

Clinical Practice Recommendations of the Swiss Society for Neuroradiology: Neuroimaging Standards for Enrollment and Disease Monitoring in Anti-Amyloid Immunotherapies.

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Alzheimer's disease (AD) is a progressive brain disorder and the most prevalent form of dementia, accounting for approximately 60–70% of dementia cases in the elderly population. The pathogenesis of AD is thought to be driven by the deposition of abnormal amyloid- β ($A\beta$) and tau forms in the brain. The accumulation of $A\beta$ 1–42 leads to the formation of extracellular amyloid plaques, which disrupt neuronal function. In addition to advanced age, the apolipoprotein E (APOE) ϵ 4 genotype has been associated with an increased risk of developing AD [1 , 2].

Recent phase 3 trials investigating early symptomatic AD, encompassing mild cognitive impairment (MCI) and the mild dementia stage of disease (CLARITY-AD and TRAILBLAZER-ALZ 2), have demonstrated a reduction in cognitive and functional decline, as well as positive changes in disease-specific biomarkers following treatment [3 , 4]. In the CLARITY-AD trial, participants receiving lecanemab (Lequemb, Eisai Company, Tokyo, Japan) experienced an approximately 30% reduction in cognitive decline over 18 months compared to the placebo group [3 , 5]. Additionally, within the treatment group, biomarkers associated with tau pathology showed a decline, suggesting that $A\beta$ -lowering therapies may modulate multiple pathophysiological mechanisms in AD. Similarly, the TRAILBLAZER-ALZ 2 trial demonstrated a 35% reduction in cognitive decline compared to placebo [4]. The outcome of the CLARITY-AD and TRAILBLAZER-ALZ 2 study poses new challenges for radiologists and neuroradiologists, as the appropriate selection of patients for anti-amyloid therapy – aiming to maximize therapeutic benefits while minimizing potential risks – requires comprehensive expertise. Additionally, the identification of treatment-related risks necessitates the development of refined imaging protocols for the monitoring of AD patients. In response to these emerging needs, the Swiss Society of Neuroradiology provides practical recommendations outlining the mandatory imaging studies required for patient enrollment and longitudinal monitoring during anti-amyloid therapy in Switzerland.

Lecanemab penetrates the brain parenchyma, where it binds to soluble aggregated forms of $A\beta$ in vivo leading to a reduction in $A\beta$ levels in AD patients [6]. This effect was demonstrated in the CLARITY-AD trial, a randomized, double-blind, placebo-controlled phase 3 study with an open-label extension phase [3]. Lecanemab demonstrated highly selective binding to $A\beta$ protofibrils, which are believed to drive AD pathophysiology both before and after amyloid plaque clearance [6]. In CLARITY-AD, treatment resulted in a significant reduction in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) score change from baseline at 18 months, compared to placebo.

Donanemab is another monoclonal antibody developed to target non-soluble A β plaques in the brains of patients with AD. The FDA approved donanemab (Kisunla, Eli Lilly and Company, Indianapolis, USA) in July 2024, followed by approval by the UK regulatory commission in October 2024 and by the EMA's Human Medicines Committee in July 2025. Donanemab is indicated "for the treatment of MCI and mild dementia due to AD in adult patients that are apolipoprotein E ϵ 4 heterozygotes or non-carriers" [7]. Donanemab selectively binds to N3pG (pyroglutamate-modified A β), a highly pathogenic, early form of A β that contributes to plaque aggregation. This interaction facilitates plaque clearance via microglial activation, thereby promoting amyloid removal from the brain.

Unlike lecanemab, which targets both soluble and insoluble forms of A β , donanemab is designed to target a more mature form of amyloid plaques, potentially reducing long-term amyloid deposition. The TRAILBLAZER-ALZ trial demonstrated a slowing in cognitive and functional decline compared to placebo, as well as significant amyloid plaque clearance on amyloid PET imaging. Donanemab was shown to be effective in patients with low-to-intermediate tau burden and in a broader population that included individuals with high tau levels [8]. Specifically, treatment with donanemab at 76 weeks was associated with 35% slowing of decline on the primary endpoint (Integrated Alzheimer's Disease Rating Scale) in the low-medium tau group compared to 22% slowing in the combined population. Consistent results, with significant slowing were observed on prespecified secondary clinical endpoints, including the CDR-SB (36% slowing in the low-medium tau group, 29% slowing in the combined population). These results imply that early diagnosis is relevant for treatment considerations.

The EMA's Human Medicines Committee (CHMP) has recommended a marketing authorization to lecanemab for treating MCI or mild dementia in patients who have one or no copy of APOE4. The marketing authorization for donanemab was communicated in July 2025. In Switzerland – by January 2026 – no anti-amyloid immunotherapies (AATs) have been approved by Swissmedic for the treatment of patients with MCI or mild dementia due to AD. The recently published recommendations of the Swiss Memory Clinics for eligibility and treatment of AATs in Switzerland differ slightly in the exclusion criteria from those established in pivotal clinical trials [9]. Nevertheless, they reflect a necessary translation of clinical trial protocols into real-world clinical workflows as recently recommended by the Alzheimer's Disease and Related Disorders Therapeutics Work Group for lecanemab [10] and donanemab [11]. Given the rapid evolution of AAT, it is the opinion of the authors to provide the SSNR recommendation in alignment with the ASNR practical considerations for radiologists to highlight the risk of amyloid-related imaging abnormalities (ARIAs).

Prior to initiating AAT, the presence of a positive amyloid biomarker is required, either through increased amyloid burden on PET imaging or decreased A β 1–42 in CSF. Very recently, the Alzheimer's Association released its first clinical practice guideline on the use of blood-based biomarker tests [12]. Additionally, a non-contrast magnetic resonance imaging (MRI) examination is mandatory before commencing treatment.

As a general recommendation, the MRI protocol should be performed at consistent field strength for individual patients (either at 1.5 or 3 Tesla). The protocol should at least include the following sequences as listed in Table 1 :

Imaging recommendations for screening and monitoring of ARIA

Either T2* or T2* and SWI in combination should be used for interpretation. Lesion quantification should rely solely on T2* numeric evaluation based on current evidence.

A screening MRI is required for all patients considered for AAT. The Alzheimer Disease and Related Disorders Therapeutics Work Groups recommends a baseline MRI within 3–6 months before enrollment, but a brain MRI within 12 months may be adequate if negative for

microhemorrhages. The presence of 1–4 baseline microhemorrhages on a brain MRI performed 7–12 months before initiating therapy should trigger a repeat examination because these patients are of high risk for additional microhemorrhages. From a practical perspective, a baseline MRI should be planned closely to the enrollment, dependent on the given resources [10].

Pre-existing cerebral microhemorrhages have been identified as a predictor of ARIA-H; therefore, according to recommendations of the American Society of Neuroradiology and the European Society of Neuroradiology patients with more than four microhemorrhages detected on baseline T2*-weighted sequences or susceptibility-weighted imaging (SWI) must be excluded from treatment. Similarly, a single macrohemorrhage >10 mm at greatest diameter or an area of superficial siderosis excludes patients from treatment.

For patients with contraindications to MRI, including those with cardiac pacemakers, implantable defibrillators, or ferromagnetic metal implants, CT imaging is not a valid alternative, and such patients are ineligible for therapy. Furthermore, the administration of treatment is restricted to patients without evidence of advanced cerebrovascular disease on baseline imaging [13]. The baseline MRI examination must be systematically assessed for the presence or absence of the following: Acute or subacute macrohemorrhage.

Microhemorrhages (>4 microhemorrhages, each <10 mm on T2*-weighted sequences constitute an exclusion criterion).

Cortical infarctions (>1.5 cm) or >2 single lacunar infarction (≤1.5 cm).

As stated previously, both 1.5- and 3-Tesla MRI scanners can be used for pre-screening. However, the higher magnetic field strength (3T) and spatial resolution increases the probability of detecting microhemorrhages, which must be accounted for when interpreting results. Changes in field strength in the individual's evaluation are not recommended and must be documented in the reports, if not avoidable. The detection of microhemorrhages is influenced by several factors, including MRI sequence parameters, post-processing techniques, and the use of 3D sequences. Lower flip angles, prolonged echo time, and extended repetition times increase sensitivity to susceptibility effects [14].

A prior study evaluating T2*-weighted MRI sequences at 1.5T and 3.0T in healthy volunteers reported an approximately 20% higher detection rate of microhemorrhages at 3T compared to 1.5T [15]. Similarly, comparative analyses of hemosiderin-sensitive T2* and SWI sequences in dementia screening reported an average increase of 1.3 microhemorrhages on SWI (4 mm thickness) compared to thin (1.6 mm) T2* images [16]. Biffi et al. [17] have recently analyzed the ARIA-H sensitivity in GRE standard sequences versus SWI in the TRAILBLAZER-6 study. Thirty-eight patients enrolled in this cohort (4.5%) would have screen-failed if SWI imaging had been used for ARIA-H assessment. Very recently, the same authors presented new data of 840 participants who had both T2*-weighted GRE and SWI MRI scans performed before the first infusion. T2*-weighted GRE and SWI sequences resulted in similar trial eligibility and similar detection rate of the presence of treatment-emergent ARIA-H. However, ARIA-H severity was greater if SWI has been used for grading. Conclusion from these two congress presentations remains preliminary; however, SWI may provide additional information to support ARIA findings. Therefore, different treatment inclusion criteria might be required in the future [18].

Given that previous clinical trials (CLARITY-AD, TRAILBLAZER-ALZ, EMERGE, and ENGAGE) used T2*-weighted imaging as inclusion criterion, all evaluations as well as decisions should currently be primarily based on T2* GRE sequences. However, we recommend to add SWI for comparison due to the latter's higher sensitivity to susceptibility changes related to hemorrhage [3 , 4 , 14 , 15].

A previously published national recommendation states that patients should be excluded from treatment if MRI reveals evidence of prior cerebral contusion, encephalomalacia, brain aneurysms or other vascular malformations, central nervous system infection, brain tumors (except for meningiomas or arachnoid cysts <1 cm at their greatest diameter), pre-existing cerebral amyloid angiopathy (CAA), and cerebral amyloid angiopathy-related inflammation (CAA-ri) or A β -related angiitis. These criteria ensure optimal patient selection and risk minimization for AATs. Amyloid positivity can be determined by amyloid PET, CSF biomarkers and more recently – by plasma biomarkers. Following the role of the neuroradiologist, the SSNR recommends applying the criteria published in AJNR on the basis of consensus discussion within an expanded American Society of Neuroradiology Alzheimer, ARIA, and Dementia Study Group, based on available clinical data and current experience in clinical practice [13].

ARIA has been identified in patients receiving AAT in AD. These imaging abnormalities are believed to reflect increased vascular fragility and with blood or protein leakage into the extracellular space. ARIA is broadly classified into two subtypes (Tables 2 , 3): ARIA-E (edema/effusion), characterized by parenchymal edema and extracellular fluid accumulation, and

ARIA-H, defined by the presence of cerebral microhemorrhages and hemosiderin deposits.

The APOE ϵ 4 genotype has been identified as the primary genetic risk factor for both ARIA-E and ARIA-H development. Individuals who are homozygous for APOE ϵ 4 are at the highest risk, whereas heterozygous carriers exhibit an intermediate risk, and APOE ϵ 4-negative individuals have the lowest susceptibility to ARIA development. A dose-dependent relationship with increased doses of anti-amyloid treatment and ARIA has been seen with both available anti-amyloid monoclonal antibodies [3].

Lecanemab is administered as an intravenous infusion every 2 weeks, with serial MRI monitoring for ARIA required prior to the 5th, 7th, and 14th infusions to assess for the emergence or progression of ARIA-related findings. For donanemab, a new titration regimen has been approved in July 2025 by the FDA. The recommended dosing regimen of donanemab is 350 mg for infusion 1, 700 mg for infusion 2, 1,050 mg for infusion 3, and 1,400 mg for infusion 4, and every 4 weeks thereafter. The previous dosing regimen was 700 mg every 4 weeks for 3 doses, then 1,400 mg every 4 weeks. According to the FDA prescribing information for donanemab, MRI monitoring is required prior to the 2nd, 3rd, 4th, and 7th infusions to screen for ARIA [11] 10. Recently, modified titration of donanemab demonstrated reduction of ARIA-E in TRAILBLAZER-ALZ 6 phase 3b study [19].

ARIA is a known adverse effect of AAT for AD, with an incidence reported in approximately 10–30% of patients treated in clinical trials for aducanumab, lecanemab, and donanemab [20]. In high-dose lecanemab recipients, ARIA (any form) was observed in 21.5% of patients, compared to 9.5% in the placebo group [21]. Among ARIA cases, approximately 12.5% were associated with vasogenic edema and effusions (ARIA-E), whereas approximately 17% were linked to hemorrhagic changes (ARIA-H). Most imaging abnormalities develop within the first 8 months of treatment titration. Adverse effects led to discontinuation of the trial agent in 6.9% of the patients, compared to 2.9% in the placebo group [3]. Of note, both studies and real-world data report much lower percentage of symptomatic ARIAs in the range of 1–2% depending on the AAT molecule and APOE genotype.

ARIA-E can present with a wide spectrum of clinical symptoms, ranging from asymptomatic findings on imaging to significant neurological deficits. Approximately 0.9–40.6% of patients receiving anti-amyloid therapies developed ARIA-E with a majority remaining asymptomatic or experiencing only mild symptoms [20 , 22 – 24]. When symptomatic, ARIA-E commonly manifests with nonspecific neurological symptoms, including: headache, dizziness or gait disturbances, confusion or mental status changes (including disorientation and cognitive fluctuations), nausea or vomiting, or focal neurological deficits (such as hemiparesis, aphasia, or visual disturbances in severe cases) [23]. ARIA-E symptoms are thought to result from transient blood-brain barrier dysfunction, leading to vasogenic edema in affected brain regions [25]. The parietal, occipital, and frontal lobes are

most commonly involved, with occasional extension into the cerebellum and brainstem. In severe cases, increased intracranial pressure and cerebral herniation may occur, necessitating urgent intervention.

Most cases of mild to moderate ARIA-E are self-limiting and resolve with modification or temporary suspension of therapy (Table 2). However, severe cases may require corticosteroid treatment to reduce inflammation and associated vasogenic edema. Serial MRI monitoring is essential to ensure resolution of ARIA-E before therapy continuation or re-initiation [10]. Decision-making for continuation depends on severity grading. ARIA-E is usually asymptomatic and self-limiting; most patients may continue or temporarily discontinue therapy [26 , 27]. The decision to continue patients with ARIA-H on AAT therapy depends on the severity and stability over time.

ARIA-E is characterized by increased signal intensity on FLAIR and T2-weighted MRI, predominantly affecting the parietal, occipital, and frontal lobes, with less frequent involvement of the cerebellum and brainstem. [13] (Fig. 1). The severity classification of ARIA-E lesions is as follows: Mild: lesions <5 cm in diameter, confined to a single location.

Moderate: characterized by one or more lesions measuring 5–10 cm in diameter.

Severe: defined by one or more large, confluent FLAIR hyperintensities exceeding 10 cm in diameter (Table 2).

a , b Patient with ARIA-E type changes seen as hyperintensities on the FLAIR images.

The hyperintense areas associated with ARIA-E are typically located in the subcortical white matter but can also extend into the cortex or deep white matter. Sulcal effusions and extracellular exudation frequently occur, leading to proteinaceous fluid accumulation and hyperintensity in CSF, referred to as the “dirty” CSF sign [27]. It may present as either focal or multifocal abnormalities across both hemispheres. DWI restriction is not an imaging feature of ARIA-E; however, DWI is recommended to rule out acute/subacute ischemia and differentiate cytotoxic edema from ARIA-E [13].

ARIA-E is typically a transient and reversible finding, with resolution observed following modification or discontinuation of therapy [28]. Follow-up imaging is essential to confirm the resolution of edema and hyperintensities, which typically occur within a few weeks to months.

ARIA-H occurs in approximately 10–20% of patients undergoing AAT and may develop in conjunction with ARIA-E [13]. ARIA-H may progress with continued immunotherapy, especially at higher dosages, though it remains asymptomatic in many cases. Unlike the vasogenic edema of ARIA-E, which is typically reversible, microhemorrhages or superficial siderosis persist even after discontinuation of therapy. The presence of multiple microhemorrhages, superficial siderosis, or lobar hemorrhage increases the risk of progressive cognitive impairment or vascular cognitive decline. These findings require careful monitoring due to their potential clinical implications, potentially predisposing patients to future intracerebral hemorrhage [29]. Serial MRI monitoring is crucial, as progression of microhemorrhages may necessitate treatment pause or permanent discontinuation. In cases of significant symptomatic hemorrhage, corticosteroids or supportive management may be required [13].

Hemosiderin deposits, including cerebral microhemorrhages and superficial siderosis, are hallmarks of ARIA-H and can be visualized on iron-sensitive sequences [30]. Microhemorrhages constitute the majority of ARIA-H abnormalities and may serve as an early indicator of treatment-related hemorrhagic risk [31] (Fig. 2 , Table 3).

a , b Patient with ARIA-H changes with signal drops on T2* images in the occipital lobes.

Key imaging features of ARIA-H are cerebral microhemorrhages, appearing as punctate hypointense foci on SWI and T2*-weighted sequences, with a preferred distribution along the gray-white matter junction. Unlike hypertensive microhemorrhages, which predominantly affect the deep brain regions, microbleeds in ARIA-H tend to involve the cortical and subcortical white matter [31]. Superficial siderosis, another hallmark of ARIA-H, appears as linear susceptibility artifacts along the cortical surface, reflecting hemosiderin deposition due to prior superficial hemorrhage or blood product leakage into the subarachnoid space. This finding is best visualized on SWI or T2*-weighted MRI, presenting as a characteristic rim-like hypointensity [31]. The severity classification of ARIA-H is as follows: Mild: ≤ 4 microhemorrhages or a single localized area of superficial siderosis.

Moderate: 5–9 microhemorrhages or two areas of superficial siderosis.

Severe: ≥ 10 microhemorrhages or >2 areas of superficial siderosis (Table 3).

Patients who are APOE $\epsilon 4$ homozygous are at a higher risk of developing ARIA-H, particularly those receiving higher AAT doses [26 , 32]. Additional risk factors for ARIA-H are age, antithrombotic use, and history of prior strokes.

The APOE $\epsilon 4$ genotype has been identified as the primary genetic risk factor for both ARIA-E and ARIA-H development. Individuals who are homozygous for APOE $\epsilon 4$ are at the highest risk, whereas heterozygous carriers exhibit an intermediate risk, and APOE $\epsilon 4$ -negative individuals have the lowest susceptibility to ARIA development.

A key determinant of ARIA risk is the specific anti-A β antibody used, providing insight into potential mechanisms underlying ARIA development [33]. Interactions between A β antibodies and CAA potentially influence the risk for ARIA-E [34]. Antibodies such as aducanumab, lecanemab, and donanemab have shown different bindings to CAA fibrils, suggesting a potential interaction with CAA and ARIA risk [3 , 4 , 35]. Notably, lecanemab has demonstrated a lower affinity for CAA in vitro and a lower incidence of ARIA in clinical trials compared to other antibodies, though direct comparisons across studies are confounded by differences in dosage regimens, administration schedules, and baseline patient characteristics, including A β burden and cognitive status [3 , 34]. A dose-dependent relationship with increased doses of anti-amyloid treatment and ARIA has been seen with both available anti-amyloid monoclonal antibodies [26].

In contrast to genetic and vascular risk factors, analyses of ARIA incidence have not identified gender differences as a significant predictor. However, Chen et al. [36] recently demonstrated a favorable risk-benefit profile in the Asian Clarity-AD region cohort. The incidence of adverse events leading to study drug dose interruption or withdrawal and adverse side effect as infusion-related reactions, ARIA-E and ARIA-H tended to be lower in the Asia region population than those of the overall population. A lower prevalence of CAA may be a possible explanation, but evidence is still limited with mixed results in the literature.

However, the limited diversity in study populations, predominantly consisting of non-Hispanic white individuals, may restrict the generalizability of these findings. Future studies with more diverse cohorts are necessary to assess potential demographic influences on ARIA risk.

The neuroimaging characteristics of ARIA closely resemble those observed in CAA-ri, a spontaneously occurring syndrome that has also been reported in association with anti-A β (auto)antibodies [25] (Fig. 3). The hallmark MRI feature of CAA-ri-associated vasogenic edema is the presence of unifocal or multifocal white matter hyperintensities that exhibit an asymmetric distribution extending into the immediately subcortical white matter. This pattern was validated in a study of 17 individuals with pathologically confirmed CAA-ri, demonstrating a 97% specificity in differentiating CAA-ri from non-inflammatory CAA in a cohort of 37 patients [37]. Notably, these MRI features are nearly identical to the brain parenchymal lesions characteristic of ARIA-E.

a Biopsy-proven CAA-ri in a 65-year-old male without AAT, axial 2 days FLAIR and axial SWI sequence, 3T MRI. Note the extensive white matter hyperintensities on T2-FLAIR that are asymmetric and extend to the immediately subcortical white matter and sulci. b Multifocal corticosubcortical hemorrhagic lesions are denoted on the SWI.

Similarly, the cortical cerebral microbleeds, cortical superficial siderosis, convexity subarachnoid hemorrhage, and lobar intracerebral hemorrhages observed in ARIA-H align with the diagnostic imaging criteria for probable CAA, as established by the pathologically validated Boston Criteria 2.0 [38]. This overlap supports a potential role of CAA in the pathogenesis of ARIA, reinforcing the need for careful differentiation.

AATs provide a new therapeutic avenue for patients with MCI or mild dementia due to AD. The risk of ARIA presents significant challenges in patient selection, monitoring, and management. EMA and UK regulatory agencies have restricted lecanemab and donanemab use to APOE ϵ 4 heterozygotes or non-carriers, citing insufficient evidence to establish a positive benefit-risk balance in homozygous carriers [39].

For neuroimaging-based risk stratification, the FDA recommends caution in patients with increased hemorrhagic risk but does not explicitly exclude individuals with preexisting lesions, if their number is not more than 4 on T2* imaging. Appropriate use recommendations for donanemab and lecanemab advise excluding patients with intracerebral hemorrhages >1 cm, any cortical superficial siderosis, or more than four cerebral microbleeds, mirroring clinical trial exclusion criteria. The contrasting stricter exclusion criteria recently recommended by the Swiss Memory Clinics Association list probable CAA, according to Boston 2.0 criteria as an exclusion criterion. Here, patients who present with one lobar hemorrhagic lesion (i.e., a single microbleed) plus one additional white matter feature would fulfill the strict interpretation for exclusion. In addition, the appropriate use recommendations suggest excluding any patient with even one area of cortical superficial siderosis from donanemab treatment, pending further safety data [11]. The role of the (neuro-)radiologist must therefore be supportive to secure the appropriate reporting of the numbers and potential origin of microbleeds for clinical decision-making.

Given the potential for symptomatic and severe ARIA, regular MRI surveillance is critical. Imaging should be performed in the early phase of the treatment and at regular intervals specified by the national authorities thereafter to detect new or progressive ARIA. If a patient develops neurological symptoms suggestive of ARIA, including headache, confusion, dizziness, or focal deficits, an emergency MRI should be performed within 24 h using the same scanner and protocol as routine monitoring to minimize bias and false-positive findings.

Differential diagnosis is essential, as several conditions can mimic ARIA on imaging. Inflammatory CAA closely resembles ARIA-E and may represent an autoimmune reaction against vascular amyloid deposits. Similarly, posterior reversible encephalopathy syndrome, progressive multifocal leukoencephalopathy, vasculitis, and subacute infarcts should be considered when evaluating ARIA-like findings [40]. Notably, ARIA-E and posterior reversible encephalopathy syndrome both predominantly affect the occipital lobes and may present with petechial hemorrhages, further complicating radiological differentiation.

The primary intervention for ARIA is modification of antibody dosing. FDA prescribing information (label) recommend suspension of therapy for moderate-to-severe radiographic ARIA-E or ARIA-H, symptomatic ARIA-E, or any symptomatic ARIA-H.

For further information, refer to the appropriate use recommendations, which differ between lecanemab and donanemab (Tables 4 , 5). Severe cases may benefit from anti-inflammatory treatment, such as intravenous methylprednisolone (1 g for 3–5 days) followed by an oral prednisone taper over 6–12 weeks, an approach commonly used in CAA-ri [41]. The impact of antithrombotic therapy on ARIA risk remains a critical concern. Patients on antiplatelet agents, such

as aspirin, were included in clinical trials, and available data do not indicate an increased ARIA risk in this population [42]. However, the safety of anticoagulants is less certain. In lecanemab trials, intracerebral hemorrhage occurred in 2.7% of anticoagulated patients compared to 0.4% of non-anticoagulated patients, including two fatal cases [42]. While donanemab data have not demonstrated a similar risk, caution is advised when prescribing anti-amyloid therapies in anticoagulated individuals until further safety data are available. A particularly high-risk scenario involves the administration of thrombolytic therapy in patients receiving anti-amyloid treatment. Two fatal cases have been reported following thrombolysis in patients on lecanemab or donanemab, raising substantial concerns about its safety. One hypothesis suggests that these patients may have had ARIA-E mimicking acute stroke, leading to inappropriate thrombolysis [43 , 44]. The FDA has issued a black box safety warning for donanemab, recommending that clinicians carefully evaluate for ARIA before administering thrombolytics, ideally with pretreatment MRI imaging. Similarly warnings are present in appropriate use recommendations for lecanemab until more safety data become available [10]. Mechanical thrombectomy without thrombolysis appears safe and remains a viable option for large vessel occlusion in patients under anti-amyloid immunotherapies.

Appropriate use recommendations for donanemab (Rabinovic et al. [11])

a Stop treatment if: any macrohemorrhage, more than 1 area of superficial siderosis (risk/benefit assessment of treatment continuation is recommended if a single area of superficial siderosis emerges during treatment), more than 10 microhemorrhages since treatment initiation, more than 2 episodes of ARIA, radiographically severe ARIA, serious symptoms of ARIA, the patient requires treatment with an anticoagulant.

Appropriate use recommendations for lecanemab (Cummings et al. [10])

a Stop treatment if: any macrohemorrhage, more than 1 area of superficial siderosis, more than 10 microhemorrhages since treatment initiation, more than 2 episodes of ARIA, severe symptoms of ARIA, the patient requires treatment with an anticoagulant.

A recent phase 3b study (NCT05738486) demonstrated a reduction in ARIA-E at the 24-week primary endpoint for people receiving a modified titration of donanemab. Patients on modified titration received a shift of one vial from the first infusion to the third infusion. The primary endpoint of the study was the proportion of participants with any occurrence of ARIA-E by week 24, and the results showed the incidence of ARIA-E was 14% in patients receiving the modified titration compared with 24% for those receiving the standard dosing regimen, a 41% lower relative risk. The largest ARIA-E reduction with the modified titration was seen in apolipoprotein E (APOE4) homozygotes, carriers of a known genetic risk factor for developing AD. In these patients, 19% had ARIA-E on the modified titration as compared to 57% on the standard dosing regimen, resulting in a 67% lower relative risk [19]. Further drugs are currently under evaluation [45]. Interim results showed that 91% of patients given the highest dose of trontinemab achieved amyloid negativity at 28 weeks, but most of this reduction was achieved rapidly with 60% amyloid reduction already seen at 8 weeks. Less than 5% of participants have experienced ARIA with brain swelling or bleeding to date, compared with an average of 13% for lecanemab and 24% for donanemab, suggesting further reduction of side effects. The latest results from the dose-expansion part (Part 2) of the Brainshuttle™ AD study of trontinemab in people with Alzheimer's disease are available [47 , 48].

To mitigate ARIA risk, patients with AD preview for AAT must undergo baseline and serial MRI assessments, with screening for preexisting cerebrovascular pathology, including microhemorrhages, cortical superficial siderosis, and CAA-ri. Regulatory agencies vary in their patient selection criteria, with some restricting use in APOE ε4 homozygous carriers due to their increased ARIA susceptibility. Management strategies for ARIA involve dose adjustments, temporary treatment suspension, and symptomatic intervention, with anti-inflammatory therapy considered in severe cases. The potential interaction between anti-amyloid therapies and antithrombotic treatments, particularly anticoagulants and thrombolytics, remains a critical safety

concern. Given the growing use of anti-amyloid immunotherapies, radiologists and neuroradiologists play a pivotal role in screening, monitoring, and guiding clinical decision-making to balance therapeutic benefits against potential risks. Standardized neuroimaging protocols and rapid response pathways for ARIA evaluation, similar to stroke and seizure units, are mandatory to ensure safe and effective treatment of AD patients undergoing anti-amyloid immunotherapies.

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