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Anti-Amyloid Therapies in Alzheimer's Disease: Current Evidence, Clinical Controversies, and the Path Forward

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ABS TRAC T

Alzheimer's disease (AD) is the leading cause of dementia globally, affecting over 55 million individuals, and represents one of the most significant unmet medical needs of our time. After more than two decades of clinical trial failures targeting the amyloid cascade hypothesis, the field has witnessed the first validated disease-modifying treatments in the form of anti-amyloid monoclonal antibodies — lecanemab (Leqembi) and donanemab (Kisunla) — whose approval by regulatory agencies marks a pivotal transition from purely symptomatic management to genuine biological intervention. The amyloid cascade hypothesis, first proposed by Hardy and Higgins in 1992, posits that the accumulation of amyloid-beta (Aβ) peptides — as soluble oligomers, protofibrils, and insoluble plaques — is the central initiating event in AD pathogenesis, driving downstream tau neurofibrillary tangle formation, neuroinflammation, synaptic loss, and neurodegeneration. Anti-amyloid monoclonal antibodies target various Aβ species with differing specificities: lecanemab preferentially binds soluble Aβ protofibrils, while donanemab targets the pyroglutamate-modified Aβ (N3pE) incorporated into established plaques. In the pivotal CLARITY AD trial, lecanemab reduced clinical decline (CDR-SB) by 27% relative to placebo over 18 months in early AD patients with confirmed amyloid pathology. TRAILBLAZER-ALZ 2 demonstrated donanemab reduced clinical decline by 35% in the low-to-medium tau subgroup. Both agents achieve near-complete amyloid clearance on PET imaging, but at the cost of amyloid-related imaging abnormalities (ARIA) — comprising cerebral oedema (ARIA-E) and microhaemorrhages (ARIA-H) — in a significant proportion of treated patients, with higher rates in APOE ε4 carriers. The accelerated approval of aducanumab in 2021 based solely on amyloid clearance as a surrogate endpoint without a consistent clinical benefit signal generated intense regulatory and scientific controversy, ultimately resulting in its market withdrawal. This review comprehensively examines the biological rationale for amyloid targeting, the molecular mechanisms and clinical profiles of approved and investigational anti-amyloid agents, the interpretation of clinical trial evidence, the ARIA safety framework, the ongoing scientific controversies surrounding the amyloid hypothesis and disease-modification validity, the challenges of translating trial efficacy to real-world practice, and the future direction of combination disease-modifying strategies in AD.

Keywords: *Alzheimer's Disease, Amyloid Cascade Hypothesis, Lecanemab, Donanemab; Aducanumab, Amyloid-Beta, Tau, ARIA, APOE ε4, CLARITY AD, TRAILBLAZER-ALZ 2, Disease Modification, Anti-Amyloid Antibody, Neurodegeneration, Dementia.*

1. INTRODUCTION

Alzheimer's disease (AD), the most prevalent form of dementia globally, afflicts over 55 million individuals worldwide, a figure projected to reach 139 million by 2050 as populations age [1]. The disease is characterised by progressive and irreversible decline in memory, language, executive function, and activities of daily living, with a clinical course spanning years to decades from the onset of pathological changes in the brain to the terminal stages of profound cognitive and functional dependency. Beyond the immeasurable personal and family burden, AD imposes an estimated global economic cost exceeding USD 1.3 trillion annually, rendering it one of the most consequential

chronic diseases of our era by virtually any metric of human and economic impact.

For the majority of the past three decades, pharmacological management of AD was confined to symptomatic agents — cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the N-methyl-D-aspartate receptor antagonist memantine — that modestly ameliorate cognitive symptoms without altering the underlying disease process [2]. This therapeutic landscape reflected both the incomplete understanding of AD pathophysiology and the extraordinary difficulty of translating mechanistic insights into effective human therapies, as evidenced by over 200 failed clinical trials between 1998 and 2021. The approval of lecanemab by the US Food and Drug Administration (FDA) in January 2022 under accelerated approval, subsequently converted to full traditional approval in July 2022, and the approval of donanemab in July 2023, mark what many in the field regard as the dawn of the disease-modifying era in Alzheimer's therapeutics — though significant controversy surrounds the magnitude of clinical benefit, the appropriate patient population, and the risk-benefit calculus in routine clinical practice.

This narrative review provides a comprehensive examination of the biological foundations of amyloid targeting in AD, the molecular mechanisms and clinical evidence for anti-amyloid monoclonal antibodies, an in-depth analysis of ARIA safety and management, the ongoing scientific controversies surrounding both the amyloid hypothesis and the clinical significance of achieved treatment effects, the challenges of real-world implementation, and the evolving landscape of combination disease-modifying strategies that may define AD therapeutics in the coming decade.

2. THE AMYLOID CASCADE HYPOTHESIS — BIOLOGICAL FOUNDATIONS

2.1 Amyloid Precursor Protein Processing and Aβ Generation

Amyloid-beta (Aβ) peptides are generated through the sequential proteolytic cleavage of the type I transmembrane amyloid precursor protein (APP) by two aspartyl proteases: beta-site APP-cleaving enzyme 1 (BACE1, beta-secretase) and the gamma-secretase complex — a multiprotein intramembrane protease comprising presenilin-1 or presenilin-2, nicastrin, APH-1, and PEN-2 [3]. Beta-secretase cleavage of APP generates a soluble ectodomain (sAPPβ) and a membrane-retained C99 fragment; gamma-secretase then cleaves C99 within the transmembrane domain to release Aβ peptides of variable length — predominantly Aβ40 (the most abundant species, constituting ~80–90% of secreted Aβ) and the more amyloidogenic Aβ42, which has a greater propensity for aggregation due to its additional hydrophobic C-terminal residues. In the non-amyloidogenic pathway, alpha-secretase cleaves APP within the Aβ domain, precluding Aβ generation and releasing neuroprotective sAPPα.

2.2 Aβ Aggregation Hierarchy and Neurotoxic Species

Aβ monomers exist in equilibrium with higher-order aggregates, progressing through a nucleation-dependent polymerisation process to form soluble oligomers, protofibrils, and ultimately insoluble amyloid fibrils that deposit as neuritic plaques [4]. The relative neurotoxicity of different Aβ species has been the subject of intensive investigation and persisting debate. The prevailing contemporary view holds that soluble oligomers and protofibrils — rather than insoluble plaques themselves — are the principal mediators of synaptic toxicity, dendritic spine loss, tau hyperphosphorylation, and neuronal death, based on evidence from experimental models and post-mortem human studies demonstrating that plaque burden correlates poorly with cognitive decline, while soluble Aβ levels show stronger associations. Pyroglutamate-modified Aβ (Aβ-pE3 or N3pE), arising from the post-translational cyclisation of the N-terminal glutamate of Aβ3-x peptides, exhibits enhanced aggregation propensity, resistance to proteolytic degradation, and seeding activity that may promote amyloid propagation — properties that informed the design of pyroglutamate-targeting antibodies including donanemab.

2.3 From Genetics to the Amyloid Cascade — Supporting Evidence

The amyloid cascade hypothesis, originally formulated by Hardy and Higgins in 1992 and later refined as the 'amyloid cascade hypothesis' by Hardy and Selkoe, receives its strongest support from human genetic data [5]. All three autosomal dominant mutations causing familial AD — in the APP gene on chromosome 21, presenilin-1 (PSEN1) on chromosome 14, and presenilin-2 (PSEN2) on chromosome 1 — increase either total Aβ production or the Aβ42:Aβ40 ratio, placing Aβ overproduction upstream of all other pathological changes. Individuals with Down syndrome (trisomy 21), who carry three copies of the APP gene, invariably develop AD pathology by their fourth decade. Conversely, an APP coding variant (A673T) that reduces BACE1 cleavage by approximately 40% is associated with protection against AD and cognitive decline in Icelandic population studies. The APOE ε4 allele — the strongest common genetic risk factor for late-onset AD — promotes Aβ aggregation and impairs Aβ clearance from the brain, further implicating Aβ metabolism as central to disease susceptibility [6].

2.4 Tau — The Downstream Executioner

While Aβ accumulation is considered the initiating event in the amyloid cascade, the downstream pathological consequences — particularly the formation of tau neurofibrillary tangles — are more directly correlated with neurodegeneration and cognitive decline

in established AD. Tau is a microtubule-associated protein whose hyperphosphorylation in AD leads to its detachment from microtubules, aggregation into paired helical filaments, and eventual deposition as neurofibrillary tangles (NFTs) [7]. The spatial progression of tau pathology — from the transentorhinal cortex and hippocampus (Braak stages I–II) through limbic structures to neocortex (stages V–VI) — follows a predictable anatomical pattern that correlates closely with the sequential loss of episodic memory, then semantic memory and language, and finally executive function and visuospatial abilities. Anti-amyloid therapies that reduce Aβ burden have been shown in clinical trials to secondarily slow tau accumulation as measured by tau PET imaging, providing in vivo human evidence for the mechanistic link between Aβ and tau — a critical validation of the cascade model.

3. THE BIOMARKER FRAMEWORK FOR CLINICAL TRIAL DESIGN AND PATIENT SELECTION

3.1 The ATN Framework

The biological definition of AD, independent of clinical symptoms, is now operationalised through the ATN (Amyloid / Tau / Neurodegeneration) biomarker framework proposed by Jack *et al*., in 2018 [8]. Within this framework, A refers to amyloid pathology (detected by amyloid PET imaging or reduced CSF Aβ42, or elevated CSF Aβ42/40 ratio or plasma Aβ42/40); T refers to tau pathology (elevated CSF phospho-tau-181 or tau PET evidence of neurofibrillary tangles); and N refers to neurodegeneration markers (CSF total tau, FDG-PET hypometabolism, or structural MRI atrophy). An individual is biologically classified as having AD only when both A and T are positive (A+T+), irrespective of clinical syndrome — a conceptual shift from the historical clinicopathological model that equated AD with dementia diagnosis.

3.2 Amyloid PET and Fluid Biomarkers

The clinical development of anti-amyloid therapies has been enabled by amyloid PET imaging — using radiotracers including florbetapir, florbetaben, and flutemetamol — which allows in vivo quantification of cortical amyloid burden in standardised centiloid units, enabling prospective confirmation of amyloid positivity for trial eligibility and serial assessment of amyloid clearance as a pharmacodynamic biomarker [9]. Cerebrospinal fluid (CSF) biomarkers — specifically the Aβ42/40 ratio (reduced in AD due to amyloid plaque sequestration of Aβ42), phospho-tau-181, and total tau — provide an alternative, widely accessible method for amyloid and tau pathology confirmation, particularly relevant in settings where PET is unavailable or cost-prohibitive. Plasma biomarkers for AD have undergone rapid development and validation, with plasma phospho-tau-217 (p-tau217) emerging as a highly accurate biomarker of amyloid and tau pathology with area under the ROC curve exceeding 0.90 for distinguishing amyloid-positive from amyloid-negative individuals, potentially enabling cost-effective population screening to identify candidates for anti-amyloid therapy without mandatory PET imaging.

3.3 The Preclinical-to-Clinical Disease Continuum

AD pathological changes — particularly amyloid deposition — precede the onset of clinical symptoms by 15–20 years, establishing a prolonged preclinical phase during which intervention may prevent or delay cognitive decline. Current anti-amyloid therapies have demonstrated benefit exclusively in the early symptomatic phase — mild cognitive impairment due to AD and mild AD dementia — where amyloid burden remains sufficient to drive ongoing pathological change but neuronal loss has not yet rendered the brain unresponsive to amyloid clearance [10]. The A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer's) trial evaluated solanezumab in cognitively unimpaired individuals with elevated amyloid PET, and its negative results — published in 2023 — dampened enthusiasm for very early amyloid targeting, though the agent's limited efficacy on soluble amyloid may have confounded interpretation. The AHEAD 3-45 trial evaluating lecanemab in preclinical AD is ongoing and represents the most definitive test of whether earlier intervention produces greater and more durable clinical benefit.

4. ANTI-AMYLOID MONOCLONAL ANTIBODIES — MECHANISMS AND CLINICAL EVIDENCE

A summary of major anti-amyloid monoclonal antibody trials is presented in Table 1.

Table 1: Summary of Major Anti-Amyloid Monoclonal Antibody Clinical Trials

Agent	Mechanism	Trial (Phase)	n	Population	Primary Outcome (CDR-SB change)	Amyloid Clearance	ARIA-E (%)
Solanezumab	Soluble Aβ monomers	EXPEDITION3 (Phase III)	2,100	Mild AD	No significant benefit (p=0.10)	Minimal	<1%
Bapineuzumab	N-terminal Aβ (aggregated)	Phase III (2 trials)	4,365	Mild-moderate	No significant	Partial	15–17%

				AD	benefit; Trials discontinued		
Gantenerumab	Fibrillar Aβ (plaques)	GRADUATE I/II (Phase III)	1,965	Early AD	No significant benefit; Trials discontinued	Near-complete	24–25%
Aducanumab	Aggregated Aβ (oligomers + plaques)	EMERGE + ENGAGE (Phase III)	3,285	Early AD (MCI/mild)	EMERGE: –22% CDR-SB (p=0.01); ENGAGE: NS; Controversial FDA approval (2021)	Near-complete	35–41%
Lecanemab (LEQEMBI®)	Soluble Aβ protofibrils (all species)	CLARITY AD (Phase III)	1,795	Early AD (MCI/mild) Confirmed amyloid	–27% CDR-SB decline vs placebo (p<0.001) Δ0.45 points	Near-complete (59.1→29.0 centiloids)	12.6%
Donanemab (KISUNLA®)	N3pE Aβ (pyroglutamate; plaques)	TRAILBLAZER - ALZ 2 (Phase III)	1,736	Early symptomatic AD; confirmed amyloid + tau	–35% CDR-SB decline vs placebo (p<0.001) (Low/med tau group)	Near-complete; discontinuation protocol	24.0%
Remternetug	Pyroglutamate Aβ plaques	Phase II/III (ongoing)	~1,600 (est.)	Early AD	Ongoing; rapid amyloid clearance observed	Near-complete (rapid)	~22% (est.)
ARIA-E = Amyloid-Related Imaging Abnormality — Edema/Effusions; CDR-SB = Clinical Dementia Rating sum of boxes; NS = not significant; MCI = mild cognitive impairment; Centiloids = standardised amyloid PET unit; AD = Alzheimer's disease							

4.1 The Era of Negative Trials — Lessons from the Past

4.1.1 Bapineuzumab

Bapineuzumab, a humanised anti-Aβ IgG1 monoclonal antibody targeting the N-terminal region of Aβ with affinity for both fibrillar and oligomeric species, was among the first anti-amyloid antibodies to enter large-scale Phase III evaluation. Two parallel Phase III trials enrolling over 4,000 patients with mild-to-moderate AD — stratified by APOE ε4 carrier status — demonstrated no significant benefit on the co-primary endpoints of cognition (ADAS-cog11) or function (DAD) in either the APOE ε4 carrier or non-carrier populations [11]. Bapineuzumab produced meaningful amyloid PET reductions and elevated CSF Aβ42 levels, confirming biological target engagement, but failed to translate amyloid reduction into clinical benefit. A high rate of vasogenic oedema (ARIA-E) — particularly in APOE ε4 carriers at rates of 15–17% — limited dose escalation and may have precluded achieving the amyloid clearance levels subsequently shown to be necessary for clinical efficacy in later trials.

4.1.2 Solanezumab

Solanezumab, which preferentially binds soluble Aβ monomers (specifically the mid-domain of Aβ), was developed based on the hypothesis that capturing soluble monomeric Aβ in the periphery and CSF — the 'peripheral sink' hypothesis — would shift the equilibrium of Aβ species away from aggregated, plaque-bound forms [12]. Three large Phase III trials (EXPEDITION 1, 2, and 3) in mild-to-moderate AD patients failed to demonstrate significant benefit on clinical endpoints, with EXPEDITION 3 — the largest and most rigorously powered — showing a non-significant trend toward slowing decline (p=0.10) in mild AD. A post-hoc analysis suggested a possible benefit in amyloid-confirmed patients, which provided the rationale for the subsequently failed A4 trial in preclinical disease. The solanezumab experience highlighted the critical importance of: (1) targeting the correct Aβ species, (2) treating at an earlier disease stage, and (3) achieving sufficient amyloid clearance as a prerequisite for clinical benefit.

4.1.3 Gantenerumab

Gantenerumab, a fully human anti-Aβ IgG1 antibody with high affinity for fibrillar Aβ and plaque-enriched species, was designed to achieve more potent amyloid clearance than prior agents through Fc receptor-mediated microglial phagocytosis. Despite demonstrating near-complete amyloid clearance on PET imaging at high doses in the open-label SCarlet RoAD extension and in Phase II studies, the two pivotal Phase III trials — GRADUATE I and GRADUATE II — enrolling a combined 1,965 patients with early AD failed to demonstrate significant cognitive benefit, with 24–25% ARIA-E rates at therapeutic doses [13]. The GRADUATE trials results were particularly challenging for the field's understanding of the amyloid hypothesis, as they demonstrated that robust plaque clearance alone is insufficient for clinical benefit — raising the possibility that co-existing tau burden, concomitant pathologies, or a missed therapeutic window may limit responsiveness to amyloid removal.

4.2 Aducanumab — A Cautionary Regulatory Episode

Aducanumab (Aduhelm, Biogen/Eisai) — a human IgG1 antibody that binds aggregated Aβ including oligomers and fibrils with greater affinity than monomers — generated the most contentious regulatory episode in the history of modern neuroscience. Its Phase III programme comprised two identically designed trials, EMERGE and ENGAGE, which were discontinued in March 2019 following a futility analysis predicting failure [14]. Upon re-analysis of a larger post-futility dataset by Biogen, EMERGE showed a 22% reduction in CDR-SB decline ($p=0.01$) at the high dose (10 mg/kg), while ENGAGE did not reach statistical significance. In June 2021, the FDA approved aducanumab under its accelerated approval pathway based on amyloid plaque reduction as a reasonably likely surrogate for clinical benefit — the first approval of any drug based solely on a biomarker surrogate for AD — despite the FDA's own Advisory Committee unanimously voting against approval (10–0, 1 uncertain) based on the inconsistent efficacy data.

The approval provoked widespread criticism from clinicians, biostatisticians, payers, and patient advocates, centring on: the statistical irregularity of using post-futility data to overturn a prospective futility analysis; the inconsistency between the two trials; the high ARIA rate (35–41% ARIA-E at 10 mg/kg); the annual list price of USD 56,000 (later reduced to USD 28,200); and the broad label covering all stages of AD irrespective of amyloid confirmation [15]. Three independent members of the FDA Advisory Committee resigned in protest. The Centers for Medicare and Medicaid Services (CMS) took the unprecedented step of restricting Medicare coverage exclusively to patients enrolled in qualifying clinical trials — effectively limiting clinical access. The episode catalysed broader discussions about surrogate endpoint validation, the appropriate evidentiary threshold for accelerated approval in neurodegenerative disease, and conflicts of interest in the FDA advisory process. Aducanumab was voluntarily withdrawn from the market by Biogen in January 2023, rendering its regulatory legacy one of controversy without clinical legacy.

4.3 Lecanemab — The First Validated Anti-Amyloid Therapy

4.3.1 Mechanism and Selectivity

Lecanemab (Leqembi, Eisai/Biogen) is a humanised IgG1 anti-Aβ monoclonal antibody derived from the murine antibody mAb158, selected for its preferential binding to large soluble Aβ protofibrils — the intermediate aggregation species proposed to be among the most neurotoxic Aβ forms — while retaining binding activity for fibrils and plaques [16]. This specificity distinguishes lecanemab from antibodies with primary affinity for insoluble plaque-bound Aβ (such as gantenerumab and donanemab) and from those targeting monomers (solanezumab), and may explain its efficacy given the proposed primacy of protofibrillar Aβ in mediating synaptic toxicity and tau propagation. Lecanemab achieves amyloid clearance through Fc-mediated microglial phagocytosis of Aβ-antibody complexes, with the resultant inflammatory activation of microglia believed to underlie the ARIA mechanism.

4.3.2 CLARITY AD Trial

The CLARITY AD Phase III trial randomised 1,795 patients with early AD — confirmed amyloid-positive MCI due to AD or mild AD dementia with CDR 0.5 or 1 — to lecanemab 10 mg/kg intravenously biweekly or placebo over 18 months [17]. The primary endpoint — change from baseline in CDR-SB — was significantly reduced by 0.45 points (27% slowing of decline) in the lecanemab group compared with placebo (1.21 vs 1.66; $p<0.001$). All five pre-specified secondary endpoints were also significantly improved, including the Alzheimer's Disease Composite Score (ADCOMS), the ADAS-cog14, and measures of functional independence and quality of life. Amyloid PET demonstrated near-complete plaque clearance, with amyloid burden falling from a mean of 77.9 centiloids at baseline to 29.0 centiloids at 18 months in the lecanemab group, representing a 59% absolute reduction compared with a modest increase in the placebo group. Plasma p-tau181 and p-tau217 showed significant reductions, as did markers of tau pathology on PET imaging, providing the first large-scale human in vivo evidence that effective Aβ clearance secondarily attenuates tau accumulation.

4.3.3 Safety and ARIA Profile

ARIA occurred in a significant proportion of lecanemab-treated patients: ARIA-E in 12.6% (vs 1.7% placebo) and ARIA-H microhaemorrhages in 17.3% (vs 9.0% placebo). Symptomatic ARIA occurred in 2.8% of lecanemab-treated patients. Three deaths potentially related to lecanemab occurred during the trial — one in

a patient receiving concomitant tissue plasminogen activator (tPA) for acute ischaemic stroke and one associated with intracerebral haemorrhage — raising concerns about safety in patients requiring anticoagulation or thrombolytic therapy [18]. APOE ε4 carriers, particularly homozygotes, demonstrated substantially higher ARIA rates: ARIA-E occurred in approximately 35–45% of APOE ε4/ε4 homozygotes in subsequent analyses, a rate that has generated significant clinical concern about the risk-benefit ratio in this subgroup, which constitutes approximately 2–3% of the population but carries the highest genetic AD risk.

4.4 Donanemab — Targeting Pyroglutamate Aβ with a Finite Treatment Course

4.4.1 Mechanism and the N3pE Epitope

Donanemab (Kisunla, Eli Lilly) is a humanised IgG1 antibody that targets the pyroglutamate-modified form of amyloid-beta (Aβ-pE3 or N3pE) present in established amyloid plaques. Pyroglutamate Aβ is generated by the post-translational cyclisation of N-terminal glutamate residues, producing a truncated Aβ species that is enriched in amyloid plaques relative to non-plaque compartments, highly prone to aggregation, and resistant to aminopeptidase-mediated degradation [19]. Donanemab's specificity for plaque-enriched pyroglutamate Aβ — compared with lecanemab's protofibril preference — reflects a complementary targeting strategy within the anti-amyloid class. Its near-complete and rapid clearance of existing plaques also enabled a novel treatment paradigm: discontinuation of therapy upon amyloid clearance to a pre-specified low threshold (less than 25 centiloids or amyloid negativity), with the rationale that the treatment course is self-limiting once its biological target has been eliminated.

4.4.2 TRAILBLAZER-ALZ 2 Trial

The TRAILBLAZER-ALZ 2 Phase III trial randomised 1,736 patients with early symptomatic AD — confirmed amyloid PET positivity — to donanemab (700 mg IV monthly for the first three doses, then 1400 mg IV monthly) or placebo, with stratification into low/medium tau and high tau subgroups based on baseline tau PET.[20] In the primary pre-specified low/medium tau population — representing patients with earlier tau pathology and higher potential for meaningful clinical response — donanemab reduced CDR-SB decline by 35% relative to placebo (1.20 vs 1.84; $p<0.001$) at 76 weeks. In the combined population (all tau levels), the reduction was 22% ($p<0.001$). Amyloid clearance was rapid and near-complete, with 76% of donanemab-treated patients in the low/medium tau group achieving amyloid negativity (below 24 centiloids) by week 76, enabling treatment discontinuation in this subset. Plasma p-tau217 demonstrated significant reductions with donanemab, with the rate of change approaching that of the placebo group after amyloid clearance, suggesting that the treatment effect may persist beyond active dosing.

4.4.3 Safety and the Treatment Discontinuation Model

ARIA-E occurred in 24.0% of donanemab-treated patients and ARIA-H microhaemorrhages in 31.4%, with symptomatic ARIA in 6.1% and serious ARIA in 1.6%. Three deaths were considered possibly related to ARIA. The higher ARIA rates compared with lecanemab likely reflect donanemab's more aggressive plaque clearance kinetics. The treatment discontinuation model — stopping the drug once amyloid is cleared — represents an important clinical innovation: if amyloid re-accumulation does not rapidly recur after discontinuation, patients may achieve durable benefit from a finite treatment course of 12–18 months, with significant implications for cumulative ARIA exposure, cost, and convenience [20]. Preliminary analyses suggest that amyloid re-accumulation after discontinuation is slow, occurring at rates of approximately 10–15 centiloids per year — significantly below the therapeutic clearance rate — suggesting sustained amyloid negativity for at least several years after a successful treatment course, though long-term data remain limited.

5. AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA) — FRAMEWORK AND MANAGEMENT

A comprehensive overview of ARIA classification, frequency, clinical presentation, and management is presented in Table 2.

Table 2: ARIA Classification, Clinical Features, and Management Framework

ARIA Type	MRI Finding	Frequency (Lecanemab / Donanemab)	Clinical Presentation	Management Approach
ARIA-E (Oedema / Effusions)	Fluid-attenuated inversion recovery (FLAIR) hyperintensity in sulci or white matter; leptomeningeal effusions	12.6% / 24.0% (any grade) Symptomatic: 2.8% / 6.1%	Often asymptomatic; headache, confusion, dizziness, visual changes, seizures (rare) in severe cases	Mild: continue, increase monitoring frequency; Moderate: suspend therapy, repeat MRI in 4–8 weeks; Severe/symptomatic: discontinue; corticosteroids for severe cases

ARIA-H (Haemosiderin deposition)	Susceptibility-weighted imaging (SWI) microhaemorrhages or superficial siderosis	Microhemorrhages: 14.0% / 31.4% Siderosis: 10.4% / 12.6%	Generally asymptomatic; severe/large microhemorrhages may cause focal neurological signs	Mild (1–4 lesions): continue with monitoring; Moderate (5–9): suspend pending MRI clearance; Severe (≥10 or siderosis): discontinue; anticoagulants: heightened caution
ARIA Risk Factors	Baseline microhaemorrhages; superficial siderosis; APOE ε4 homozygosity (highest risk); concomitant anticoagulation; hypertension	APOE ε4/ε4: ARIA-E ~40–45% (lecanemab)	APOE ε4 carriers have 3–4x higher ARIA-E risk; ARIA most common in first 6 months; ε4 homozygotes at highest risk	Pre-treatment: baseline brain MRI; APOE genotyping (recommended); anticoagulant review; strict BP control; MRI at weeks 13, 26 minimum; ARIA-specific MRI protocol

5.1 Pathophysiological Mechanism of ARIA

ARIA is believed to arise through a two-stage process: the antibody-mediated removal of vascular amyloid (cerebral amyloid angiopathy, CAA) from perivascular spaces triggers an inflammatory response — mediated by Fc receptor activation on perivascular macrophages and microglia — that transiently increases blood-brain barrier permeability, producing perivascular oedema, sulcal effusions (ARIA-E), and microhaemorrhages (ARIA-H) [21]. This mechanism explains the higher ARIA incidence with antibodies targeting plaque-bound versus soluble Aβ species, the dose-dependency of ARIA, and the concentration of ARIA events in the early months of treatment when the rate of amyloid clearance — and associated vascular amyloid mobilisation — is most rapid. The APOE ε4 allele, which is independently associated with greater CAA burden, further amplifies ARIA risk by increasing the substrate of vascular amyloid available for antibody-mediated removal.

5.2 Clinical Significance and Risk Stratification

The majority of ARIA events — both ARIA-E and ARIA-H — are asymptomatic and detected only on protocol-mandated MRI surveillance, with spontaneous resolution on repeat imaging in most cases [22]. Symptomatic ARIA is less common but can manifest as headache, dizziness, confusion, focal neurological deficits, or — in rare severe cases — seizures and aphasia. Fatal ARIA, while documented, occurs at very low absolute rates in the trials (<0.5%), though the clinical severity in individual patients can be profound. Risk stratification for ARIA requires pre-treatment assessment of APOE genotype, baseline MRI for microhaemorrhages and superficial siderosis, anticoagulant and antiplatelet medication review, and blood pressure optimisation. APOE ε4/ε4 homozygotes face ARIA-E rates of approximately 40–45% with lecanemab and receive heightened scrutiny in prescribing guidance, with some neurologists arguing that the risk-benefit ratio in this genotype warrants careful individual counselling prior to treatment initiation.

6. SCIENTIFIC AND CLINICAL CONTROVERSIES

6.1 Is the Magnitude of Clinical Benefit Clinically Meaningful?

Perhaps the most widely debated issue in the anti-amyloid field is whether the statistically significant reductions in CDR-SB decline — 0.45 points for lecanemab and approximately 0.67 points for donanemab in their respective primary populations — translate into clinically meaningful benefit that patients, caregivers, and clinicians can detect and value in everyday life [23]. The CDR-SB is scored from 0 to 18, with a minimal clinically important difference (MCID) estimated at approximately 1.0–2.0 points depending on the analytical method and study context. The absolute treatment effect of approximately half a point over 18 months is substantially smaller than the estimated MCID, leading some experts to argue that the approved treatments produce effects that are detectable statistically but imperceptible to the vast majority of individual patients and caregivers in the short term.

Proponents of clinical meaningfulness counter-argue on several grounds: the percentage slowing of progression (27–35%) rather than absolute point differences better reflects the disease-modifying nature of the treatment; the observed effects are expected to compound over time as amyloid clearance prevents further tau accumulation, potentially producing increasingly divergent trajectories over 3–5 years; individual responders within the overall population may experience substantially larger benefits than the population mean; and delayed institutionalisation — even by several months — has profound societal and caregiving value [24]. The FDA and EMA have taken different positions: the FDA granted full approval based on demonstrated clinical benefit, while the EMA's Committee for Medicinal Products for Human Use (CHMP) issued an initial negative opinion for lecanemab in 2023, citing uncertainty about the clinical

relevance of the benefit, though the final regulatory determination continued to be evaluated. This regulatory divergence reflects genuine scientific uncertainty that the field has not yet resolved.

6.2 Does the Amyloid Hypothesis Fully Explain AD?

Decades of failed anti-amyloid trials have fuelled scepticism about whether Aβ is truly the causal driver of AD or merely a bystander or epiphenomenon of the disease process. Proponents of alternative hypotheses point to the tau hypothesis — in which tau propagation is the proximate cause of neurodegeneration — and suggest that the modest clinical benefits of amyloid clearance reflect targeting a marker rather than the disease mechanism [25]. The inflammatory hypothesis proposes that activated microglia and reactive astrocytes, driven by multiple triggers including but not limited to amyloid, are the principal mediators of neuronal death, supported by the genetic burden of AD risk variants in immune-related genes (TREM2, CLU, CR1, ABCA7, BIN1). The vascular hypothesis implicates cerebrovascular pathology — including CAA, blood-brain barrier breakdown, and reduced cerebral blood flow — as either an independent cause or a critical cofactor in AD neurodegeneration.

The partial but significant clinical benefits of lecanemab and donanemab provide the strongest human in vivo evidence yet that Aβ reduction does slow clinical progression, lending credibility to the amyloid cascade hypothesis as at least partially correct. However, the limited magnitude of benefit also argues that Aβ alone is insufficient to fully explain AD pathogenesis and that additional pathological processes — tau, neuroinflammation, vascular pathology, TDP-43, alpha-synuclein co-pathology — continue to drive disease independently of amyloid once the cascade has been initiated [26]. This multimodal pathological reality underlies the growing consensus that combination disease-modifying strategies — targeting amyloid, tau, and inflammation simultaneously or sequentially — will ultimately be required to achieve the substantial and sustained clinical benefits that the field aspires to deliver.

6.3 The Data Integrity Controversy

A significant and troubling dimension of the amyloid hypothesis controversy emerged in 2022, when Vanderbilt University neuroscientist Matthew Schrag and investigative journalist Charles Piller, writing in Science, raised concerns about potential data manipulation in a 2006 Nature paper by Lesné *et al.*, that claimed to identify a specific toxic Aβ oligomer species (Aβ*56) as causally linked to cognitive impairment in mice [27]. Subsequent independent analyses identified multiple instances of apparently manipulated Western blot images across several papers from the Ashe laboratory reporting on Aβ*56, raising questions about whether a body of preclinical research that had influenced the direction of the field for over a decade was built on unreliable foundations. The University of Minnesota conducted an investigation, and several papers were retracted or issued expressions of concern. While Aβ*56 was not a direct therapeutic target for any major clinical programme, the episode triggered broader soul-searching about the reliability of the preclinical amyloid literature and the peer review process in high-impact journals.

6.4 Who Should Be Treated — The Patient Selection Dilemma

The approval of lecanemab and donanemab is specifically indicated for early AD — MCI due to AD and mild AD dementia with confirmed amyloid positivity — yet the practical implementation of this patient selection in routine clinical and public health systems presents formidable challenges [28]. Amyloid PET, the gold standard for treatment eligibility confirmation, costs approximately USD 4,000–6,000 per scan in the United States and is not universally covered by insurance. CSF lumbar puncture with biomarker analysis is more widely accessible but carries procedural barriers. Plasma biomarkers such as p-tau217 offer promise as low-cost accessible screening tools, but performance characteristics for treatment decision-making in routine clinical practice have not yet been fully validated at the population level. The optimal CDR staging and amyloid centiloid thresholds for treatment eligibility, the role of tau PET in patient selection (as demonstrated by the tau-stratified results in TRAILBLAZER-ALZ 2), and the management of patients with extensive baseline cerebrovascular pathology remain incompletely defined.

6.5 Equity, Access, and Cost

The annual cost of lecanemab in the United States was set at USD 26,500, with donanemab at approximately USD 32,000 for a full treatment course. Beyond the drug cost, a comprehensive anti-amyloid treatment programme involves amyloid confirmation imaging, baseline and serial MRI surveillance (at minimum at weeks 13 and 26 for ARIA monitoring), infusion centre access (biweekly for lecanemab), APOE genotyping, and specialist neurology oversight — collectively representing a cost burden that is likely to make these treatments inaccessible to a large proportion of eligible patients in both high-income and low-to-middle-income country settings [29]. The Institute for Clinical and Economic Review (ICER) assessed lecanemab as not cost-effective at the USD 26,500 price point, estimating that it would need to be priced at approximately USD 8,900–21,500 to meet conventional cost-effectiveness thresholds. The differential access that will inevitably emerge between well-resourced tertiary memory clinics and underserved community settings raises profound questions of health equity, particularly given that Black and Hispanic Americans — who are disproportionately represented among AD patients — have been substantially underrepresented in

the clinical trials that established the treatment's evidence base.

7. TRANSLATING TRIAL EVIDENCE TO REAL-WORLD PRACTICE

7.1 The Role of Memory Clinics and Diagnostic Infrastructure

The real-world delivery of anti-amyloid therapies requires a substantially enhanced diagnostic and monitoring infrastructure that does not currently exist at scale in most healthcare systems. The identification of eligible patients demands cognitive screening capable of detecting MCI — a notoriously underdiagnosed condition in primary care settings where the MMSE remains the predominant screening tool — followed by specialist evaluation, biomarker confirmation of amyloid pathology, neuroimaging, and APOE genotyping [30]. Memory clinics at academic medical centres are well-positioned to deliver this infrastructure, but their capacity is limited relative to the estimated 6 million Americans and 50 million individuals globally with AD dementia, let alone the substantially larger preclinical and MCI populations who might benefit. The development of scalable diagnostic pathways — incorporating plasma biomarker screening in primary care, facilitated specialist referral, and community-based infusion delivery — will be critical to realising the population-level impact of disease-modifying therapy.

7.2 Management of Anticoagulation and Surgical Risk

The three potentially ARIA-related deaths in the lecanemab and donanemab trials — including one patient who received tPA for acute ischaemic stroke — highlight a critical real-world safety concern for patients on anticoagulants, antiplatelet agents, or who may require emergency thrombolytic therapy [31]. Current prescribing information for lecanemab contraindicates use in patients on anticoagulants and recommends careful risk-benefit assessment for those on antiplatelet agents. In patients with concurrent atrial fibrillation — who are both at elevated risk of ischaemic stroke and may require anticoagulation — the choice between stroke prevention and ARIA risk management presents a genuine clinical dilemma without an established evidence-based solution. Emergency department clinicians and neurologists must be aware that patients receiving anti-amyloid therapy face heightened haemorrhagic risk with thrombolytic agents, requiring modified management algorithms for acute ischaemic stroke presentation.

7.3 Biomarker-Guided Treatment Monitoring

The integration of plasma biomarkers — particularly p-tau217, p-tau181, and the Aβ42/40 ratio — into treatment monitoring protocols offers a potentially cost-effective approach to tracking treatment response and detecting early evidence of amyloid re-accumulation after treatment discontinuation [32]. Several academic centres have implemented plasma biomarker panels as part of their anti-amyloid therapy monitoring programmes, using serial p-tau217 trajectories as an accessible proxy for amyloid PET re-evaluation. Whether plasma biomarker-guided monitoring can replace or substantially defer follow-up amyloid PET and tau PET imaging — thereby reducing the cost and logistical burden of post-approval monitoring — is being actively investigated in real-world cohort studies and may materially influence the economic case for anti-amyloid therapy as reimbursement negotiations progress.

8. BEYOND AMYLOID — COMPLEMENTARY AND COMBINATION THERAPEUTIC STRATEGIES

8.1 Anti-Tau Therapies

Given the stronger correlation between tau pathology and cognitive decline compared with amyloid burden, anti-tau strategies represent the most advanced complementary therapeutic approach to amyloid targeting. Multiple anti-tau monoclonal antibodies have been evaluated, including semorinemab (anti-tau IgG4), gosuranemab (anti-N-terminal tau), and tilavonemab, with mixed results in Phase II trials. Zagotenemab (LY3303560), an anti-aggregated tau antibody, showed a possible signal in a Phase II study in early AD, though without statistical significance [33]. The combination of amyloid clearance to arrest the initiating cascade with tau clearance or aggregation prevention to address the downstream executioner represents the most mechanistically coherent disease-modification strategy, and combination trials pairing lecanemab with tau-targeting agents are in early planning or initiation phases. Small molecule tau aggregation inhibitors — including LMTM (TRx0237), a second-generation methylene blue derivative — have not demonstrated consistent Phase III benefit in isolation.

8.2 Neuroinflammation and TREM2 Targeting

The genetic architecture of late-onset AD is substantially dominated by immune and inflammatory pathways: APOE, BIN1, CLU (clusterin), ABCA7, and rare coding variants in TREM2 (triggering receptor expressed on myeloid cells 2) collectively account for a large proportion of the genetic risk of sporadic AD, with TREM2 variants (particularly R47H) conferring a risk elevation comparable to APOE ε4 in heterozygous form [34]. TREM2 is expressed on microglia and plays a critical role in microglial activation, phagocytic clearance of amyloid and cellular debris, and the transition from homeostatic to disease-associated microglial states. AL002c (ALECTOR/AbbVie), a TREM2-activating antibody, has entered Phase II trials in AD, with the goal of enhancing microglial amyloid clearance capacity. Anti-neuroinflammatory strategies including selective tau phosphorylation inhibitors, NLRP3 inflammasome inhibitors, and interleukin-1 receptor antagonists are also under investigation as potential adjuncts to amyloid-targeting therapy.

8.3 Synaptic and Neuroprotective Approaches

Synaptic loss — occurring early in the AD disease continuum and correlating closely with cognitive impairment — represents an attractive therapeutic target independent of amyloid and tau accumulation. Xanamem (UE2343), a selective 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor that reduces cortisol signalling in the brain, and simufilam, a synthetic peptide targeting filamin A-mediated aberrant signalling, represent novel mechanistic approaches whose clinical development has encountered challenges [35]. Brain-derived neurotrophic factor (BDNF) mimetics, TrkB receptor agonists, and insulin signalling modulators represent additional neuroprotective strategies under investigation, with the shared goal of enhancing neuronal resilience to amyloid and tau-mediated injury.

8.4 Secretase Inhibitors and Modulators

Small molecule inhibitors of beta-secretase (BACE1 inhibitors — verubecestat, atabecestat, lanabecestat, umibecestat) failed comprehensively in Phase II and III trials, predominantly due to dose-limiting cognitive side effects attributable to disruption of non-APP BACE1 substrates including neuregulin-1, a critical regulator of myelination and synaptic plasticity [36]. Gamma-secretase modulators (GSMs) — which selectively shift Aβ production toward shorter, less amyloidogenic peptides without globally inhibiting gamma-secretase activity — represent a more selective approach with a potentially improved side-effect profile compared with pan-gamma-secretase inhibitors. Several GSMs have entered early clinical evaluation, and the identification of potent, selective compounds without Notch pathway interference remains an active area of medicinal chemistry.

9. FUTURE DIRECTIONS

9.1 Prevention Trials in Preclinical AD

The most ambitious and potentially transformative application of anti-amyloid therapy is prevention — treating cognitively unimpaired individuals with elevated amyloid burden before clinical symptoms emerge, with the goal of arresting or indefinitely delaying the disease course. The AHEAD 3-45 trial is evaluating lecanemab in two cohorts of amyloid-positive cognitively normal individuals — one with intermediate amyloid (AHEAD 3 study) and one with elevated amyloid (AHEAD 45 study) — representing the most rigorous prospective test of whether earlier treatment produces greater and more durable benefit [37]. The GENERATION HD1 trial (gantenerumab in PSEN1 mutation carriers) and studies within the Alzheimer's Prevention Initiative (API) familial AD trial and the DIAN-TU (Dominantly Inherited Alzheimer Network Trials Unit) network represent additional prevention paradigm investigations, leveraging the predictable disease course in autosomal dominant AD to test amyloid clearance at defined pre-symptomatic stages.

9.2 Plasma Biomarkers as Treatment Eligibility Gatekeepers

The widespread adoption of plasma p-tau217 and other plasma AD biomarkers as pre-screening tools for amyloid PET referral holds the potential to dramatically expand the accessibility of anti-amyloid therapy eligibility assessment, reducing reliance on costly imaging and invasive CSF sampling [38]. Validation studies demonstrate that plasma p-tau217 has a positive predictive value for amyloid PET positivity exceeding 85–90% at optimised thresholds, sufficient to substantially reduce unnecessary amyloid PET referrals when used as a first-line screen. Integration of plasma biomarker testing into primary care electronic health record workflows — triggered by standardised cognitive complaints or a positive brief cognitive screen — could enable a scalable population-level funnel for identifying anti-amyloid therapy candidates.

9.3 Subcutaneous and Oral Administration Formats

The intravenous administration requirement for currently approved anti-amyloid antibodies — every two weeks for lecanemab and monthly for donanemab — represents a significant practical barrier to broad access, requiring infusion centre infrastructure, nursing staff, and substantial patient time commitment [39]. Subcutaneous formulations of both lecanemab and donanemab are in clinical development, with Phase III data expected in the near term; if approved, subcutaneous self-administration would substantially reduce the logistical and infrastructure burden of anti-amyloid therapy and could transform the treatment experience for eligible patients. Small molecule BACE1 modulators and gamma-secretase modulators under development would, if successful, offer the additional convenience of oral administration.

9.4 Next-Generation Anti-Amyloid Agents

Remternetug (LY3372993, Eli Lilly), a second-generation anti-pyroglutamate Aβ antibody with enhanced Fc-mediated plaque clearance activity compared with donanemab, has demonstrated exceptionally rapid amyloid clearance in Phase II studies and is progressing to Phase III evaluation with an anticipated faster clearance timeline of 12–15 months. Gene therapy approaches targeting APP expression, APOE4-to-APOE2 editing, and tau gene silencing via antisense oligonucleotides represent next-generation interventions at earlier stages of development with transformative long-term potential [40]. The convergence of improved patient selection through plasma biomarkers, more potent and rapidly acting antibodies, combination disease-modifying strategies, and scalable delivery models holds genuine promise for substantially improving the clinical impact of anti-amyloid therapy over the coming decade.

10. CONCLUSION

Anti-amyloid therapies have arrived at a pivotal inflection point in Alzheimer's disease medicine. After more than two decades of relentless clinical trial failures and scepticism about the centrality of amyloid in disease pathogenesis, the demonstrations of significant — albeit modest — clinical slowing of progression with lecanemab and donanemab in well-defined early AD populations represent the first validated evidence that biological modification of the amyloid cascade translates into measurable clinical benefit in human AD. The 27% slowing of CDR-SB decline with lecanemab in CLARITY AD and the 35% slowing with donanemab in TRAILBLAZER-ALZ 2's low/medium tau population are statistically unambiguous and biologically coherent, supported by robust pharmacodynamic biomarker data demonstrating amyloid clearance, secondary tau attenuation, and neuroinflammatory marker reductions.

Yet the controversies that surround this milestone are substantive and legitimate: the absolute magnitude of clinical benefit is small relative to the minimal clinically important difference for individual patients; the aducanumab episode has underscored the risks of surrogate endpoint-based approvals; ARIA represents a clinically real and potentially serious safety concern that disproportionately affects the highest-risk APOE ε4 genotype; cost and access barriers threaten to confine these treatments to the privileged; and the data integrity concerns that surfaced regarding foundational amyloid oligomer research — while not directly related to the approved agents — have appropriately prompted scrutiny of preclinical evidence standards in the field.

For the practising neurologist, geriatrician, and primary care physician, the message from the current evidence is nuanced: anti-amyloid therapy offers a real but modest benefit in carefully selected early AD patients with confirmed amyloid positivity, manageable ARIA risk in most but not all subgroups, and a treatment infrastructure requirement that challenges current healthcare system capabilities. For the field as a whole, the approval of lecanemab and donanemab is best understood not as the destination but as a proof-of-concept milestone validating the amyloid cascade hypothesis in human disease and establishing the biological plausibility of disease modification — a foundation upon which combination strategies targeting amyloid, tau, neuroinflammation, and synaptic biology may ultimately deliver the transformative outcomes that Alzheimer's patients and families urgently need.

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