Rhode Island STROKE SYMPOSIUM

THE WARREN ALPERT Medical School
BROWN UNIVERSITY

ARIA Detection and Safety Management

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DISCLOSURE

- I have the following financial relationships to disclose:
- Advisor, Consultant, Speaker and Research funding (received to institution) with Biogen, Lilly, and Roche
- My talk will not include any off-label discussion

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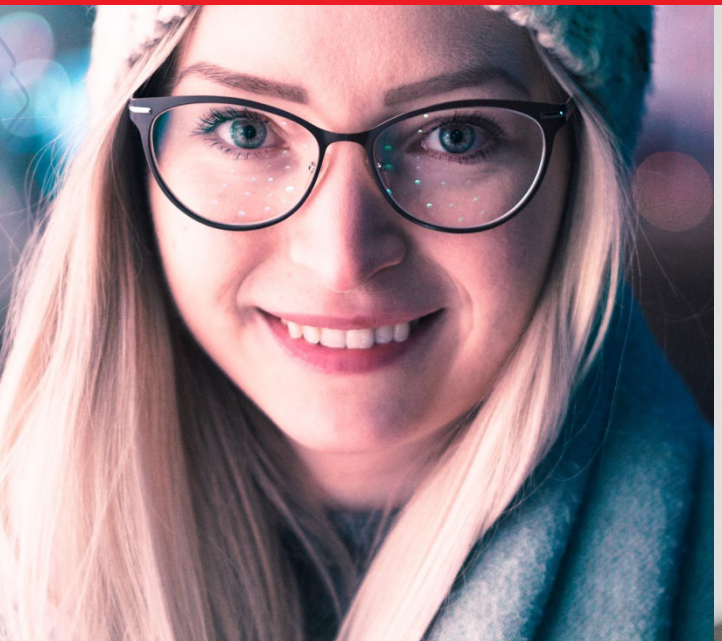
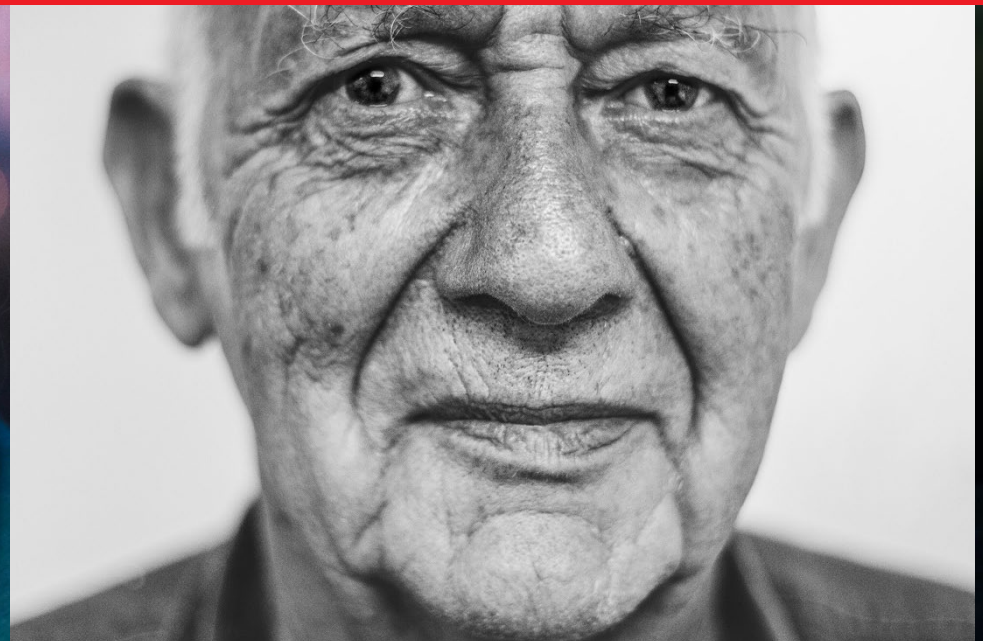
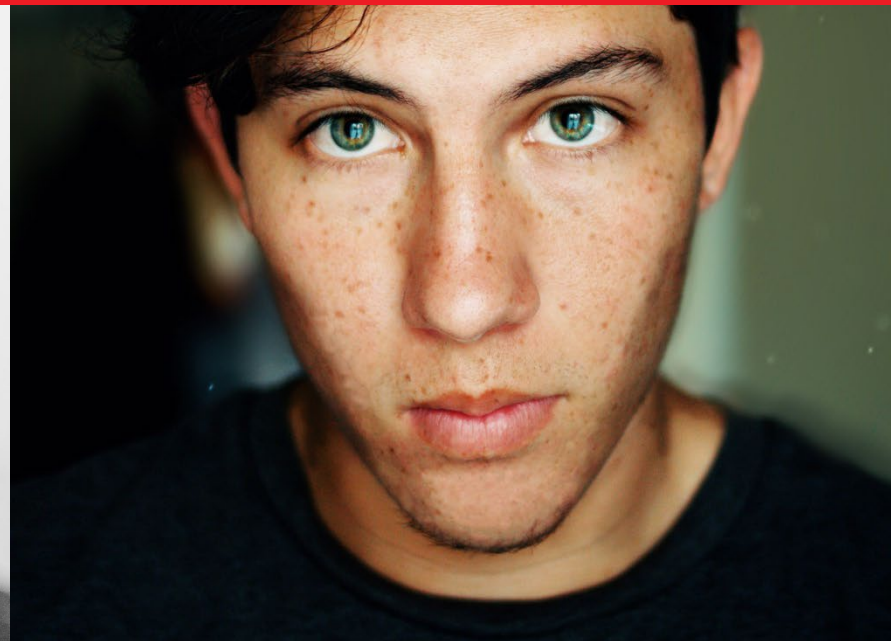
ARIA Detection and Safety Management







Key Risk Factors Associated with ARIA

- ApoE4 copy number
- Dose of drug
- Underlying CAA

Rates of ARIA-E in Phase 3 by Amyloid-lowering Treatment

	Bapineuzumab[1] (0.5 mg/kg)	Aducanumab[2] (10 mg/kg)	Gantenerumab[3] (1020 mg sq)	Lecanemab[4] (10 mg/kg)	Donanemab[5] (1,400 mg)
Combined	**11.6%**	**35.2%**	**24.9%**	**12.6%**	**24.0%**
ApoE4 -/- (noncarriers)	4.2%	20.3%	13.1%	5.4%	15.7%
ApoE4 +/- (heterozygotes)	11.4%	41.0%	24.5%	10.9%	22.8%
ApoE4 +/+ (homozygotes)	27.3%	66.0%	47.8%	32.6%	40.6%

1. Salloway S; NEJM 2014;370(4):322-333. doi:10.1056/NEJMoa1304839
2. Salloway S; *JAMA-N*. 2022;79(1):13-21. doi:10.1001/jamaneurol.2021.4161
3. Bateman; NEJM 2023 (In Press)
4. van Dyck CH; NEJM. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948
5. Sims JR. *JAMA*. 2023;330(6):512–527. doi:10.1001/jama.2023.13239

Approximately 1.5% of all pt treated have a serious ARIA event

ARIA and *APOE*

ARIA by *APOE* ε4 Carrier Status

No./Total No. (%)[a,b]	Placebo (N=870)	Donanemab (N=850)
ARIA-E		
Non-carrier	2/250 (0.8)	40/255 (15.7)
Heterozygous carrier	9/474 (1.9)	103/452 (22.8)
Homozygous carrier	5/146 (3.4)	58/143 (40.6)
ARIA-H[c]		
Non-carrier	28/250 (11.2)	48/255 (18.8)
Heterozygous carrier	57/474 (12.0)	146/452 (32.3)
Homozygous carrier	30/146 (20.5)	72/143 (50.3)

[a] Based on MRI.
[b] Participants with missing *APOE* ε4 carrier status are excluded.
[c] Treatment-emergent microhemorrhage is based on new incidents of microhemorrhages. Treatment-emergent superficial siderosis is based on new or worsening superficial siderosis.

- Participants with at least 1 serious ARIA event[d]
  - ARIA-E: 12 *APOE* ε4 carriers and 1 non-carrier
  - ARIA-H: 3 *APOE* ε4 carriers and 1 non-carrier

[d] SAEs are by AE reporting
Abbreviations: *APOE* = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities-edema/effusions; ARIA-H = amyloid-related imaging abnormalities-hemorrhage/hemosiderin deposition; MRI = magnet resonance imaging; N, n = number of participants

Sims, JAMA 2023

ARIA

- Typically occurs early and is transient and manageable in a clinical trial setting
- 75% of cases are asymptomatic
- Symptoms can include headache, dizziness, unsteadiness, confusion and visual disturbance
- More serious cases can occur and can be fatal

ARIA-Related Fatalities

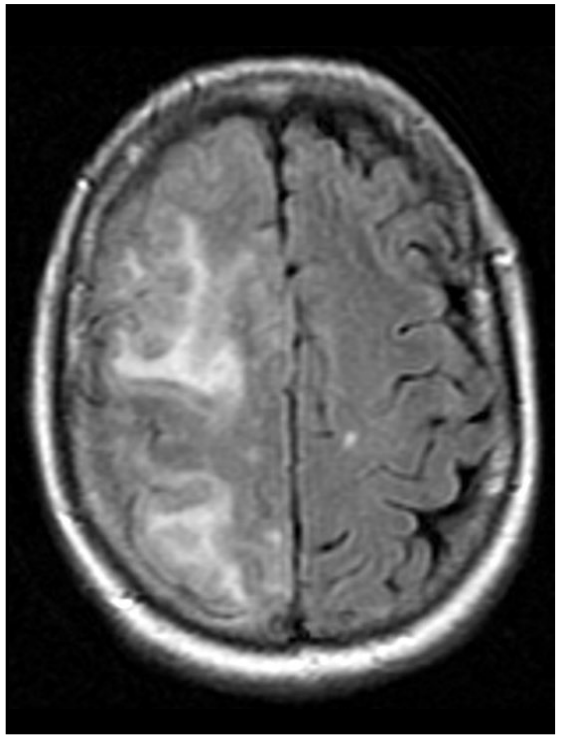
12 known fatalities

- 3 ICH, 2 with a large single area of siderosis and 1 on anticoagulation and ASA, all non-carriers
- 9 severe edema resembling CAAri, all ApoE4 carriers including 4-4,4
  - 2 of those had a focal presentation and received a thrombolytic with multiple hemorrhages
  - 3 had refractory status epilepticus
  - 8 had clear warning signs preceding the fatal event

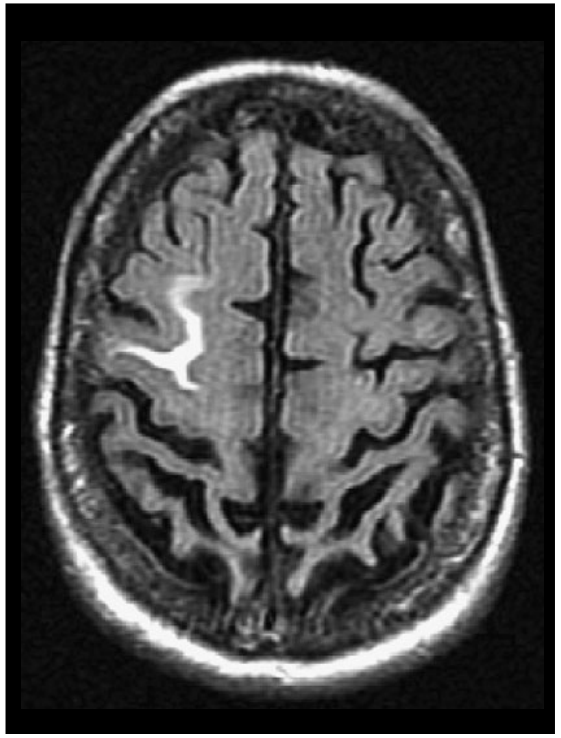
Salloway, Neurology 2024, Briard, Neurology 2024, Sims, JAMA 2023, Castellani, NEJM 2023, Solopova, Nat Comm 2023, AlzForum 2024

Classification and Subtypes of ARIA

ARIA-E (Effusion)

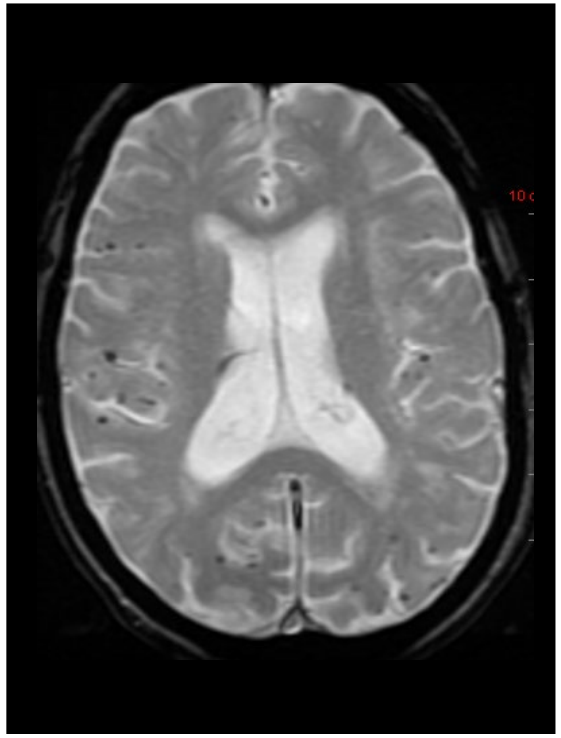


Cerebral Effusion

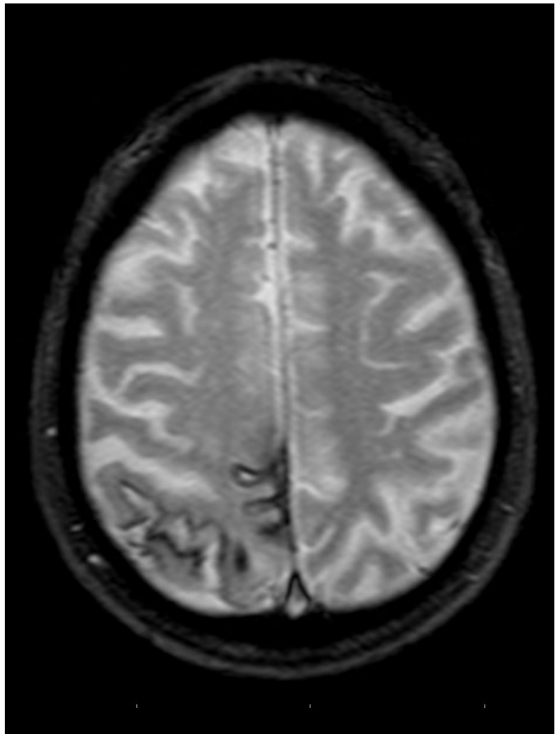


Sulcal Effusion

ARIA-H (Hemorrhage)



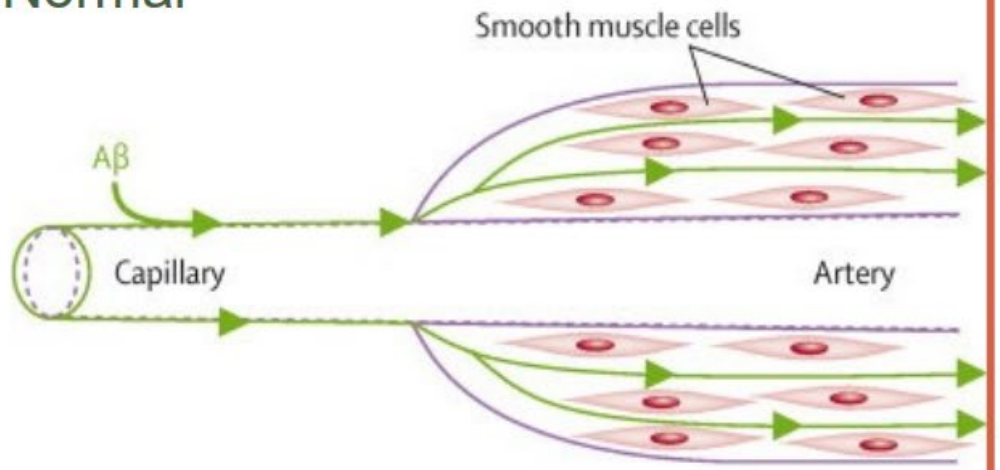
Cerebral Microbleeds



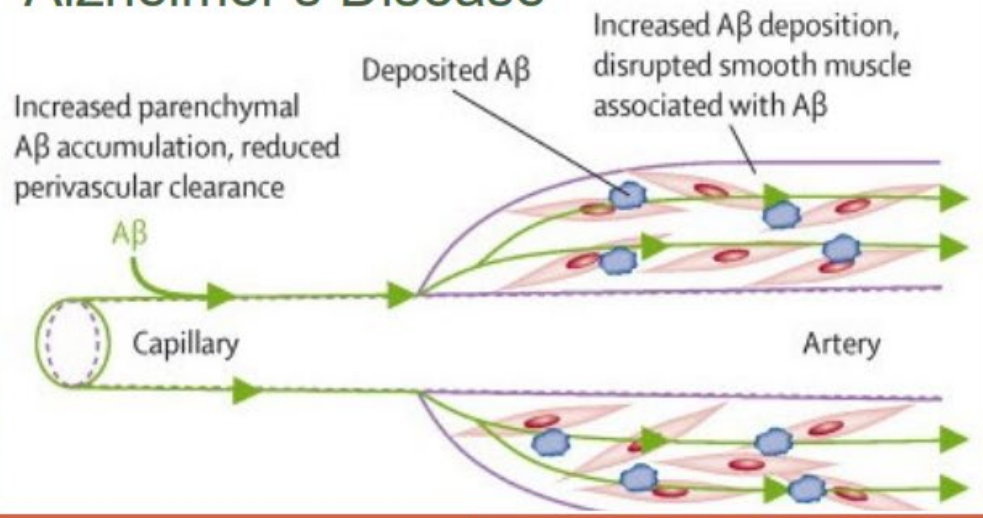
Superficial Siderosis

- ARIA-**E** (**E**ffusion type) – leakage of **fluid** across the BBB
- ARIA-**H** (**H**emorrhage type) – leakage of **blood** across the BBB

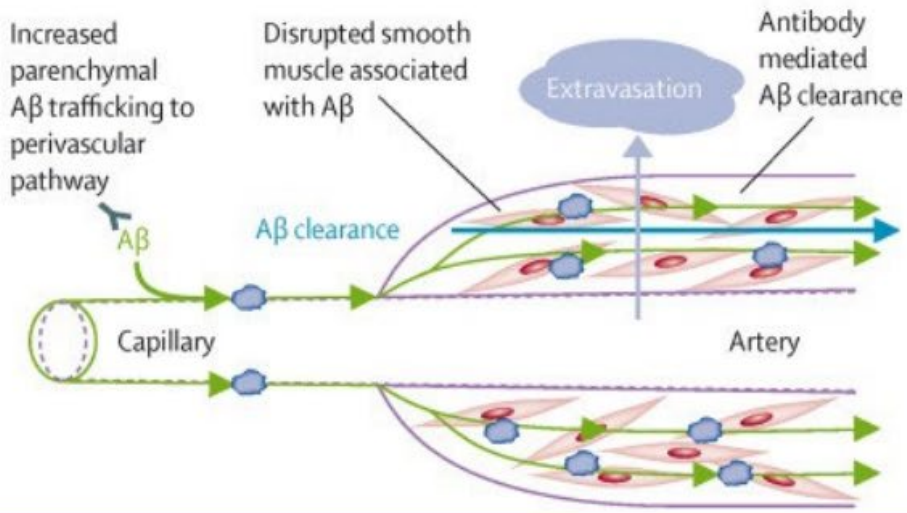
Normal



Alzheimer's Disease

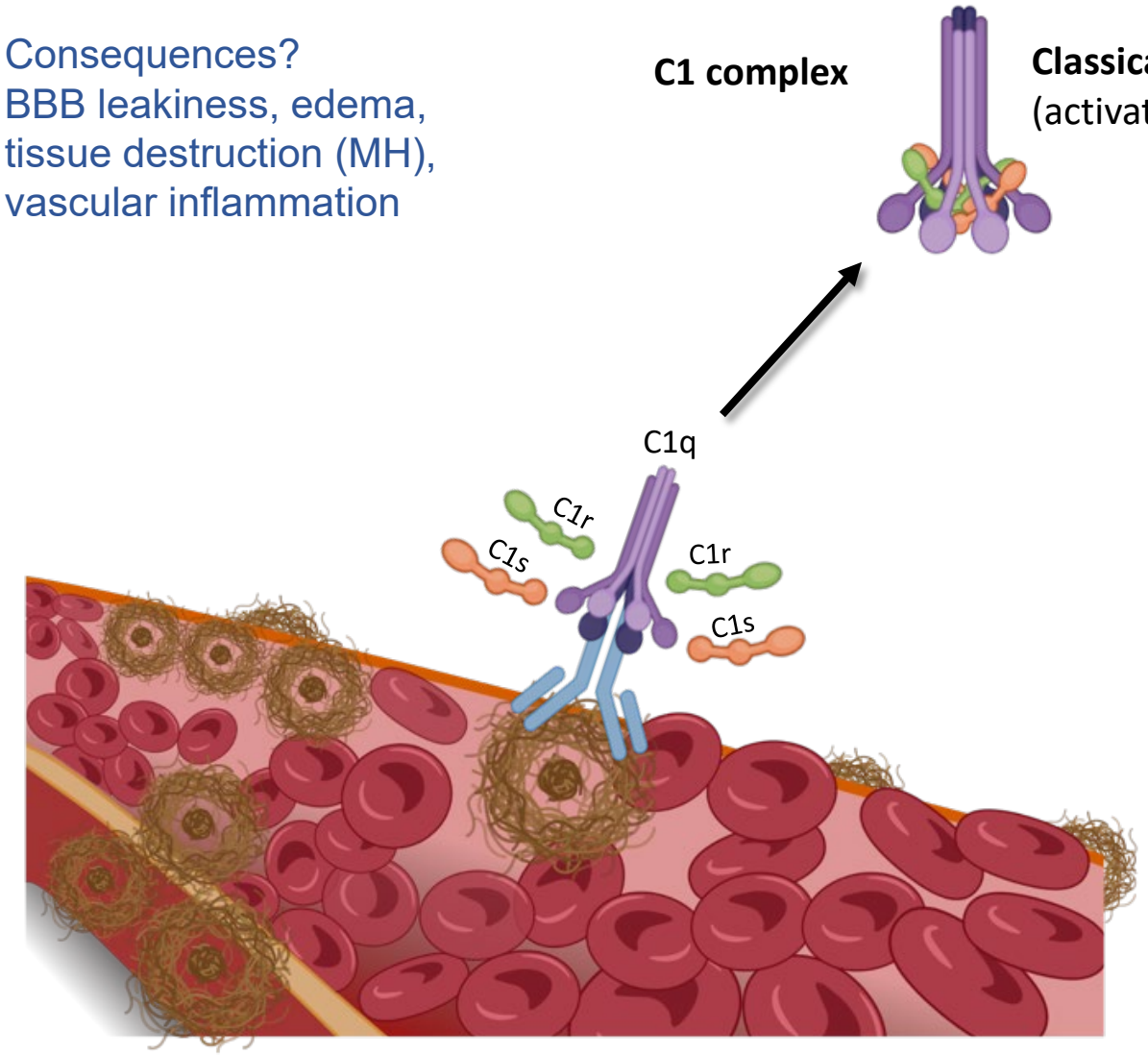


Immunization

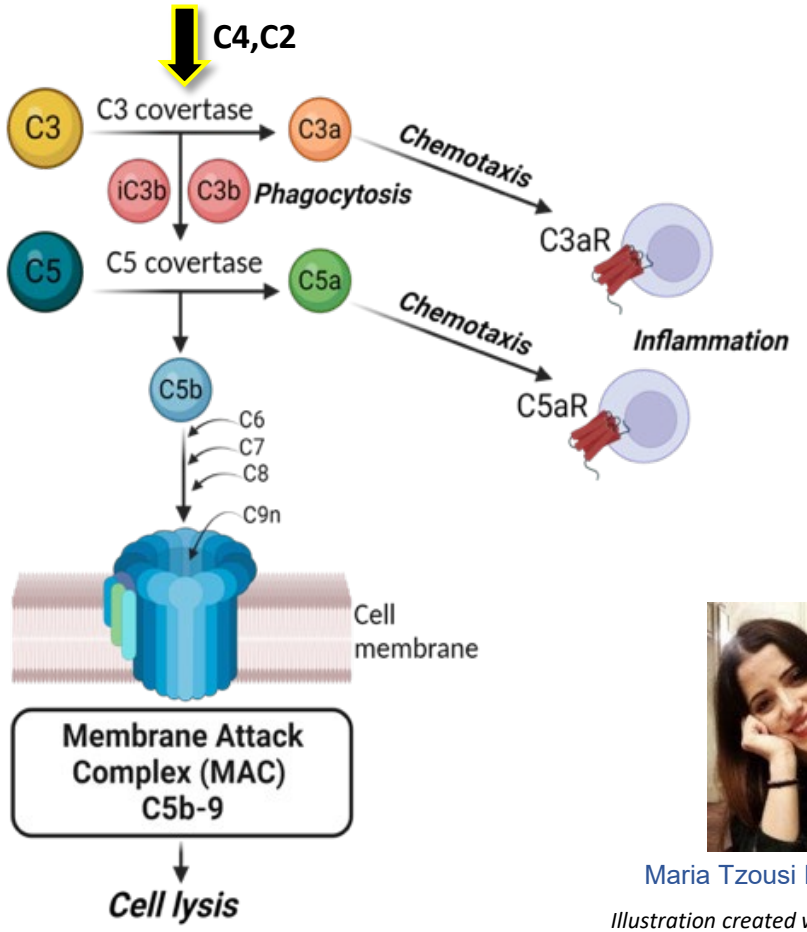


A hypothetical mechanism for anti-amyloid mAb related ARIA

Consequences?
BBB leakiness, edema, tissue destruction (MH), vascular inflammation



Classical complement pathway
(activated by antigen-antibody binding)



Maria Tzousi Papavergi

Illustration created with Biorender.com

Limiting Serious Outcomes

- Appropriate patient selection
- Early detection and careful management of ARIA
- Safety guidelines in emergency settings

Selecting Appropriate Patients

- Screening guided by the FDA label, phase 3 trials and AUR
  - MCI or mild dementia
  - MMSE 22-30
  - Amyloid + on CSF or amyloid PET, possibly plasma
  - MRI exclusions- > 4 microhemorrhages, > 1 small area of superficial siderosis, severe white matter changes, > 2 lacunar infarcts or any territorial infarct, ICH
  - ApoE testing
  - Do not treat patients on anticoagulation, antiplatelets OK

Cummings et al, J Prevention of Alz Dis, 2022, 2023, FDA Prescribing Information, Pittock, Neurology 2023

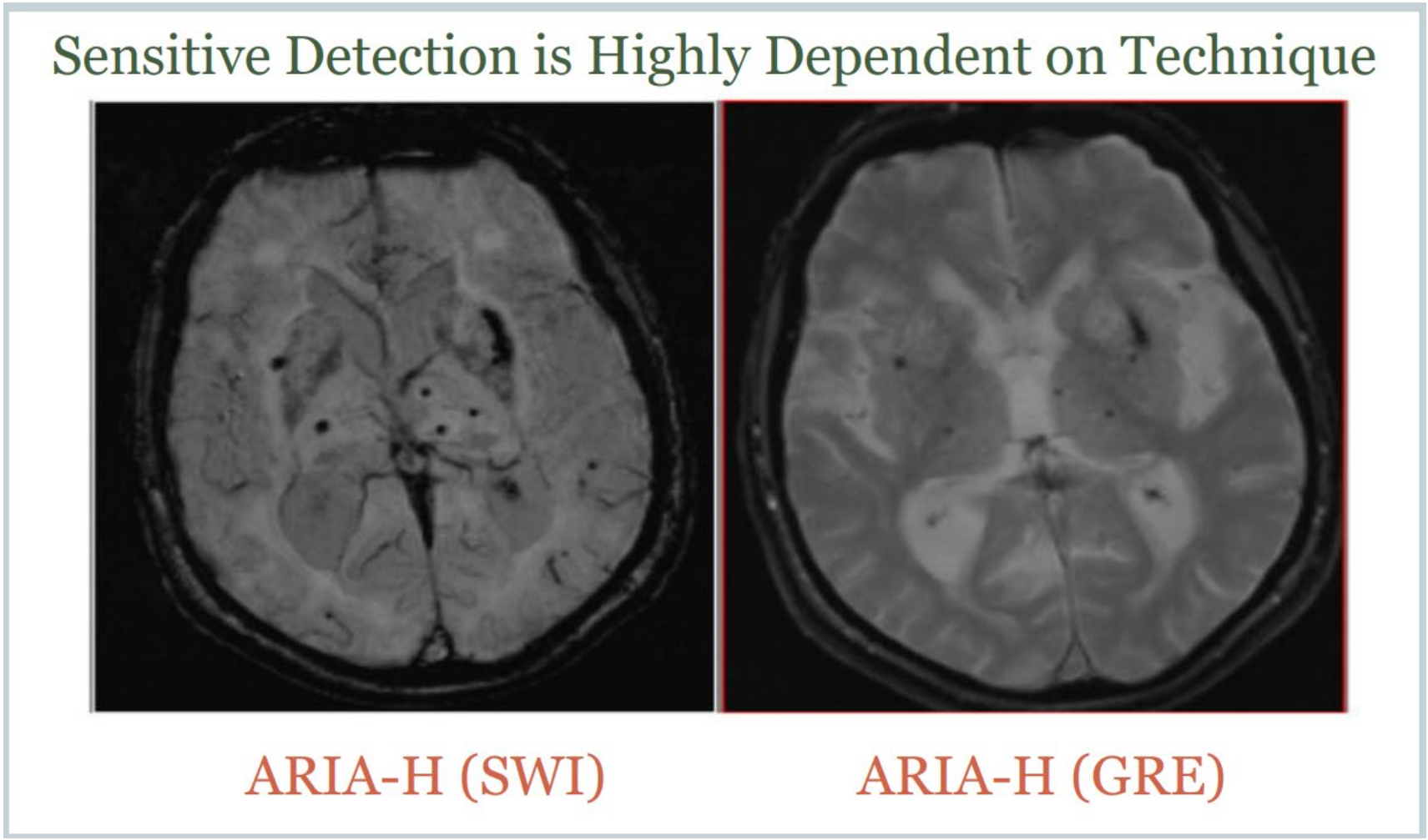
MRI Acquisition Protocols to Detect and Monitor ARIA

MRI Protocol: Standards for Detection of ARIA in Clinical Trials

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

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

SWI vs. GRE



Sperling, Alz and Dementia, 2011

ARIA Detection and Management

Figure 1. MRI monitoring for lecanemab

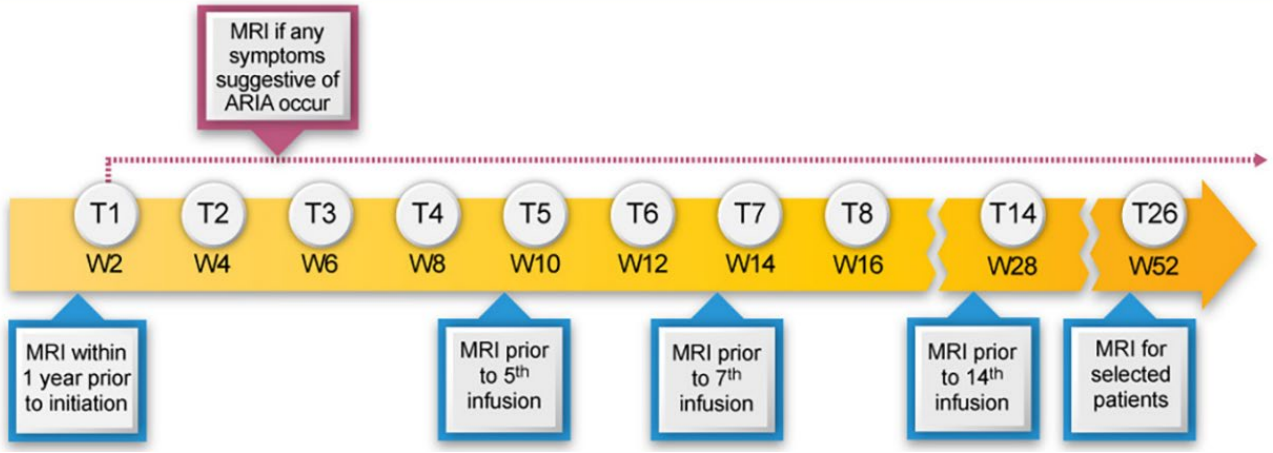
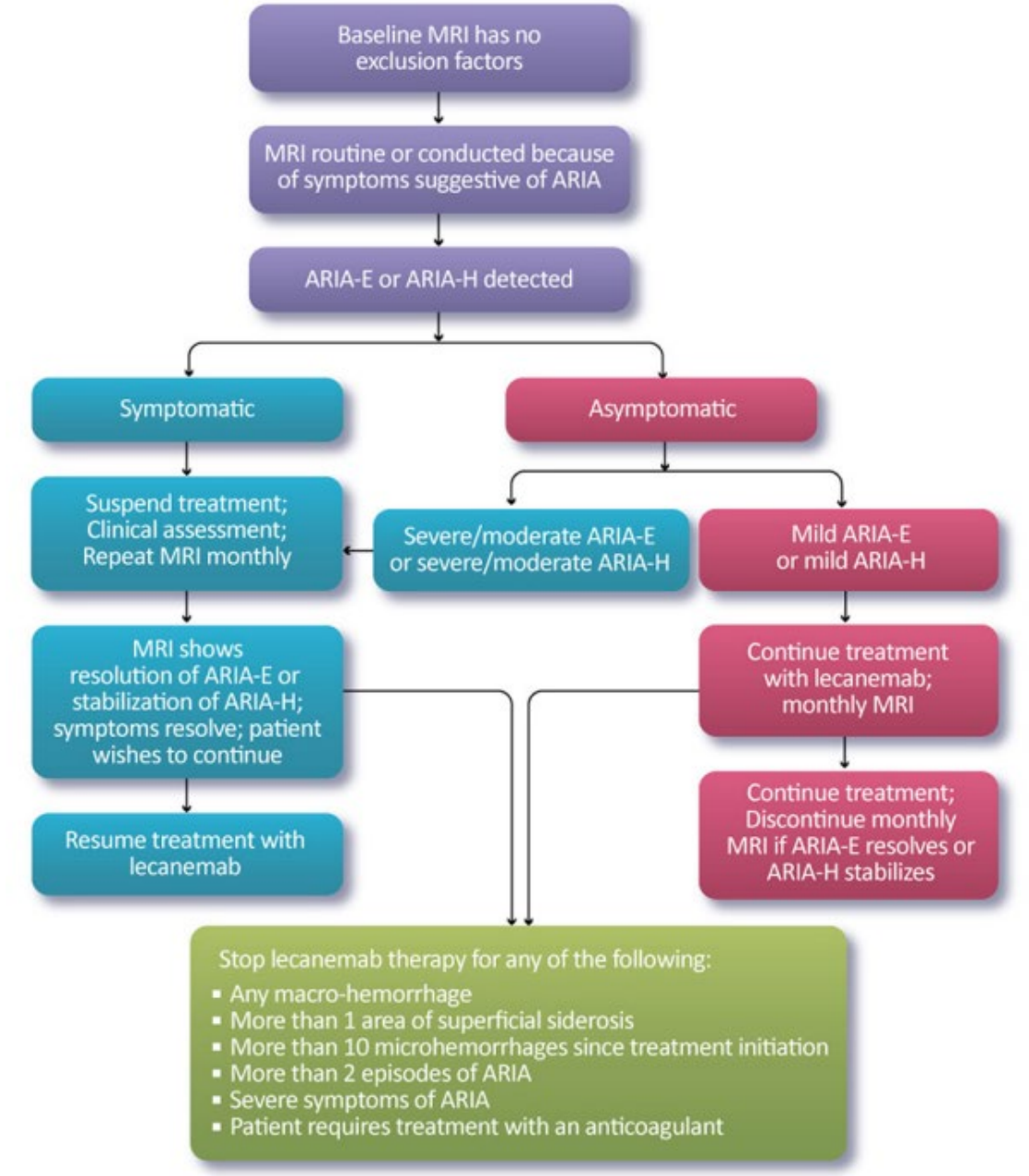


Figure 2. Monitoring and management of ARIA



Cummings, JPAD 2023

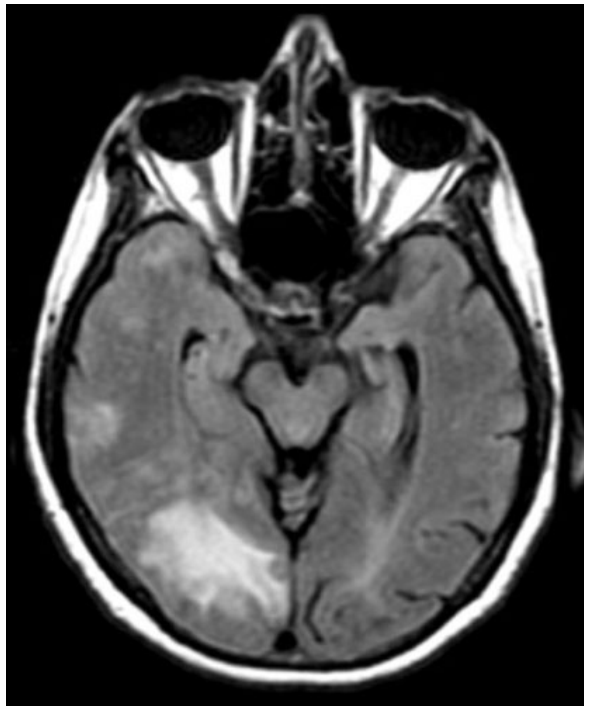
Characterizing ARIA Radiographic Severity

ARIA MRI Classification Criteria

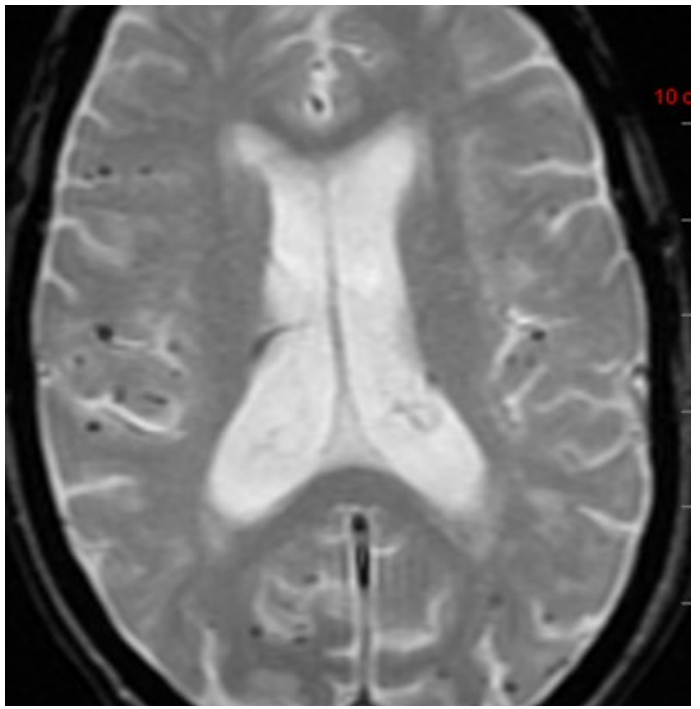
ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortical white matter in **1** location **<5 cm**	FLAIR hyperintensity **5-10 cm**, or **more than one site** of involvement, each measuring **<10 cm**	FLAIR hyperintensity measures **>10 cm**, often with significant subcortical white matter and/or sulcal involvement; **≥1 separate sites** of involvement might be noted
ARIA-H microhemorrhage	**≤4** new incident microhemorrhages	**5-9** new incident microhemorrhages	**≥10** new incident microhemorrhages
ARIA-H superficial siderosis	**1** focal area of superficial siderosis	**2** focal areas of superficial siderosis	**>2 focal areas** of superficial siderosis

Lecanemab-irmb [PI]. Approved 2023. Revised January 2023; Aducanumab-avwa [PI]. Approved 2021. Revised August 2023.

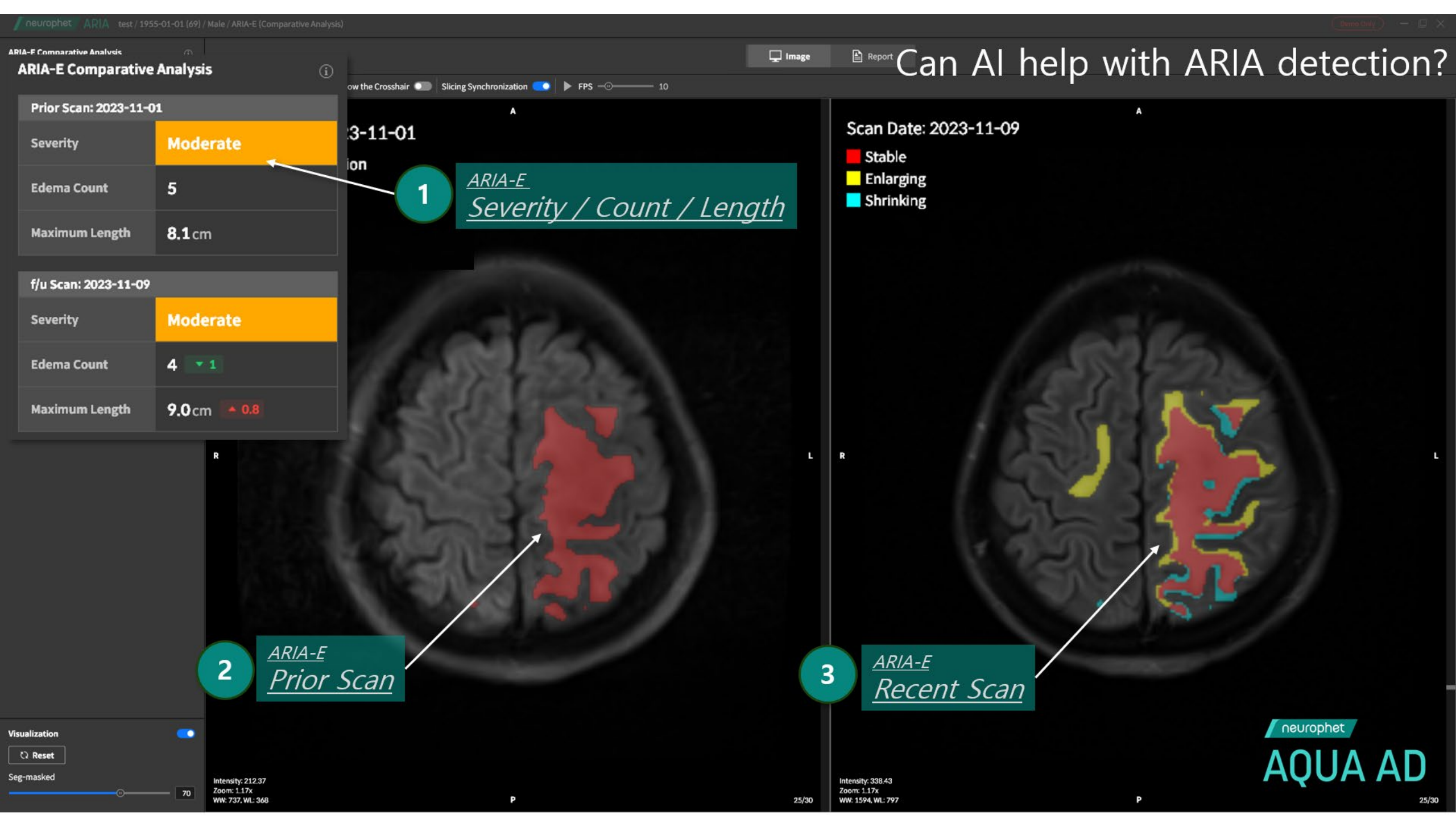
Mild ARIA-E



Moderate ARIA-E



Severe ARIA-H


Can AI help with ARIA detection?
ARIA-E Comparative Analysis
Prior Scan: 2023-11-01
Severity
Moderate
Edema Count
5
Maximum Length
8.1 cm
f/u Scan: 2023-11-09
Severity
Moderate
Edema Count
4
1
Maximum Length
9.0 cm
0.8
Image
Report
Slicing Synchronization
FPS
10
1
ARIA-E
Severity / Count / Length
2
ARIA-E
Prior Scan
3
ARIA-E
Recent Scan
Scan Date: 2023-11-09
Stable
Enlarging
Shrinking
Visualization
Reset
Seg-masked
70
Intensity: 212.37
Zoom: 1.17x
WW: 737, WL: 368
25/30
Intensity: 338.43
Zoom: 1.17x
WW: 1594, WL: 797
25/30
neurophet
AQUA AD

Evaluation of Possible ARIA in Emergency Settings

- Close communication between outpatient and hospital teams
- Awareness of amyloid-lowering Rx, ApoE, prior episodes of ARIA
  - Flag in EMR, pt bracelet
- ARIA may present with focal signs and symptoms or seizures
- Rapid eval of etiology to include MRI
- Limit use of thrombolytics
- Prompt use of pulse steroids and seizure management
- Update stroke Get With The Guidelines

Symptoms of ARIA Can Mimic Ischemic Stroke

- 70-year-old patient, ApoE ε3/ε4 carrier, screening MRI with focal lesions of white matter disease
- 7 days after the 5th dose of donanemab, developed headache and slurred speech; hospitalized for ischemic stroke
- Computed tomography (CT)/CT angiogram/CT perfusion of head/neck with no findings suggestive of ischemia or vessel blockages
- Tenecteplase was administered and altered mental status developed one hour later
- Repeat imaging obtained
  - CT scan showed multiple hemorrhages in the bilateral hemispheres
  - MRI with severe ARIA-E, superficial siderosis; macrohemorrhage in the left temporal, left occipital, left parietal, and right frontal lobes; and bilateral intraventricular hemorrhages
- The patient died due to bilateral intraparenchymal hemorrhage and acute hypoxic respiratory failure four days later

- 65 yo E4,4
- Lecanemab OLE
- ER eval for possible CVA
- Multi-focal ICH following TPA
- Post-mortem severe CAA and angiitis

The NEW ENGLAND JOURNAL of MEDICINE

Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke

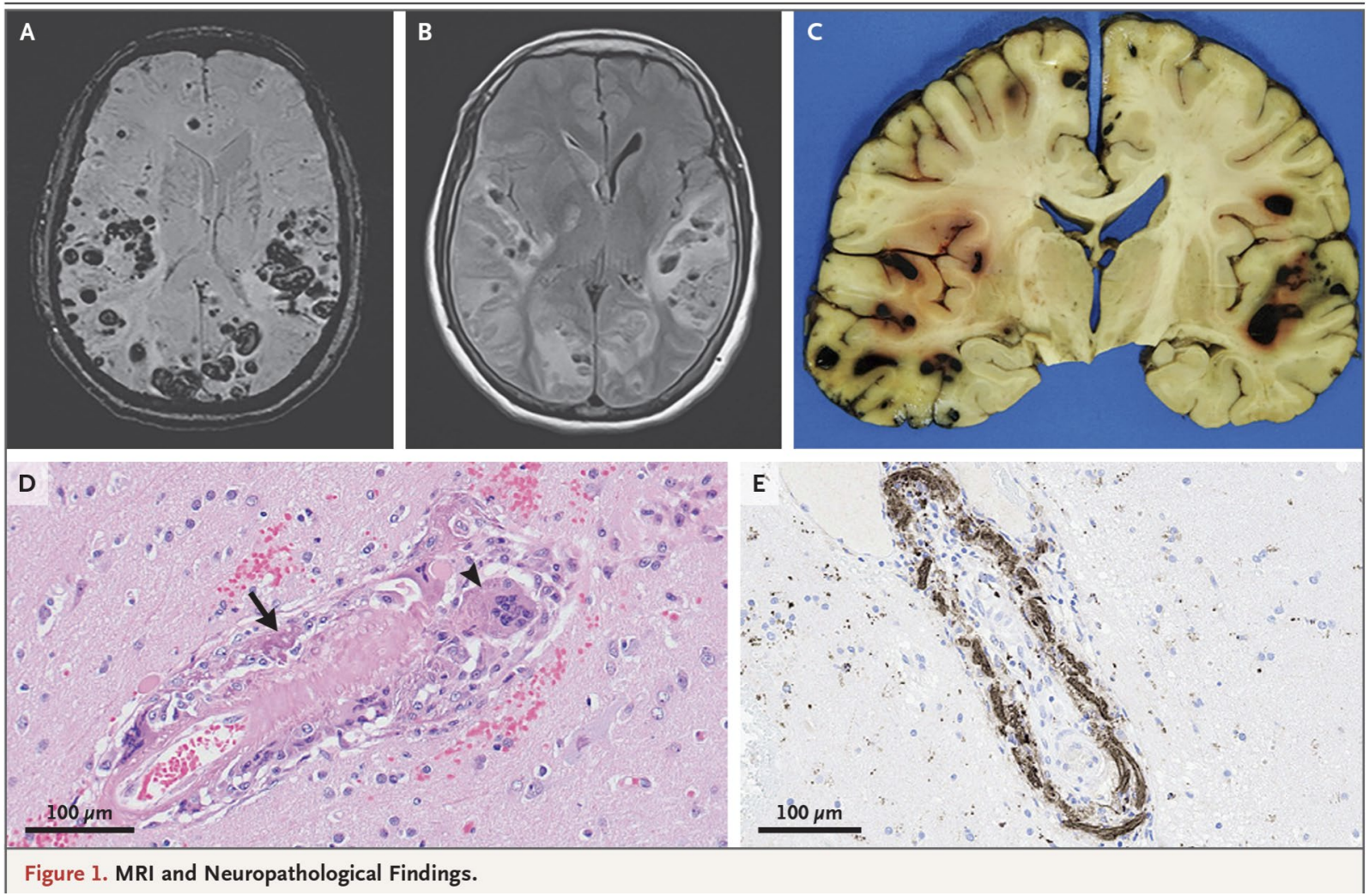


Figure 1. MRI and Neuropathological Findings.

N Engl J Med 2023; 388:478-479. DOI: 10.1056/NEJMc2215148

ARIA-Mitigation Strategies in Development

- TYK2/JAK1 inhibitor to decrease inflammation related to ARIA
- Modulation of ApoE4-related lipid dysmetabolism
- Anti-ApoE HAE-4 antibody
- GLP-1 agonist to decrease inflammation
- Anti-C1s mAb to block the complement cascade

Limiting Serious Outcomes

- Careful patient selection with a favorable risk:benefit profile
- Heed the warning signs
- Standardize MRI reporting
- Close communication between outpatient and hospital teams with updated stroke guidelines
- Ensure timely reporting of SAE’s

Heed the Warning Signs

- E4,4
- Significant CAA
- Treatment with anticoagulation
- Prior episodes of ARIA
- Atypical headache
- Encephalopathy