Poster number: 98357

Identifying and Characterizing Comorbid Cerebral Amyloid Angiopathy in ADNI Participants Using Boston Criteria Version 2.0

For US HCPs Only
Scan to View Congress Material Presented

Robert W. Deering[1]; Neal S. Parikh[1]; Sasikiran Goteti[1]; Ying He[1]; Luc Bracoud[2]; Andreja Avbersek[3]; Joseph A. Chiarappa[3]; Farshid Sepehrband[3]

[1]Alnylam Pharmaceuticals, Inc., Cambridge, MA, USA; [2]Clario Inc., Lyon, France; [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Conclusions

- **Cerebral amyloid angiopathy (CAA) is a leading cause of hemorrhagic stroke and is often comorbid with Alzheimer's disease (AD).**
- **In this analysis of Alzheimer's Disease Neuroimaging Initiative (ADNI) participants, probable CAA (as defined by Boston Criteria version 2.0[1]) was identified in approximately 25% of cognitively impaired participants.**
- ***Apolipoprotein E4* (*APOE4*) homozygosity, higher Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores, and older age were significantly associated with probable CAA.**
- **These findings have informed the design of an ongoing Phase 2 study in CAA to include individuals with cognitive impairment/dementia.**
  - **Mivelsiran is an investigational first-in-class RNA interference therapeutic designed to target amyloid-beta precursor protein (APP) in patients with CAA (cAPPricorn-1; NCT06393712).**
- **Whether the findings of this analysis apply to patients with other presentations of CAA, apart from cognitive impairment, requires investigation.**

Background

- CAA is a debilitating and progressive cerebrovascular disease characterized by deposition of amyloid-beta (Aβ) in blood vessels, leading to hemorrhagic and nonhemorrhagic disease manifestations.[2]
- CAA is often comorbid with AD, but also independently contributes to cognitive decline.[3]
- Patients with AD and comorbid CAA are often excluded from treatment with Aβ-targeting monoclonal antibodies by appropriate use recommendations, owing to an increased risk of amyloid-related imaging abnormalities and hemorrhage.[4,5]
- Investigational treatments for AD and CAA have recently entered clinical development, and limited data are available to inform inclusion criteria and clinical trial design.

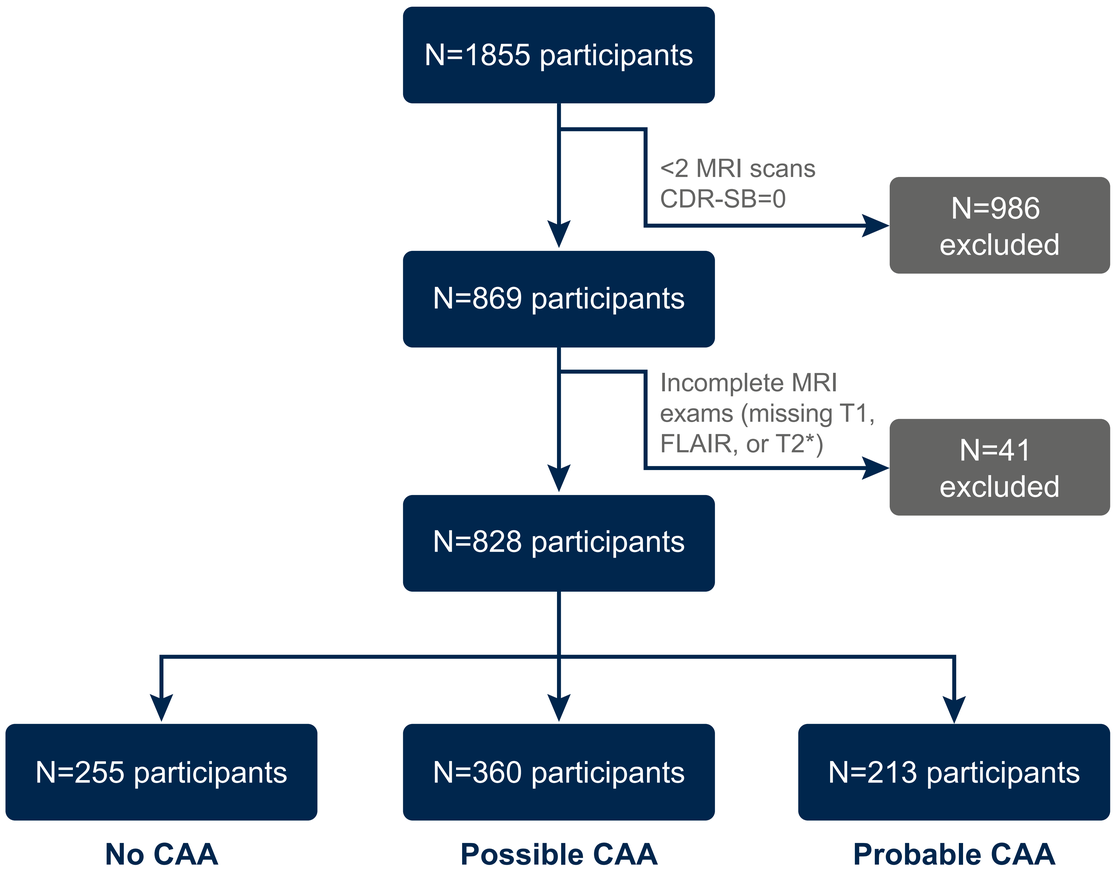
Objective

- This study aimed to estimate the proportion of ADNI participants who have probable CAA by systematically applying Boston Criteria version 2.0, and to evaluate characteristics associated with probable CAA in this population.

Methods

- Participants in ADNI were included if they had cognitive symptoms or deficits (at least one CDR-SB score of >0) and at least two magnetic resonance imaging (MRI) scans appropriate for CAA adjudication. Participants with incomplete MRI exams were excluded (**Figure 1**).

Figure 1. Participant Selection Flowchart



CAA, cerebral amyloid angiopathy; CDR-SB, Clinical Dementia Rating-Sum of Boxes; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

- 3D T1-weighted, fluid-attenuated inversion recovery (FLAIR), and T2* Gradient Echo MRI sequences from the ADNI database were evaluated by blinded neuroradiologists to categorize participants as having no CAA, possible CAA, or probable CAA, using the Boston Criteria version 2.0.
- The clinical criteria required by Boston Criteria version 2.0 were considered met if the participant had cognitive impairment as demonstrated by a CDR-SB score >0.
- A 10% sample was randomly selected to be read by two neuroradiologists in addition to the counts provided by ADNI to evaluate inter-reader variability of cerebral microbleed count.
- Univariate analyses were conducted to compare baseline characteristics between participants with probable CAA versus no/possible CAA.
- Variables found to be significant (p<0.05) in the univariate analysis, along with others deemed clinically relevant, were included in a multivariable logistic regression model to identify factors associated with the likelihood of probable CAA. The final model retained only variables that remained statistically significant (p<0.05) after model selection.

REFERENCES

1. Charidimou A *et al. Lancet Neurol* 2022;21(8):714–25.
2. Koemans EA *et al. Lancet Neurol* 2023;22(7):632–42.
3. Boyle PA *et al. Neurology* 2015;85(22):1930–6.
4. Rabinovici GD *et al. J Prev Alzheimers Dis* 2025;12(5):100150.
5. Cummings J *et al. J Prev Alzheimers Dis* 2023;10(3):362–77.

Disclosures: RWD, **NSP**, **SG**, and **YH** are employees of and shareholders in Alnylam Pharmaceuticals. **LB** is an employee of Clario. **AA**, **JAC**, and **FS** are employees of Regeneron Pharmaceuticals.

Results

Participant Population

- Based on the Boston Criteria version 2.0, of 828 participants who met the inclusion criteria, 25.7% had probable CAA, 43.5% had possible CAA, and 30.8% did not have CAA (**Figure 1**).
- Of those with probable CAA, 46.9% had mild cognitive impairment and 44.6% had dementia (**Table 1**); median CDR-SB score was 3 (interquartile range, 1–5).
- Participants with probable CAA frequently had cardiovascular disease (69.0%), history of antithrombotic medication use (63.2%), or comorbid hypertension (53.1%), and were current or former smokers (40.2%).
- High interobserver agreement was observed for cerebral microbleed detection; attribution of probable CAA would have been affected in <5% of the subsample based on reader variability (intraclass correlation coefficient, 0.92; 95% confidence interval, 0.89–0.94).

Table 1. Baseline Characteristics and Univariate Analysis of Participants with Probable CAA Versus No/Possible CAA

Characteristic	Total (N=828)	Probable CAA (N=213)	No/Possible CAA (N=615)	*p* Value
Age (years), mean (SD)	76.7 (7.8)	78.6 (7.3)	76.1 (7.9)	**<0.01**
Weight (kg), mean (SD)[a]	76.4 (16.3)	76.8 (16.4)	76.2 (16.3)	0.64
Male sex	461 (55.7)	130 (61.0)	331 (53.8)	0.07
Race				
White	774 (93.5)	199 (93.4)	575 (93.5)	0.97
Other[b]	54 (6.5)	14 (6.6)	40 (6.5)	
Ethnicity				
Hispanic/Latino	26 (3.1)	3 (1.4)	23 (3.7)	0.09
Not Hispanic/Latino or unknown	802 (96.9)	210 (98.6)	592 (96.3)	
Hypertension	409 (49.4)	113 (53.1)	296 (48.1)	0.22
Stroke	13 (1.6)	4 (1.9)	9 (1.5)	0.67
Cardiovascular disease[c]	436 (67.4)	120 (69.0)	316 (66.8)	0.60
History of antithrombotic medication use[c]	404 (62.4)	110 (63.2)	294 (62.2)	0.80
Current or former smoker[c]	253 (39.1)	70 (40.2)	183 (38.7)	0.72
Cognitive status				
CN	81 (9.8)	18 (8.5)	63 (10.2)	
MCI	433 (52.3)	100 (46.9)	333 (54.1)	0.07
Dementia	314 (37.9)	95 (44.6)	219 (35.6)	
CDR-SB score, mean (SD)	3.4 (3.2)	4.1 (3.7)	3.2 (3.0)	**<0.01**
***APOE4* status**				
***E4* noncarrier**	417 (50.4)	84 (39.4)	333 (54.1)	
***E4* heterozygote**	311 (37.6)	88 (41.3)	223 (36.3)	**<0.01**
***E4* homozygote**	100 (12.1)	41 (19.2)	59 (9.6)	

Data are reported as n (%) except as stated otherwise. Univariate analyses were conducted to compare probable vs no/possible CAA. Denominators for select covariates differed from group total owing to variable data availability.
[a]Data for this covariate were available for n = 806, 210, and 560 for the total, probable CAA, and no/possible CAA groups, respectively.
[b]American Indian/Alaskan, Asian, Black, Hawaiian/Other Pacific Islander, more than one, unknown.
[c]Data for this covariate were available for n = 647, 174, and 473 for the total, probable CAA, and no/possible CAA groups, respectively.
APOE4, *apolipoprotein E4*; CAA, cerebral amyloid angiopathy; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CN, cognitively normal; MCI, mild cognitive impairment; SD, standard deviation.

Factors Associated with Probable CAA

- Multivariable logistic regression identified older age, higher CDR-SB score, and *APOE4* homozygosity as independently and significantly associated with probable CAA (p<0.05) (**Table 2**).

Table 2. Factors Associated with Having Probable CAA in the ADNI Cohort

Participant Characteristic	Odds Ratio (95% CI)	*p* Value
Multivariable logistic regression: full model		
Age	1.06 (1.03–1.09)	**<0.01**
Sex (male vs female)	1.32 (0.90–1.93)	0.16
Ethnicity (Hispanic/Latino vs not Hispanic/Latino or unknown)	0.14 (0.02–1.13)	0.07
Hypertension (yes vs no)	1.30 (0.90–1.88)	0.17
History of antithrombotic medication use (yes vs no)	0.81 (0.55–1.20)	0.29
Cognitive status (MCI vs CN)	0.85 (0.44–1.65)	0.63
Cognitive status (dementia vs CN)	0.68 (0.30–1.55)	0.36
CDR-SB score	1.11 (1.02–1.20)	**0.01**
***APOE* status: *E4* homozygotes (yes vs no)**	2.31 (1.35–3.95)	**<0.01**
Multivariable logistic regression: final model after stepwise selection[a]		
Age	1.06 (1.03–1.09)	**<0.01**
CDR-SB score	1.08 (1.02–1.13)	**<0.01**
***APOE* status: *E4* homozygotes (yes vs no)**	2.38 (1.40–4.03)	**<0.01**

[a]Final model includes variables with significant p values (p<0.05) following model selection.
ADNI, Alzheimer's Disease Neuroimaging Initiative; *APOE*, *apolipoprotein*; CAA, cerebral amyloid angiopathy; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CI, confidence interval; CN, cognitively normal; MCI, mild cognitive impairment.

Acknowledgments: Data used in the preparation of this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Thank you to the participants, their families, investigators, study staff, and collaborators for their participation. Editorial assistance provided by Elizabeth Coe of PharmaGenesis Cardiff, Cardiff, UK, was funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice (GPP) guidelines.
Funding: This study was funded by Alnylam Pharmaceuticals.

If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.

Presented at the Alzheimer's Association International Conference (AAIC) 2025, July 27–31, 2025, Toronto, ON, Canada