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ANTI-AMYLOID MONOCLONAL ANTIBODIES IN ALZHEIMER DISEASE: WEIGHING MODEST CLINICAL BENEFIT AGAINST ARIA RISK, COST AND HEALTH SYSTEM READINESS IN LOW- AND MIDDLE-INCOME COUNTRIES

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ABSTRACT

Lecanemab and donanemab are the first drugs shown in phase 3 trials to slow clinical decline in early symptomatic Alzheimer disease by removing cerebral amyloid. Over roughly 18 months, lecanemab reduced progression on the Clinical Dementia Rating Sum of Boxes (CDR-SB) by 0.45 points, and donanemab by 0.67 points in its primary low/medium tau population. These are relative slowings of about a quarter to a third, yet neither difference reaches published thresholds for a minimal clinically important difference. The cost of that benefit is amyloid-related imaging abnormalities (ARIA). Oedema or effusion developed in 12.6% of lecanemab

and 24.0% of donanemab recipients, rose to about one in three among APOE ε4 homozygotes, and was occasionally fatal. Safe prescribing therefore depends on biomarker confirmation of amyloid, APOE genotyping, repeated MRI, infusion capacity and clinicians able to recognise ARIA. This review appraises the efficacy and safety evidence and then tests it against conditions in low- and middle-income countries (LMICs), home to more than 60% of people with dementia and to most of the projected rise from 57.4 million cases in 2019 to 152.8 million in 2050. Low-income countries have fewer than one CT scanner and 1.9 radiologists per million people, and one year of donanemab in India costs about 17 times national per capita gross domestic product in drug acquisition alone. At current prices and capacity, population-wide use is neither affordable nor safe in most LMICs. A staged model is proposed: timely diagnosis and risk-factor control for everyone, locally validated blood-biomarker triage at referral hubs, and antibody treatment confined to accredited centres with mandatory registries and prices negotiated against demonstrated value.

Keywords: Alzheimer disease; amyloid beta-peptides; monoclonal antibodies; lecanemab; donanemab; amyloid-related imaging abnormalities; developing countries; health care costs.



1. Introduction

Dementia is becoming a disease of poorer countries. The Global Burden of Disease forecasting collaboration estimated 57.4 million people with dementia in 2019 and projected 152.8 million by 2050, with the steepest proportional increases in North Africa and the Middle East (367%) and eastern sub-Saharan Africa (357%), against 53% in high-income Asia Pacific and 74% in western Europe ¹. More than 60% of people with dementia already live in low- and middle-income countries (LMICs) ², and the worldwide cost of the condition was put at US\$1.3 trillion in 2019 ³. In India, nationally representative data from the Longitudinal Aging Study in India, Diagnostic Assessment of Dementia (LASI-DAD) give a prevalence of 7.4% among adults aged 60 years and above, roughly 8.8 million people ⁴.

Into this setting have come the amyloid-targeting monoclonal antibodies. Lecanemab and donanemab each met their primary endpoints in large phase 3 trials ^{5,6}, and both now hold marketing authorisation in the European Union, China and India, among other markets ⁷⁻¹². Whether they work, in the narrow sense of clearing amyloid and shifting a rating scale, is settled. They do. The open question for most of the world's patients is different: whether a benefit measured in fractions of a scale point, bought with a real risk of brain oedema and haemorrhage and delivered through a pathway designed for well-staffed memory clinics, is a sound use of money in health systems that still fail to diagnose most dementia.

High-income payers have debated this at length ^{13,14}. LMICs have had less voice, although the regulatory decisions are now reaching them. This review first appraises efficacy and safety, then cost, and then sets the treatment pathway against what LMIC health systems can currently supply. The argument is that population-level adoption is premature in most LMICs, but that a narrow, staged model is defensible, provided it is built on diagnostic capacity worth having whether or not antibodies are ever prescribed.

2. Scope and approach

This is a narrative review. PubMed, Europe PMC, regulator and health-technology assessment websites (FDA, EMA, NICE) and manufacturer disclosures were searched for January 2020 to September 2026, using the terms lecanemab, donanemab, aducanumab, amyloid-related imaging abnormalities, eligibility, cost-effectiveness, health system capacity and low- and middle-income countries. Phase 3 randomised trials and their extensions, systematic reviews, appropriate-use recommendations and health-technology assessments were given priority; conference abstracts were excluded. The pivotal trials differ in primary endpoint, population and dosing, so no new pooling was attempted, and published meta-analyses are cited instead ^{15,16}. Prices appear in the currency of the source, and every conversion is stated.



3. What the trials show

3.1 Aducanumab: an instructive false start

The first antibody to reach the market did so on contested evidence. EMERGE and ENGAGE, identically designed phase 3 trials halted for futility and later reanalysed, disagreed: high-dose aducanumab slowed CDR-SB progression by 0.39 points (95% CI 0.09 to 0.69) in EMERGE, whereas the ENGAGE point estimate favoured placebo by 0.03¹⁷. Across both trials, ARIA with oedema or effusion (ARIA-E) developed in 35.2% of participants given 10 mg/kg, about a quarter of them symptomatic¹⁸. The sponsor withdrew the drug in 2024¹⁹. For LMIC regulators the lesson is specific. Approval on a surrogate, amyloid removal, ran ahead of clinical evidence, and the surrogate is not what patients experience.

3.2 Lecanemab and donanemab: consistent, small effects

Two trials moved the debate from argument to data (Table 1). Clarity AD randomised 1795

people with mild cognitive impairment or mild dementia and confirmed amyloid pathology to lecanemab 10 mg/kg every two weeks or placebo⁵. At 18 months CDR-SB had worsened by 1.21 points with lecanemab and 1.66 with placebo, a difference of 0.45 (95% CI 0.23 to 0.67), and amyloid fell by 59.1 centiloids relative to placebo in the PET substudy. TRAILBLAZER-ALZ 2 selected 1736 participants on amyloid and tau PET and gave monthly donanemab until amyloid cleared⁶. On its primary endpoint, the integrated Alzheimer's Disease Rating Scale (iADRS), the difference was 3.25 points in the low/medium tau population and 2.92 in the combined population (35.1% and 22.3% slowing); CDR-SB differences were 0.67 and 0.70. By week 76, 76.4% of donanemab recipients had reached amyloid clearance, which is what allows dosing to stop.

Table 1. Pivotal phase 3 trials of anti-amyloid monoclonal antibodies in early Alzheimer disease.

Trial (antibody, regimen)	Population (n randomised)	Primary endpoint result	CDR-SB difference vs placebo (95% CI)	ARIA-E, drug vs placebo	ARIA-H, drug vs placebo
EMERGE and ENGAGE (aducanumab, up to 10 mg/kg IV every 4 weeks) ^{17,18}	Early AD, amyloid PET positive	CDR-SB: benefit in EMERGE only	EMERGE -0.39 (-0.69 to -0.09); ENGAGE +0.03 (-0.26 to 0.33)	35.2% at 10 mg/kg, both trials	Not extracted
Clarity AD (lecanemab, 10 mg/kg IV every 2 weeks) ⁵	MCI or mild dementia due to AD, amyloid positive (1795)	CDR-SB at 18 months	-0.45 (-0.67 to -0.23)	12.6% vs 1.7%	17.3% vs 9.0%
TRAILBLAZER-ALZ 2 (donanemab, IV every 4 weeks, stopped on amyloid clearance) ⁶	Early symptomatic AD, amyloid and tau PET selected (1736)	iADRS at 76 weeks: 3.25 (low/medium tau), 2.92 (combined)	-0.67 (-0.95 to -0.40) low/medium tau; -0.70 combined	24.0% vs 2.1%	31.4% vs 13.6%

Both trials were large, adequately powered and consistent in direction across secondary endpoints. Two features limit how far their

results travel. Selection was strict: participants needed confirmed amyloid, little vascular disease on MRI and, for donanemab, a qualifying tau



PET profile, so the trial populations were healthier and better characterised than patients seen in routine practice ²⁰. And frequent ARIA and infusion reactions (26.4% versus 7.4% with lecanemab ⁵) gave raters and participants chances to guess allocation, a route by which subjective rating scales can drift; neither the direction nor the size of any such bias has been established.

Relative slowing flatters. A 27% slowing of a 1.66-point decline is 0.45 points on an 18-point scale.

3.3 Is the effect clinically meaningful?

Anchor-based estimates of the minimal clinically important difference (MCID) on CDR-SB are 0.98 points in mild cognitive impairment and 1.63 points in mild AD dementia ²¹, and no pivotal trial's mean difference reaches even the lower figure (Figure 1a). Supporters reply that an MCID describes change within a person, whereas a between-group difference in the rate of decline accumulates if the effect persists. That reply is reasonable, and it makes durability the decisive issue.

Independent syntheses have been severe. A meta-analysis of 19 publications (23,202 participants, eight antibodies) found a pooled CDR-SB difference of 0.18 points, with no outcome exceeding its MCID and a number needed to harm of 9 for ARIA-E ¹⁵. The 2026 Cochrane review of 17 trials and 20,342 participants judged effects on cognition and function absent or trivial and estimated 107 additional ARIA-E cases per 1000 people treated ¹⁶. Because both analyses pool failed compounds

with the two effective ones, they understate what lecanemab and donanemab achieve; the qualitative verdict, a small benefit against a frequent harm, still holds for the two drugs taken alone.

3.4 Durability

The strongest case for these drugs rests on longer follow-up, where the evidence is weaker by design. The Clarity AD open-label extension reported continued separation between early-start and delayed-start groups through 36 months ²². The TRAILBLAZER-ALZ 2 extension reported a CDR-SB difference of 1.2 points (95% CI 0.7 to 1.7) at three years between early-start participants and an external comparison cohort from the Alzheimer's Disease Neuroimaging Initiative ²³. That figure crosses the MCID for mild cognitive impairment, but the comparison is observational, against people recruited, assessed and scheduled differently, without rater blinding. Delayed-start separation is the more credible signal of disease modification, and it is modest. Neither extension yet answers what payers ask: does treatment delay loss of independence, institutional care or death?

4. ARIA and other harms

4.1 Mechanism

ARIA covers two MRI phenotypes that follow antibody-mediated removal of amyloid, particularly from vessel walls affected by cerebral amyloid angiopathy: ARIA-E, vasogenic oedema or sulcal effusion on FLAIR sequences, and ARIA-H, microhaemorrhage or superficial siderosis on susceptibility-weighted



imaging²⁴. Most episodes are silent and found only on scheduled scans. Symptomatic episodes bring headache, confusion, visual disturbance or seizures, and a few progress to status epilepticus or macrohaemorrhage. Efficacy and harm share a mechanism, which is why the antibodies that clear plaque fastest have produced the most ARIA.

4.2 Frequency and the APOE $\epsilon 4$ gradient

In Clarity AD, ARIA-E occurred in 12.6% of lecanemab and 1.7% of placebo recipients, and ARIA-H in 17.3% and 9.0%⁵. Donanemab rates were roughly double: ARIA-E 24.0% versus 2.1%, with 52 of 205 cases symptomatic, and ARIA-H 31.4% versus 13.6%; three deaths in the

donanemab arm were judged treatment related⁶ (Figure 1b). Risk climbs with APOE $\epsilon 4$ dose. Lecanemab-associated ARIA-E affected 5.4% of non-carriers, 10.9% of heterozygotes and 32.6% of homozygotes in the core study²⁵ (Figure 1c), and 34.5% of homozygotes once open-label exposure was added²⁶. On this gradient the European Commission restricted both drugs to APOE $\epsilon 4$ non-carriers and heterozygotes^{7,8}, and United States appropriate-use recommendations require genotyping and explicit risk counselling before the first dose^{25,27}. Genotyping is thus a condition of safe prescribing rather than a refinement, and it is not a routine test in most LMIC public laboratories.

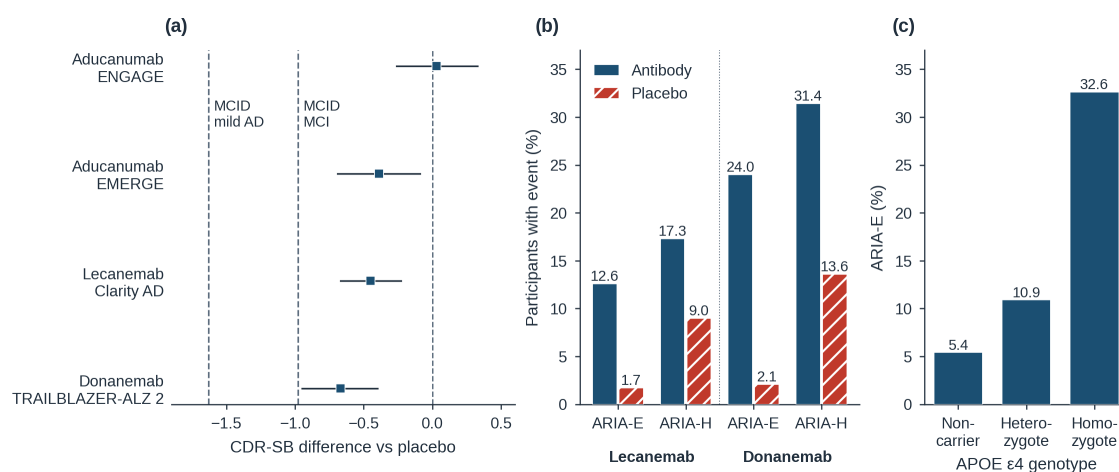


Figure 1. Clinical benefit of anti-amyloid antibodies is small relative to published thresholds of clinical importance, whereas ARIA is common and genotype dependent. (a) Treatment minus placebo difference in CDR-SB at the end of the double-blind period (76 to 78 weeks) with 95% confidence intervals; negative values favour the antibody. Dashed lines mark the anchor-based minimal clinically important differences of 0.98 points (MCI) and 1.63 points (mild AD dementia)²¹. Donanemab is shown for its primary low/medium tau population. (b) Incidence of ARIA-E and ARIA-H with lecanemab (Clarity AD, $n = 1795$) and donanemab (TRAILBLAZER-ALZ 2, $n = 1736$) versus placebo. (c) Lecanemab-associated ARIA-E by APOE $\epsilon 4$ genotype in the Clarity AD core study.

4.3 Haemorrhage, anticoagulation and brain volume

Serious harm clusters where ARIA meets anticoagulation. A lecanemab-treated patient

given intravenous tissue plasminogen activator for suspected stroke developed multiple cerebral haemorrhages and died²⁸, and appropriate-use recommendations exclude people taking



anticoagulants²⁵. Where stroke teams cannot see a patient's treatment record or obtain rapid MRI, as in many LMIC emergency departments, the risk that ARIA is mistaken for ischaemic stroke and thrombolysed is concrete. A separate and unexplained signal is accelerated loss of whole-brain volume with ventricular enlargement in treated participants, consistent across trials in a meta-analysis²⁹; whether this reflects removal of amyloid and associated inflammation or loss of neural tissue remains unknown.

4.4 Mitigation

Dosing strategy can lower ARIA without sacrificing amyloid removal. In TRAILBLAZER-ALZ 6, a more gradual donanemab titration reduced ARIA-E at 24 weeks from 23.7% with the original schedule to 13.7%³⁰, and at 18 months from 24.2% to 15.6%, with symptomatic ARIA-E falling from 4.8% to 2.8%³¹. Mitigation reduces, but does not remove, the need for surveillance: appropriate-use recommendations place MRI at baseline and three or four further times within roughly the first six months of therapy^{25,27}.

5. Cost and value

Prices were set in high-income markets and then exported. Lecanemab launched in the United States at US\$26,500 a year, whereas the Institute for Clinical and Economic Review put its health-benefit price benchmark at US\$8,900 to US\$21,500³². Donanemab was priced at US\$695.65 per vial, or US\$32,000 for 12 months (13 infusions)³³. Acquisition is only part of the bill, since diagnostic confirmation, genotyping,

infusion visits, surveillance MRI and ARIA management all add cost. For the European Union, Jönsson and colleagues estimated 5.4 million potentially eligible people and annual spending above EUR 133 billion at United States prices, more than half of total EU pharmaceutical expenditure¹³. In England, final draft guidance from the National Institute for Health and Care Excellence (NICE) in June 2025 recommended neither drug: for lecanemab, the committee's preferred incremental cost-effectiveness ratio was GBP 93,769 per quality-adjusted life year, against a usual threshold of GBP 20,000 to 30,000¹⁴. That guidance was reopened on appeal in 2026. The gap between price and value has not closed.

In LMICs the arithmetic is harsher. Donanemab launched in India in May 2026 at INR 91,688 per 350 mg vial¹¹. The labelled first-year course uses 46 vials, the quantity implied by the United States price for 13 infusions, which comes to about INR 4.2 million, or roughly US\$44,000 at the exchange rate reported at launch. With India's 2024 gross domestic product per capita at US\$2,592³⁴, one year of the drug alone costs about 17 times average annual per capita output, before any MRI, genotype or infusion charge. Lecanemab reached India in August 2026 at INR 21,682 per vial with weight-based dosing every two weeks¹²; in China it launched in 2024 at CNY 2,508 per 200 mg vial⁹. The Brazilian Academy of Neurology judged the drugs not cost-effective above US\$25,000 a year and advised restricting any use to public reference centres³⁵. Where outpatient medicines are



largely paid out of pocket, as across much of South Asia and sub-Saharan Africa, prices of this order mean that access will follow wealth rather than clinical need.

6. Health system readiness in LMICs

The antibody is the smallest part of the intervention. Safe treatment is a chain (Figure 2a): recognition of cognitive symptoms, specialist assessment, confirmation of amyloid, APOE genotyping, a baseline MRI read by a radiologist trained in ARIA, an infusion service, scheduled surveillance scans, and an emergency pathway that recognises ARIA and withholds thrombolysis. In most LMICs every link is weak, and a chain fails at its weakest link (Table 2).

6.1 Eligibility

Few patients qualify even where the system is strong. In the population-based Mayo Clinic Study of Aging, 47% of 237 amyloid-positive people with mild cognitive impairment or mild dementia met the Clarity AD inclusion criteria, but only 8% remained eligible after every exclusion was applied, and 17.4% under relaxed criteria²⁰ (Figure 2b). No comparable estimate exists for any LMIC. The exclusions target vascular brain injury, bleeding risk and anticoagulation, so the higher burden of uncontrolled hypertension and cerebrovascular disease in many LMIC populations would plausibly shrink the eligible fraction further, and late presentation moves many people past the mild stage at which the drugs were tested.

6.2 Diagnosis and biomarkers

Amyloid confirmation is the first bottleneck. PET and cerebrospinal fluid assays are confined to a few tertiary centres, and a survey across Latin America named funding and infrastructure as the main barriers to biomarker use³⁶. Blood tests offer the likeliest way round. In Swedish primary and secondary care cohorts, a plasma p-tau217 based test classified amyloid status with about 90% accuracy, compared with 61% for primary care physicians and 73% for dementia specialists using standard evaluation³⁷, and in May 2025 the United States Food and Drug Administration cleared the first plasma p-tau217 to amyloid- β 1-42 ratio assay for specialist use³⁸. These assays have not been validated at scale in South Asian, African or Latin American populations, where chronic kidney disease and different pre-test probabilities could move cut-offs, so local validation has to come first.

6.3 Imaging for safety

MRI is the rate-limiting step for safety. Low- and middle-income countries have fewer than one CT scanner per million inhabitants against almost 40 in high-income countries, low-income countries have 1.9 radiologists per million against 97.9, and the gap for MRI is wider still³⁹. Each treated patient needs four or five scans in the first six months, each with susceptibility-weighted and FLAIR sequences and a reader able to grade ARIA^{25,27}. Where one scanner serves a district or a province, surveillance at that density would displace imaging for stroke, trauma and cancer.



6.4 Workforce, infusion capacity and waiting times

The combined neurological workforce is 0.1 per 100,000 people in low-income countries and 7.1 per 100,000 in high-income countries⁴⁰. Even in the United States, modelling projected waits of about 50 months for specialist assessment if referral followed brief cognitive screening and about 12 months if a positive blood biomarker were required first⁴¹; in six European countries, capacity limits were projected to leave over a million people with mild cognitive impairment progressing to dementia while waiting⁴². No LMIC has an equivalent model, but the direction is not in doubt. Infusion chairs are a further constraint for a drug given every two weeks. The August 2025 approval of a weekly subcutaneous

lecanemab autoinjector for maintenance after 18 months of intravenous treatment⁴³, and the finite, clearance-guided course of donanemab, ease that burden without removing it.

6.5 Opportunity cost

Every rupee, real or naira spent on antibody therapy is unavailable for care that reaches more people. The 2024 Lancet Commission attributed about 45% of dementia risk to 14 potentially modifiable factors, among them hypertension, hearing loss, air pollution, low education and untreated vision loss⁴⁴, many of them more prevalent in LMICs. Blood pressure control, hearing aids and caregiver support cost little per person and reach populations that no infused biologic can. This is not an argument against innovation; it is an argument about sequence.

Table 2. Requirements for safe anti-amyloid therapy, the constraint in LMIC settings, and a staged response.

Requirement	Evidence of constraint	Staged response
Diagnosis at the MCI or mild dementia stage	About 8.8 million people with dementia in India ⁴ ; only 8% of amyloid-positive people eligible even in a high-income cohort ²⁰	Stage 1: primary care diagnosis with locally adapted tools; risk-factor control; caregiver support
Confirmation of amyloid	PET and CSF assays limited to tertiary centres; funding and infrastructure the main barriers in Latin America ³⁶	Stage 2: plasma p-tau217 triage after local validation ³⁷
APOE ε4 genotyping	ARIA-E 32.6% in homozygotes ²⁵ ; test not routine in public laboratories	Mandatory at accredited centres; homozygotes excluded
MRI at baseline and 3 to 4 further scans in about 6 months	Fewer than 1 CT scanner per million in LMICs; 1.9 radiologists per million in low-income countries; MRI gap wider ³⁹	Stage 3: treat only where on-site MRI with ARIA-trained reporting exists
Specialist assessment and infusion capacity	Neurological workforce 0.1 versus 7.1 per 100,000 ⁴⁰ ; about 50-month waits projected even in the United States ⁴¹	Hub-and-spoke referral; blood-test triage; subcutaneous maintenance where approved ⁴³
Affordability	First-year donanemab in India about INR 4.2 million, about 17 times per capita GDP ^{11,34}	Local health-technology assessment; value-based, pooled or tiered pricing; conditional reimbursement
Emergency safety	Fatal haemorrhage after thrombolysis during lecanemab treatment ²⁸	Alert cards or electronic flags; stroke-unit protocols requiring imaging review before thrombolysis

CSF, cerebrospinal fluid; GDP, gross domestic product; LMIC, low- and middle-income country; MCI, mild cognitive impairment.

7. A staged pathway for LMICs

The evidence reviewed here does not support outright rejection. It supports a sequence in which the investments needed for antibody



therapy are also those that improve dementia care generally (Figure 2a).

The first stage belongs in every setting: timely diagnosis in primary care with brief cognitive tools adapted to local language and schooling, management of modifiable risk factors, and support for caregivers, in line with the WHO global action plan ³. Without it, no downstream therapy has patients to treat.

At regional referral hubs, a second stage adds blood-biomarker triage once assays have been validated locally, so that specialist and imaging time goes to people likely to have Alzheimer pathology. In the United States model this single step cut projected waits by about three-quarters ⁴¹.

The third stage, antibody therapy, should be confined to a small number of accredited centres treating rigorously selected patients: APOE ε4

non-homozygotes, not anticoagulated, meeting trial-derived criteria and able to attend surveillance. Accreditation should require on-site MRI with ARIA-trained reporting, a written ARIA management protocol, an alert card or electronic flag that blocks thrombolysis without neuroimaging review, and enrolment of every patient in a national registry with standardised outcomes. Purchasers carry two further obligations. Prices should be negotiated against value shown in local health-technology assessment, ideally through pooled or tiered procurement, and any public reimbursement should be time limited and conditional on registry evidence. National assessment bodies such as Health Technology Assessment in India and Brazil's CONITEC are placed to set these terms before private-market uptake defines the standard of care.

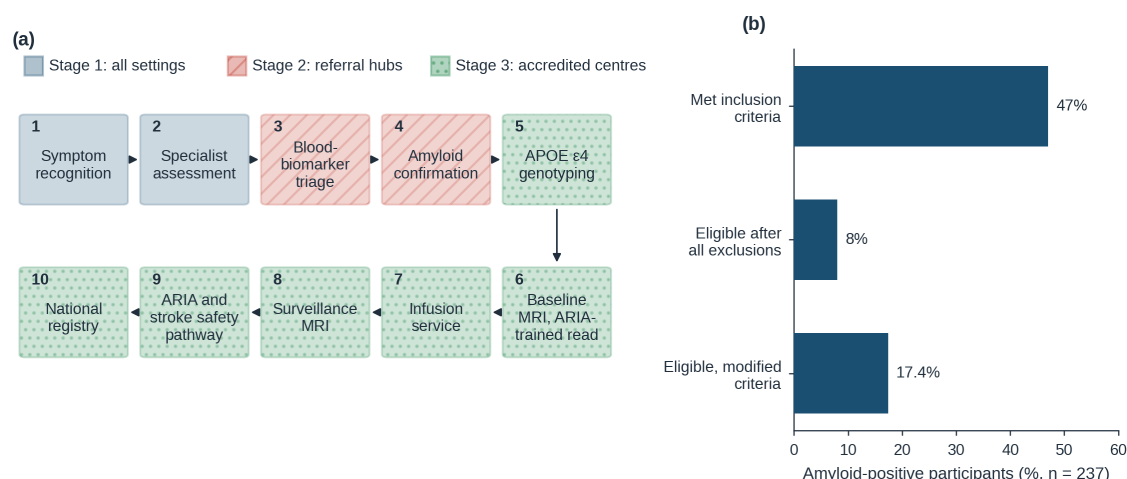


Figure 2. Safe anti-amyloid therapy depends on a long care chain, and only a small fraction of amyloid-positive patients qualify even in a high-income population. (a) Steps required before and during treatment, grouped into the three stages proposed for LMICs; each step is a prerequisite for the next, and the treatment steps (stage 3) presuppose all earlier ones. (b) Eligibility cascade among 237 amyloid-positive participants with MCI or mild dementia in the population-based Mayo Clinic Study of Aging: proportion meeting Clarity AD inclusion criteria, remaining eligible after all exclusions, and eligible under modified criteria ²⁰.



8. Evidence gaps that would change decisions

Four kinds of study would alter policy in LMICs. Population-based eligibility estimates, modelled on the Mayo Clinic analysis²⁰ and run in cohorts such as LASI-DAD⁴, would show how many people could ever qualify. Validation of plasma p-tau217 assays against amyloid PET in South Asian, African and Latin American populations, with local comorbidity profiles, would show whether the cheapest diagnostic route is trustworthy. Registries recording ARIA incidence, time to MRI and serious adverse events outside trial conditions matter because trial safety depended on services that LMIC hospitals often lack. And cost-effectiveness analyses built on local costs, care pathways and willingness-to-pay thresholds should replace ratios transferred from high-income assessments. Trials of dosing strategies that cut ARIA and scan burden in the manner of TRAILBLAZER-ALZ 6³⁰, and trials powered for time to institutional care would help every health system, but most of all those with the fewest scanners.

9. Conclusions

Lecanemab and donanemab show that removing amyloid can slow the clinical course of early Alzheimer disease. At 18 months the slowing falls short of conventional thresholds of clinical importance, and it carries a frequent, genotype-dependent risk of brain oedema and haemorrhage that obliges intensive MRI surveillance. In India a year of donanemab costs many times average

annual income, and the diagnostic, imaging and specialist capacity that safe use requires is missing from most LMIC public systems. For LMICs the defensible course is to build diagnosis, biomarker triage and registries first, confine treatment to accredited centres, and pay no more than local evidence shows the drugs are worth. What decides their long-term place is whether extension signals are confirmed on outcomes families recognise, above all time to loss of independence.

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