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Adverse Effects ARIA (ARIA-E and ARIA-H) in Aducanumab and Lecanemab According to APOE Genotype: Systematic Review of the Literature

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ABSTRACT

Introduction: Alzheimer's Disease (AD) is characterized by cerebral accumulation of β-amyloid (Aβ) plaques and tau tangles, leading to progressive cognitive decline. Monoclonal antibodies targeting Aβ, such as aducanumab and lecanemab, have demonstrated plaque reduction and slowed clinical deterioration by 25–40%, but their use is complicated by Amyloid-Related Imaging Abnormalities (ARIA), Manifesting as Vasogenic Edema (ARIA-E) and microhemorrhages or siderosis (ARIA-H).

Objective: To systematically review the incidence and characteristics of ARIA-E and ARIA-H in patients treated with aducanumab or lecanemab, stratified by APOE ε4 genotype.

Methods: A systematic review of Randomized Clinical Trials (RCTs) was conducted. PubMed, Embase, Web of Science, CENTRAL, and Scopus were searched through June 2025 for RCTs reporting ARIA adverse events by APOE genotype. Trials involving adult AD or mild cognitive impairment patients with documented APOE status and imaging-assessed ARIA were included. Data extraction and Cochrane RoB 2.0 bias assessment were performed by two independent reviewers, with narrative synthesis of ARIA incidence and management strategies.

Results: Four RCTs met inclusion criteria. In phase 3 CLARITY-AD (lecanemab), overall ARIA-E incidence was 13.6%; among APOE ε4/ε4 homozygotes it rose to 34.5% versus 6.9% in non-carriers (principal result), with most cases mild/moderate and resolving within 3–6 months. Symptomatic ARIA-E occurred in 3.3% and serious events in 1.1% of all treated patients.

Discussion: APOE ε4 carriage, especially homozygosity, markedly elevates ARIA risk with anti-Aβ antibodies. Pre-treatment genotyping is recommended to tailor safety monitoring: ε4/ε4 individuals may benefit from slower dose titration, more frequent MRI surveillance during the first 6–12 months, and stricter criteria for treatment interruption. These strategies aim to optimize therapeutic benefit while minimizing ARIA-related harm.

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Introduction

Alzheimer's Disease (AD) is the most common cause of dementia and primarily affects older adults. Its pathophysiology is characterized by the accumulation of beta-amyloid (Aβ) peptide and tau protein in the brain, which has prompted the development of Aβ-targeted therapies as a disease-modifying strategy [1]. In recent years, monoclonal antibodies such as Lecanemab and Donanemab have been approved for treating patients with early-stage AD, showing efficacy in reducing cerebral amyloid burden and slowing clinical decline by an estimated 25 %–40 % [2,3].

Nevertheless, the use of these therapies is associated with a significant safety profile, particularly with the emergence of Amyloid-Related Imaging Abnormalities (ARIA, by its English acronym). The most common manifestations include vasogenic

edema (ARIA-E) and microhemorrhages or cortical siderosis (ARIA-H), which in some cases can be severe or even fatal [2,3].

A growing body of evidence indicates that the apolipoprotein E genotype, especially the ε4 allele, is a relevant risk factor for the occurrence of ARIA. In recent clinical studies, the incidence of ARIA-E in patients treated with Lecanemab was 32.6 % in APOE ε4 homozygotes compared with 5.4 % in non-carriers; with Donanemab, this incidence reached 41 % in homozygotes [3]. This has raised clinical concern regarding the prescription of these therapies in genetically predisposed patients, underscoring the need for an individualized approach to therapeutic selection.

In this context, it is essential to systematically review the available clinical evidence on the relationship between the APOE ε4 genotype and the occurrence of ARIA-type adverse events when using anti-amyloid therapies. This synthesis aims to provide relevant information to guide safe and effective clinical decision-making in the treatment of Alzheimer's disease.

Methods

Study Design

This was a systematic review of controlled clinical trials investigating the occurrence of Amyloid-Related Imaging Abnormalities (ARIA)–related adverse events in carriers of different APOE allele genotypes, with special attention to ε4 allele carriers.

Selection Criteria

Study Types

Only Randomized Clinical Trials (RCTs), published in peer-reviewed scientific journals, were included. This decision was made to ensure the highest possible internal validity and to minimize the risk of bias in estimating intervention effects.

Participant Types

Adult participants (≥18 years) with a diagnosis of Alzheimer's disease or mild cognitive impairment consistent with amyloid accumulation, in whom APOE genotype was determined and ARIA adverse events were assessed.

Intervention/Exposure Types

The exposure of interest was the presence of one or two APOE ε4 alleles. ARIA adverse events were compared across genotypes (ε4 homozygotes, heterozygotes, and non-carriers).

Outcome Types

Primary Outcomes

Incidence of ARIA-E (edema) and ARIA-H (hemorrhage) in relation to the different APOE genotypes.

Secondary Outcomes

Severity of ARIA adverse events.
Treatment discontinuation due to ARIA.
Differences in clinical management of ARIA by genotype.

Search Methods for Study Identification

Electronic Searches

Systematic searches were conducted in MEDLINE (via PubMed), Embase, Web of Science, CENTRAL, and Scopus from inception through June 2025. Combinations of MeSH and free-text terms were used, including "APOE," "Apolipoprotein E4," "ARIA," "amyloid-related imaging abnormalities," "Alzheimer's disease," and "adverse effects."

Searching Other Resources

Reference lists of included studies and relevant previous reviews were screened. Unpublished trials were sought on ClinicalTrials.gov and the WHO ICTRP.

Data Collection and Analysis

Study Selection

Two independent reviewers screened titles and abstracts, followed by full-text assessments. Discrepancies were resolved by consensus or by a third reviewer.

Data Extraction and Management

Data were extracted using a standardized template capturing study characteristics, population details, APOE genotyping method, presence and type of ARIA, and clinical outcomes. Inter-reviewer consistency was verified (Table 1).

Table 1: Included Studies Characteristics Summary

Study (Design)	Population (Criteria)	Intervention (Comparator)	Primary Efficacy Outcome	Key Efficacy Findings
Honig et al. [7]	Participants with early Alzheimer's disease; inclusion based on clinical diagnosis and biomarker confirmation	Lecanemab vs. placebo	Change in Clinical Dementia Rating–Sum of Boxes (CDR-SB)	Lecanemab significantly slowed decline in CDR-SB compared to placebo
Rosenstiel et al. [6]	APOE ε4 carriers with early Alzheimer's disease (n≈26 in aducanumab arm)	Aducanumab vs. placebo	Amyloid PET SUVR reduction at 24 months	Aducanumab led to dose-dependent amyloid reduction
Burkett et al. [4]	Participants from EMERGE and ENGAGE trials with early Alzheimer's disease (n=3285)	Aducanumab (10 mg/kg) vs. placebo	ARIA incidence and safety management profile	ARIA-E incidence was 35.2% in 10 mg/kg group, mostly asymptomatic
Salloway et al. [14]	Same as Burkett et al.: Patients from EMERGE and ENGAGE trials (n=3285)	Aducanumab (10 mg/kg) vs. placebo	ARIA incidence and radiographic/clinical characterization	ARIA-E occurred in 35.2% of patients, most within first 32 weeks; 26% were symptomatic

Assessment of Risk of Bias

The Cochrane RoB 2.0 tool was applied to each trial, evaluating the domains of selection, comparability, and outcome measurement.

Bias Control

Handling of Missing Data

Authors of studies with incomplete data were contacted. If no response was received, data were reported as unavailable, and the impact was assessed via sensitivity analyses.

Assessment of Reporting Bias

Publication bias was evaluated by visually inspecting funnel plots and conducting statistical tests when at least 10 studies were included.

A narrative synthesis of the findings was undertaken.

Results

Figure 1 shows the study selection process. A total of 87 records were identified through database searches (PubMed, EMBASE, and LILACS). After removing 4 duplicate records, 83 titles and abstracts were screened, of which 51 were excluded for not addressing the research question. Thirty-two full-text articles were assessed, and 28 were excluded for the following reasons: 14 were review articles, 9 were case reports, 3 were observational or genetic studies, and 2 were technical guidelines or expert recommendations. Ultimately, 4 studies were included in the systematic review.

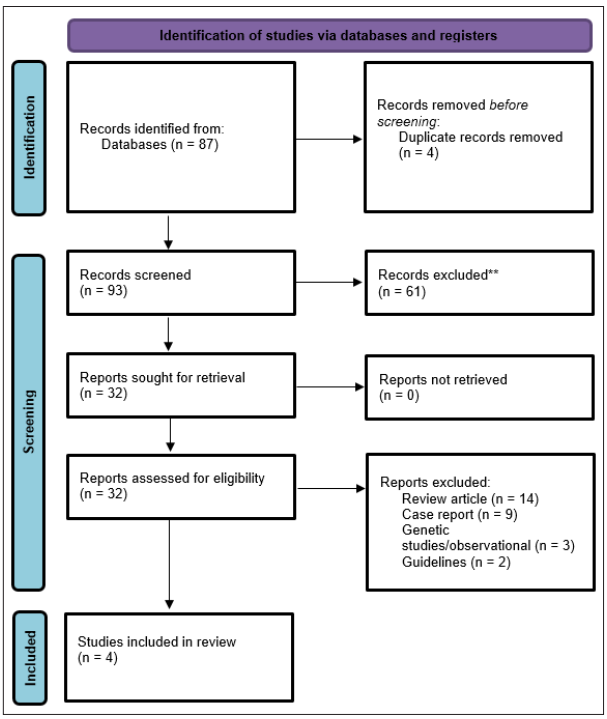

Figure 1: PRISMA Flow Diagram

In this context, anti–β-amyloid monoclonal antibodies such as Aducanumab and Lecanemab have been evaluated in clinical trials for the treatment of early-stage Alzheimer's disease. Although they have demonstrated efficacy in reducing amyloid plaques, one of the main challenges in their clinical use is the occurrence of Amyloid-Related Imaging Abnormalities (ARIA), presenting as either cerebral edema (ARIA-E) or hemorrhages (ARIA-H). These adverse reactions have been the subject of intensive study, particularly in relation to genetic factors such as the APOE ε4 genotype, which appears to significantly increase the risk of developing ARIA [4-7].

In the phase 3 EMERGE and ENGAGE trials, the safety and efficacy of Aducanumab were evaluated in patients with mild cognitive impairment or mild dementia due to Alzheimer's disease. In the combined analysis, the most frequent adverse event in the high-dose group (10 mg/kg) was ARIA, occurring in 41.3 % of treated patients (425/1,029). The most common manifestation was ARIA-E (35.2 %), while ARIA-H included microhemorrhages (19.1 %) and superficial siderosis (14.7 %). The majority of ARIA-E events were detected during the first eight infusions. Clinically, 26.0 % of ARIA-E cases were symptomatic, with predominant symptoms of headache (46.6 %), confusion (14.6 %), and dizziness (10.7 %). Only 1.4 % of cases were serious and required hospitalization [4].

The APOE ε4 genotype was a key determinant of ARIA incidence with Aducanumab. In EMERGE/ENGAGE, ARIA-E incidence among carriers was 43.0 %, compared with 20.3 % in non-carriers, yielding an estimated relative risk of 2.1. In the phase 1b PRIME study, ε4/ε4 homozygotes exhibited a 66 % incidence of ARIA-E, versus 36 % in heterozygotes. Despite the higher incidence, ARIA severity and symptomatology did not differ significantly between genetic groups. Genome-wide association studies (GWAS) confirmed APOE ε4 as the principal genetic determinant of ARIA, with odds ratios of 4.3 for ARIA-E and 7.8 for ARIA-H [5,6].

The phase 3 CLARITY-AD trial assessed the safety profile of Lecanemab in early Alzheimer's patients. The overall incidence of ARIA-E was 13.6 % and ARIA-H was 16.0 %, considerably lower than with Aducanumab. Among APOE ε4 carriers, ARIA-E incidence rose to 16.8 %, and in homozygotes reached 34.5 %, compared with 6.9 % in non-carriers. Most cases were mild or moderate and resolved within 3 to 6 months. Only 3.3 % of cases were symptomatic. The rate of serious events was 1.1 %, with no deaths directly attributable to treatment [7].

Clinical management of ARIA according to APOE genotype has gained practical relevance. Genotyping is recommended before treatment initiation, particularly to adjust monitoring and expectations in ε4 carriers. For Aducanumab, a progressive dose-titration strategy was implemented to reduce ARIA risk, especially in carriers. In cases of moderate or severe ARIA, temporary treatment interruption, radiological evaluation for resolution, and enhanced clinical surveillance are advised. In both drugs, the presence of the ε4 allele influenced not only ARIA frequency but also the need to modify safety and monitoring strategies in Alzheimer's patients [4-7].

Overall, risk-of-bias assessment of the included studies revealed considerable heterogeneity in methodological quality (Table 2). Honig demonstrated low risk of bias across all domains except for some concerns regarding missing outcome data [7]. In contrast, Rosenstiel, Burkett and Salloway exhibited concerns in multiple domains [4-6]. Specifically, high risk of bias due to deviations from intended interventions was identified in Rosenstiel and Burkett, as well as high risk from missing outcome data in these two and in Salloway. Additionally, some concerns were noted in randomization, outcome measurement, and selection of reported results in most studies, suggesting methodological limitations that could affect the internal validity of their findings.

Table 2: Risk of Bias (RoB2)

Domain	Honig [7]	Rosenstiel [6]	Burkett [4]	Salloway [14]
Random process	Low	Some concerns	Some concerns	Some concerns
Intervention deviation	Low	High	High	Low
Missing data	Some concerns	High	High	High
Outcome measure	Low	Some concerns	Some concerns	Low
Reported results	Low	Some concerns	Some concerns	Some concerns

Discussion

Amyloid-Related Imaging Abnormalities (ARIA) represent the most frequent and clinically relevant adverse effect of anti-amyloid therapies in Alzheimer's disease. They are divided into two main types: ARIA-E (cerebral edema or sulcal effusion) and ARIA-H (microhemorrhages and superficial siderosis). These alterations, usually asymptomatic or of mild and transient presentation, are detected by magnetic resonance imaging in clinical trials. Between 74 % and 85 % of ARIA-E episodes reported with anti-amyloid antibodies (aducanumab, donanemab, lecanemab) were clinically silent, and over 80 % resolved spontaneously within 16 weeks. However, given the possibility of severe cases-such as extensive cerebral edema or symptomatic hemorrhages these events require careful monitoring during treatment [4,8-10].

Aducanumab has shown a high incidence of ARIA in the EMERGE and ENGAGE trials, with approximately 41 % of patients in the high-dose group (10 mg/kg) experiencing some form of ARIA, of which 35.2 % corresponded to ARIA-E and 19.1 % to microhemorrhages (ARIA-H). This incidence is strongly associated with APOE genotype, particularly among carriers of the ε4 allele. In homozygotes (ε4/ε4), the ARIA-E rate reached 66 %, compared with 36 % in heterozygotes. Although most of these events were mild and asymptomatic, 26 % were symptomatic and approximately 6 % required treatment discontinuation [4,11]. By contrast, lecanemab, evaluated in the CLARITY-AD trial, demonstrated a considerably lower overall ARIA frequency: 13.6 % for ARIA-E and 16.0 % for ARIA-H. Again, ε4 carriers exhibited greater susceptibility, with ARIA-E rates of 32.6 % in homozygotes and 10.9 % in heterozygotes, versus only 5.4 % in non-carriers. Moreover, symptomatic cases were significantly less frequent with lecanemab [12,13].

The available evidence supports implementing an individualized clinical approach based on APOE genotype for administering anti-amyloid therapies. Pre-treatment genotyping is recommended, especially to inform patients of their risk profile and to tailor imaging follow-up. In ε4/ε4 homozygotes, slow dose-titration schemes, avoidance of concomitant anticoagulant use, and stricter criteria for treatment suspension in the event of ARIA are advised. Additional measures—such as more frequent MRI monitoring during the first 6 to 12 months and differentiated informed consent—are also proposed. These strategies help optimize the balance between efficacy and safety, particularly in individuals genetically predisposed to severe adverse events [10,14-16].

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