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RESEARCH ARTICLE

Relationship between use of anti-platelet agents, oral anti-coagulants, and Aβ burden with cerebral microhemorrhages in cognitively asymptomatic adults

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Abstract

INTRODUCTION: Cerebral microhemorrhages (CMHs) are detectable by magnetic resonance imaging (MRI). CMHs in deep brain regions are linked to hypertensive vasculopathy, while those in lobar regions with amyloid beta (Aβ) deposition in blood vessels. This study aims to determine the association between anti-thrombotic treatment and CMH prevalence among cognitively asymptomatic adults, and to assess the role of Aβ markers, apolipoprotein E (*APOE*) ε4 carrier status, and cardiovascular risk factors in CMH development.

METHODS: Using baseline data from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) and Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) studies, we examined CMH presence via 3T MRI, along with medication use, *APOE* ε4 carrier status, medical history, and blood pressure.

RESULTS: Our analysis showed a significantly higher prevalence of CMHs in the A4 cohort (17.3%) compared to the LEARN cohort (2.6%).

DISCUSSION: Factors such as male sex, age, Aβ markers, and *APOE* ε4 status were significantly associated with higher CMH prevalence in the A4 cohort. However, anti-thrombotic treatment did not show association with overall CMHs.

KEYWORDS
amyloid beta, anti-thrombotic treatment, asymptomatic Alzheimer's disease, cerebral amyloid angiopathy, cerebral microhemorrhages

Highlights

- Male sex, age > 75, amyloid beta (Aβ) burden, and apolipoprotein E (*APOE*) ε4 homozygosity are significantly associated with higher prevalence of CMHs (cerebral microhemorrhages) in a cohort of cognitively asymptomatic individuals.

Marcus D. Gay and Dobri Baldaranov contributed equally to this study.

- Male sex, age > 75, Aβ burden, and *APOE* ε4 homozygosity are significantly associated with higher prevalence of lobar CMHs in a cohort of cognitively asymptomatic individuals.
- Anti-platelet or anti-coagulant usage were not associated with an increased prevalence of CMHs in either brain location or overall, in a cohort of cognitively asymptomatic individuals.
- History of a lipid disorder is associated with a higher prevalence of lobar CMHs in a cohort of cognitively asymptomatic individuals.

1 | BACKGROUND

Cerebral microhemorrhages (CMHs) are the product of extravasation of blood from small intracerebral vessels, and manifest as hypointense lesions on T2*-weighted gradient echo magnetic resonance imaging (MRI).[1] While generally an incidental finding, several studies have demonstrated that their location is acting as a marker of specific pathologic processes. For example, histologic examination of patients who suffered from an intracerebral hemorrhage (ICH) showed the basal ganglia, thalami, and brain stem as preferred locations in hypertensive patients.[2] On the other hand, findings that have informed the pathologically validated Boston Criteria for the diagnosis of probable cerebral amyloid angiopathy (CAA) have implicated CMHs located in lobar brain regions as a marker for CAA.[3] CMHs have been studied to predict risk for other pathologies with pathogenesis related to neurovascular injury. This has proved true as CMHs have been associated with a higher risk of lobar ICH recurrence and ischemic stroke.[4–6] Investigations into CMHs have contributed to the growing body of evidence that suggests that vascular pathology plays a pivotal role in cognitive deterioration: impaired cognitive performance, executive function, and processing speed along with an increased risk of dementia, including Alzheimer's disease (AD) dementia.[6,7]

Efforts have been made to uncover the prevalence of CMHs in different populations to allow the identification of individuals at high risk for symptomatic cerebrovascular pathology (ICH, ischemic stroke, hypertensive vasculopathy, CAA) and cognitive decline. Studies evaluating the prevalence of CMHs are further supporting the association of amyloid beta (Aβ) burden (measured by positron emission tomography [PET]) with lobar, but not deep, CMHs.[8]

There is existing uncertainty of the management and interpretation of incidentally found CMHs, for example, if found in individuals on anti-thrombotic treatment. Oral anti-coagulant (OAC) use is important to investigate because it has been shown not only to increase the risk of lobar and deep ICH in large cohort studies such as the Framingham Heart Study[9] but also the risk of symptomatic ICH.[10] A recent meta-analysis has observed an association with OAC usage and CMH prevalence.[11] Many of the individuals included in studies that comprised the meta-analysis had other medical comorbidities, and their baseline cognitive status was unknown; thus, the relationship between OACs and CMH prevalence in cognitively asymptomatic adults, such as those in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study and the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) study, is still to be determined. One recent investigation showed that anti-coagulant use was associated with the presence of CMHs in a cognitively normal population.[12] Along a similar line, the association between anti-platelet agents and CMHs has been a focus of investigation due to the prevalence of anti-platelet use in cerebrovascular disease. In terms of CMHs, acetylsalicylic acid was associated with CMHs in patients who had suffered from hemorrhagic stroke but not ischemic stroke or transient ischemic attack.[13] Other studies have found no association between anti-platelet use and CMHs in those with hemorrhagic stroke.[14] However, anti-platelet agents have been shown to be associated with an increased risk of recurrence of ICH after controlling for covariates.[15]

In our study we examined the relationship between anti-thrombotic treatment, and the prevalence of CMHs in different brain regions (deep and lobar) among older cognitively asymptomatic adults with no recent cerebrovascular events. Importantly, we analyzed our results among two different populations: with elevated Aβ burden in the brain as confirmed by PET (A4 study), and without elevated Aβ burden (LEARN study). One recent study in the same population found that having two apolipoprotein E (*APOE*) ε4 alleles was a risk factor for CMH in the A4 study, while having one *APOE* ε4 allele was not a risk factor in either A4 or LEARN.[16] Our analysis expands on this work by looking at the different brain regions to uncover possible risk factors that may be associated with pathophysiologic mechanisms related to deep or lobar CMHs. Therefore, our analysis evaluated Aβ burden as both a unique variable and as an effect modifier related to anti-thrombotic use. Identifying risk factors and medications that amplify or mitigate CMH development in this high-risk population could help inform clinical decisions targeted at avoiding the neuropathology associated with CMHs.[17]

2 | METHODS

2.1 | Participant inclusion

We sought to perform a cross-sectional study to investigate the factors associated with the prevalence of CMHs among participant with

elevated Aβ and those without elevated Aβ on brain PET. To accomplish this, we used the screening data of all participants that completed the MRI stage at screening for the A4 study (NCT02008357) and the LEARN study (NCT02488720).

The screening process for A4 and LEARN is described in detail elsewhere but we will provide an overview here.[18] First, it is important to understand that LEARN and A4 are sister studies that are distinguished by the presence of elevated Aβ in the participants in A4. Potential participants in A4 and LEARN were eligible for screening if they were between the ages of 65 and 85, did not have evidence of cognitive impairment (a Mini-Mental State Examination [MMSE] score between 25 and 30, a global Clinical Dementia Rating [CDR] score of 0, and a Logical Memory II score between 6 and 18), were not taking medications for AD dementia, lived independently, and had a partner who could provide collateral information regarding the participant's functioning. Furthermore, those with serious or unstable medical conditions, as deemed by the investigators, were ineligible for the study. However, those with stable and common conditions that were not expected to interfere with the analysis of safety or efficacy for the studies, such as diabetes, hypertension, or controlled atrial fibrillation, were included. Four thousand four hundred eighty-six individuals met these criteria and subsequently underwent florbetapir Aβ PET imaging.

RESEARCH IN CONTEXT

1. **Systematic review**: The prevalence of cerebral microhemorrhages (CMHs) in asymptomatic Alzheimer's disease (AD) is still unclear and the literature (PubMed) is limited as well as about their association with the use of anti-thrombotic treatment. However, the literature is supportive of the general finding that the use of anti-thrombotic treatment together with amyloid beta (Aβ) load have been shown to increase the risk of lobar and deep intracerebral hemorrhage.
2. **Interpretation**: Our work is showing that the association between having elevated brain Aβ load and CMH prevalence persists not only in general but also when looking at CMH distribution by different locations in the brain. The other important finding in this study is the absence of an association between anti-thrombotic treatment and total CMH prevalence regardless of Aβ load.
3. **Future directions**: Our results suggest that anti-thrombotic use may not be a risk factor for CMH development in the preclinical AD population and lead to discussion on this now widely used exclusion criteria for most of the AD trials. However, more data are needed to increase the confidence of such a decision.

2.2 | PET imaging

^{18}F-florbetapir PET imaging was used to evaluate if participants had elevated cerebral Aβ and were therefore eligible to participate in the A4 study. Cerebral Aβ status was determined by an algorithm that combined a mean cortical standardized uptake value ratio (SUVR) using a whole cerebellar reference region and a qualitative visual reading. Individuals with a mean SUVR > 1.15 were automatically considered Aβ+. Individuals with a mean SUVR between 1.10 and 1.15 were Aβ+ if two independent readers concluded that the read was positive for evidence of cerebral Aβ pathology qualitatively. Those with a mean SUVR < 1.10, or those with a mean SUVR between 1.10 and 1.15 without consensus from two different readers were considered Aβ−. Those considered Aβ+ (n = 1323) continued to screen for the A4 trial while those who were Aβ− were eligible to screen for the LEARN study until a target size of 500 LEARN participants was reached. Individuals in each screening cohort underwent a screening 3T MRI.

2.3 | Brain MRI and characterization of CMHs

The screening 3T MRIs were used to obtain the outcomes of interest: total CMHs, CMHs located in lobar brain regions, and CMHs located in deep brain regions. The A4 and LEARN trials collaborated with neuroradiologists at the Mayo Clinic to obtain data regarding CMHs in the manner identical to that used in the Alzheimer's Disease Neuroimaging Initiative (ADNI), described elsewhere in detail.[19] Briefly, the following sequences acquired on 3T MRI were used: 3D T1-weighted magnetization-prepared rapid gradient echo, axial T2*-weighted gradient echo, and axial T2-weighted fluid-attenuated inversion recovery. Definite CMHs were identified by trained image analysts and secondarily confirmed by two experienced radiologists at Mayo Clinic. Small (< 10 mm), homogenous, hypointense lesions that were dissociable from small vessels were counted as definite CMHs. Possible CMHs were read but were not included in this study. The location of CMHs was determined by propagating the identified CMHs to a coordinate system and comparing the visualized CMH to an automated anatomic labeling atlas.[20] This comparison allowed the radiologists to characterize the CMH as either deep/infratentorial or lobar. Double rating was used, and a test of inter-reader reliability between the two radiologists on definite versus non-definite CMH was 85%.[19]

2.4 | Other variables

The data collected during the screening process for LEARN and A4 were used to obtain the different independent variables that were studied. Data for different medications that each participant self-reported taking were recorded during the screening process. These data were used to categorize individuals by whether they used anti-platelet drugs, anti-hypertensive drugs, and OACs at the time the data were collected during screening. Everyone was assigned a "yes" or "no" for each drug category based on whether they were taking a medication that fit into one of the three classes. Data on each

participant's medical history were obtained through self-report and review of medical records. Information on height, weight, and blood pressure measurement were obtained through the ascertainment of vital signs during screening visits. Patients were classified as being hypertensive at visit if they had either a systolic blood pressure ≥ 140 or a diastolic blood pressure ≥ 90. This definition of hypertension corresponds with stage 2 hypertension according to the 2017 American College of Cardiology guidelines.[21] However, this higher cutoff was chosen given that it aligns with the definition used by the International Society of Hypertension, the National Institute for Health Care and Excellence (NICE), and the 2013 American College of Cardiology guidelines, making it more applicable internationally as well as temporally with prior research in the field of CMHs and hypertension.[22,23]

2.5 | Statistical analysis

We calculated descriptive statistics for all demographic variables (Table 1). The continuous variable of participant age was summarized by mean and standard deviation and compared between LEARN and A4 by a two-sample *t* test. Nominal categorical variables (e.g., sex, hypertension at visit), were compared via a chi-squared test. Finally, categorical variables with multiple categories were compared using analysis of variance.

The distribution of CMHs was analyzed among the combined population of A4 and LEARN (Table 2), and in each study separately (Tables 3 and 4). The proportion of those in A4 with any CMH, a deep CMH, and a lobar CMH compared to those in LEARN was evaluated with a chi-squared test. The proportions of those with different categories for given exposures were evaluated for A4 (Table 3) and LEARN (Table 4) separately and were stratified by CMH location. Again, the proportions were compared by a chi-squared test to evaluate statistical significance.

Multivariable analysis was performed using binary logistic regression tests to obtain adjusted odds ratios. While the primary univariate measure of association was a prevalence ratio, which has the advantage of ease of interpretation, the adjusted measure of association was an odds ratio given the increased statistical assumptions needed to obtain adjusted prevalence ratios. In the comparison of the odds of CMHs between A4 and LEARN in Table 2, the logistic regression analysis included age > 75, sex, OAC use, anti-platelet agent use, antihypertensive use, *APOE* ε4 status, and prevalence of lipid disorders as covariates to create a multivariable analysis. These variables were chosen as covariates given that they were statistically different in a head-to-head comparison of the two populations in Table 1. Therefore, selectively using these covariates in the model helped to use the least number of variables possible to ensure model accuracy. In Tables 2 and 3, which focused on analysis of variables as potential risk factors in A4 and LEARN, all variables that were analyzed in a univariate fashion were included in the binary logistic regression. The Durbin–Watson test was used to check the assumption that the different predictor variables are independent of each other for each model in Tables 2, 3, and 4. Based on this test, we failed to reject the null hypothesis that the errors of different predictor variables auto-correlated, providing evidence that the independence assumption was met. Finally, it was visually checked that the residual errors had a mean value near zero for each model.

All analysis was done in R version 3.6.2. Tables were created using the "tableone" package in R (https://github.com/kaz-yos/tableone).

3 | RESULTS

The demographic and exposure statistics of the cohort by A4 versus LEARN enrollment are reported in Table 1. Of the total population of 1803 individuals, the majority (1263), were amyloid eligible for the A4 study. Participants in the A4 study were older (mean [standard deviation] age of 72.05 [4.86] years vs. 70.08 [4.4] years for those in LEARN, $p < 0.001$) and more likely to have one or two *APOE* ε4 alleles (7.9% *APOE* ε4 homozygotes in A4 vs. 0.6% in LEARN and 45.3% *APOE* ε4 carriers vs. 20.7% in LEARN, $p < 0.001$). The distribution of the proportion of those speaking different languages was significantly different between the A4 population and the LEARN population ($p < 0.05$). The most prominent difference in the language category was that 1.5% of individuals in A4 spoke Japanese as a primary language, owing to A4 being a more global study with sites in Japan. Among the total population at the time of enrollment, a higher proportion of those in LEARN had been prescribed an anti-platelet agent (48.9% of those in LEARN vs. 35.3% in A4, $p < 0.001$), an anti-hypertensive (48.1% of those in LEARN vs. 33.2% in A4, $p < 0.001$), and an OAC (9.6% of those in LEARN vs. 3.1% in A4, $p < 0.001$). There was no significant difference in the distribution of race, ethnicity, sex, marital status, and the proportion of those with a hypertensive-range blood pressure at their initial clinic visit between LEARN and A4. The prevalence of cardiovascular risk factors was similar between the A4 and LEARN populations, with the exception that there was a higher prevalence of lipid disorders in A4 (36.4% in A4 vs. 29.4% in LEARN, $p = 0.005$). Despite the significant difference in the proportion of participants receiving OACs, there was a similar proportion of atrial fibrillation in the two groups (2.4% in A4 vs. 1.9% in LEARN, $p = 0.61$).

Table 2 serves as an overview of the distribution of CMHs by location in both A4 and LEARN. Both overall and after adjusting for covariates that were significantly different between A4 and LEARN, a significantly higher proportion of those in A4 (17.3%) had at least one CMH in any location compared to LEARN (2.6%, $p < 0.001$). The prevalence of having at least one CMH was 6.66 times greater among those in A4 compared to those in LEARN ($p < 0.001$) and the odds were 6.85 times higher after adjusting for covariates ($p < 0.001$). The prominence of CMHs in A4 compared to LEARN persisted when dividing CMHs by brain region. That is, a higher proportion of participants in A4 had CMHs in deep brain regions (5.0% vs. 1.9% in LEARN, $p = 0.003$) and in lobar regions (13.9% vs. 1.1% in LEARN, $p < 0.001$) compared to those in the LEARN study. The unadjusted strength of association, as measured by the prevalence ratios of those in A4 compared to LEARN, was greater for CMHs located in lobar brain regions, compared to deep brain regions (non-overlapping confidence intervals). However, after

TABLE 1 Study population.

	Total population	A4	LEARN	*p* value
n	1803	1263	540	
Sex = female (%)	1070 (59.3)	740 (58.6)	330 (61.1)	0.34
AGE (mean [SD])	71.46 (4.8)	72.05 (4.86)	70.08 (4.4)	<0.001
Ethnicity (%)				0.76
Hispanic or Latino	55 (3.1)	37 (2.9)	18 (3.3)	
Not Hispanic or Latino	1731 (96.0)	1213 (96.0)	518 (95.9)	
Unknown or not reported	17 (0.9)	13 (1.0)	4 (0.7)	
Race (%)				0.37
American Indian or Alaskan Native	20 (1.1)	11 (0.9)	9 (1.7)	
Asian	39 (2.2)	27 (2.1)	12 (2.2)	
Black or African American	49 (2.7)	34 (2.7)	15 (2.8)	
Unknown or not reported	9 (0.5)	8 (0.6)	1 (0.2)	
White	1686 (93.5)	1183 (93.7)	503 (93.1)	
Language (%)				0.016
English	1777 (98.6)	1239 (98.1)	538 (99.6)	
Japanese	19 (1.1)	19 (1.5)	0 (0.0)	
Spanish	7 (0.4)	5 (0.4)	2 (0.4)	
Marital status (%)				0.13
Divorced	246 (13.6)	179 (14.2)	67 (12.4)	
Married	1292 (71.7)	903 (71.5)	389 (72.0)	
Never married	74 (4.1)	45 (3.6)	29 (5.4)	
Unknown/other	23 (1.3)	20 (1.6)	3 (0.6)	
Widowed	168 (9.3)	116 (9.2)	52 (9.6)	
Medication usage = yes (%)				
Anti-platelet usage[a]	710 (39.4)	446 (35.3)	264 (48.9)	<0.001
Anti-hypertensive usage[b]	679 (37.7)	419 (33.2)	260 (48.1)	<0.001
Oral anti-coagulant usage[c]	91 (5.0)	39 (3.1)	52 (9.6)	<0.001
Hypertension at visit[d]	673 (37.6)	486 (38.5)	187 (34.6)	0.14
APOE ε4 allele status:				<0.001
2 *APOE* ε4 alleles	103 (5.7)	100 (7.9)	3 (0.6)	
1 *APOE* ε4 allele	684 (37.9)	572 (45.3)	112 (20.7)	
No *APOE* ε4 alleles	1016 (56.4)	591 (46.8)	425 (78.7)	
Cardiovascular risk factors (%)				
History of hypertension	794 (44.0)	545 (43.2)	249 (46.1)	0.27
History of a lipid disorder[e]	619 (34.3)	460 (36.4)	159 (29.4)	0.005
Currently obese******	451 (25.0)	308 (24.4)	143 (26.5)	0.38
History of diabetes mellitus	118 (6.5)	89 (7.0)	29 (5.4)	0.22
Prevalence of atrial fibrillation	40 (2.2)	30 (2.4)	10 (1.9)	0.61

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study; ACE, angiotensin-converting enzyme; ADP, adenosine diphosphate; *APOE*, apolipoprotein E; ARB, angiotensin receptor blocker; BP, blood pressure; LEARN, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration study; SD, standard deviation.

[a]Anti-platelet usage is defined as using an ADP receptor blocker at any dose or aspirin at a dose greater than or equal to 81 mg at baseline.

[b]Use of an anti-hypertensive medication is defined as the use of a diuretic, ARB, ACE inhibitor, calcium channel blocker, or beta-blocker at baseline.

[c]Oral anti-coagulant usage is defined as the use of warfarin, a direct thrombin inhibitor, or a factor Xa inhibitor.

[d]Hypertension at visit was defined as a systolic BP ≥ 140 or a diastolic BP ≥ 90.

[e]History of a lipid disorder was defined as anyone with any derangements in cholesterol; therefore, those with only hypertriglyceridemia were excluded.

TABLE 2 Distribution of cerebral microhemorrhages.

	Any CMH					Deep CMH				Lobar CMH				Combined Lobar and Deep CMH				
Study	No	Yes	Prevalence ratio	*p*	Adjusted* odds ratio	*p*	No	Yes	Prevalence ratio	Adjusted odds ratio	*p*	No	Yes	Prevalence ratio	Adjusted odds ratio	*p*	No	Yes	Prevalence ratio	Adjusted odds ratio	*p*
LEARN (%)	526 (97.4)	14 (2.6)	6.66 (3.92, 11.32)	<0.001	6.85 (4.01, 12.64)	<0.001	530 (98.1)	10 (1.9)	2.69 (1.39, 5.21)	3.01 (1.53, 6.53)	0	534 (98.9)	6 (1.1)	12.54 (5.59, 28.12)	11.36 (5.36, 29.35)	<0.001	538 (99.6)	2 (0.4)	4.49 (1.06, 19.08)	3.51 (0.94, 22.90)	0.1
A4 (%)	1045 (82.7)	218 (17.3)					1200 (95.0)	63 (5.0)				1087 (86.1)	176 (13.9)				1242 (98.3)	21 (1.7)			0

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study; *APOE*, apolipoprotein E; CMH, cerebral microhemorrhages; LEARN, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration study.
*The logistic regression analysis included age > 75, sex, OAC use, anti-platelet agent use, anti-hypertensive use, *APOE ε4* status, and prevalence of lipid disorders as covariates to create a multivariable analysis.

adjusting for covariates, there was no significant difference between the strength of association (odds ratio) for CMHs located in lobar versus deep brain regions.

Table 3 focuses on the A4 population and shows the relationships between different exposure variables and the presence of CMHs, subdivided by location, as response variables. Male sex, age > 75 years, and *APOE ε4* homozygosity were exposures that were significantly associated with a higher prevalence of CMHs. All four of these significant variables were only significantly associated with lobar, and not deep, CMHs when subdividing by location in the multivariable model. Antiplatelet or anti-coagulant usage were not associated with an increased prevalence of CMHs in either brain location or overall. Among the various cardiovascular risk factors, the history of a lipid disorder was significantly associated with overall and lobar CMHs. Other cardiovascular risk factors, other than the history of a lipid disorder, were not associated with the prevalence of CMHs in the A4 population.

Table 4 is the LEARN counterpart to Table 3 in that it shows the relationship between different exposure variables with the prevalence of total CMHs, and CMHs subdivided by location, as dependent variables. Among the variables studied, none were associated with an increased or decreased prevalence of overall CMHs in the LEARN cohort. When subdividing by location, only OAC usage was significantly associated with an increased prevalence of CMHs; however, this association was not seen when correcting for covariates in the multivariable model.

4 | DISCUSSION

The results replicated the findings that the A4 cohort had a significantly higher prevalence of CMHs compared to the LEARN cohort published in a previous study.[16] This work expands upon these prior results by showing that the association between enrollment in the A4 study (i.e., having elevated brain amyloid) and CMH prevalence persists when looking at CMHs by different locations in the brain. While not statistically significant, the magnitude of the association was greater between elevated brain amyloid and lobar CMH prevalence than elevated brain amyloid and deep CMH prevalence (Table 2). The finding of the strong association between elevated brain Aβ, as represented by enrollment in A4, and a higher prevalence of lobar CMHs was expected as prior studies have demonstrated positive correlations between brain Aβ and lobar CMH burden.[8,24,25] However, these same studies did not demonstrate a relationship between brain Aβ and deep CMHs. This begs the question on the results here demonstrating such a strong relationship between elevated brain Aβ and deep/subcortical CMHs (Table 2). A study has shown that infratentorial CMHs were present in 18% of individuals in a cohort of people with presumed or definite CAA.[26] In the same study, the presence of supratentorial CMHs was associated with an increased prevalence of infratentorial CMHs, suggestive that a very high amyloid burden could be associated with CMHs in all brain regions, not just lobar/supratentorial CMHs. Thus, a possible difference between the relative amyloid burdens of the participants in the A4 study and other studies could explain the discrepancy. Future work directly comparing the Centiloid/SUVR values to measure amyloid

TABLE 3 Distribution of cerebral microhemorrhages in A4 participants.

	Any CMH						Deep CMH						Lobar CMH					
A4 study	No	Yes	Prevalence ratio	*p*	Adjusted odds ratio	*p*	No	Yes	Prevalence ratio	*p*	Adjusted odds ratio	*p*	No	Yes	Prevalence Ratio	*p*	Adjusted odds ratio	*p*
n (%)	1045 (82.7)	218 (17.3)					1200 (95.0)	63 (5.0)					1087 (86.1)	176 (13.9)				
Sex (%)																		
Female	632 (85.4)	108 (14.6)	1.44 (1.13, 1.83)	0.003	1.47 (1.09, 1.99)	0.012	710 (95.9)	30 (4.1)	1.56 (0.96, 2.52)	0.07	1.47 (0.87, 2.48)	0.15	654 (88.4)	86 (11.6)	1.48 (1.13, 1.95)	0.005	1.52 (1.09, 2.12)	0.13
Male	413 (79.0)	110 (21.0)					490 (93.7)	33 (6.3)					433 (82.8)	90 (17.2)				
Age (%)																		
<75	786 (84.8)	141 (15.2)	1.51 (1.18, 1.94)	0.001	1.67 (1.20, 2.31)	0.002	889 (95.9)	38 (4.1)	1.82 (1.11, 2.96)	0.016	1.72 (0.99, 2.94)	0.051	813 (87.7)	114 (12.3)	1.5 (1.13, 1.99)	0.005	1.67 (1.17, 2.38)	0.005
>75	259 (77.1)	77 (22.9)					311 (92.6)	25 (7.4)					274 (81.5)	62 (18.5)				
Anti-platelet use(%)																		
No	677 (82.9)	140 (17.1)	1.02 (0.79, 1.31)	0.87	0.90 (0.65, 1.24)	0.52	778 (95.2)	39 (4.8)	1.13 (0.69, 1.85)	0.64	1.03 (0.59, 1.77)	0.911	701 (85.8)	116 (14.2)	0.95 (0.71, 1.27)	0.71	0.82 (0.60, 1.16)	0.26
Yes	368 (82.5)	78 (17.5)					422 (94.6)	24 (5.4)					386 (86.5)	60 (13.5)				
Anti-hypertensive use(%)																		
No	702 (83.2)	142 (16.8)	1.08 (0.84, 1.39)	0.56	0.80 (0.51, 1.23)	0.3	805 (95.4)	39 (4.6)	1.24 (0.76, 2.03)	0.39	0.87 (0.43, 1.80)	0.7	729 (86.4)	115 (13.6)	1.07 (0.80, 1.42)	0.65	0.95 (0.59, 1.55)	0.83
Yes	343 (81.9)	76 (18.1)					395 (94.3)	24 (5.7)					358 (85.4)	61 (14.6)				
Oral anti-coagulant use (%)																		
No	1013 (82.8)	211 (17.2)	1.04 (0.53, 2.06)	0.91	0.88 (0.33, 2.11)	0.79	1163 (95.0)	61 (5.0)	1.03 (0.26, 4.06)	0.97	1.06 (0.15, 4.15)	0.94	1053 (86.0)	171 (14.0)	0.92 (0.40, 2.10)	0.84	0.65 (0.20, 1.74)	0.43
Yes	32 (82.1)	7 (17.9)					37 (94.9)	2 (5.1)					34 (87.2)	5 (12.8)				
APOE ε4 allele status(%)																		
2 *APOE* ε4 alleles	72 (72.0)	28 (28.0)	1.65 (1.15, 2.38)	0.008	2.10 (1.26, 3.42)	0.004	94 (94.0)	6 (6.0)	1.01 (0.44, 2.35)	0.98	1.12 (0.41, 2.59)	0.81	75 (75.0)	25 (25.0)	1.97 (1.32, 2.94)	0.001	2.49 (1.45, 4.17)	0.0007
1 *APOE* ε4 allele	482 (84.3)	90 (15.7)	0.93(0.72, 1.21)	0.58	0.94 (0.68, 1.29)	0.71	550 (96.2)	22 (3.8)	0.65 (0.39, 1.09)	0.1	0.66 (0.38, 1.15)	0.15	496 (86.7)	76 (13.3)	1.05 (0.78, 1.41)	0.76	1.08 (0.76, 1.53)	0.68
No *APOE* ε4 allele	491 (83.1)	100 (16.9)	ref		ref		556 (94.1)	35 (5.9)	ref		ref		516 (87.3)	75 (12.7)	ref		ref	

(Continues)

TABLE 3 (Continued)

	Any CMH						Deep CMH						Lobar CMH					
A4 study	No	Yes	Prevalence ratio	*p*	Adjusted odds ratio	*p*	No	Yes	Prevalence ratio	*p*	Adjusted odds ratio	*p*	No	Yes	Prevalence Ratio	*p*	Adjusted odds ratio	*p*
Hypertensive at visit (%)																		
No	649 (83.5)	128 (16.5)	1.12 (0.88, 1.44)	0.35	1.05 (0.77, 1.43)	0.75	742 (95.5)	35 (4.5)	1.28 (0.79, 2.07)	0.32	1.17 (0.74, 3.08)	0.56	672 (86.5)	105 (13.5)	1.08 (0.82, 1.43)	0.58	1.02 (0.72, 1.42)	0.93
Yes	396 (81.5)	90 (18.5)					458 (94.2)	28 (5.8)					415 (85.4)	71 (14.6)				
History of hypertension (%)																		
No	606 (84.4)	112 (15.6)	1.25 (0.98, 1.59)	0.072	1.40 (0.92, 2.13)	0.12	688 (95.8)	30 (4.2)	1.45 (0.90, 2.35)	0.13	1.54 (0.74, 3.08)	0.24	623 (86.8)	95 (13.2)	1.12 (0.85, 1.48)	0.41	1.11 (0.69, 1.77)	0.66
Yes	439 (80.6)	106 (19.4)					512 (93.9)	33 (6.1)					464 (85.1)	81 (14.9)				
History of diabetes																		
No	970 (82.6)	204 (17.4)	0.91 (0.55, 1.49)	0.69	0.74 (0.38, 1.33)	0.33	1114 (94.9)	60 (5.1)	0.66 (0.21, 2.06)	0.47	0.52 (0.12, 1.51)	0.29	1009 (85.9)	165 (14.1)	0.88 (0.50, 1.56)	0.66	0.76 (0.36, 1.44)	0.42
Yes	75 (84.3)	14 (15.7)					86 (96.6)	3 (3.4)					78 (87.6)	11 (12.4)				
Currently obese																		
No	792 (82.9)	163 (17.1)	1.05 (0.79, 1.38)	0.75	1.09 (0.76, 1.54)	0.65	906 (94.9)	49 (5.1)	0.89 (0.50, 1.58)	0.68	0.87 (0.45, 1.60)	0.67	822 (86.1)	133 (13.9)	1.00 (0.73, 1.38)	0.99	1.07 (0.72, 1.58)	0.72
Yes	253 (82.1)	55 (17.9)					294 (95.5)	14 (4.5)					265 (86.0)	43 (14.0)				
History of a lipid disorder																		
No	679 (84.6)	124 (15.4)	1.32 (1.04, 1.69)	0.024	1.41 (1.04, 1.92)	0.03	763 (95.0)	40 (5.0)	1.00 (0.61, 1.65)	0.99	1.00 (0.57, 1.70)	0.99	705 (87.8)	98 (12.2)	1.39 (1.06, 1.83)	0.019	1.5 (1.07, 2.09)	0.017
Yes	366 (79.6)	94 (20.4)					437 (95.0)	23 (5.0)					382 (83.0)	78 (17.0)				

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease study; *APOE*, apolipoprotein E; CMH, cerebral microhemorrhages.

TABLE 4 Distribution of cerebral microhemorrhages in LEARN participants.

LEARN study	Any CMH						Deep CMH						Lobar CMH					
	No	Yes	Prevalence ratio	*p*	Adjusted* odds ratio	*p*	No	Yes	Prevalence ratio	*p*	Adjusted odds ratio	*p*	No	Yes	Prevalence ratio	*p*	Adjusted odds ratio	*p*
n (%)	526 (97.4)	14 (2.6)					530 (98.1)	10 (1.9)					534 (98.9)	6 (1.1)				
Sex (%)																		
Female	320 (97.0)	10 (3.0)	0.63 (0.20, 2.0)	0.42	0.54 (0.13, 1.80)	0.35	322 (97.6)	8 (2.4)	0.39 (0.08, 1.83)	0.22	2.42 (0.03, 1.18)	0.12	328 (99.4)	2 (0.6)	3.14 (0.59, 17.0)	0.21	3.07 (0.49, 2.48)	0.24
Male	206 (98.1)	4 (1.9)					208 (99.0)	2 (1.0)					206 (98.1)	4 (1.9)				
Age (%)																		
Less than or equal to 75 years	450 (97.4)	12 (2.6)	0.99 (0.23, 4.33)	0.99	0.95 (0.13, 4.30)	0.95	454 (98.3)	8 (1.7)	1.48 (0.32, 6.84)	0.61	1.23 (0.15, 6.65)	0.83	456 (98.7)	6 (1.3)	0 (0, n/a)	0.31	0 (0, n/a)	0.99
Greater than 75 years	76 (97.4)	2 (2.6)					76 (97.4)	2 (2.6)					78 (100)	0 (0)				
Anti-platelet use(%)																		
No	271 (98.2)	5 (1.8)	1.88 (0.64, 5.54)	0.24	2.35 (0.73, 8.24)	0.16	274 (99.3)	2 (0.7)	4.18 (0.90, 19.5)	0.06	5.07 (1.12, 3.58)	0.053	273 (98.9)	3 (1.1)	1.05 (0.21, 5.13)	0.96	0.85 (0.12, 5.46)	0.87
Yes	255 (96.6)	9 (3.4)					256 (97.0)	8 (3.0)					261 (98.9)	3 (1.1)				
Anti-hypertensive use(%)																		
No	270 (96.4)	10 (3.6)	0.43 (0.14, 1.36)	0.14	0.31 (0.06, 1.42)	0.15	273 (97.5)	7 (2.5)	0.46 (0.12, 1.77)	0.34	2.44 (0.04, 1.45)	0.13	275 (98.2)	5 (1.8)	0.22 (0.03, 1.83)	0.22	1.35 (0.01, 1.62)	0.15
Yes	256 (98.5)	4 (1.5)					257 (98.8)	3 (1.2)					259 (99.6)	1 (0.4)				
Oral anti-coagulant use (%)																		
No	477 (97.7)	11 (2.3)	2.56 (0.74, 8.88)	0.13	2.62 (0.51, 10.2)	0.2	481 (98.6)	7 (1.4)	4.02 (1.07, 15.09)	0.03	3.65 (0.63, 1.71)	0.11	483 (99.0)	5 (1.0)	1.88 (0.22, 15.76)	0.56	1.72 (0.07, 14.6)	0.67
Yes	49 (94.2)	3 (5.8)					49 (94.2)	3 (5.8)					51 (98.1)	1 (1.9)				
APOE ε4 allele status (%)																		
2 *APOE* ε4 alleles	3 (100)	0 (0)	0.00 (0.00, n/a)	1	0 (0.00, n/a)	1	3 (100)	0 (0)	0.00 (0.00, n/a)	1	0 (0.00, n/a)	1	3 (100)	0 (0)	0 (0, n/a)	1	0 (0, n/a)	1
1 *APOE* ε4 allele	109 (97.3)	3 (2.7)	1.03 (0.29, 3.65)	0.96	1.17 (0.25, 4.20)	0.82	110 (98.2)	2 (1.8)	0.95 (0.20, 4.41)	0.95	1.34 (0.18, 6.62)	0.74	110 (98.2)	2 (1.8)	1.90 (0.35, 10.23)	0.45	1.50 (0.19, 8.85)	0.67

(Continues)

TABLE 4 (Continued)

	Any CMH						Deep CMH						Lobar CMH					
LEARN study	No	Yes	Prevalence ratio	*p*	Adjusted* odds ratio	*p*	No	Yes	Prevalence ratio	*p*	Adjusted odds ratio	*p*	No	Yes	Prevalence ratio	*p*	Adjusted odds ratio	*p*
No *APOE* ε4 alleles	414 (97.4)	11 (2.6)	ref		ref		417 (98.1)	8 (1.9)	ref		ref		421 (99.1)	4 (0.9)	ref		ref	
Hypertensive at visit (%)																		
No	346 (98.0)	7 (2.0)	1.89 (0.67, 5.30)	0.22	1.92 (0.62, 5.88)	0.25	348 (98.6)	5 (1.4)	1.89 (0.55, 6.44)	0.3	1.76 (0.45, 6.75)	0.4	349 (98.9)	4 (1.1)	0.94 (0.17, 5.11)	0.95	1.05 (0.13, 6.10)	0.96
Yes	180 (96.3)	7 (3.7)					182 (97.3)	5 (2.7)					185 (98.9)	2 (1.1)				
History of hypertension (%)																		
No	282 (96.9)	9 (3.1)	0.65 (0.22, 1.9)	0.43	1.04 (0.21, 4.62)	0.96	285 (97.9)	6 (2.1)	0.78 (0.22, 2.73)	0.7	1.20 (0.19, 6.79)	0.84	287 (98.6)	4 (1.4)	0.58 (0.11, 3.16)	0.53	1.29 (0.10, 1.27)	0.84
Yes	244 (98.0)	5 (2.0)					245 (98.4)	4 (1.6)					247 (99.2)	2 (0.8)				
History of diabetes																		
No	498 (97.5)	13 (2.5)	1.35 (0.18, 10.0)	0.77	1.23 (0.06, 8.79)	0.86	502 (98.2)	9 (1.8)	1.96 (0.26, 14.93)	0.51	1.85 (0.08, 1.55)	0.62	506 (99.0)	5 (1.0)	3.52 (0.43, 29.2)	0.22	1.63 (0.06, 1.79)	0.72
Yes	28 (96.6)	1 (3.4)					28 (96.6)	1 (3.4)					28 (96.6)	1 (3.4)				
Currently obese																		
No	388 (97.7)	9 (2.3)	1.54 (0.53, 4.53)	0.43	1.83 (0.48, 6.20)	0.35	391 (98.4)	6 (1.6)	1.85 (0.53, 6.46)	0.33	2.23 (0.46, 9.85)	0.29	394 (99.2)	3 (0.8)	2.78 (0.57, 13.60)	0.19	3.70 (0.50, 2.49)	0.17
Yes	138 (96.5)	5 (2.5)					139 (97.2)	4 (2.8)					140 (97.9)	3 (2.1)				
History of a lipid disorder																		
No	369 (96.9)	12 (3.1)	0.40 (0.09, 1.76)	0.21	4.70 (0.07, 1.85)	0.34	373 (97.9)	8 (2.1)	0.60 (0.13, 2.79)	0.51	7.26 (0.10, 3.32)	0.71	376 (98.7)	5 (1.3)	0.48 (0.05, 4.07)	0.49	0.49 (0.02, 3.46)	0.54
Yes	157 (98.7)	2 (1.3)					157 (98.7)	2 (1.3)					158 (99.4)	1 (0.6)				

Abbreviations: *APOE*, apolipoprotein E; CMH, cerebral microhemorrhages; LEARN, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration study.

burden between different studies could help elucidate the possibility of a dose–response relationship between cerebral beta-amyloidosis and deep CMHs. This work focused on the distribution of CMH prevalence in relation to OAC use, anti-platelet use, and cardiovascular risk factors, while future work in our group will examine brain amyloid within the A4 cohort as a predictor variable in a longitudinal study.

The findings among the A4 group corroborate prior findings that *APOE* ε4 homozygosity, older age, and male sex were associated with increased odds of CMHs in the A4 population.[16] The results expand upon the prior work in the A4 cohort by showing that the associations involving *APOE* ε4 homozygosity are driven by the subgroup with CMHs located in lobar brain regions. Moreover, our results corroborate findings from the Mayo Clinic Study of Aging, which demonstrated an association between *APOE* ε4 carrier status and incident CMHs in lobar, but not deep, brain regions.[27] The relationship between *APOE* ε4 homozygosity and lobar CMHs was expected, and the lack of a relationship between *APOE* ε4 homozygosity and deep CMHs exemplifies the stronger relationship between Aβ and CMHs in lobar brain regions compared to deep regions. It should be noted that the smaller percentage of participants aged > 75 (14% in LEARN vs. 27% in A4) and the small number of ε4/ε4 individuals in LEARN ($n = 3$) may have reduced the sensitivity to detect an effect of these well-known risk factors for CMHs in LEARN (in contrast to A4).

The finding that a history of a lipid disorder was associated with both overall and lobar CMHs in the A4 group but not in the LEARN group also expands on prior work. Prior work to elucidate the relationship between cholesterol levels and CMHs has been somewhat mixed. In the large cohort of the Rotterdam scan study, serum cholesterol levels were not associated with incident CMHs, and they were inversely associated with the incidence of deep CMHs.[28] The CIRCLE study also found that low low-density lipoprotein cholesterol levels were associated with an increased risk of CMHs.[29] In a cohort of 232 young and middle-aged patients in China, dyslipidemia was independently associated with the prevalence of lobar CMH.[30] The observed relationship between high cholesterol levels and an increased prevalence of CMHs in A4 is interesting and not consistent with all prior findings, potentially identifying those with high cerebral amyloid as a unique group. Furthermore, the finding that medical history of lipid abnormalities in the A4 group with elevated brain amyloid but not in the LEARN group suggests that abnormal lipid metabolism may compound the risk of CMHs associated with elevated cerebral amyloid. Prior work from an Australian group demonstrated that the presence of midlife dyslipidemia and an *APOE* ε4 allele was associated with greater late-life cerebral amyloid deposition than the presence of an *APOE* ε4 allele alone.[31] This finding suggests a possible etiology for the observed association between lipid disorders and lobar CMHs seen in this study in that abnormal lipid metabolism may augment cerebral amyloid deposition in those with the *APOE* ε4 allele. A link between lipid metabolism and brain amyloid deposition would explain why a history of lipid disorders was not associated with CMHs in the LEARN cohort, as those with elevated brain amyloid were excluded from LEARN. Furthermore, a possible link between dyslipidemia and elevated brain amyloid would explain the higher prevalence of lipid disorders in the A4 cohort compared to the LEARN cohort despite similar proportions of other cardiovascular risk factors (Table 1).

There were several other differences between the results observed in the A4 group and the LEARN group. We found male sex and older age to be associated with CMH prevalence only in the A4 group. These are well-known risk factors for CMHs; however, they were not observed in the LEARN group. When stratified based on brain Aβ level our results suggest that elevated brain Aβ may be an effect modifier of these risk factors and may be an intermediary through which they exert their effect on CMH development.

There are several important negative findings in our results. The lack of association between anti-platelets and CMHs in either group is one of the most important negative findings. A prior meta-analysis observed an association between anti-platelet usage and CMHs only in lobar brain regions, but not in deep brain regions.[32] Our study does not demonstrate an association between anti-platelet usage and lobar CMHs in cognitively asymptomatic adults, a unique exclusion criterion that was not present in many of the studies included in the meta-analysis. This finding suggests that anti-platelet use may not be a risk factor for CMH development in the preclinical AD population.

The other important negative finding in this study is the absence of an association between OAC usage and total CMH prevalence in either the A4 or LEARN groups. This finding is important because recent research shows that atrial fibrillation is related to dementia independent of strokes.[33] This finding raises the question of whether OACs, which are commonly prescribed for those with atrial fibrillation, could contribute to dementia through a pathway such as CMHs. Our finding is reassuring against this possibility. However, there was an observed association between OAC usage and the prevalence of deep CMHs in the LEARN group unadjusted analysis, but there was no association when adjusting for covariates (Table 4). This finding is interesting and informs next steps to evaluate if those with predominantly hypertensive arteriolosclerosis-mediated small vessel disease could have a predisposition to developing CMHs in deep brain regions due to OAC use. The lack of an association between OAC usage and deep CMHs in the A4 group is interesting, and a possible explanation could be that some deep CMHs in the A4 group are mediated by very high amyloid burden, thus drowning out the effect of CMHs. To date, it is uncertain if more conservative anti-coagulant strategies would be beneficial in those with CMHs. Despite the association between OAC usage and CMH prevalence in the LEARN group, the lack of association between OAC usage and overall CMH prevalence is still reassuring against the need for more conservative anti-coagulation strategy, though a longitudinal study would provide more clinically informative evidence. In addition, it should be acknowledged that there were very few individuals on OACs in A4 (3.1%). Though the generalizability of this finding to other populations may be limited. As in this study history of hypertension was not significantly associated with deep CMHs, although known risk factor for the development of deep CMHs, which is a known risk factor for the development of deep CMHs. It is possible that the history of hypertension did not confer as much of an increased risk of CMHs in these relatively healthy populations compared to others. There was still a higher prevalence of deep CMHs among those with

hypertension in both cohorts, though not to a statistically significant extent.

There were several limitations to this study that should be considered, including the cross-sectional nature of our investigation and lack of quantification of medication dosage or duration spent taking the medication. Finally, we did not correct for indication for medication prescription, although this should be somewhat offset by the fact that medically unstable participants were excluded from A4 and LEARN enrollment. The number of participants in our study was the major strength of the study. To our knowledge, this is the largest study that examines factors associated with CMH prevalence.

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CONSENT STATEMENT

All studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline, and local regulatory requirements. The study protocols were approved by an independent ethics committee or institutional review board at each study site. All patients provided written consent before the start of the study. All studies were registered at ClinicalTrials.gov: A4 Study (NCT02008357) and LEARN Study (NCT02488720).

CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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