REVIEW ARTICLE

Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics

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Abstract

Excess accumulation and aggregation of toxic soluble and insoluble amyloid-β species in the brain are a major hallmark of Alzheimer's disease. Randomized clinical trials show reduced brain amyloid-β deposits using monoclonal antibodies that target amyloid-β and have identified magnetic resonance imaging signal abnormalities called amyloid-related imaging abnormalities (ARIA) as possible spontaneous or treatment-related adverse events. This review provides a comprehensive state-of-the-art conceptual review of radiological features, clinical detection and classification challenges, pathophysiology, underlying biological mechanism(s), and risk factors/predictors associated with ARIA. We summarize the existing literature and current lines of evidence with ARIA-edema/effusion (ARIA-E) and ARIA-hemosiderosis/microhemorrhages (ARIA-H) seen across anti-amyloid clinical trials and therapeutic development. Both forms of ARIA may occur, often early, during anti-amyloid-β monoclonal antibody treatment. Across randomized controlled trials, most ARIA cases were asymptomatic. Symptomatic ARIA-E cases often occurred at higher doses and resolved within 3–4 months or upon treatment cessation. *Apolipoprotein E* haplotype and treatment dosage are major risk factors for ARIA-E and ARIA-H. Presence of any microhemorrhage on baseline MRI increases the risk of ARIA. ARIA shares many clinical, biological, and pathophysiological features with Alzheimer's disease and cerebral amyloid angiopathy. There is a great need to conceptually link the evident synergistic interplay associated with such underlying conditions to allow clinicians and researchers to further understand, deliberate, and investigate on the combined effects of these multiple pathophysiological processes. Moreover, this review article aims to better assist clinicians in detection (either observed via symptoms or visually on MRI), management based on appropriate

use recommendations, and general preparedness and awareness when ARIA is observed as well as researchers in the fundamental understanding of the various antibodies in development and their associated risks of ARIA. To facilitate ARIA detection in clinical trials and clinical practice, we recommend the implementation of standardized MRI protocols and rigorous reporting standards. With the availability of approved amyloid-β therapies in the clinic, standardized and rigorous clinical and radiological monitoring and management protocols are required to effectively detect, monitor, and manage ARIA in real-world clinical settings.

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Abbreviations: Aβ = amyloid-β; APOE = apolipoprotein E; ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality-edema/effusion; ARIA-H = amyloid-related imaging abnormality- hemosiderosis/microhemorrhages; AUR = Appropriate use recommendations; CAA = cerebral amyloid angiopathy; CAA-ri = cerebral amyloid angiopathy-related inflammation; CAD = computer-aided diagnosis; FDA = Food and Drug Administration; FLAIR = fluid-attenuated inversion recovery**;** GRE = gradient recalled echo; IgG = Immunoglobulin G; mH = microhemorrhage; P-tau = phosphorylated tau; RCT = randomized clinical trial; sAβ = soluble Aβ; SWI = susceptibility weighting imaging; TE = echo time

Introduction – Historical Background & Definition of ARIA

Alzheimer's disease is a primary neurodegenerative disease leading to a clinical dementia syndrome, which is projected to affect 152.8 million people by 2050 worldwide.[1] Translational studies support a descriptive hypothetical model of Alzheimer's disease pathophysiology, characterized by the accumulation of aggregated amyloid-β (Aβ) species into plaques. This precedes clinical manifestations by 20–30 years, neuroinflammation, and the spreading of phosphorylated tau and neuronal loss.[2,3] Currently, monoclonal antibodies that remove Aβ from the brain are in several late-stage randomized clinical trials (RCTs).[4-6]

The use of anti-Aβ antibodies has been associated with treatment-emergent MRI signal abnormalities,[7] coined amyloid-related imaging abnormalities (ARIAs) at the Alzheimer's Association Research Roundtable in 2011.[8] ARIA covers two classes of MRI signal abnormalities. ARIA-edema/effusion (ARIA-E) refers to the extravasation of fluid resulting in interstitial vasogenic edema or sulcal effusion in the leptomeningeal/subpial space.[8,9] These

manifest as hyperintense parenchymal or sulcal abnormalities such as changes to cortical folds on T2-weighted and fluid-attenuated inversion recovery [FLAIR] sequence images (representative MRI images of ARIA-E shown in **Figure 1**).[8-10] ARIA-hemosiderosis/microhemorrhages (ARIA-H) refers to microhemorrhages (mH) or macrohemorrhages observed as hypointense hemosiderin deposition. These reflect iron accumulation following the breakdown of extravasated hemoglobin on gradient recalled echo (GRE)/T2* images or with enhanced visualization processing by susceptibility weighting imaging (SWI) sequences.[8,11,12] Under the rigorous protocols and conditions of clinical trials, ARIA-E/H have generally been asymptomatic and have usually resolved within 3–4 months with dose adjustment, suspension, or discontinuation.[13-15] In the minority of cases when ARIA-E was symptomatic, most were of mild or moderate severity. Rare serious or severe neurological symptoms may require hospitalization and specific monitoring and management (e.g., intensive care unit admission, electroencephalography, corticosteroids, antiepileptics).[7,13-15] The recent accelerated approvals of anti-Aβ antibodies by the United States Food and Drug Administration (FDA)[16,17] underscores the importance of safety monitoring and effectively managing ARIA in the real-world clinical setting. This state-of-the-art review provides an overview of the radiological features, detection and classification challenges, pathophysiology, and risk factors/predictors associated with ARIA.

Radiological Features of ARIA

ARIA-E

ARIA-E is characterized as the extravasation of fluid resulting in interstitial vasogenic edema or sulcal effusion in the leptomeningeal/subpial space.[8,9] ARIA-E severity is heavily dependent on the location and extent of the abnormality (**Table 1**).[8-10,18-20] The sulcal effusion/exudates in ARIA-E may reflect leakage of proteinaceous fluid that is limited to the leptomeningeal/subpial space.[8,9] Both forms of ARIA-E are typically transient and are not associated with restricted diffusion, thus differentiating it from ischemia.[9]

ARIA-H

ARIA-H is typically characterized as cerebral microhemorrhages and/or hemosiderosis. Rare macrohemorrhages have been reported in patients treated with anti-Aβ antibodies. Most cases

were asymptomatic, with antibody treatment being discontinued.[14,21,22] mH are described as lesions (≤10 mm or ≤5 mm in diameter) in brain imaging where actual size criteria depend on the study.[8,14,21,22] The GRE/T2* MRI sequence has a superior sensitivity to FLAIR and turbo spin-echo T2. This enables the detection of small quantities of blood products associated with the mH of ARIA-H.[23] The antibody-associated hemosiderin deposits identified on imaging consist of mH, macrohemorrhages, and superficial siderosis (representative MRI images of ARIA-H are shown in **Figure 1**).

ARIA-H mH are generally small, circular, or elliptical, very low intensity (compared with surrounding brain matter) lesions in the brain parenchyma on GRE/T2* MRI sequences.[8] mH likely result from microruptures in blood vessels in cortical regions and leakage of small amounts of iron-containing blood products into adjacent brain parenchyma.[8,24]

ARIA-H superficial siderosis typically manifests as curvilinear low intensities on GRE/T2* MRI sequences located near the brain surface. A distinction between the ARIA-H subtypes is that in superficial siderosis, the leakage of blood traverses into the adjacent subpial space or the subarachnoid compartment. In mH, leakage traverses into the perivascular space and surrounding vessel wall.[8] Similar to ARIA-H mH, the number of areas affected by superficial siderosis determines its severity (**Table 1**).[18]

Pathophysiological Mechanisms and Commonalities Between Alzheimer's Disease, Cerebral Amyloid Angiopathy and ARIA

Commonalities Between Alzheimer's Disease and Cerebral Amyloid Angiopathy

The accumulation and deposition of Aβ plays a shared role in the pathology of Alzheimer's disease and cerebral amyloid angiopathy (CAA).[25] In CAA, Aβ deposition favors the vascular wall while in Alzheimer's disease, Aβ deposition occurs in the brain parenchyma.[25] CAA is frequently detected in up to 90% of patients with Alzheimer's disease and in approximately 50% of elderly above the age of 80.[26] Similar to Alzheimer's disease, CAA pathology is shown to likely occur years before any symptomatic manifestations.[27] When CAA manifestations occur,

they often present broadly and consist of cognitive decline, lobar intracranial hemorrhage, or intermittent focal neurological symptoms.[25,27] Despite the overlapping pathology of Aβ deposition in CAA and Alzheimer's disease but with different focal points of vascular or parenchyma respectively, the physiological consequence diverge.[25] In CAA, Aβ deposition in the walls of small- and medium-sized blood vessels leads to downstream effects including gradual vessel stiffening and vessel-wall fragility.[25,28-30] Impairment of Aβ degradation and/or clearance may increase CAA severity through diverting Aβ to perivascular drainage pathways.[31] CAA often results in tissue injury leading to hemorrhagic or ischemic brain injury while Alzheimer's disease elicits loss of neurons and synapses.[25] It has also been shown that CAA is associated with Alzheimer's disease dementia independent of amyloid plaque and tau tangle pathology, further highlighting the substantial heterogeneity underlying the current clinical biological construct of Alzheimer's disease.[32,33]

In a minority of patients, CAA may trigger an autoimmune inflammatory reaction known as CAA-related inflammation (CAA-ri). CAA-ri often occurs spontaneously and can trigger the occurrence of ARIA.[34,35] The MRI findings of CAA and CAA-ri closely resemble ARIA-H and ARIA-E, respectively.[35,36]

Putative Pathophysiological Mechanisms of ARIA

In Alzheimer's disease, brain parenchymal Aβ plaques are associated with gradual loss of cerebral vascular integrity and reduced perivascular clearance.[10,11,25,30] In patients with pre-existing Aβ vascular pathology, anti-Aβ immunization may temporarily increase vascular vulnerability due to breakdown of plaques in response to immunization. This increases the mobilization of Aβ aggregates from the parenchyma and vasculature.[10,11,25,37] Aβ40 is the predominant species in vascular walls. Aβ aggregation and deposition may increase the progression of CAA (features of CAA are described in the subsequent sections).[30,38] Aβ42 deposits are the major species in the parenchymal plaques.[25] Anti-Aβ antibodies bind to accessible Aβ in the vasculature, further disrupting its vascular integrity.[25] Since perivascular clearance pathways are impaired in Alzheimer's disease and Aβ alterations take place within the walls of blood vessels, an immune response against vessels is initiated, increasing vascular

permeability.[11] Although often co-localized and disseminated over time, the amyloid vascular accumulation suggests a potential synergy in pathophysiological mechanism.[11]

ARIA-H may be caused by anti-Aβ-mediated displacement of Aβ from the plaques in the parenchyma to vessel walls, which increases the severity of potentially pre-existing CAA. This results in subsequent extravasation and ultimately leakage of blood products through damaged vessel walls.[11,25,37]

In 49% of ARIA-E cases, ARIA-H co-occurred.[9] mH may often present and accumulate over time in areas where ARIA-E is resolving or recently resolved.[9] This suggests a considerable overlap in underlying pathophysiological mechanisms.[9] In particular, vascular Aβ accumulation and clearance as potential mechanisms support the frequent co-occurrence of ARIA-E and ARIA-H. Further research and familiarity with MRI findings are warranted for proper detection, monitoring, and management of ARIA.[9]

Lessons from Active Aβ Immunotherapy

The imaging features of the meningoencephalitis and cortical hemorrhages experienced with active Aβ immunotherapy with AN1792 (Elan Pharmaceuticals) are similar to ARIA.[21,39-43] However, pathological information for ARIA from passively immunized patients for comparison with findings from AN1792 is lacking. Neuropathologic studies of patients treated with AN1792 suggest that anti-Aβ antibodies bind to and disrupt brain Aβ plaques. Solubilized Aβ is then translocated to the vasculature where it accumulates in arterial and capillary walls, putatively the intramural peri-arterial drainage pathway,[44] increasing CAA severity.[45] This may provoke vascular inflammation analogous to spontaneous CAA-ri and potentially focal removal of Aβ from CAA-affected vessels mediated by the antibodies. The overall effect is vascular leakage of fluid resulting in ARIA-E (effusion) and blood leakage resulting in ARIA-H (mH).[46] Poorly understood mechanistic aspects include whether Aβ is transported to the vasculature in association with antibody (i.e., in the form of immune complexes) as a conjugate to apolipoprotein E (APOE) or as unassociated soluble Aβ.[47] Regarding ARIA-E, the role of astrocyte end-feet and aquaporin4, which control water flux across the blood-brain barrier, as a cellular and molecular locus of neuro-vascular interaction is hypothetical.[48] The common co-occurrence of ARIA-E and ARIA-H – with mH appearing in areas where ARIA-E is resolving or

resolved – highlights the dynamic aspects of plaque removal as ARIA co-localizes with foci of Aβ removal as demonstrated by PET scanning.[11]

Roles of Therapeutic Variables

Factors associated with the magnitude of extravasation events following anti-Aβ immunization include: the extent of age-related ischemic vasculature changes, the severity of underlying CAA, the extent and magnitude of transport of soluble Aβ to the vessel wall followed by antibody-mediated removal of Aβ from vessel walls, and the amount of local inflammation represented by infiltration of microglia and T-cells to the area due to anti-Aβ complexes at the vessel wall (**Figure 2**).[11,25,37] Repeated anti-Aβ antibody therapy may reduce the total Aβ burden, attenuating the risk of extravasation events owing to continued clearance of vascular Aβ and enhanced vessel wall integrity, however, this requires further and long-term study.[11]

RCTs suggest that antibodies binding to different epitopes and recognizing different Aβ conformations (monomers, oligomers, protofibrils, fibrils) play a role in ARIA rate variance.[49] Higher rates of ARIA are found in antibodies against the N-terminus compared with antibodies targeting mid- and C-terminal regions of Aβ.[25] The latter antibodies mobilize fewer Aβ due to their binding propensity to monomeric or oligomeric Aβ.[25] Despite higher rates of ARIA, antibodies against the N-terminus of Aβ were most effective in reducing the Aβ burden.[49]

The isotype form of the anti-Aβ antibody (Immunoglobulin G (IgG)1, IgG2, IgG4) and the selectivity for specific Aβ forms (soluble or deposited forms) were additional considerations that trigger ARIA or CAA-like manifestations.[50] IgG1 anti-Aβ triggered ARIA-E and ARIA-H events while IgG2 and IgG4 anti-Aβ were less likely to actuate CAA-like manifestations.[50] Antibodies more selective in targeting soluble Aβ forms were less likely to bind to cerebrovascular deposits, unlike those targeting insoluble forms.[50] This may help emphasize that ARIA and CAA share commonalities in their pathophysiological mechanisms and the predisposition of certain groups to ARIA.

Commonalities Between CAA and ARIA

CAA has many clinical, pathophysiological, and neuroimaging features similar to ARIA.[8,25,51] The most significant evidence of shared pathophysiology between ARIA and CAA is spontaneous ARIA-E triggered by CAA-ri in the early stages of sporadic and familial Alzheimer's disease.[25,51] CAA-ri (aka Aβ-related angiitis) occurs in a minority of patients where the clinical presentation, neuroimaging features, and association with *APOE ε4* are similar to ARIA-E in patients with Alzheimer's disease receiving immunotherapy.[25,52] The active stage of CAA-ri is characterized by activation of microglia, T-cells, and Aβ-containing multinucleated large cells surrounding CAA-positive vessel walls, signifying a spontaneous anti-antibody autoimmune response via Aβ-autoantibodies.[25,30,52] Furthermore, the MRI findings of CAA and CAA-ri closely resemble ARIA-H and ARIA-E respectively.[35,36] In phase 2 trial of bapineuzumab, vasogenic edema, now commonly referred to as ARIA-E, occurred spontaneously with CAA, was transient in nature, and resolved on MRI upon discontinuation.[53] Similarly, cerebral microhemorrhages, now commonly referred to as ARIA-H, have been shown to occur spontaneously in up to 19%, 32%, and 38% of cognitively normal elderly, Alzheimer's disease patients, and individuals with mild cognitive impairment, respectively.[54] ARIA-H is also considered a complication of CAA and small vessel angiopathy.[54]

Clinical Presentation and Management of ARIA

Identifying symptoms commonly seen with ARIA may assist treating clinicians in implementing a strategy for appropriate detection, classification, monitoring, and management. ARIA-E and ARIA-H events are predominantly reported in patients on active anti-Aβ antibody therapy. However, occasional cases are reported in cognitively normal patients on the usual course of Alzheimer's disease as well as in patients receiving a placebo treatment.[22,55]

ARIA-E events during various clinical trials are found to be mostly clinically asymptomatic with symptomatic cases accounting for 6.1% to 39.3% depending on the investigational therapeutics and doses, with the most commonly reported symptoms being headache, confusion, vomiting, visual, or gait disturbance.[6,10,22,56-59] Management of ARIA-E in RCTs, particularly decisions around continuing, reducing the dose, or withdrawing anti-Aβ antibody therapy, were drug-

specific and dose-dependent. Most cases of ARIA-E resolved within a span of weeks to months after withholding or discontinuing anti-Aβ antibody.[11,54,57]

Appropriate use recommendations (AUR) for the available anti-Aβ antibodies with accelerated FDA approval for treating patients with early Alzheimer's disease have proposed ways to potentially mitigate the risk of ARIA.[13,15,60] In general, AURs are written by community experts not as a guideline but as a complement to prescribing information to help physician in treatment decision and management. Despite AURs being tailored to each specific anti-amyloid antibody, the common considerations for the anti-amyloid antibodies include clinician awareness of individual's medical history and APOE genotype status. AURs for anti-amyloid therapeutics to date propose a framework for evaluation and management protocols in cases when severe symptoms or signs may be due to ARIA. This includes urgent assessments and early treatment initiation of high-dose steroids. Current AURs propose continued dosing through asymptomatic mild ARIA with serial MRI monitoring.[13,15,60] In asymptomatic moderate ARIA cases, a dose suspension with serial MRI monitoring is recommended.[15,60] Whereas, in cases of severe symptomatic or recurrent ARIA of even mild severity (more than two episodes), treatment discontinuation is recommended.[15,60] In some instances when ARIA was quite severe or symptoms were considered serious, corticosteroids have been empirically administered to alleviate symptoms and reduce recurrence, as with treatment of CAA-ri.[13,34,53]

If medical conditions requiring anticoagulation (atrial fibrillation, deep vein thrombosis, pulmonary embolism) emerge, therapy must be discontinued.[13,60] Previous clinical trials have shown that concomitant anti-amyloid treatment with anticoagulants, antiplatelets, or antithrombotics is associated with increased risk of ARIA, particularly ARIA-H warranting potential exclusion in these patient populations.[12,60,61] As new therapies become available, the establishment of uniform guidelines and recommendations on ARIA management will be imperative in ensuring patient safety.

Risk Factors of CAA and Commonalities with Alzheimer's Disease

APOE ε4 genotype is a significant risk factor for CAA, Alzheimer's Disease, and ARIA.[8,25,30,62-64] APOE, primarily synthesized by astrocytes and microglia, binds to Aβ peptides with high

avidity, amplifying the emergence of Aβ fibrils.[25] The *APOE ε4* genotype and low Aβ42:40 ratio may promote CAA.[63] Since Aβ40 contributes to inhibiting fibril formation, it is another important component of developing severe CAA.[63] The *APOE ε2* genotype is a risk factor for CAA-related intracerebral hemorrhage despite evidence suggesting *ε2* carriers have protective effects against AD.[65,66] Additional risk factors of CAA include older age and superficial siderosis, the latter being often characterized as ARIA-H in clinical trial context.[36,67]

Risk Factors and Predictors of ARIA

The three main risk factors for ARIA are exposure to anti-Aβ antibody, presence of pre-existing microhemorrhages, and *APOE ε4* carrier status (**Figure 1)**.[7,11,19,22,57,58] The presence of baseline mH increases risk for developing ARIA-H with anti-Aβ antibody therapy.[12,35] The extent and incidence of ARIA may vary across anti-Aβ antibody therapies likely attributing to the differing mechanisms of action, therapeutic properties, and selectivities to amyloid confirmations.

Results from a retrospective analysis of bapineuzumab trials found the greatest incidence of ARIA-E when the two highest drug doses were used (hazard ratio of 3 in patients receiving 2 or 1 mg/kg dose).[11] *APOE ε4* carriers treated with anti-Aβ antibodies had a greater risk of developing ARIA compared with non-carriers; those who were *APOE ε4* homozygous were at greatest risk (**Table 2**).[11,22] *APOE* genotyping should be suggested for patients considering anti-Aβ antibody drug initiation to enable better risk evaluation, to allow for better patient/family counseling and informed decisions, and to optimize safety monitoring and management of potential treatment-emergent ARIA.[30,60]

Other ARIA-H risk factors include the extent of brain parenchymal or vascular Aβ deposition, and the level of pre-existing CAA.[12] Severe CAA or brain MRI-detected baseline mH increase ARIA risk.[19,68] It is recommended to identify past medical conditions that may predispose to ARIA or increase the likelihood of ARIA-related complications. Such medical conditions include pre-existing autoimmune or inflammatory conditions, seizures, transient ischemic attacks, cerebrovascular disease, or substantial changes in the brain white matter.

Protein biomarkers (particularly CSF biomarkers) have potential application in the detection, monitoring, and management of ARIA.[68,69] In particular, CSF Aβ autoantibodies are seen in spontaneous ARIA-like events (i.e., CAA-ri), providing a better understanding of the

pathophysiology.[68,70] This may also hold promise as a future biomarker for ARIA surveillance and management.[68,70] Recovery from ARIA (following application of appropriate management protocols) is associated with reductions in CSF tau, phosphorylated tau (P-tau), total tau, Aβ40, and autoantibody concentration.[68,71] Analysis of baseline protein CSF biomarkers as potential predictors of future ARIA requires further investigation.[71] Similarities in pathophysiological mechanisms between CAA-ri and ARIA are not fully understood. Past evidence supports the use of CSF Aβ autoantibodies as a valid biomarker in CAA-ri diagnosis.[51,68] Future studies should assess whether these findings apply to ARIA, and whether monitoring CSF Aβ autoantibodies in patients with Alzheimer's disease treated with anti-Aβ antibodies offers a viable safety biomarker of ARIA-related adverse events.[51,68]

Prevalence of ARIA in the Research Population

Although most often associated with anti-amyloid trials, ARIA has also been observed in the natural course of Alzheimer's disease at lower rates. In patients with Alzheimer's disease dementia who have not received anti-Aβ antibody therapy, ARIA-E prevalence is <0.1% to 0.8% while ARIA-H prevalence is between 9.2% and 33%.[55,72] Previously reported studies suggest that an increase in age correlates to higher odds of ARIA-H and mH rates in Aβ+ populations.[55]

In Phase 3 clinical trials, baseline prevalence of ARIA-E was low (~0.1% and 0.8% depending on the anti-Aβ antibody being tested).[11,22,73] For ARIA-H, the prevalence of spontaneous mH in the general older adult population was relatively high.[74,75] In the population-based Rotterdam Scan Study (N=1062), 17.8% of participants aged 60–69 had mH. The prevalence increased to 38.3% in those aged ≥80 years.[74] A meta-analyses based on five prevalence studies found that mH were present in 23% of patients with AD.[76] In contrast to mH, the prevalence of superficial siderosis was much less common (0.7% in the Rotterdam Study population).[77]

A systematic review of 22 RCTs, 11 secondary analyses of RCTs, and a case report, comprising a total of 15,508 adult patients, found that ARIA-H and ARIA-E generally manifested early during the study course.[7] Most ARIA-E cases resolved spontaneously once treatment was withheld; though in cases of severely symptomatic ARIA, empirical use of steroids has been reported.[7] The recurrence rates for ARIA-E after dose re-initiation or adjustment varied from

13.8% to 25.6% across RCTs.[7] In contrast, ARIA-H cases were generally found to be asymptomatic.[7]

Detection and Classification Challenges in ARIA

Since the clinical significance of asymptomatic ARIA remains unclear, RCTs include a contingent ARIA protocol as a precaution.[78] Contingent ARIA protocols may require un-blinding in the case of dose suspensions or need for repeated MRIs. Therefore, treatment allocation can be disclosed to all stakeholders (caregivers, patients, and investigators) potentially affecting outcome assessments, especially those requiring caregiving reports.[78] Future ARIA protocols should consider a blinded radiologist to read the magnetic resonance images and include a placebo arm to avoid potential knowledge bias.[78]

ARIA-H detection and classification can be challenging due to the small lesion sizes and the apparent similarity with other types of brain microbleeds.[30] Accurately and consistently measuring the size criteria of mH requires access to advanced technical features.[8] Furthermore, the problem may be amplified by the 'blooming effect'. This is where the apparent size of the mH on MRI appears bigger than the size of the histologically defined area of the hemosiderin deposited in the tissue.[8,30] Therefore, training neuroradiologists and using a standardized MRI protocol to quantify the number of mH present is important. Such challenges associated with identification and differentiation between suspected CAA, microhemorrhages, or hemosiderin deposits (often designated as ARIA-H) are of particular importance when the potential use of anti-amyloid antibody is expanded to include individuals with vascular comorbidities.[30] Thus, there may be a need for consensus or re-definition of terminology for these patient populations in the future. From a technical perspective of image acquisition, MRI sequences that enhance signal loss due to micro-gradients in tissue are typically used for the detection of mH and superficial siderosis. The two general approaches include GRE/T2* and SWI.

Based on the original Alzheimer's Association Research Roundtable Workgroup, at minimum, the MRI assessment should be obtained with a 1.5T scanner, 2D T2* GRE scan sequence (to identify ARIA-H), T2 FLAIR (to identify ARIA-E) with slice thickness ≤5mm and echo time ≥20 milliseconds (**Figure 3)**.[8] If available, the MRI assessment should be obtained with a 3T magnet and include SWI sequences as they are more sensitive at detecting mH.[30] It is

recommended to obtain a brain MRI at the time or within 3–4 months of initiating treatment. It is still acceptable if obtained within the past year. Optimally, the same scanner, sequence, magnetic field strength, and protocol should be used for a given individual to improve reliability and ensure patient safety.

Reliable automated algorithms for the identification of mH or superficial siderosis from medical images are not available.[8] Determination of a mH or superficial siderosis is based on visual inspection of MRI images by experts. There may be variation among experienced MRI readers owing to factors including features of the image acquisition and image artifacts.[8] A trial using the Brain Observer MicroBleed Scale found reduced interrater disagreement in the number of mH in MRI images, highlighting its potential utility.[79] Recognizing the technical challenges of detecting ARIA, the Alzheimer's Association Workgroup provided guidance on how technical consistency and a uniform neuroradiological approach to ARIA might be accomplished (**Figure 3**).[8] In contrast to ARIA, a greater consensus regarding the initial work-up and diagnosis of suspected CAA exists. This is likely due to experience in diagnosing CAA in clinical practice and the availability of validated grading criteria.

Moreover, a quantitative scoring or rating scale and a severity index may uncover the potential relationship between ARIA and clinical symptoms and/or outcomes in a patient.[8,18] This is successfully implemented in CAA and will be useful for diagnosing ARIA in anti-Aβ antibody therapies. Currently, one ARIA-E visual rating scale has been proposed to grade imaging findings.[20] The scoring sheet ranges from 0 (no abnormalities) to 5 (abnormalities in the entire lobe) and is arranged by region (i.e. frontal, parietal, occipital, temporal, central, and infratentorial). It considers three different imaging features: sulcal hyperintensity, parenchymal hyperintensity, and gyral swelling.[20] An MRI severity index of ARIA-E and ARIA-H was adapted by the Advisory Committee Briefing Document.[18] This index is divided into three severity categories (mild, moderate, and severe), based on the size and site of involvement in ARIA-E and the number of mH or focal areas involved in ARIA-H.[18] Given the complexity of ARIA, relatively small sample sizes utilizing such tools currently, and varying experience and expertise levels, further validation of existing and new scales are warranted to assess the clinical relevance of ARIA and its possible implications on management.

Future Directions and Conclusions

Existing evidence highlights the significant impact of ARIA in the natural course of Alzheimer's disease and on the use of anti-Aβ antibodies to treat early Alzheimer's disease. In light of the accelerated FDA approvals of two anti-Aβ therapies,[16,17] current recommendations underline the need for standardized ARIA detection, monitoring, and management protocols in real-world clinical settings.[8,13] Management protocols related to therapeutic options, which may in specific cases include steroids, anticonvulsants, or other symptomatic agents, are important to have, *a priori*, in place and will likely evolve as clinical knowledge expands regarding optimal monitoring and management of ARIA.

Current recommendations focus largely on stated requirements for the MRI scanner and associated sequence. It is acknowledged that interrater variability might be a challenge.[8] The use of a quantitative computer-aided diagnosis (CAD), which combines computational algorithms and clinician's evaluation of the MRI images,[80] may support the successful diagnosis of ARIA (e.g., given the difficulties of ARIA-H diagnosis). Future clinical trials involving anti-Aβ antibodies should consider using CAD methodology once it is validated.

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Competing interests

Dr. Hampel is an employee of Eisai Inc. He serves as Reviewing Editor for the Journal Alzheimer's & Dementia and does not receive any fees or honoraria since May 2019.

He is inventor of 11 patents and has received no royalties:

• In Vitro Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Patent Number: 8916388

• In Vitro Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases Patent Number: 8298784

• Neurodegenerative Markers for Psychiatric Conditions Publication Number: 20120196300

• In Vitro Multiparameter Determination Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Publication Number: 20100062463

• In Vitro Method for The Diagnosis and Early Diagnosis of Neurodegenerative Disorders Publication Number: 20100035286

• In Vitro Procedure for Diagnosis and Early Diagnosis of Neurodegenerative Diseases Publication Number: 20090263822

• In Vitro Method for The Diagnosis of Neurodegenerative Diseases Patent Number: 7547553

• CSF Diagnostic in Vitro Method for Diagnosis of Dementias and Neuroinflammatory Diseases Publication Number: 20080206797

• In Vitro Method for The Diagnosis of Neurodegenerative Diseases Publication Number: 20080199966

• Neurodegenerative Markers for Psychiatric Conditions Publication Number: 20080131921

• Method for diagnosis of dementias and neuroinflammatory diseases based on an increased level of procalcitonin in cerebrospinal fluid: Publication number: United States Patent 10921330

Dr. Atri has received in the past ten years, or may receive, honoraria for consulting; participating in independent data safety monitoring boards; providing educational lectures, programs, and materials; or serving on advisory boards for AbbVie, Acadia, Allergan, the Alzheimer's Association, Axovant, AZ Therapies, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, JOMDD, Lundbeck, Merck, Roche/Genentech, Novo Nordisk, Qynapse, Sunovion, Suven, and Synexus. Dr. Atri receives book royalties from Oxford University Press for a medical book on dementia. Dr. Atri receives institutional research grant/contract funding from NIA/NIH 1P30AG072980, AZ DHS CTR040636, Washington University St Louis, and Gates Ventures. Dr. Atri's institution receives/received funding for

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Prof Nicoll has been consultant/advisor relating to Alzheimer immunotherapy programmes for Elan Pharmaceuticals, GlaxoSmithKline, Novartis, Roche, Janssen, Pfizer and Biogen.

Dr. Cho and Dr. Elhage are employees of Eisai Inc.

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Figure 1 Main Characteristics of ARIA. Figure reproduced with permission from [1]Barakos et al. 2022; [2]Cogswell et al. 2022. ARIA are MRI signal abnormalities that present as edema/effusion (ARIA-E) or microhemorrhage/superficial siderosis (ARIA-H). ARIA-E refers to the leakage of proteinaceous fluid while ARIA-H refers to leakage of small amounts of iron-containing blood products. Three main risk factors across both ARIA classes include exposure to anti-Aβ antibody treatment, presence of pretreatment microhemorrhages, and *APOE-ε4* carrier status. Biomarkers (i.e., CSF, PET) as potential predictors of future ARIA require further investigation.[71]

Figure 2 Proposed Pathophysiological Mechanisms for ARIA. ARIA may occur due to the pathologic deposition of amyloid in cerebral blood vessel walls (also known as cerebral amyloid angiopathy) or upon introduction of monoclonal antibodies that remove Aβ plaque.[8,25,51] The loss of vascular integrity and impaired clearance often leads to an immune response (inflammation) in the vessel wall. Such effects transiently weaken the vessels leading to leakage of proteinaceous fluid and blood, resulting in ARIA-E or ARIA-H, respectively. Some evidence suggests that with repeated immunization, the risk of extravasation tends to decrease, subsequently decreasing the risk of ARIA.[8,25,51] Abbreviations: sAβ = soluble Aβ.

Figure 3 MRI Protocols for Detection of ARIA in an Anti-Amyloid Therapy Clinical Trial. [1]Due to the limited availability of higher field units in certain centers, the use of 1.5T scanners is suggested as a minimum standard despite the greater sensitivity often found with high-field strength scanners. The implementation of more sensitive MRI measures e.g., SWI to detect ARIA-H should be balanced against the clinical importance of such findings. While a brain MRI obtained within the past year may be acceptable if there have been no clinical changes since the scan was performed, it is preferable to obtain a brain MRI when initiating treatment or within 3–4 months of beginning treatment.[8] Abbreviations: T = Tesla.

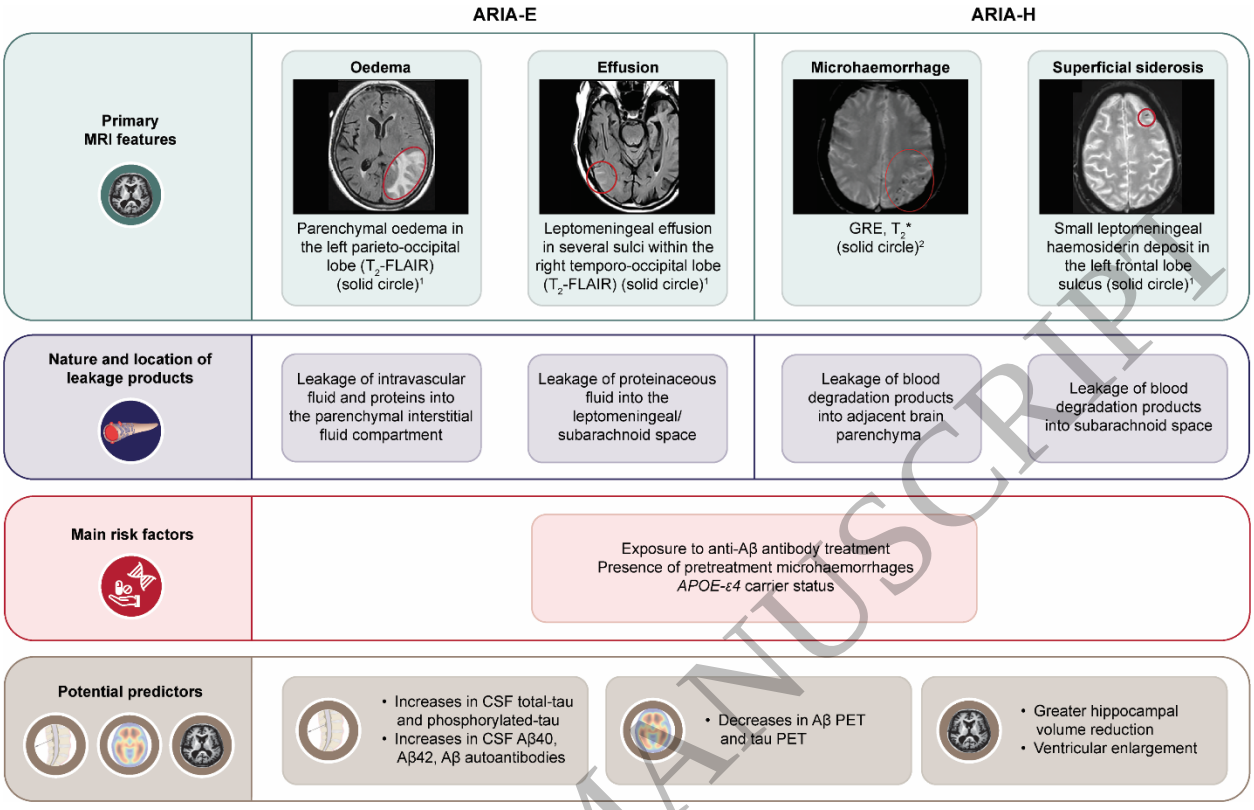

Figure 1
285x182 mm (x DPI)

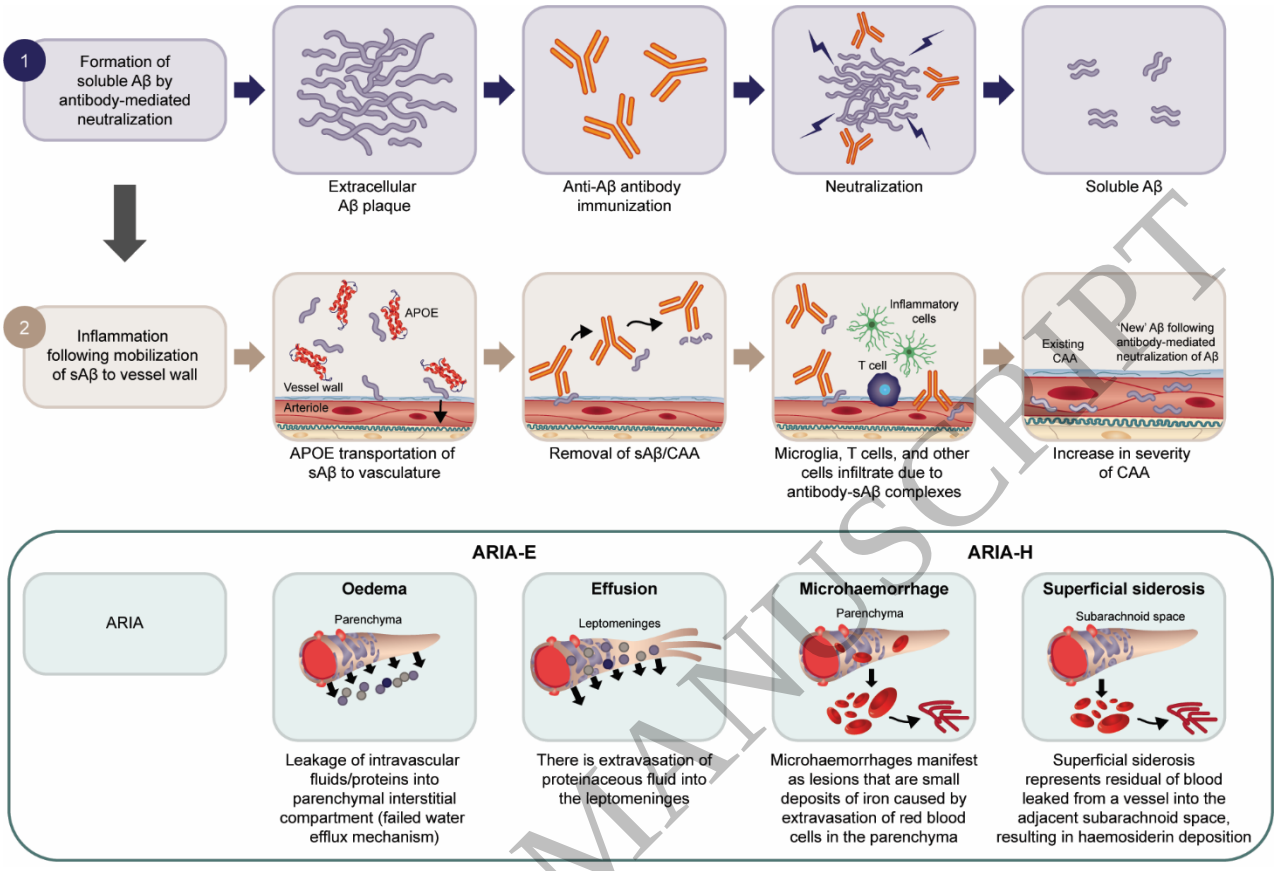

Figure 2
168x114 mm (x DPI)

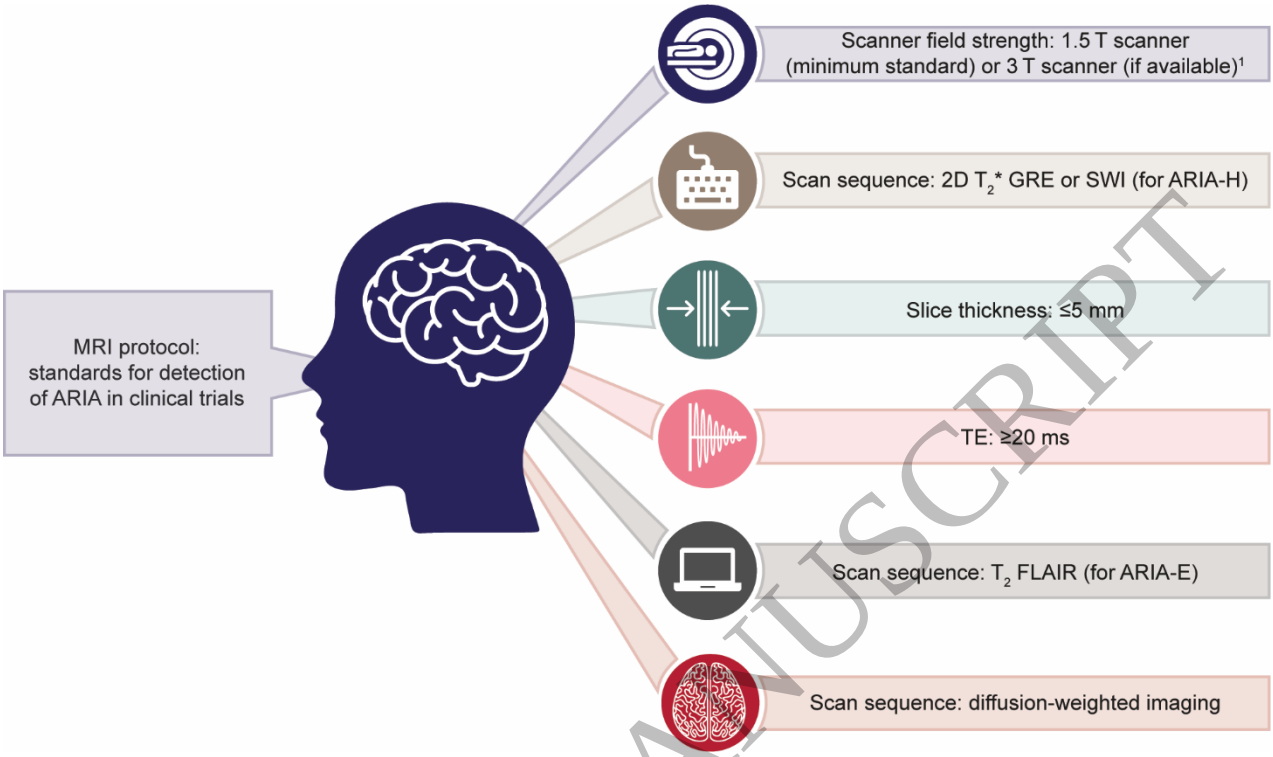

Figure 3
168x99 mm (x DPI)

Table 1 MRI Rating Scale for ARIA-E and ARIA-H

ARIA type	Radiographic severity		
	Mild	**Moderate**	**Severe**
ARIA-E			
Size	<5 cm	5–10 cm	>10 cm
Location	Confined to a single site within sulcus or cortex/subcortical white matter	Observed in one or multiple brain locations	Significant involvement in the sulcus or subcortical white matter in one or more distinct sites
ARIA-H			
New incident microhemorrhages	≤4	5–9	≥10
Focal areas of superficial siderosis	1	2	>2

Table 2 ARIA Findings by *APOEε4*

Patients with Alzheimer's disease treated with bapineuzumab	**Sperling *et al.*[11]: Retrospective analysis of ARIA-E**		**Arrighi *et al.*[12]: Prospective secondary analysis of ARIA-H < 1cm**
***APOE ε4* genotype**	**Patients who experienced ARIA-E (n; %)**	**HR (95% CI; *P*-value)**	**HR (95% CI)**
Non-carriers	5 (6.8)	1.00 (reference)	1.00 (reference)
Heterozygote	18 (17.6)	3.62 (1.30, 10.08; 0.01)	4.16 (1.09, 15.91)
Homozygote	12 (36.4)	7.28 (2.53, 20.95; <0.01)	14.79 (3.92, 55.74)
Patients with Alzheimer's disease treated with solanezumab	**Carlson *et al.*[22]: ARIA-E summary table**		
***APOE ε4* genotype**	**ARIA-E sulcal and/or parenchymal: n**	**Maximum ARIA-E severity: n**	**ARIA-H at time of ARIA-E: n**
EXPEDITION			
Non-carriers	Parenchymal: 1	Mild: 1	>10: 1
Heterozygote	Sulcal: 1	Mild: 1	2–5: 1
Homozygote	Sulcal: 1	Severe: 1	2–5: 1
EXPEDITION 2			
Non-carriers	Parenchymal: 3	Mild: 2 Severe: 1	>10: 1 N/A: 2
Heterozygote	Parenchymal: 1	Severe: 1	6–10: 1
Homozygote	Parenchymal: 1	Moderate: 1	1: 1
EXPEDITION EXT			
Non-carriers	Parenchymal: 3	Mild: 2 Moderate: 1	>10: 2 0: 1
Heterozygote	Sulcal: 1 Parenchymal: 1	Mild: 1 Moderate: 1	>10: 1 0: 1
Homozygote	Sulcal: 1 Parenchymal: 1	Mild: 2	>10: 1 2–5: 1

Abbreviations: CI = confidence interval; HR = hazard ratio; N/A = not available.