3. Efficacy and Safety of Recently Approved Anti-Amyloid Monoclonal Antibodies in Early Alzheimer's Disease: A Systematic Review and Meta-Analysis

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Background: Alzheimer's disease (AD) is the leading cause of dementia worldwide and affects over 55 million people. Lecanemab and donanemab are anti-amyloid monoclonal antibodies that flag the abnormal amyloid-beta plaques for removal by the immune system. Recent phase 3 trials have demonstrated significant slowing of clinical decline. However, the magnitude of clinical benefit, comparative efficacy across cognitive and functional domains, and the safety profile including the incidence of amyloid-related imaging abnormalities (ARIA) require pooled quantitative synthesis. **Objective:** To quantitatively synthesise the efficacy and safety of lecanemab and donanemab against placebo in patients with early AD, with a focus on cognitive outcomes, amyloid clearance, and ARIA incidence. **Methods:** A systematic search of reputable electronic databases was conducted with predefined keywords: "Alzheimer disease", "dementia", "lecanemab", "donanemab", "anti-amyloid antibody", "CDR-SB", "ARIA". All searches were conducted on January 5, 2026 and ranged from inception of databases to January 2026. Eligible studies included RCTs involving adults with early AD receiving lecanemab or donanemab versus placebo. Primary outcomes focused on changes in CDR-SB score and ARIA incidence. Secondary outcomes included amyloid PET clearance and performance on cognitive subscales (ADAS-Cog). Risk of bias was assessed using the Cochrane RoB 2.0 tool and demonstrated a low risk of bias across all five methodological domains. **Results:** Our systematic review and meta-analysis included the two Phase 3 trials (CLARITY AD with lecanemab and TRAILBLAZER-ALZ 2 with donanemab) involving a total of 3531 participants with early Alzheimer's disease. Anti-amyloid monoclonal antibodies consistently showed clinical decline when compared to placebo over the span of 18 months. In CLARITY AD (n=1795), lecanemab reduced CDR-SB worsening by 0.45 points, parallel to a 27% slowing of decline. Secondary outcomes showed similar benefits, such as a 1.44 -point advantage on ADAS-Cog14 and improved daily functioning on ADCS-MCI-ADL (+2.0 points). In TRAILBLAZER-ALZ 2 (n=1736), donanemab produced comparable effects. The drug slowed iADRS decline by 3.25 points (35.1% slowing) and CDR-SB progression by 0.67 points (36% slowing), among patients with low to medium tau pathology. Benefits were somewhat similar in the overall population. Both agents achieved substantial amyloid plaque reduction on PET imaging: lecanemab lowered levels by 59.12 centiloids, lowering the mean post-treatment burden below the positivity threshold, while donanemab reduced centiloids by approximately 87-88 and produced amyloid clearance in 76-80% of treated patients. Safety findings showed increased amyloid-related imaging abnormalities. ARIA-E occurred in 12.6% (lecanemab) and 24% (donanemab) of treated patients versus roughly 2% on placebo. ARIA-H rates were similarly elevated. APOE ε4 carriers faced a significantly higher ARIA risk. **Conclusion:** In patients with early Alzheimer's disease, lecanemab and donanemab moderately slow cognitive and functional decline while producing strong amyloid clearance. These benefits come at the cost of significantly elevated ARIA risk, especially among APOE ε4 carriers. These therapies represent a meaningful first step in disease modification, yet their modest clinical effects highlight the need for longer-term data and better strategies to identify those most likely to benefit.

Key Words: Alzheimer's disease, Immunotherapy, Amyloid beta peptides, cognitive dysfunction, drug-related side effects

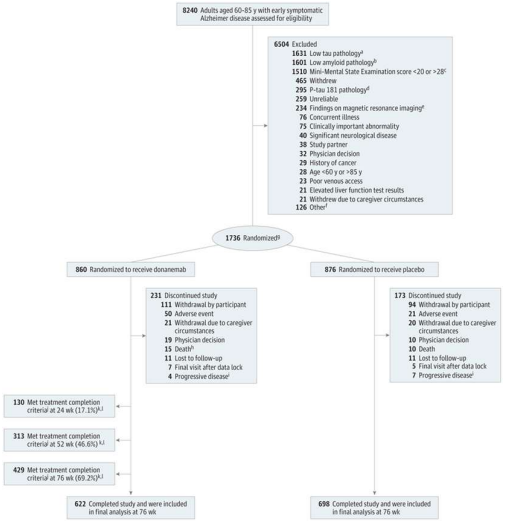

Figure 1. Participant Flow in a Trial of Donanemab for Early Symptomatic Alzheimer Disease

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