33], lends strong support to recommendations from the UK's Medicines and Healthcare products Regulatory Agency and the EMA to exclude them from treatment eligibility. Our data provide a quantitative evidence base for these recommendations and underscore the necessity of mandatory ApoE4 genotyping prior to initiating lecanemab. However, such restrictions are not included in the current FDA prescribing information, highlighting a key area of ongoing regulatory divergence.

We also observed significant heterogeneity in the incidence of ARIA between the two RCTs (12 % vs. 21 %). This discrepancy is likely explained by the marked difference in the proportion of ApoE4 carriers in their study populations (30.4 % vs. 69.0 %), further highlighting that the ApoE4 status of a cohort is a primary determinant of the observed incidence of ARIA.

4.2. *IRRs prophylaxis and management*

IRRs are the most frequently reported AEs in patients receiving lecanemab, with a pooled incidence of 26 %. Yet, the substantial heterogeneity observed (I^2 = 82.1 %) indicates a potential origin of variability in this context. When the analysis was restricted to studies implementing a defined pre-infusion prophylaxis regimen—including acetaminophen and loratadine—heterogeneity was entirely resolved (I^2=0.0 %). These findings strongly suggest that the observed variability in IRR rates is a modifiable factor contingent on clinical management.

This finding is particularly relevant to ongoing discussions regarding the optimal management of IRRs. Clinically, IRRs generally manifest as mild, transient symptoms, rarely necessitating treatment discontinuation. Nevertheless, recommendations for routine premedication remain inconsistent. For example, the Alzheimer's Disease and Related Disorders Therapeutics Work Group (ADRD TWG) advocates various

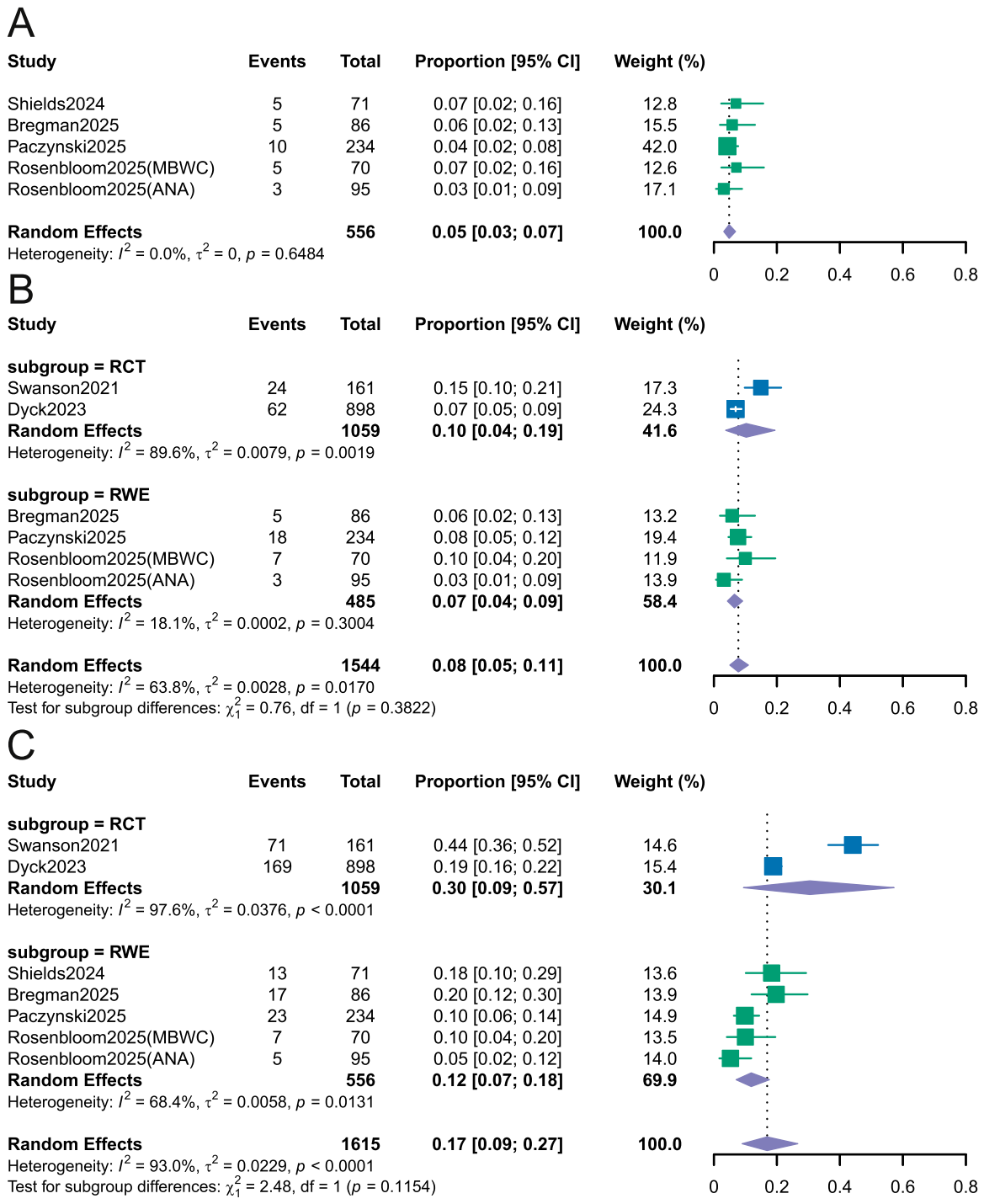

Fig. 5. Forest plot of proportion of discontinuation. A. Due to ARIA in RWE studies; B. Due to AEs in RCTs and RWE studies; C. Due to any-reason in RCTs and RWE studies.

strategies including diphenhydramine, acetaminophen, or low-dose oral corticosteroids for prophylaxis, whereas the EMA does not recommend routine premedication [34].

Our analysis indicated that a prophylactic regimen comprising acetaminophen and loratadine was associated with a consistent and predictable IRR incidence. In contrast, diphenhydramine has demonstrated both limited efficacy in preventing IRRs and the potential for serious adverse behavioral effects [25,35]. These findings underscore the importance of carefully weighing the risk-benefit profile of each prophylactic agent. Collectively, these findings highlight the urgent need for further research to establish an optimal and standardized infusion protocol for lecanemab.

4.3. *Tolerability and acceptability in RCTs and real-world settings*

Following recommendations from the ADRD TWG and the EMA, discontinuation of lecanemab is warranted for severe AEs, including severe radiographic or symptomatic ARIA, severe IRRs, major hemorrhage, or other serious treatment-emergent complications [12,34]. The occurrence of such events is a primary determinant of drug tolerability in clinical practice.

Our analysis of real-world data revealed that the discontinuation rate

due to any AE was 7 %, while the rate due to ARIA specifically was 5 %. The proximity of these two figures strongly suggests that severe ARIA is the primary determinant of safety-related treatment discontinuation. This highlights the critical importance of regular monitoring and timely, effective management of ARIA to help patients remain on this potentially disease-modifying therapy.

In addition to ARIA, other serious AEs can also lead to the discontinuation of lecanemab, as previously discussed. Our analysis revealed that a notable discrepancy emerged between the phase 2b (15 %) and phase 3 (7 %) trials for AE-related discontinuation. This discrepancy likely reflects the smaller sample size ($N = 161$ vs. $N = 898$) and limited experience with AE management during the earlier phase 2b trial. In contrast to this inter-trial variability, the four RWE studies reported a consistent AE-related discontinuation rate around 7 %, suggesting a more standardized management approach in routine practice.

With respect to acceptability, our analysis revealed a stark contrast in the all-cause discontinuation rates between the two pivotal RCTs (44 % vs. 19 %). This profound heterogeneity ($I^2 = 97.6$ %) may be explained by a regulatory decision that required immediate withdrawal of all 25 ApoE4 carriers who had not yet reached six months of treatment. This highlights how sensitive all-cause discontinuation rates in RCTs can be to protocol-specific events, potentially limiting their generalizability.

In contrast, the reasons for discontinuation in real-world settings are more directly tied to clinical practice. Our findings, showing a 12 % all-cause discontinuation rate in RWE, reflect a different set of drivers. While tolerability issues, primarily severe ARIA, are a major factor, discontinuation in the real world is also influenced by practical considerations such as patient preference, caregiver burden, and economic constraints. Therefore, while AE-related discontinuation rates reflect drug tolerability, the all-cause discontinuation rate in RWE provides a more holistic measure of treatment acceptability and persistence in a routine clinical environment.

4.4. Symptomatic ARIA and serious cerebral adverse events in lecanemab treatment-related fatalities

In our meta-analysis, the pooled incidence of ARIA was 19 %, comprising 10 % for ARIA-E, 11 % for ARIA-H, and 6 % for concurrent ARIA-E and ARIA-H. Among these, symptomatic ARIA occurred in 3 % of patients with lecanemab, accounting for approximately one-sixth of all ARIA cases, and showed highly consistent rates across both RCTs and RWE studies. Reported symptoms associated with ARIA included headache, visual disturbances, confusion, dizziness, seizures, aphasia, and psychosis. Beyond the ApoE4 gene-dose effect identified in our analysis, Paczynski et al. demonstrated that symptomatic ARIA risk is strongly associated with baseline Clinical Dementia Rating (CDR) and MMSE scores, and with the severity of clinical symptoms, highlighting the need for early diagnosis and treatment of AD [23].

No fatalities associated with lecanemab were reported across the RCTs and RWE studies included in our analysis. To provide a more comprehensive evaluation of safety, we queried the FAERS database using the terms "BAN2401", "LECANEMAB", "LECANEMAB IRMB", "LECANEMAB IRMB LEQEMBI" and "LEQEMBI" [36]. We found that, as of the second quarter of 2025, 2761 lecanemab-related cases had been reported, including 1006 serious and 112 fatal cases. Although the causal relationship between lecanemab and death remains uncertain, fifteen cases were associated with serious cerebral AEs, including ARIA, brain edema, and intracerebral hemorrhage (ICH); notably, eight of these deaths were related to ARIA.

In addition, in the most recent safety data from the OLE phase of the CLARITY study, nine deaths were reported, four of which were considered related to lecanemab. Three deaths occurred in the context of serious cerebral AEs, irrespective of whether these events were the direct cause of death [18]. One fatality occurred in an 85-year-old male ApoE4 non-carrier with cardiovascular disease, receiving apixaban, who developed a symptomatic macrohemorrhage consistent with ARIA-H [18]. A second fatality involved a 77-year-old ApoE4 homozygous female whose MRI showed radiographically severe ARIA-E with 51 microhemorrhages and autopsy confirmed severe cerebral amyloid angiopathy (CAA) [37]. A third death occurred in a 63-year-old ApoE4 homozygous female who developed acute multifocal ICH, severe CAA, and vasculitis following tPA administration for left middle cerebral artery occlusion [38,39]. Collectively, these observations underscore that lecanemab should be used with particular caution in patients who are receiving or require anticoagulant therapy, given the elevated risk of serious cerebral AEs. The ADRD TWG recommends withholding lecanemab in such patients and resuming treatment only if anticoagulation is no longer medically indicated [12].

Although FAERS data and the OLE phase of RCTs do not meet the criteria for inclusion in meta-analyses, as noted above, these data nonetheless indicate the substantial contribution of serious cerebral AEs to lecanemab-related mortality. They also highlight the importance of timely MRI monitoring, early recognition, and prompt discontinuation or intervention, thereby providing important complementary evidence to our meta-analysis.

4.5. Strengths and limitations

The widespread clinical implementation of lecanemab for AD is constrained by high costs [40], narrow patient eligibility [41–46], a shortage of qualified healthcare personnel [47] and a high incidence of AEs, which have limited large-scale RWE and underscore the relevance of our systematic synthesis of safety data. In this study, we evaluated lecanemab safety across both RCTs and real-world settings. Its strengths include a comprehensive literature search, adherence to PRISMA guidelines, and pre-specified subgroups analyses. Our findings underscore the clinical importance of identifying ApoE4 genotype prior to initiating lecanemab therapy and highlight the crucial need to optimize and standardize the management of ARIA and IRRs, thereby informing clinical decision-making for clinicians, patients, caregivers, healthcare systems, payers, and policymakers.

Nonetheless, several limitations should be acknowledged. First, the total number of included studies, particularly RCTs ($N = 2$), was limited, which may have affected the precision of the pooled estimates. Second, the single-arm design of the included RWE studies precluded a direct estimation of lecanemab-specific risk, as AEs were also reported in the placebo arms of the RCTs; consequently, our analysis reports overall event incidence rather than attributable risk. Third, substantial variation in follow-up duration across studies represents a potential source of heterogeneity that could not be fully accounted for, although one included study reported no significant time-ARIA interaction [22]. Finally, residual heterogeneity in some pooled estimates likely reflects underlying variability in patient characteristics and clinical practice patterns.

5. Conclusions

This meta-analysis provides a comprehensive synthesis of lecanemab safety profiles, drawing on evidence from both RCTs and real-world studies. The incidence of ARIA was found to be strongly influenced by ApoE4 genotype, emphasizing the importance of pre-treatment genotyping for risk stratification and informed consent. Severe ARIA was identified as the principal driver of safety-related treatment discontinuation, highlighting the necessity of standardized ARIA management protocols to increase treatment tolerability. Furthermore, standardized pre-infusion regimens have emerged as critical for effective IRR management. Collectively, these insights provide a robust evidence base to guide the safe and optimized clinical application of lecanemab.

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

We have not used any AI at all.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained from all participants in this study.

CRediT authorship contribution statement

Lin Qi: Writing – review & editing, Writing – original draft, Methodology, Data curation. **Fangxue Zheng:** Writing – review & editing, Writing – original draft, Software, Methodology, Data curation. **Mengjiao Tu:** Writing – review & editing, Software, Methodology, Data curation. **Reema Abdullah:** Writing – review & editing. **Yilei Zhao:** Writing – review & editing. **Xinhui Su:** Validation, Supervision. **Dan Zhou:** Writing – review & editing, Validation, Supervision. **Guoping Peng:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

We would like to thank the researchers and participants of the studies included in this meta-analysis on the safety profiles of lecanemab.

We did not receive any funding or financial support for this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100473.

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