White paper

A clinician's guide to detecting and diagnosing ARIA in Alzheimer's disease patients

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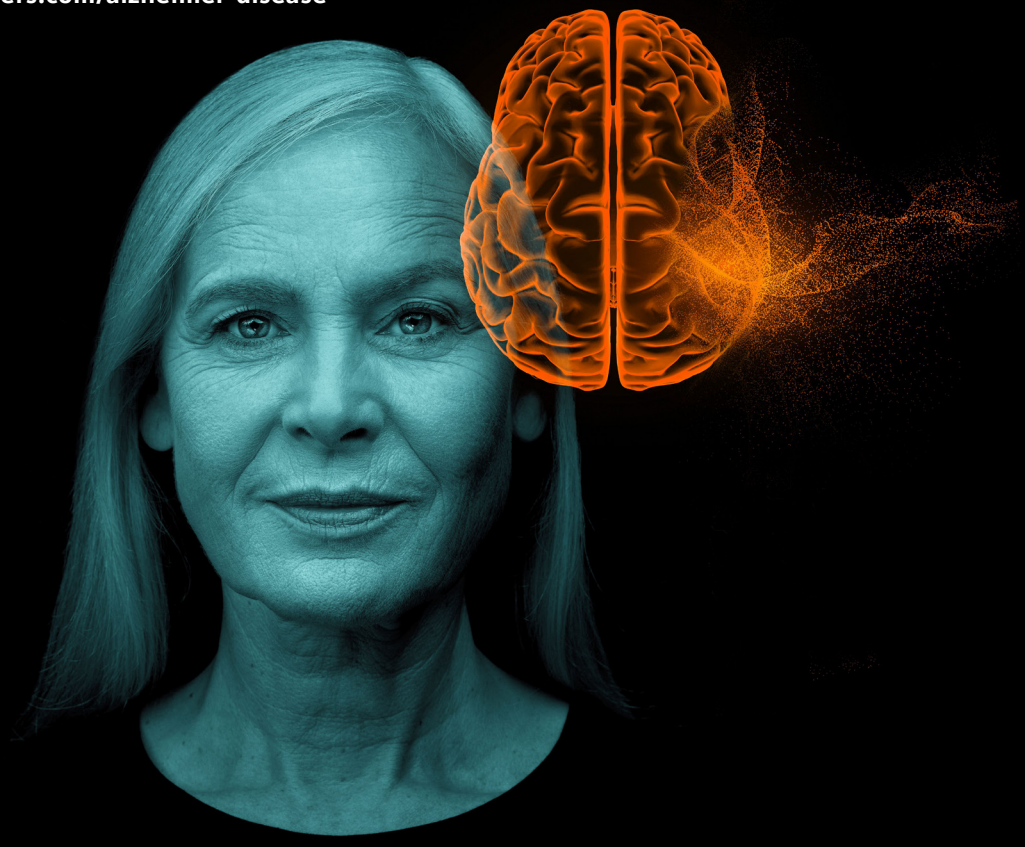

We're in a new era for Alzheimer's disease treatment. With recent approvals of novel amyloid-targeting therapies, Alzheimer's disease – the seventh leading cause of death worldwide [1] – may one day be a thing of the past. However, in the quest to advance the treatment and management of this silent pandemic, a new challenge has emerged: the detection and management of Amyloid-Related Imaging Abnormalities (ARIA). Characterized by ARIA-E (edema) and ARIA-H (hemorrhage), ARIA poses significant implications for patient care, highlighting the necessity for accurate diagnosis, meticulous imaging monitoring, and early therapeutic intervention.

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Abstract

In the rapidly evolving landscape of Alzheimer's disease treatment, the quest for effective therapies has brought to light a critical challenge: the detection and management of amyloid-related imaging abnormalities (ARIA), which may result from anti-amyloid disease modifying therapies. Encompassing both ARIA-E (edema) and ARIA-H (hemorrhage), ARIA represents a spectrum of MRI-detectable changes that can complicate the clinical management of patients undergoing amyloid-targeting therapies. And clinicans play a critical role in precisely detecting and diagnosing ARIA to ensure patient safety and support the effective delivery of treatment.

This guide is designed to equip clinicians with the essential knowledge and practical strategies needed to navigate the complexities of ARIA detection, delving into MRI techniques that reveal the subtle, yet significant, imaging abnormalities associated with ARIA. By providing a comprehensive overview of current best practices, from optimizing MRI sequences to interpreting findings and making informed treatment decisions, this article aims to enhance diagnostic precision and improve patient outcomes. As we advance in our fight against Alzheimer's disease, mastering ARIA detection is not just a necessity – it's a cornerstone of responsible and effective patient management in the era of innovative therapies.

Contents

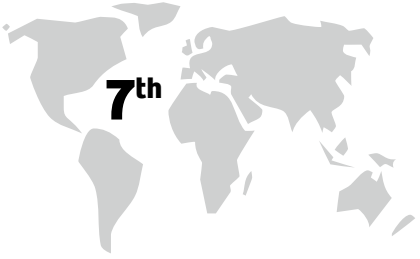
Alzheimer's disease: An increasing challenge for healthcare providers

Globally, an estimated 55 million people [1] are currently living with dementia. By 2050, the number of new dementia cases is projected to more than double, affecting up to 139 million people. [1]

Alzheimer's disease (AD) is the most common neurodegenerative disease worldwide [2] and most common form of dementia accounting for over 60–80 % of all dementia cases. [3] Clinically characterized by a gradual decline in cognitive function, memory, and reasoning abilities, AD progresses through mild, moderate, and severe stages, eventually leading to complete dependency and death. Pathologically, AD is marked by the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles in the brain, leading to neuronal loss and brain atrophy. The presence of Aβ plaques is one of the defining features of the disease. [4]

Although the underlying pathophysiology of AD is complex, the prevailing theory postulates that Aβ accumulation directly results in synaptic dysfunction, neurodegeneration, and, ultimately, clinical symptoms. [5-7] As a result, the AD drug development pipeline consists of many disease-modifying treatments, such as immunotherapy with monoclonal antibodies, that typically target the cessation of Aβ formation or facilitate plaque removal. [8] These AD therapies can cause side effects described as amyloid-related imaging abnormalities (ARIA). [9]

In 2019, Alzheimer's was the **7th leading cause of death** worldwide. [1]



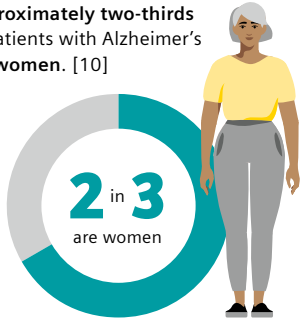
Between 2000 and 2019, the **mortality rates from AD increased**. [10]

33% aged 65 to 74

51% aged 75 to 84

78% aged 85 & older

Approximately two-thirds of patients with Alzheimer's are **women**. [10]



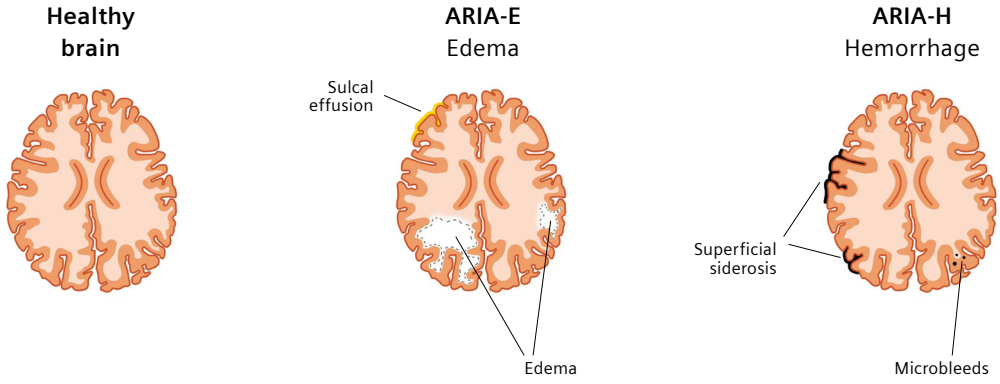
What is ARIA?

In July 2010, the Alzheimer's Association Research Roundtable convened a working group comprising academic and industry representatives, which first introduced "ARIA" as a term encompassing a spectrum of magnetic resonance imaging (MRI) findings observed in patients receiving anti-Aβ immunotherapies for AD. Recognizing the potential development of ARIA in patients undergoing monoclonal antibody treatment for AD, the working group established recommendations regarding inclusion and exclusion criteria, as well as safety monitoring for AD clinical trials. [9]

Significant advances have been made in our understanding of ARIA since the 2010 working group. ARIA refers to imaging findings seen exclusively on MRI, and depending on the MRI appearance, two types of ARIA are recognized: ARIA-E, which is characterized by edema and effusion, and ARIA-H, which is characterized by microhemorrhages and superficial siderosis. [9]

What causes ARIA?

ARIA is an inherently imaging-based phenomenon that emerges in patients with AD undergoing treatment with novel amyloid-targeting therapies, such as Bapineuzumab, Solanezumab, Aducanumab, Lecanemab and Donanemab. [11,12] Although the mechanisms underlying ARIA are not fully understood, the current hypothesis is that these abnormalities occur due to the breakdown of the blood-brain barrier as a result of the binding of monoclonal antibodies to accumulated Aβ in the cerebral parenchyma and vasculature. [9] This binding leads to amyloid clearance, resulting in loss of vessel wall integrity and vessel leakiness of proteinaceous fluid (ARIA-E) and heme products (ARIA-H). [9]



"ARIA is an inherently image-based phenomenon. The diagnosis of ARIA depends on the radiologic diagnosis. Radiologist education and understanding of how to interpret these cases is crucial."

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ARIA-E vs. ARIA-H

ARIA-E and ARIA-H are both associated with amyloid-targeting therapies used in the treatment of AD, but they differ in their underlying pathology and imaging characteristics (Figure 1). [11] Both ARIA-E and ARIA-H typically occur early in the treatment course (within six months), and approximately 90% of patients are asymptomatic, underscoring the importance of routine imaging monitoring. [11]

Pathophysiology of ARIA-E (edema and effusion)
ARIA-E involves the leakage of fluid into the brain parenchyma or into the subarachnoid space, resulting in cerebral edema or effusions. Detected through MRI scans, ARIA-E appears as regions of hyperintensity on T2-weighted FLAIR (fluid-attenuated inversion recovery) sequences. ARIA-E may present as local mass effect and gyral swelling. [13]

Pathophysiology of ARIA-H (microhemorrhages and superficial siderosis)
ARIA-H involves microhemorrhages or small areas of bleeding within the brain tissue, leading to the deposition of hemosiderin (a blood breakdown product). [14] Detected through MRI scans, particularly on T2*-weighted and susceptibility-weighted imaging (SWI) sequences, ARIA-H appears as hypointense (dark) spots on these MRI sequences, indicating areas of microbleeding. [14]

ARIA-E, ARIA-H, and Cerebral Amyloid Angiopathy (CAA)
ARIA-E and ARIA-H have similar MRI findings to cerebral amyloid angiopathy (CAA). Both ARIA and CAA are related to the deposition of Aß in cerebral blood vessels, which compromises the integrity of the vascular walls and the blood-brain barrier. [9] This compromised integrity can lead to fluid leakage, causing edema in ARIA-E and inflammatory CAA, and to microhemorrhages or hemosiderin deposits, as seen in ARIA-H and CAA-associated microbleeds. [9]

CAA is frequently detected in up to 90% of patients with AD. [10] And clinically, ARIA and CAA present with overlapping symptoms, such as headaches, cognitive decline, seizures, and focal neurological deficits, reflecting the underlying vascular and inflammatory processes. Therefore, the only real distinguishing feature between ARIA and CAA is clinical context: ARIA only occurs in individuals undergoing treatment with amyloid lowering agents, whereas CAA has been shown to be associated with AD independent of amyloid plaque and tau tangle pathology. [11,12]

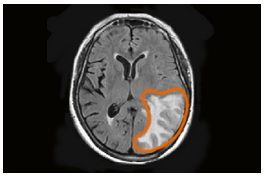
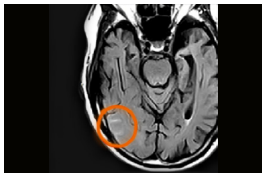
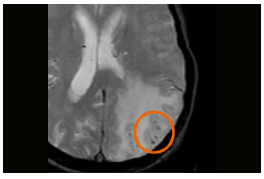
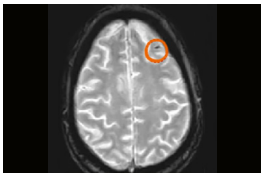
	ARIA-E		ARIA-H	
	Edema	Effusion	Microhemorrhage	Superficial siderosis
Primary MRI features				
	Parenchymal edema in the left parieto-occipital lobe (T2 FLAIR) *(solid circle)*	Leptomeningeal effusion in several sulci within the right temporo-occipital lobe (T2 FLAIR) *(solid circle)*	Several small parenchymal microbleeds in the left occipital lobe (T2*) *(solid circle)*	Small leptomeningeal hemosiderin deposit in the left frontal lobe sulcus (T2*) *(solid circle)*
Nature and location of leakage products	Leakage of intravascular fluid and proteins into the parenchymal interstitial fluid compartment	Leakage of proteinaceous fluid into the lepto-meningeal/subarachnoid space	Leakage of blood degradation products into adjacent brain parenchyma	Leakage of blood degradation products into subarachnoid space

Figure 1: Main characteristics of ARIA-E and ARIA-H. ARIA-E is characterized by the presence of parenchymal edema and sulcal effusions. ARIA-H is usually seen in combination with ARIA-E and is characterized by the presence of parenchymal microhemorrhages (most common) and sulcal/leptomeningeal hemosiderin deposits. [11]

Risk factors for ARIA

The primary risk factor for both ARIA-E and ARIA-H is apolipoprotein E (APOE) ϵ4 allele carriership. Patients with the APOE ϵ4 allele tend to have higher Aβ loads in both brain tissue and blood vessels. This increased amyloid burden is thought to enhance perivascular Aβ clearance under antibody treatment, which in turn heightens vascular permeability. [9] This heightened permeability allows protein-rich fluid and red blood cells to leak out, leading to ARIA-E and ARIA-H, respectively (Figure 2). [9] Therefore, genetic testing prior to treatment initiation is crucial for clinicians to identify patients at higher risk for ARIA.

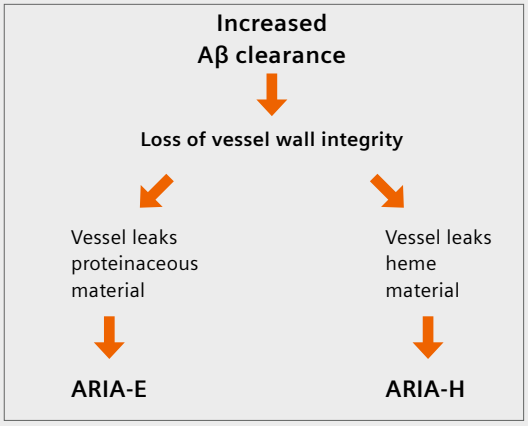


Figure 2: Pathophysiology of ARIA. The current hypothesis is that these abnormalities occur due to the breakdown of the blood-brain barrier as a result of the binding of monoclonal antibodies to accumulated Aβ in the cerebral parenchyma and vasculature. [9] This binding leads to increased amyloid clearance, resulting in loss of vessel wall integrity and vessel leakiness of proteinaceous fluid (ARIA-E) and heme products (ARIA-H).

Additional risk factors

High dosages of anti-Aβ immunotherapies: ARIA-E demonstrates an additional dose dependence, occurring more frequently at higher doses of anti-Aβ immunotherapies due to greater mobilization of Aβ. [9]

Antithrombotic medications: Previous clinical trials have shown that concomitant anti-amyloid treatment with anti-coagulants, antiplatelets or antithrombotics is associated with increased risk of ARIA-H, warranting potential exclusion in these patient populations. [9]

Existing microhemorrhages: Patients who already have cerebral microbleeds or CAA at baseline are at higher risk for developing additional microhemorrhages with anti-amyloid therapy. [11]

Age: Advanced age can increase susceptibility to ARIA-E and ARIA-H due to cumulative vascular damage and decreased repair mechanisms. [15]

"When ARIA develops, it is typically identified on MRI scans that are routinely implemented for monitoring patients that are [administered] monoclonal antibody therapies. Typically, every patient will have five MRI scans in their first year of treatment. They'll have a baseline MRI scan prior to the start of therapy, which is typically within three to six months prior to the start of therapy. And then they will have four follow-up MRI scans in the first year. Typically, ARIA is an incidental finding, with over 90% of patients being asymptomatic. And it's most common in the first six months of therapy. MRI surveillance is crucial for the safe administration of these treatments."

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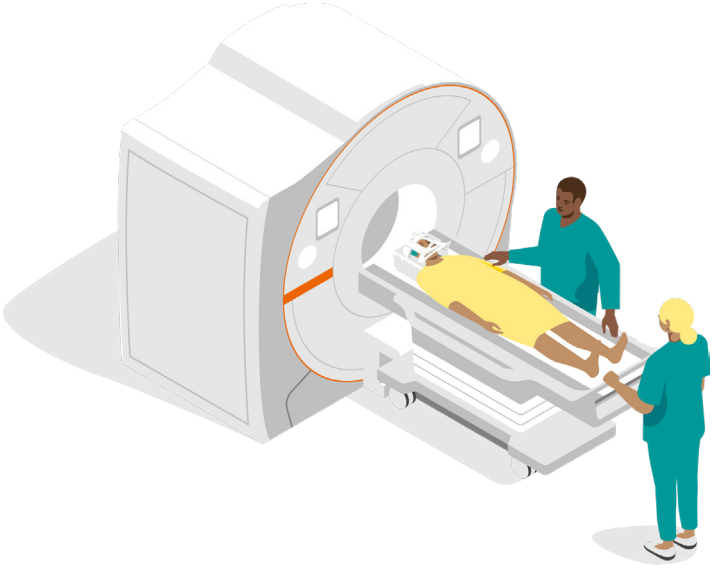
Detecting, monitoring, and managing ARIA

Regular MRI is required to detect and monitor different forms of ARIA during initiation of approved antiamyloid therapies, such as Lecanemab and Donanemab. [16] The guidelines for using MRI to detect ARIA typically include protocols for baseline imaging, regular monitoring, and managing detected abnormalities. These guidelines aim to ensure early detection and appropriate intervention to mitigate potential risks associated with amyloid-targeting treatments. In this next section, we provide the key imaging characteristics of ARIA-E and ARIA-H detection.



Imaging characteristics of ARIA-E

ARIA-E is easily detected using T2-weighted FLAIR MRI sequences, [17] examplary T2 FLAIR images are shown in Figure 3. FLAIR is particularly effective for highlighting abnormalities in brain tissue by suppressing the signal from cerebrospinal fluid, thereby enhancing the visibility of pathologies like edema. Prolonged signals on T2 FLAIR sequences within the brain (intra-axial) represent the presence of edema, prolonged signals outside the brain (extra-axial) represent effusion or exudate in the sulci or leptomeningeal spaces. [18]

ARIA-E appears as areas of increased signal intensity (hyperintensity) in the cortical and subcortical regions of the brain. [17] The hyperintense areas may also show mild swelling of the gyri (the ridges of the brain's surface) (Figure 1). This indicates localized swelling due to fluid accumulation. In some ARIA-E cases, there can be a slight mass effect, which means the swelling may cause pressure on adjacent brain structures. This can be seen as displacement or compression of nearby brain tissue. [18]

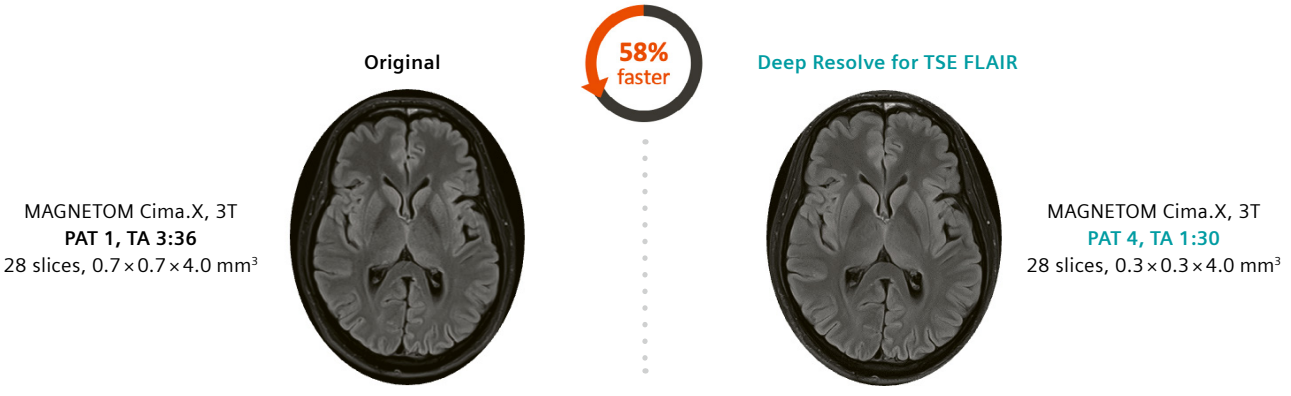


Figure 3: Comparison of conventional and advanced brain scans using the MAGNETOM Cima.X 3T system. The left image shows a conventional brain scan (PAT 1, TA 3:36) captured with the MAGNETOM Cima.X 3T scanner, highlighting standard resolution and contrast. The right image demonstrates the use of Siemens Healthineers' Deep Resolve for TSE FLAIR (PAT 4, TA 1:30), offering enhanced image clarity and detail, as well as a 58% faster scanning time.

When ARIA-E affects the sulci, it might be mistaken for leptomeningeal processes if the radiologist is not aware that the patient is undergoing monoclonal antibody therapy for AD. ARIA-E more frequently affects the occipital lobes than the parietal, frontal, and temporal lobes. It is much less common in the cerebellum. [14] Having baseline MRI images before starting amyloid-targeting therapy is crucial. These baseline images allow for the detection of subtle changes that occur later, making it easier to identify and diagnose ARIA-E accurately.

Imaging characteristics of ARIA-H

ARIA-H is detected on MRI using long echo time (TE) T2*-weighted gradient echo (GRE) sequences. These sequences are sensitive to magnetic susceptibility differences caused by hemosiderin deposits that appear as markedly hypointense signals in the brain parenchyma or sulci. ARIA-H can also be detected through SWI, a technique that uses high-resolution 3D spoiled GRE acquisition, providing higher spatial resolution and increased sensitivity compared to conventional T2*-weighted GRE sequences. [9] SWI can detect hemosiderin, calcification, and iron deposits with greater accuracy. [9] Exemplary SWI images are shown in Figure 4.

On T2*-weighted GRE and SWI sequences, ARIA-H appears as areas of hypointense signal due to the presence of hemosiderin deposits in the brain tissue. T2*-weighted GRE sequences augment the effects of local field variations and spin dephasing caused by microhemorrhages, resulting in susceptibility-related signal loss, commonly referred to as "blooming." [9] This makes microhemorrhages more visible (Figure 1).

The imaging characteristics of ARIA-H are similar to those seen in CAA, a condition where amyloid deposits in the walls of cerebral blood vessels, leading to hemorrhages. However, ARIA-H typically affects the lobar regions of the brain, especially at the gray-white matter junction or cortex. This means the hemorrhages are more common in the outer parts of the brain, unlike hypertensive hemorrhages which usually occur in the deep gray matter structures of the brain. [9]

ARIA-H is usually not visible on CT scans or standard MRI sequences like T1-weighted, T2-weighted, FLAIR or diffusion-weighted imaging (DWI). [9] These sequences lack the sensitivity to detect the small, subtle changes caused by hemosiderin deposits. Therefore, long-TE T2*-weighted GRE and susceptibility-weighted imaging (SWI), are the preferred MRI techniques for detecting ARIA-H due to their sensitivity to hemosiderin. [9]

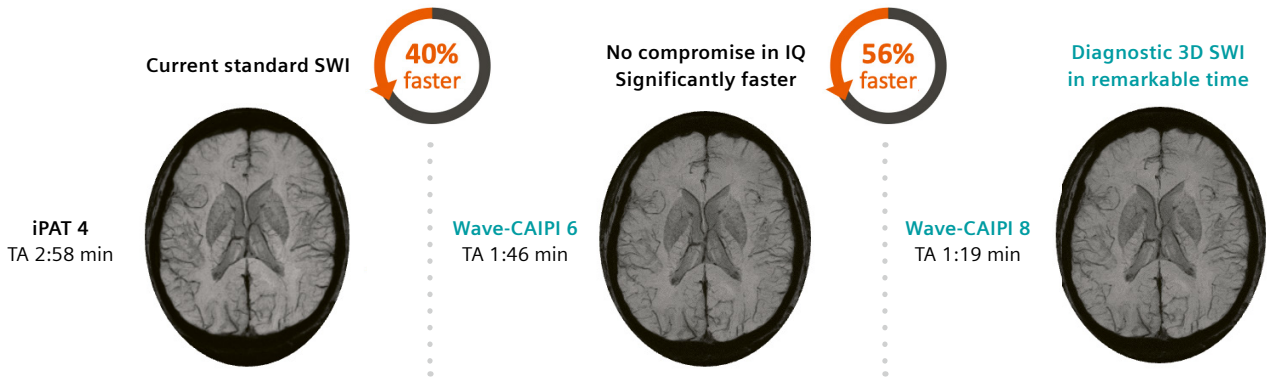


Figure 4: Comparison of brain scans using standard and advanced SWI techniques. The first image shows a brain scan with current standard SWI using iPAT 4 (TA 2:58 mins), offering a high-quality but longer acquisition time. The second image highlights a faster scan using Wave-CAIPI 6 (TA 1:46 mins) with no compromise in image quality (IQ), reducing scan time significantly. The third image features a diagnostic 3D SWI using Wave-CAIPI 8 (TA 1:19 mins), delivering remarkable time efficiency while maintaining excellent diagnostic clarity, ideal for rapid yet precise brain imaging.

Field strength of MRI magnet in ARIA detection

Field strength of the MRI magnet matters for the detection of ARIA. Higher field strength magnets, such as 3 Tesla (3T) compared to 1.5 Tesla (1.5T), offer several advantages in the detection of ARIA-E and ARIA-H.

So, several consensus documents are now recommending 3T MRI machines over 1.5T. [19] The use of low-field 0.55T MRI machines is currently under investigation for detecting ARIA, particularly in resource-limited settings. [19] However, low-field MRI has reduced SNR, reduced susceptibility-weighting, and longer scan times, which can result in lower image resolution and quality. [20]

Here's how field strength impacts ARIA detection:

- **Improved Signal-To-Noise Ratio (SNR):**
  3T magnets provide a higher SNR compared to 1.5T magnets. This improved SNR enhances the overall quality of the images, making subtle abnormalities more detectable. [21] The increased SNR is particularly useful in detecting the subtle changes associated with ARIA, such as small areas of edema or microhemorrhages. [14]

- **Enhanced sensitivity to susceptibility effects:**
  Higher field strength increases sensitivity to magnetic susceptibility effects. [14] This is critical for detecting ARIA-H, where hemosiderin deposits create susceptibility artifacts. [18] The enhanced sensitivity at 3T improves the visualization of microhemorrhages, which appear as hypointense areas on susceptibility-weighted sequences.

- **Higher spatial resolution:**
  At higher field strength, the intrinsically higher SNR can be traded for higher spatial resolution imaging. This means that the images can show finer details, which is essential for detecting small or subtle ARIA lesions. Better spatial resolution also helps in precisely localizing and characterizing the extent of ARIA-related changes in the brain. [22]

- **Longer TE:**
  At higher field strengths, longer echo times can be used without compromising image quality. This is beneficial for T2*-weighted and SWI sequences, which rely on longer TEs to enhance susceptibility effects. Longer TEs at higher field strengths also improve the detection of hemosiderin deposits, making it easier to identify and quantify microhemorrhages. [23]

Importance of consistency in MRI imaging parameters

MRI protocols for ARIA detection must be standardized. Since guidelines for use of MRI to detect ARIA when administering amyloid-targeting therapies typically include protocols for baseline imaging, regular monitoring, and managing detected abnormalities, it is crucial that there is consistency in imaging parameters.

It is ideal to use the same MRI field strength (e.g., 3T), the same MRI machine vendor (e.g., Siemens Healthineers), and the same scanner model for all serial exams of a patient. [24] Consistency in these factors helps ensure that images are comparable over time. In addition, using identical MRI sequences (i.e. either use T2*-weighted GRE OR SWI) and the same sequence parameters (e.g., echo time, repetition time) across all exams ensures uniformity in the images obtained (Figure 5). [24]

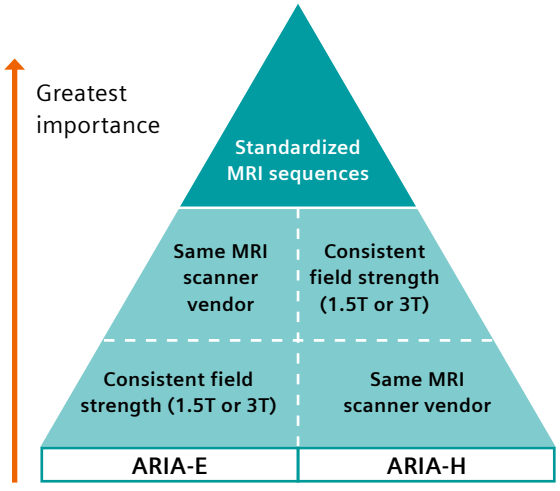


Figure 5: Key factors impacting MR imaging of ARIA [24] Maintaining consistency and standardization in MRI imaging parameters – such as using the same field strength, vendor, scanner model, and identical sequences with the same parameters – is crucial for the accurate assessment of ARIA over time. [24] Field strength particularly affects the detection of ARIA-H, while differences in MRI vendors can impact the appearance and detection of ARIA-E, especially in the occipital white matter. [24] Uniform imaging protocols help ensure reliable and comparable results across serial exams.

Consistency and standardization in imaging protocols are critical for accurately assessing and monitoring ARIA. [24] Variations in imaging parameters can lead to differences in image appearance, making it difficult to detect subtle changes or to compare images over time. [24] For example, the field strength of the MRI (e.g., 1.5T vs. 3T) has a significant impact on the detection of ARIA-H. Higher field strength enhances the sensitivity to magnetic susceptibility effects, making it easier to detect hemosiderin deposits and microhemorrhages. Consequently, field strength should not be changed during the course of baseline MRI and ARIA monitoring as this has direct impact on the detection of ARIA, particularly ARIA-H.

Similarly, different MRI vendors may have slight variations in how they generate and display images. These differences can affect the appearance of brain regions, particularly the occipital white matter. This variability can impact the detection and assessment of ARIA-E, where subtle changes in the white matter need to be accurately identified.

Optimization of MRI sequences for ARIA detection

MRI sequences must be optimized for the effective detection of ARIA for three key reasons:

1. **Subtle abnormalities:** ARIA often presents with subtle changes that can be easily missed without high sensitivity and resolution.
2. **Specificity:** ARIA-E and ARIA-H require different imaging characteristics for accurate detection.
3. **Consistency:** To monitor ARIA progression or resolution over time, consistent and optimized imaging protocols are essential.
4. **Rule out stroke:** To differentiate symptomatic ARIA-E from stroke, i.e. ischemia, a diffusion-weighted imaging (DWI) scan should be performed.

Optimized MRI sequences for ARIA-E detection

For ARIA-E detection, T2-weighted FLAIR sequences enhance the visibility of edema by suppressing the signal from cerebrospinal fluid, allowing better contrast of abnormal fluid accumulation in the brain parenchyma. In addition, DWI sequences help differentiate vasogenic edema (seen in ARIA-E) from cytotoxic edema (seen in acute infarct, i.e. stroke).

Optimized MRI sequences for ARIA-H detection

For ARIA-H detection, T2*-weighted GRE sequences are sensitive to magnetic susceptibility effects caused by blood breakdown products like hemosiderin. SWI provides enhanced sensitivity and spatial resolution for detecting small hemorrhages and hemosiderin deposits. Even small microbleeds appear as dark spots, providing greater detail than T2*-weighted GRE.

Clinical applications

MRI sequences must be optimized for ARIA detection to enhance sensitivity and specificity to the subtle changes associated with ARIA-E and ARIA-H. This involves using high field strength, selecting appropriate sequences, and adjusting sequence parameters. MRI sequences for ARIA monitoring can be found on the website of the American Society of Neuroradiology (ASNR) or directly downloaded from the MAGNETOM World website from Siemens Healthineers. *https://www.asnr.org/education-resources/alzheimers-webinar-series/* or *https://www.magnetomworld.siemens-healthineers.com/clinical-corner/protocols/neurology-neurography/asnr*

"MRI sequences need to be optimized for ARIA detection. In fact, all of the key MRI vendors have prepared specific ARIA detection protocols in collaboration with the ASNR ..."

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Impact of MRI findings on treatment decision-making

MRI findings of ARIA-E and ARIA-H play a crucial role in treatment decision-making for patients receiving amyloid-targeting therapies.

Detection and monitoring

Baseline imaging
Before starting amyloid-targeting therapies, baseline MRI scans are performed to identify any pre-existing abnormalities. [25] This helps in distinguishing new ARIA findings from chronic changes.

Regular monitoring
Routine MRI scans are conducted during treatment to detect new or worsening ARIA-E and ARIA-H. [17] This regular monitoring helps in early detection and timely intervention.

ARIA-E assessment

Severity: Mild ARIA-E typically involves small areas of cortical-subcortical hyperintensity with mild gyral swelling. Mild cases might be monitored without immediate changes to therapy. With moderate to severe ARIA-E, larger areas of hyperintensity with significant mass effect or effusion indicate more severe edema. [17] These cases often require more immediate intervention (Figure 6).

Treatment modifications: If moderate or severe ARIA-E is detected, treatment with amyloid-targeting therapy is often paused to prevent further complications. If the patient is symptomatic (e.g., headaches, confusion), additional treatments, such as corticosteroids, may be considered to reduce inflammation and edema. [16] Patients with ARIA-E typically undergo follow-up MRI scans after a pause in treatment to assess resolution. Once ARIA-E has resolved or significantly improved, therapy may be cautiously resumed, often at a lower dose.

ARIA-H assessment

Severity: Small, isolated hypointense spots (microhemorrhages) on T2*-weighted or SWI sequences might be monitored closely without immediate therapy changes. [26] Extensive or confluent areas of hypointensity indicating significant bleeding may necessitate more immediate and aggressive management (Figure 6).

Treatment modifications: In cases of extensive ARIA-H, amyloid-targeting therapy is typically paused to prevent further bleeding. Although ARIA-H may be asymptomatic, any new neurological symptoms (e.g., seizures, focal neurological deficits) are closely monitored and managed. [16] The presence of ARIA-H may lead to a re-evaluation of the risks versus benefits of continuing amyloid-targeting therapy. In some cases, therapy may be discontinued altogether if the risk is deemed too high.

ARIA-Class	Mild	Moderate	Severe
ARIA-E (Edema, effusion, exudate)	FLAIR hyperintensity measuring **<5** cm in one site	FLAIR hyperintensity measuring **5–10** cm, or signal at **>1** site with each measuring **<10** cm	FLAIR hyperintensity measuring **>10** cm in one or more separate sites
ARIA-H (Microhemorrhages)	**1 to 4** new microhemorrhages	**5 to 9** new microhemorrhages	**10 or more** new microhemorrhages
ARIA-H (Superficial siderosis)	**1** focal area of superficial siderosis	**2** focal areas of superficial siderosis	**More than 2** focal areas of superficial siderosis

Figure 6: ARIA severity grading scale. ARIA can be categorized by radiographic severity as mild, moderate, or severe according to hyperintense signal measuring (ARIA-E) or the presence of new microhemorrhages or focal areas of superficial siderosis (ARIA-H). [14]

ARIA management

MRI findings of ARIA-E and ARIA-H are integral to the management of patients on amyloid-targeting therapies. They help in assessing the severity of ARIA, guiding modifications in therapy, and ensuring patient safety. Regular monitoring and timely intervention based on MRI findings are essential to optimize treatment outcomes and minimize complications. Clinicians must follow established guidelines and protocols, such as those from the Food and Drug Administration (FDA) and other regulatory bodies, which provide recommendations on managing ARIA.

For Lecanemab, patients require a baseline MRI scan as well as follow-up scans before the 5th, 7th, and 14th infusion. An additional follow-up MRI scan is recommended prior the 26th infusion in patients who are APOE4 carriers or in those who showed evidence of ARIA (with or without symptoms) on earlier MRIs. [27]

For Donanemab patients need also a baseline scan and follow-up scans prior the 2nd, 3rd, 4th, and 7th infusion. An additional follow-up MRI scan is recommended prior the 12th infusion in higher-risk individuals (e.g., APOE4 carriers, patients with previous ARIA events earlier in treatment). [28]

ARIA is often asymptomatic and detected incidentally during routine MRI surveillance rather than through the presentation of symptoms. When ARIA does cause symptoms, they are usually unspecific and can include headaches, confusion, visual disturbances, visuospatial impairment, and apraxia. Although rare, some severe cases of ARIA have been reported, which required intensive care unit admissions due to significant symptoms. Typically, clinical symptoms of ARIA often resolve on their own when the amyloid-targeting treatment is paused or withdrawn. In some cases, based on the severity of ARIA, adjustments to the treatment dose or complete discontinuation may be necessary to manage symptoms and prevent further complications. [11]

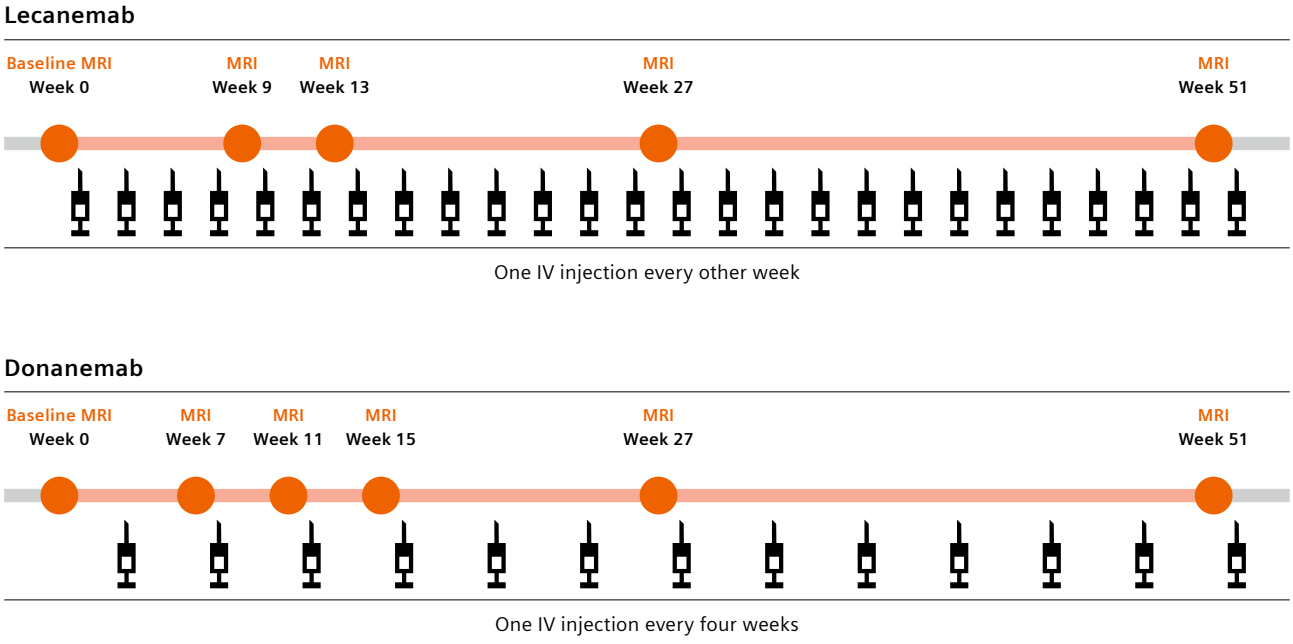

Figure 7: Recommended MRI Monitoring Schemes.

Mastering ARIA detection

As the prevalence of AD continues to rise, clinicians face an unprecedented challenge in managing this complex and debilitating condition. The increasing burden of Alzheimer's care demands that healthcare professionals be well-prepared to navigate the multifaceted aspects of treatment and patient management. Central to this preparation is the integration of advanced diagnostic tools and monitoring techniques, particularly the detection and management of ARIA.

ARIA assessment, encompassing both ARIA-E and ARIA-H, is a critical component in the management of Alzheimer's patients undergoing amyloid-targeting therapies. Effective ARIA detection through MRI is essential for tailoring treatment plans, minimizing potential risks, and optimizing therapeutic outcomes. By staying vigilant in monitoring ARIA, clinicians can better address treatment-related complications, adjust therapies as needed, and ultimately improve the quality of care for patients. As the burden of AD grows, mastering ARIA detection and monitoring will be integral to ensuring that patients receive the safest and most effective treatment possible.

References

[1] "Faktenzentrale Demenz". https://www.dzne.de/aktuelles/hintergrund/faktenzentrale

[2] "Alzheimer's Disease and Dementia: What Healthcare Practitioners Need to Know." www.thedoctors.com/articles/alzheimers-disease-and-dementia-what-healthcare-practitioners-need-to-know/

[3] "Alzheimer's Association Report. 2024 Alzheimer's disease facts and figures." Alzheimer's & Dementia 2024; 3708 - 3821https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13809

[4] "Pathology of Alzheimer's Disease – an Overview | ScienceDirect Topics." Sciencedirect.com, 2012, https://www.sciencedirect.com/topics/medicine-and-dentistry/pathology-of-alzheimers-disease

[5] Scheltens P, De Strooper B, Kivipelto M,et al. "Alzheimer's disease." Lancet 2021; 397:1577–1590, https://pmc.ncbi.nlm.nih.gov/articles/PMC8354300/

[6] Ono K, Watanabe-Nakayama T. "Aggregation and structure of amyloid β-protein." Neurochem Int 2021; 151:105208, https://www.sciencedirect.com/science/article/abs/pii/S0197018621002540?via%3Dihub

[7] Selkoe DJ, Hardy J. "The amyloid hypothesis of Alzheimer's disease at 25 years." EMBO Mol Med 2016; 8:595–608, https://pmc.ncbi.nlm.nih.gov/articles/PMC4888851/pdf/EMMM-8-595.pdf

[8] JL Cummings et al.: "Alzheimer's disease drug development pipeline: 2025;" Alzheimer's Dement. 2025;11:e70098; https://doi.org/10.1002/trc2.70098

[9] Roytman, Michelle, et al. "Amyloid-Related Imaging Abnormalities: An Update." American Journal of Roentgenology, vol. 220, no. 4, 2 Nov. 2022, https://www.ajronline.org/doi/10.2214/AJR.22.28461

[10] "Alzheimer's Association Report. 2023 Alzheimer's disease facts and figures." Alzheimer's & Dementia 2023; 1598 - 1695, https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13016

[11] Hampel, Harald, et al. "Amyloid-Related Imaging Abnormalities (ARIA): Radiological, Biological and Clinical Characteristics." Brain, 6 June 2023, https://academic.oup.com/brain/article/146/11/4414/7191051

[12] Gaillard, Frank. "Amyloid Related Imaging Abnormalities (ARIA) | Radiology Reference Article | Radiopaedia.org." Radiopaedia, radiopaedia.org/articles/amyloid-related-imaging-abnormalities-aria

[13] VandeVrede, Lawren, et al. "Symptomatic Amyloid-Related Imaging Abnormalities in an APOE ε4/ε4 Patient Treated with Aducanumab." Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, vol. 12, no. 1, Jan. 2020, https://doi.org/10.1002/dad2.12101.

[14] Cogswell, P.M., et al. "Amyloid-Related Imaging Abnormalities with Emerging Alzheimer Disease Therapeutics: Detection and Reporting Recommendations for Clinical Practice." American Journal of Neuroradiology, vol. 43, no. 9, 11 Aug. 2022, pp. E19–E35, https://www.ajnr.org/content/early/2022/08/25/ajnr.A7586

[15] Doran, Sarah, et al. "Risk factors in developing amyloid related imaging abnormalities (ARIA) and clinical implications" Front Neurosci. 2024, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10834650/

[16] Withington, Charles G., and R. Scott Turner. "Amyloid-Related Imaging Abnormalities with Anti-Amyloid Antibodies for the Treatment of Dementia due to Alzheimer's Disease." Frontiers in Neurology, vol. 13, 23 Mar. 2022,www.ncbi.nlm.nih.gov/pmc/articles/PMC8985815/, https://doi.org/10.3389/fneur.2022.862369.

[17] Amit Kumar Agarwal, et al. "Amyloid-Related Imaging Abnormalities in Alzheimer Disease Treated with Anti–Amyloid-β Therapy." Radiographics, vol. 43, no. 9, 1 Sept. 2023, https://doi.org/10.1148/rg.230009.

[18] Barakos, J., et al. "Detection and Management of Amyloid-Related Imaging Abnormalities in Patients with Alzheimer's Disease Treated with Anti-Amyloid Beta Therapy." The Journal of Prevention of Alzheimer's Disease, 2022, https://doi.org/10.14283/jpad.2022.21.

[19] Graves, Martin John. "3 T: The Good, the Bad and the Ugly." The British Journal of Radiology, vol. 95, no. 1130, 1 Feb. 2022, https://doi.org/10.1259/bjr.20210708.

[20] Sarracanie, Mathieu, and Najat Salameh. "Low-Field MRI: How Low Can We Go? A Fresh View on an Old Debate." Frontiers in Physics, vol. 8, 12 June 2020, https://doi.org/10.3389/fphy.2020.00172.

[21] Caruso, Damiano, et al. "Magnetic Resonance of Rectal Cancer Response to Therapy: An Image Quality Comparison between 3.0 and 1.5 Tesla." BioMed Research International, vol. 2020, 10 Oct. 2020, pp. 1–8, www.ncbi.nlm.nih.gov/pmc/articles/PMC7576357/, https://doi.org/10.1155/2020/9842732.

[22] Verma, Gaurav, and Priti Balchandani. "Ultrahigh field MR Neuroimaging" Top Magn Reson Imaging. 2019 Jun, https://pmc.ncbi.nlm.nih.gov/articles/PMC6784841/

[23] Vachha, Behroze, and Susie Y. Huang. "MRI with Ultrahigh Field Strength and High-Performance Gradients: Challenges and Opportunities for Clinical Neuroimaging at 7 T and Beyond." European Radiology Experimental, vol. 5, no. 1, 26 Aug. 2021, https://doi.org/10.1186/s41747-021-00216-2.

[24] Franceschi, AM. "Amyloid-Related Imaging Abnormalities (ARIA): An Update." Powerpoint and lecture presented at: ECR 2025; 27 Feb. 2025

[25] Yu FF. "Invited Commentary: Radiologist's Role in Anti-Amyloid Therapy for Alzheimer Disease." RadioGraphics. 2023;43(9). doi:https://doi.org/10.1148/rg.230205

[26] Haller, Sven, et al. "Cerebral Microbleeds: Imaging and Clinical Significance." Radiology, vol. 287, no. 1, Apr. 2018, pp. 11–28, https://pubs.rsna.org/doi/10.1148/radiol.2018170803. Accessed 21 Jan. 2021.

[27] J. Cummings et al. Lecanemab: "Appropriate Use Recommendations." The Journal of Prevention of Alzheimer's Disease 2023. https://doi.org/10.14283/jpad.2023.30

[28] G.D. Rabinovici et al. Donanemab: "Appropriate use recommendations." The Journal of Prevention of Alzheimer's Disease 2025. https://doi.org/10.1016/j.tjpad.2025.100150

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[1] *Personalization of diagnosis, therapy selection and monitoring, aftercare, and managing health.*

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