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ORIGINAL RESEARCH

Common Medications and Intracerebral Hemorrhage: The ARIC Study

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BACKGROUND: Antiplatelets, anticoagulants, and statins are commonly prescribed for various indications. The associations between these medications and the risk of intracerebral hemorrhage (ICH) and cerebral microbleeds (CMBs) are unclear.

METHODS AND RESULTS: We performed a retrospective study of the ARIC (Atherosclerosis Risk in Communities) study cohort, recruited from 4 US communities in 1987 to 1989 with follow-up. In 2011 to 2013, a subset (N=1942) underwent brain magnetic resonance imaging with CMB evaluation. Time-varying and any antiplatelet, anticoagulant, or statin use was evaluated at subsequent study visits in participants not on each medication at baseline. To determine the hazard of ICH and odds of CMB by medication use, logistic and Cox proportional hazard models were built, respectively, adjusting for the propensity to take the medication, concomitant use of other medications, and cognitive, genetic, and radiographic data. Of 15 719 individuals during up to 20 years of follow-up, 130 participants experienced an ICH. The adjusted hazard of ICH was significantly lower among participants taking an antiplatelet at the most recent study visit before ICH versus nonusers (hazard ratio [HR], 0.53; 95% CI, 0.30–0.92). Statin users had a significantly lower hazard of an ICH compared with nonusers (adjusted HR, 0.13; 95% CI, 0.05–0.34). There was no association of CMB and antiplatelet, anticoagulant, or statin use in adjusted models.

CONCLUSIONS: In this US community-based study, antiplatelet and statin use were associated with lower ICH hazard, whereas no association was noted between CMBs and antiplatelets, anticoagulants, and statins. Further study is needed to understand the differential roles of these medications in cerebral microhemorrhages and macrohemorrhages.

Key Words: cohort studies ■ intracerebral hemorrhage ■ medications

See Editorial by Gutierrez

Antiplatelets, anticoagulants, and statins are commonly prescribed for a variety of indications. Although guidelines delineate when to initiate these medications,[1–3] it is unclear whether these medications are associated with long-term risk of intracerebral hemorrhage (ICH) and cerebral microbleeds (CMBs) in the United States.

ICH risk in patients who take these medications has been studied,[4–7] but results have been conflicting and limited by short follow-up, settings in countries other than the United States, and difficulty accounting for confounders, such as age, concomitant use of other medications, and radiographic and genetic information. There was no increased risk of ICH in older participants randomized to aspirin for primary prevention in the ASPREE (Aspirin in Reducing Events in the Elderly) trial.[8] Similarly, a meta-analysis of 5 randomized controlled trials demonstrated no increased risk of ICH with aspirin (odds ratio [OR], 1.64; 95% CI, 0.72–3.74) over 2.5 years.[9] In contrast, another meta-analysis of 3 years of aspirin use did identify increased risk of ICH.[4]

CMBs are associated with hypertensive arteriopathy and cerebral amyloid angiopathy,[10] and their accumulation is associated with an 8-fold increased risk

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CLINICAL PERSPECTIVE

What Is New?

- Antiplatelets, anticoagulants, and statins are commonly used; however, their longitudinal impact on cerebral hemorrhagic risk is relatively unknown.
- During nearly 20 years of follow-up in the ARIC (Atherosclerosis Risk in Communities) study, we observed a lower hazard of intracerebral hemorrhage among participants who had a prior exposure to either an antiplatelet or a statin in analyses adjusted for the propensity to be prescribed each medication as well as apolipoprotein E genotype, having an ischemic stroke, and concomitant use of a medication in the other class.
- In cross-sectional analyses adjusted for the propensity of being prescribed each medication and markers of small-vessel disease, there was no significant association between exposure to an antiplatelet, anticoagulant, or statin and the presence of cerebral microbleed on magnetic resonance imaging; long-term use of antiplatelets and statins was linked with lower risk of intracerebral hemorrhage in this retrospective, observational study.

What Are the Clinical Implications?

- There may be differential cerebral bleeding risk profiles associated with antiplatelet, anticoagulant, and statin use longitudinally.
- Future studies are needed to discern the hemorrhagic effects of these medications while accounting for medication indication and markers of cerebral small-vessel disease.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
ASPREE	Aspirin in Reducing Events in the Elderly
CMB	cerebral microbleed
ICH	intracerebral hemorrhage

of ICH.[11] Studies have demonstrated significantly elevated risk or no link between the use of statins,[12,13] aspirin,[14–17] or warfarin[15,18] and CMB presence, with a lack of consensus in the magnitude of these effects.

It is thus important to characterize the relationships between exposure to commonly used medications in the United States and the risks of ICH and CMB while accounting for demographic, clinical, radiographic, and genetic factors to guide clinical decision-making. We explore in a longitudinal, US community-based cohort (the ARIC [Atherosclerosis Risk in Communities] study), the associations of statins, antiplatelets, and anticoagulants with the development of ICH and the prevalence of CMB.

METHODS

This retrospective observational study was approved by the Institutional Review Boards for each ARIC study affiliated institution. All participants provided informed consent. Requests to access the data sets from researchers trained in human subject confidentiality may be sent to ARICpub@unc.edu.

Study Population

Participants were members of the ARIC study, a prospective, population-based cohort recruited from 4 US communities. Each ARIC study field center (Washington County, Maryland; suburbs of Minneapolis, MN; Jackson, MS; and Forsyth County, North Carolina) recruited nearly 4000 participants in 1987 to 1989, for 15 792 total participants ranging from age 45 to 64 years. Because of small numbers, as is standard in the ARIC study, all non-White or non-Black participants and all Black participants from Washington County and Minnesota were excluded, resulting in 15 719 participants. The design and objectives of the ARIC study are published elsewhere.[19] ARIC study participants were interviewed for demographic, social, and clinical information, provided samples for serologic tests, and underwent other tests at the baseline visit and every 3 years at visits thereafter through 1998 (visit 2: 1990–1992; visit 3: 1993–1995; and visit 4: 1996–1998), with a fifth in-person visit in 2011 to 2013, the end point of our study. Participants were contacted by telephone annually. A follow-up telephone call from 2004 to 2007 was used to obtain medication data given the large gap between visits 4 and 5. When analyzing the association of each medication with hemorrhage outcomes, we excluded participants who were taking the medication at visit 1 to prevent left-truncation bias.

Hemorrhage Definition

ICH outcome was identified via surveillance and annual follow-up telephone calls. If a hospitalization is reported, records are obtained for data abstraction. Cases in the ARIC study were defined as probable or definite ICH in accordance with the National Survey of Stroke criteria, including the following: (1) computed tomography or magnetic resonance imaging (MRI) demonstrating an intraparenchymal hematoma, (2) demonstration of ICH

on autopsy or surgery, or (3) (a) at least 1 major or 2 minor neurologic deficits, (b) a bloody spinal fluid on lumbar puncture, and (c) cerebral angiography showing an avascular mass effect and no evidence of aneurysm or arteriovenous malformation.[20] A probable ICH did not have computed tomography/MRI available, but met criteria 3a, 3b, and 3c with decreased level of consciousness lasting 24 hours or until death. Of patients with strokes in the ARIC study, 98% underwent computed tomography or MRI. The criteria were implemented by a computer algorithm with additional physician review of medical records, with adjudication by a second physician in the event of discordance.

The outcome of CMB was identified by 3-T brain MRI with T2*gradient echo sequences from 2011 to 2013 in participants who underwent this visit 5 imaging study (N=1942).[21] Participants were eligible for a brain MRI if there was no contraindication for an MRI and they met one of the following criteria: (1) had previous MRI scans from 2004 to 2006, (2) had low cognitive test scores or a decline on longitudinal testing, or (3) were from an age-stratified sample of remaining individuals. There were sampling fractions assigned by the ARIC study for participants <80 and ≥80 years of age to approximate the age distribution for those selected with cognitive impairment to reach a goal of nearly 2000 scans. The 3-T MRIs with 3.3-mm slices and repetition time/echo time 200/20 ms were reviewed centrally (MRI reading center, Mayo Clinic) for CMBs.[22] CMBs were defined as homogeneous lesions of hemosiderin deposits ≤10 mm in diameter, as detected visually by trained image analysts and confirmed by a radiologist, all of whom were blinded to the exposures of the medications of interest. This analysis only used definite CMBs (85% interrater agreement on definite and not definite CMB; κ=68%).[22,23] The presence and location of CMBs (anywhere; lobar or cortical gray; subcortical or periventricular; deep within the basal ganglia, thalamus, corpus callosum, internal, external, and extreme capsule; or infratentorial in the brainstem and cerebellum) in the brain were recorded.[22] Topographic location was identified by transforming the T2*gradient echo into the participant's T1 image space, followed by a discrete cosine transformation of this space, obtained by statistical parametric mapping unified segmentation of the T1 image.[23] A parcellated anatomic atlas is linked to each participant's anatomic MRI. We analyzed the presence of a CMB in any location and in the lobar, subcortical, and deep regions. No subgroup analysis of brainstem CMBs was performed because of the known heterogeneity of cerebellar CMBs, as demonstrated in a radiopathologic study.[24]

Medications

The study exposures were antiplatelet, anticoagulant, and statin medications. These data were obtained by extracting medication names or the generic product identification codes from medication inventory lists compiled by ARIC study staff from medication containers brought by participants at every in-person visit (Table 1). To estimate duration of medication use, time between 2 consecutive visits was calculated if the medication was documented at both. If the medication was taken at 1 of 2 consecutive visits, then we assumed that the patient took the medication for the entirety of the intervening time period until the date of the visit when not documented. Time fragments of medication use were added to determine cumulative years of medication use. We analyzed the hazard of ICH by medication status in 2 groups to establish temporality: (1) participants who took the medication of interest during follow-up and, if an ICH occurred, necessarily at the most recent visit before the date of ICH versus those who were never exposed; and (2) participants who took the medication at any point during follow-up versus those who were never exposed. When analyzing the odds of the presence of a CMB on the visit 5 MRI, a participant was classified as a user of each medication class if there was any exposure to the medication of interest during the study period.

Propensity Score Covariates

We created a propensity score for taking each medication class to address confounding by indication. This score was derived from variables at visit 1, or midlife, to predict use of each medication from visits 2 to 5. The variables of the propensity score were chosen a priori as they may influence medication prescription and outcomes, and are available to a community practitioner. Date of birth, sex, race, and education were self-reported. Clinical data consisted of smoking (self-report; defined as ever versus never), hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, based on the average of the last 2 of 3 measurements, or use of antihypertensive medication over the past 2 weeks), diabetes mellitus (fasting glucose ≥126 mg/dL or nonfasting glucose ≥200 mg/dL, physician diagnosis of diabetes mellitus, or takes a diabetes mellitus medication), coronary heart disease (myocardial infarction evident on adjudicated ECG, history of myocardial infarction, history of heart surgery, history of coronary bypass, or history of balloon angioplasty), and heart failure (taking heart failure medications or meeting a Gothenburg score of 3, based on cardiac and pulmonary symptoms as well as use of diuretics and/or digitalis[25]). Low-density lipoprotein was calculated as follows: total cholesterol–high-density lipoprotein–(total triglycerides/5). Serum creatinine was measured in mg/dL. The use of either of the other

Table 1. Codes Available to Extract Medication Use by ARIC Study Visit

MSRA		MSRB		MSRC04		MSRD04		AFU		MSRF	
Medication	Code	Medication	Code	Medication	Code	Medication	Code	Medication	Code	Medication	GPI No.
Aspirin	Strings	Aspirin	102055	Aspirin	102055	Aspirin	102055	Aspirin	Strings	Clopidogrel	85158020100320
Dipyridamole	Strings	Dipyridamole	107599	Buffered aspirin (Bufferin)	102092	Buffered aspirin (Bufferin)	102092	Warfarin	Strings	Aspirin	64100010000315
Warfarin	Strings	Warfarin	109474	Dipyridamole	107599	Dipyridamole	107599	Simvastatin	Strings		64100010000605
Lovastatin	Strings	Lovastatin	110753	Warfarin	119474	Warfarin	109915	Dipyridamole	Strings		64100010000307
				Lovastatin	110753	Lovastatin	110753	Atorvastatin	Strings	Dipyridamole	85159902206920
				Pravastatin	Strings	Pravastatin	121480	Clopidogrel	Strings	Warfarin	83200030200303
				Simvastatin	Strings	Simvastatin	102354	Dabigatran	Strings		83200030200305
						Atorvastatin	121495	Lovastatin	Strings		83200030200310
							119740				83200030200313
											83200030200315
											83200030200317
											83200030200320
											83200030200325
										Edoxaban	8337003020
										Rivaroxaban	8337006000
										Dabigatran	8333703020
										Apixaban	83370010000320
										Simvastatin	39400075000320
											39400075000330
											39400075000340
											39400075000360
										Atorvastatin	39400010100310
											39400010100320
											39400010100330
											39400010100350
										Rosuvastatin	39400060100305
											39400060100310
											39400060100340
										Pravastatin	39400065100330
											39400065100340
										Lovastatin	39400050000305
											39400050000310
										Pitavastatin	39400058100330

ARIC indicates Atherosclerosis Risk in Communities; AFU, Phone call between Visits 4 and 5; GPI, Visit 5; MSRA, Visit 1; MSRB, Visit 2; MSRC, Visit 3; and MSRD, Visit 4.

medications classes at visit 1 was determined, as described in the Medications section.

Risk Factors for Adjustment

Although the propensity score includes variables readily available to clinicians before initiating medications, we also adjusted for important covariates associated with increased risk of ICH and CMB.

In models evaluating ICH, we considered ischemic stroke,[26] APOE (apolipoprotein E) genotype (ε2 and/or ε4),[27] and use of the other 2 medication classes during follow-up. Potential ischemic strokes were identified by the same surveillance method as ICHs.[28] An ischemic stroke was included if the event occurred before or at the date of the ICH or during the time up to the end of the participant's study period if there was no ICH. APOE genotyping, performed by a TaqMan assay (Applied Biosystems, Foster City, CA),[29] was categorized by genotype into the following categories: ε3/ε3, at least one ε2 and no ε4 allele, at least one ε4 and no ε2 allele, and both an ε2 and an ε4 allele. Participants who opted out of release of genetic information for research were excluded from analyses including APOE.

When evaluating CMB presence on visit 5 MRIs, we considered these covariates: APOE genotype,[30] percentage of white matter occupied by hyperintense signal,[31] the presence of either mild cognitive impairment or dementia at visit 5,[32] and use of the other 2 medication classes from visits 2 to 5. To calculate white matter hyperintensity percentage, axial fluid-attenuated inversion recovery images from the MRI obtained in 2011 to 2013 were centrally segmented into voxels to measure leukoaraiosis volume.[33] Percentage of white matter occupied by leukoaraiosis was dichotomized to less than or equal to versus more than the sample mean. Cognitive function at visit 5 was determined by expert review and computer algorithm, using standard criteria, including neuropsychological assessments and informant interviews, and classified as normal, mild cognitive impairment, or dementia.[34–36] All 1942 participants with MRI gradient echo data underwent visit 5 cognitive testing.

Statistical Analysis

Participants were compared in groups determined by use of each medication at any point during follow-up from ARIC study visit 2 onwards. Univariate analyses were performed using Student *t* tests and χ^2 tests, comparing individuals by medication use. Statistical analyses were performed in SAS 9.4.

Creation of Propensity Scores

We constructed separate propensity scores for taking an antiplatelet, anticoagulant, or statin at any point from visits 2 to 5 using visit 1 variables, by multivariable logistic regressions.[37] Multivariable logistic regressions were built to model the odds of taking each of the medications of interest from visits 2 to 5 as a function of visit 1 variables. The variables were entered into a propensity score estimation, including quadratic, spline, and interaction terms, and were retained in the final model if the covariate's associated $P \leq 0.2$. The predicted propensity score values were then binned into quintiles for use as adjustment covariates for the primary analyses. The balance of the propensity scores was assessed by computing the mean standardized differences of each variable in the score across the 5 score quintiles, with a prespecified threshold of balance <0.10.[38]

Analysis of ICH Outcome

We determined the hazard of an ICH during visits 2 to 5 associated with each medication class by Cox proportional hazard regression models, with visit 2 as the time of origin. Participants were censored at the end of the administrative censoring date (December 31, 2013) or when lost to follow-up.

To study the association of contemporaneous medication use and ICH, we performed Cox regression analyses to ascertain the hazard of an ICH when taking each medication class during follow-up and at the most recent visit before the ICH if the event occurred versus no exposure to the medication of interest before ICH or censoring, excluding participants with ICH and remote medication use. To understand the impact of any medication use, remote or concurrent, we also analyzed the hazard of ICH in participants who were exposed to the medications at any time before the ICH versus those who were never exposed before an ICH or censoring. Each model was assessed for proportionality of hazards by including an interaction term of the time-varying covariate of medication use and the log of survival time for each Cox proportional hazard model with a prespecified threshold of violation of the assumption if $P<0.05$.

We performed Cox proportional hazard regression analysis with a static and time-varying variable representing medication use (any exposure from visit 2–5). The static model assigns time of nonexposure within the medication use group toward the hazard of the outcome and models the future occurrence of an outcome based on a possible future exposure. In contrast, the time-varying variable denotes 5 possible periods of medication exposure, demarcated by the dates of each visit and the telephone call, allowing reevaluation of a participant's exposure status at each time interval. Proportionality of hazards was tested for each model.

Model 1 represents the unadjusted hazard of an ICH as a function of the medication use, model 2 adjusted for the propensity quintile of taking that medication, and model 3 adjusted for the propensity quintile

of concomitant use of either of the other medication classes, occurrence of an ischemic stroke, and APOE genotype.

Sensitivity Analyses

A sensitivity analysis was performed to determine whether there was an overarching medication compliance bias among ARIC study participants who have ICH versus not. This was tested by analyzing the use of thyroid replacement medications. We chose to study the use of levothyroxine in association with the occurrence of ICH as it was a commonly prescribed medication during the ARIC study period and its use is not associated with a risk of ICH in the literature. We hypothesized that there is no difference in the proportions of participants with ICH versus participants without ICH who use levothyroxine and that there is no hazard of ICH by levothyroxine use.

To further assess the validity of the method used in this study to assess medication effects, we studied the impact of antihypertensive medication use as uncontrolled systemic blood pressure is an established risk factor for ICH. We hypothesized that patients with ICH were less likely to have taken an antihypertensive medication before the onset of ICH and that there would be a lower hazard of ICH with antihypertensive use.

Analysis of CMB Outcome

We separately analyzed the likelihood of CMB presence on MRI as a function of use of each medication of interest from visits 2 to 5. Because MRIs were only performed at visit 5, logistic regressions were used to evaluate the following: CMB anywhere, lobar CMB, subcortical CMB, and deep CMB, as a function of any use of each medication class from visits 2 to 5. The logistic regression models were constructed with survey weights accounting for the MRI sampling strategy. Model 1 was unadjusted, model 2 was adjusted for propensity quintile, and model 3 was adjusted for concomitant use of either of the other medication classes, APOE genotype, white matter hyperintensity percentage category, and mild cognitive impairment or dementia.

Data Availability

Requests for data from qualified investigators can be directed to the corresponding author.

RESULTS

Univariate Analysis

Antiplatelet Use

The antiplatelet study cohort consisted of 14 471 participants not taking an antiplatelet at visit 1, of whom 7458 took an antiplatelet at some point from visits 2 to 5. The mean follow-up time was 17.4 (SD, 6.8) years for antiplatelet users and 18.5 (SD, 6.4) years for antiplatelet nonusers. Among antiplatelet users, 44% took an antiplatelet at >1 visit. The median time of antiplatelet use was 11.8 (interquartile range, 6.0–15.1) years. Antiplatelet users had more comorbidities, took a statin during follow-up, and were less likely to have both APOE ε2 and ε4 alleles (Tables 2 and 3). A total of 124 participants had an ICH during follow-up (0.76% among antiplatelet users and 0.97% among antiplatelet nonusers); however, 23 of these ICHs occurred at a time remote to antiplatelet use among antiplatelet users. The average time from documented antiplatelet use and ICH among remote users was 6.9 (SD, 5.5) years. Among antiplatelet users with recent exposure if an ICH occurred and antiplatelet nonusers, 0.4% of antiplatelet users (N=29) and 1% of antiplatelet nonusers (N=72) developed an ICH (P<0.001). Among the 1801 participants who underwent a visit 5 MRI, 23.75% of antiplatelet users and 24.14% of antiplatelet nonusers were noted to have a CMB (P=0.857).

Anticoagulant Use

The anticoagulant study cohort consisted of 15 719 participants not taking an anticoagulant at visit 1, of whom 846 took an anticoagulant from visits 2 to 5. Mean follow-up time was 17.8 (SD, 6.9) years for anticoagulant users and 18.0 (SD, 6.6) years for anticoagulant nonusers. Of anticoagulant users, 16% took an anticoagulant at >1 visit. Anticoagulant users took the medication for a median of 6.0 (interquartile range, 3.5–9.4) years. Anticoagulant users were older, had more comorbidities, and were more likely to have an ischemic stroke and cognitive impairment. There was no difference in the proportion of ICH by anticoagulant use (0.35% among anticoagulant users and 0.86% among anticoagulant nonusers; P=0.168). Among the 1942 who underwent a visit 5 MRI, anticoagulant users compared with nonusers were more likely to have any CMB (34.2% versus 23.9%, respectively; P=0.012) and lobar CMB (18.1% versus 8.4%, respectively; P<0.001).

Statin Use

The statin cohort contained 15 711 participants not on a statin at visit 1. A statin was used by 4229 participants at some point from visits 2 to 5. The mean time to ICH or censoring was 19.8 (SD, 5.6) years among statin users and 17.3 (SD, 6.9) years among statin nonusers. Nearly 28% of statin users took a statin at >1 visit for a median of 6.8 (interquartile range, 5.7–13.3) years. Statin users were younger, had higher low-density lipoprotein levels, had ≥1 APOE ε4 allele, and used an

Table 2. Baseline Characteristics of Participants by Use of Each Medication of Interest

Visit 1 Characteristics	Antiplatelet Use				Anticoagulant Use				Statin Use			
	Antiplatelet Cohort (N=14 471)	Any Use From Visit 2–5 (N=7458)	No Use From Visit 2–5 (N=7013)	*P* Value	Anticoagulant Cohort (N=15 719)	Any Use From Visit 2–5 (N=846)	No Use From Visit 2–5 (N=14 873)	*P* Value	Statin Cohort (N=15 711)	Any Use From Visit 2–5 (N=4229)	No Use From Visit 2–5 (N=11 482)	*P* Value
Age, y	54.1 (5.8)	54.1 (5.7)	54.2 (5.9)	0.040	54.2 (5.8)	55.0 (5.6)	54.1 (5.8)	<0.001	54. 2 (5.8)	53.1 (5.4)	54.5 (5.8)	<0.001
Male sex	6325 (44.0)	3478 (46.6)	2847 (41.2)	<0.001	6988 (44.8)	470 (55.6)	6518 (44.1)	<0.001	6998 (44.8)	1909 (45.1)	5089 (44.7)	0.638
White race	10 264 (71.4)	5906 (79.2)	4358 (63.1)	<0.001	11 416 (73.1)	663 (78.4)	10 753 (72.8)	<0.001	11 408 (73.1)	3361 (79.5)	8047 (70.7)	<0.001
High school education or higher	10.795 (75.3)	5936 (79.7)	4859 (70.5)	<0.001	11 875 (76.2)	671 (79.4)	11 204 (76.0)	0.023	11 866 (76.2)	3455 (81.9)	8411 (74.0)	<0.001
Hypertension	5017 (35.1)	2495 (33.6)	2522 (36.7)	<0.001	5434 (35.0)	368 (43.8)	5066 (34.5)	<0.001	5432 (35.0)	1390 (33.0)	4042 (35.7)	0.002
Diabetes mellitus	1715 (12.1)	802 (10.8)	913 (13.4)	<0.001	1851 (12.0)	97 (11.6)	1754 (12.0)	0.702	1844 (11.9)	463 (11.0)	1381 (12.3)	0.037
LDL, mg/dL	137.7 (39.2)	139.2 (38.5)	136.0 (40.0)	<0.001	137.6 (39.3)	137.8 (37.8)	137.6 (39.4)	0.910	137.6 (39.3)	150.9 (39.1)	132.7 (38.2)	<0.001
Coronary artery disease	590 (4.2)	367 (5.01)	223 (3.31)	<0.001	736 (4.8)	74 (8.9)	662 (4.6)	<0.001	747 (4.9)	228 (5.5)	519 (4.7)	0.032
Ever smoker	8281 (57.7)	4272 (57.3)	4009 (58.1)	0.345	9100 (58.3)	512 (60.5)	8588 (58.2)	0.180	9105 (58.4)	2377 (56.2)	6728 (59.2)	0.001
Serum creatinine, mg/dL	1.10 (0.40)	1.10 (0.21)	1.12 (0.53)	0.018	1.11 (0.42)	1.13 (0.19)	1.11 (0.43)	0.005	1.11 (0.42)	1.10 (0.19)	1.12 (0.48)	0.002
APOE genotype				0.030				0.244				<0.001
>1 ε2, no ε4	1973 (14.2)	1025 (14.3)	948 (14.2)		2081 (13.8)	102 (12.7)	1979 (13.9)		2083 (13.9)	477 (11.8)	1606 (14.6)	
>1 ε4, no ε2	3839 (27.7)	1928 (26.9)	1911 (26.9)		4174 (27.8)	225 (28.0)	3949 (27.7)		4171 (27.8)	1169 (28.8)	3002 (27.4)	
ε2 and ε4 alleles	434 (3.1)	209 (2.9)	225 (3.4)		470 (3.1)	17 (2.1)	453 (3.2)		472 (3.1)	106 (2.6)	366 (3.3)	

Mean (SD) values are presented if continuous, and number (percentage) values are presented if categorical. APOE indicates apolipoprotein E; and LDL, low-density lipoprotein.

Table 3. Occurrence of ICH or Ischemic Stroke and Concomitant Medication Use Over the Duration of the Study Period From Visit 2 to 5 and Clinical and Radiographic Variables Assessed at Visit 5 by Medication Group

Variables	Antiplatelet				Anticoagulant				Statin			
	Antiplatelet Cohort (N=14 471)	Any Use From Visit 2–5 (N=7458)	No Use From Visit 2–5 (N=7013)	P Value	Anticoagulant Cohort (N=15 719)	Any Use From Visit 2–5 (N=846)	No Use From Visit 2–5 (N=14 873)	*P* Value	Statin Cohort (N=15 711)	Any Use From Visit 2–5 (N=4229)	No Use From Visit 2–5 (N=11 482)	*P* Value
Variables assessed in all participants												
ICH	124 (0.86)	57 (0.76)	67 (0.97)	0.184	130 (0.83)	3 (0.35)	127 (0.86)	0.168	130 (0.83)	16 (0.38)	114 (0.99)	<0.001
Ischemic stroke before or at time of ICH or censoring	1065 (7.41)	566 (7.59)	499 (7.22)	0.399	1136 (7.27)	133 (15.72)	1003 (6.79)	<0.001	1134 (7.27)	277 (6.55)	857 (7.53)	0.036
Concomitant antiplatelet use	…	…	…	…	8449 (53.75)	488 (57.68)	7961 (53.53)	0.0183	8425 (53.62)	3195 (75.55)	5230 (45.55)	<0.001
Concomitant anticoagulant use	789 (5.46)	417 (5.59)	372 (5.30)	0.448	…	…	…	…	885 (5.63)	361 (8.54)	524 (4.56)	<0.001
Concomitant statin use	3876 (26.78)	2866 (38.43)	1010 (14.40)	<0.001	4263 (27.12)	358 (42.32)	3905 (26.26)	<0.001	…	…	…	…
	N=1801	**N=1221**	**N=580**		**N=1942**	**N=117**	**N=1825**		**N=1939**	**N=928**	**N=1011**	
Variables assessed in participants present at visit 5 who underwent MRI and cognitive testing												
Any CMB	430 (23.88)	290 (23.75)	140 (24.14)	0.857	476 (24.51)	40 (34.19)	436 (23.89)	0.012	476 (24.55)	247 (26.62)	229 (22.65)	0.043
Lobar CMB	155 (8.68)	109 (9.02)	46 (7.97)	0.464	173 (8.98)	21 (18.10)	152 (8.40)	<0.001	173 (9.00)	91 (9.92)	82 (8.15)	0.175
Subcortical CMB	348 (19.48)	228 (18.86)	120 (20.80)	0.333	386 (20.04)	31 (26.72)	355 (19.61)	0.064	386 (20.07)	191 (20.83)	195 (19.38)	0.429
Deep CMB	48 (2.69)	29 (2.40)	19 (3.29)	0.275	53 (2.75)	4 (3.45)	49 (2.71)	0.557	53 (2.76)	23 (1.20)	30 (2.98)	0.526
White matter hyperintensity percentage	3.99 (3.57)	4.07 (3.51)	3.82 (3.67)	0.153	3.98 (3.56)	4.62 (3.45)	3.94 (3.57)	0.047	3.98 (3.57)	4.12 (3.68)	3.86 (3.45)	0.106
Cognitive impairment	1571 (26.74)	1101 (27.17)	470 (25.81)	0.278	1700 (26.48)	175 (34.45)	1525 (25.79)	<0.001	1699 (26.50)	901 (28.62)	798 (24.46)	<0.001

Mean (SD) values are presented if continuous, and number (percentage) values are presented if categorical. CMB indicates cerebral microbleed; ICH, intracranial hemorrhage; and MRI, magnetic resonance imaging.

anticoagulant or antiplatelet. Statin users were likely to be diagnosed with an ischemic stroke and cognitive impairment. Sixteen statin users developed an ICH compared with 114 statin nonusers (0.4% versus 1.0%; $P<0.001$). Only 7 of these ICHs occurred in context of remote statin use before the ICH. The mean time from documented statin use to ICH among remote users was 11.8 (SD, 2.7) years. Among statin users with recent exposure if an ICH occurred and statin nonusers, 0.1% of statin users (N=4) and 1% of statin nonusers (N=119) developed an ICH ($P<0.0001$). Among the 1939 who underwent a visit 5 MRI, there were more CMBs overall in the statin group (26.6% versus 22.7%, respectively; $P=0.043$).

Propensity Score

Tables 4 through 6 displays the visit 1 variables used to create a propensity score for each medication class. Although standardized differences were above the prespecified threshold of 0.10 for many baseline variables, after stratification by propensity quintile, the mean standardized differences across propensity strata were ≥0.10 for only 2 variables: age (mean standardized difference, 0.108) and coronary artery disease (mean standardized difference, 0.108) for anticoagulant use, indicating reasonably well-balanced groups.

Multivariable Analyses

Intracerebral Hemorrhage

There were 130 participants in the ARIC study with a definite or probable ICH (Table 2). The proportionality of hazards assumption was met for every medication class analysis with interaction $P\geq0.05$. The paucity of events in the anticoagulant group precluded meaningful survival analysis for this medication.

In the analysis of recent antiplatelet use if an ICH occurred versus antiplatelet nonuse, there was a significantly lower hazard of ICH among antiplatelet users versus nonusers maintained in all 3 models (Figure [A]; model 1 hazard ratio [HR], 0.36 [95% CI, 0.21–0.61]; model 2 HR, 0.50 [95% CI, 0.29–0.88]; model 3 HR, 0.53 [95% CI, 0.30–0.92]) with the same directionality using static and time-varying antiplatelet exposure. There was a significantly lower hazard of ICH among antiplatelet users at any point during follow-up versus nonusers when considering time-varying use of antiplatelets in the unadjusted model (Figure [B]; model 1 HR, 0.56 [95% CI, 0.37–0.85]), but the association lost significance with subsequent adjustments. HRs obtained with static and time-varying antiplatelet use maintained the same directionality. There were no significant interactions between antiplatelet use and APOE genotype, having an ischemic stroke, or concomitant anticoagulant or statin use on the ICH hazard when the interaction terms were included in model 3.

When analyzing statin users exposed to the medication class including only those with recent use if an ICH occurred versus statin nonusers, time-varying use of statins was associated with a significantly lower hazard of ICH during follow-up in all unadjusted and adjusted models (Figure [A]; model 1 HR, 0.15 [95% CI, 0.06–0.33]). The directionality of HRs was the same with static and time-varying antiplatelet use. The hazard of an ICH was significantly lower with statin use at any point as a time-varying covariate compared with nonuse, and this remained significant in sequentially adjusted models (Figure [B]; model 2 HR, 0.24 [95% CI, 0.12–0.47]; model 3 HR, 0.21 [95% CI, 0.10–0.45]). Again, there were no significant interactions between statin use and the other risk factors in model 3.

Sensitivity Analyses

We analyzed levothyroxine use as documented by study staff inspection of participants' medication containers at each study visit (Tables S1 and S2). There were 1109 participants who took levothyroxine anew after visit 1 before an ICH or, if no ICH occurred, the administrative date of censoring. Eight participants with ICH took levothyroxine before this event (6.3%), whereas 1101 (7.3%) of participants without ICH took levothyroxine before the administrative censoring date ($P=0.6643$). The unadjusted HR of an ICH of levothyroxine use was neither statistically significant in the static use model (HR, 0.74; 95% CI, 0.36–1.52) nor statistically significant in the time-varying model (HR, 1.08; 95% CI, 0.56–2.07). This sensitivity analysis demonstrates the lack of a medication compliance bias in this study. Furthermore, it also lends credence to the HR estimates noted in this study because no increased hazard of ICH was noted among levothyroxine users, as expected.

We additionally analyzed antihypertensive medication use at each study visit. There were 7241 participants who took an antihypertensive anew after visit 1 and before either an ICH or the administrative censoring date. Participants who developed an ICH were significantly less likely to have taken an antihypertensive medication during the study period of interest before the ICH than those who did not develop an ICH (37.5% versus 49.1%; $P=0.0117$). In the unadjusted static model, participants who took an antihypertensive medication had a significantly lower hazard of ICH during follow-up (HR, 0.56; 95% CI, 0.38–0.83). In the unadjusted time-varying model, the ICH hazard was again lower among participants taking an antihypertensive medication (HR, 0.66; 95% CI, 0.44–0.99). This expected result further validates the method used to assess the associations between medications of interest and ICH in this study.

Table 4. Propensity Score Assessment for Antiplatelet Use

Without Propensity Score Stratification				With Propensity Score Stratification														
				Propensity Score Quintile 1			Propensity Score Quintile 2			Propensity Score Quintile 3			Propensity Score Quintile 4			Propensity Score Quintile 5			
Variable	Proportion of Antiplatelet Users	Proportion of Antiplatelet Nonusers	Std. Diff.	Proportion of Antiplatelet Users	Proportion of Antiplatelet Nonusers	Std. Diff.	Proportion of Antiplatelet Users	Proportion of Antiplatelet Nonusers	Std. Diff.	Proportion of Antiplatelet Users	Proportion of Antiplatelet Nonusers	Std. Diff.	Proportion of Antiplatelet Users	Proportion of Antiplatelet Nonusers	Std. Diff.	Proportion of Antiplatelet Users	Proportion of Antiplatelet Nonusers	Std. Diff.	Mean Std. Diff.
Aged >54 y	0.463	0.473	0.017	0.482	0.481	0.001	0.580	0.569	0.019	0.515	0.518	0.006	0.471	0.461	0.015	0.316	0.329	0.022	0.013
Men	0.466	0.412	0.089	0.392	0.427	0.059	0.285	0.290	0.009	0.100	0.092	0.022	0.434	0.414	0.033	0.973	0.973	0.001	0.025
White race	0.792	0.631	0.304	0.459	0.378	0.134	0.611	0.578	0.054	0.989	0.987	0.017	0.998	0.997	0.012	0.998	0.999	0.013	0.046
High school education or higher	0.797	0.705	0.179	0.497	0.451	0.076	0.531	0.539	0.013	0.876	0.856	0.049	0.935	0.954	0.067	0.978	0.970	0.041	0.049
CAD	0.050	0.033	0.067	0.014	0.017	0.024	0.026	0.019	0.036	0.017	0.016	0.006	0.029	0.024	0.025	0.126	0.109	0.042	0.027
Hypertension	0.336	0.367	0.053	0.456	0.449	0.012	0.405	0.442	0.062	0.207	0.206	0.003	0.371	0.356	0.025	0.268	0.255	0.022	0.025
Diabetes mellitus	0.108	0.134	0.066	0.174	0.200	0.055	0.147	0.147	0.001	0.079	0.093	0.041	0.098	0.079	0.053	0.058	0.056	0.006	0.031
LDL >160 mg/dL	0.268	0.251	0.031	0.113	0.117	0.012	0.373	0.358	0.025	0.323	0.345	0.038	0.173	0.187	0.030	0.309	0.301	0.015	0.024
Ever smoker	0.573	0.581	0.013	0.589	0.636	0.078	0.666	0.651	0.025	0.505	0.480	0.041	0.500	0.504	0.007	0.622	0.595	0.045	0.039
Creatinine> mean	0.358	0.345	0.023	0.376	0.410	0.056	0.268	0.281	0.023	0.129	0.145	0.038	0.331	0.303	0.048	0.628	0.630	0.003	0.033
Anticoagulant at visit 1	0.003	0.006	0.035	0.013	0.017	0.029	0.002	0.003	0.022	0.003	0.009	0.065	0.001	0.002	0.009	0.001	0.003	0.040	0.033
Statin at visit 1	0.006	0.003	0.030	0.002	0.003	0.013	0.002	0.002	0.010	0.004	0.004	0.004	0.002	0.001	0.021	0.016	0.007	0.071	0.024

Std. Diff. values among antiplatelet users and nonusers for each visit 1 variable represented in the propensity score for taking the medication from visit 2 to 5 without and with propensity quintile stratification, yielding mean Std. Diff. values. CAD indicates coronary artery disease; LDL, low-density lipoprotein; and Std. Diff., standardized difference.

Table 5. Propensity Score Assessment for Anticoagulant Use

Without Propensity Score Stratification				With Propensity Score Stratification																
				Propensity Score Quintile 1			Propensity Score Quintile 2			Propensity Score Quintile 3			Propensity Score Quintile 4			Propensity Score Quintile 5			Mean Std. Diff.
Variable	Proportion of Anticoagulant Users	Proportion of Anticoagulant Nonusers	Std. Diff.	Proportion of Anticoagulant Users	Proportion of Anticoagulant Nonusers	Std. Diff.	Proportion of Anticoagulant Users	Proportion of Anticoagulant Nonusers	Std. Diff.	Proportion of Anticoagulant Users	Proportion of Anticoagulant Nonssers	Std. Diff.	Proportion of Anticoagulant Users	Proportion of Statin Nonusers	Std. Diff.	Proportion of Anticoagulant Users	Proportion of Anticoagulant Nonusers	Std. Diff.	
Aged >54 y	0.546	0.464	0.134	0.084	0.117	0.091	0.424	0.576	0.250	0.458	0.522	0.105	0.676	0.625	0.088	0.715	0.717	0.004	0.108
Men	0.556	0.441	0.189	0.105	0.101	0.011	0.242	0.271	0.054	0.477	0.463	0.023	0.553	0.580	0.043	0.875	0.827	0.113	0.049
White race	0.784	0.728	0.107	0.590	0.550	0.065	0.647	0.674	0.047	0.745	0.762	0.033	0.883	0.838	0.110	0.878	0.876	0.006	0.052
High school education or higher	0.794	0.760	0.068	0.695	0.677	0.032	0.616	0.624	0.014	0.837	0.817	0.043	0.782	0.810	0.056	0.890	0.904	0.037	0.036
CAD	0.089	0.046	0.135	0.000	0.013	0.159	0.020	0.016	0.025	0.000	0.013	0.163	0.021	0.016	0.029	0.251	0.168	0.164	0.108
Hypertension	0.438	0.345	0.155	0.074	0.124	0.143	0.283	0.220	0.118	0.288	0.260	0.051	0.463	0.449	0.022	0.662	0.660	0.003	0.067
Diabetes mellitus	0.116	0.120	0.011	0.126	0.121	0.013	0.172	0.136	0.081	0.072	0.099	0.081	0.117	0.106	0.030	0.095	0.106	0.030	0.047
LDL >160 mg/dL	0.265	0.260	0.009	0.137	0.175	0.088	0.394	0.356	0.064	0.190	0.220	0.063	0.346	0.319	0.045	0.240	0.236	0.007	0.053
Smoking	0.605	0.582	0.039	0.547	0.504	0.072	0.515	0.565	0.081	0.556	0.575	0.032	0.606	0.613	0.010	0.700	0.666	0.059	0.051
Creatinine> mean	0.448	0.349	0.163	0.105	0.087	0.049	0.242	0.240	0.005	0.340	0.316	0.042	0.415	0.437	0.037	0.745	0.695	0.092	0.045
Antiplatelet at visit 1	0.121	0.082	0.101	0.000	0.005	0.097	0.030	0.058	0.117	0.046	0.043	0.011	0.122	0.115	0.018	0.262	0.209	0.102	0.069
Anticoagulant at visit 1	0.007	0.005	0.023	0.011	0.000	0.099	0.010	0.002	0.080	0.000	0.003	0.080	0.000	0.007	0.119	0.015	0.012	0.023	0.080

Std. Diff. values among anticoagulant users and nonusers for each visit 1 variable represented in the propensity score for taking the medication from visit 2 to 5 without and with propensity quintile stratification, yielding mean Std. Diff. values. CAD indicates coronary artery disease; LDL, low-density lipoprotein; and Std. Diff., standardized difference.

Table 6. Propensity Score Assessment for Statin Use

Without Propensity Score Stratification				With Propensity Score Stratification														
				Propensity Score Quintile 1			Propensity Score Quintile 2			Propensity Score Quintile 3			Propensity Score Quintile 4			Propensity Score Quintile 5			
Variable	Proportion of Statin Users	Proportion of Statin Nonusers	Std. Diff.	Proportion of Statin Users	Proportion of Statin Nonusers	Std. Diff.	Proportion of Statin Users	Proportion of Statin Nonusers	Std. Diff.	Proportion of Statin Users	Proportion of Statin Nonusers	Std. Diff.	Proportion of Statin Users	Proportion of Statin Nonusers	Std. Diff.	Proportion of Statin Users	Proportion of Statin Nonusers	Std. Diff.	Mean Std. Diff.
Aged >54 y	0.400	0.495	0.158	0.673	0.740	0.120	0.572	0.545	0.044	0.419	0.456	0.062	0.375	0.369	0.011	0.271	0.264	0.012	0.050
Men	0.451	0.447	0.007	0.472	0.466	0.010	0.471	0.422	0.080	0.423	0.427	0.006	0.452	0.459	0.011	0.467	0.473	0.009	0.023
White race	0.795	0.707	0.170	0.559	0.531	0.045	0.685	0.686	0.002	0.734	0.747	0.024	0.820	0.804	0.033	0.926	0.919	0.021	0.025
High school education or higher	0.819	0.740	0.159	0.497	0.530	0.055	0.725	0.742	0.032	0.847	0.811	0.079	0.866	0.852	0.031	0.889	0.887	0.004	0.040
CAD	0.055	0.047	0.031	0.053	0.036	0.065	0.043	0.046	0.012	0.026	0.038	0.057	0.051	0.048	0.011	0.075	0.064	0.035	0.036
Hypertension	0.330	0.357	0.046	0.454	0.437	0.027	0.363	0.326	0.065	0.295	0.335	0.071	0.305	0.317	0.020	0.301	0.297	0.008	0.038
Diabetes mellitus	0.110	0.123	0.032	0.151	0.145	0.014	0.122	0.114	0.022	0.096	0.117	0.057	0.106	0.099	0.019	0.090	0.089	0.004	0.023
LDL >160 mg/dL	0.372	0.219	0.271	0.019	0.022	0.022	0.077	0.073	0.013	0.125	0.153	0.068	0.352	0.343	0.015	0.737	0.691	0.084	0.040
Smoking	0.562	0.592	0.049	0.645	0.682	0.063	0.585	0.589	0.007	0.553	0.558	0.010	0.567	0.559	0.014	0.543	0.540	0.005	0.020
Creatinine >mean	0.364	0.352	0.019	0.365	0.363	0.005	0.362	0.345	0.028	0.368	0.333	0.058	0.354	0.365	0.019	0.365	0.358	0.010	0.024
Antiplatelet at visit 1	0.094	0.080	0.041	0.071	0.064	0.023	0.101	0.079	0.060	0.064	0.079	0.046	0.073	0.081	0.025	0.135	0.120	0.037	0.038
Anticoagulant at visit 1	0.004	0.005	0.017	0.006	0.013	0.058	0.004	0.003	0.010	0.001	0.001	0.002	0.001	0.001	0.000	0.005	0.003	0.026	0.019

Std. Diff. values among statin users and nonusers for each visit 1 variable represented in the propensity score for taking the medication from visit 2 to 5 without and with propensity quintile stratification, yielding mean Std. Diff. values. CAD indicates coronary artery disease; LDL, low-density lipoprotein; and Std. Diff., standardized difference.

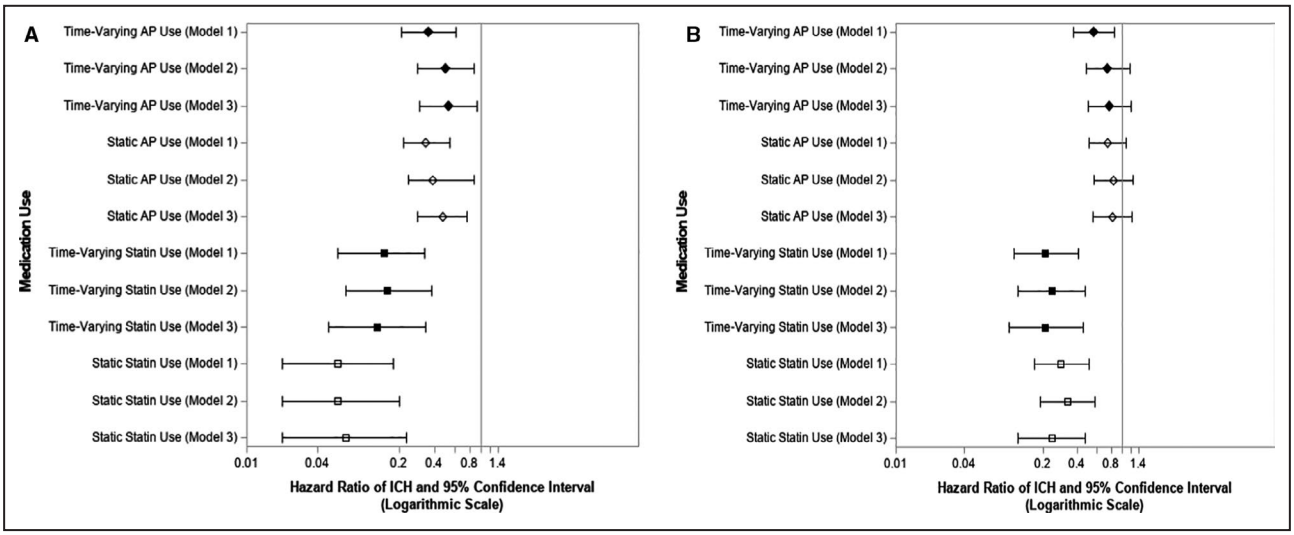

Figure. Medication use and the hazard of an intracerebral hemorrhage (ICH).
Unadjusted and adjusted hazard ratios of ICH by use of medications of interest during follow-up and at the most recent study visit just before ICH if the event occurred vs nonuse (**A**); and use of medications of interest at any point during follow-up before ICH vs nonuse (**B**). The hazards of ICH as function of medication use as both a static and a time-varying covariate were modeled. Model 1 was unadjusted, model 2 was adjusted for propensity quintile to take the medication, and model 3 was adjusted for propensity quintile, concomitant use of either of the other medication classes during follow-up, occurrence of an ischemic stroke, and apolipoprotein E genotype. AP indicates antiplatelet.

CMBs in Any Location

Neither antiplatelet nor statin use was associated with having a CMB in any location (Table 7). The odds of a CMB were higher among anticoagulant users (OR, 1.64; 95% CI, 1.04–2.59), but this association dissipated with adjustments. There was no significant interaction between antiplatelet use and APOE genotype, concomitant anticoagulant or statin use, white matter hyperintensity percentage, and cognitive status in predicting the odds of any CMB in model 3.

Lobar CMBs

Neither antiplatelet nor statin use was associated with the presence of a lobar CMB. Anticoagulant users were at significantly higher risk of having a lobar CMB in the unadjusted model (model 1 OR, 1.96; 95% CI, 1.14–3.36), but not after adjustments. There were no significant interactions between any of the medications of interest and the other risk factors in model 3.

Subcortical and Deep CMBs

Medication exposure was not associated with subcortical or deep CMBs.

DISCUSSION

This study delineates associations between medications with hemorrhagic potential (namely, antiplatelets, anticoagulants, and statins) and ICH and CMBs in the population-based and longitudinal ARIC study cohort. Antiplatelet and statin use were associated with significantly lower risks of ICH longitudinally. There was an increased risk of CMB among anticoagulant users, but not after adjusting for the propensity for taking these medications and markers of small-vessel disease presence and severity.

The protective effects of antiplatelets and statins against ICH in our study may be partly explained by their biochemical mechanisms at sites of action in the cerebral vasculature. These medications may be safeguards of arterial vessel wall integrity because of their antithrombotic and anti-inflammatory properties. Antiplatelets prevent platelet aggregation and thrombosis, precluding platelet-endothelium interaction that leads to a proinflammatory cascade and atherosclerotic wall damage.[39] In addition to their lipid-lowering activity, statins upregulate platelet and endothelial NO synthase and platelet-derived NO,[40] resulting in less platelet-mediated arterial thrombosis and fragility. Thus, long-term antiplatelet and statin use may prevent arterial wall compromise and consequent hemorrhage.[41] These medications also decrease the risk of ischemic stroke, thus indirectly preventing hemorrhagic conversion. The strength of the protective association of these medications, however, was preserved even after adjusting for ischemic stroke occurrence, suggesting that their influences extend beyond preventing an acute, macrothrombotic event. The results from our study are similar to the findings in RESTART (Restart or Stop Antithrombotics Randomized Trial).

Table 7. Medication Use and Prevalence of CMB

Medication	Model 1*	Model 2†	Model 3‡
Any CMB			
Any antiplatelet	1.07 (0.81–1.40)	1.05 (0.79–1.40)	1.00 (0.74–1.35)
Any anticoagulant	1.64 (1.04–2.59)	1.44 (0.91–2.29)	1.21 (0.75–1.97)
Any statin	1.21 (0.95–1.56)	1.29 (0.98–1.70)	1.23 (0.92–1.64)
Lobar CMB			
Any antiplatelet	1.24 (0.80–1.91)	1.17 (0.75–1.82)	1.04 (0.66–1.64)
Any anticoagulant	1.96 (1.14–3.36)	1.65 (0.95–2.88)	1.34 (0.76–2.35)
Any statin	1.27 (0.86–1.87)	1.30 (0.86–1.97)	1.16 (0.76–1.76)
Subcortical CMB			
Any antiplatelet	1.04 (0.78–1.38)	1.07 (0.80–1.45)	1.01 (0.74–1.38)
Any anticoagulant	1.51 (0.94–2.43)	1.38 (0.85–2.24)	1.23 (0.74–2.05)
Any statin	1.12 (0.85–1.46)	1.19 (0.88–1.61)	1.15 (0.84–1.57)
Deep CMB			
Any antiplatelet	0.69 (0.33–1.42)	0.64 (0.29–1.42)	0.56 (0.25–1.23)
Any anticoagulant	1.27 (0.43–3.76)	1.14 (0.39–3.37)	0.94 (0.31–2.85)
Any statin	0.78 (0.48–1.25)	0.81 (0.49–1.33)	0.79 (0.47–1.32)

Data are given as odds ratio (95% CI). Unadjusted and unadjusted odds ratios for CMB, lobar CMB, subcortical CMB, and deep CMB are given as a function of any exposure to each medication of interest during the study period. CMB indicates cerebral microbleed.

*Unadjusted model.

†Model adjusted for propensity score quintile.

‡Model adjusted for propensity score quintile, apolipoprotein E genotype, white matter hyperintensity volume, cognitive status, and any concomitant use of the other 2 medication types from visit 2 to visit 5.

The trial demonstrated that participants randomized to an antiplatelet after an ICH were less likely to have a recurrent ICH during the 4 years of follow-up (HR, 0.51; 95% CI, 0.25–1.03; P=0.06).[42] The authors postulated the mechanisms included prevention of ischemic stroke and thereby hemorrhagic transformation, prevention of arterial thrombosis, which can trigger hemorrhage, and mitigation of inflammation, which might be a key mechanism for the development of ICH.

Our results contrast with observational studies demonstrating no or increased ICH risk with aspirin[4,7,9,43,44]; however, the follow-up in these studies was at most 5 years. The protective effect of antiplatelet use in our study may reflect the longer duration of exposure to prevent vascular remodeling and longer follow-up needed to identify ICH events as arteriopathy accrues in those not exposed. Furthermore, the results from some of these studies, which were conducted outside the United States, may not be generalizable to the US population with its specific risk factors for ICH attributable to lifestyle behaviors as well as genetic composition. Finally, there is variability by the intracranial compartment studied. For instance, the clinical trial, ASPREE, demonstrated an elevated risk of ICH with aspirin use with respect to subdural or extradural hemorrhage, but no association with ICH. Finally, observational studies are prone to confounding by indication and selection biases, which we attempted to directly address in this study.

The protective effect of statin use in our study also differs from the result of the post hoc analysis of the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study, which demonstrated that statin use was associated with increased risk of ICH among patients with stroke (HR, 1.68; 95% CI, 1.09–2.59).[45] This secondary prevention trial only included subjects with a prior stroke with likely already fragile vasculature, and the antithrombotic property of statins may have prevailed. In our study, we did not exclude participants with prior stroke and adjusted the effects of statin use for the occurrence of an interim ischemic stroke, after which the protective effect was maintained. A study of 345 531 individuals in Israel followed up for 9.5 years also noted a significantly protective effect of statin use against ICH (HR, 0.68; 95% CI, 0.58–0.79), suggesting that long-term statin use in the general population may prevent the occurrence of vasculopathy that results in ICH.[46]

Anticoagulant use was associated with a significantly higher risk of any and lobar CMBs, but not after adjustment for demographics and markers of the presence and severity of small-vessel disease. Our finding is consistent with results from the Rotterdam Study, which followed up 1062 participants who ever took an antithrombotic and underwent a brain MRI in the Netherlands.[15] To our knowledge, there have not been any other large studies assessing longitudinal anticoagulant use and the prevalence of CMBs. Antiplatelet

use did not confer any additional risk of CMB in our study, unlike in the Rotterdam Study, which observed an elevated risk of lobar CMB among aspirin users and no association with deep or infratentorial CMBs. One explanation may be the differences in antiplatelets taken. For instance, a low number of Rotterdam Study participants on platelet aggregation inhibitor specifically took aspirin (n=67). There is also substantial variation in APOE allelic distribution by geography, which may support the differential association of antiplatelet use and CMB.[47] Further studies are needed to help elucidate the interactions between the specific platelet aggregation medications and the neurovascular unit.

We addressed several potential sources of bias. To minimize reporting bias, we assessed medication use from lists or containers brought to each visit or read from during telephone calls. To account for nonrandom use of medications, we included commonly available variables at midlife, which may predict future use of medications by adjusting for well-balanced propensity scores. A sensitivity analysis did not demonstrate a compliance bias, thus bolstering the validity of the primary analyses. The index time for study entry was set at visit 2, and participants on a medication of interest at visit 1 were excluded for each analysis to prevent left-truncation bias. Time-varying covariates were used to mitigate biasing the HR with fixed, static medication exposure, which inflates exposed time at risk. Although a more appropriate method, it relies on an assumption of participation, taking the medication from one visit to just before the next, which occurred nearly every 3 to 6 years. Once cardiovascular disease is diagnosed, rarely does the indication for one of these medications resolve. In a study of ARIC study participants, 97.8% have reported that their degree of medication adherence is either medium or high. Thus, it is within the realm of possibilities that the medication was used for a major duration of the time interval. Nevertheless, further studies are needed with more granular medication adherence data to confirm the findings in this study.

There were several limitations of our study. The propensity score method, unlike randomization, does not balance unmeasured confounders. Because all non-White or non-Black and all Black participants from Washington County and Minnesota were excluded, the generalizability of these results to other races/ethnicities is limited. The time intervals between follow-up visits were lengthy. To that end, we inserted data from the intervening follow-up telephone call for the longest interval between visits 4 and 5. Relatively few participants experienced ICH, underpowering our interaction and subgroup analyses. Only 4 patients with ICH underwent the visit 5 MRI, of whom 3 demonstrated the presence of a CMB; thus, further details about the imaging correlates of the clinical ICH events could not be determined. The interrater reliability of CMB detection was 85%; however, given that the raters were blinded to medication use, we have little reason to believe there was heterogeneity in CMB rating by treatments. Data from only 1 MRI visit were available, so it is theoretically possible that the microbleeds visualized on the visit 5 MRI preceded entry into the study. However, given the average age of participants at visit 1 was 54 years and the prevalence of CMB in participants aged 50 to 59 years has been reported at 6.5% to 11.5%, it is possible that most CMBs seen on the visit 5 MRI were accrued during the study period.[48] Although the CMB analysis of this study was cross-sectional, future studies are needed to assess interval changes in the number of CMBs as a function of medication use, and acquisition of visit 6 MRI data may present such an opportunity.

This study presents the risks of developing ICH and having CMBs in participants from 4 US regions with use of antiplatelets, anticoagulants, and statins. Our findings suggest that there may be differential bleeding risk profiles of each medication for intracerebral microhemorrhage and macrohemorrhage. These results, derived from a large, longitudinal US cohort, are hypothesis generating and may provide justification for future studies testing the hemorrhagic effects of these medications while accounting for medication indication and small-vessel disease markers.

ARTICLE INFORMATION

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Author Contributions: Dr Sharma designed and conceptualized study; analyzed and interpreted data; drafted and revised the manuscript; and conducted the statistical analysis. Drs Matsushita, Wu, Jack, Mosley, and Fornage revised the manuscript for intellectual content. Dr Griswold assisted with data analysis and interpretation; and revised the manuscript for intellectual content. Dr Gottesman designed the study; assisted with analysis and interpretation of data; and revised the manuscript.

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Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Codes available to extract anti-hypertensive medication usage by ARIC Visit.

Visit 1	Visit 2	Visit 3	Visit 4	Annual Follow-Up Phone Call 2004-2007	Visit 5
Apresazide	109534	109534	109534	Amlodipine	37600040000305
Calan	107371	107371	107371	Apresazide	36992002130320
Captopril	109516	109516	109516	Atenolol	37600040000310
Cardizem	108955	108955	108955	Benazepril	37600040000110
Catapress	118787	118787	118787	Benicar	36400010100305
Chlorthalidone	110671	110671	110671	Caduet	37500020000305
Clonidine	117658	117658	117658	Calan	37500020000310
Diltiazem	116025	116025	116025	Captopril	33100040100315
Dyazide	105684	105684	105684	Captopril/Hydrochlorothia	37990002300330
Furosemide	110239	110239	110239	Cardizem	37990002300315
HCTZ	115606	115606	115606	Cartia	37990002300105
Hydralazine	112492	112492	112492	Catapress	32100025007520
Hydrochlorot	119344	119344	119344	Chlorthalidone	32100020000405
Hydrochlorothiazide	106000	106000	106000	Clonidine	36201010100315
Inderal	109963	109963	109963	Diltiazem	34000020007570
Inderide	112023	112023	112023	Diovan	36100010000310
Isordil	101475	101475	101475	Dyazide	33100040107025
Isosorbide	111651	111651	111651	Enalapril	34000030100420
Lozol	117661	117661	117661	Felodipine	34000030100410
Maxzide	102382	102382	102382	Furosemide	33200020000305
Metholazone	104461	104461	104461	HCTZ	33200020000303
Minipres	121446	121446	121446	Hydralazine	33200020000310
Moduretic	115074	115074	115074	Hydrochlorot	34000010107040
Nifedipine	116867	116867	116867	Hydrochlorothiazide	34000010107030
Normazide	109480	109480	109480	Hyzaar	34000010106910
Normodyne	119682	119682	119682	Inderal	33100040107040
Prazosin	107888	107888	107888	Inderide	36150080000320
Prinivil	121424	121424	121424	Isordil	36994002700370
Prinzide	107870	107870	107870	Isosorbide	36150080000330
Procard	116017	116017	116017	Lisinopril	36994002700350
Procardia	109495	109495	109495	Lozol	36150080000340
Propranolol	104472	104472	104472	Maxzide	34000020007550
Spironolactone				Metholazone	36100030000310
Triameter				Minipres	36100030000310
Verapamil				Moduretic	36100030000330
					36100030000305
					36991802550320
					34000003100330
					34000003100340
					34000003100320

Zestril				Nadalol Nifedipine Normazide Normodyne Norvasc Prazosin Prinivil Prinzide Procard Procardia Propranolol Spironolactone Terazosin Triameter Verapamil Zestril	36991802550320 36100030000315 36150040200330 36994002450320 36150040200340 36993002050340 36993002050320 36150055200340 36994002500320 36100050000140 33300007000310 33300007000320 33300007000330 36202040100115 36991802550305 36991802550310 36202005100320 36202005100340 36994002450340 36150040200330 36991802550305 36100020100310 36992002100310 33200020000303 36994002600340 36991502200160 36991502200140 36992002130320 36201010100305 36994503450330 36991802650330

Table S2. Codes available to extract thyroid medication usage by ARIC Visit.

Visit 1	Visit 2	Visit 3	Visit 4	AFU	Visit 5
Levothroid Levothyroxine Synthroid Thyroid	110586	110586	110586	Levothroid Levothyroxine Synthroid Thyroid	28100010100310 28100010100315 28100010100317 28100010100320 28100010100322 28100010100325 28100010100327 28100010100330 28100010100335