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The advent of monoclonal antibodies targeting amyloid-beta-namely **lecanemab** and **donanemab**-has reshaped the therapeutic landscape of Alzheimer's disease (AD). Both agents modestly slow cognitive and functional decline in patients with early symptomatic AD, marking a long-awaited shift toward disease-modifying treatment. However, **response is not uniform**, and **the decision to initiate therapy requires careful clinical, imaging, and biomarker-based triage**.

This article synthesizes the most up-to-date 2025 data to guide clinicians on **who should-and should not-receive anti-amyloid therapy**, with practical insights for implementation in real-world practice.

Early Stage Disease Is Crucial

The **single most reliable predictor of benefit** is **clinical stage**. In both the **CLARITY AD** (lecanemab) and **TRAILBLAZER-ALZ 2** (donanemab) trials, **patients with mild cognitive impairment (MCI) or mild AD dementia** derived the greatest benefit.

- **CDR Global Score**: 0.5–1.0
- **CDR Sum of Boxes (CDR-SB)**: ≤6.5
- **MMSE**: Lecanemab (22–30), Donanemab (20–30)
- **FAST**: Stages ≤4

Patients with **moderate or severe dementia** (e.g., CDR ≥2.0 or FAST stage ≥5) had limited or no benefit and were excluded from clinical trials.

Tau Pathology: A Predictor of Efficacy

- **Baseline tau burden** is a powerful determinant of therapeutic response.
- **Low to intermediate tau pathology**, measured via **CSF p-tau217** or **tau PET**, is strongly associated with **greater slowing of cognitive decline**.
- **High tau burden** is linked to **reduced or absent benefit**, particularly in late-stage patients.

In open-label extensions of lecanemab, **some low-tau patients improved over 3 years**, an unprecedented finding in AD treatment.

***Implication**: **Tau staging should be integrated into the treatment decision** whenever feasible.*

Fluid Biomarkers: Confirming Target Engagement

Anti-amyloid therapies induce predictable **biological shifts** that can support therapeutic monitoring:

- ↓ **p-tau181, p-tau217 and GFAP**: Reflect reduced tau phosphorylation and astrocytic inflammation.
- ↑ **Aβ42/40 ratio (CSF and plasma)**: Indicates amyloid plaque clearance.
- ↓ **rate of NfL increase**: Suggests slowed axonal injury and correlates with clinical benefit.

These biomarkers provide **mechanistic reassurance**, though **they do not replace clinical evaluation** or predict response independently.

Neuroimaging: Eligibility, Risk, and Safety

- **Amyloid via PET**
  - Required for therapy initiation.
  - Degree of baseline amyloid load **does not predict clinical response**, but is critical for diagnosis.
- **Tau via PET**
  - Optional but **strongly prognostic**.
  - Tau-PET not commercially available
  - High tau = lower likelihood of benefit.
- **MRI**
  - **Safety gatekeeper**. Required for ARIA risk stratification.
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Exclusion criteria:

- ≥ 4 Cerebral Microhemorrhages
  - **Definition**: Cerebral microbleeds are small (<10 mm) areas of chronic blood deposition visible on susceptibility-weighted MRI sequences (SWI or GRE).
  - **Clinical Implication**: The presence of **more than four microbleeds** is associated with an elevated risk of **amyloid-related imaging abnormalities–hemorrhagic (ARIA-H)** and may suggest underlying **cerebral amyloid angiopathy (CAA)**. This threshold was used in both CLARITY AD and TRAILBLAZER-ALZ 2 trials to exclude high-risk patients.
- Cortical Superficial Siderosis (cSS)

  - **Definition**: cSS refers to the deposition of hemosiderin along the superficial layers of the cerebral cortex, especially in sulcal regions, typically detected using SWI or GRE imaging.
  - **Clinical Implication**: **Any evidence of cSS is an absolute contraindication** to anti-amyloid monoclonal antibodies. It is considered a radiologic hallmark of **advanced CAA** and strongly predicts ARIA-H and intracerebral hemorrhage.

- Macrohemorrhage >10 mm
  - **Definition**: Macrohemorrhages are intraparenchymal hemorrhages greater than 10 mm in diameter.
  - **Clinical Implication**: A prior history of **spontaneous lobar macrohemorrhage**, especially in a patient with amyloid positivity, is highly suggestive of CAA. Anti-amyloid therapies are contraindicated due to the risk of recurrence and potential for **catastrophic ARIA-H events**.
- Multiple Lacunar Infarcts
  - **Definition**: Small (3–15 mm) deep infarcts in the basal ganglia, thalamus, internal capsule, or brainstem due to occlusion of penetrating arteries.
  - **Implication**: Reflects chronic small vessel ischemia. **>2 lacunar infarcts**, or a single **strategic infarct**, indicate vascular compromise and may increase the risk of ARIA or complicate interpretation of treatment response.
- Severe white matter disease (Fazekas Score >2)
  - **Definition**: Grade 3 periventricular WMH: extending into deep white matter and/or Grade 3 deep WMH: confluent hyperintensities.
  - **Clinical Implication**: Extensive WMH (Fazekas 3) increases susceptibility to ARIA-E and is associated with **mixed vascular-amyloid pathology**. It may also suggest an impaired glymphatic system or fragile blood-brain barrier.
- Radiologic Signs of CAA-ri (Cerebral Amyloid Angiopathy–Related Inflammation)
  - **Definition**: A inflammatory condition in amyloid-laden vessels presenting with subacute cognitive decline, seizures, and asymmetric T2/FLAIR hyperintensities +/- edema.
  - **MRI Features**: Patchy, confluent white matter edema; asymmetric signal changes; mass effect.
- Radiologic Signs of ABRA (Amyloid Beta-Related Angiitis):
  - **Definition**: A subtype of CAA-ri with histologic evidence of vasculitis.

- **Implication**: Absolute exclusion due to potential for fulminant disease and poor outcomes if triggered by immunotherapy.

Clinical and Genetic Predictors

- **APOE ε4**
  - Homozygotes are at **increased risk for ARIA-E/H**, especially with donanemab.
  - APOE ε4 does **not negate benefit**, but mandates enhanced monitoring.
  - **Genotyping is recommended** prior to therapy initiation.
- **Sex**
  - Subgroup data (e.g., Clarity AD) suggest **men may experience greater benefit**, although this remains exploratory.
- **Age**
  - **No consistent differences in efficacy** across age brackets.
  - Very old adults may have **mixed pathology**, which could diminish clinical gains.

Who Should *Not* Be Treated?

Clinical Exclusions

- Moderate-to-severe dementia (CDR ≥2, MMSE <20)
- Rapid progression inconsistent with AD
- Recent stroke or TIA (within 12 months)
- Use of anticoagulants (e.g., warfarin, DOACs, heparin)
- Active seizure disorder or seizure in past 12 months
- **Systemic Illness**
  - Uncontrolled hypertension (MAP >93 mmHg)
  - Active bleeding/clotting disorders (platelet count <50k, INR >1.5)
  - Active malignancy or history within 5 years (unless in remission)
  - End-stage organ disease (ESRD, advanced liver disease)
  - Immunosuppression or autoimmune disease on systemic therapy

- **Other Exclusions**
    - Inability to undergo MRI (e.g., metal implants, claustrophobia)
    - Pregnancy or lactation
    - Inadequate care partner support

MRI-Based Exclusions

- 4 microbleeds
- Any cSS
- Macrohemorrhage >10 mm
- Extensive white matter disease
- Signs of CAA-ri/ABRA

The "Goldilocks" Responders

Ideal candidates are in the therapeutic "sweet spot":

- Clinical diagnosis of **MCI or mild AD dementia**
- **Amyloid-positive** (PET or CSF)
- **Low-to-intermediate tau** burden
- **No MRI signs of CAA**, cSS, or extensive microbleeds
- **Not on anticoagulants**
- **Stable systemic health**
- APOE ε4 status known and discussed
- Supportive care partner and informed consent obtained

Summary: 2025 Clinical Insights

Predictor	Effect on Response
Low tau pathology (CSF/tau PET)	↑↑ Strongest predictor of response
CDR 0.5–1 / Early therapy	↑ Clinical stabilization or mild improvement
Slow NfL rise	↑ Slower decline trajectory

↓ p-tau217, ↓ GFAP	↑ Biologic effect confirmation
↑ Aβ42/40 (CSF/plasma)	↑ Target engagement, not clinical outcome
APOE ε4 homozygosity	↔ Benefit, ↑ ARIA risk
Male sex	↑ Possibly greater benefit (needs validation)
Significant CAA on MRI	↓ Contraindicated due to ARIA risk
Age	↔ No consistent impact

Conclusion

Anti-amyloid therapies are not one-size-fits-all. As we enter the biomarker era of Alzheimer's care, the success of **lecanemab and donanemab** depends on **precision in diagnosis, staging, and safety triage**. The 2025 data support a **"Goldilocks" model**: early, not too early; pathologic but not too advanced; and cognitively symptomatic yet not too impaired.

Clinicians are now challenged not just to treat, but to treat **wisely**-identifying who stands to benefit and who might be harmed. This is the future of Alzheimer's medicine, and it has already begun.

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