Stroke

CLINICAL AND POPULATION SCIENCES

Cerebral Microbleeds

Relationship to Antithrombotic Medications

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BACKGROUND AND PURPOSE: Cerebral microbleeds (CMBs) are represented by small areas of hemosiderin deposition, detected on brain magnetic resonance imaging (MRI), and found in ≈23% of the cognitively normal population over age of 60 years. CMBs predict risk of hemorrhagic and ischemic stroke. They correlate with increased cardiovascular mortality. In this article, we sought to determine in a population-based study whether antithrombotic medications correlate with CMBs and, if present, whether the association was direct or mediated by another variable.

METHODS: The study consisted of 1253 participants from the population-based Mayo Clinic Study of Aging who underwent T2* gradient-recalled echo magnetic resonance imaging. We tested the relationship between antithrombotic medications and CMB presence and location, using multivariable logistic-regression models. Ordinal logistic models tested the relationship between antithrombotics and CMB frequency. Using structural equation models, we assessed the effect of antithrombotic medications on presence/absence of CMBs and count of CMBs in the CMB-positive group, after considering the effects of age, sex, vascular risk factors, amyloid load by positron emission tomography, and apoE.

RESULTS: Two hundred ninety-five participants (26.3%) had CMBs. Among 678 participants taking only antiplatelet medications, 185 (27.3%) had CMBs. Among 95 participants taking only an anticoagulant, 43 (45.3%) had CMBs. Among 44 participants taking an anticoagulant and antiplatelet therapy, 21 (48.8%) had CMBs. Anticoagulants correlated with the presence and frequency of CMBs, whereas antiplatelet agents were not. Structural equation models showed that predictors for presence/absence of CMBs included older age at magnetic resonance imaging, male sex, and anticoagulant use. Predictors of CMB count in the CMB-positive group were male sex and amyloid load.

CONCLUSIONS: Anticoagulant use correlated with presence of CMBs in the general population. Amyloid positron emission tomography correlated with the count of CMBs in the CMB-positive group.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: anticoagulants ■ hemorrhage ■ ischemic stroke ■ magnetic resonance imaging ■ positron emission tomography

Cerebral microbleeds (CMBs) are a risk factor for intracerebral hemorrhage (ICH)[1,2] and are associated with increased risk of dementia[3] and mortality.[4] The prevalence of CMBs increases significantly with age, approaching forty percent by the age of 80 years.[5] Established risk factors for CMBs include age, male sex, and hypertension.[5–7] Antithrombotic medications have also been associated with increased risk of developing CMBs,[8,9] but few population-based studies have evaluated this association, and these studies have not included amyloid positron emission tomography (PET). Recently, we demonstrated that amyloid burden measured by PET, particularly in the occipital region, was associated with CMB risk.[5] The objectives of this study were to determine

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Nonstandard Abbreviations and Acronyms

CMBs	cerebral microbleeds
DOACs	direct oral anticoagulants
GRE	gradient recall echo
ICH	intracranial hemorrhage
PET	positron emission tomography
PiB	Pittsburgh Compound B
SEMs	structural equation models
SUVR	standardized uptake value ratio

in a population-based cohort (1) whether antithrombotic medications are associated with CMBs, and if so, (2) whether such association was direct and, therefore, possibly causal, or mediated by another variable.

METHODS

Data from the Mayo Clinic Study of Aging including data from this study are available upon request.

Study Participants

Participants were enrolled in the Mayo Clinic Study of Aging, a longitudinal, population-based study of cognitive decline among Olmsted County, MN, residents. All residents were enumerated using the Rochester Epidemiology Project medical records–linkage system and randomly selected in an age- and sex-stratified design for enrollment in the study.[10] The full design of the Mayo Clinic Study of Aging has been previously published.[11]

Mayo Clinic Study of Aging participants without contraindications were invited to undergo brain magnetic resonance imaging (MRI) imaging and PET imaging. In October 2011, T2* gradient recall echo (GRE) sequences were added to the MRI neuroimaging protocol. Participants imaged with T2* GRE sequences between October 2011 and December 2017 were included in this study.

Clinical Data Retrieval

Clinical data, including history of diabetes, smoking, hypertension, history of stroke, and dyslipidemia, were abstracted by a nurse from the detailed medical records included in the Rochester Epidemiology Project medical records–linkage system.[10] Criteria for atrial fibrillation were based on physician diagnosis, electrocardiographic evidence of atrial fibrillation, or treatment for atrial fibrillation using the medical records–linkage system from the Rochester Epidemiology Project and abstracted by trained research nurses. Trained study coordinators ascertained current medications and the length of use at each clinical visit.

Considered antiplatelet agents included aspirin, clopidogrel, ticagrelor, or prasugrel. Antiplatelet use was characterized as any of the above medications, ≥3× per week. Anticogulants included warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. Because of a lower number of participants on direct oral anticoagulants (5 on direct oral anticoagulants [DOACs] with CMBs compared with 7 on DOACs without CMBs), we combined warfarin and the direct oral anticoagulants into an anticoagulation category. Participants on both anticoagulant medications and antiplatelet medications were included in both groups for analysis.

MRI Examination and Identification of CMBs

All images were obtained using 3T MRI scanners. The complete details of the acquisitions were previously published.[12] A T2* GRE (repetition time/echo time=200/20 ms; flip angle=12°; in-plane matrix=256×224; phase field of view=1.00; slice thickness=3.3 mm; acquisition time, 5 minutes). On the MRI, CMBs are defined according to consensus criteria.[3] The full details of CMB acquisition have been previously published.[5] Briefly, CMBs were identified by trained image analysts and then confirmed by a vascular neurologist or radiologist experienced in interpreting the T2* GRE images. The interrater agreement was 87%, corresponding to good agreement (κ, 0.68), and the intrarater reliability based on blinded reading on 2 separate occasions was excellent (κ statistic, 0.86).

CMBs were classified as lobar with or without cerebellar CMBs and deep/infratentorial CMBs with or without cerebellar CMBs. Cerebellar-only microbleeds were categorized as lobar if they were in the cerebellar cortex or vermis or deep if in the cerebellar white matter.[13]

11C-Pittsburgh Compound B PET Acquisition

Amyloid PET imaging was completed with 11C-Pittsburgh Compound B (PiB). PET images were acquired with a PET/computed tomography operating in 3-dimensional mode (DRX, GE Healthcare, Waukesha, WI). The details of PET acquisition were previously published.[14,15] Attenuation-corrected PiB PET images were processed using our in-house, fully automated pipeline.[16] This includes coregistration of each participant's structural MRI to their PiB PET image, spatial normalization to template space, and smoothing. Regions of interest are propagated from an MRI template to be used in PiB PET analyses. Gray- and white-matter sharpening was applied, during which voxels with a higher likelihood of being cerebral spinal fluid than either gray or white matter were excluded from the regions of interest statistics.

A global cortical PiB PET standardized uptake value ratio (SUVR) was calculated as the voxel size-weighted median uptake in the precuneus, anterior and posterior cingulate, prefrontal, orbitofrontal, parietal, and temporal regions of interest after normalization to the uptake in the cerebellar crus gray matter.[17] We also calculated an occipital SUVR normalized to the cerebellar crus gray matter.

Patient Consents

The Mayo Clinic Study of Aging was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Written informed consent was obtained from all participants before they joined the study.

Statistical Analysis

Demographic and clinical characteristics of the participants were summarized using means and SDs for continuous

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variables and counts and percentages for categorical variables; groups were compared using the *t* test or χ^2 test. Additional testing was adjusted for age and sex. The tests for continuous variables were performed with ANCOVA models, and categorical variables were assessed with logistic-regression models. The distributions of the continuous variables were examined for approximate symmetry and normality using plots; PiB SUVR was subsequently log-transformed for statistical tests to reduce a positive skew. For PiB SUVR, we reported means and SDs on the original scale and *P* values for tests using the log transformation. The participants were first classified in a binary fashion based on presence of CMB (CMB present/absent) by location (any CMB, lobar only, deep only) and then into 4 categorical CMB groups based on number of CMBs (0, 1, 2–4, 5+) to determine an association between increasing frequency of CMBs and β-amyloid burden. Multivariable logistic models were developed to test the relationship between CMBs, antithrombotic medications, and β-amyloid burden by location. Multivariable ordinal logistic models were used to test the relationship between β-amyloid burden and antithrombotics with increasing CMB frequency. Because of the low frequency of individuals with multiple deep CMBs, the ordinal regression model for deep CMBs was split into 3 groups: none, 1, 2+. Potential covariates in these models included age, sex, hypertension, APOE4 carrier status, diabetes, dyslipidemia, and smoking (ever/never), but only those covariates significant at $P<0.05$ were retained in the final models. For each model, we report coefficients and their associated SEs, odds ratios or common odds ratios and 95% CIs, and *P* values. We included results for the intercept terms to allow expected probabilities to be calculated if desired. Brant tests were used to assess the proportional odds assumptions in the ordinal logistic regressions. If the test was significant, then a partial proportional odds model allowing for nonproportional odds was used.

We fit structural equations models (SEMs) to predict CMBs. Amyloid SUVR was log-transformed to better meet modeling assumptions. We fit separate models for total, lobar, and deep CMBs. We first fit a full model for each of the form in Figure 1, with almost all possible associations between five levels of variables (plotted from left to right). Level 1 consisted of age at MRI (age), sex (male), *APOE* ε4 carrier status (APOE4), and smoking (ever/never), level 2 consisted of hypertension, diabetes, dyslipidemia, and atrial fibrillation, level 3 consisted of anticoagulant use and antiplatelet use, level 4 consisted of amyloid PET (log-transformed), and level 5 consisted of CMB divided into 2 components: presence or absence of CMBs and count of CMBs among those with at least one CMB (the CMB-positive group). Each arrow in the SEM represents a linear regression of predictors (to the left) on an outcome (to the right). Where the outcome was binary, the arrow represents a logistic regression. For CMB as an outcome, the SEMs used a negative binomial hurdle model. The hurdle model consisted of

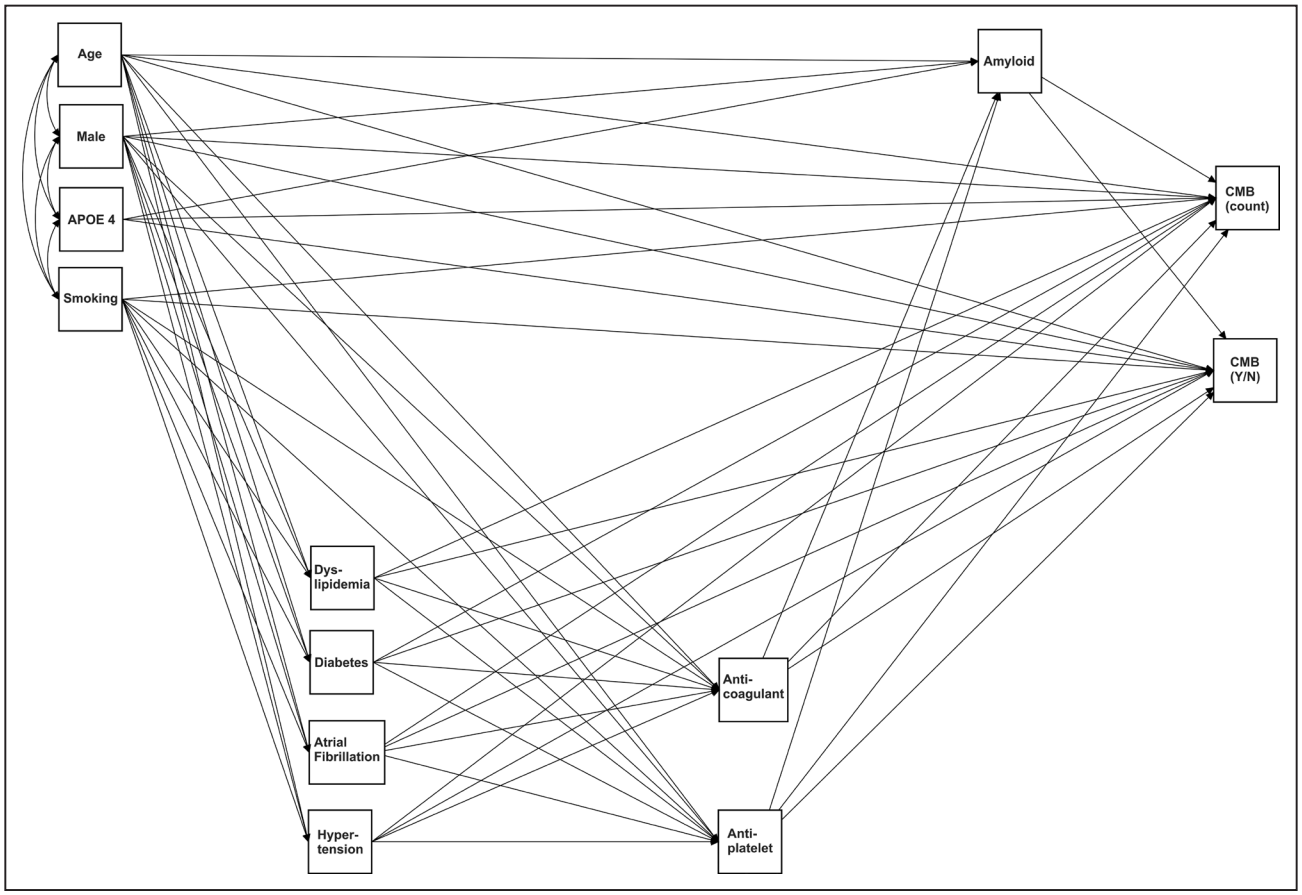

Figure 1. Full structural equation model model for prediction of cerebral microbleeds (CMBs).
This diagram presents the variables under consideration and the maximum number of associations (arrows) we could find in this specified structure. Variables can affect other variables to their right, as denoted by the arrows. Pruning removes nonsignificant arrows from this structure to produce parsimonious models. N indicates no; and Y, yes.

2 stages: (1) a logistic-regression model for predicting having ≥1 CMBs versus no CMBs, which constitutes the hurdle, and (2) a truncated negative binomial model for predicting the count of CMBs in the CMB-positive group. The idea is that a hurdle needs to be crossed to get to the events (CMB) stage, individuals with no CMBs have not crossed the hurdle, and predictors involved in the 2 stages need not be the same. As a sensitivity analysis, we compared results using a truncated approximate Poisson distribution (setting the dispersion parameter to 0.001) to the truncated negative binomial. The 2 approaches produced similar models, but the Bayesian Information Criterion values were much worse with the approximate Poisson. This appears to be from overdispersion in the counts, where the conditional variance is greater than the conditional mean. The negative binomial distribution models the overdispersion. Based on prior work, *APOE* ε4 and amyloid PET were considered as a pathway separate from cardiovascular risk variables. SEMs require a weak causal ordering of the variables to be specified before running any models and allow us to account for complex relationships between the variables, rather than simply adjusting for confounding variables through simple or multiple linear regression. Each level in the SEM analysis is assumed to come later than preceding levels in a causal framework, and any variable can cause changes to variables lying in higher levels. Variables lying between lower and higher levels are mediators. We report regression coefficients with their associated standard errors and *P* values. The coefficients give the predicted change in the outcome (higher level) variable per unit increase in the predictor (lower level) variable. For logistic regressions, the coefficients are estimated log odds ratios and exponentiated coefficients estimate odds ratios. For the truncated negative binomial models, the coefficients estimate change in the log of the counts, and exponentiated coefficients estimate incidence rate ratios. We also developed models with occipital amyloid PiB SUVR instead of global amyloid SUVR because occipital amyloid may have a stronger association with cerebral amyloid angiopathy.

The SEMs were fitted with Mplus version 8.3 structural equations software. We used full information maximum likelihood to handle missing values. We pruned the full models to parsimonious models using *P* values and Bayesian Information Criterion.

RESULTS

The demographics of the study cohort by CMB status are reported in Table 1. A total of 1253 participants underwent MRI imaging T2* GRE sequences and were included in the analysis. Of these participants, 1162 (93%) underwent concurrent ^{11}C-PiB PET scans. At the time of MRI, 50 participants had a history of clinical stroke, 23 participants had a diagnosis of dementia, and 10 participants had a history of ICH.

Of the 1253 participants, there were 295 (26.3%) participants with CMBs. Participants with CMBs were older (mean [SD] age 78.5 [8.4] years versus 72.6 without CMBs, *P*<0.001), more likely male (192 [65%]

Table 1. Characteristics Based on Presence of a CMB

	None; n=958	CMB present; n=295	*P* value*	Adjusted *P* value†
Age, y	72.6 (8.4)	78.5 (8.4)	<0.001	
Males, n (%)	474 (49%)	192 (65%)	<0.001	
*APOE*4, n (%) [8]‡	270 (28%)	84 (29%)	0.95	0.45
Education, y [1]‡	14.7 (2.6)	14.7 (2.6)	0.71	0.69
PiB SUVR [91]‡	1.57 (0.39)	1.73 (0.48)	<0.001	0.058
Diabetes, n (%) [1]‡	170 (18%)	55 (19%)	0.71	0.38
Hypertension, n (%) [1]‡	603 (63%)	220 (75%)	<0.001	0.24
Dyslipidemia, n (%) [1]‡	788 (82%)	245 (83%)	0.67	0.46
Smoker, n (%)	444 (46%)	138 (47%)	0.90	1.00
Atrial fibrillation, n (%) [1]‡	82 (9%)	67 (23%)	<0.001	0.001
Warfarin, n (%)	45 (5%)	38 (13%)	<0.001	0.013
Direct oral anticoagulant, n (%)	7 (1%)	5 (2%)	0.14	0.75
Aspirin, n (%)	485 (51%)	182 (62%)	<0.001	0.23
Clopidogrel, ticagrelor or prasugrel, n (%)	23 (2%)	12 (4%)	0.13	0.71
Any antiplatelet, n (%)	493 (51%)	185 (63%)	<0.001	0.27
Any anticoagulants Tx, n (%)	52 (5%)	43 (15%)	<0.001	0.017
Any antithrombotic, n (%)	532 (56%)	207 (70%)	<0.001	0.17
Both anticoagulant and antiplatelet, n (%)	13 (1%)	21 (7%)	<0.001	0.002

Means and SDs are on the original scale, but due to skewness, the statistical tests were done on the log transformation of PiB SUVR. CMB indicates cerebral microbleed; PiB, Pittsburgh Compound B; and SUVR, standardized uptake value ratio.

*P values for differences between groups come from a *t* test for the continuous variables and a χ^2 test for the categorical variables.

†P values adjusted for age and sex for differences between groups come from an ANCOVA for the continuous variables and a logistic regression for the categorical variables.

‡No. of individuals missing data (denoted within brackets).

versus 474 [49%], $P<0.001$), and more likely hypertensive (220 [75%] versus 587 [62%] $P<0.001$). PiB SUVR was higher in those with CMBs (1.73 [0.48] versus those without CMBs 1.57 [0.39] $P<0.001$). Of 295 participants with CMBs, there were 227 (77%) with a lobar-only location; 41 (14%) were deep-only and 27 (9%) were mixed; and 171 (58%) had 1 CMB, 88 (30%) had 2 to 4 CMBs, and 36 (12%) had ≥5 CMBs.

Antiplatelet treatment was more common in those with CMBs (185 [63%] versus 493 [51%], $P<0.001$) but was no longer significant after adjusting for age and sex. Similarly, anticoagulant treatment was more common in those with CMBs (43 [15%] versus 52 [5%] $P<0.001$) and remained significantly different after adjusting for age and sex. Among 678 participants taking only antiplatelet medications, 185 (27.3%) had CMBs. Among 95 participants taking only an anticoagulant, 43 (45.3%) had CMBs. Among 44 participants taking an anticoagulant and antiplatelet therapy, 21 (48.8%) had CMBs.

Multivariable logistic regressions, including participants with at least one CMB as the outcome variable and with nonmissing predictors (n=1162), showed associations between age, male sex, and anticoagulants with the presence of a CMB (Table 2). Replacing global PiB SUVR with occipital PiB SUVR did not change the results. No interaction between global PiB SUVR and anticoagulants was found (Table I in the Data Supplement). Similar results were found when looking at the presence of at least 1 lobar-only CMB.

Multivariable proportional odds ordinal logistic regressions (n=1162) with increasing total CMB frequency (0, 1, 2–4, 5+) as the response variable showed associations between age, male sex, PiB SUVR, and anticoagulants with a higher number of CMBs (Table 3). Lobar CMBs showed similar results, although log(PiB) was not significant going from 0 to 1 CMB. Deep CMBs were split into 3 groups: none, 1, 2+ due to lower numbers. Again, there was no interaction between anticoagulant and amyloid load with regards to increasing CMBs. Excluding the DOAC participants did not significantly change our findings (results not shown). The proportional odds assumption was met for the total CMB model (Brant $P=0.18$) and deep CMB model ($P=0.10$). The proportional odds assumption was not met for the lobar CMB model ($P=0.04$). Lobar CMB results thus come from a partial proportional odds model not requiring the proportional odds for log(PiB).

Table 2. Factors Associated With Presence or Absence of CMBs

	Estimate (SE)	Odds ratio (95% CI)	*P* value
Any CMB present			
Intercept	−6.950 (0.681)	…	<0.001
Age	0.068 (0.009)	1.07 (1.05–1.09)	<0.001
Male	0.473 (0.150)	1.60 (1.20–2.15)	0.002
Log PiB SUVR	0.626 (0.330)	1.87 (0.98–3.57)	0.058
Anticoagulants	0.684 (0.241)	1.98 (1.24–3.18)	0.005
Any lobar CMB present			
Intercept	−7.433 (0.728)	…	<0.001
Age	0.071 (0.010)	1.07 (1.05–1.09)	<0.001
Male	0.606 (0.160)	1.83 (1.34–2.51)	<0.001
Log PiB SUVR	0.616 (0.343)	1.85 (0.94–3.63)	0.073
Anticoagulants	0.564 (0.247)	1.76 (1.08–2.85)	0.023
Any deep CMB present			
Intercept	−6.930 (1.183)	…	<0.001
Age	0.050 (0.016)	1.05 (1.02–1.09)	0.002
Log PiB SUVR	0.552 (0.551)	1.74 (0.59–5.11)	0.32
Anticoagulants	0.316 (0.393)	1.37 (0.63–2.96)	0.42

CMB indicates cerebral microbleed; PiB, Pittsburgh Compound B; and SUVR, standardized uptake value ratio.

Table 3. Factors Associated With CMB Frequency by Location

	Estimate (SE)	Odds ratio (95% CI)	*P* value
Total CMBs			
Age	0.069 (0.009)	1.07 (1.05–1.09)	<0.001
Male	0.481 (0.147)	1.62 (1.21–2.16)	0.001
Log PiB SUVR	0.763 (0.319)	2.14 (1.15–4.01)	0.017
Anticoagulants	0.574 (0.224)	1.78 (1.14–2.76)	0.011
Intercepts			
None:1	7.036 (0.668)	…	<0.001
1:2–4	8.167 (0.680)	…	<0.001
2–4:5+	9.544 (0.701)	…	<0.001
Lobar			
Age	0.071 (0.010)	1.07 (1.05–1.09)	<0.001
Male	0.615 (0.158)	1.86 (1.37–2.54)	<0.001
Log PiB SUVR (none:1)	0.570 (0.341)	1.77 (0.91–3.45)	0.095
Log PiB SUVR (1:2–4)	1.387 (0.440)	4.00 (1.69–9.48)	0.002
Log PiB SUVR (2–4:5+)	2.074 (0.745)	7.96 (1.85–34.27	0.005
Anticoagulants	0.524 (0.237)	1.69 (1.06–2.69)	0.027
Intercepts			
None:1	7.460 (0.719)	…	<0.001
1:2–4	9.135 (0.760)	…	<0.001
2–4:5+	10.986 (0.883)	…	<0.001
Deep			
Age	0.052 (0.016)	1.05 (1.02–1.09)	0.001
Log PiB SUVR	0.550 (0.549)	1.73 (0.59–5.09)	0.32
Anticoagulants	0.287 (0.393)	1.33 (0.62–2.88)	0.46
Intercepts			
None:1	7.053 (1.190)	…	<0.001
1:2+	8.528 (1.213)	…	<0.001

Ordinal logistic models with CMB as the response where total CMBs and Lobar are split into 4 groups: none, 1, 2–4, 5+. Deep is split into 3 groups: none, 1, 2+ due to lower numbers. Total and deep CMB model results from proportional odds models, lobar CMB results from partial proportional odds model where proportional odds for log PiB was not required. CMB indicates cerebral microbleed; PiB, Pittsburgh Compound B; and SUVR, standardized uptake value ratio.

SEM Results

The initial full model considered for the SEMs is presented in Figure 1. This diagram presents the variables under consideration and the maximum number of associations we could find in this specified structure. The SEMs were then pruned to parsimonious versions by removing nonsignificant associations. The main results for the final model predicting CMBs (any) are summarized in Figure 2A and 2B and Table 4. Increasing age at MRI and *APOE* ε4 were predictors of higher amyloid burden at baseline. Increasing age and male sex were predictors of atrial fibrillation. Increasing age, male sex, and atrial fibrillation were predictors of anticoagulant use. Increasing age, male sex, and anticoagulant use predicted having at least one CMB. Male sex and amyloid burden predicted the count of CMBs in the CMB-positive group.

Replacing occipital amyloid for global amyloid did not substantively change any of the findings (results not shown). We replaced any CMB with lobar CMB (results not shown), and the results were similar to total CMBs. The full model was of the same general form.

For the deep CMB SEM (Figure 2B), increasing age at MRI and smoking predicted hypertension, increasing age, and hypertension predicted having at least one CMB, and increasing age and *APOE* ε4 predicted the count of CMBs in the CMB-positive group.

To evaluate a potential synergistic relationship between amyloid and anticoagulants, an anticoagulant×amyloid interaction was added to the models. No interaction term was significant.

DISCUSSION

In this population-based study, anticoagulant use—but not antiplatelet use—was associated with increasing CMB burden after adjusting for potential confounders. The SEM results suggested that anticoagulants were involved in the processes leading to getting CMBs, but not to the count of CMBs in the CMB-positive group which was predicted by amyloid load. This study expands upon findings of prior population-based studies by demonstrating (1) a relationship between the presence of CMBs with anticoagulants but not antiplatelet agents; (2) a possible causal pathway for the development of CMBs in the setting of cerebral amyloid and antithrombotic use.

We looked for, but failed to find, an anticoagulant×amyloid interaction to our models. This does not exclude a synergistic relationship between amyloid and anticoagulant use among patients with clinical cerebral amyloid angiopathy. But even if the relationship between amyloid burden and anticoagulant use is additive, it suggests a higher bleeding risk in high-risk patients (those on anticoagulants) with high amyloid burden as opposed to a lower amyloid burden.

Similar to the Rotterderdam study, we found an association between anticoagulant use and CMBs. Additionally, in the Rotterdam study, greater INR variability was associated with CMBs.[8] The association between CMBs and anticoagulant use is clinically relevant in the general population. Among those with atrial fibrillation taking anticoagulation, the burden of CMBs is associated with future ICH risk.[18,19] Our additional finding that amyloid is independently associated with CMB risk is important because it suggests that cerebral amyloid angiopathy might contribute to a subset of these CMBs, with potential implications for the risk of anticoagulant-associated intracranial hemorrhage.[20] Therefore, individuals with cerebral amyloid angiopathy on anticoagulation have 2 independent risk factors for CMBs, which might place them at an elevated risk of clinical intracranial hemorrhage.

Due to our low numbers of DOAC users, this study cannot determine whether the use of DOACs mitigates the association of anticoagulation with CMBs. In a study of ICH patients, the presence of CMBs was similar between vitamin K antagonist–associated ICH and DOAC-associated ICH, but the burden of CMBs and the frequency of those with >5 CMBs were lower in the DOAC-ICH cases.[21] Because DOACs are associated with a lower CMB burden and correlate with a decreased risk of ICH, we anticipate performing a future follow-up study to investigate the risk of CMBs in those on DOACs versus vitamin K antagonists will be possible as the number of DOAC users increases over time.

In the Rotterdam study, antiplatelet agents were associated with CMB presence, with aspirin use related to the development of lobar CMBs[22] and clopidogrel users having a greater number of deep or infratentorial CMBs.[9] In the Framingham study, antiplatelet agents were associated with deep or infratentorial CMBs.[6] In contrast, antithrombotic use was not associated with CMBs in the Northern Manhattan Study.[23] The current study found no association between antiplatelet use and CMBs. The association may depend on the population studied. In a pooled analysis of patients with ICH and ischemic stroke/transient ischemic attack, the association with antiplatelet agents and CMBs was such that the association was driven by one study population.[24]

The relationship between anticoagulants and CMBs was location dependent. In the SEMs, we did not see an effect of anticoagulants or antiplatelets on the risk of deep CMBs. The SEMs demonstrated a relationship between vascular risk factors of smoking and hypertension and deep CMB risk. The findings of vascular risk factors being associated with deep CMBs are consistent with prior studies.[7,25] The SEMs may have allowed the relationship between hypertension and deep CMBs to become more apparent compared with the regression models due to an indirect effect of older age at MRI through hypertension on CMB risk in addition to the direct relationship of hypertension on deep CMB risk.

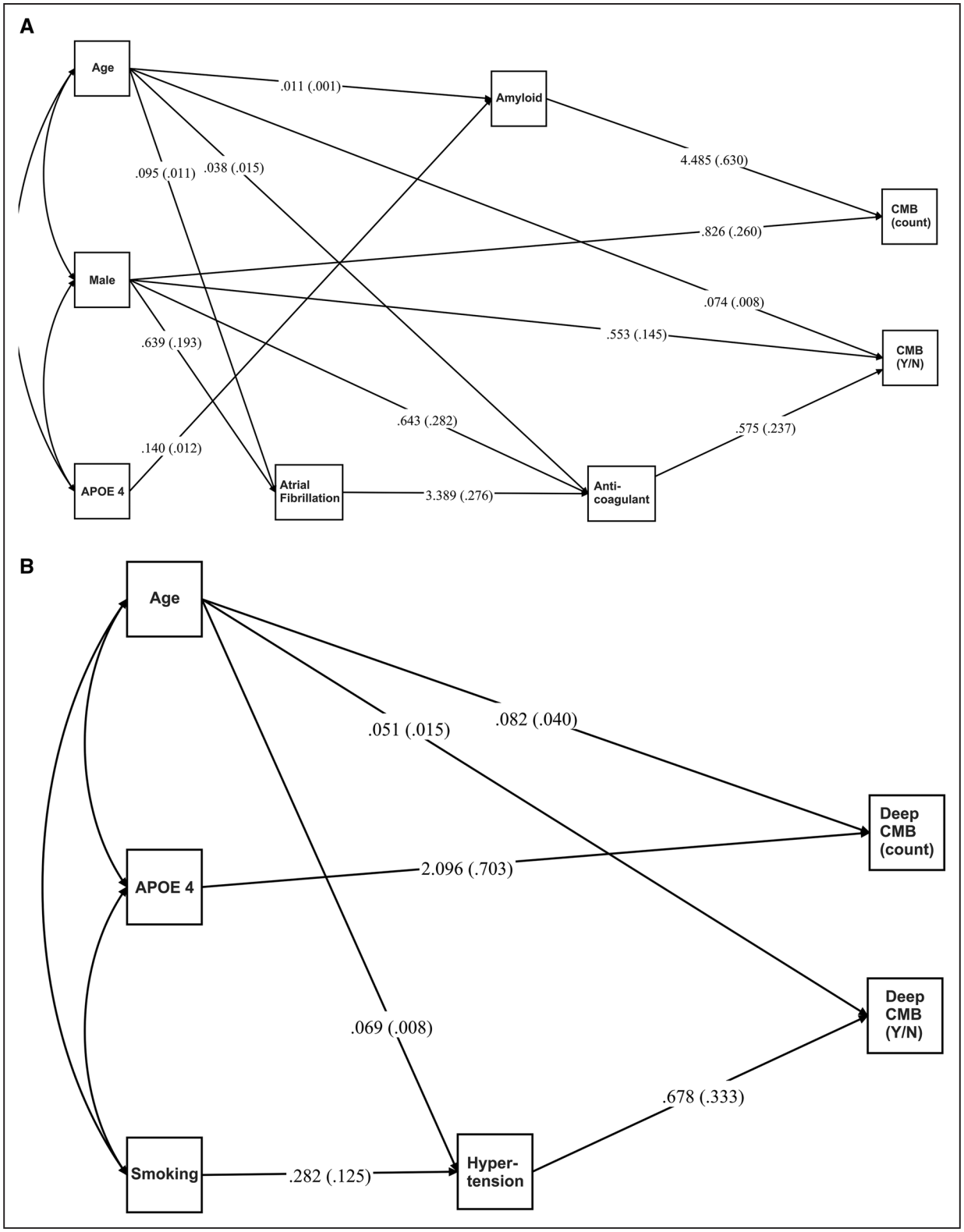

Figure 2. Pruned structural equation model (SEM) for predicting cerebral microbleed (CMB) risk.
A, Pruned SEM predicting any CMB (deep or lobar) risk. Arrows show significant associations ($P<0.05$). *P* values are found in Table 4. The numbers on the arrows are coefficients (SE). **B**, Pruned SEM for predicting deep CMB risk. N indicates no; and Y, yes.

A prior multicenter study of patients with transient ischemic attack or stroke showed that although CMBs were associated with intracranial hemorrhage, the risk of ischemic stroke outweighed the risk of hemorrhage even in those that had a CMB pattern consistent with cerebral amyloid angiopathy.[26] Whether the risk of ICH

Table 4. Direct Effects on CMB Risk and CMB Counts (1+)

Direct effect	Estimate (SE)	OR (95% CI) or IRR (95% CI)	*P* value
Age→Afib	0.095 (0.011)	1.100 (1.076–1.124)	<0.001
Male→Afib	0.639 (0.193)	1.895 (1.298–2.766)	0.001
Age→anticoagulant	0.038 (0.015)	1.039 (1.009–1.070)	0.012
Male→anticoagulant	0.643 (0.282)	1.902 (1.094–3.306)	0.022
Afib→anticoagulant	3.389 (0.276)	29.64 (17.25–50.91)	<0.001
Age→log(PiB)	0.011 (0.001)		<0.001
APOE→ log(PiB)	0.140 (0.012)		<0.001
Age→CMB (Y/N)	0.074 (0.008)	1.077 (1.060–1.094)	<0.001
Male→CMB (Y/N)	0.553 (0.145)	1.738 (1.308–2.310)	<0.001
Anticoagulant→ CMB (Y/N)	0.575 (0.237)	1.777 (1.117–2.828)	0.015
Male→CMB (count)	0.826 (0.260)	2.284 (1.372–3.802)	0.001
Log(PiB)→CMB (count)	4.485 (0.630)	88.68 (25.80–304.8)	<0.001
Direct effects on deep CMB risk			
Age→Htn	0.069 (0.008)	1.071 (1.055–1.088)	<0.001
Smoke→Htn	0.282 (0.125)	1.326 (1.038–1.694)	0.024
Age→CMB (Y/N)	0.051 (0.015)	1.052 (1.022–1.084)	0.001
Htn→CMB (Y/N)	0.678 (0.333)	1.970 (1.026–3.784)	0.042
Age→CMB (count)	0.082 (0.040)	1.085 (1.004–1.174)	0.039
APOE→CMB *(count)*	2.096 (0.703)	8.134 (2.051–32.26)	0.003

Afib indicates atrial fibrillation; CMB, cerebral microbleed; Htn, hypertension; IRR, incidence rate ratios; No, no; OR, odds ratio; PiB, Pittsburgh Compound B; and Y, yes.

would outweigh the risk of ischemic stroke in those on anticoagulants for primary prevention of ischemic stroke remains unclear, but in this population-based study, anticoagulants were associated with an increased risk of CMBs.

Strengths of this study include that the analysis was conducted on a large cohort from a population-based study with a significant proportion of the participants undergoing amyloid PET imaging and the use of 3T MRI scans for the assessment of CMBs. The study also has several limitations. We may have underestimated the relationship between CMBs and antithrombotics because the study used T2* GRE sequence CMB detection which is less sensitive than susceptibility-weighted imaging. In addition, although PiB PET can detect vascular amyloid deposition, PIB binds to parenchymal plaques and therefore it is not specific for vascular amyloid; we attempted to control for this by also investigating occipital amyloid burden, which may be more specific for vascular amyloid.[27,28] Although SEMs are helpful in understanding and exploring the associations between the variables in the models, estimating direct and indirect effects, and suggesting mediation and causality, they do not alone prove causality. Furthermore, the current study is cross-sectional, and a longitudinal study is necessary to confirm possible causal associations. Also, because clinical practice has evolved towards using DOACs rather than vitamin K antagonists, the findings are not generalizable to all patients on anticoagulation and the study will need to be repeated with a larger number of patients taking DOACs.

CONCLUSIONS

In conclusion, our findings support a possible causal association between anticoagulant use and higher risk of developing a CMB in the general population, whereas amyloid burden predicted higher CMB count among those with a CMB. In contrast, we found no association between CMBs and antiplatelet agents. Although prescribing anticoagulation to patients with additional factors directly associated with higher risk of CMBs (ie, older age, male sex, higher amyloid burden) may result in more CMBs, whether this increases the risk of ICH requires further investigation.

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Supplemental Materials

Online Table I

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