CMEO BriefCase

ARIA Alert: Timely Recognition in the Emergency Department

This activity is supported by an educational grant from Lilly.

CME OUTFITTERS

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Lenox Hill Hospital
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Learning Objective

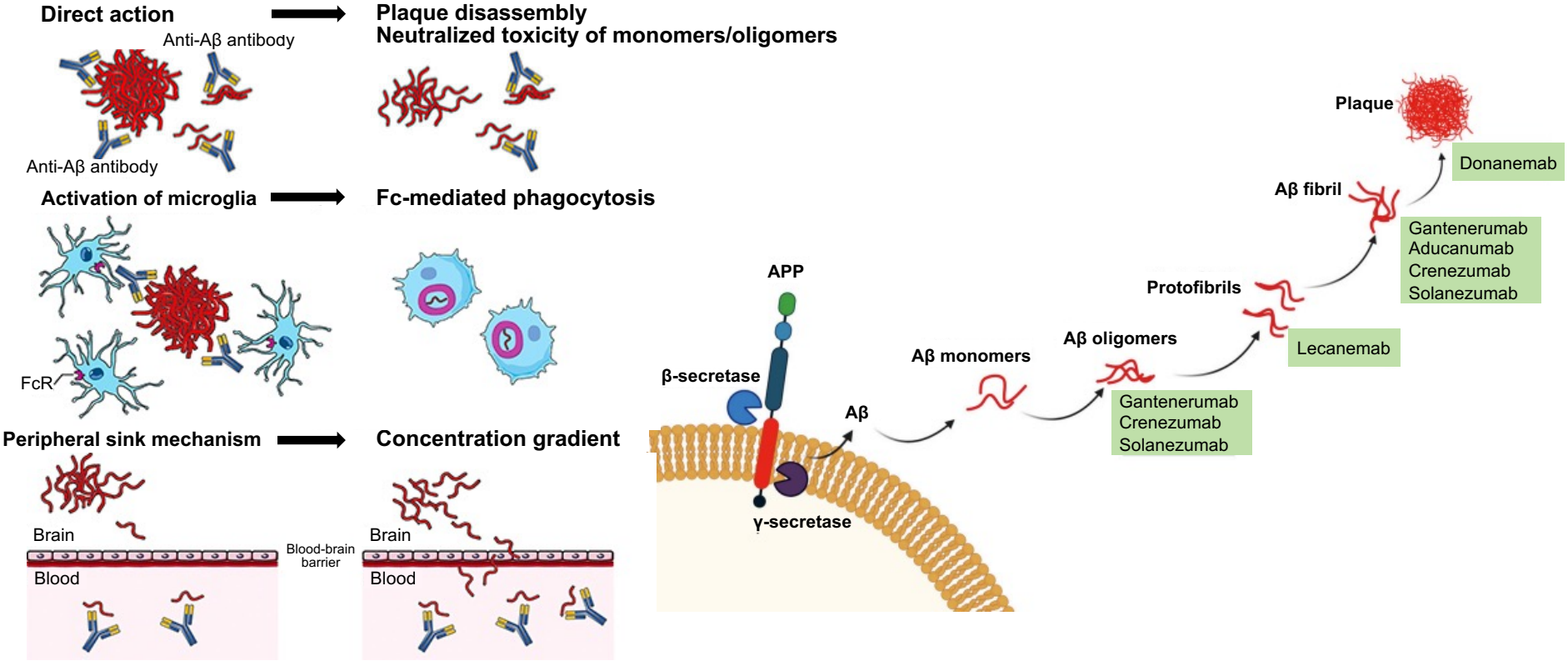
Differentiate ARIA from other conditions with a similar presentation in emergency care settings.

Audience Response

How familiar are you with amyloid-related imaging abnormalities (ARIA) in patients who are receiving amyloid-targeting treatments (ATTs)?

A. Not familiar
B. Somewhat familiar
C. Familiar
D. Very familiar

What Is an Amyloid-Targeting Treatment (ATT)?



Aβ = amyloid-β; APP = amyloid precursor protein; FcR = Fc receptor

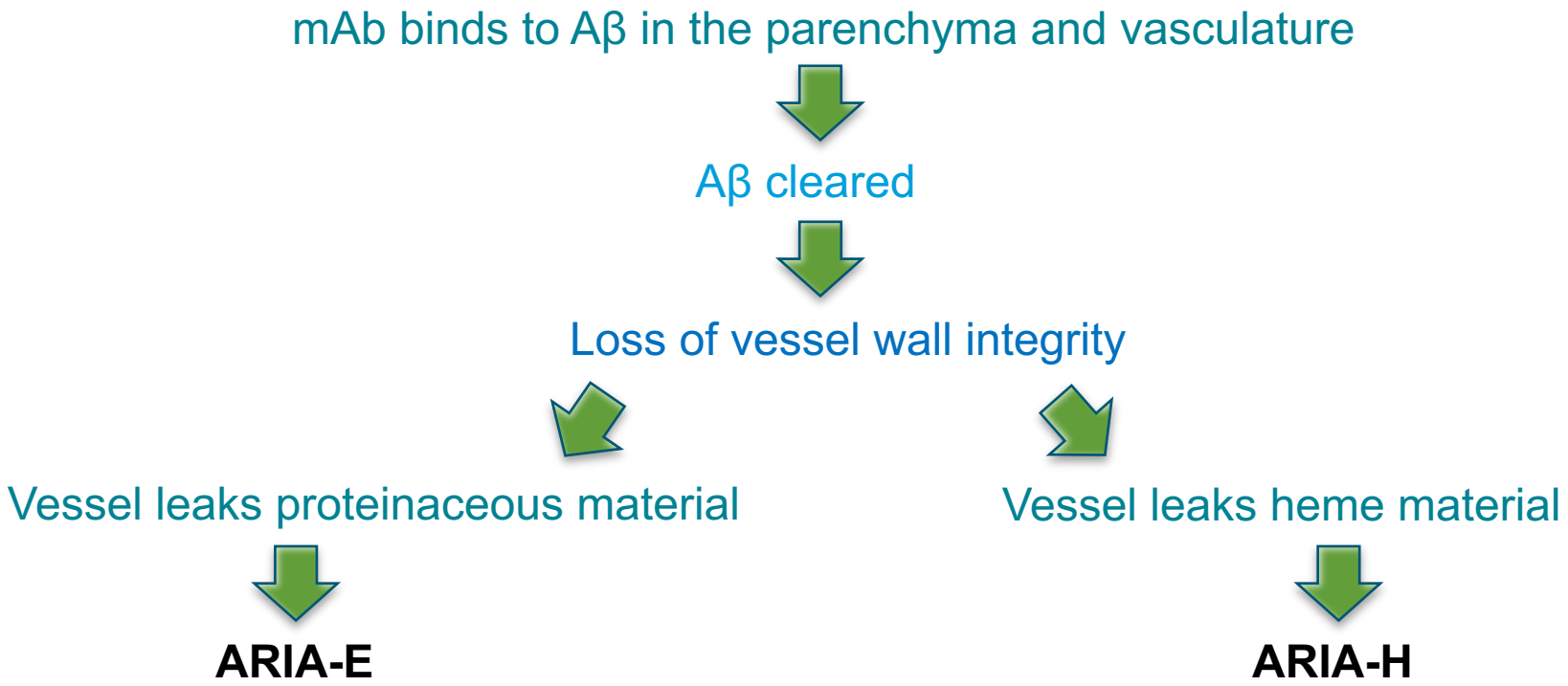
Zampar S, Wirths O. Immunotherapy targeting amyloid-β peptides in Alzheimer's disease. In: *Alzheimer's Disease: Drug Discovery*. 2020: pp. 23-49. https://exonpublications.com/index.php/exon/article/view/257. Vogt AS, et al. *Int J Mol Sci*. 2023;24(4):3895.

Patient Case: Jacqueline (she/her/hers)

- 60-year-old female presents to the emergency department with her partner at 12:45am
- Chief complaint: headache, some nausea, and partner reports that the patient has been more confused and has not been able to complete normal daily activities
- Past medical history: AD, dyslipidemia, and depression
- Jacqueline started an ATT 6 weeks ago for early AD; genetic testing had revealed that she is a carrier of *APOE4*
- She denies any sudden numbness, weakness, or trouble speaking

AD = Alzheimer's disease; *APOE4* = a form of apolipoprotein E gene

Pathophysiology of ARIA: Hypothesis



ARIA-E = ARIA with edema or effusion; ARIA-H = ARIA with microhemorrhages; mAb = monoclonal antibody

Barakos J, et al. *J Prev Alz Dis.* 2022;2(9):211-220.

Patient Case: Jacqueline (she/her/hers)

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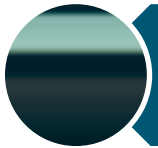
ARIA Symptoms

- Most cases of ARIA are asymptomatic (~ 74%)
- When ARIA is symptomatic, symptoms are nonspecific
- Symptoms can also include visual disturbances, acute/subacute onset of focal neurological deficits, gait disturbance, and seizures



Headache

Confusion/altered mental status

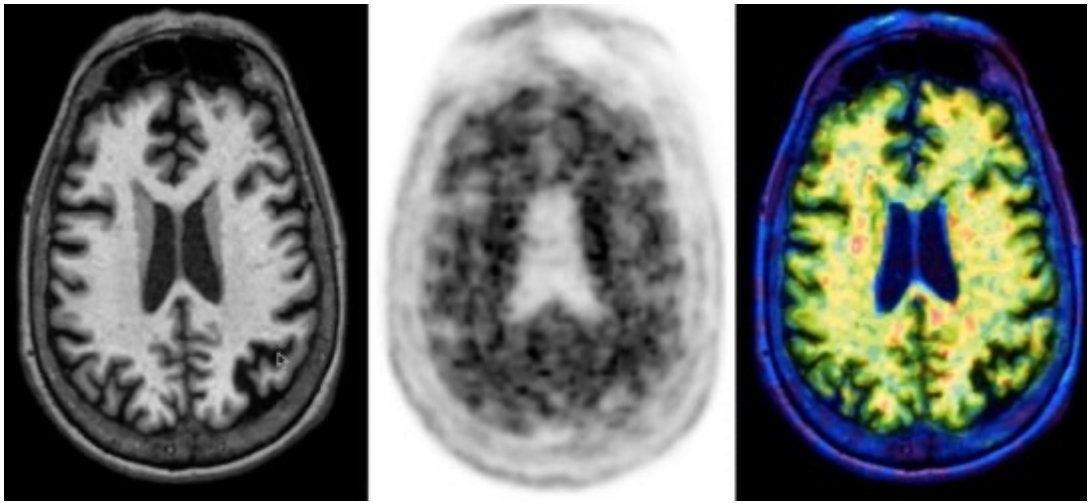
Dizziness/vertigo

Nausea/vomiting

Leqembi® (lecanemab-irmb) [package insert]. Nutley, NJ: Eisai Inc.; Revised 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf. Salloway S, et al. *JAMA Neurol*. 2022;79(1):1-10.

Aβ-Related Cerebral Pathologies: Alzheimer's Disease

- Aβ leads to cerebral pathology in two distinct pathways:
  - Cerebral cortex amyloid deposits → Aβ42 peptide → Alzheimer's disease
  - Blood vessel amyloid deposits → Aβ40 peptide → cerebral amyloid angiopathy



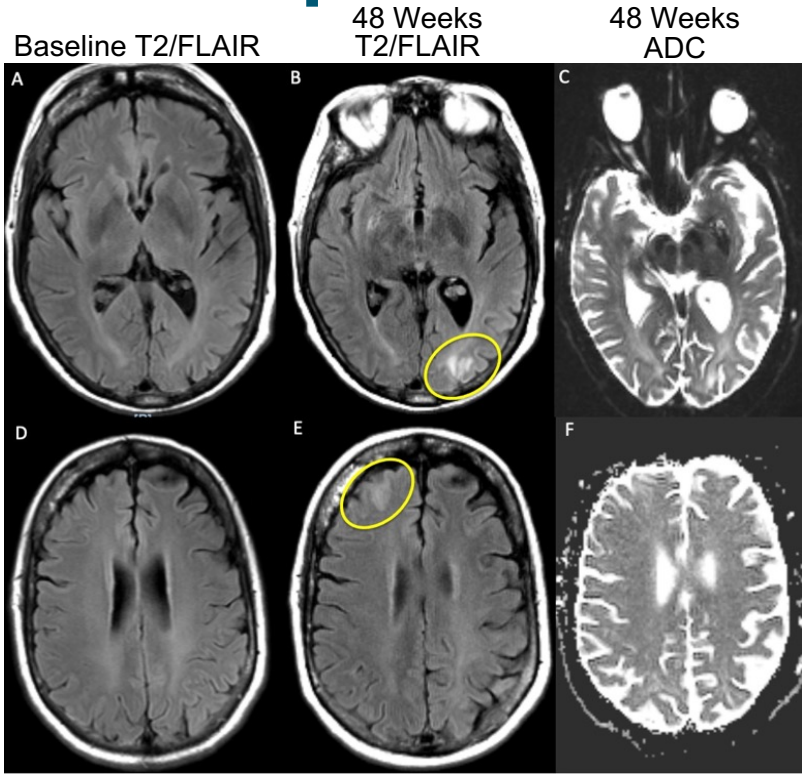
Left: 3D-T1WI showing biparietal atrophy more pronounced on the left
Middle: florbetapir PET showing abnormal cortical accumulation of amyloid
Right: fused PET/MRI (positive)

MRI = magnetic resonance imaging; PET = positron emission tomography

Hampel H, et al. *Mol Psychiatry.* 2021;26(10):5481-5503. Irizarry BA, et al. *J Biol Chem.* 2021;297(5):101259.

Back to Patient Case: Jacqueline

- T2/FLAIR prolongation with associated gyral swelling involves the left occipital and right frontal lobes (yellow circles)
- No restricted diffusion on ADC map to suggest superimposed cytotoxic edema



ADC = apparent diffusion coefficient; FLAIR = fluid-attenuated inversion recovery

Audience Response

What type of ARIA does the patient, Jacqueline, have?

A. ARIA-H; mild severity on MRI, mild symptoms
B. ARIA-H; moderate severity on MRI, mild symptoms
C. ARIA-E; moderate severity on MRI, moderate symptoms
D. ARIA-E; severe on MRI, moderate symptoms

MRI for ARIA Detection

- Clinical trial protocols of ATTs include regular MRI monitoring for ARIA
- ARIA is most often *asymptomatic,* but it is critical to identify and manage ARIA appropriately as it can be symptomatic, severe, and even deadly

Type of ARIA	Severity of MRI Abnormality		
	Mild	Moderate	Severe
ARIA-E			
Size of FLAIR hyperintensity (sulcus and/or cortical subcortical white matter)	< 5 cm at one site	5-10 cm at one site or < 10 cm at multiple sites	> 10 cm in one or more separate sites
ARIA-H			
Number of new microhemorrhages	1-4	5-9	≥ 10
Number of focal areas of superficial siderosis	1	2	≥ 3

Roytman M, et al. *Am J Roentgenol*. 2023;220:562-574. Leqembi® (lecanemab-irmb) [package insert]. Nutley, NJ: Eisai Inc.; Revised 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf. Salloway S, et al. *JAMA Neurol.* 2022;79(1):1-10.

ARIA-E and ARIA-H on MRI Plus Clinical Symptoms

Management Guidance from Lecanemab Prescribing Information

Clinical Symptom Severity	ARIA-E Severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing	Suspend dosing
Mild	May continue dosing based on clinical judgment	Suspend dosing	
Moderate or Severe	Suspend dosing		

Clinical Symptom Severity	ARIA-H Severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing	Suspend dosing
Symptomatic	Suspend dosing	Suspend dosing	

Leqembi® (lecanemab-irmb) [package insert]. Nutley, NJ: Eisai Inc.; Revised 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf. Salloway S, et al. *JAMA Neurol.* 2022;79(1):1-10.

Audience Response

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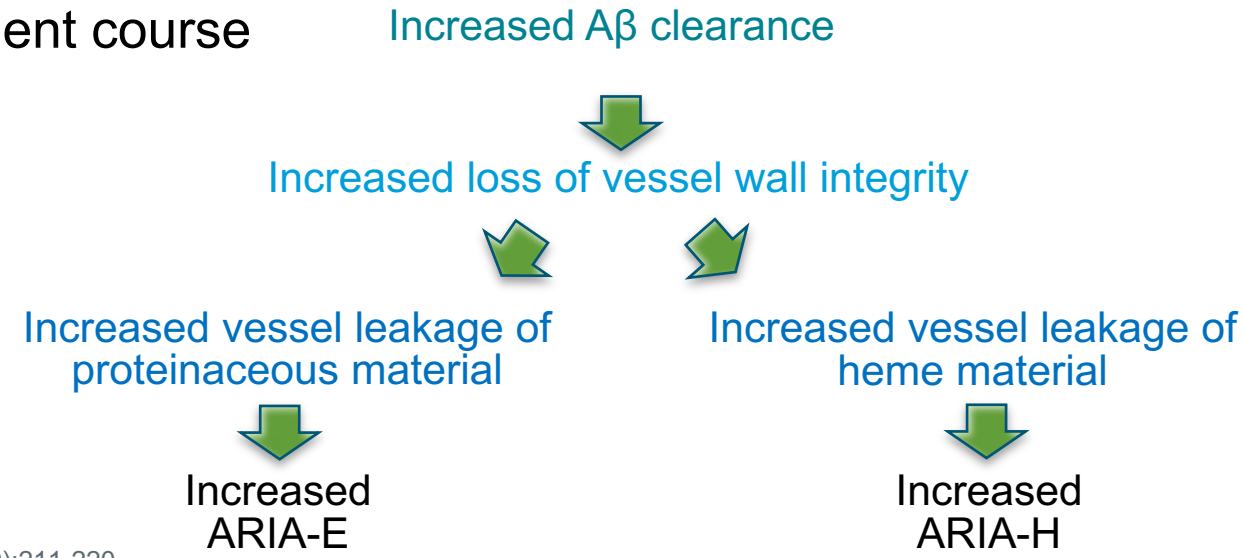
B. ARIA-H; moderate severity on MRI, mild symptoms
C. ARIA-E; moderate severity on MRI, moderate symptoms
D. ARIA-E; severe on MRI, moderate symptoms

Risk Factors for ARIA

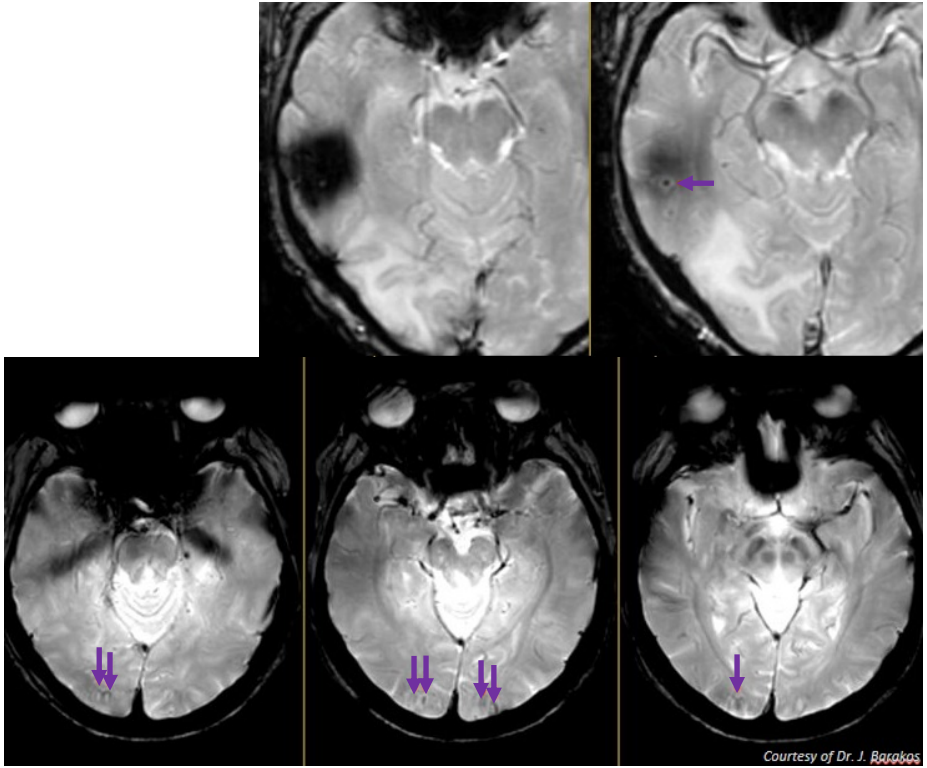
- Apolipoprotein E (ApoE) ε4 allele carriership is the main risk factor for both ARIA-E and ARIA-H
- ApoE ε4 carriers exhibit higher parenchymal and vascular Aβ loads
- Pretreatment microhemorrhages
- Early in the treatment course



Barakos J, et al. *J Prev Alz Dis.* 2022;2(9):211-220.

Pitfalls: ARIA-H Mimics

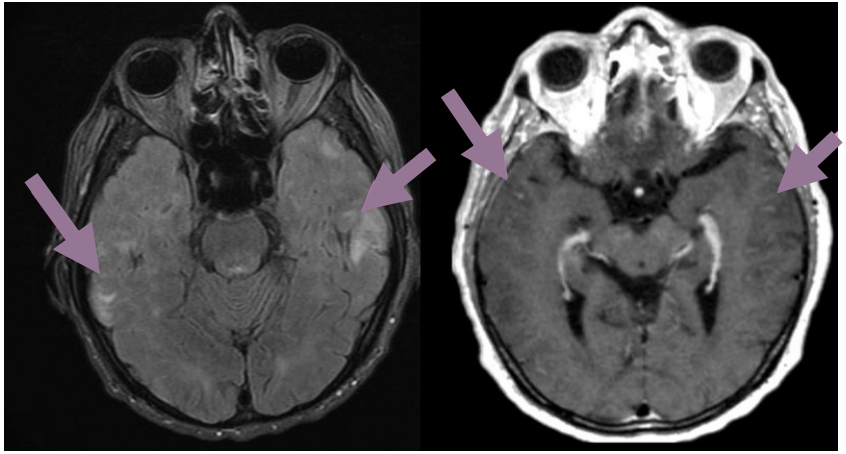
- Susceptibility artifacts can appear as hypointense foci near areas of expected susceptibility
  - Example: top right near the interface of the temporal bone
- Artifact in the phase-encoding direction in the region of the torcula can mimic siderosis or microhemorrhages
  - Example: bottom row shows artifact in the phase-encoding direction



Cogswell PM, et al. *AJNR Am J Neuroradiol*. 2022. https://www.ajnr.org/content/early/2022/08/25/ajnr.A7586.

Pitfalls: ARIA-E Mimics

- Incomplete CSF suppression and/or susceptibility artifact
- Superior CSF suppression offered by the nonselective inversion pulse of 3D FLAIR makes it the preferred sequence for assessing ARIA-E (?clinical utility?)
- Similar MRI findings may be seen with PRES, evolving subacute ischemia, inflammatory CAA
- **History of mAb therapy is crucial**

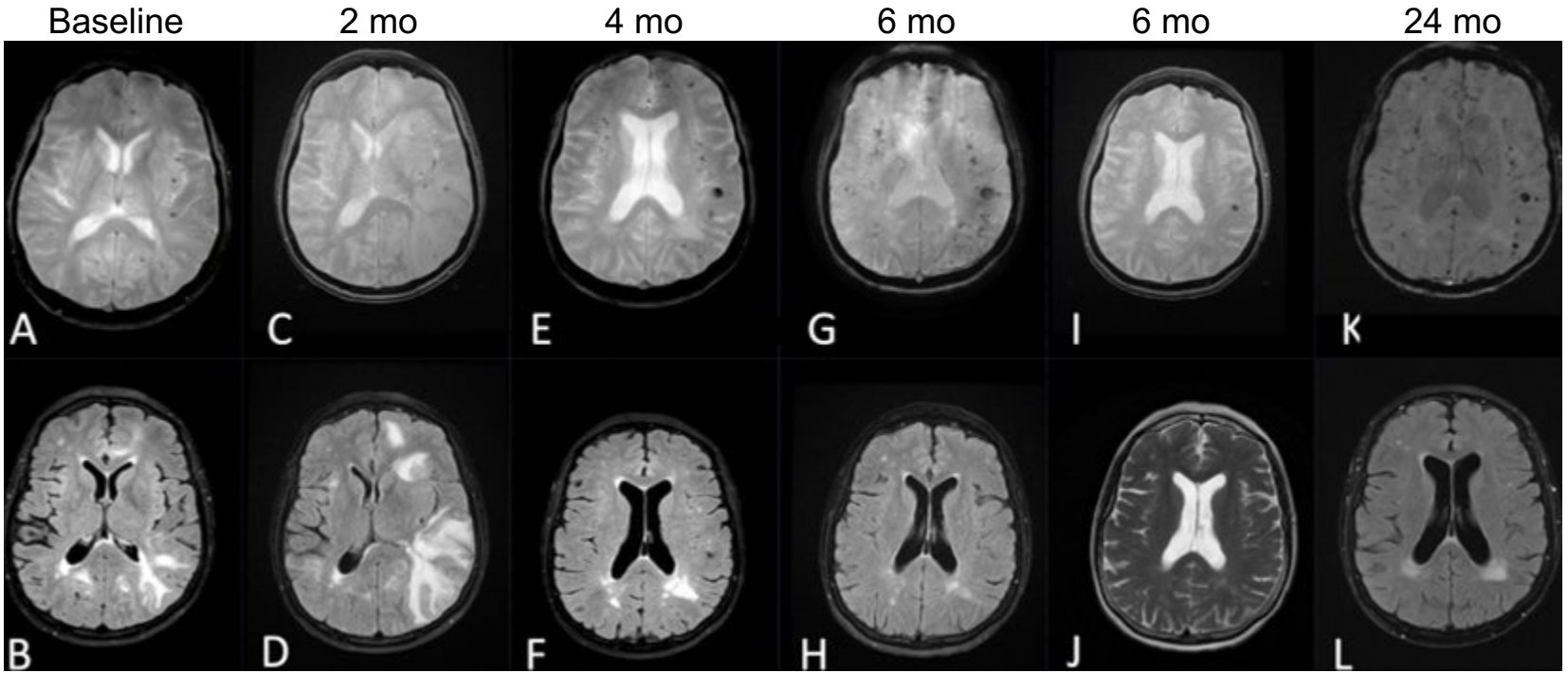


Example of bitemporal vasogenic edema and leptomeningeal enhancement in a patient without history of mAb therapy and CAA-related inflammation or amyloid-related beta angiitis
ARIA-E would appear similar

CAA = cerebral amyloid angiopathy; CSF = cerebrospinal fluid; PRES = posterior reversible encephalopathy syndrome

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

Pitfalls: Scan Technique



Variation in surveillance scan protocols and scanner used makes it difficult to assess microbleeds and/or siderosis and changes in appearance of FLAIR hyperintensities

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

Incidence of ARIA Among ATTs in Phase III Clinical Trials

Incidence of ARIA-E			
	Placebo	3-6 mg/kg aducanumab	10 mg/kg aducanumab
Aducanumab EMERGE ENGAGE	2% 3%	26% 26%	35% 36%
		10 mg/kg lecanemab every 2 weeks	
Lecanemab CLARITY AD	1.7%	12.6%	
		700 mg donanemab monthly for first 3 months, then 1,400 mg for up to 72 weeks	
Donanemab TRAILBLAZER ALZ 2	2%	24%	

Incidence of ARIA-H			
	Placebo	3-6 mg/kg aducanumab	10 mg/kg aducanumab
Aducanumab EMERGE ENGAGE	7% 6%	16% 16%	20% 19%
		10 mg/kg lecanemab every 2 weeks	
Lecanemab CLARITY AD	9%	17.3%	
		700 mg donanemab monthly for first 3 months, then 1,400 mg for up to 72 weeks	
Donanemab TRAILBLAZER ALZ 2	14%	31%	

Haeberlein B, et al. *J Prev Alzheimers Dis*. 2022;9(2):197-210. Sims JR, et al. *JAMA*. 2023;330(6):512-527. van Dyck CH, et al. *N Engl J Med.* 388(1):9-21.

Concurrent Use of Antithrombotic and ATT

EMERGE and ENGAGE (aducanumab)	Clarity AD (lecanemab)	TRAILBLAZER-ALZ 2 (donanemab)
• Antiplatelet or anticoagulant use was excluded from these trials	• Antithrombotic use was permitted • Antithrombotic medications were not associated with increased risk of ARIA • Three deaths in open-label extension were associated with the use of anticoagulants or acute thrombolytics	• Antithrombotic use was permitted • Antithrombotic medications were not associated with increased risk of ARIA • Of the three deaths from brain bleeding during the trial, none were on anticoagulants

Haeberlein B, et al. *J Prev Alzheimers Dis*. 2022;9(2):197-210. Sims JR, et al. *JAMA*. 2023;330(6):512-527.
van Dyck CH, et al. *N Engl J Med.* 388(1):9-21. Leqembi® (lecanemab-irmb) [package insert]. Nutley, NJ: Eisai Inc.; Revised 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf.

ARIA Imaging Protocol

BRAIN WITHOUT: ARIA PROTOCOL

Booking Time	
Contrast Type:	
Preparation:	
Post Processing:	3D

Indications: ALZHEIMER'S DISEASE FOR PATIENTS ON OR POTIENTIELLY BEING EVALUTED TO START THE DRUG ADUHELM (ADUCANUMAB). FOR REDUCING AMYLOID PLAQUE

General Comments: THIS PROTOCOL SHOULD ONLY BE RUN IF THE SCRIPT SPECIFICALLY REQUESTS 'ARIA' PROTOCOL. TO BE PERFORMED ON SIEMENS 3T(PREFERRED) OR SIEMENS 1.5T (I.E. 1.5T ONLY MR CONDITIONAL IMPLANT). EXAM SHOULD BE ASSIGNED TO DR. ANA FRANCESCHI

FOR SIEMENS SCANNERS WITHOUT LICENSE FOR 3D SWI, A 3D GRE T2* WITH FLOW COMP IN BOTH DIRECTIONS HAS BEEN SET UP. minIP thick section 10/1 MPR's need to be created off of raw data.

SAG 3D T1 & SAG 3D T2 FLAIR: CREATE MPR'S (INLINE/AUTO OR MANUAL IN 3D) AX AND COR 1MM. COVER WHOLE HEAD.

Coverage: : SKULL BASE TO VERTEX. POSITION AXIAL SLICES PARALLEL TO AC/PC

Injection protocol Notes: USUALLY NON-CONTRAST UNLESS CONTRAST REQUESTED ON THE SCRIPT/REFERRAL

SIEMENS 1.5T/3T	GENERAL PARAMETERS	GE 1.5T/3T	GENERAL PARAMETERS
SAG 3D T1 MPRGAGE		SIEMENS ONLY	
SAG 3D T2 FLAIR		SIEMENS ONLY	
AX 3D SWI		SIEMENS ONLY	
AX T2 FLAIR		SIEMENS ONLY	
AX T2		SIEMENS ONLY	
AX T1 FLAIR		SIEMENS ONLY	
AX DWI		SIEMENS ONLY	

NeuroQuant® ARIA-E

ARIA-E Screening Report

Patient Information

Patie t Name: ARIA-E
Referring MD:

Age: 61 Sex: F
Patie t ID: ID 123456

Report Information

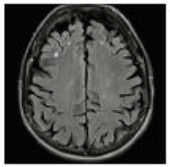
Scan Date: 2022-10-26
Prior Scan Date: 2022-09-19

Site Information

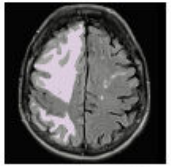
Site Information:
Imaging Center XYZ

Brain Structure Vizualization

Baseline

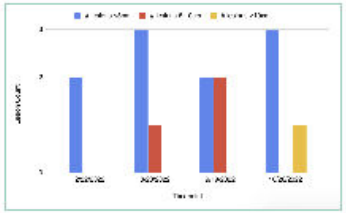


Current



Lesion

Longitudinal Analysis



ARIA-E Summary

	Max Diameter (cm)	Change from Baseline (cm)	Type	L / R	Locatio	Severity
Lesion 1	14.22	+3.45	Parenchymal	R	Frontal	Severe
Lesion 2	4.07	+0.32	Parenchymal	L	Frontal	
Lesion 3	3.62	-0.07	Parenchymal	R	Parieto-Occipital	
Lesion 4	3.23	+0.12	Parenchymal	R	Frontal	

Scan Information

Scan Date	Slice Thickness (mm)	Slice Gap	Manufacturer	Model	Field Strength
2022-10-26	4 mm	0	Siemens	Espree	3.0
2022-09-19	4 mm	0	Siemens	Espree	3.0

ARIA-E Radiographic Severity Grading

	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	1 locatio < 8m	1 locatio 5 10 cm OR > 1locatio each < 10 cm	1 morelocatio > 10 cm

cortechs.ai

NeuroQuant® ARIA-H

ARIA-H Screening Report

Patient Information

Patie t Name: ARIA-H
Referring MD:

Age: 61 Sex: F
Patie t ID: ID123456

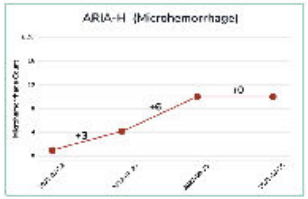
Report Information

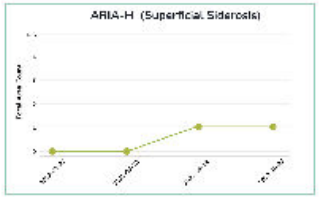
Scan Date: 2022-10-26
Prior Scan Date: 2022-09-19

Site Information

Site Informatio:
Imaging Center XYZ

Longitudinal Analysis





ARIA-H Summary

	Total	Occipital	Parietal	Frontal	Temporal	Cerebellum	Deep Gray	Brainstem	Severity
Current MCH Count	10	4	3	0	2	1	0	0	Moderate
Baseline MCH Count	1	1	0	0	0	0	0	0	
Change from Baseline MCH	+9	+3	+3	0	+2	+1	0	0	
Current SS Count	1	1	0	0	0	0	0	0	Mild
Baseline SS Count	0	0	0	0	0	0	0	0	
Change from Baseline SS	+1	+1	0	0	0	0	0	0	

MCH - Microhemorrhage SS - Superficial Siderosis

Scan Information

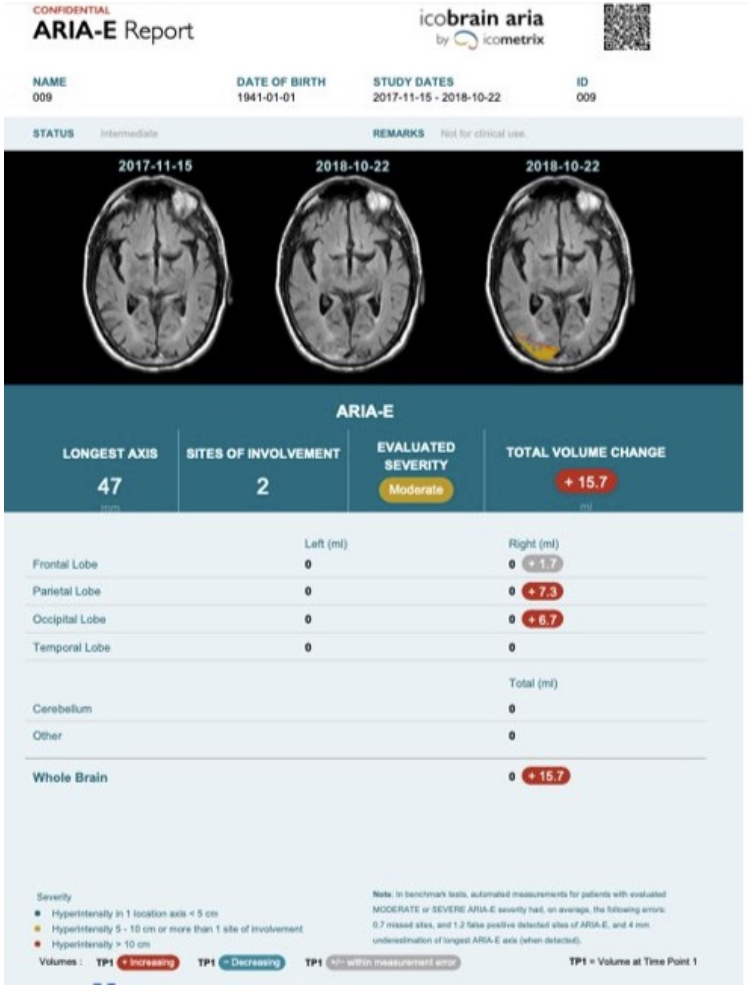
Scan Date	Slice Thickness (mm)	Slice Gap	Manufacturer	Model	Field Strength
2022-10-26	4 mm	0	Siemens	Espree	3.0
2022-09-19	4 mm	0	Siemens	Espree	3.0

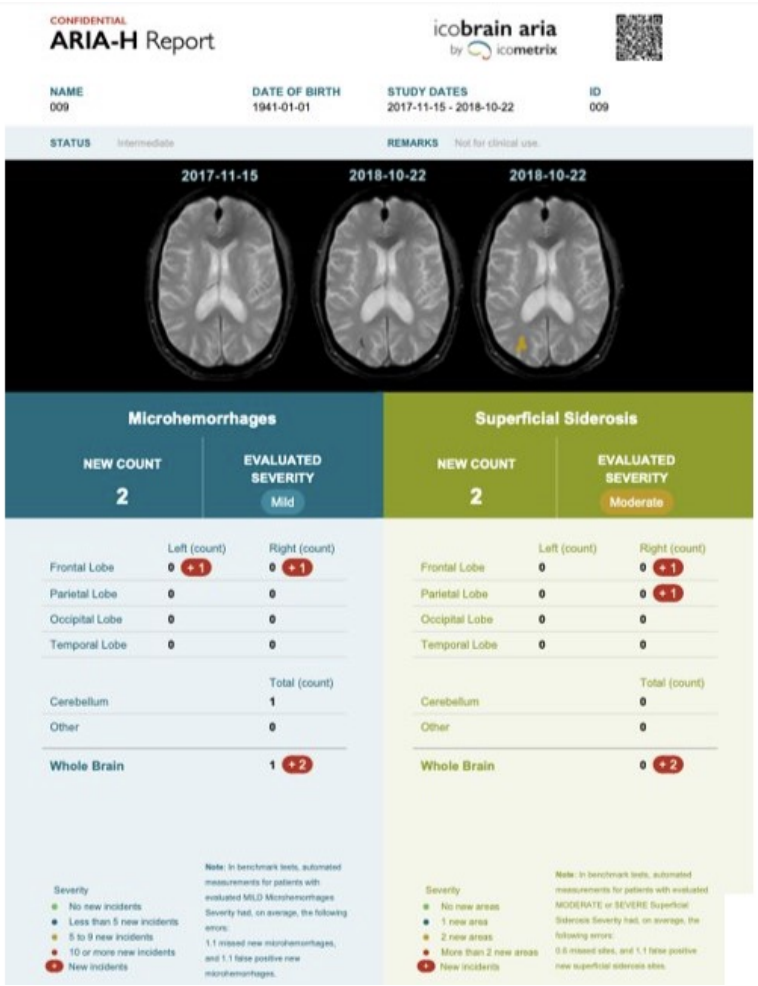
ARIA-E Radiographic Severity Grading

		Radiographic Severity		
		Mild	Moderate	Severe
ARIA-H	Microhemorrage	< 4	5 - 9	> 10
ARIA-H	Superficia Siderosis	1 focal area	2 focal areas	> focal areas

cortechs.ai

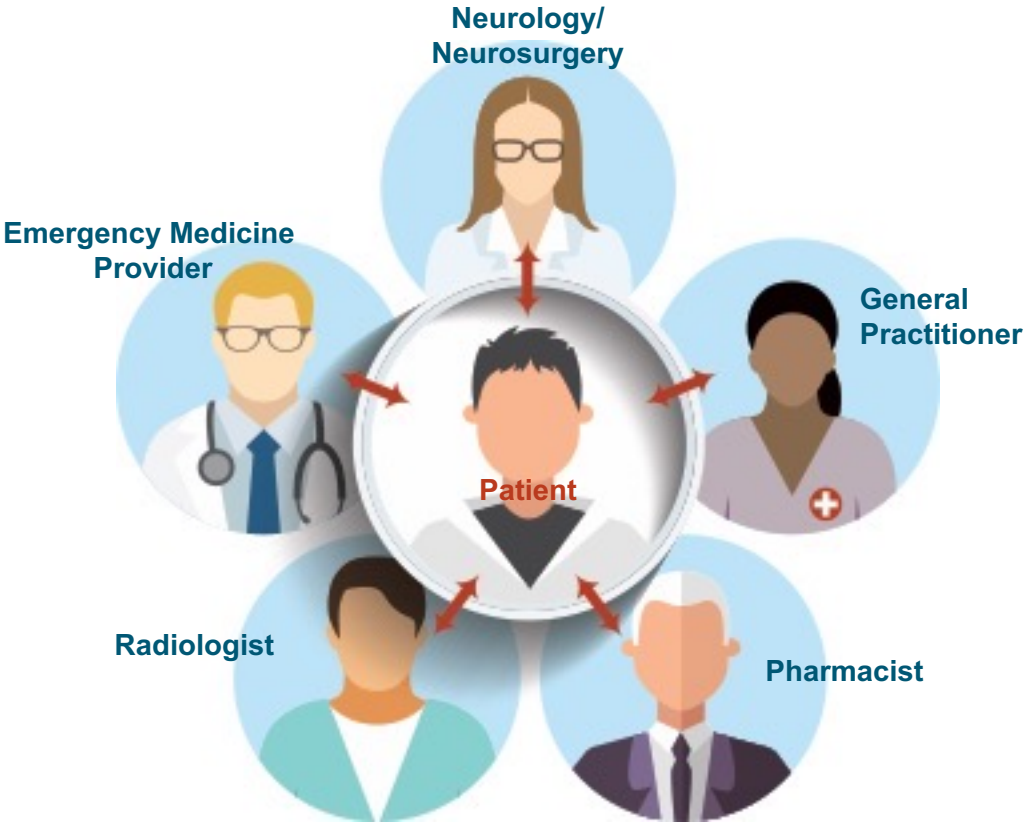
Cortechs.ai Website. 2021. https://www.cortechs.ai/insight/aria-blog/.





Van Hecke W, Maes C. icometrix Website. 2023. https://icometrix.com/resources/a-new-era-in-the-management-of-patients-with-alzheimers.

Team-Based Approach for the Management of ARIA in the Emergency Department



Audience Response

How familiar are you with amyloid-related imaging abnormalities (ARIA) in patients who are receiving amyloid-targeting treatments (ATTs)?

A. Not familiar
B. Somewhat familiar
C. Familiar
D. Very familiar

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Identify patient-related risk factors, timing of occurrence of ARIA-like MRI or clinical symptoms, and the presence of ATTs to facilitate a timely diagnosis of ARIA
- Recognize ARIA-E and ARIA-H mimics so that an appropriate team-based approach (that includes a knowledgeable neuroradiologist) can most accurately and rapidly diagnose and manage ARIA for patients who are on ATTs

CMEO BriefCase 2

What to Do: My Patient in the ED May Have ARIA

CMEO BriefCase 3

How to Treat ARIA in Emergency Settings: Timely Communication with Multi-Disciplinary Colleagues

www.cmeoutfitters.com/practice/alzheimers-disease-hub/

Alzheimer's Disease Education Hub

A robust hub of education and resources for your patients

https://www.cmeoutfitters.com/practice/alzheimers-disease-hub/

CME OUTFITTERS

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.