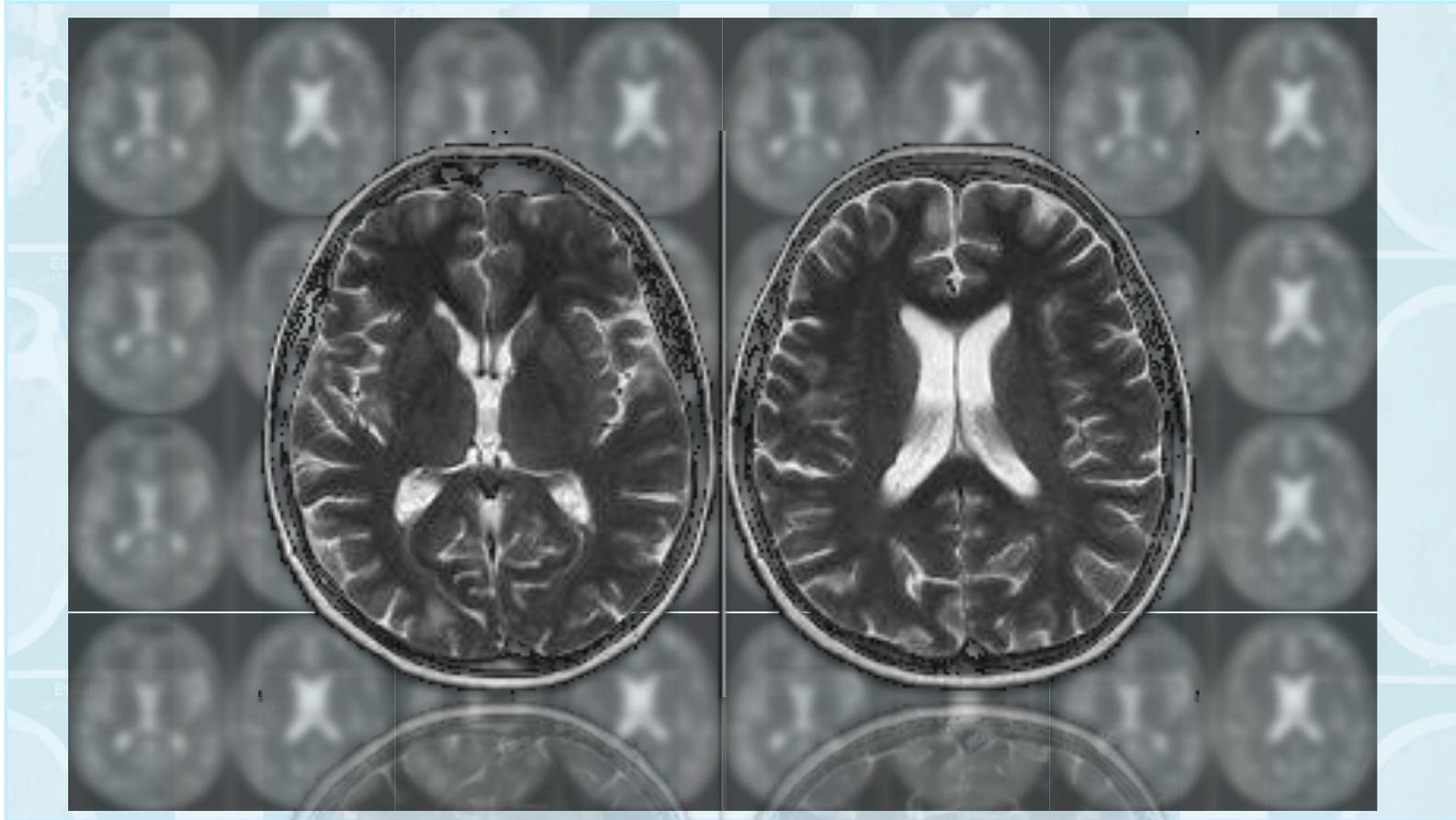


# Understanding Amyloid-Related Imaging Abnormalities (ARIA): For the Radiologist

# Outline slide



**Introducing ARIA**

**Pathophysiology**

**Deeper focus on ARIA**

**Clinical manifestation of ARIA**

**Diagnosis of ARIA**

**Management of ARIA**

# Introducing ARIA

# Introduction to Alzheimer's disease

## What is Alzheimer's



AD is a multifactorial and heterogeneous neurodegenerative disorder, accounting for 60–80% of dementia cases<sup>1,2</sup>

## Alzheimer's pathology



The presence of amyloid-beta and tau, synaptic failure, and neuronal dysfunction are common features of AD and are suggested to play a pivotal role in cognitive dysfunction<sup>3–6</sup>

Amyloid deposition visualized on a PET scan<sup>7</sup>  
Image from Chapleau M, et al. (2022)<sup>7</sup>



These pathological changes can begin many years before (~15–20 years) before the development of symptoms<sup>4,5</sup>

1. Kazim SF, Iqbal K. Mol Neurodegener 2016;11:50; 2. Alzheimer's Association. Alzheimers Dement. 2022;18(4):700–789; 3. Serrano-Pozo A, et al. Cold Spring Harb Perspect Med 2011;1:a006189; 4. Jack CR, et al. Alzheimers Dement 2018;14:535–562; 5. Bateman RJ, et al. N Engl J Med 2012;367:795–804; 6. Bennet AD, et al. Arch Neurol 2004;61:378–384; 7. Chapleau M, et al. J Nucl Med. 2022 Jun;63(Suppl 1):13S-19S

# What is ARIA?

- ARIA is a consequence of the presence of amyloid in cerebral blood vessel walls (cerebral amyloid angiopathy [CAA]).<sup>1</sup> CAA can cause spontaneous ARIA in patients with AD and the risk of ARIA is increased with monoclonal antibodies that remove amyloid plaques<sup>1</sup>
- Studies have suggested that ARIA-E and ARIA-H may be caused by disruption of vessels with CAA and the risk is increased by the clearance of A $\beta$  from cerebral vessels, but other mechanisms are also hypothesized<sup>2</sup>
- An Alzheimer's Association workgroup defined the term **“amyloid-related imaging abnormalities” or “ARIA,”** in AD based on MRI findings which is subdivided into ARIA-E or ARIA-H<sup>1</sup>
  - ARIA-E: parenchymal vasogenic edema or sulcal effusions detected on FLAIR sequences<sup>3</sup>
  - ARIA-H: microhemorrhages, superficial hemosiderin deposition (superficial siderosis) detected on T2\*GRE sequences<sup>3</sup>
- **Most cases of ARIA in patients treated with monoclonal antibodies that remove amyloid plaque are asymptomatic; however, ARIA-E may have concurrent symptoms such as headache, confusion, dizziness, and nausea; less likely, gait disturbances, visual impairment, and rarely seizures.<sup>4</sup> ARIA can be serious, and life-threatening and may require intervention beyond withholding treatment to address symptoms<sup>5</sup>**

ARIA, amyloid-related imaging abnormalities; ARIA-E: ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo

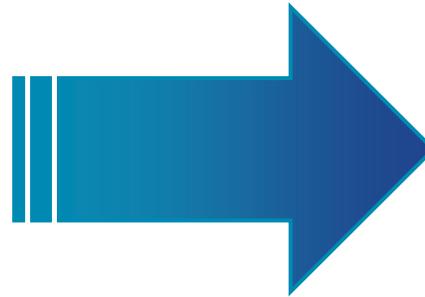
1. Sperling RA, et al. *Alzheimers Dement*. 2011;7:367–385; 2. Sperling RA, et al. *Lancet Neurol*. 2012;11:241–249; 3. Barakos J, et al. *J Prev Alzheimers Dis*. 2022;9(2):211–220; 4. Salloway S, et al. *JAMA Neurol*. 2022;79(1):13–21; 5. Cummings J, et al. *J Prev Alzheimers Dis* 2022;9:221–230

# Emerging therapies aiming to remove amyloid beta (A $\beta$ )

## Monoclonal antibodies that remove amyloid



Strategies to target and remove amyloid are based on our understanding that interfering with the underlying pathophysiologic mechanisms of the disease process could **slow disease progression**, but need to be initiated early in the course of disease given these changes begin in the early stages of disease<sup>1</sup>



## Amyloid-related imaging abnormalities

Interfering/removing the amyloid deposition in the brain that has built up over years can impact the vessel vasculature in the brain which can result in signal changes identifiable on MRI: **“amyloid-related imaging abnormalities or ARIA”<sup>2</sup>**

**ARIA is a known adverse reaction of monoclonal antibodies that remove amyloid plaque for AD**

A $\beta$ , amyloid beta; ARIA: Amyloid-related imaging abnormalities; AD: Alzheimer's Disease  
1. Bateman RJ, et al. N Engl J Med 2012;367:795–804; 2. Sperling RA, et al. Alzheimers Dement. 2011;7:367–385

# Neuroimaging: ARIA-E and ARIA-H

ARIA-E

Interstitial vasogenic edema or sulcal effusion that manifests as parenchymal or sulcal hyperintensities

ARIA-H

Microhemorrhages (mH) are observed as <1cm hypointense hemosiderin deposition in the parenchyma  
Superficial siderosis is observed as linear hypointense hemosiderin deposition in the leptomeningeal/subpial space

## Primary MRI features

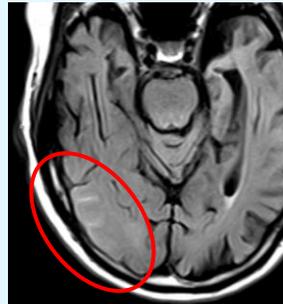
ARIA-E

Edema



FLAIR hyperintense;  
parenchymal edema  
in left occipital-parietal lobe<sup>a</sup>

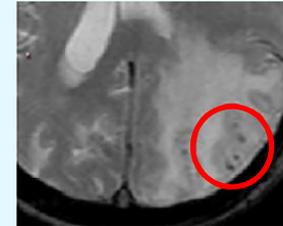
Effusion



FLAIR hyperintense;  
increased MRI signal in sulci within right  
temporal-occipital lobe<sup>a</sup>

ARIA-H

Microhemorrhage



Punctate foci of signal void on T2\*GRE in  
an area of parenchymal edema<sup>a</sup>

Superficial siderosis



New right temporal superficial siderosis  
on axial T2\*GRE imaging<sup>b</sup>

**Intracerebral hemorrhage (also termed macrohemorrhage):**

Rare lobar intracerebral hemorrhage occurs spontaneously in AD and with monoclonal antibodies that remove amyloid, related to underlying CAA<sup>2</sup>

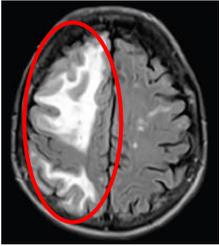
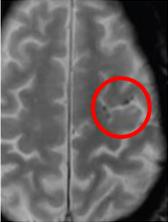
Figures reproduced from <sup>a</sup>Barakos et al (2022); <sup>b</sup>Cogswell et al (2022).

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; CAA, cerebral amyloid angiopathy; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo; mH, microhemorrhage; MRI, magnetic resonance imaging; SWI, susceptibility weighted imaging.

1. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 2. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

# ARIA-E and ARIA-H

ARIA is an umbrella term used to describe two types of imaging abnormalities<sup>1</sup>

	ARIA-E <sup>1,2</sup>	ARIA-H <sup>1,2</sup>
PRIMARY DIAGNOSTIC IMAGING SEQUENCE	FLAIR	T2* GRE
NATURE OF LEAKAGE PRODUCTS	Proteinaceous fluids	Blood-degradation products
LOCATION OF INCREASED VASCULAR PERMEABILITY	<b>Parenchyma:</b> vasogenic edema <b>Leptomeninges:</b> sulcal effusions (i.e., exudates)	<b>Parenchyma:</b> microhemorrhages (typically defined as <10 mm) and intracerebral hemorrhage (≥10 mm) <b>Leptomeninges:</b> superficial hemosiderin deposits (superficial siderosis)
EVALUATION OF SEVERITY	MRI severity scales <sup>3</sup> and assessment of symptoms	The number of microhemorrhages and hemosiderin deposits on MRI and assessment of symptoms
IMAGE	 <p>ARIA-E seen on FLAIR images demonstrating increased signal in multiple regions of the right hemisphere, affecting both gray and white matter<sup>4</sup></p>	 <p>ARIA-H seen on T2* GRE MRI. MRI reveals several microhemorrhages (&lt;10 mm; red circle)<sup>4</sup></p>

ARIA, amyloid-related imaging abnormalities; ARIA-E: ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; MRI, magnetic resonance imaging.

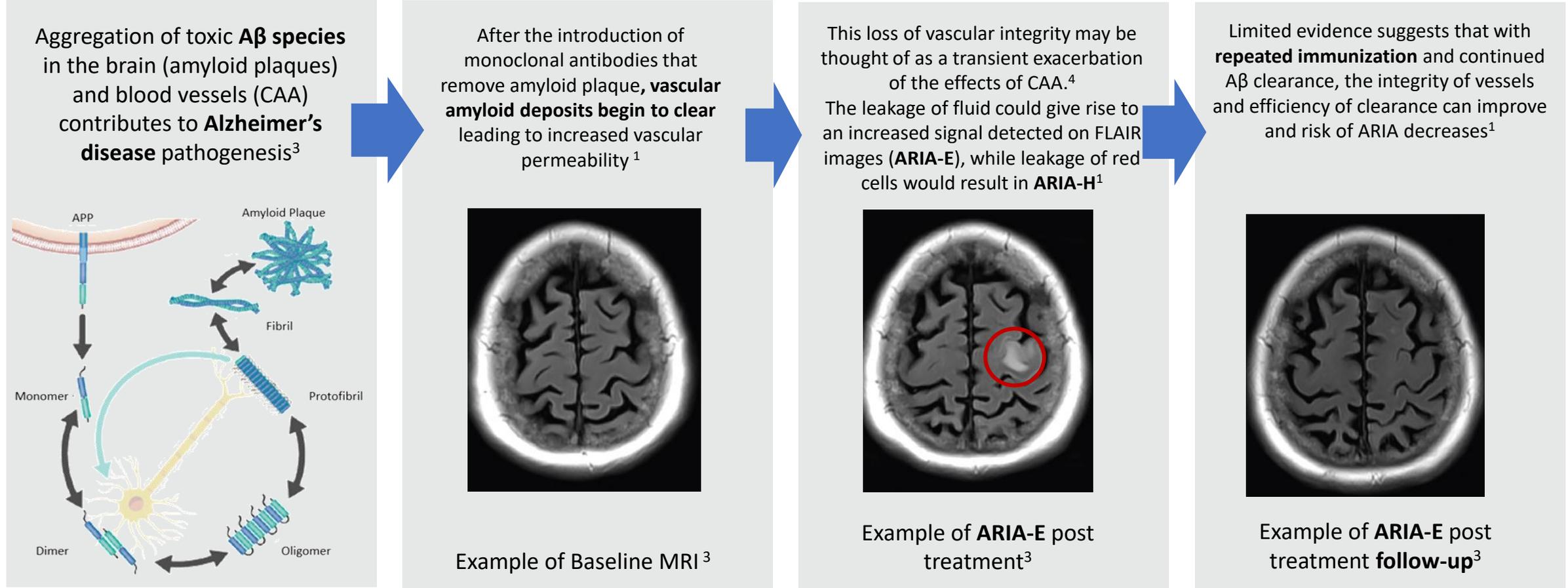
1. Sperling RA, et al. *Alzheimers Dement*. 2011;7:367–85; 2. Barakos J, et al. *AJNR Am J Neuroradiol*. 2013;34:1958–965; 3. Barkhof F, et al. *AJNR Am J Neuroradiol*. 2013;34:1550–1555; 4. Cogswell PM, et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19–E35



# Pathophysiology

# Hypothesized pathophysiology of ARIA

ARIA is a consequence of the presence of amyloid in cerebral blood vessel walls (cerebral amyloid angiopathy [CAA]), which can cause spontaneous ARIA in patients with AD.<sup>1</sup> The increased occurrence of ARIA-E seen with treatments that remove amyloid plaques is thought to be due to the removal of vascular amyloid and disruption of amyloid in blood vessel walls.<sup>1</sup> Other mechanisms are also hypothesized.



MRI images from Cogswell et al (2022);<sup>3</sup> figure adapted from Hampel et al. (2021)<sup>4</sup>

$A\beta$ , Amyloid beta; ARIA: Amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage

1. Sperling RA, et al. *Alzheimers Dement.* 2011;7:367–385; 2. Barakos, J et al. *J Prev Alzheimer's Dis* 2022; 9(2):211–220; 3. Cogswell, PM et al. *AJNR Am J Neuroradiol.* 2022;43(9):E19–E35; 4. Hampel H, et al. *Nature.* 2021;26:5481–5503

# Cerebral Amyloid Angiopathy (CAA) presentation and Cerebral Amyloid Angiopathy-related inflammation (CAA-ri)

## What is CAA?



CAA is a type of cerebrovascular disorder characterized by the accumulation of A $\beta$  peptide within the leptomeninges and small/medium-sized cerebral blood vessels in patients with or without AD symptoms<sup>1</sup>

## CAA presentation



A $\beta$  deposition results in fragile vessels that may present with microhemorrhages, superficial hemosiderosis, or intracerebral hemorrhage (macrohemorrhage)<sup>1</sup>

## CAA-ri



CAA-ri is a rare and potentially life-threatening autoimmune response to vascular amyloid complication of CAA.<sup>2</sup> It can be a treatment-reversible disease, responsive to immunosuppressive therapies<sup>3</sup>

A $\beta$ , amyloid- $\beta$ ; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; CAA-ri, CAA-related inflammation.

1. Kuhn J, Sharman T. Cerebral Amyloid Angiopathy. 2022 Jun 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan; 2. Grasso, D et al. Radiol Case Rep. 2021 Sep.;16(9):2514-2521; 3. Antolini, L et al. Neurology 2021;97:e1809–e1822

# Commonalities in pathophysiology between CAA-ri and ARIA

While ARIA and CAA-ri are separate entities, they share a number of similarities:

## Risk factors



Increased number of microbleeds  
and *APOE ε4* genotype

## Location



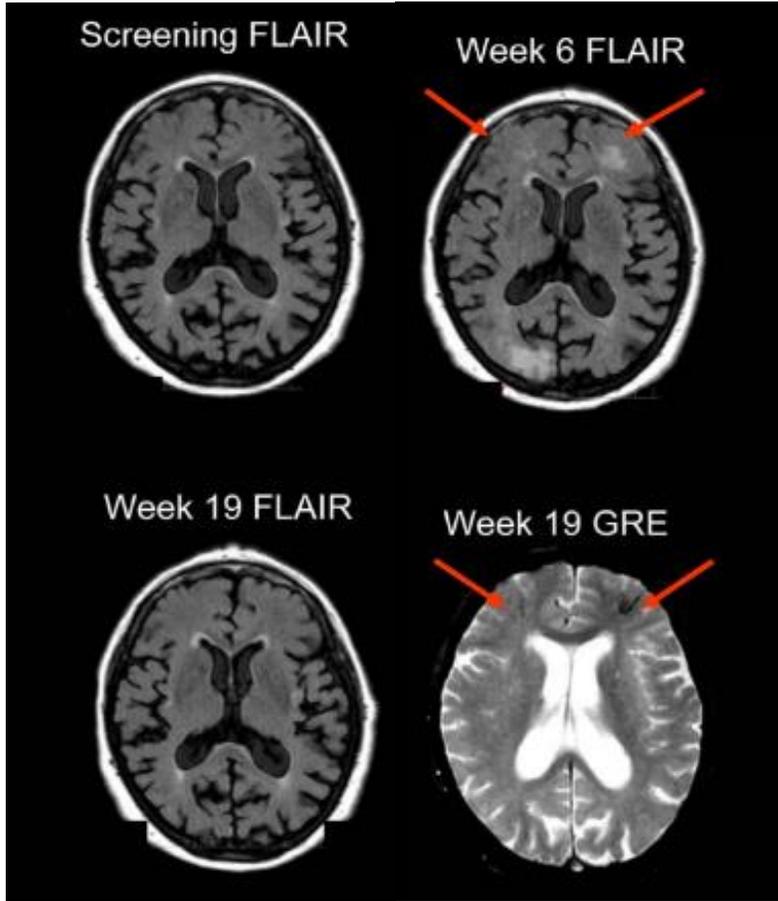
CAA develops to a greater extent in  
cortical and leptomeningeal vessels  
(the locations where ARIA occurs)

## Syndrome resemblance



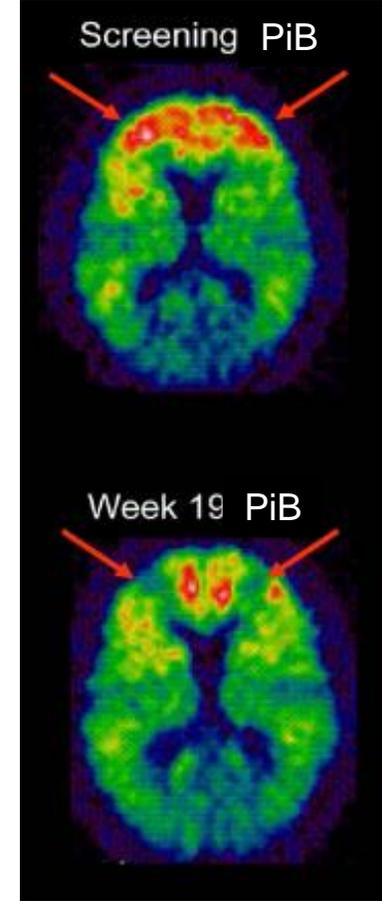
Infiltration of inflammatory cells  
(microglia, T cells, and  
 $A\beta$ -containing multinucleated  
cells) in CAA-ri suggests possible  
spontaneous anti- $A\beta$  immunization

# Relationship between amyloid removal with monoclonal antibodies and ARIA-E and ARIA-H



At **Week 6**, FLAIR MRI reveals bifrontal parenchymal hyperintensity (ARIA-E), which resolves by **Week 19**

At **Week 19**, T2\*GRE sequence reveals the development of bifrontal microhemorrhages (ARIA-H)



**Baseline** PiB retention consistent with high fibrillar burden

**Week 19** PiB uptake is reduced representing clearance of fibrillar amyloid from plaque and cerebral vessels

**Reduced PiB retention is temporally and regionally associated with ARIA-E and ARIA-H**

ARIA-E: ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; FLAIR, fluid-attenuated inversion recovery; GRE, gradient-recalled echo; MRI, magnetic resonance imaging; PiB-PET, Pittsburgh compound B-positron emission tomography  
Sperling RA, et al. Lancet Neurol 2012;11:241–249



# Deeper focus on ARIA

# ARIA-E

## Parenchymal signal abnormalities (ARIA-E edema)

- Imaging features of **ARIA-E edema** are thought to reflect **leakage of intravascular fluid and proteins** into the **parenchymal interstitial compartment**<sup>1</sup>
- Parenchymal signal abnormalities can be quite subtle in a single region, multifocal, or nearly pan-hemispheric<sup>2</sup>



Figure from Barakos et al (2022)<sup>4</sup>

## Sulcal FLAIR hyperintensities (ARIA-E effusion)

- The imaging features of **ARIA-E effusion** are thought to reflect **leakage or effusion of proteinaceous fluid from meningeal vessels**<sup>2</sup>
- Sulcal FLAIR hyperintensity in the leptomeningeal or sulcal space may be seen in isolation or near gray matter disturbances<sup>2</sup>



Figure from Barakos et al (2022)<sup>4</sup>

**Additional analyses are required to confirm the prevalence of spontaneous ARIA-E<sup>3</sup>**  
**In clinical trials, the rate of spontaneous ARIA-E in the placebo arm over 18 months has been found to range between 0.8% and 3.0%<sup>5-8</sup>**

AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E: ARIA-edema/effusion; FLAIR, fluid-attenuated inversion recovery.

1. Barakos J, et al. *AJNR Am J Neuroradiol.* 2013;34:1958–1965; 2. Sperling RA, et al. *Alzheimers Dement.* 2011;7:367–385; 3. Carlson C, et al. *Alzheimers Dement.* 2011;396–401; 4. Barakos J, et al. *J Prev Alzheimers Dis.* 2022;9(2):211–220;

5. Budd-Haeberlein S, et al. *J Prev Alzheimers Dis* 2022;9:197–210; 6. van Dyck C, et al. *N Eng J Med* 2023;388:9–21; 7. Ostrowitzki S, et al. *Alzheimers Res Ther.* 2017;9(1):95; 8. Vandenberghe R, et al. *Alzheimers Res Ther.* 2016;8:18.

# ARIA-H

## Microhemorrhages

- Small deposits of iron in the brain **parenchyma** in the form of **hemosiderin**<sup>1</sup>
- Typically manifest as new **hypointense lesions on T2\*GRE MRI sequences** (typically defined by a cutoff of **<10 mm**)<sup>2</sup>
- Thought to represent residua of a small leakage of blood from a vessel into **adjacent tissue**<sup>1</sup>
- The baseline prevalence of microhemorrhages is estimated to be 15.3%<sup>3</sup>
  - This prevalence increases with age: ~17% in people aged 60–69 years, ~29% in people aged 70–79 years, and ~36% in people aged 80–97 years<sup>3</sup>
- **Less commonly, macrohemorrhages (≥10 mm) can also occur**<sup>2</sup>

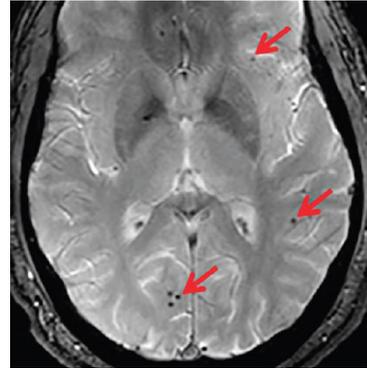


Figure from Cogswell et al (2022)<sup>4</sup>

## Superficial Siderosis

- **Curvilinear low intensities on T2\*GRE MRI sequences** that lie adjacent to the surface of the brain<sup>1</sup>
- Attributed to the deposition of iron in the form of **hemosiderin** and is thought to represent residua of leakage of blood from a vessel into the **adjacent subarachnoid space or the periadventitial compartment**<sup>1</sup>
- The baseline prevalence of superficial siderosis is estimated to be 0.21% in those aged 50–69 years and 1.43% in those >69 years old<sup>5</sup>

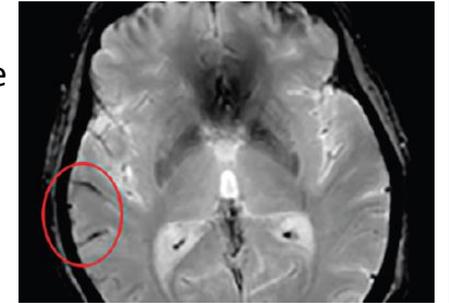


Figure from Cogswell et al (2022)<sup>4</sup>

ARIA-H: ARIA-hemosiderin/hemorrhage; GRE, gradient-recalled echo; MRI, magnetic resonance imaging.

1. Sperling RA, et al. *Alzheimers Dement*. 2011;7:367-385. 2. Barakos J, et al. *AJNR Am J Neuroradiol*. 2013;34:1958-1965. 3. Poels MM, et al. *Stroke*. 2010;41:S103-S106

4. Cogswell PM, et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19-E35; 5. Pichler M, et al. *Stroke*. 2017;48:3210-3214



# Clinical manifestations of ARIA

# Clinical manifestations of ARIA



In most cases, ARIA is **asymptomatic**.<sup>1</sup> Moreover, most cases **occur early** in the treatment course and **decrease with increased duration** of exposure<sup>1,2</sup>



The most commonly reported symptoms of ARIA-E are transient and nonspecific and include **headache, confusion, dizziness, nausea and neuropsychiatric symptoms**; **less frequent symptoms include fatigue, visual impairment, blurred vision, and gait disturbance**<sup>1,3</sup>



Infrequently, severe symptoms occur (e.g., encephalopathy, focal neurologic symptoms, seizures), requiring hospitalization and specific treatments (e.g., intensive care unit admission, electroencephalography, corticosteroids, antiepileptics).<sup>1,4</sup> **ARIA can be serious and life-threatening**<sup>4</sup>

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion

1. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 2. Sperling RA, et al. Lancet Neurol 2012;11:241–249 3. Salloway S, et al. JAMA Neurol. 2022;79(1):13–21;; 4. Cummings J, et al. J Prev Alzheimers Dis 2022;9:221–230

# ARIA experience from clinical trials



ARIA is more common in *APOE ε4* carriers<sup>1,2</sup>



Most cases of ARIA-E and ARIA-H are asymptomatic and usually recognized as incidental ARIA during follow-up evaluation on MRI<sup>1,2</sup>



Most cases of ARIA-E occur early in the treatment course and decrease with increased duration of exposure.<sup>1-3</sup> ARIA-E and ARIA-H may occur concurrently<sup>3</sup>



Most cases of ARIA-E resolve completely. Depending on severity, treatment may be continued, be interrupted, or discontinued.<sup>1,4,5,6</sup> Some cases may require specific treatments or even hospitalization.<sup>6</sup> ARIA-H stabilizes but can remain on subsequent imaging<sup>3,7</sup>



Re-dosing following resolution is generally associated with a low rate of ARIA recurrence<sup>4,5</sup>

*APOE ε4*, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; MRI, magnetic resonance imaging

1. Sperling R, et al. Lancet Neurol 2012;11:241–249; 2. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 3. Barakos J, et al. AJNR Am J Neuroradiol. 2013;34(10):1958–1965; 4. Ketter N, et al. J Alzheimers Dis 2017;57:557–573;

5. Ostrowitzki S, et al. Alzheimers Res Ther 2017;9:95; 6. Cummings J, et al. J Prev Alzheimers Dis 2022;9:221–230; 7. Salloway S, et al. JAMA Neurol. 2022;79(1):13–21;

# Diagnosis of ARIA

# ARIA risk factors

## Main risk factors:



***APOE*  $\epsilon$ 4 carrier status<sup>1-3</sup>**



**Pre-treatment microhemorrhage<sup>2,3</sup>**

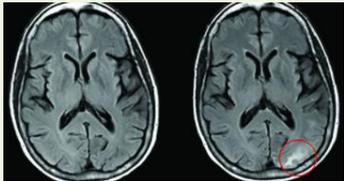
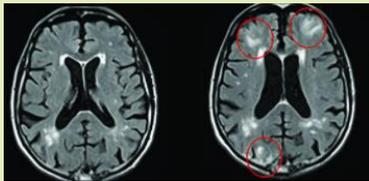
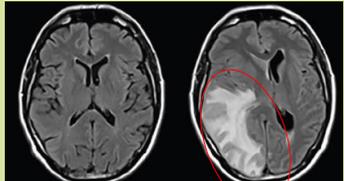
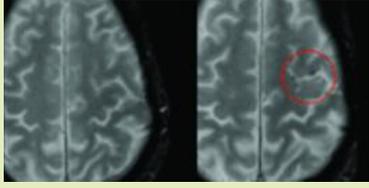
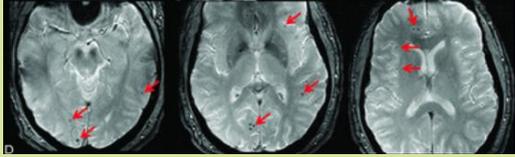


**Treatment with  
monoclonal antibodies  
that remove amyloid<sup>2,3</sup>**

APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities (includes ARIA-E and ARIA-H); ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage;  
1. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304; 2. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 3. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

# Grading scale for determining radiographic severity of ARIA

ARIA-E, ARIA-H microhemorrhage, and ARIA-H superficial siderosis are each categorized by radiographic severity (mild to severe) based on the following criteria

	Mild	Moderate	Severe
<p><b>ARIA-E</b> Sulcal and/or cortical/ subcortical FLAIR hyperintensity</p>	<p>1 location &lt;5 cm</p>  <p>Baseline Posttreatment</p>	<p>1 location 5–10 cm OR &gt;1 location each &lt;10 cm</p>  <p>Baseline Posttreatment</p>	<p>1 more location &gt; 10 cm</p>  <p>Baseline Posttreatment</p>
<p><b>ARIA-H</b> Superficial siderosis</p>	1 focal area	2 focal areas	> 2 focal areas
<p><b>ARIA-H</b> Number of new Microhemorrhages</p>	<p>≤4</p>  <p>Baseline Posttreatment &lt;5 treatment-emergent microhemorrhages</p>	<p>5–9</p>  <p>Baseline Posttreatment 5 treatment-emergent microhemorrhages</p>	<p>≥10</p>  <p>Posttreatment At least 12 treatment-emergent microhemorrhages (arrows)</p>

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-vasogenic edema; ARIA-H, ARIA-microhemorrhages or hemosiderosis  
Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

Figure adapted from Cogswell et al (2022)

# Recommended MRI protocols for detection of ARIA

MRI protocol:  
standards for detection  
of ARIA in clinical trials



Figure adapted from Barakos et al, (2022)<sup>3</sup>



3T scanner  
(recommended)  
1.5T scanner (minimal)<sup>1,2</sup>

High field strength scanners have greater sensitivity but limited availability. The use of 1.5T is endorsed as a minimum standard<sup>2</sup>



Slice thickness<sup>2</sup>:  $\leq 5$  mm

Thinner slices increase resolution but should be balanced against the loss in signal-to-noise ratio<sup>2</sup>



TE<sup>2</sup>:  $\geq 20$  ms

Longer TE increases sensitivity to detection<sup>2</sup>



2D T2\*GRE or SWI (for  
ARIA-H)<sup>2,3</sup>

To identify superficial siderosis and microhemorrhages (ARIA-H) T2\*GRE and SWI are MRI sequences used to improve the detection and visualization of microhemorrhages<sup>2</sup>



T2-FLAIR (for ARIA-E)<sup>2</sup>

To monitor brain edema or sulcal effusion (ARIA-E)<sup>3</sup>



Diffusion-weighted  
imaging (DWI)<sup>3</sup>

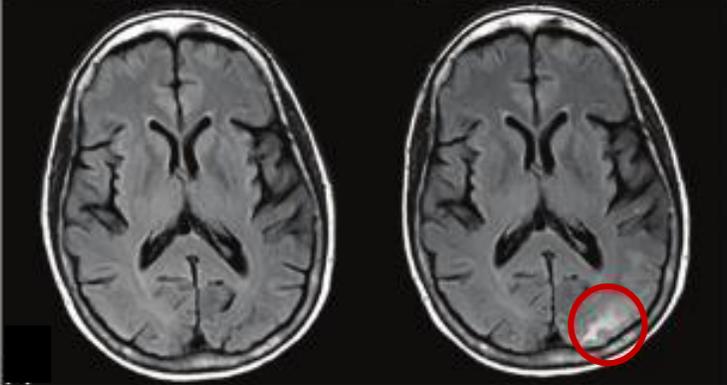
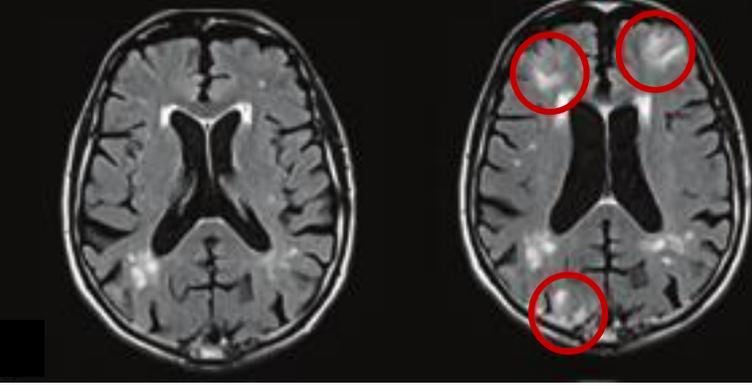
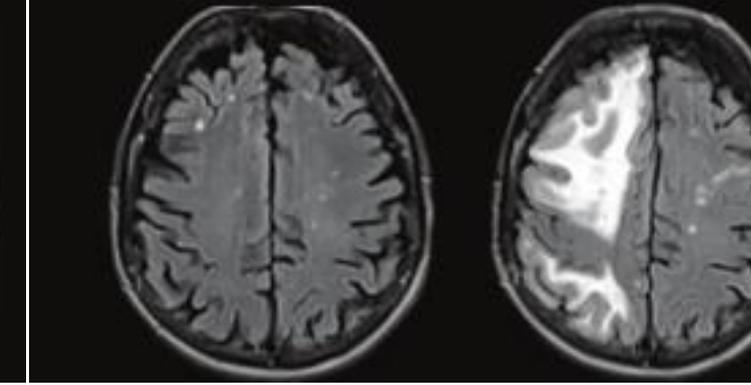
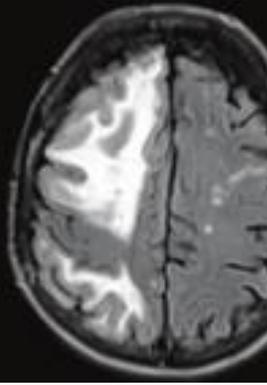
Recommended for differential diagnosis<sup>3</sup>

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient recalled echo; MRI, magnetic resonance imaging; T2-FLAIR, T2-weighted fluid attenuated inversion recovery; TE, echo time; SWI, susceptibility weighted imaging.

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385; 3. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220

# Detection of ARIA-E, parenchymal edema, and corresponding grading

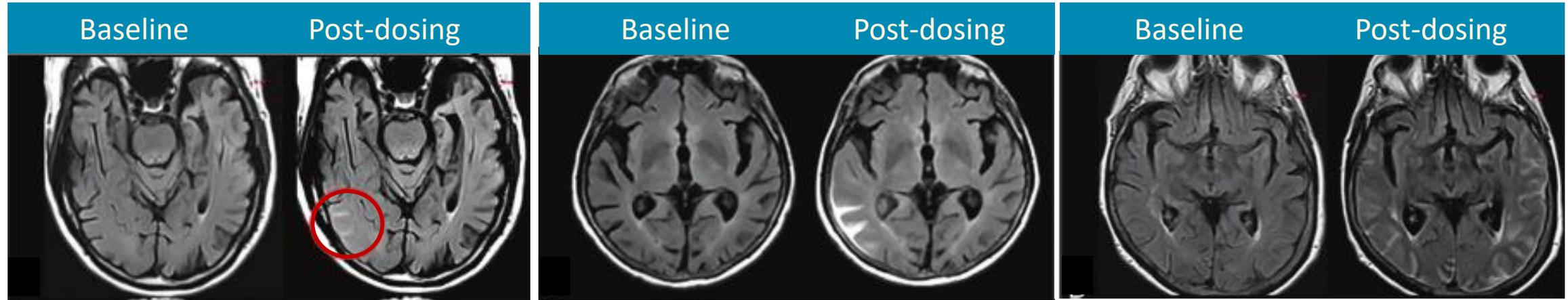
All figures adapted from Cogswell, PM et. al (2022)

Baseline		Post-dosing		Baseline		Post-dosing		Baseline		Post-dosing	
											
<b>Mild ARIA-E</b> T2-FLAIR hyperintense signal in the left parietooccipital subcortical white matter with mild local mass effect and sulcal effacement measuring <5 cm the transverse dimension		<b>Moderate ARIA-E</b> New multifocal, patchy T2-FLAIR hyperintense signal in the bifrontal and right occipital subcortical white matter, each region measuring <5 cm. A single region measuring <5 cm would be classified as mild; >1 yields a moderate ARIA-E classification as long as each region is <10 cm in diameter		<b>Severe ARIA-E</b> Development of extensive T2-FLAIR hyperintense signal throughout the right frontal and parietal lobes measuring >10 cm Associated mass effect and sulcal effacement throughout much of the right cerebral hemisphere							

Data shown of 3 different patients  
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion, T2-FLAIR, T2-weighted fluid attenuated inversion recovery;  
Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19-E35

# Detection of ARIA-E, sulcal effusion, and corresponding grading

All figures adapted from Cogswell, PM et. al (2022)



## Mild ARIA-E

New sulcal T2-FLAIR hyperintense signal in the right temporal-occipital lobe measuring <5 cm in transverse dimensions

## Moderate ARIA-E

New T2-FLAIR sulcal effusion involving the right posterior temporal and parietal lobes measuring 5–10 cm

## Severe ARIA-E

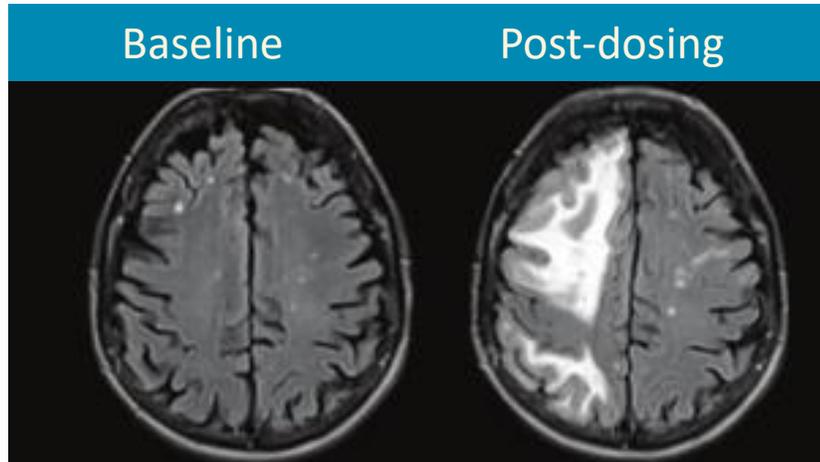
Extensive T2-FLAIR sulcal effusion involving the bilateral temporal and occipital lobes measuring  $\geq 10$  cm in extent

Data shown of 3 different patients

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; MRI, magnetic resonance imaging; T2-FLAIR, T2-weighted fluid attenuated inversion recovery

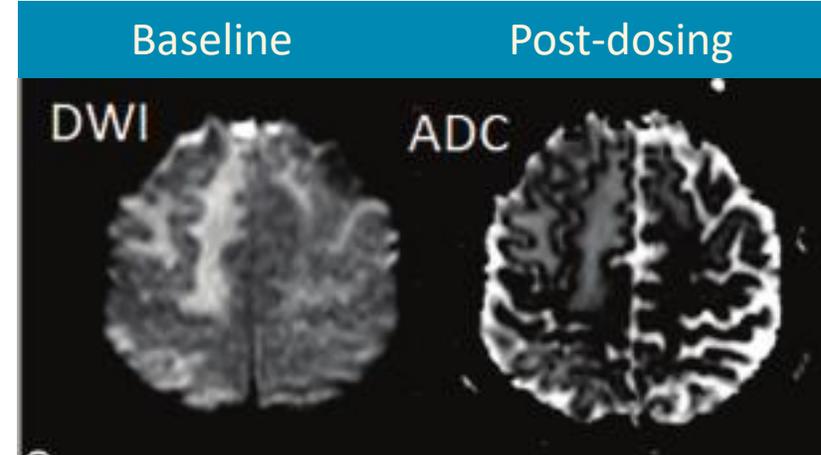
Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

# Differentiating ARIA-E from Ischemic Stroke



## Severe ARIA-E

Development of extensive T2-FLAIR hyperintense signal throughout the right frontal and parietal lobes measuring >10 cm (severe ARIA-E). Associated mass effect and sulcal effacement throughout much of the right cerebral hemisphere



Hyperintense signal on Diffusion Weighted Imaging (DWI) is confirmed to be T2 shine-through on the Apparent Diffusion Coefficient (ADC) map, differentiating ARIA-E from acute ischemia or other cause of cytotoxic edema

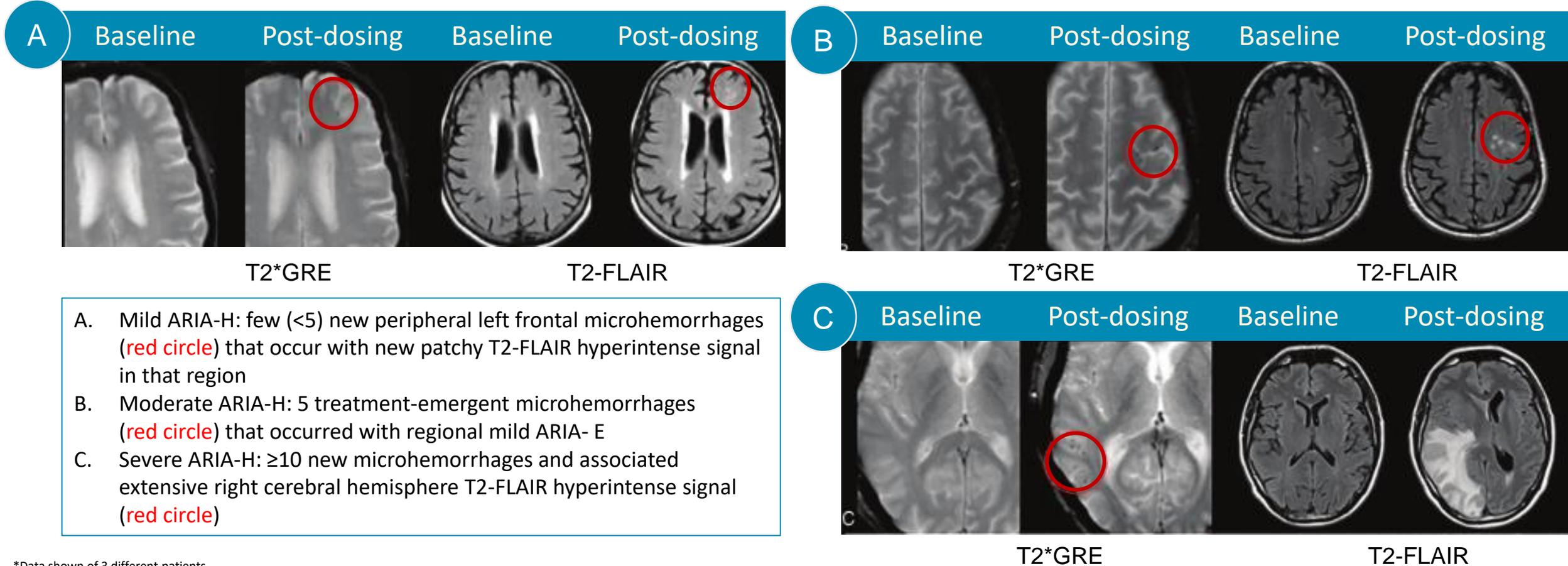
Data shown of 3 different patients

ADC, Apparent Diffusion Coefficient; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; DWI, diffusion-weighted imaging; T2-FLAIR, T2-weighted fluid attenuated inversion recovery

Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19-E35

# Detection of ARIA-H, microhemorrhage, co-occurring with ARIA-E

A leakage of heme products in the parenchyma, as a result of ARIA-E, can result in microhemorrhages\*

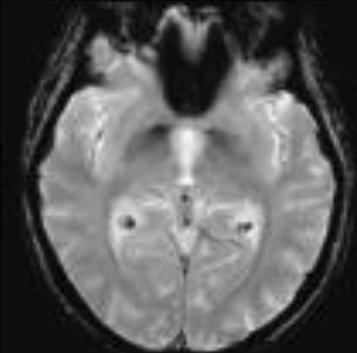
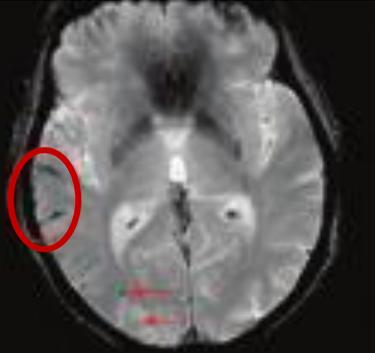
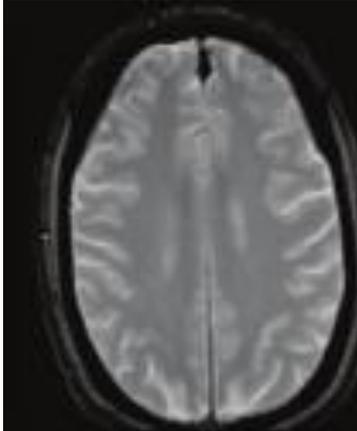


- A. Mild ARIA-H: few (<5) new peripheral left frontal microhemorrhages (red circle) that occur with new patchy T2-FLAIR hyperintense signal in that region
- B. Moderate ARIA-H: 5 treatment-emergent microhemorrhages (red circle) that occurred with regional mild ARIA-E
- C. Severe ARIA-H:  $\geq 10$  new microhemorrhages and associated extensive right cerebral hemisphere T2-FLAIR hyperintense signal (red circle)

\*Data shown of 3 different patients

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; GRE, gradient recalled echo; T2-FLAIR, T2-weighted fluid attenuated inversion recovery  
Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19-E35

# Detection of ARIA-H, superficial siderosis, and corresponding grading

Baseline		Post-dosing		Axial T2*GRE imaging
		<b>Mild ARIA-H</b> Post-dosing: new right temporal superficial siderosis involves contiguous sulci when viewed over multiple slices (siderosis, red circle). This patient also had 2 treatment-emergent microhemorrhages in the right occipital lobe (microhemorrhage, red arrows)		
Baseline		Post-dosing		
		<b>Moderate ARIA-H</b> Two regions of treatment-emergent superficial siderosis in the right greater-than-left frontal lobes (red circle and arrow)		

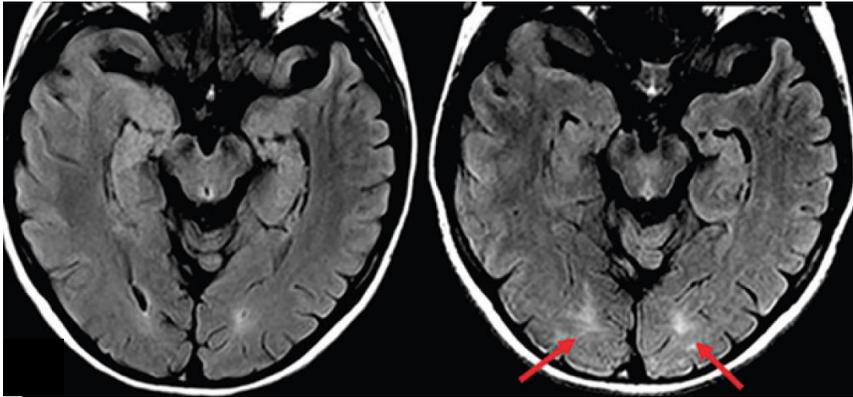
Figures adapted from Cogswell et al. (2022)

Data shown of 2 different patients  
ARIA, amyloid-related imaging abnormalities; ARIA-H: ARIA-hemosiderin/hemorrhage; GRE, gradient recalled echo  
Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

# Potential interpretation pitfalls of MRI when detecting ARIA-E

If a patient is imaged on different scanners, it may be difficult to distinguish true ARIA-E versus technical variation<sup>1</sup>

Vendor 1: Time-point 1      Vendor 2: Time-point 2



T2-FLAIR hyperintense signal in the bilateral occipital white matter that may be mistaken for subtle ARIA-E, which appears to be new from the prior examination on vendor 1

Figure reproduced with permission from Cogswell et al (2022).

White matter signal may differ with scan technique and field strength, such as the use of 3D versus 2D FLAIR

Shading artifacts and scanner or sequence variability may make identification and interpretation of ARIA-E versus artifacts difficult

- Axial T2-FLAIR images from two time points with the two scans performed on different vendor scanners
- Repeat imaging of participant on vendor 1 showed that the apparent abnormality was resolved

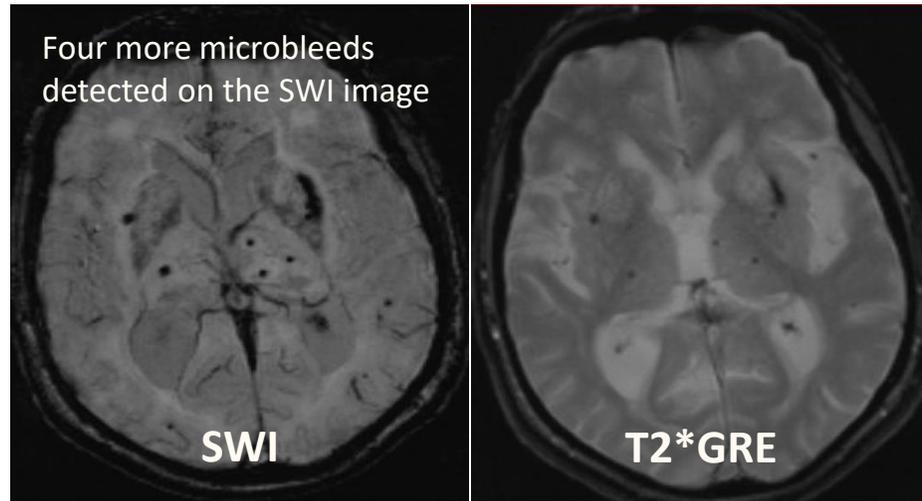
ARIA-E can be identified using T2-weighted FLAIR sequences, but can be entirely obscured with T2-weighted imaging<sup>2</sup>

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; MRI, magnetic resonance imaging; T2-FLAIR, T2-weighted fluid attenuated inversion recovery

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35. 2. Barakos J, et al. AJNR Am J Neuroradiol 2013;34:1958–1965

# Potential interpretation pitfalls of MRI when detecting ARIA-H

SWI is a more sensitive technique for detection of microhemorrhages than T2\* GRE images<sup>1</sup>



Images acquired from the same patient on the same day  
Figure reproduced with permission from Sperling et al (2011).

Enhanced sensitivity with SWI is accomplished by forming both a magnitude and a phase image and multiplying the magnitude image by the phase image<sup>3</sup>

The conspicuity of microhemorrhages can be increased based on sequence and magnetic field strength<sup>2</sup>

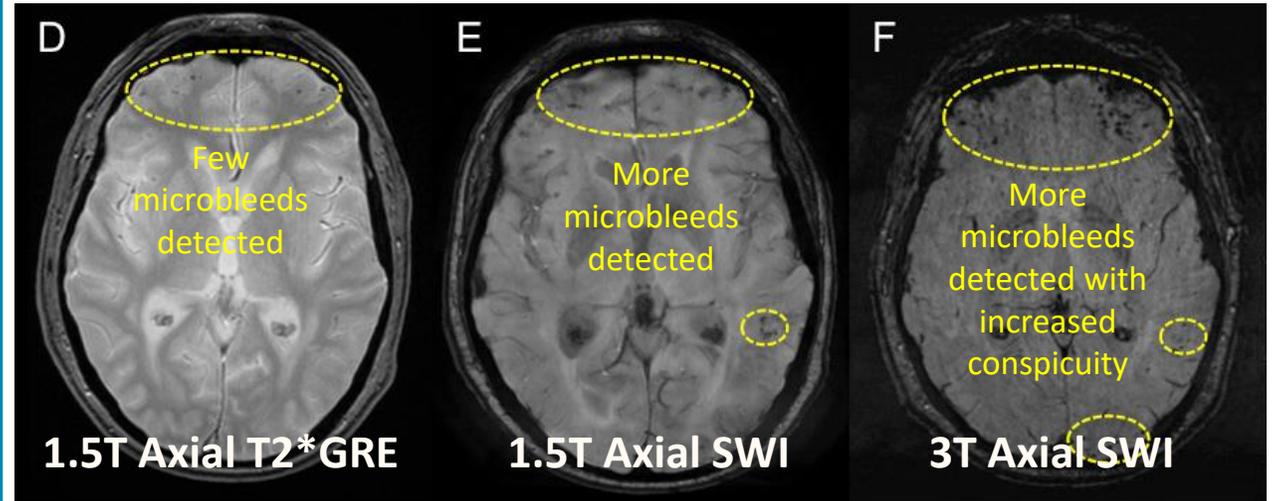


Image of a patient with spontaneous intracerebral hemorrhage  
Figure reproduced with permission from Puy et al (2021).

Thick-section acquisitions may make it difficult to distinguish a mH from a vessel flow void<sup>3</sup>

ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA-hemosiderin/hemorrhage; GRE, gradient-recalled echo; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging.

1. Sperling RA, et al. *Alzheimers Dement*. 2011;7(4):367–385; 2. Puy L, et al. *J Neurol Neurosurg Psychiatry*. 2021;92(6):598–607; 3. Cogswell PM, et al. *AJNR Am J Neuroradiol*. 2022;43(9):E19–E35

# Differentiating ARIA from other pathologies

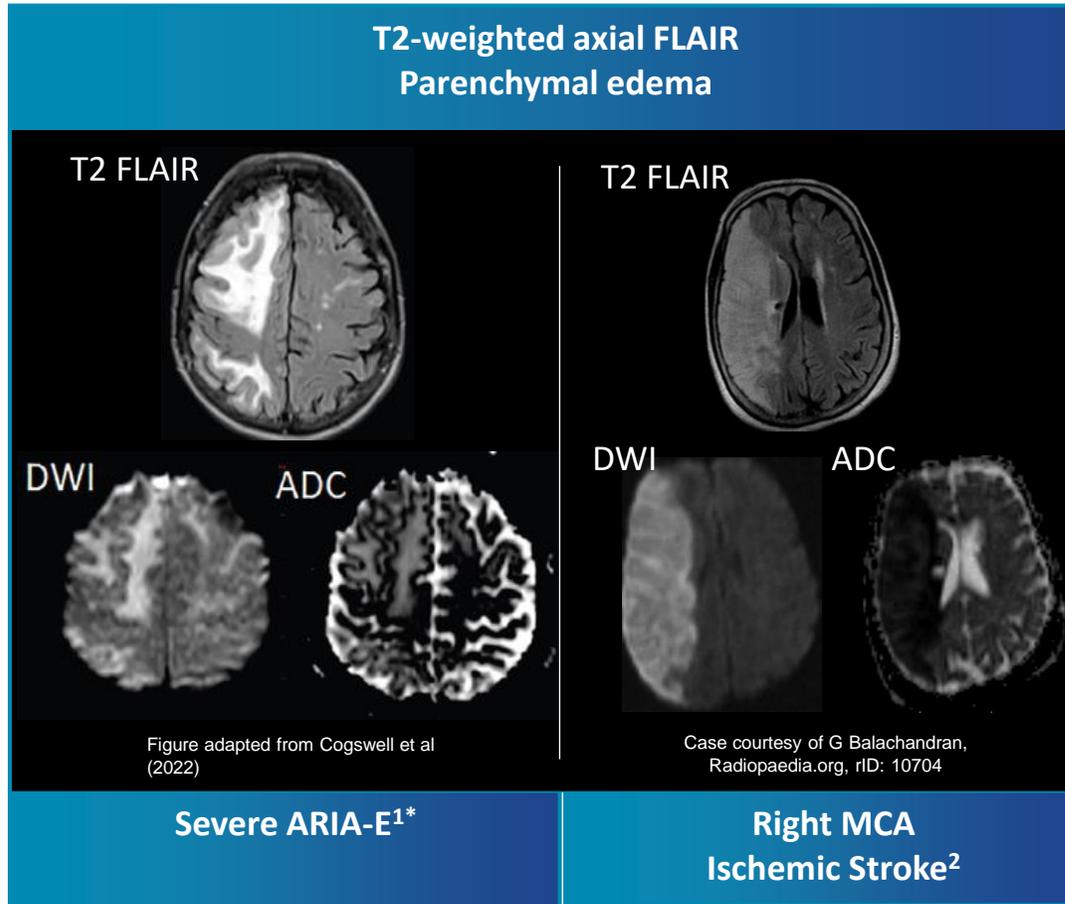
ARIA-E or ARIA-H should be considered as the presumptive diagnosis when signal abnormalities on MRI are identified in patients recently exposed to monoclonal antibodies that remove amyloid plaque and in whom no evidence of any other inciting cause or underlying lesion can be found<sup>1</sup>

- In a suspected ARIA case, the full clinical picture must be taken into account before a diagnosis is confirmed<sup>1</sup>
- MRI is key for the diagnosis and differential diagnosis of ARIA<sup>2</sup>
- CT would not be expected to detect milder forms of ARIA-edema/effusion (ARIA-E) and is insensitive to the detection of microhemorrhages and siderosis (ARIA-H)<sup>2</sup>
- Training should be provided to ensure reliable diagnosis of ARIA<sup>2</sup>

ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA- edema/effusion; ARIA-H: ARIA-hemosiderin/hemorrhage; CT, computed tomography

1. Barakos J, et al. AJNR Am J Neuroradiol 2013;34:1958–1965; 2. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220

# Differential diagnosis: acute ischemic stroke



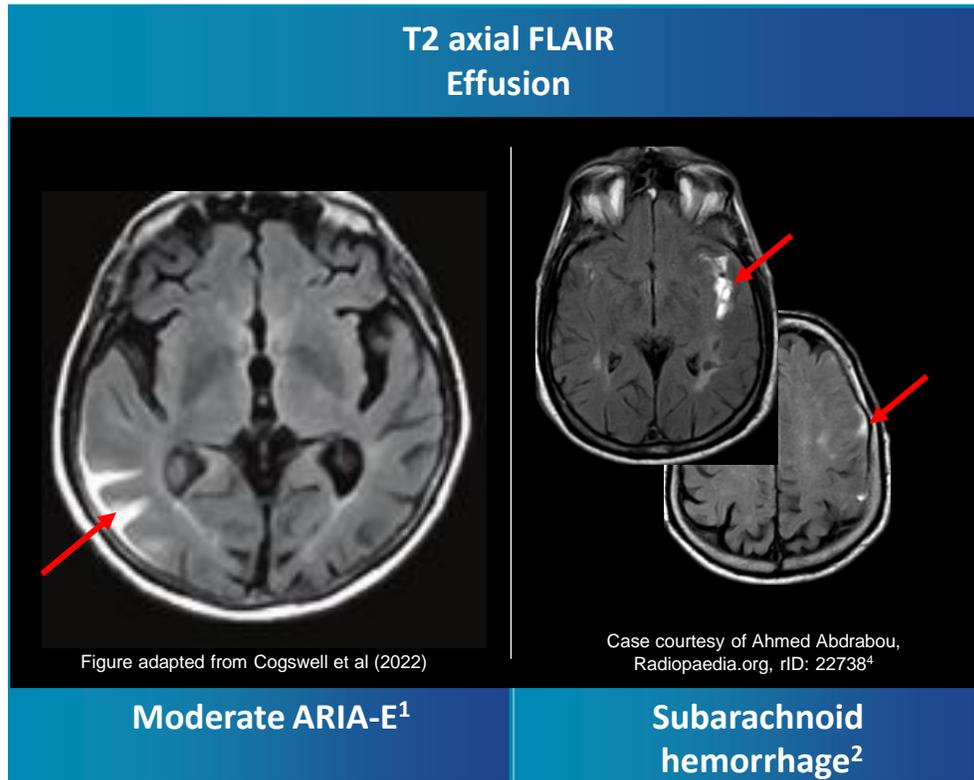
- Parenchymal FLAIR hyperintensity of ARIA-E edema may be mimicked by ischemic stroke<sup>3</sup>
- Diffusion weighted imaging (DWI) is needed to differentiate between ARIA-E and ischemic stroke<sup>3</sup>
- Signs and symptoms of ischemic stroke include: acute onset, hemiparesis, dysphasia or dysarthria, facial paresis, paresthesia, eye movement abnormalities, and visual field defects<sup>4</sup>
- Knowing if a patient is on monoclonal antibodies that remove amyloid helps with determining the diagnosis of ARIA<sup>3</sup>

\*Hyperintense signal on DWI is confirmed to be T2 shiethrough on the ADC map, differentiating ARIA-E from acute ischemia or other cause of cytotoxic edema

ADC, Apparent Diffusion Coefficient; ARIA-E, ARIA-edema/effusion; DWI, diffusion-weighted imaging; T2-FLAIR: T2 Fluid attenuated inversion recovery; MCA, middle cerebral artery

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Bhuta S, et al. Radiopaedia.org <https://radiopaedia.org/articles/13401>; 3. Barakos, J et al. AJNR AM J Neuroradiol 2013;34:1958-1965; 4. Yew KS, et al. Am Fam Physician. 2015;91(8):528–36

# Differential diagnosis: subarachnoid hemorrhage

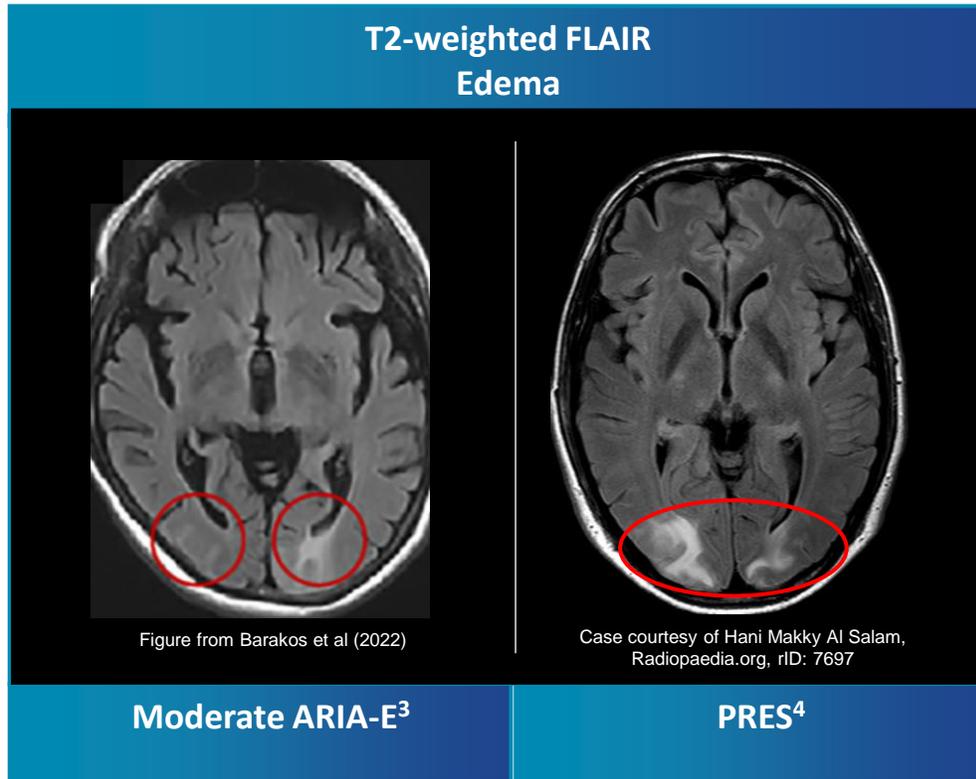


- Leptomeningeal FLAIR hyperintensity of ARIA-E effusion may be mimicked by SAH<sup>3</sup>
- Differentiating ARIA and SAH requires a systematic clinical and diagnostic approach<sup>3</sup>
- Subarachnoid hemorrhage typically presents with a number of signs and symptoms: severe headache accompanied by nausea or vomiting<sup>4</sup>
- Decreased level of consciousness and focal neurological signs can also be present<sup>4</sup>

ARIA-E, ARIA-edema/effusion; SAH, subarachnoid hemorrhage; T2-FLAIR, T2-Fluid-attenuated inversion recovery

1. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35; 2. Abdrabou A. Radiopaedia.org <https://doi.org/10.53347/rID-22738>; 3. Barakos, J et al. AJNR AM J Neuroradiol 2013;34:1958-1965; 4. Tetsuka S, et al. BMC Neurol 2016;16:196

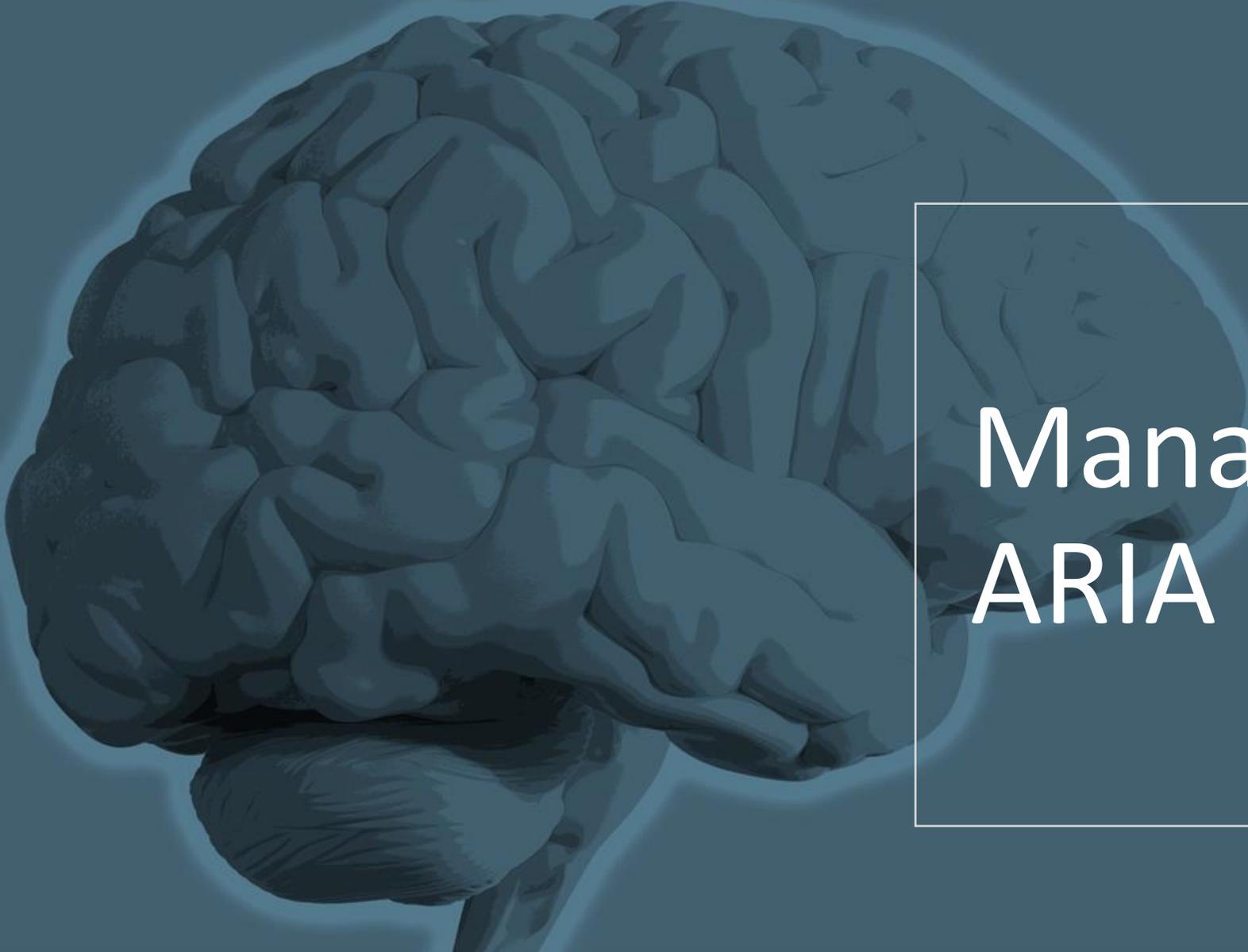
# Differential diagnosis: Posterior Reversible Encephalopathy Syndrome (PRES)



- PRES could resemble ARIA-E on imaging<sup>1</sup>
- PRES frequently develops from cytotoxic medication or disorders such as preeclampsia, sepsis, renal disease, or autoimmune disorders<sup>2</sup>
- Signs of PRES<sup>2</sup>:
  - Encephalopathy, epileptic seizures, visual disturbances, and focal neurological deficits
- Less specific signs include:<sup>2</sup>
  - Headache, nausea, vomiting
- In this case, clinical history is **important for differentiation**

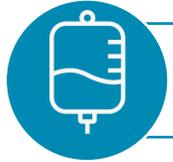
ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; T2-FLAIR, T2-Fluid-attenuated inversion recovery

1. Barakos, J et al. AJNR AM J Neuroradiol 2013;34:1958-1965; 2. Fischer M, et al. J Neurol 2017;264:1608-1616 3. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211-220; 4. Gaillard F, et al. <https://doi.org/10.53347/rID-1915>



# Management of ARIA

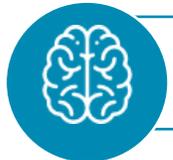
# Management of ARIA



Refer to prescribing information of monoclonal antibodies that remove amyloid for monitoring and management guidelines of ARIA



Discuss ARIA and associated symptoms with patients and care partners before treatment initiation including the importance of MRI monitoring and seeking urgent evaluation in the case of ARIA clinical symptoms<sup>1,2</sup>



MRI should be used to assess for ARIA symptoms where possible; CT scans can be deficient for detecting radiographic findings, particularly ARIA-H, owing to its relatively low spatial definition and resolution vs MRI<sup>3</sup>



ARIA is most frequently detected on routine surveillance MRIs in patients who are clinically asymptomatic, highlighting the need for monitoring early in the course of therapy<sup>4</sup>



In cases of severe or serious ARIA-E or ARIA-H, monitoring neurologic status closely and early empiric administration of high dose intravenous corticosteroids should be considered<sup>1</sup>

ARIA, amyloid-related imaging abnormalities (due to ARIA-E and ARIA-H); ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemosiderin/hemorrhage; CT, computed tomography; MRI, magnetic resonance imaging.

1. Cummings J, et al. J Prev Alzheimers Dis 2022;9:221–230; 2. Cummings J et al. Alzheimers Dement. 2021;7(1):e12179 3. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 4. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35.

To access a growing repository of educational resources on ARIA, please scan the QR code or access the platform by the following link:  
[www.UnderstandingARIA.com](http://www.UnderstandingARIA.com)

This information is intended for healthcare professionals only.

