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Real-world effectiveness of monoclonal antibody lecanemab versus acetylcholinesterase inhibitors in Alzheimer's disease: a target trial emulation

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Abstract

Background:

Acetylcholinesterase inhibitors (AChEIs) provide symptomatic relief in Alzheimer's disease (AD), whereas lecanemab may modify disease progression; however, real-world evidence on its safety and clinical impact remains limited. Therefore, this study aimed to compare the safety and effectiveness of initiating lecanemab versus AChEIs in patients with mild cognitive impairment (MCI) or AD.

Methods:

Using the TriNetX US electronic health record network, we conducted a retrospective cohort study including individuals diagnosed with MCI or AD between July 2023 and September 2025. A target trial emulation with 1:1 propensity score matching and Cox models estimated comparative risks.

Results:

Lecanemab was associated with a fivefold higher incidence of neuroimaging abnormalities than AChEIs, while 1-year treatment persistence was similar (53.4% vs 52.5%). After matching, 589 patients were included in each cohort. Compared with AChEIs, lecanemab was associated with significantly lower risks of behavioral and psychological symptoms of dementia (BPSD) (HR, 0.52; 95% CI, 0.36–0.77) and emergency visits (HR, 0.66; 95% CI, 0.51–0.85), but a higher risk of hospitalization (HR, 1.31; 95% CI, 1.03–1.67). Lecanemab was also associated with lower use of antipsychotics (HR, 0.47; 95% CI, 0.32–0.70), antidepressants (HR, 0.60; 95% CI, 0.43–0.85),

melatonin/orexin antagonists (HR, 0.61; 95% CI, 0.42–0.88), antibiotics (HR, 0.61; 95% CI, 0.44–0.86), and antifungals (HR, 0.57; 95% CI, 0.37–0.88), whereas steroid use was higher among lecanemab users (HR, 2.19; 95% CI, 1.55–3.10).

Conclusions:

Compared with an AChEI-based conventional care strategy, lecanemab initiation was associated with comparable treatment persistence and lower observed risks of BPSD, emergency visit as well as reduced use of psychotropic and infection-related medications in exploratory analyses. However, the higher incidence of neuroimaging abnormalities associated with lecanemab, along with increased risks of hospitalization and corticosteroid use, likely reflects proactive clinical monitoring and management of amyloid-related imaging abnormalities (ARIA). While residual confounding cannot be excluded and results warrant cautious interpretation , these exploratory findings warrant further validation in biomarker-confirmed cohorts and head-to-head randomized trials.

Key Words:

Alzheimer’s disease; Lecanemab; Acetylcholinesterase inhibitors; Behavioral and psychological symptoms of dementia; Amyloid-related imaging abnormalities; Real-world evidence

Background

With rapidly aging populations worldwide, Alzheimer's disease (AD) has become a growing public imperative, demanding urgent attention and innovative interventions to address this escalating healthcare challenge[1]. Traditional pharmacological management has relied primarily on symptomatic treatment with acetylcholinesterase inhibitors (AChEIs), which provide modest and temporary improvement in cognitive and behavioral symptoms by enhancing cholinergic signaling[2]. However, these agents do not modify the underlying disease pathology.

Monoclonal antibodies (mAbs) targeting amyloid-β (Aβ)[3] have been approved by the U.S. Food and Drug Administration (FDA), including aducanumab, lecanemab, and donanemab, for patients with AD[4]. A randomized controlled trial has demonstrated that lecanemab reduced amyloid biomarkers and produced a moderate reduction in cognitive and functional decline over 18 months compared with placebo[5]. However, these benefits were accompanied by a notable incidence of treatment-related adverse events. Specifically, the incidence of amyloid-related imaging abnormalities - edema or effusion (ARIA-E) and amyloid-related imaging abnormalities - hemorrhage (ARIA-H) were 12.5% and 17.3%, respectively, in patients receiving lecanemab[5]. A recent systematic review and meta-analysis reported that, relative to AChEIs, mAbs were associated with a slower rate of cognitive decline, without significant differences in safety outcomes, including acceptability, tolerability, serious adverse events, or all-cause mortality[6]. However, evidence from real-world practice remains scarce. It remains uncertain whether the efficacy–safety profile observed in clinical trials can be replicated in routine care settings, and whether mAb therapy confers additional clinical benefits beyond cognitive improvement.

This study aimed to evaluate the safety, behavioral, and physical outcomes, as well as the risk of using symptom-directed medications, between patients initiating lecanemab and those receiving AChEIs in a real-world clinical setting. Specifically, we examine treatment persistence and longitudinal ARIA to understand adherence patterns and practical feasibility in routine clinical care.

Methods

Data source

Data were obtained from TriNetX, a large federated health research network that integrates deidentified EHRs from more than 275 million patients across academic medical centers, specialty physician practices, and community hospitals worldwide[7]. We used deidentified electronic health record (EHR) data collected for clinical practice and administrative purposes, with optional linkage to administrative claims when available. Available data elements include demographic characteristics, diagnoses, procedures, medications, laboratory tests, genomics, and health care utilization. Data on TriNetX are ingested in near real time through periodic synchronizations, ensuring that the network reflects up-to-date clinical activity. For this analysis, we used the TriNetX US Collaborative Network, the major TriNetX dataset and a federated EHR platform comprising data from 71 health care organizations across the United States. All diagnoses were identified using ICD-10 codes, and medications were identified using RxNorm codes. Analyses were conducted using available data without formal imputation, as missingness in key variables was

minimal in the TriNetX database. The Kaohsiung Medical University Hospital Institutional Review Board (KMUHIRB-E(I)-20250199) approved the research protocol. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies and the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) guidelines for target trial emulations.

Study Design, Cohort, and Treatment Strategies

We applied a target trial emulation framework to emulate a randomized comparison of initiating lecanemab versus AChEIs among patients with AD or mild cognitive impairment (MCI) on several important clinical outcomes[8, 9]. This approach aims to replicate the key components of a randomized controlled trial (RCT) using real-world observational data[10] (see eTable 1 for the protocol of the target trials).

Eligible participants were adults aged ≥45 years who had medical encounters with participating health care organizations between 1 July 2023 and 30 September 2025 and received a diagnosis of AD or MCI. The lower age threshold was selected to capture potential early-onset Alzheimer's disease cases and to enhance generalizability to real-world populations. Patients with a history of donanemab or aducanumab use before cohort entry were excluded. In addition, we excluded patients with prior diagnoses of vascular dementia or cognitive deficits following cerebrovascular disease, defined using ICD-10-CM codes F01* (vascular dementia), I69.31* (cognitive deficits following cerebral infarction), I69.81* (cognitive deficits following other

cerebrovascular disease), and I69.91* (cognitive deficits following unspecified cerebrovascular disease) to reduce inclusion of individuals with mixed or non-Alzheimer's pathology. To improve comparability between treatment groups and approximate early-stage disease, we restricted inclusion to patients initiating treatment within 90 days after a diagnosis of MCI or AD. Participants were assigned to one of two treatment strategies: (1) the lecanemab group (initiated lecanemab within 90 days after diagnosis) or (2) the AChEI group (initiated donepezil, rivastigmine, or galantamine within 90 days after diagnosis, with no prior exposure to any anti-amyloid monoclonal antibody). Diagnosis codes were used only to identify the eligible MCI or AD population before treatment initiation, whereas drug initiation defined time zero and outcome follow-up began after this index date.

Outcomes

The primary outcomes were safety-focused, including 1-year treatment persistence of lecanemab versus AChEIs and the incidence and prevalence of abnormal neuroimaging findings and ARIA-proxy composite events. For the analysis of 1-year treatment persistence, patients who initiated lecanemab or AChEIs between 1 July 2023 and 30 September 2024 were included to ensure adequate follow-up duration. The incidence and prevalence of abnormal neuroimaging findings and ARIA-proxy composite events were calculated at half-year intervals throughout the study period; therefore, data were available up to June 2025. Because ARIA (amyloid-related imaging abnormalities) lacks specific ICD-10-CM codes, we used a composite proxy definition encompassing: G93.6 (cerebral edema), I61.9 (nontraumatic intracerebral hemorrhage,

unspecified), I62.9 (nontraumatic intracranial hemorrhage, unspecified), and R90.89 (other abnormal findings on diagnostic imaging of the central nervous system).

Exploratory secondary outcomes were evaluated in an intention-to-treat–like framework and included behavioral and psychological symptoms of dementia (BPSD), anxiety disorder, emergency visits, hospitalizations, falls, delirium, infections, and symptom-directed medication use[11-14]. Medications of interest included antipsychotics, antidepressants, benzodiazepines, melatonin/orexin antagonists, steroids, antibiotics, antifungals, and anti-inflammatory drugs. For both primary and exploratory secondary outcomes, follow-up began at treatment initiation and continued until the first occurrence of the outcome of interest, death, the end of available follow-up, or the end of the study period, whichever occurred first. Patients were analyzed according to the treatment strategy initiated at time zero, regardless of subsequent discontinuation. To improve comparability for exploratory secondary analyses, individuals with prior AChEI exposure before cohort entry were excluded from the lecanemab cohort. Accordingly, the comparator cohort consisted of AChEI initiators without lecanemab exposure at baseline, while the lecanemab cohort was restricted to patients without prior AChEI exposure before treatment initiation.

Emulation of the Target Trials

We included covariates based on a combination of literature review, clinical expertise, and their availability within the dataset. All baseline covariates used for propensity-score matching, including demographics, comorbidities, prior medication use, and healthcare utilization variables, were

assessed using information available before time zero, up to the day before the index date. The 68 covariates included demographic characteristics, race/ethnicity, sex, broad ICD-10 diagnostic categories reflecting baseline disease burden, specific neuropsychiatric and medical comorbidities, medication classes, dementia-related medications, and healthcare utilization indicators. Specifically, we additionally accounted for major disease domains, including nervous system disorders, mental, behavioral, and neurodevelopmental disorders, circulatory, endocrine/metabolic, musculoskeletal, genitourinary, digestive, respiratory, infectious, hematologic/immune, neoplastic, injury-related, sensory, and skin disorders. We also included psychiatric comorbidity domains such as anxiety-related disorders, mood disorders, psychotic disorders, substance use disorders, and behavioral syndromes associated with physiological disturbances.

To further address treatment-selection differences and outcome-related baseline risks, we incorporated a broad range of medication classes, including central nervous system medications, antidepressants, antipsychotics, anticonvulsants, sedatives/hypnotics, cardiovascular medications, anticoagulants, antiparkinson agents, antineoplastics, antimicrobials, analgesics, gastrointestinal medications, vitamins, and other commonly used medication categories. Dementia-related medications, including memantine, donepezil, rivastigmine, and galantamine, were also included. In addition, healthcare utilization was captured using inpatient and emergency encounter variables.

We used propensity score matching to emulate randomization, adjusting for 68 baseline covariates. A logistic regression model estimated the probability of assignment to the lecanemab versus AChEIs. Using greedy nearest-neighbor matching with a 0.1 caliper, patients from the smaller cohort were matched to those in the larger cohort with comparable scores. A standardized mean difference <0.1 was considered indicative of adequate balance[10]. The details of the covariates are listed in Table 1. No post-baseline exposures, post-index diagnoses, or post-index outcomes were used to define eligibility, exclusions, or propensity-score covariates.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. Continuous variables were reported as means with SDs or medians with IQRs, and categorical variables as frequencies and percentages.

Treatment persistence of lecanemab and AChEI was evaluated among patients initiating therapy within one year after diagnosis. Persistence was defined by continuing medication records assessed at 3-month intervals over a 12-month follow-up. The incidence proportion, incidence rate (per person-time at risk), and prevalence of abnormal neuroimaging findings and the ARIA-proxy composite were calculated at half-year intervals. Between-group differences in time-to-event outcomes were estimated using Cox proportional hazards regression models. For all statistically significant outcomes, we calculated E-values to assess the potential impact of unmeasured confounding. The E-value represents the minimum strength of association that an unmeasured

confounder would need to have with both the exposure and the outcome to fully explain away the observed hazard ratio. E-values were calculated for both the point estimate and the confidence limit closest to the null, with larger values indicating greater robustness[15].

We conducted three sensitivity analyses to assess the robustness of findings. First, we conducted an observational analogue of a per-protocol sustained-treatment analysis, given that treatment discontinuation is common with AChEI therapy[16]. Patients were considered sustained users if they demonstrated adequate medication use during both the 0–90-day and 180–270-day intervals following treatment initiation, indicating continued therapy for at least six months. Follow-up for this analysis began on day 181. This design was intended to reduce exposure misclassification and evaluate outcomes under sustained treatment exposure, but was interpreted as conditional on treatment persistence. Second, we performed a 30-day lagged analysis excluding outcomes occurring within the first 30 days after treatment initiation, to reduce potential reverse causation and the influence of early events that may reflect baseline clinical differences rather than treatment effects. Third, we performed a fixed 1-year follow-up analysis, in which follow-up was truncated at 365 days for both treatment groups, to improve comparability of observation time and minimize bias due to differential follow-up across groups. All statistical analyses were performed using the TriNetX Analytics Platform and R software (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Population

A total of 1337 patients were included in the lecanemab cohort and 58262 in the AChEIs cohort at baseline. After propensity score matching, each cohort consisted of 589 patients. 11.1% of participants in the lecanemab group and 6.1% in the AChEI group were younger than 65 years. The participant selection flow diagram is presented in Figure 1. As shown in Table 1, all baseline demographic and clinical characteristics were balanced after matching, with standardized differences <0.1 across all covariates. Among the covariate “Mental, Behavioral and Neurodevelopmental Disorders,” the most common comorbidities in both groups were depression (40.62% in the lecanemab group vs 48.17% in the AChEI group) and anxiety (48.20% vs 49.71%, respectively).

Persistence of Lecanemab versus AChEIs

Figure 2 presents treatment persistence over time between lecanemab (n=946) and AChEIs (n=50,224). The lecanemab persistence rates were 78.0% at 3 months, 67.5% at 6 months, 62.1% at 9 months, and 53.4% at 12 months. The AChEIs persistence rates were 83.9% at 3 months, 72.0% at 6 months, 56.3% at 9 months, and 52.5% at 12 months.

Incidence and Prevalence of Abnormal Neuroimaging Findings and ARIA

The incidence proportion of abnormal neuroimaging findings (Figure 3) in the lecanemab group increased progressively from 1.3% in 2023 to 4.8% in 2024, then decreased to 3.9% in 2025. The incidence rate of abnormal neuroimaging findings in the lecanemab group rose from 2.58

cases/100 person-years in 2023 to 9.82 cases/100 person-years in 2024, then decreased to 8.45 cases/100 person-years in 2025. The prevalence of abnormal neuroimaging findings in the lecanemab group increased from 4.0% in 2023 to 17.6% in 2025. The AChEIs group showed lower incidence and prevalence of abnormal neuroimaging findings throughout the study period. The incidence proportion of abnormal neuroimaging findings in the AChEIs group ranged from 0.8% to 1.1% between 2023 and 2025. The incidence rate increased from 1.56 cases/100 person-years in 2023 to 2.32 cases/100 person-years in 2024, then decreased to 1.76 cases/100 person-years in 2025. The prevalence of abnormal neuroimaging findings in the AChEIs group rose from 4.3% in 2023 to 8.1% in 2025.

The ARIA-proxy composite events demonstrated a similar trend (eFigure 1). The incidence proportion of ARIA in the lecanemab group remained stable at 1.1% through 2024, rising thereafter to 4.1% in 2025. The incidence rate of ARIA in the lecanemab group increased from 2.30 cases/100 person-years in 2023 to 8.80 cases/100 person-years in 2025. Prevalence of ARIA in the lecanemab group rose gradually from 1.4% in 2023 to 11.5% in 2025. The AChEIs group exhibited lower ARIA incidence and prevalence throughout the study period. The incidence proportion of ARIA in the AChEIs group was 0.4% in 2023 and increased to 0.7% in 2025. The incidence rate rose from 0.77 cases/100 person-years in 2023 to 1.57 cases/100 person-years in 2025. The prevalence of ARIA in the AChEIs group gradually increased from 3.1% in 2023 to 5.5% in 2025.

The Secondary Clinical Outcomes

Figure 4 displays the adjusted hazard ratios (HRs) for behavioral symptoms, safety outcomes, healthcare utilization, and symptom-directed medications. Compared with AChEIs, lecanemab was associated with significantly lower risks of BPSD (HR, 0.52; 95% CI, 0.36–0.77; E-value: 3.26, CI lower bound 1.92), emergency visit (HR, 0.66; 95% CI, 0.51–0.85; E-value: 2.40, CI lower bound 1.63), while a nonsignificant trend toward lower risk of genitourinary infection was also observed (HR, 0.72; 95% CI, 0.51–1.02). However, lecanemab was associated with a significantly higher risk of hospitalization compared with AChEIs (HR, 1.31; 95% CI, 1.03–1.67; E-value: 1.95, CI lower bound 1.21).

For symptom-directed medication use, lecanemab was associated with significant lower risks of antipsychotics (HR, 0.47; 95% CI, 0.32–0.70; E-value: 3.66, CI lower bound 2.22), antidepressants (HR, 0.60; 95% CI, 0.43–0.85; E-value: 2.72, CI lower bound 1.63), melatonin/orexin antagonists (HR, 0.61; 95% CI, 0.42–0.88; E-value: 2.66, CI lower bound 1.53), antibiotics (HR, 0.61; 95% CI, 0.44–0.86; E-value: 2.66, CI lower bound 1.60), and antifungals (HR, 0.57; 95% CI, 0.37–0.88; E-value: 2.90, CI lower bound 1.53) than AChEIs. However, lecanemab was associated with a significantly higher risk of steroid use compared with AChEIs (HR, 2.19; 95% CI, 1.55–3.10; E-value: 3.80, CI lower bound 2.47). We conducted several sensitivity analyses to assess the robustness of our findings, with the results presented in eFigures 2–4. The overall pattern of the secondary outcomes remained consistent with the main analysis, with most results favoring lecanemab.

Discussion

To our knowledge, this is the first real-world, head-to-head target trial emulation comparing initiation of lecanemab versus AChEIs therapy on safety, behavioral, and physical outcomes. We found that the treatment persistence was generally comparable between initiating lecanemab and AChEIs, indicating that lecanemab use was feasible and sustainable in real-world clinical practice. In exploratory analyses, lecanemab initiation was associated with lower observed risks of BPSD and emergency visits, and its users required fewer psychotropic and infection-related medications compared with those receiving only AChEIs. Most significant associations demonstrated moderate to strong robustness, with E-values exceeding 2.0 for reductions in BPSD, emergency visits, antipsychotic use, antidepressant use, melatonin/orexin antagonist use, antibiotic use, and antifungal use, as well as the increased risk of steroid use, suggesting that a relatively strong unmeasured confounder would be required to fully explain these findings. In contrast, the association with hospitalization showed only marginal robustness (E-value = 1.95), indicating that this result could potentially be more susceptible to residual confounding. Overall, these findings support the relative stability of most observed associations, while highlighting hospitalization as outcomes with greater sensitivity to unmeasured confounding. We conducted several sensitivity analyses, and the results for the secondary outcomes were consistent with the main analysis, reinforcing the robustness of our findings. However, these potential benefits were weighed against the higher risks of abnormal neuroimaging findings and ARIA, hospitalization, and steroid use in this study.

We found that the treatment persistence was comparable between lecanemab and AChEIs, while the lecanemab group showed higher incidence of abnormal neuroimaging findings and ARIA-proxy composite events ; however, ARIA events are likely underestimated due to reliance on ICD-10 codes, particularly for asymptomatic cases that may not be routinely documented. In addition, we did not observe an increased risk of emergency visits among patients receiving lecanemab. In the combined Core and open-label extension populations of the lecanemab clinical trial[5, 17], the most frequently reported adverse events were infusion-related reactions (24.5%), ARIA-H (16.0%), COVID-19 infection (14.7%), ARIA-E (13.6%), and headache (10.3%). ARIA-E typically appears within 3–6 months of treatment[18]and can be asymptomatic or manifest with mild symptoms such as headache, confusion, dizziness, nausea, and vomiting. However, in rare cases, it may lead to severe outcomes including seizures, pronounced neurological deficits, significant brain edema, or life-threatening intracerebral hemorrhage[19]. An analysis of the U.S. FDA Adverse Event Reporting System (FAERS) identified 811 adverse event reports associated with lecanemab in AD patients, with a median onset of 44 days post-administration[20]. In a tertiary hospital study, ARIA occurred in 18.6% of patients, with most cases being asymptomatic, and showed no significant impact on Mini-Mental State Examination scores[21]. A retrospective observational study including 3155 patients demonstrated high short-term persistence, with 87.6% of patients remaining on therapy at four months[22]. In brief, our study showed that treatment discontinuation rates were not excessive and that emergency visit rates were approximately 34%

lower, indicating that most ARIA-related events were manageable in real-world clinical practice.

Our study extends prior RCTs by demonstrating potential benefits of lecanemab on behavioral and physical outcomes in everyday clinical settings. While RCTs have primarily focused on cognitive endpoints and amyloid reduction[5], our results showed lower risks of BPSD and emergency visits among lecanemab users. A prior systematic review and meta-analysis indicated slower cognitive decline with mAbs without differences in safety or mortality outcomes compared with AChEIs[6]. However, the impact on behavioral, psychiatric, and physical measures had not been well established. By addressing this gap, our study provides new evidence supporting the broader clinical benefits of lecanemab beyond cognition. These findings align with the hypothesized effects of amyloid clearance, including reduced neuroinflammation and preserved neural integrity[23], which may enhance behavioral and physical functioning. The potential mechanisms might be explained by lecanemab's disease-modifying effects, which reduces amyloid-β protofibrils and downstream neuroinflammation[24]. Therefore, patients may have slowing cognitive and functional decline and stabilizing emotional regulation and daily functioning—ultimately leading to fewer behavioral symptoms and reduced secondary complications.

We further observed that lecanemab users required fewer symptomatic medications, including antipsychotics, antidepressants, melatonin/orexin antagonists, antibiotics and antifungals. This reduction in medication use may reflect both improved symptom control and a lower burden of comorbid complications. The large longitudinal CATIE-AD cohort study concluded that atypical

antipsychotic use in AD patients was associated with worsening cognitive and functional decline equivalent to about a year's faster deterioration compared to placebo[25]. Benzodiazepines in older adults are consistently associated with well-documented adverse outcomes, including falls, fractures, sedation, and increased risk of pneumonia[26]. Minimizing polypharmacy is particularly important in dementia care, as excessive medication use is linked to increased risks of adverse events, falls, cognitive worsening, and mortality[27, 28]. Therefore, the favorable trend toward reduced psychotropic and symptomatic drug use supports lecanemab's potential to simplify treatment regimens and improve safety in real-world management.

Although lecanemab was associated with fewer emergency visits, it was also associated with a significantly higher risk of hospitalization compared with AChEIs (HR, 1.31). The reasons for this finding cannot be determined from our data. In community-dwelling populations with generally mild AD, hospitalization affects nearly two-thirds of patients over a median follow-up of 3 years. The leading causes of admission include syncope or falls, ischemic heart disease, gastrointestinal disease, pneumonia, and delirium[29]. A large register-based cohort study of over 70,000 patients further demonstrated that individuals with AD experience substantially higher rates of infections and infection-related hospitalizations than matched controls, likely driven by systemic inflammation, infections, delirium, and caregiver-related challenges[30]. A nationwide Finnish cohort found that recent, especially prolonged, hospitalizations markedly increased the risk of antipsychotic use in community-dwelling AD patients[31]. Moreover, a prospective cohort study highlighted that hospitalization complicated by delirium was strongly associated with adverse

outcomes, including increased risks of death, institutionalization, and accelerated cognitive decline[32]. In our study, lecanemab was associated with lower risks of BPSD and emergency visits, suggesting potential benefits in reducing some common triggers of acute care use. This discrepancy may reflect differences in the nature of admissions—while emergency visits often indicate acute or behavioral crises, hospitalizations among lecanemab-treated patients may more commonly involve planned monitoring or management of treatment-related imaging abnormalities. However, this interpretation needs to be confirmed in future studies. In addition, we observed a significantly higher risk of steroid use among patients initiating lecanemab compared with those receiving AChEIs (HR, 2.19). This finding is likely related to the management of ARIA, particularly cases presenting with symptomatic cerebral edema, where steroids are frequently used in clinical practice to mitigate neuroinflammatory responses. The increased use of steroids therefore may reflect a downstream indicator of ARIA-related clinical management rather than a direct pharmacologic effect of lecanemab itself. This result further supports the importance of close radiological and clinical monitoring during treatment initiation and early treatment phases. Overall, these findings highlight the complex interplay between treatment-related safety events, disease-related complications, and healthcare utilization, underscoring the need for proactive monitoring and individualized management in clinical practice.

Our study has several strengths. We applied a target trial emulation framework, allowing us to mimic the design of a randomized trial while using real-world data. Propensity score matching ensured comparability of baseline characteristics across treatment groups. The large sample size

enabled evaluation of both behavioral and physical outcomes, which have been underexplored in prior comparative studies. In addition, E-value analyses suggested that the observed associations would require relatively strong unmeasured confounding to be fully explained away, and three sensitivity analyses yielded results consistent with the primary findings, further supporting the robustness of our results. Nevertheless, several limitations should be acknowledged. First, we could not conduct subgroup analysis of AD and MCI, because the sample size of MCI was too small. Second, despite rigorous matching, residual confounding cannot be completely excluded. We lacked detailed clinical measures of disease stage (e.g., cognitive scores) and information on amyloid confirmation, which may have resulted in heterogeneity in disease severity and underlying pathology between groups. These differences may have contributed to variations in behavioral outcomes and use of psychoactive medications. Third, outcome assessment relied on ICD-10 codes, which may introduce misclassification bias, and ARIA detection depends on neuroimaging frequency, which may vary across healthcare settings. As a result, ARIA events are likely underestimated, particularly for asymptomatic cases that may not be routinely documented; therefore, ARIA-related findings in this study should be considered exploratory. Finally, although our results suggest potential clinical advantages of lecanemab over AChEIs, these results should be interpreted with caution, and further studies in biomarker-confirmed AD populations and head-to-head randomized trials are needed to validate these findings.

Conclusions

In real-world practice, patients receiving lecanemab therapy showed comparable persistence rate

compared with those receiving only AChEIs despite a higher incidence rate of ARIA-proxy composite events. Exploratory analyses suggested lower observed risks of BPSD and emergency visit as well as reduced use of psychotropic and infection-related medications among patients initiating lecanemab. However, its associated higher risks of hospitalization and steroid use likely reflect the proactive inpatient management required for ARIA rather than treatment failure. Although our findings suggest potential clinical advantages of lecanemab over AChEIs, these results may be influenced by residual confounding and should be interpreted with caution. Accordingly, the exploratory secondary outcomes should be regarded as hypothesis-generating rather than definitive evidence of comparative treatment effectiveness. Future studies in biomarker-confirmed Alzheimer's disease populations and head-to-head randomized trials are needed to validate these findings.

List of abbreviations

Aβ: amyloid-β; AChEIs: acetylcholinesterase inhibitors; AD: Alzheimer's disease; ARIA: amyloid-related imaging abnormalities; ARIA-E: amyloid-related imaging abnormalities – edema or effusion; ARIA-H: amyloid-related imaging abnormalities – hemorrhage; BPSD: behavioral and psychological symptoms of dementia; CATIE-AD: Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Disease; CI: confidence interval; COVID-19: coronavirus disease 2019; EHR: electronic health record; FDA: U.S. Food and Drug Administration; FAERS: Food and Drug Administration Adverse Event Reporting System; HR: hazard ratio; ICD-10-CM: International

Classification of Diseases, Tenth Revision, Clinical Modification; IQR: interquartile range; KMUHIRB: Kaohsiung Medical University Hospital Institutional Review Board; mAbs: monoclonal antibodies; MCI: mild cognitive impairment; RCT: randomized controlled trial; SD: standard deviation; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TARGET: Transparent Reporting of Observational Studies Emulating a Target Trial.

Declarations

Ethics approval and consent to participate

This study was approved by the Kaohsiung Medical University Hospital Institutional Review Board (KMUHIRB-E(I)-20250199). The requirement for informed consent was waived because the study used deidentified electronic health record data from the TriNetX network.

Consent for publication

Not applicable. The manuscript contains no individual person's data in any form.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CYL and CWH designed the study and performed data acquisition and analysis. PTT, YYF, and YHL contributed to data interpretation and methodological supervision. YCK and FCY supported statistical analysis and data visualization. BS, TT, and AFC assisted with manuscript editing and provided final approval of the submitted manuscript. CSL and TWH provided overall study supervision, critically revised the manuscript, and served as corresponding authors. All authors read and approved the final manuscript.

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Not applicable.

Figures title and legends

Figure 1

Title: Participant selection flow diagram

Legend: This figure illustrates the selection process of participants included in the analysis, beginning with all eligible individuals and applying predefined inclusion and exclusion criteria to identify the final study cohorts for lecanemab and acetylcholinesterase inhibitor treatment.

Abbreviations: AD, Alzheimer's disease; AChEI, acetylcholinesterase inhibitor; MCI, mild cognitive impairment

Figure 2

Title: Persistence of lecanemab versus acetylcholinesterase inhibitors in real-world practice

Legend: The figure presents treatment persistence over time among patients receiving lecanemab compared with those treated with acetylcholinesterase inhibitors in real-world clinical settings.

Abbreviations: AChEI, acetylcholinesterase inhibitor.

Figure 3

Title: Abnormal neuroimaging findings over time in real-world practice: lecanemab versus AChEIs

Legend: This figure compares the longitudinal occurrence of abnormal neuroimaging findings among patients treated with lecanemab and those receiving acetylcholinesterase inhibitors.

Abbreviations: AChEI, acetylcholinesterase inhibitor.

Figure 4

Title: Adjusted hazard ratios for behavioral symptoms, safety outcomes, healthcare utilization, and symptom-directed medications

Legend: This figure displays the adjusted hazard ratios for (A) behavioral and psychological symptoms of dementia, major safety outcomes, and healthcare utilization, and for (B) the use of symptom-directed medications among patients treated with lecanemab versus acetylcholinesterase inhibitors. Abbreviations: AChEI, acetylcholinesterase inhibitor; CI, confidence interval; Events_A, number of events in the acetylcholinesterase inhibitor group; Events_L, number of events in the lecanemab group; GU, genitourinary; HR, hazard ratio; LmAB, lecanemab; Total_A, total number in the acetylcholinesterase inhibitor group; Total_L, total number in the lecanemab group.

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Table 1. Basic characteristics of the Study Population

Characteristics, n (%)	Cohort 1 (n=1337)	Cohort 2 (n=58262)	SMD [a] before matching	Cohort 1 (n=589) after matching	Cohort 2 (n=589) after matching	SMD [a] after matching
Age at index, mean	72.01	76.25	0.5313	72.56	72.46	0.0116
White	1206 (90%)	45945 (79%)	0.3176	533 (90%)	530 (90%)	0.0172
Not Hispanic or Latino	1159 (87%)	43406 (75%)	0.3118	504 (86%)	500 (85%)	0.0191
Asian	27 (2%)	2359 (4%)	0.1185	12 (2%)	15 (3%)	0.0340
Black or African American	22 (2%)	5325 (9%)	0.3365	12 (2%)	12 (2%)	0.0000
Female	736 (55%)	34957 (60%)	0.1059	316 (54%)	307 (52%)	0.0306
Male	601 (45%)	23305 (40%)	0.1048	273 (46%)	282 (48%)	0.0272
Diseases of the nervous system	1327 (99%)	37429 (64%)	1.0167	583 (99%)	583 (99%)	0.0000
Mild neurocognitive disorder due to known physiological condition	138 (10%)	316 (1%)	0.4419	49 (8%)	44 (7%)	0.0315
Mental, behavioral and neurodevelopmental disorders	1241 (93%)	31849 (55%)	0.9622	532 (90%)	539 (92%)	0.0414
Mental disorders due to known physiological conditions	1199 (90%)	21087 (36%)	1.3299	505 (86%)	515 (87%)	0.0498
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	354 (26%)	11882 (20%)	0.1440	140 (24%)	123 (21%)	0.0694
Mood [33] disorders	307 (23%)	12367 (21%)	0.0418	126 (21%)	111 (19%)	0.0636
Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	10 (1%)	999 (2%)	0.0877	10 (2%)	10 (2%)	0.0000
Mental and behavioral disorders due to psychoactive substance use	47 (4%)	3056 (5%)	0.0846	24 (4%)	32 (5%)	0.0639
Behavioral syndromes associated with physiological disturbances and physical factors	46 (3%)	1647 (3%)	0.0352	20 (3%)	21 (4%)	0.0093
Diseases of the circulatory system	754 (56%)	34645 (60%)	0.0622	344 (58%)	355 (60%)	0.0380
Endocrine, nutritional and metabolic diseases	773 (58%)	35211 (60%)	0.0533	331 (56%)	335 (57%)	0.0137
Diseases of the musculoskeletal system and connective tissue	558 (42%)	27054 (46%)	0.0949	233 (40%)	214 (36%)	0.0665
Diseases of the genitourinary system	338 (25%)	19638 (34%)	0.1856	148 (25%)	159 (27%)	0.0426
Diseases of the digestive system	344 (26%)	18157 (31%)	0.1207	143 (24%)	141 (24%)	0.0080
Diseases of the respiratory system	255 (19%)	13711 (24%)	0.1091	120 (20%)	107 (18%)	0.0560
Certain infectious and parasitic diseases	155 (12%)	7828 (13%)	0.0557	68 (12%)	70 (12%)	0.0106
Diseases of the blood and blood-forming organs and certain disorders involving the immune	151 (11%)	10306 (18%)	0.1824	63 (11%)	73 (12%)	0.0531

mechanism						
Neoplasms	267 (20%)	10512 (18%)	0.0491	119 (20%)	109 (19%)	0.0430
Injury, poisoning and certain other consequences of external causes	210 (16%)	11875 (20%)	0.1218	100 (17%)	106 (18%)	0.0268
Diseases of the eye and adnexa	201 (15%)	8451 (15%)	0.0149	92 (16%)	94 (16%)	0.0093
Diseases of the ear and mastoid process	197 (15%)	7824 (13%)	0.0375	75 (13%)	68 (12%)	0.0364
Diseases of the skin and subcutaneous tissue	232 (17%)	10175 (17%)	0.0030	99 (17%)	80 (14%)	0.0900
Congenital malformations, deformations, chromosomal abnormalities, and genetic disorders	32 (2%)	1396 (2%)	0.0002	16 (3%)	16 (3%)	0.0000
Factors influencing health status and contact with health services	883 (66%)	35899 (62%)	0.0922	375 (64%)	387 (66%)	0.0426
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	27 (2%)	1417 (3%)	0.0280	14 (2%)	16 (3%)	0.0216
Central nervous system medications	1077 (81%)	32884 (56%)	0.5375	331 (56%)	329 (56%)	0.0068
Central nervous system medications, other	858 (64%)	7745 (13%)	1.2247	114 (19%)	107 (18%)	0.0304
Antidepressants	511 (38%)	16014 (27%)	0.2300	168 (29%)	150 (25%)	0.0689
Antidepressants, other	504 (38%)	15488 (27%)	0.2397	166 (28%)	150 (25%)	0.0613
Antipsychotics	56 (4%)	4060 (7%)	0.1214	25 (4%)	35 (6%)	0.0773
Anticonvulsants	114 (9%)	6167 (11%)	0.0701	40 (7%)	38 (6%)	0.0137
Sedatives/Hypnotics	234 (18%)	9831 (17%)	0.0166	89 (15%)	89 (15%)	0.0000
Lithium salts	10 (1%)	83 (0.1%)	0.0910	10 (2%)	10 (2%)	0.0000
Cardiovascular medications	649 (48%)	31843 (55%)	0.1226	251 (43%)	241 (41%)	0.0344
Anticoagulants	64 (5%)	8853 (15%)	0.3524	22 (4%)	16 (3%)	0.0577
Antiparkinson agents	14 (1%)	2290 (4%)	0.1859	10 (2%)	10 (2%)	0.0000
Antineoplastics	32 (2%)	1792 (3%)	0.0418	12 (2%)	10 (2%)	0.0251
Antimicrobials	364 (27%)	18069 (31%)	0.0835	146 (25%)	147 (25%)	0.0040
Analgesics	311 (23%)	18234 (31%)	0.1812	116 (20%)	122 (21%)	0.0254
Anesthetics	264 (20%)	10762 (18%)	0.0324	103 (17%)	85 (14%)	0.0835
Genitourinary medications	343 (26%)	14289 (25%)	0.0260	138 (23%)	122 (21%)	0.0655
Gastrointestinal medications	364 (27%)	20348 (35%)	0.1670	133 (23%)	129 (22%)	0.0163
Respiratory tract medications	383 (29%)	19468 (33%)	0.1032	162 (28%)	147 (25%)	0.0580
Hormones/Synthetics/Modifiers	502 (38%)	23526 (40%)	0.0581	202 (34%)	194 (33%)	0.0288
Immunological agents	410 (31%)	20364 (35%)	0.0914	192 (33%)	187 (32%)	0.0182
Musculoskeletal medications	228 (17%)	11540 (20%)	0.0711	95 (16%)	85 (14%)	0.0472
Pharmaceutical aids/reagents	232 (17%)	13949	0.1633	90 (15%)	91 (15%)	0.0047

		(24%)				
Autonomic medications	185 (14%)	6906 (12%)	0.0593	67 (11%)	67 (11%)	0.0000
Rectal, local	139 (10%)	8050 (14%)	0.1050	63 (11%)	72 (12%)	0.0480
Vitamins	184 (14%)	9511 (16%)	0.0717	59 (10%)	49 (8%)	0.0589
Blood products/modifiers/volume expanders	146 (11%)	12974 (22%)	0.3087	47 (8%)	45 (8%)	0.0127
Otic agents	68 (5%)	4005 (7%)	0.0755	24 (4%)	21 (4%)	0.0266
Central nervous system stimulants	25 (2%)	896 (2%)	0.0257	10 (2%)	10 (2%)	0.0000
Antivertigo agents	25 (2%)	1382 (2%)	0.0349	10 (2%)	12 (2%)	0.0251
Antihemorrhagics	20 (2%)	796 (1%)	0.0109	10 (2%)	10 (2%)	0.0000
Donepezil	661 (49%)	0 (0%)	1.3984	0 (0%) [b]	0 (0%)	0.0000
Rivastigmine	110 (8%)	0 (0%)	0.4234	0 (0%) [b]	0 (0%)	0.0000
Galantamine	36(3%)	0 (0%)	0.2352	0 (0%) [b]	0 (0%)	0.0000
Memantine	243 (18%)	3376 (6%)	0.3883	84 (14%)	80 (14%)	0.0196
Prior hospitalization	274 (20%)	9574 (16%)	0.1048	125 (21%)	133 (23%)	0.0328
Prior emergency visit	141 (11%)	11730 (20%)	0.2684	61 (10%)	65 (11%)	0.0220

Values are presented as n (%) unless otherwise indicated

[a] SMD: standardized mean difference; A standardized mean difference <0.1 was considered indicative of adequate balance

[b] Individuals with prior AChEI exposure before cohort entry were excluded from the lecanemab cohort.

Graphical Abstract

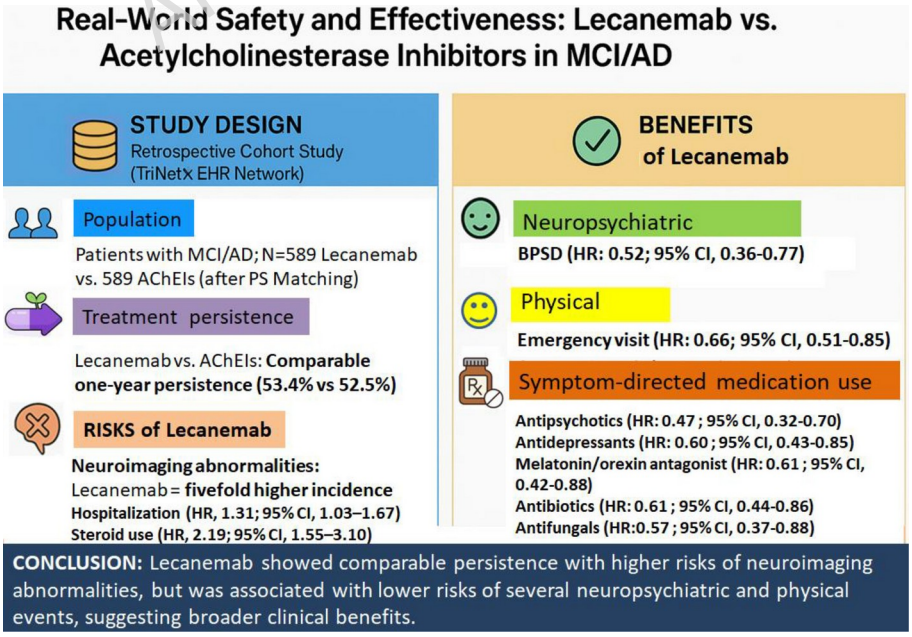


Figure 1

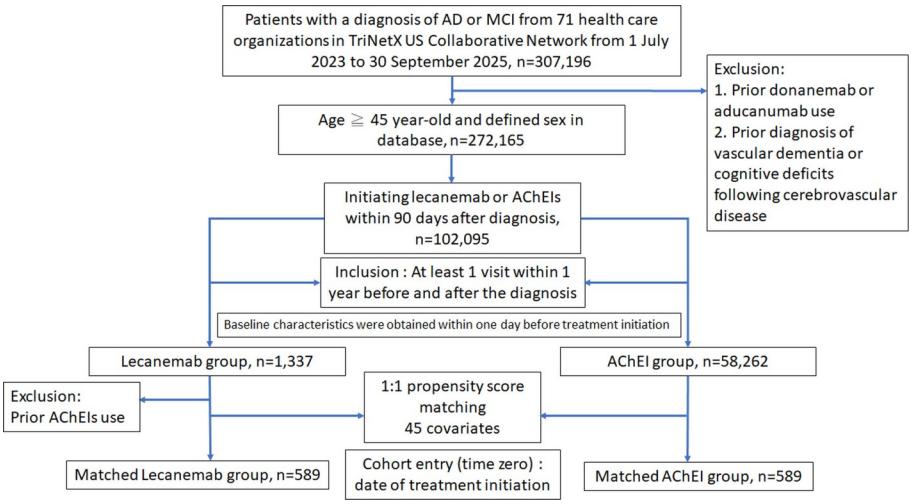


Figure 2

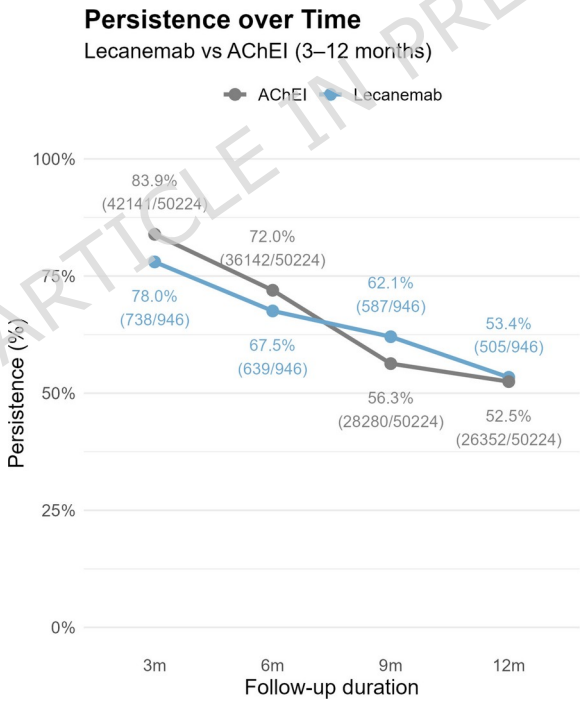
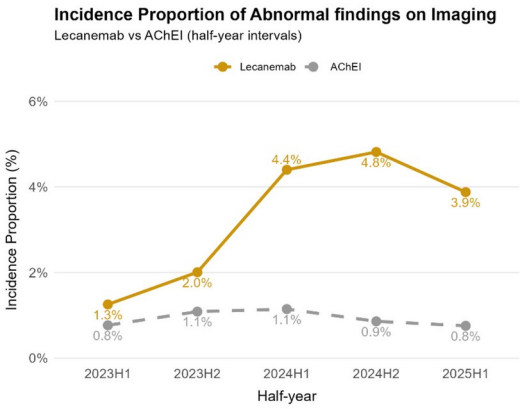
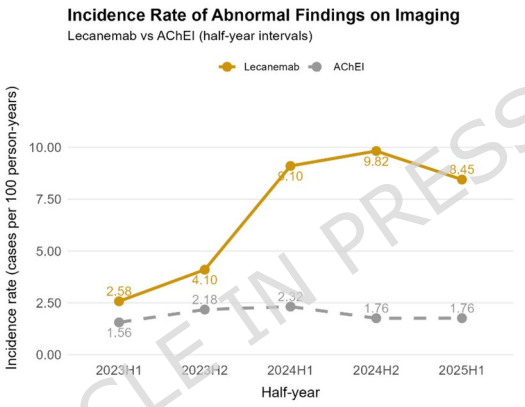


Figure 3

(A)



(B)



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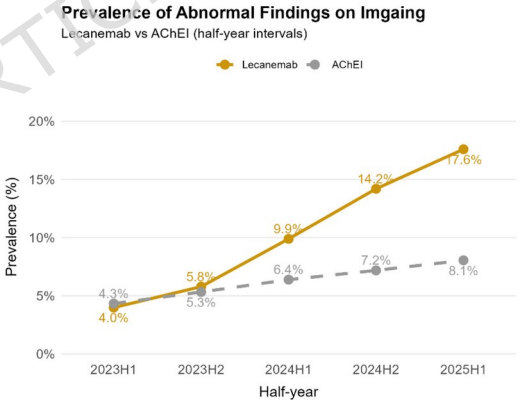
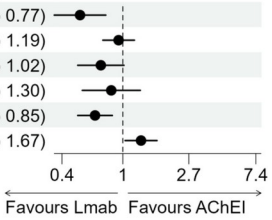


Figure 4

(A)

	LmAB		AChEI		
Outcome	**Total_L**	**Events_L**	**Total_A**	**Events_A**	**HR (95% CI)**
BPSD	445	39	397	77	0.52 (0.36 to 0.77)
Anxiety Disorder	579	126	579	152	0.94 (0.74 to 1.19)
GU Infection	579	52	579	86	0.72 (0.51 to 1.02)
Pulmonary Infection	579	34	579	52	0.84 (0.54 to 1.30)
Emergency	579	90	579	162	0.66 (0.51 to 0.85)
Hospitalization	579	142	579	129	1.31 (1.03 to 1.67)



(B)

	LmAB		AChEI		
Outcome	**Total_L**	**Events_L**	**Total_A**	**Events_A**	**HR (95% CI)**
Antipsychotics	478	34	462	83	0.47 (0.32 to 0.70)
Antidepressants	321	50	316	95	0.60 (0.43 to 0.85)
Benzodiazepines	589	92	589	131	0.80 (0.61 to 1.04)
Melatonin/Orexin Antagonists	589	43	589	86	0.61 (0.42 to 0.88)
Steroids	275	70	392	66	2.19 (1.55 to 3.10)
Antibiotics	589	53	589	102	0.61 (0.44 to 0.86)
Antifungals	589	32	589	62	0.57 (0.37 to 0.88)
Anti-inflammatory Drugs	589	84	589	132	0.76 (0.58 to 1.00)