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APOE ε4 and Risk of Intracranial Hemorrhage in Patients With Atrial Fibrillation Taking Apixaban

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IMPORTANCE The *APOE* ε4 variant is causally linked to cerebral amyloid angiopathy and is a risk factor for intracranial hemorrhage (ICH) among warfarin-treated patients with atrial fibrillation. Nevertheless, its impact on those treated with apixaban remains unknown.

OBJECTIVE To test the hypothesis that *APOE* ε4 allele carriership is associated with an increased risk of ICH in patients with atrial fibrillation taking apixaban.

DESIGN, SETTING, AND PARTICIPANTS This cohort study involved data from the All of Us Research Program, a longitudinal, population-based study in the United States. Inclusion criteria were age older than 50 years, history of atrial fibrillation, and anticoagulation with apixaban. Participants with a history of ischemic stroke or ICH were excluded. Up to 3 years of follow-up data were available. Data were collected from 2017 to 2022 and analyzed from November 2023 to December 2024.

EXPOSURE *APOE* ε2, ε3, and ε4 were ascertained using variants rs429358 and rs7412. *APOE* ε4 was modeled dichotomously (noncarriers [no alleles] vs carriers [1 or 2 alleles]).

MAIN OUTCOMES AND MEASURES Incident ICH, including any new intraparenchymal, subdural, or subarachnoid hemorrhage after initiation of apixaban therapy.

RESULTS Of 413 477 All of Us participants, 2038 were eligible. Their mean (SD) age was 71 (9) years; 918 (45%) were female, 1120 (55%) were male, and 1710 (83%) had European ancestry. Among these participants, 483 (23.7%) were carriers of at least 1 *APOE* ε4 allele. After a median follow-up of 2.9 years, 26 participants sustained an ICH (cumulative incidence, 1.5%; 95% CI, 1.0%-2.2%), of whom 12 (cumulative incidence, 3.1%; 95% CI, 1.7%-5.3%) were carriers and 14 (cumulative incidence, 1%; 95% CI, 0.6%-1.7%) were noncarriers ($P = .007$). Multivariable Cox proportional hazard models confirmed this association: compared with noncarriership, *APOE* ε4 carriership was associated with a 3-fold increase in the risk of ICH (hazard ratio, 3.07; 95% CI, 1.42-6.65). *APOE* information improved the discrimination of risk prediction scores (C statistic of 0.74 and 0.68 for models with and without *APOE*, respectively; $P = .03$).

CONCLUSIONS AND RELEVANCE Further research is needed to evaluate whether cerebral amyloid angiopathy mediates the observed association and whether *APOE* e4 information improves clinical decision-making about anticoagulation therapy in patients with atrial fibrillation. The latter is important now that *APOE* information is used in clinical settings to guide antiamyloid treatment for Alzheimer disease and has been returned to millions of persons by direct-to-consumer genotyping companies.

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Supplemental content

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Atrial fibrillation, a highly prevalent cardiac arrhythmia, substantially contributes to global morbidity and mortality.[1] Effective management of atrial fibrillation often involves anticoagulant therapy, such as warfarin, or direct oral anticoagulants like apixaban, to mitigate the risk of thromboembolic events.[1] However, this treatment is not without risks, as it increases the possibility of serious hemorrhages such as intracranial hemorrhage (ICH), a feared and potentially fatal event.[1] Because of this subtle balance of benefits and risks, clinical decision-making tools that estimate the risk of thromboembolic and bleeding events have a important role in guiding the decision to initiate and continue anticoagulant therapy. As an example, the HAS-BLED score captures several ICH risk factors to estimate an individual patient's bleeding risk and, in turn, guides clinicians in the careful consideration of initiating anticoagulant therapy.[2]

The ε4 variant within the *APOE* gene is a strong risk factor for ICH[3] as it has been shown to double the risk of spontaneous ICH.[4] Among patients treated with warfarin for atrial fibrillation, *APOE* ε4 was associated with a 2-fold increase in the risk of ICH, and information on *APOE* status was shown to improve prediction models for ICH.[5] Despite this compelling evidence, the role of *APOE* ε4 as a risk factor for ICH in patients with atrial fibrillation treated with direct oral anticoagulants has not been studied. One reason for the lack of data on this question has been the absence of large cohorts of patients treated with these anticoagulants with available genetic information.

We leveraged genetic data from the largest population study to date conducted in the US to test the hypothesis that individuals with atrial fibrillation taking apixaban and carrying at least 1 *APOE* ε4 allele are at increased risk of ICH. We chose apixaban because it is the most widely used and cost-effective direct oral anticoagulant for the prevention of ischemic stroke in patients with atrial fibrillation.[6,7] Filling this knowledge gap is important because nearly 25% of individuals in the US carry at least 1 *APOE* ε4 allele, making it a prevalent polymorphism with clinical implications.[8] Importantly, direct-to-consumer genetic testing companies are changing the field of personalized medicine by returning *APOE* data to their customers around the world.[9] In addition, *APOE* information is now being actively used in clinical practice to select patients for treatment with the antiamyloid treatment lecanemab, as clinical trial data showed an increased risk of amyloid-related imaging abnormalities (a feared complication of this therapy) in *APOE* ε4 carriers.[10] As a result, current appropriate use recommendations advocate for *APOE* genotyping in all candidates for lecanemab before initiating treatment to inform risk discussions and help guide safety considerations.[11] The widespread access to genetic information coupled with the clear role of *APOE* in existing precision medicine strategies could significantly facilitate the integration of genetic information into risk-stratification tools used for clinical decision-making in patients with atrial fibrillation who are anticoagulation candidates.

Key Points

Question Does the *APOE* ε4 allele increase the risk of intracranial hemorrhage among patients with atrial fibrillation who are treated with apixaban?

Findings In this cohort study that evaluated 2038 patients who had atrial fibrillation on apixaban and no history of stroke, carriers vs noncarriers of 1 or 2 *APOE* epsilon ε4 alleles exhibited a 3-fold increase in intracranial hemorrhage risk over a median follow-up of 2.9 years.

Meaning *APOE* epsilon ε4 is a significant risk factor for intracranial hemorrhage in patients with atrial fibrillation on apixaban; additional research is needed to identify the mediating biological mechanisms and evaluate the utility of adding *APOE* information to existing risk stratification tools for bleeding complications.

Methods

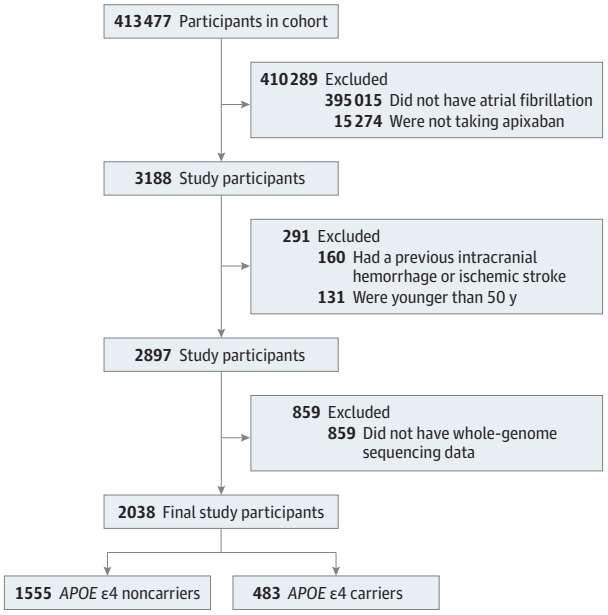
Study Design, Setting, and Participants

We performed a genetic association study nested within the All of Us Research Program.[12] The National Institutes of Health All of Us Research Program is a large ongoing prospective population study within the United States that aims to enroll 1 million individuals 18 years and older. All of Us welcomes participants from all backgrounds to reduce disparities in medical research, with the goal of returning individual information to participants. Among persons who consent, All of Us aims to collect survey questionnaires capturing detailed past and present medical data, electronic health records, physical measurements (ie, blood pressure, height, weight), and genomic information (ie, whole-genome sequencing). More information regarding All of Us, its design, and logistics is available elsewhere.[13] Inclusion criteria for the current nested study were age older than 50 years, presence of atrial fibrillation, and ongoing anticoagulation with apixaban started after an atrial fibrillation diagnosis. This specific age cutoff is often used in studies of spontaneous and anticoagulant-associated ICH to minimize the inclusion of other causes of ICH (eg, vascular malformations and tumors) that are more frequent in younger patients.[4] Exclusion criteria were histories of ischemic stroke or ICH. The All of Us institutional review board approved the protocol and study, and all participants or their legally designed surrogates provided written informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Ascertainment of Atrial Fibrillation and Apixaban Treatment

Atrial fibrillation was ascertained using a combination of codes from Systematized Nomenclature of Medicine (SNOMED)[14]; *International Classification of Diseases, Ninth Revision (ICD-9)*[15]; and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*),[16] as shown in eTable 1 in Supplement 1. We ascertained apixaban use using a combination of Multum,[17] National Drug Code,[18] Veterans Health Administration National Drug File,[19] and RxNorm codes[20] (eTable 2 in Supplement 1).

Figure 1. Assembly of Analytical Sample



The flow chart was originally designed using BioRender software.

Genomic Data and *APOE* Status

Consenting participants gave 15 mL of blood for genetic analysis, with saliva samples as an alternative when blood collection was not feasible.[13] To date, 312 945 participants have provided their genetic data, yielding 245 388 short-read whole-genome sequencing samples. These data encompass more than 1.03 billion single-nucleotide variations and insertion/deletion sites. Uniformity in genomic data was ensured by standardizing the library construction protocol (PCR Free Lapa HyperPrep), sequencing equipment (NovaSeq 6000), and bioinformatics tools (DRAGEN version 3.4.12), which also facilitate sample quality control metrics for variant calling, all of which are reported to the Data and Research Center.[13] The single-nucleotide variations rs429358 and rs7412 were used to determine *APOE* ε2, ε3, and ε4 genotype status for each participant. In primary analyses, we removed participants with C/T genotype for both rs429358 and rs7412 (n = 49) that result in ambiguous ε status that can correspond to either ε1/ε3 or ε2/ε4.[21,22]

Outcome Ascertainment

The primary outcome was incident ICH, which was defined as any nontraumatic intraparenchymal, subdural, or subarachnoid hemorrhage sustained after apixaban initiation. The secondary outcomes were intraparenchymal hemorrhage, ischemic stroke, and the composite of ischemic stroke and ICH. The latter has been used to evaluate net clinical benefit in studies evaluating anticoagulants among patients with atrial fibrillation.[23] We did not include subdural and subarachnoid hemorrhages as secondary outcomes because of their low prevalence. In accordance with the All of Us Data and Statistics Dissemination policy, counts under 20 are typically not reported; however, we obtained an exception for this study (see the section "Data Availability"). These outcomes were ascertained from individual-level electronic health records, clinical notes, and self-report data using a combination of SNOMED, *ICD-9*, and *ICD-10* codes,[14-16] shown in eTable 3 in Supplement 1.

Covariates

Sex and smoking were ascertained via questionnaire data while age at apixaban initiation was calculated using participants' date of birth and date of apixaban initiation, the latter obtained via electronic health records. Overweight and obesity were calculated using participants' body mass index (≥25 and ≥30, respectively). Body mass index was calculated as weight in kilograms divided by height in meters squared by the All of Us core team using height and weight measured at study enrollment. Genetic ancestry and the first 3 genetic principal components (a standard measure to control for population stratification in population genetics) were calculated using principal component analysis by the All of Us team during standard genetic quality control. All other cardiovascular risk factors and comorbidities were ascertained from individual-level electronic health records, clinical notes, and self-report data using SNOMED, *ICD-9*, and *ICD-10* codes, shown in eTable 4 in Supplement 1.[14-16]

Statistical Analyses

Discrete data are presented as counts (percentage), and continuous variables as median (IQR) or mean (SD), as appropriate. We used time-to-event analyses to ascertain risks for the primary and secondary outcomes from the date of apixaban initiation to the outcome date. Participants were censored at the time of death or 3 years after apixaban initiation as it was the point when 80% of participants had completed their follow-up.

First, we evaluated the cumulative incidence and respective 95% CIs of our outcomes using cumulative incidence functions, accounting for death as a competing risk. We also applied Gray tests to assess the equality of cumulative incidence functions, reporting the associated *P*. We then plotted the respective Kaplan-Meier curves comparing *APOE* ε4 carriership vs noncarriership and reported log-rank test *P*. Multivariable Cox proportional hazard models were used to evaluate time to our primary and secondary outcomes across carriership of *APOE* ε4, while accounting for potential confounders and reporting hazard ratios (HRs) and CIs. We use a complete case approach, where participants without data on the exposure, outcome, or covariates of interest were excluded. We confirmed the proportional hazards assumption in our primary analysis using Schoenfeld residuals. We used 3 hierarchical models for our multivariable Cox regressions. Model 1 adjusted for age, sex, genetic ancestry, the first 3 genetic principal components (which were chosen because they provided the optimal fit for our models), and *APOE* ε2 carriership status, following the approach used in several previous studies on the role of *APOE* in intracerebral hemorrhage.[4,5,24] Models 2 and 3 incorporated covariates that have been identified as risk factors for ICH in prior research,[25,26] cardiovascular risk factors (hypertension, hyperlipidemia, smoking, diabetes,

Table 1. Baseline Characteristics of the Study Population

Variable	No. (%)		
	APOE ε4 noncarriers (n = 1555)	*APOE* ε4 carriers (n = 483)	*P* value[a]
Demographic and genetic variables			
Age, mean (SD), y	72 (9)	70 (9)	.004
Sex			.70
Female	692 (44.5)	226 (46.8)	
Male	863 (55.5)	257 (53.2)	
Genetic ancestry[b]			.02
European	1325 (85.2)	385 (79.7)	
Non-European	230 (14.8)	98 (20.3)	
Cardiovascular risk factors			
Hypertension	1319 (84.8)	409 (84.7)	>.99
Diabetes	544 (35.0)	172 (35.6)	.80
Hyperlipidemia	1240 (79.7)	400 (82.8)	.11
Overweight and obesity (BMI ≥25)[b]	1175 (75.6)	377 (78.1)	.30
Smoking			.10
Current	110 (7.1)	34 (7)	
Former	655 (42.1)	214 (44.3)	
Physiologic variables, mean (SD)			
Systolic BP, mm Hg	126 (12)	125 (14)	.20
Diastolic BP, mm Hg	74 (8)	75 (8)	.30
BMI[b]	31 (8)	31 (8)	.90
LDL cholesterol, mg/dL	89 (27)	95 (28)	<.001
Hemoglobin A_{1c}, %	6.10 (1.07)	6.12 (1.34)	.20
Comorbidities			
Coronary artery disease	329 (21.2)	115 (23.8)	.20
Heart failure	512 (32.9)	179 (37.1)	.20
Chronic obstructive pulmonary disease	303 (19.5)	86 (17.8)	.40
Chronic kidney disease	8 (0.5)	7 (1.4)	.06

Abbreviations: BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein.

SI conversion factor: To convert LDL cholesterol to mmol/L, multiply values by 0.0259.

[a] The statistical tests used were the Wilcoxon rank sum test, Pearson χ^2 test, and Fisher exact test as appropriate.

[b] In accordance with All of Us Data and Statistics Dissemination policies, non-European ancestries with low participant counts (African, American, Asian) were combined into a single non-European category to prevent participant re-identification.

[c] Calculated as weight in kilograms divided by height in meters squared.

and overweight/obesity), and comorbidities (history of coronary artery disease, heart failure, chronic obstructive pulmonary disease, and chronic kidney disease), respectively. Following standard analytical practices, *APOE* ε4 was modeled dominantly as carriers (1 or 2 alleles) vs noncarriers (no alleles).[24]

We performed 4 separate sensitivity analyses. First, we repeated the primary analysis but only among persons of European genetic ancestry. Second, we modeled *APOE* ε4 in an additive (0, 1, or 2 alleles) and a recessive (0 or 1 allele vs 2 alleles) fashion separately. Third, although most participants with atrial fibrillation require lifelong anticoagulation, a portion of them discontinued apixaban.[27,28] To account for this clinical scenario, we repeated the analysis after excluding all patients who discontinued apixaban before the end of the study follow-up. Fourth, we repeated the analysis including patients with C/T genotypes for both rs429358 and rs7412, assuming that because of the rarity of ε1/ε3, these participants were ε2/ε4. Also, we tested for interaction using product terms between *APOE* ε4 carriership and characteristics known to be associated with increased hemorrhagic risks (sex, age, hypertension, diabetes, hyperlipidemia, statins, antiplatelets, chronic kidney disease, and HAS-BLED score). HAS-BLED is a validated and frequently used score that uses clinical variables (hypertension, abnormal liver and kidney function, previous stroke, bleeding history or predisposition, labile international normalized ratio for patients taking warfarin, age >65 years, and concomitant antiplatelet drugs or alcohol use) to evaluate bleeding risk in patients about to start anticoagulant therapy.[2] Also, we compared the predictive ability of the HAS-BLED score to that of the same score plus the addition of the *APOE* genotype for ICH. For this, we used logistic regression and receiver-operator characteristic curves. We used the likelihood ratio test to compare the models' C statistics.

Finally, we conducted 2 separate additional analyses. First, we repeated the primary analysis using *APOE* ε2 carriership as exposure, using only a dominant model because of the limited sample size of *APOE* ε2 homozygotes. Second, to better understand if the association seen for *APOE* ε4 translates to other direct oral anticoagulants, we repeated the primary analysis in a sample of patients with atrial fibrillation taking rivaroxaban, the other direct oral anticoagulant with sufficient data in All of Us. However, because of power limitations, we could not conduct regression analyses in this group. All analyses were conducted from November 2023 to December 2024 using the R statistical package version 4.2.2 (R Foundation)[29] for all statistical analyses and PLINK 1.9 (open source)[30,31] for *APOE* status ascertainment.

Data Availability

Data from the All of Us Research Program are publicly available.[32] We used release version 7, which includes data from all participants who enrolled from the beginning of the program on May 30, 2017, to June 23, 2022. All data access and analyses were conducted within a secure informatic workspace provided by the National Institutes of Health. We

Table 2. Three-Year Cumulative Incidences for the Primary and Secondary Outcomes According to *APOE* ε4 Carriership With Death as a Competing Risk

Outcomes	Cumulative incidence (95%CI), %		
	APOE ε4 noncarriers (n = 1555)	*APOE* ε4 carriers (n = 483)	*P* value[a]
Primary analysis			
ICH	1 (0.6-1.7)	3.10 (1.7-5.3)	.007
Secondary analyses			
Intraparenchymal hemorrhage	0.88 (0.5-1.5)	2.8 (1.5-4.9)	.006
Ischemic stroke	4.80 (3.5-6.4)	4.90 (2.8-8.1)	.90
Ischemic stroke–ICH composite	4.20 (3.2-5.5)	6.30 (4.1-9.1)	.13

Abbreviation: ICH, intracranial hemorrhage.

[a] The statistical test used was the cumulative incidence function reporting a Gray test for equality of cumulative incidence functions' *P*.

obtained an exception from the All of Us Research Access Board to report certain low participant counts that would otherwise be restricted (record number 116).

Results

Among the 413 477 All of Us participants, 2038 were included in the final analytical sample (**Figure 1**). As shown in eTable 5 in Supplement 1, relative to the general All of Us cohort, our final analytical sample was older (mean age, 71 years vs 51 years) and had a higher prevalence of European ancestry (84% vs 54%) and cardiovascular comorbidities (ie, coronary artery disease prevalence of 22% vs 2.6%). The latter is probably due to the selection of a cohort of patients with atrial fibrillation. Of note, *APOE* ε2 carriership was 15% and 13% in the cohort and the final study sample, respectively, values intermediate to those from prior reports of *APOE* ε allele frequencies among participants mainly of European ancestry.[33,34] eTable 6 in Supplement 1 compares the baseline characteristics between the 2038 participants with atrial fibrillation receiving apixaban with whole-genome sequencing data (ie, final study sample) and those without it (n = 859), showing that most variables were balanced between both groups except for a higher prevalence of comorbidities among those without genetic data. eTable 7 in Supplement 1 shows the distribution of *APOE* ε genotypes across the final analytical sample.

As detailed in Figure 1, this study's analytical sample comprised 1555 *APOE* ε4 noncarriers (76.3%) and 483 *APOE* ε4 carriers (23.7%). **Table 1** outlines their baseline characteristics: the mean (SD) age was 71 (9) years; 918 (45%) were female, and 1120 (55%) were male. *APOE* ε4 noncarriers were older, had a higher prevalence of European ancestry, and had lower baseline values for low-density lipoprotein cholesterol. Other variables did not differ significantly between the groups. Participants had a median time of 10.6 months from atrial fibrillation diagnosis to the initiation of apixaban treatment. Over a median (IQR) follow-up of 2.9 years (1.7-3.0), 26 participants experienced an ICH (cumulative incidence, 1.5%; 95% CI, 1.0%-2.2%), 23 an intraparenchymal hemorrhage (cumulative incidence, 1.3%; 95% CI, 0.9%-2.0%), and 55 an ischemic stroke (cumulative incidence, 3.3%; 95% CI, 2.5%-4.3%), and 78 sustained the composite outcome of ischemic stroke or ICH (cumulative incidence, 4.7%; 95% CI, 3.7%-5.8%).

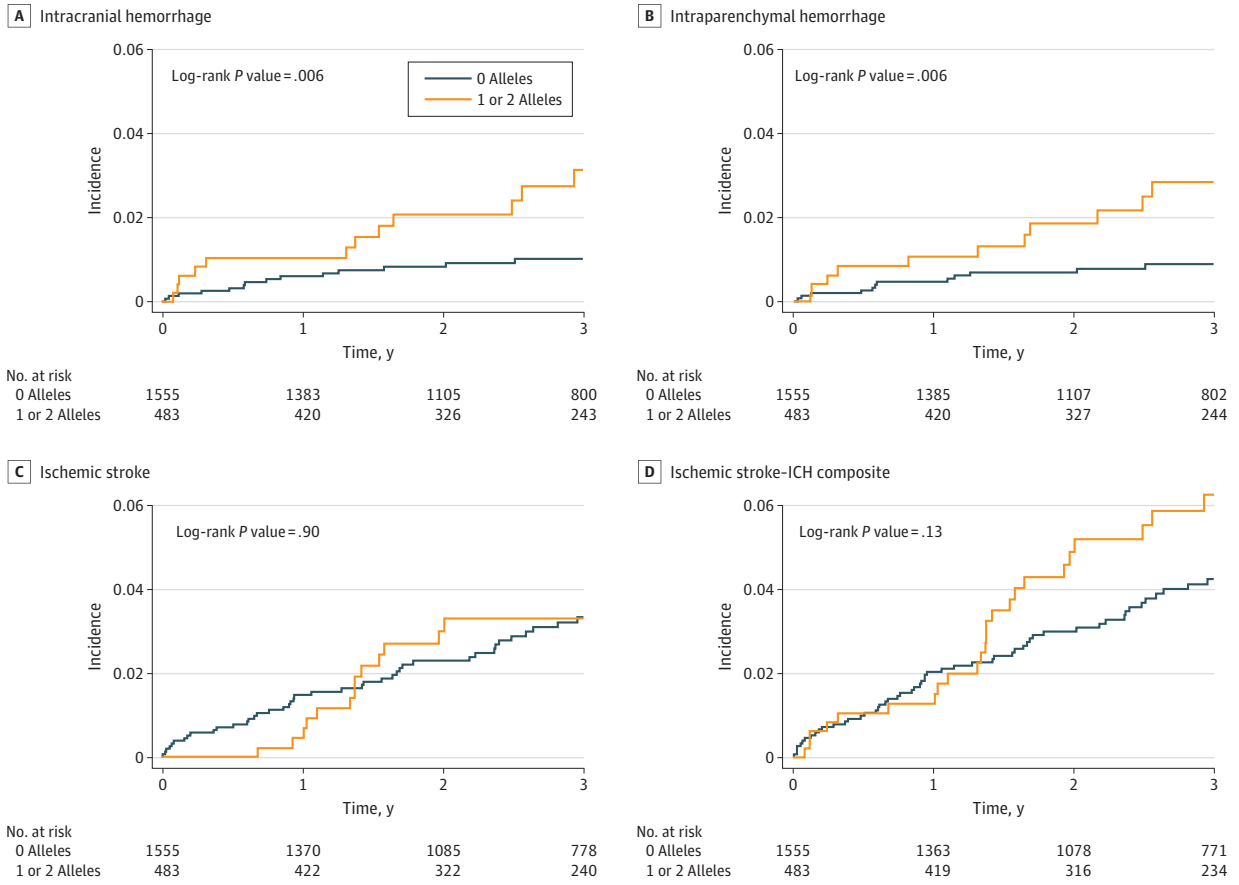
Primary Analysis: Intracranial Hemorrhage

After a median follow-up of 2.9 years, 14 of 1555 *APOE* ε4 noncarriers had sustained an ICH (cumulative incidence, 1%; 95% CI, 0.6%-1.7%). In comparison, among 483 *APOE* ε4 carriers, 12 participants experienced an ICH (cumulative incidence, 3.10%; 95% CI, 1.7%-5.3%) (**Table 2**). **Figure 2**A shows the cumulative number of ICHs for *APOE* ε4 noncarriers and carriers in the primary analysis during the complete follow-up period. Cox proportional hazard models confirmed these results, showing a more than 3-fold increase in the risk of ICH (model 3: HR, 3.07; 95% CI, 1.42-6.65). Schoenfeld residuals confirmed that the Cox proportional hazards assumption was met (eFigure 1 in Supplement 1). Results for the other covariate models were similar (**Table 3**). Sensitivity analysis investigating only participants of European ancestry and modeling *APOE* ε4 additively showed similar results, while modeling *APOE* ε4 in a recessive fashion yielded nonsignificant results (eTables 8 and 9 in Supplement 1). Also, results remained consistent after excluding all participants who stopped apixaban use during the study follow-up (n = 229) and after including participants with ambiguous rs429358 and rs7412 genotypes (eTable 8 in Supplement 1). No interaction analyses were significant.

Secondary Analyses: Intraparenchymal Hemorrhage, Ischemic Stroke, and the Composite of Ischemic Stroke and ICH

Among 1555 *APOE* ε4 noncarriers, 12 participants experienced an intraparenchymal hemorrhage (cumulative incidence, 0.88%; 95% CI, 0.5%-1.5%), 42 sustained an ischemic stroke (cumulative incidence, 4.80%; 95% CI, 3.5%-6.4%), and 54 experienced an ischemic stroke or an ICH (cumulative incidence, 4.20%; 95% CI, 3.2%-5.5%). Among the *APOE* ε4 carriers, 11 participants experienced an intraparenchymal hemorrhage (cumulative incidence, 2.80%; 95% CI, 1.5%-4.9%), 13 sustained an ischemic stroke (cumulative incidence, 4.90%; 95% CI, 2.8%-8.1%), and 24 had an event within the ischemic stroke–ICH composite (cumulative incidence, 6.30%; 95% CI, 4.1%-9.1%) (Table 2). Figure 2B-D shows the cumulative incidence of these secondary outcomes by *APOE* ε4 status. Cox proportional hazard models recapitulated these findings, indicating that *APOE* ε4 carriers had more than 3 times the likelihood of experiencing an intraparenchymal hemorrhage (model 3: HR, 3.70; 95% CI, 1.36-8.38). Results were not statistically significant for ischemic stroke (model 3: HR, 0.82; 95% CI, 0.43-1.57) or the com-

Figure 2. Cumulative Event Curves for the Primary and Secondary Outcomes by *APOE* ε4 Carrier Status



Shown are the unadjusted number of events across strata of *APOE* ε4 carriership with their respective log-rank *P*. The primary outcome (A) was incidence of intracranial hemorrhage (ICH); secondary analyses (B-D) included other stroke types and a composite outcome. *APOE* ε4 noncarriers are those with 0 alleles, while *APOE* ε4 carriers are those with 1 or 2 alleles.

posite of ischemic stroke and ICH (model 3: HR, 1.33; 95% CI, 0.80-2.21). Results were similar for all the other covariate models across all outcomes (Table 3).

Comparison of Predictive Power

The HAS-BLED score is a widely used tool to predict the risk of major hemorrhage in patients with atrial fibrillation. It includes hypertension, abnormal liver and kidney function, history of previous stroke or bleeding, labile international normalized ratio, age older than 65 years, and concomitant antiplatelet drugs or alcohol use as risk predictors. In this study population, the HAS-BLED score had a C statistic of 0.68 (for reference, the C statistic from the original HAS-BLED report among individuals using oral anticoagulants was 0.69).[2] The model including the HAS-BLED score plus *APOE* information had a C statistic of 0.74 (likelihood ratio test $P = .03$) (eFigure 2 in Supplement 1).

Additional Analyses

Both cumulative incidence and multivariable Cox proportional hazard results analyzing the association of *APOE* ε2 carriership and ICH were nonsignificant (eTables 10 and 11 in Supplement 1). Finally, in a sample of 209 All of Us participants with atrial fibrillation on rivaroxaban, we found a nonsignificant increased risk of ICH among *APOE* ε4 carriers (eTable 12 in Supplement 1).

Post Hoc Power Calculations

We conducted post hoc power calculations to evaluate the possibility of false-positive results due to limited statistical power. We modeled *APOE* dominantly and assumed an effective sample size of 2038 study participants, 483 *APOE* ε4 carriers, a baseline risk of ICH (in the population of atrial fibrillation patients treated with apixaban) of 1.5%, and 2.9 years of follow-up. With these assumptions, the present study had 80%, 85%, and 90% power to detect an absolute risk of ICH in the *APOE* ε4 population of 2.6%, 2.8%, and 3%, respectively.

Discussion

In this large genetic association study of patients with atrial fibrillation treated with apixaban, we found that carriership of 1 or 2 *APOE* ε4 alleles was associated with a 3-fold increase in the

Table 3. Cox Proportional Hazard Regression Results for Carriers and Noncarriers of the *APOE* ε4 Genotype and the Primary and Secondary Analyses Outcomes of Interest

	Model 1[a]		Model 2[b]		Model 3[c]	
Outcome	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary analysis						
ICH	3.49 (1.49-8.18)	.004	3.61 (1.52-8.55)	.004	3.07 (1.42-6.65)	.004
Secondary analyses						
Intraparenchymal hemorrhage	4.15 (1.65-10.50)	.003	4.35 (1.71-11.10)	.002	3.70 (1.63-8.38)	.002
Ischemic stroke	0.91 (0.49-1.71)	.80	0.91 (0.48-1.70)	.80	0.82 (0.43-1.57)	.50
Ischemic stroke–ICH composite	1.42 (0.86-2.33)	.20	1.44 (0.87-2.36)	.20	1.33 (0.80-2.21)	.30

Abbreviation: HR, hazard ratio; ICH, intracranial hemorrhage.

[a] Model 1 covariates: age, sex, genetic ancestry, and the first 3 genetic principal components.

[b] Model 2 covariates: model 1 covariates plus hypertension, hyperlipidemia, diabetes, smoking, and body mass index ≥25 (calculated as weight in kilograms divided by height in meters squared).

[c] Model 3 covariates: model 1 and 2 covariates plus coronary artery disease, heart failure, chronic obstructive pulmonary disease, and chronic kidney disease.

risk of ICH during the first 3 years after initiation of anticoagulation. These results were confirmed in sensitivity analyses that restricted the study population to persons of European ancestry, modeled *APOE* ε4 carriership additively, and excluded participants who stopped apixaban intake during the study follow-up. We also found that carriership of 1 or 2 *APOE* ε4 alleles was associated with a 3-fold increase in the risk of intraparenchymal hemorrhage. Importantly, the addition of *APOE* information to existing risk stratification tools for ICH in patients with atrial fibrillation led to improvements in their predictive power.

Our findings align with previous research demonstrating a link between *APOE* ε4 carriership and increased risk of spontaneous ICH (not associated with anticoagulation). A large-scale genetic association case-control study involving 2189 ICH cases and 4041 controls found that *APOE* ε4 carriers had a 2-fold higher risk of both lobar and deep ICH compared with noncarriers.[4] This finding was further corroborated by a meta-analysis of existing studies for ICH, irrespective of location.[3] Regarding other anticoagulants, a previous case-control study involving a total of 382 ICH cases and 1385 controls showed a 2-fold increased risk for warfarin-associated ICH among *APOE* ε4 carriers.[5] Of note, we found a higher point estimate for the risk of ICH associated with *APOE* ε4 carriership in our study, suggesting that the pathophysiology of the interaction between factor X inhibition (apixaban's mechanism of action) and *APOE* may be different from that observed in patients treated with warfarin. It is also important to note that apixaban has been shown to reduce by half the risk of ICH when compared with warfarin (0.24% vs 0.47, respectively).[35]

Our study provides new insights into the pathophysiological determinants of ICH in patients treated with apixaban, one of the most widely used, safe, and cost-effective direct oral anticoagulants.[6] The *APOE* ε4 variant is causally linked to cerebral amyloid angiopathy, a relatively frequent form of cerebral small vessel disease that affects older adults.[36] This vasculopathy makes the brain vasculature more prone to bleeding in the form of microhemorrhages, intraparenchymal hemorrhages, and subdural hemorrhages.[37] Given what is known about the effect of *APOE* ε4 on ICH risk mediated through cerebral amyloid angiopathy, it is likely that a similar paradigm applies to apixaban-related ICH. Confirmation by follow-up studies of the role of cerebral amyloid angiopathy would therefore provide valuable mechanistic information as well as a useful risk factor to consider when evaluating the risks and benefits of anticoagulation in patients with atrial fibrillation.

Our findings also underscore the importance of genetics in personalizing pharmacological therapy, aiding clinicians in identifying high-risk patients and tailoring anticoagulant strategies. The *APOE* ε variants have played a central role in the field of precision medicine because of their effect on ICH, coronary artery disease, and, most importantly, Alzheimer disease, as well as early studies demonstrating that sharing *APOE* status with patients is safe and feasible.[38] The general public and the medical community are both increasingly aware of the potential applications of *APOE* information in clinical practice and research. This awareness is driven by recent media attention to the role of *APOE* e4 status in Alzheimer disease,[39] the widespread use of direct-to-consumer genetic testing[40] (which often includes *APOE* information), the recent introduction of large-scale population studies like All of Us[12] (that plans to return genetic information to the hundreds of thousands of genotyped participants), and the emergence of concrete examples of genetic-based precision medicine strategies. One important example of the latter involves the antiamyloid medication lecanemab, the first disease-modifying treatment for Alzheimer disease approved by the US Food and Drug Administration. Current appropriate use recommendations advocate for *APOE* genotyping in all candidates to receive this new medication to inform risk discussions and help guide safety considerations because clinical trial data showed an increased risk of amyloid-related imaging abnormalities in *APOE* ε4 carriers.[10,11] With the *APOE* ε4 allele present in at least a quarter of the US population,[8] there is a unique opportunity to enhance personalized medicine and anticoagulant risk stratification.

Strengths and Limitations

Our study has at least 3 significant strengths. First, unlike previous investigations that analyzed the association between *APOE* ε4 and ICH using a case-control design, our research used a genetic association design using prospectively collected data. This approach is particularly effective for examining gene-environment interactions in complex diseases, as it assesses

exposures and risk factors before disease onset.[41] Second, our sample size was very similar to other well-powered genetic association studies analyzing both genetic factors and direct oral anticoagulants.[42] Third, the consistency of our findings across multiple analytical models and sensitivity analyses lends additional credibility to our results.

However, our study has limitations. First, because we used electronic health record data to ascertain intraparenchymal hemorrhage, we could not distinguish between lobar and deep hemorrhages, making it difficult to determine the relative contribution of hypertension and cerebral amyloid angiopathy to each hemorrhage subtype. Future studies that include detailed neuroimaging profiling are needed to understand if these associations apply to all subtypes of intraparenchymal hemorrhage. Second, because more than 80% of study participants were of European ancestry, our results may not be generalizable to other ancestral groups. Further studies are needed to determine whether comparable differences are also observed for increased apixaban-associated ICH risk in other ancestral groups. Finally, because of the lack of other genetic studies in the US evaluating patients with atrial fibrillation treated with apixaban, we were unable to externally validate the prediction analyses.

Conclusions

Our study suggests an increased risk of ICH in *APOE* ε4 carriers with atrial fibrillation who are treated with apixaban. These findings highlight the potential role of cerebral amyloid angiopathy in causing ICH in these patients and point to the possibility of incorporating and developing personalized, genetically informed approaches for anticoagulant therapy. Importantly, these results should not be interpreted as evidence that apixaban should be avoided in this patient population. Instead, our results address an important knowledge gap related to the role of *APOE* ε4 in this specific ICH population and support the need for future studies focused on developing and refining risk assessment tools that include genetic information.

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