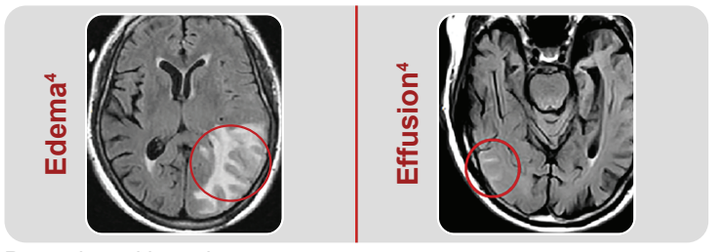
Amyloid Related Imaging Abnormalities

General Overview for the Specialist and Prescriber

Amyloid Related Imaging Abnormalities (ARIA)

- A **spectrum** of **MRI signal abnormalities** associated with **amyloid clearance** in the **brain**[1-3]
- Can occur spontaneously but more frequently observed during treatment with **amyloid-targeting therapies**[1-3]
- There are two types of ARIA: **ARIA-E** and **ARIA-H**[2-4]
  - Both types may be observed on the same scan[5]
  - ARIA type is determined by nature of **leakage product** and **location**[2,5]
- **Monoclonal antibodies** directed against aggregated forms of beta amyloid carry a boxed warning regarding the **increased risk for causing ARIA**, which can be serious and life threatening[1-3]
- **Identification of ARIA** prior to initiation of therapy and ongoing **monitoring via MRI** imaging are crucial during treatment with amyloid-targeting therapies[1-3]

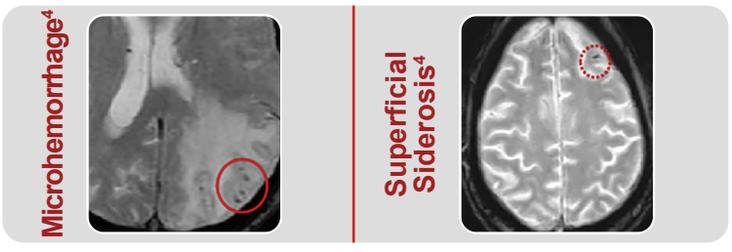
ARIA-E Vasogenic Edema and/or Sulcal Effusion



Parenchymal hyperintense signal on T2 FLAIR

Leptomeningeal sulcal surface hyperintense signal on T2 FLAIR

ARIA-H Hemosiderin Deposits



Punctate foci of signal void on T2* GRE

Sulcal signal hypointensity on T2* GRE

Radiographic Severity Monitoring[5]

	Mild	Moderate	Severe
ARIA-E: Sulcal and/or cortical /subcortical FLAIR hyperintensity Measured in single greatest dimension	1 site <5 cm	1 site 5-10 cm, or >1 site each <10 cm	≥1 site(s) >10 cm
ARIA-H: Number of new* microhemorrhages	≤4	5-9	≥10
ARIA-H: Superficial siderosis	1 focal area	2 focal areas	>2 focal areas
*New: cumulative number from baseline			

Clinical Symptom Severity Monitoring[6-8]

Asymptomatic:
No symptoms noted, no disruption of daily activities

Mild:
Symptoms noted, no disruption of daily activities

Moderate:
Symptoms sufficient to reduce or affect normal daily activities

Severe:
Incapacitating with inability to perform normal daily activities

Headache | Confusion/ Dizziness | Nausea

Less frequent: Neuropsychiatric symptoms | Gait disturbance | Visual disturbance/ Blurred vision

Uncommon: Seizure

ARIA Monitoring and Management: General Principles[1-3, 6-8]

- Baseline ARIA evaluation and periodic monitoring with MRI are recommended during treatment with amyloid-targeting therapies
- Refer to prescribing information for monoclonal antibodies directed against beta amyloid for ARIA monitoring and management guidelines
- Patients experiencing symptoms suggestive of ARIA should undergo clinical evaluation, including MRI if indicated
- If ARIA is observed on MRI, careful clinical evaluation should be performed. Dose suspension or discontinuation may be considered based on the presence of symptoms and/or radiographic severity
- If required, treatment of ARIA revolves around close monitoring of neurologic status and administration of supportive therapy, which may include corticosteroids
- There is limited experience in patients who continued dosing through ARIA-E
- There is limited data for dosing patients who experienced recurrent episodes of ARIA-E

Abbreviations: **ARIA-E** = Amyloid Related Imaging Abnormalities-Edema/Effusion; **ARIA-H** = Amyloid Related Imaging Abnormalities-Hemosiderin deposits; **FLAIR** = Fluid-Attenuated Inversion Recovery; **GRE** = Gradient Recalled Echo; **MRI** = Magnetic Resonance Imaging.

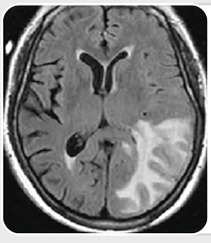
1. Salloway S, MD et al. JAMA Neurol. 2022;79:13-21. **2.** Filippi M et al. JAMA Neurol. 2022;79:291-304. **3.** Sperling RA et al. Alzheimer's Dement. 2011;7:367-385. **4.** Figure adapted from Barakos J et al. J Prev Alz Dis. 2022;9:211-220. Copyright © licensed under CC-BY-4.0 (https://creativecommons.org/licenses/by/4.0/). Modified from original by cutting. **5.** Cogswell PM et al. Am J Neurol. 2022;43:e19-35. **6.** Cummings J et al. J Prev Alz Dis. 2023;10:362-377. **7.** Cummings J et al. J Prev Alz Dis. 2022;9:221-230. **8.** Cummings J et al. J Prev Alz Dis. 2021;4:398-410.

Amyloid Related Imaging Abnormalities

ARIA-E versus ARIA-H

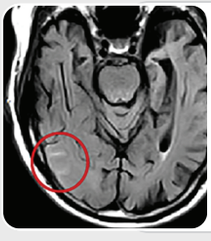
- There are two types of Amyloid Related Imaging Abnormalities (ARIA): **ARIA-E** and **ARIA-H**[1]
  - **ARIA-E** visualized on MRI as **signal hyperintensity** on **T2 FLAIR**[2]
  - **ARIA-H** visualized on MRI as **signal hypointensity** by use of **GRE/T2*** or **SWI sequences**[2]

Edema[1]



ARIA-Edema example image: Hyperintensity on T2 FLAIR in left parieto-occipital lobe, consistent with parenchymal edema

Effusion[1]

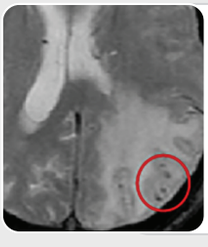


ARIA-Effusion example image: Hyperintensity on T2 FLAIR in the sulci within the right temporo-occipital lobe, consistent with effusion

ARIA-E Vasogenic Edema and/or Sulcal Effusion[2,3]

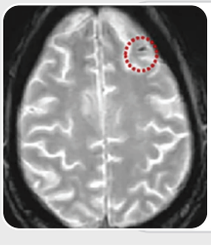
Nature of leakage products	Proteinaceous fluids
Location of increased vascular permeability	**Parenchyma:** vasogenic edema **Leptomeninges:** sulcal effusions (i.e., exudates)
Primary diagnostic imaging sequence	T2 FLAIR
Evaluation of severity	MRI severity scales[4]

Microhemorrhage[1]



ARIA-Microhemorrhage example image: Punctate foci of signal void on T2* GRE in an area of parenchymal edema, consistent with microhemorrhage

Superficial Siderosis[1]



ARIA-Siderosis example image: Signal hypointensity in right temporal area on T2* GRE, consistent with superficial siderosis on axial

ARIA-H Hemosiderin Deposits[2,3]

Nature of leakage products	Blood-degradation products
Location of increased vascular permeability	**Parenchyma:** microhemorrhage (<10 mm) and intracerebral hemorrhage (≥10 mm) **Leptomeninges:** superficial hemosiderin deposits (superficial siderosis)
Primary diagnostic imaging sequence	T2* GRE and/or SWI
Evaluation of severity	Number of microhemorrhages and hemosiderin deposits on MRI

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1. Figure adapted from Barakos J et al. J Prev Alz Dis. 2022;9:211-220. Copyright © licensed under CC-BY-4.0 (https://creativecommons.org/licenses/by/4.0/). Modified from original by cutting. **2.** Barakos J et al. Am J Neuroradiol. 2013;34:1958-1965. **3.** Sperling RA et al. Alzheimer's Dement. 2011;7:367-385. **4.** Barkhof F et al. Am J Neurol. 2013;34:1550-1555.

Amyloid Related Imaging Abnormalities

Pathophysiology of ARIA

Hypothesized Pathophysiology

- Amyloid-targeting therapies **remove deposited Aβ** in cerebral vasculature[1,2]
- Amyloid clearance is hypothesized to result in **increased vascular permeability**[1,2]
- Vascular drainage system is overloaded, leading to **leakage of fluid** (hyperintensity on T2 FLAIR indicative of ARIA-E) and/or **red blood cells** (T2* GRE images indicative of ARIA-H)[1,2]

Similarities to Cerebral Amyloid Angiopathy

Hypothesized pathophysiology of ARIA is based on similar mechanisms, image findings, and clinical outcomes seen in Cerebral Amyloid Angiopathy (CAA)[3-5]

- CAA is characterized by pathological Aβ deposition in cerebral microvasculature
- CAA is common among older adults and frequently coexists with Alzheimer's disease
- CAA has imaging features similar to those of ARIA but occurs in the absence of amyloid-targeting mAb treatment
- CAA may help explain occurrence of ARIA in placebo arms

Risk Factors

APOE ε4 carrier[1,5,6]

Presence of microhemorrhages prior to treatment with amyloid-targeting mAbs[1,5]

Amyloid-targeting mAb treatment [1,5]

ARIA-related Findings from Clinical Trials

Use of amyloid-targeting therapies was associated with **increased risk of ARIA** compared to placebo[1]

ARIA is usually asymptomatic, although rarely serious and life-threatening events can occur, and usually identified via protocol-specified surveillance MRI scans[2,6]

Most cases occurred **early in the treatment course** with risk decreasing as treatment continued although it can occur at any time[6,7]

Radiographically, **ARIA-E tended to resolve** over time[5], whereas **ARIA-H tended to stabilize** and remain visible on subsequent imaging[1]

Increased risk of ARIA-H was observed in some trials when **amyloid-targeting therapies** were given in combination with **antithrombotic medications**. Therefore, additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to patients already being treated with amyloid-targeting therapies[8]

Abbreviations: **APOE** = Apolipoprotein E; **ARIA-E** = Amyloid Related Imaging Abnormalities-Edema/Effusion; **ARIA-H** = Amyloid Related Imaging Abnormalities-Hemosiderin deposits; **ATT** = Amyloid-Targeting Therapy; **CAA** = Cerebral Amyloid Angiopathy; **FLAIR** = Fluid-Attenuated Inversion Recovery; **GRE** = Gradient Recalled Echo; **mAb** = Monoclonal Antibody; **MRI** = Magnetic Resonance Imaging.

1. Sperling RA et al. Alzheimer's Dement. 2011;7:367-385. **2.** Sperling RA et al. Lancet Neurol. 2012;11:241-249. **3.** Grasso D et al. Radiol Case Rep. 2021;16:2514-2521. **4.** Brenowitz WD et al. Neurobiol Aging. 2015;36:2702-2708. **5.** Cogswell PM et al. Am J Neuroradiol. 2022;43:e19-35. **6.** Filippi M et al. JAMA Neurol. 2022;79:291-304. **7.** Salloway S et al. JAMA Neurol. 2022;79:13-21. **8.** Arrighi HM et al. JNNP. 2016;87(1):106-112.

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Detecting ARIA: Recommended MRI Protocol[2]

- Imaging protocol standardization is necessary to ensure consistent accuracy for diagnosing ARIA, and specific parameters are needed to achieve cross-platform standardization[1]

3T scanner (recommended), 1.5T scanner (minimal)[1,2]	High field scanners have greater sensitivity but limited availability. The use of 1.5T is endorsed as a minimum standard[2]
Slice thickness[2]: ≤5 mm	Thinner slices increase resolution but should be balanced against the loss in signal-to-noise ratio[2]
TE[2]: ≥20 ms	Longer TE increases sensitivity to detection[2]
2D T2* GRE or SWI (for ARIA-H)[2,3]	To identify superficial siderosis and microhemorrhages (ARIA-H) T2* GRE and SWI MRI sequences are used to improve detection and visualization of microhemorrhages[2]
T2 FLAIR (for ARIA-E)[2]	To monitor brain edema or sulcal effusion (ARIA-E)[3]
DWI[3]	Recommended for differential diagnosis[3]
3D T1-GE (optional)[1]	Anatomical[1]

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1. Pinter NK et al. Alzheimer's Dement. 2022;18(Suppl. 5):e065547. **2.** Cogswell PM et al. Am J Neurol. 2022;43:e19-35. **3.** Sperling RA et al. Alzheimer's Dement. 2011;7:367-385. **4.** Barakos J et al. J Prev Alz Dis. 2022;9:211-220.