# Understanding the relationship between Amyloid-Related Imaging Abnormalities (ARIA) and Apolipoprotein E (APOE)

# Objectives

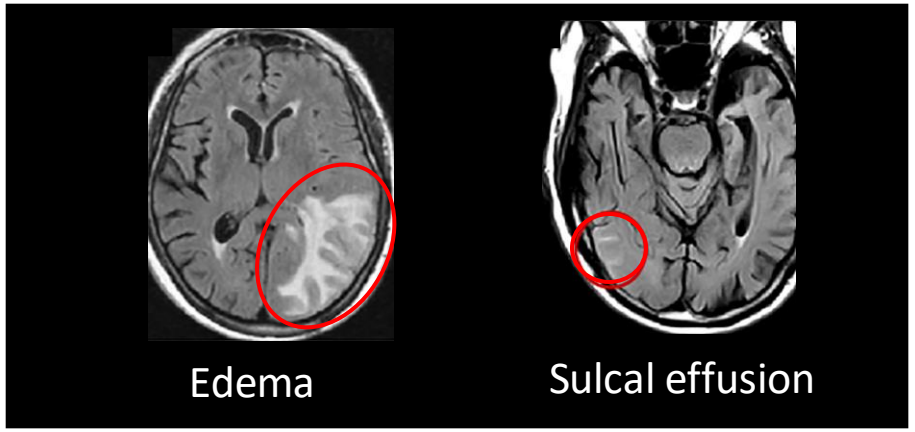
- Define ARIA and describe the two subtypes, ARIA-E and ARIA-H
- Understand the hypothesized pathophysiology of ARIA
- Describe the risk of ARIA based on *APOE* genotype
- Understand the relationship between *APOE*, AD, CAA, and ARIA
- Discuss the implications of *APOE* testing in AD clinical care

AD, Alzheimer's disease; APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities (edema/effusion); ARIA-H, amyloid-related imaging abnormalities (hemosiderin/hemorrhage); CAA, cerebral amyloid angiopathy

# ARIA

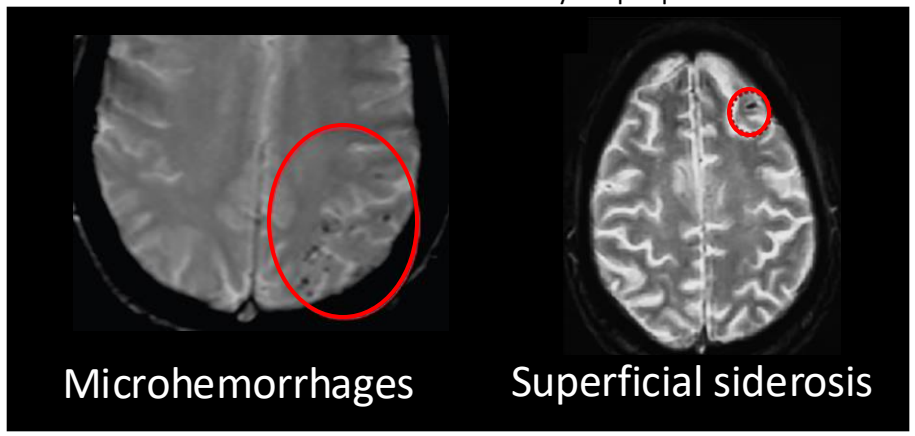
- **Amyloid-related imaging abnormalities,** or **"ARIA",** are MRI abnormalities that can occur spontaneously in Alzheimer's disease (AD), and the risk is increased with monoclonal antibodies that remove amyloid [1]
- ARIA is subdivided into **ARIA-E** (edema/effusion) or **ARIA-H** (hemosiderin/hemorrhage) [2]
- ARIA-E and -H may occur **concurrently** [3]
- **ARIA** is a consequence of the presence of amyloid in cerebral blood vessel walls (cerebral amyloid angiopathy [CAA]) [5].

Example of **ARIA-E** after monoclonal antibody treatment that removes amyloid plaque [3]




MRI images from Barakos et al (2022) [3]

Example of **ARIA-H** after monoclonal antibody treatment that removes amyloid plaque [3,4]




MRI images from Cogswell et al [4] and Barakos et al (2022) [3]

AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities (edema/effusion); ARIA-H, amyloid-related imaging abnormalities (hemosiderin/hemorrhage); CAA, cerebral amyloid angiopathy; MRI, magnetic resonance imaging

References: 1. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220 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. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35. 5. Sperling RA, et al. Alzheimers Dement. 2011;7(4):367–385

# Hypothesized pathophysiology of ARIA

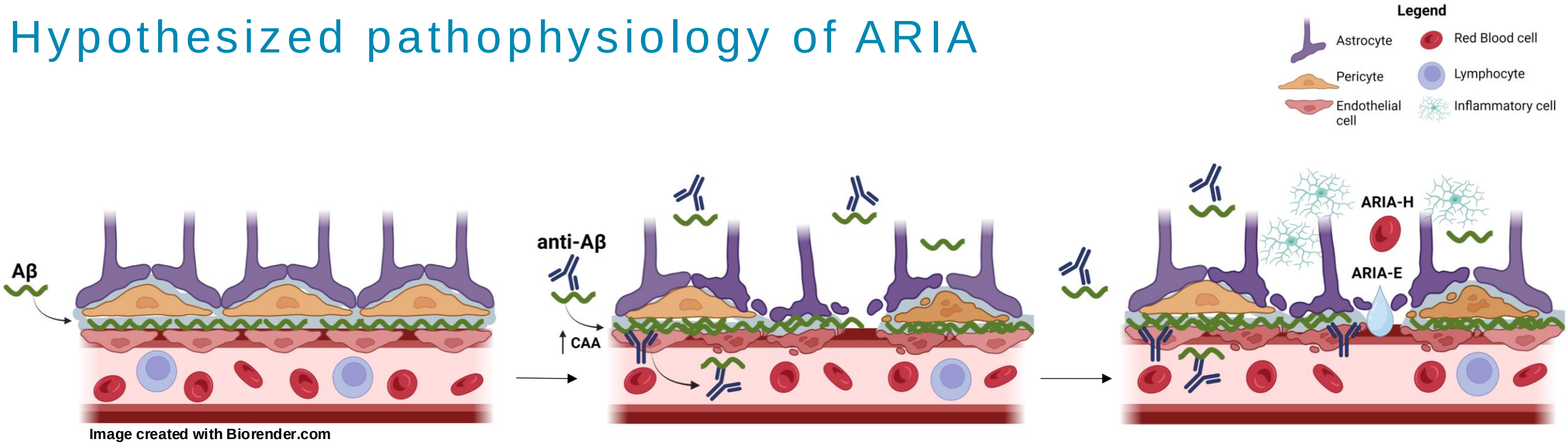



Image created with Biorender.com

Aggregation of toxic **amyloid β** (Aβ) species in the brain and vessels contributes to AD pathogenesis[1]

After the introduction of monoclonal antibodies that remove amyloid plaques, **amyloid deposits begin to clear**, leading to increased vascular permeability[1]

This **loss of vascular integrity** with vascular remodeling may be thought of as a transient exacerbation of cerebral amyloid angiopathy (CAA), similar to CAA-ri[1-3]

The **leakage of fluid** could give rise to an increased signal detected on MRI sequences(ARIA-E), while **leakage of red blood cells** would result in ARIA-H[1]

Aβ, amyloid beta; AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities (edema/effusion); ARIA-H, amyloid-related imaging abnormalities (hemosiderin/hemorrhage); CAA, cerebral amyloid angiopathy; CAA-ri, cerebral amyloid angiopathy-related inflammation; MRI, magnetic resonance imaging

References: 1. Hampel H, et al. Brain. 2023;doi:10.1093/brain/awad188. 2. Koemans EA, et al. *Lancet Neurol.* 2023;22:632-642; 3. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

# CAA-ri and ABRA

| Cerebral Amyloid Angiopathy-related inflammation (CAA-ri) | Two subtypes of inflammatory CAA | Amyloid Beta-related angiitis (ABRA) |
|---|---|---|

## Neuropathological Differentiation

| Perivascular inflammation but spares vessel wall; perivascular cuffs composed of lymphocytes with foreign body giant cells near amyloid deposits[1] | True vasculitis with lymphocytes infiltrating vessel wall and granuloma formation[1] |
|---|---|

## Shared Features

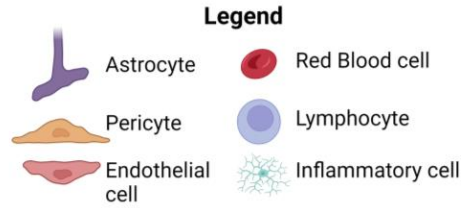
- Clinical features: headache, decreased consciousness, behavioral change, focal neurological signs, seizures[1]
- Imaging diagnosis: MRI with unifocal or multifocal, asymmetric T2/FLAIR white matter hyperintensities extending to subcortical white matter, leptomeningeal enhancement, and cortical/subcortical hemorrhages (microbleeds, macrohemorrhage, or superficial siderosis)[1]
- Pathophysiology: Amyloid deposition from CAA induces an inflammatory response leading to perivascular or mural vascular inflammation[1]

***ARIA, CAA-ri, and ABRA may represent different manifestations along a spectrum of inflammatory responses directed against amyloid beta causing leptomeningeal and parenchymal inflammation[1]***

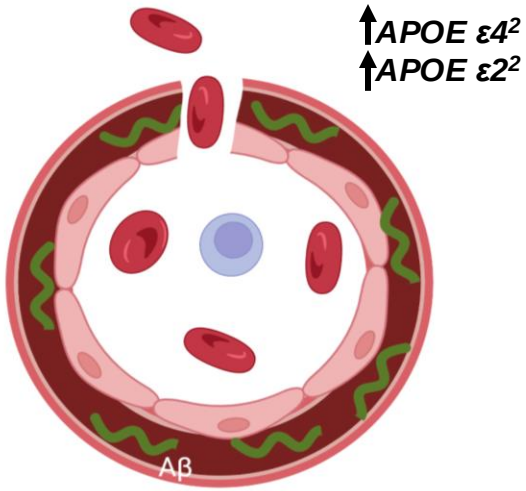
ABRA, amyloid beta-related angiitis; ARIA, amyloid-related imaging abnormalities; CAA, cerebral amyloid angiopathy; CAA-ri, cerebral amyloid angiopathy-related inflammation; FLAIR, fluid attenuated inversion recovery

1. Chwalisz, BK. *J Neurol Sci*. 2021;424:117425

# Relationship between CAA, CAA-ri, ABRA, and ARIA




## Cerebral amyloid angiopathy (CAA)

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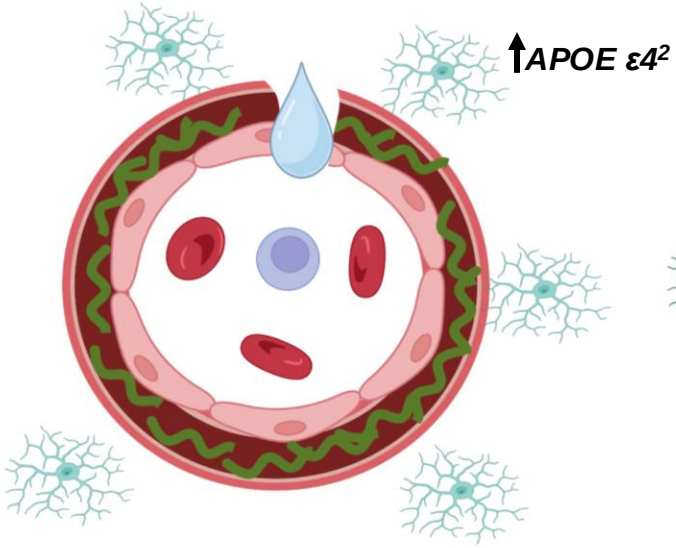
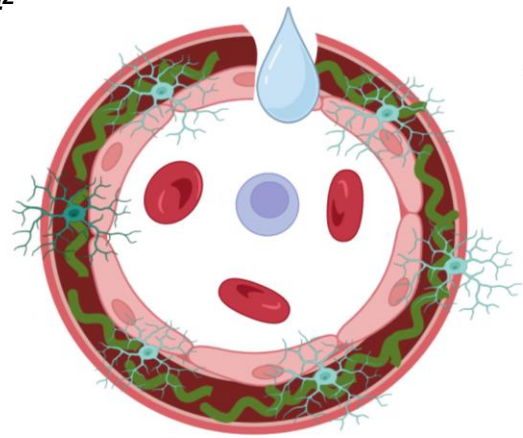
Deposition of amyloid β in blood vessels results in CAA, sometimes leading to hemorrhage[1]

## Cerebral amyloid angiopathy-related inflammation (CAA-ri)



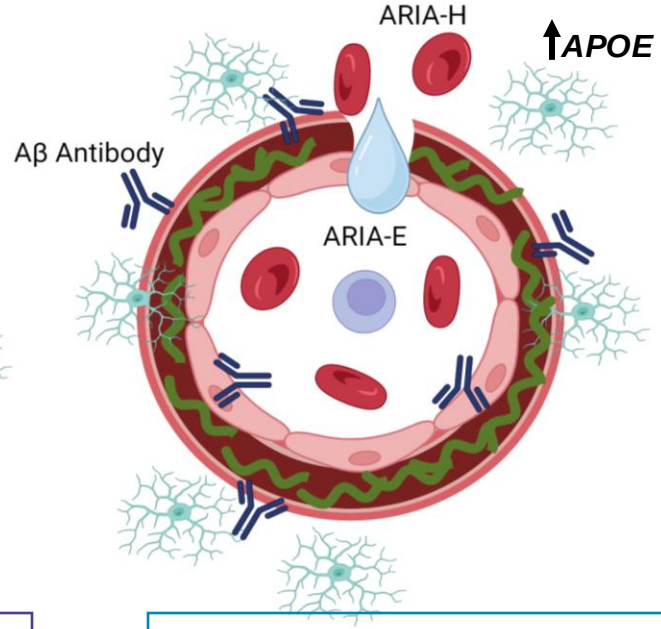

Perivascular inflammatory response to amyloid beta in blood vessels leads to CAA-ri[1]

## Amyloid beta-related Angiitis (ABRA)



Transmural inflammation with vasculitis in response to amyloid beta in blood vessels leads to ABRA[1]

## Amyloid-related Imaging abnormalities (ARIA)




Monoclonal antibodies targeting amyloid β lead to inflammation, fluid extravasation and/or hemorrhage[2]

ABRA, amyloid beta-related angiitis; APOE, apolipoprotein E; APOE ε2, apolipoprotein E ε2; APOE ε4, apolipoprotein E ε4 ARIA, amyloid related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities (edema/effusion); ARIA-H, amyloid-related imaging abnormalities (hemosiderin/hemorrhage); CAA, cerebral amyloid angiopathy; CAA-ri, cerebral amyloid angiopathy-related inflammation

References: 1. Chwalisz, BK. *J Neurol Sci*. 2021;424:117425; 2. Hampel H, et al. Brain. 2023;doi:10.1093/brain/awad188

# Increased risk of CAA and ARIA in *APOE ε4* carriers

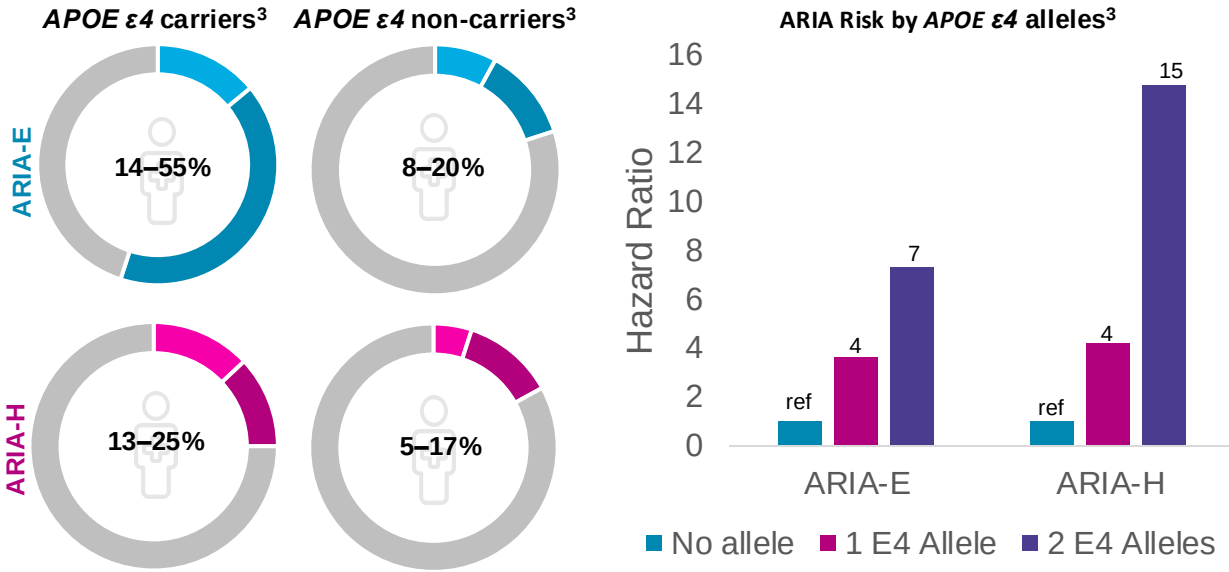
## Among patients in the general population and memory clinics

The *APOE ε4* allele is a risk factor for cerebral amyloid angiopathy **(CAA)**, with similar underlying pathophysiology to AD[1]

*APOE ε4* allele is a risk factor for spontaneously occurring **ARIA**[1] and **spontaneous intracerebral hemorrhage** related to CAA[2]

## In trials of monoclonal antibodies that remove amyloid plaque in patients with AD

The presence of one or more *APOE ε4* alleles is:
- a risk factor for **ARIA-E** and **ARIA-H**[1]




AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities (edema/effusion); ARIA-H, amyloid-related imaging abnormalities (hemosiderin/hemorrhage); CAA, cerebral amyloid angiopathy

References: 1. Greenberg SM, et al. Nat Rev Neurol. 2020;16:30-42; 2. Carpenter AM, et al. *Nat Rev* Neurol, 2016;12:40-49; 3. Filippi M, et al. *JAMA Neurology*. 2022; 79:291-304

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# *APOE* and AD pathophysiology

APOE is a lipid-binding protein with cholesterol and lipid transport functions[1]

The human *APOE* gene has three major polymorphic alleles: *APOE ε2, ε3, ε4*[1]

The three allelic variants differ in their **risk of developing AD**:[1]

- *ε2* decreases the risk of developing AD (odds ratio ~0.6)[1], although when *ε2* is recessive to *ε4* (*ε2/ε4*) there is a higher risk of developing AD[1]
- *ε3* is the most common allele used for reference[1]
- *ε4* increases the risk of developing AD[1]

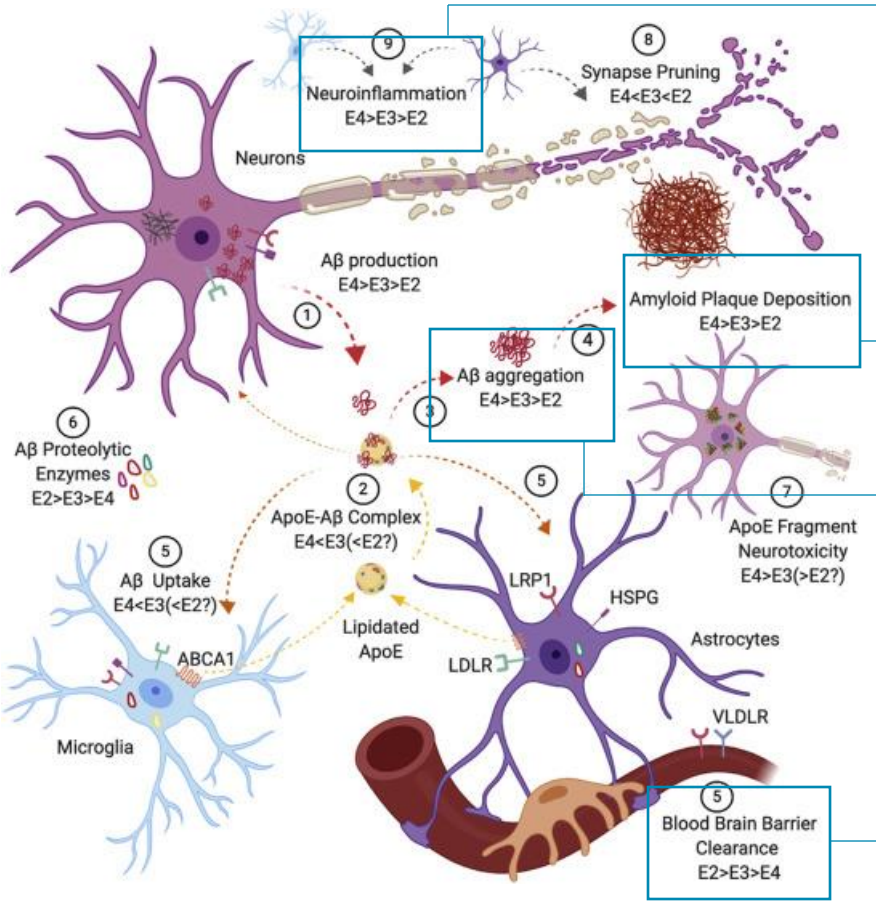


Image from Raman S, et al. Neurobiol Dis. 2020;138:104788

*APOE* **modulates** microglia-mediated **neuroinflammation** in AD[1]

*APOE ε4* carriers have **earlier and greater Aβ deposition** in plaques and vessels[1,2]

*APOE ε4* is associated with **loss of BBB** integrity and increased cerebrovascular leakiness[1,3]

*APOE ε4* carriers have **impaired Aβ clearance** from the brain[1]

Aβ, amyloid beta; AD, Alzheimer's disease; APOE ε2, apolipoprotein E ε2; APOE ε3, apolipoprotein E ε3; APOE ε4, apolipoprotein E ε4; BBB, blood-brain barrier

References: 1. Yamazaki Y, et al. Nat Rev Neurol. 2019;9:501-518; 2. Greenberg SM, et al. Nat Rev Neurol. 2020;16:30-42; 3. Tai LM, et al. Acta Neuropathol. 2016;131:709-723. 4. Raman S, et al. Neurobiol Dis. 2020;138:104788

# APOE and ARIA pathophysiology

| | |
|---|---|
| *APOE ε4* carriers have **earlier and greater Aβ deposition** in plaques and vessels[1,2] | with advanced CAA, exposure to anti-Aβ monoclonal antibodies may result in **increased solubilization of Aβ**, thus overwhelming Aβ clearance, leading to ARIA[3] |
| *APOE ε4* carriers have **impaired Aβ clearance** from the brain[2] | also resulting in **higher** perivascular **accumulation of Aβ** and subsequent CAA[1] |
| *APOE ε4* is associated with **loss of BBB** integrity and increased cerebrovascular leakiness[4] | that may **contribute to ARIA** due to extravasation from vessels[3] |
| *APOE* **modulates** microglia-mediated **neuroinflammation** in AD[2] | *APOE ε4* is a **risk factor** for CAA-ri, which involves infiltration of immune cells as a spontaneous Aβ response, similar to ARIA pathophysiology[1] |

Aβ, amyloid beta; AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; BBB, blood-brain barrier; CAA, cerebral amyloid angiopathy; CAA-ri, cerebral amyloid angiopathy-related inflammation

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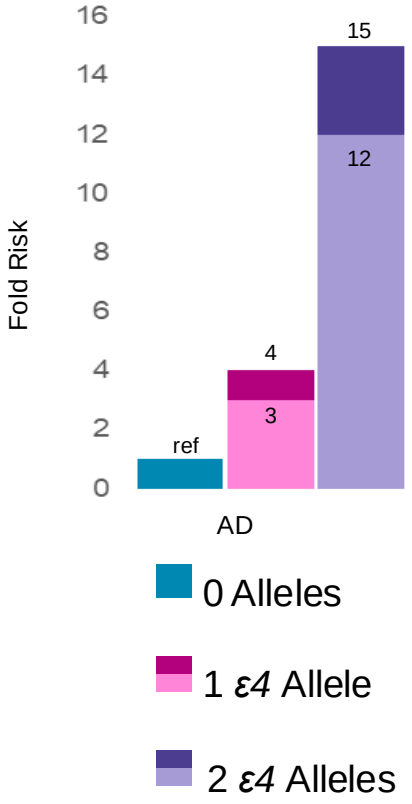
# *APOE* and risk of AD and ARIA

## Risk of developing AD

*APOE ε4* heterozygous increases the risk of developing AD **3-4 fold** in Caucasians[1,2]

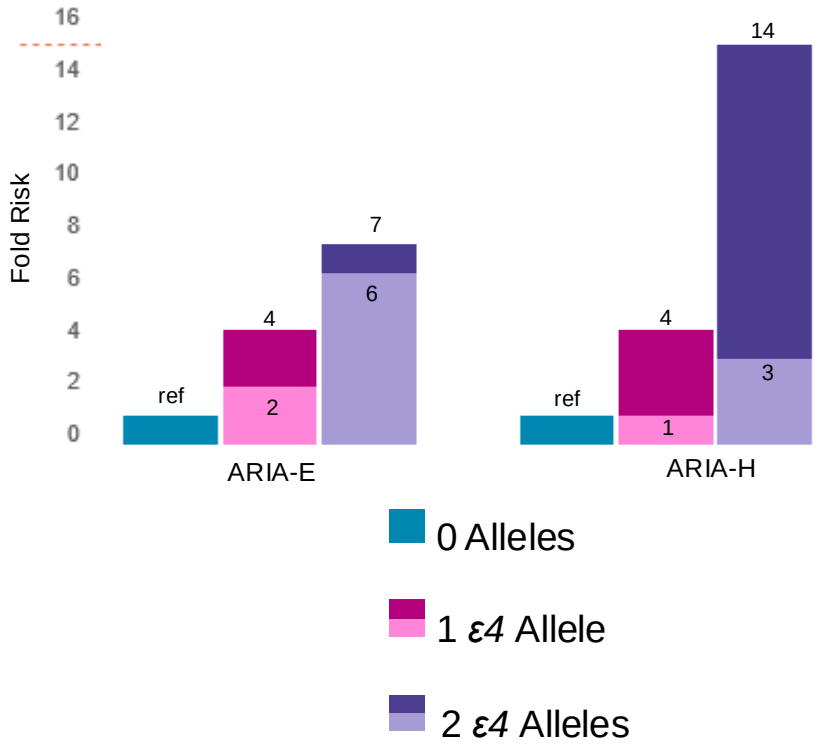
*APOE ε4* homozygous increases the risk of developing AD **12-15 fold** in Caucasians[1,2]




## Risk of ARIA

*APOE ε4* heterozygous increases the risk of developing ARIA-E **2-4 fold**[3,4] and ARIA-H **1-4 fold**[4,5]

*APOE ε4* homozygous increases the risk of developing ARIA-E **6-7 fold**[3,4] and ARIA-H **3-14 fold**[4,5]




AD, Alzheimer's disease; *APOE ε4*, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities (edema/effusion); ARIA-H, amyloid-related imaging abnormalities (hemosiderin/hemorrhage)

References: 1. Yamazaki Y, et al. *Nat Rev Neurol*. 2019;9:501-518. 2. Farrer LA, et al. *JAMA*. 1997;278:1349-1356. 3. Sperling R, et al. *Lancet Neurology*. 2012;11:241-249. 4. van Dyck CH, et al. *NEJM*. 2023;388(1):9-21 5. Arrighi HM, et al. *J Neurol Neurosurg Psychiatry*. 2016;87:106-112;

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# Benefits of *APOE* testing in AD clinical care

- Helps inform the risk of developing **ARIA** when deciding to initiate treatment with anti-Aβ monoclonal antibodies and the need for heightened clinical monitoring[1,2]
- Participation in clinical trials or preventative therapies for early intervention[3]

Aβ, amyloid beta; AD, Alzheimer's disease; APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities

1. Filippi M, et al. *JAMA Neurology*. 2022; 79:291-304. 2. Cummings, J, et al. *JPAD*. 2023;10:362-377 3. Lopez Lopez, C. *et al. Alzheimers Dement (N Y)* 2019;5:216-227.

# Recommendations for *APOE* testing in AD clinical care

- The **decision to perform genetic testing** is complex since the implication of results goes beyond considerations of specific treatments[1]
- **It is recommended that health care providers discuss *APOE ε4* testing** as part of the overall discussion of the benefit/risk of treatment options for AD, and the risk that *APOE ε4* confers for ARIA[2].
- Prior to genetic testing, health care providers should **provide genetic counseling and education** to discuss the considerations of *APOE ε4* testing with patients and family members[1]

AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities

1. Roberts JS & Uhlmann WR. *Prog Neurobiol*; 2013;110:89-101. 2. Cummings J, et al. J Prev Alzheimers Dis. 2023;10(3):362-377.

# Potential considerations of *APOE* testing in AD clinical care

Randomized controlled trials have generally shown **no impact on depression or anxiety** with disclosing APOE results, although there is **increased distress** in those who are *ε4* carriers[1,2]

APOE test results may have **significant implications for family members** given familial inheritance of *ε4* allele[1,3]

**Not all insurance companies** currently cover APOE testing (except for symptomatic individuals) in the United States, although it is available through direct-to-consumer (DTC) tests[1,4]. Further studies investigating the effect of DTC tests on individuals receiving APOE testing for AD are needed[4]

In the United States, the Genetic Information Nondiscrimination Act (GINA) (2008) prohibits employers and insurance companies from using genetic information to make hiring decisions or for insurance coverage/premiums, but this does not apply to **long-term care (LTC) insurance**[5]. Other countries have varied guidelines and policies on use of genetic testing[4]

AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; DTC, direct-to-consumer; GINA, Genetic Information Nondiscrimination Act; LTC, long-term care

1. Roberts JS & Uhlmann WR. *Prog Neurobiol*; 2013;110:89-101. 2. Green RC, et al. *NEJM*. 2009;361:245-254 3. Largent EA, et al. *J Alzheimers Dis.* 2021;84:1015-1028. 4. Galuzzi S, et al. *Biomedicines*.2022;10:1-15. 5. Chapman CR, et al. *Journal of Law and the Biosciences 2020;*7(1):lsz016

# Key Points

***APOE ε4* carriers**

**Increased risk of:**

- AD[1]
- CAA[2]
- CAA-ri[3]
- ARIA-E[4]

## ARIA and *APOE ε4*

- ARIA is subdivided into:
  - **ARIA-E** (edema/effusion)[5] or
  - **ARIA-H** (hemosiderin/hemorrhage)[5]
- ARIA can occur **spontaneously** or **following treatment** with monoclonal antibodies that remove amyloid[4]
- The presence of one or more *APOE ε4* alleles is:
  - a risk factor ARIA-E and ARIA-H[2]

- *APOE ε4* testing in **clinical practice is a complex decision** with implications beyond consideration for AD treatment
- Health care providers should discuss the implications of *APOE ε4* testing as part of the overall discussion of the benefit/risk of treatment options for AD[6]

AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; ARIA, amyloid-related imaging abnormalities ARIA-E, amyloid-related imaging abnormalities (edema/effusion); ARIA-H, amyloid-related imaging abnormalities (hemosiderin/hemorrhage); CAA, cerebral amyloid angiopathy; CAA-ri, cerebral amyloid angiopathy-related inflammation.

1. Yamazaki Y, et al. Nat Rev Neurol. 2019;9:501-518. 2. Greenberg SM, et al. Nat Rev Neurol. 2020;16:30-42. 3. Chwalisz, BK. *J Neurol Sci*. 2021;424:117425 4. Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220. 5. Filippi M, et al. JAMA Neurol. 2022;79(3):291–304 6. Roberts JS & Uhlmann WR. Prog Neurobiol; 2013;110:89-101