Journal of the American Heart Association

ORIGINAL RESEARCH

High Mortality Rates Among Patients With Non-Traumatic Intracerebral Hemorrhage and Atrial Fibrillation on Antithrombotic Therapy Are Independent of the Presence of Cerebral Amyloid Angiopathy: Insights From a Population-Based Study

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BACKGROUND: Intracerebral hemorrhage (ICH) risk is higher in elderly patients with atrial fibrillation on antithrombotic therapy as well as those with cerebral amyloid angiopathy (CAA). We investigated if mortality among patients with atrial fibrillation on antithrombotic therapy presenting with non-traumatic ICH was influenced by underlying CAA.

METHODS AND RESULTS: We used the Rochester Epidemiology Project to identify 6045 patients with atrial fibrillation aged >55 years on anticoagulation or antiplatelet therapy from 1995 to 2016. Seventy-four patients in this cohort presented with non-traumatic ICH. Medical records including imaging data were reviewed to identify those with CAA and record baseline variables and outcomes of interest; 38 of our 74 patients (51.4%) (mean age 81.5 years) met Modified Boston Criteria for possible or probable CAA. Twenty-six of 74 patients (35%) died during the first 30 days while 56 of the 74 (76%) patients died by 10 years follow-up after index ICH. Overall mortality was not significantly different between the CAA and non-CAA groups at any point of time during follow-up (P=0.89) even amongst patients restarted on anticoagulation +/– antiplatelet (n=19) (P=0.46) or those patients restarted only on antiplatelet therapy (n=22) (P=0.66). Three of the 41 patients who restarted on antithrombotic therapy had a recurrent ICH; these 3 patients met criteria for possible or probable CAA.

CONCLUSIONS: Although more than half of our patients with atrial fibrillation on antithrombotic therapy and non-traumatic ICH met Modified Boston Criteria for CAA, CAA did not significantly influence the high mortality seen in this cohort.

Key Words: anticoagulants ■ antiplatelet agent ■ antithrombotics ■ atrial fibrillation ■ cerebral amyloid angiopathy ■ intracerebral hemorrhage

The risk of cardioembolic stroke from atrial fibrillation (AF) steeply increases with age, closely paralleling the incidence of AF itself and that of hypertension in individuals aged ≥80 years.[1,2] Although there is strong evidence supporting anticoagulation therapy (AC) in the elderly to reduce the high risk of cardioembolic stroke associated with AF,[3,4] it is often underutilized in this population for the fear of intracerebral hemorrhage (ICH).[5,6] Previous studies suggest that between 56% and 85% of elderly patients with AF

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For Sources of Funding and Disclosures, see page 11.

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CLINICAL PERSPECTIVE

What Is New?

- A retrospective population-based study to investigate mortality in patients with atrial fibrillation (AF) aged >55 years on antithrombotic therapy presenting with non-traumatic intracerebral hemorrhage (ICH).
- Low 1.22 % crude incidence rate of non-traumatic ICH in our cohort after an average of 6 years exposure to anticoagulation therapy.
- There were 51.4% of our patients with AF on antithrombotic therapy who had non-traumatic ICH and met Modified Boston Criteria for possible or probable cerebral amyloid angiopathy, and the overall mortality was high in our cohort with 35% at 30 days and 76% at 10 years after the index ICH.

What Are the Clinical Implications?

- Clinicians should consider the high possibility of underlying cerebral amyloid angiopathy in patients with AF aged ≥55 years presenting with non-traumatic ICH.
- No difference in overall mortality or recurrent ICH in patients with AF with or without cerebral amyloid angiopathy findings on index ICH imaging when restarted on warfarin or antiplatelet agents.
- Future larger prospective studies may be needed to explore the impact of direct oral anticoagulants or left atrial appendage occlusion devices on mortality and risk of recurrent ICH in patients with AF with cerebral amyloid angiopathy findings on index ICH imaging.

Nonstandard Abbreviation and Acronyms

AC	Anticoagulation Therapy
AF	Atrial fibrillation
AP	Antiplatelet Therapy
CAA	Cerebral Amyloid Angiopathy
ENGAGE AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48
ICH	Intracerebral Hemorrhage
RE-LY	Randomized Evaluation of Long-term Anticoagulant Therapy
ROCKET AF	Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

are not anticoagulated despite any clear contraindications.[3,6] Up to 50% of patients discontinue AC within the first 3 years (30% in the first year),[7] partly because of fear of ICH. Although better compliance rates have been reported with direct oral anticoagulants,[8] physicians anticoagulating elderly patients for AF are often faced with a difficult dilemma as the currently available risk assessment tools like the hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly (HAS-BLED) scoring systems do not factor the presence of cerebral amyloid angiopathy (CAA) and its associated risk of ICH.[9]

CAA has been increasingly recognized as an important cause of lobar ICH in the elderly[10,11] with a prevalence of moderate-to-severe CAA occurring in 18.9% of individuals at autopsy.[12] CAA occurs because of beta-amyloid deposition within the walls of cerebral arteries, arterioles, and capillaries leading to weakness and potential rupture of the vessel wall.[13,14] Advancements in neuroimaging have improved detection of CAA before ICH, but it is unclear how the presence of CAA should impact AC treatment in patients with AF, as lobar ICH because CAA carries a mortality rate up to 55%[10,11,15] and patients with CAA-related lobar ICH are at a significantly increased risk of recurrent hemorrhage compared with patients with a hypertensive related deep ICH.[16,17]

Most studies investigating the risk of ICH among patients with AF[3] are not population-based and do not distinguish between underlying causes of ICH. The objectives of our study were to (1) determine the incidence and describe the outcomes associated with non-traumatic ICH in elderly patients with AF on AC and/or antiplatelet therapy (AP) and (2) investigate the impact of imaging findings suggestive of CAA on mortality and recurrence of ICH in these patients.

METHODS

The data, methods used in the analysis, and materials used to conduct this research study will be made available to any researcher for purposes of reproducing the results upon reasonable request.

We used data from the Rochester Epidemiology Project to identify our cohort for this study.[18] The Rochester Epidemiology Project has maintained a comprehensive medical records linkage system for nearly half a century for almost all people residing in Olmsted County, Minnesota, USA. This database contains medical records for all patients within Olmsted County and codifies their diagnoses using *International Classification of Diseases* (*ICD-9*) codes and a unique internal research code.[19,20]

There were 6045 patients aged >55 years who identified with AF on oral AC +/– AP from 1995 to 2016 using the Rochester Epidemiology Project database. All patients aged >55 years presenting from 1995 to 2016 with diagnosis of non-traumatic ICH who had AF and were on oral AC +/– AP or AP alone were included for analysis. The decision to only include patients that were aged >55 years was based on Modified Boston Criteria for diagnosing CAA. The medical records, including brain imaging, were reviewed for each patient to establish the etiology of ICH, determine baseline characteristics, antithrombotic regimen, and outcomes including recurrent ICH and overall mortality associated with index non-traumatic ICH. We reviewed the medical record for all available encounters for each patient included in the study to gather information on start, continuation, discontinuation, and resumption of antithrombotic therapy until their last available follow-up or death. After detailed individual chart review, we excluded patients if they were not on active antithrombotic therapy use (only remote history) at the time of index ICH or had evidence of traumatic etiology (Figure 1). We estimated the overall incidence of non-traumatic ICH in our population cohort and calculated the outcomes of interest such as recurrent ICH, overall mortality and mortality associated with antithrombotic therapy re-initiation in relationship to their CAA status and other risk factors.

Brain imaging (both computed tomography and magnetic resonance imaging scans) and clinical characteristics of all patients with non-traumatic ICH was reviewed by a neurologist (S.E.) to determine whether they met Modified Boston Criteria for diagnosis of CAA and we used it to classify patients into possible or probable CAA and non-CAA categories.[21] In the subset of patients who underwent brain magnetic resonance imaging, we assessed hemorrhage location, number, and location of cerebral microbleeds, and evidence of prior convexal subarachnoid hemorrhage or superficial siderosis. Hemosiderin sensitive sequences include Gradient Echo and susceptibility weighted imaging sequences. Deep hemorrhage was defined as any hemorrhage within the brainstem, deep grey matter including thalamus or basal ganglia, or internal capsule. Lobar hemorrhage was defined as any hemorrhage located superficial to deep grey structures in the cortical or subcortical region. In the context of hypertension, the presence of any deep hemorrhage was attributed to hypertensive arteriopathy. We excluded patients with a known underlying vascular lesion or tumor, hemorrhagic conversion of ischemic stroke, or hemorrhage secondary to trauma.

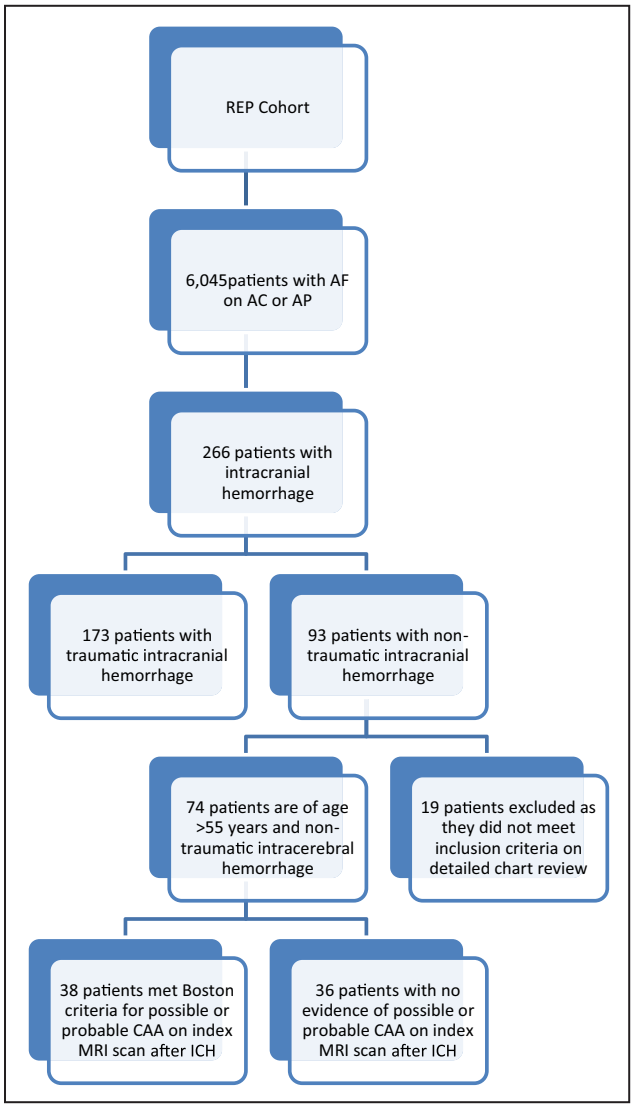

Figure 1. Study design.
AC indicates anticoagulation therapy; AF, atrial fibrillation; AP, antiplatelet therapy; CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; and REP, Rochester Epidemiology Project.

Institutional Review Boards for Mayo Foundation as well as the Olmsted Medical Center approved of this study. As this was a retrospective chart review, patient consent was not required.

Statistical Analysis

Categorical variables are presented as frequency (percentage) and continuous variables as mean ± SD. Comparisons between dichotomous subgroups were performed using the Pearson χ^2 test for categorical

variables and the Student *t*-test for continuous variables. Cox proportional hazards models were used to model long-term outcomes, adjusting for re-start of AC/AP and CAA status. The Kaplan–Meier method was used to evaluate survival, with group comparisons made using the log-rank test. Probability (*P*) values <0.05 were considered statistically significant. Statistical analyses were completed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Among the initial cohort of 6045 patients on AC+/–AP for AF, 266 patients presented with ICH. Among those 266 patients, 93 patients were identified to have suffered a non-traumatic ICH on initial screening and review; hemorrhage location revealed 43 deep (46%), 39 lobar (42%), 7 cerebellar (7.5%), 3 intra-ventricular (3.2%), and 1 convexal subarachnoid (1.1%) hemorrhages (Table 1). The etiology, distribution and location of all the ICH for the patients in our cohort are detailed in Table 1. Among 93 patients with ICH, 19 were excluded from the study analyses after detailed chart review revealed no active AC or AP at the time of index ICH (only remote history) or evidence of possible traumatic etiology documented in the chart, leaving 74 patients in the final study cohort (Figure 1).

Seventy-four of the 6045 patients (mean age 81 years, interquartile range of 76.5 to 86.6 years) were on antithrombotic therapy at the time of spontaneous ICH, representing a crude incidence of 1.22% among a cohort of patients who are >55 years with AF on antithrombotic therapy which translates to 167 per 100 000 patient-years, after a total of 38 815.18 patient-years of exposure and follow-up. 38 of these 74 patients (51.4%) (mean age, 81.5 years) met Modified Boston Criteria for possible (29 patients) or probable (9 patients) CAA (Table 2). All 74 patients had head computed tomography scans at time of index hemorrhage, and 51 patients had a brain magnetic resonance imaging during their acute hospitalization; of these, 26 had gradient echo sequences, 13 had susceptibility-weighted sequences, and 12 had neither. Twenty-five of these patients had evidence of cerebral microbleeds and 6 of them had evidence of cortical superficial siderosis.

Table 1. Etiology, Location, and Distribution of the ICH Bleeds

Type of Bleed	Location	No. of Patients
Non-traumatic ICH	Total	93
	Deep	43
	Lobar	39
	Cerebellar	7
	Convex SAH	1
	Primary IVH	3

ICH indicates intracerebral hemorrhage; IVH, intra-venticular hemorrhage; and SAH, sub-arachnoid hemorrhage.

In our study, the CHA_2DS_2-VASc scores among those who suffered a non-traumatic ICH ranged from 2 to 8 and the HAS-BLED scores ranged from 1 to 5. Baseline comorbidities and CHA_2DS_2-VASc scores between CAA and non-CAA groups were not significantly different but the baseline HAS-BLED scores were significantly lower in the CAA group (*P*=<0.01) (Table 2).

Before the index ICH, 65 patients were on AC+/-AP (warfarin, 61; direct oral anticoagulants, 3; heparin, 1) and 9 patients were on only AP (8 single and 1 dual). 36 patients (49%) were on AC only (warfarin or direct oral anticoagulant or heparin) while 29 patients (39%) were on both anticoagulation and antiplatelet agents. Rates of anticoagulation or antiplatelet therapy use were not different between possible/probable CAA and the non-CAA groups (*P* value=0.60) (Table 2). The average duration on AC before index bleed was 6.9 years in CAA and 5.2 years in non-CAA groups (*P* value=0.25) (Table 2).

Among the 61 patients on warfarin at the time of the index non-traumatic ICH, 59 patients had international normalization ratio values available at the time of the bleed while 2 patients did not. Multivariate analysis for mortality adjusted for international normalization ratio values (*P* value=0.29) at the time of index ICH and their CAA status (*P* value=0.52) was not statistically significant (Table 3).

When reviewing the outcomes of these patients, 26 of the 74 (35%) patients died during the first 30 days while 56 of the 74 (76%) patients were dead at 10 years of follow-up after index non-traumatic ICH. Kaplan-Meier mortality curves at 1, 2, 5, or 10 years were not significantly different between the CAA and non-CAA groups (Figure 2) (*P*=0.89) (Tables 4 and 5 and Figures 3 and 4); 41 of the 48 (85%) patients who survived the index ICH were restarted on either AC (10 patients) or only AP (22 patients), while 9 patients were restarted on both with an average duration of 4.5 years following index non-traumatic ICH. Out of the 19 patients restarted on AC (only AC or AC and AP), 6 of them were restarted on direct oral anticoagulants while the other 13 on warfarin. Among these 48 patients, there was no significant difference in recurrent ICH/mortality at 1, 2, 5, or 10 years between patients restarted on AC, AP, both, or none or when subset to possible/probable CAA status (Tables 6 and 7).

The 41 patients restarted on AC/AP had a total of 185.25 person-years of exposure to AC or AP; 3 of the 41 patients suffered a recurrence of ICH, and all 3 patients met criteria for possible/probable CAA on their baseline imaging (Table 2). But recurrent ICH was not statistically significant between CAA and non-CAA groups (*P* value=0.81) (Figure 5).

Table 2. Patient Characteristics and Outcomes

Variable	Overall (n=74)		No Evidence of CAA (n=36)		Possible/probable CAA (n=38)		*P* Value
Age, y	81.1	(7.4)	80.7	(8.5)	81.5	(6.2)	0.66
Sex, n (%)							0.50
Men	34	(46%)	18	(50%)	16	(42%)	
Women	40	(54%)	18	(50%)	22	(58%)	
Race, n (%)							0.16
White	72	(97%)	36	(100%)	36	(95%)	
Asian	2	(3%)	0	(0%)	2	(5%)	
Tobacco use, n (%)							0.58
No use	36	(49%)	19	(53%)	17	(45%)	
Past use	35	(47%)	15	(42%)	20	(53%)	
Current	3	(4%)	2	(6%)	1	(3%)	
Alcohol use, n (%)							0.98
No use	44	(59%)	21	(58%)	23	(61%)	
Past use	12	(16%)	6	(17%)	6	(16%)	
Current	18	(24%)	9	(25%)	9	(24%)	
Diabetes mellitus, n (%)							0.14
None	55	(74%)	24	(67%)	31	(82%)	
Not on treatment	8	(11%)	7	(19%)	1	(3%)	
On orals	5	(7%)	2	(6%)	3	(8%)	
On insulin	6	(8%)	3	(8%)	3	(8%)	
Hyperlipidemia, n (%)							0.11
None	28	(38%)	13	(36%)	15	(39%)	
Not on treatment	42	(57%)	19	(53%)	23	(61%)	
On treatment	4	(5%)	4	(11%)	0	(0%)	
Hypertension, n (%)							0.13
None	12	(16%)	7	(19%)	5	(13%)	
Not on treatment	59	(80%)	26	(72%)	33	(87%)	
On treatment	3	(4%)	3	(8%)	0	(0%)	
Coronary artery disease, n (%)	26	(36%)	11	(31%)	15	(39%)	0.47
Peripheral vascular disease, n (%)	8	(11%)	4	(11%)	4	(11%)	0.94
Stroke/TIA, n (%)	22	(30%)	10	(28%)	12	(32%)	0.72
HAS-BLED score	2.4	(1.0)	2.8	(0.8)	2.1	(0.9)	<0.001*
CHA_2DS_2-VASc score	4.3	(1.3)	4.1	(1.2)	4.4	(1.4)	0.36
Hemorrhage type, n (%)							
Clinical hemorrhage	74	(100%)	36	(100%)	38	(100%)	
Hemorrhage location, n (%)							<0.001*
Deep	32	(45%)	32	(89%)	0	(3%)	
Lobar	34	(45%)	1	(3%)	33	(84%)	
Cerebellar	5	(7%)	0	(0%)	5	(13%)	
Primary IVH	3	(4%)	3	(8%)	0	(0%)	
Prior antiplatelet use, n (%)							0.39
None	36	(49%)	17	(47%)	19	(50%)	
Aspirin	32	(43%)	15	(42%)	17	(45%)	
Clopidogrel	1	(1%)	0	(0%)	1	(3%)	
Both	5	(7%)	4	(11%)	1	(3%)	
Prior anticoagulant use, n (%)							0.44
None	9	(12%)	6	(17%)	3	(8%)	
Warfarin	61	(82%)	28	(78%)	33	(87%)	

(*Continued*)

Table 2. Continued

Variable	Overall (n=74)		No Evidence of CAA (n=36)		Possible/probable CAA (n=38)		*P* Value
Direct oral anticoagulant	3	(4%)	2	(6%)	1	(3%)	
Heparin	1	(1%)	0	(0%)	1	(3%)	
Prior anticoagulant/antiplatelet use, n (%)							0.60
Anticoagulation only	36	(49%)	17	(47%)	19	(50%)	
Aspirin or clopidogrel only	8	(11%)	5	(14%)	3	(8%)	
Both aspirin and clopidogrel only	1	(1%)	1	(3%)	0	(0%)	
Anticoagulation and antiplatelet	29	(39%)	13	(36%)	16	(42%)	
Years of prior anticoagulant use	6.0	(5.9)	6.9	(5.8)	5.2	(6.0)	0.25
Anticoagulant/antiplatelet re-started, n (%)							0.45
None	33	(45%)	16	(44%)	17	(45%)	
Anticoagulation only	10	(14%)	3	(8%)	7	(18%)	
Aspirin or clopidogrel only	20	(27%)	10	(28%)	10	(26%)	
Both aspirin and clopidogrel only	2	(3%)	2	(6%)	0	(0%)	
Anticoagulation and Antiplatelet	9	(12%)	5	(14%)	4	(11%)	
Years of re-started AC/AP use	4.5	(3.7)	4.0	(2.7)	5.0	(4.5)	0.36
Mortality, # events (K-M)							0.89
1 y	31	(42%)	14	(39%)	17	(45%)	
2 y	34	(46%)	17	(47%)	17	(45%)	
5 y	44	(62%)	23	(66%)	21	(58%)	
10 y	56	(89%)	28	(91%)	28	(88%)	
Myocardial infarction, # events (K-M)							0.99
1 y	0	(0%)	0	(0%)	0	(0%)	
2 y	1	(3%)	1	(5%)	0	(0%)	
5 y	2	(6%)	1	(5%)	1	(6%)	
10 y	2	(6%)	1	(5%)	1	(6%)	
Ischemic stroke, # events (K-M)							0.60
1 y	1	(2%)	0	(0%)	1	(5%)	
2 y	1	(2%)	0	(0%)	1	(5%)	
5 y	2	(6%)	1	(8%)	1	(5%)	
10 y	3	(12%)	1	(8%)	2	(14%)	
Recurrent ICH, # events (K-M)							0.14
1 y	1	(2%)	0	(0%)	1	(4%)	
2 y	1	(2%)	0	(0%)	1	(4%)	
5 y	1	(2%)	0	(0%)	1	(4%)	
10 y	3	(28%)	0	(0%)	3	(44%)	
Recurrent ICH/mortality, # events (K-M)							0.89
1 y	31	(42%)	14	(39%)	17	(45%)	
2 y	34	(46%)	17	(47%)	17	(45%)	
5 y	44	(62%)	23	(66%)	21	(58%)	
10 y	56	(89%)	28	(91%)	28	(88%)	

AC indicates anticoagulation therapy; AP, antiplatelet therapy; CAA, cerebral amyloid angiopathy; ICH, intra cerebral hemorrhage; IVH, intraventricular hemorrhage; K-M, Kaplan–Meier; and TIA, transient ischemic attack.

DISCUSSION

This study examined the epidemiology of non-traumatic ICH in patients aged ≥55 years on antithrombotic therapy for AF using the Rochester Epidemiology Project medical records linkage system for the Olmsted County, Minnesota. We also explored the association between outcomes of the non-traumatic ICH and presence of possible/probable CAA findings on their index ICH imaging. Our main findings are:

1. Patients aged >55 years with AF on AC or AP seem to have a relatively low 1.22 % crude

Table 3. Ten-Year Time-Dependent Model for Mortality Adjusted for INR at the Time of Index ICH and Their CAA Status - Analysis of Maximum Likelihood Estimates

Variable	Chi-Square	Probability>Chi-Square	HR	95% HR CI	
Possible/Probable CAA	0.41	0.52	1.21	0.67	2.19
INR	1.13	0.28	1.12	0.30	1.38

CAA indicates cerebral amyloid angiopathy; HR, hazard ratio; and INR, international normalization ratio.

incidence rate of non-traumatic ICH after an average of 6 years exposure to AC.

2. Over half of patients with AF on antithrombotic therapy who had non-traumatic ICH met Modified Boston Criteria for possible or probable CAA. Notably, these patients with possible or probable CAA had relatively low HAS-BLED scores before index ICH.
3. The overall mortality was high in our cohort with 35% at 30 days and 76% at 10 years after the index ICH and was not significantly different between the CAA and non-CAA groups after the index ICH regardless of whether AC or AP drugs were restarted or not.

Incidence of Non-Traumatic ICH in Patients With AF on AC and Implications of Underlying CAA

A recent inpatient database study from The Netherlands suggested that the incidence of non-traumatic ICH per 100 000 patient-years was 37.2 in patients aged >55 to 74 years but increased to 176.3 among patients aged 75 to 94 years in 2010 as compared with our incidence of 167 per 100 000 patient-years, after a total of 38 815.18 patient-years of exposure and follow-up.[22] The incidence of ICH itself also increases with advanced age along with that of CAA.[23] Our incidence of non-traumatic ICH is similar to the older cohort of The Netherlands study (aged 75–94 years) as the median age of our study population (81 years) was closer to that age group. Another population based study looking at incidence of intracranial hemorrhage in patients with AF using 23 657 anonymous patient records (both Medicare records and chart-abstracted data) from 3586 hospitals in all 50 US states reported incidence of non-traumatic intracranial hemorrhage among patients not at high-fall risk to be 800 per 100 000 patient years.[24] Given only 48.9% of those patients were on warfarin at discharge and approximately only 42% to 46%[25,26] of all intracranial hemorrhages are attributable to non-traumatic ICH, the adjusted incidence of non-traumatic ICH in patients with AF on warfarin for this cohort would be around 165 to 180 per 100 000 patient years which is again similar to that reported in our study.

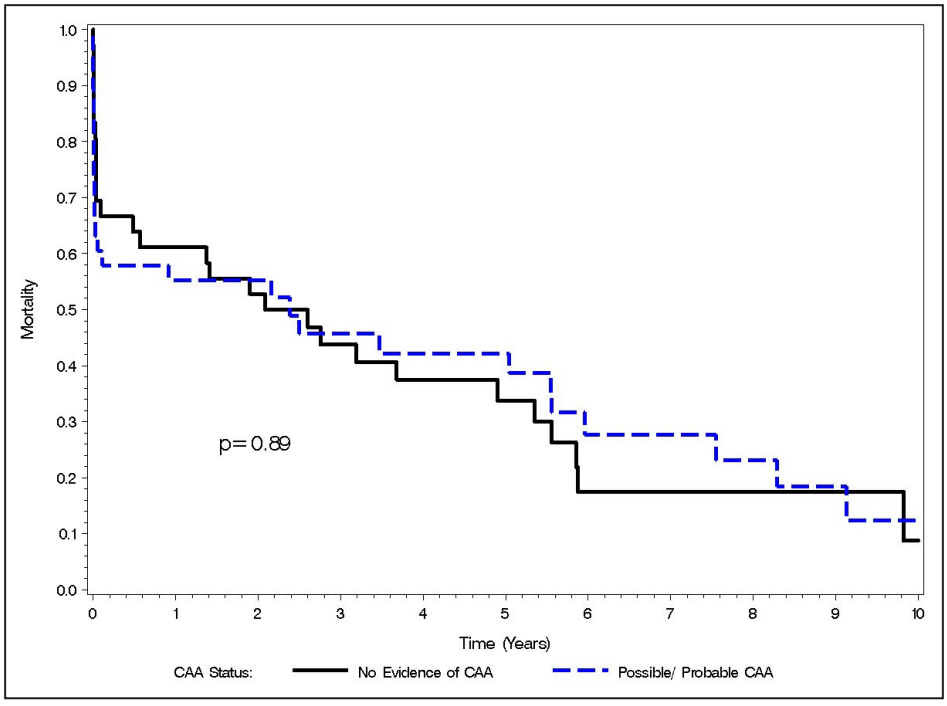

Figure 2. Kaplan–Meier curve for mortality for all 74 patients, stratified by CAA status.
CAA indicates cerebral amyloid angiopathy.

Table 4. Mortality in Patients Re-Started on Anticoagulants

Variable	No Evidence of CAA (n=8)		Possible/ Probable CAA (n=11)		*P* Value
Mortality, # events (K-M)					0.46
1 y	0	(0%)	2	(18%)	
2 y	2	(25%)	2	(18%)	
5 y	4	(50%)	2	(18%)	
10 y	5	(63%)	5	(45%)	

CAA indicates cerebral amyloid angiopathy; and K-M, Kaplan–Meier.

Both autopsy and clinical studies suggest that about 12% to 20% of all ICHs in elderly are related to CAA.[12,27–29] In our study cohort 51.4% patients with non-traumatic ICH met Modified Boston Criteria for possible/probable CAA. We report a higher incidence of CAA in our cohort as compared with other studies (12%–20%) but this may be partly because of preselection and limiting our study population to patients with AF on antithrombotics and use of Modified Boston Criteria to diagnose CAA (as supposed to pathological diagnosis) along with relatively older patient population.

Mortality Associated With Non-Traumatic ICH In Patients With AF on Antithrombotics in the Context of CAA Findings on Their Index ICH Imaging

The RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study reports the 30-day mortality for non-traumatic ICH to be between 46% to 52%.[26] In the ROCKET-AF (Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation- Thrombolysis in Myocardial Infarction 48) trial, the overall mortality associated with ICH was 37.5% (48/122) and 46.6% (14/30), respectively, in the warfarin arms of both studies but this included both traumatic and spontaneous ICH.[25,30]

The 30-day mortality associated with non-traumatic ICH in our cohort of patients with AF on antithrombotic therapy was around 35% and not significantly different between the CAA and non-CAA groups. The overall mortality in our cohort was high (76%) which probably relates to longer follow-up (10 versus 2 years) and an older patient population (81.5 years versus <75 years) in our study as compared with other studies. The high overall mortality seen in our study is consistent with the mortality reported among patients with AF in the original cohort of the Framingham Heart Study. The study reported a 10-year mortality of 61.5% in men and 57.6% in women with AF aged >55 to 74 years but increased up to 91.2% in men and 93.9% in women aged 75 to 84 years.[31]

Risk of Recurrent ICH In Patients With CAA and the Use Of HAS-BLED Scoring System

CAA is a well-known cause of lobar ICH but there are limited data on the effect of antithrombotic therapy on recurrence of ICH in patients with CAA.[9,32] Antithrombotic therapy could increase the prevalence of lobar microbleeds[33] and their risk of conversion into clinically manifest macrobleeds in patients with CAA.[34] Incidence of recurrent intracerebral hemorrhage following lobar hemorrhage may vary from 2.5% to 28.2%, while it is significantly lower in non-lobar hemorrhage (1.3%–10.6%).[35,36] This may suggest an increased risk of ICH recurrence in patients with CAA because of its association with lobar hemorrhage, which may be further potentiated with use of antithrombotic therapy. In our study, 3 out of the 41 patients restarted on antithrombotic therapy suffered a recurrent ICH despite low baseline HAS-BLED scores (<3). Although all 3 patients had evidence of possible or probable CAA on their scans for index ICH, we did not see a statistically significant difference in recurrent ICH rates between CAA and non-CAA groups among patients restarted on antithrombotic therapy. This may be because of a small cohort (41 patients) and low event rate (only 3 patients with recurrent ICH). However, the possibility of an increased risk of recurrent ICH in elderly patients

Table 5. Mortality in Patients Re-Started on Antiplatelets and Not Anticoagulants

Variable	No Evidence of CAA (n=12)		Possible/Probable CAA (n=10)		*P* Value	
Mortality, # events (K-M)					0.66	
1 y	2	(17%)	0	(0%)		
2 y	3	(25%)	0	(0%)		
5 y	4	(33%)	3	(33%)		
10 y	8	(70%)	6	(79%)		

CAA indicates cerebral amyloid angiopathy; and K-M, Kaplan–Meier.

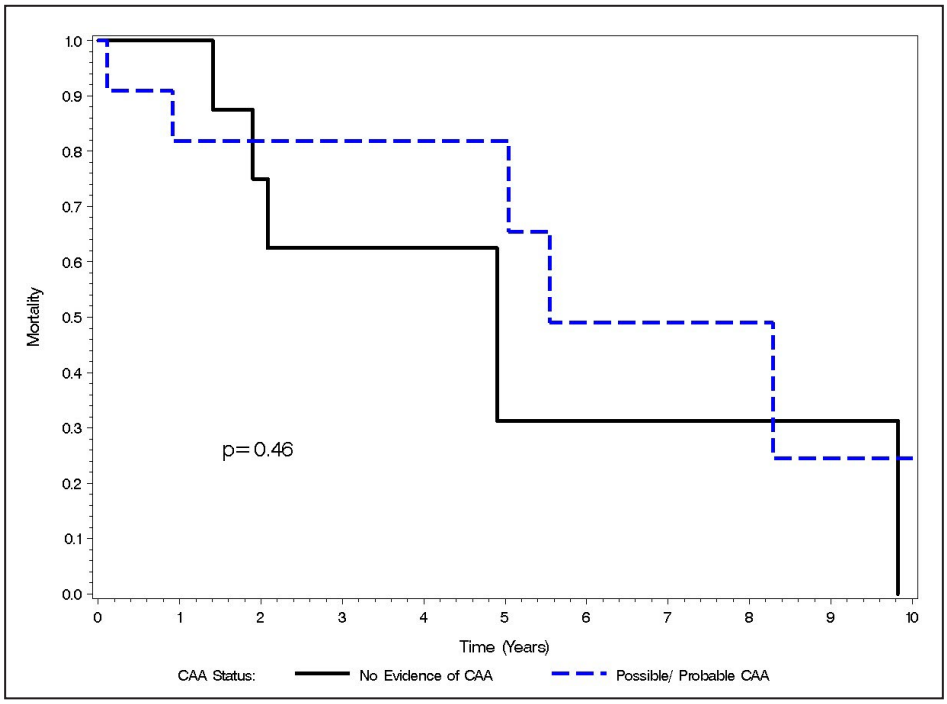

Figure 3. Kaplan–Meier curve for mortality for the 19 patients re-started on anticoagulation therapy, stratified by CAA status.
CAA indicates cerebral amyloid angiopathy.

with CAA findings when restarted on antithrombotic therapy (despite low baseline HAS-BLED scores [<3]) may need to be further explored in future large prospective or randomized trials.

Limitations

The main strength of our study lies in its population-based design. Yet, the relatively low number of patients with ICH, most notably recurrent ICH, limited

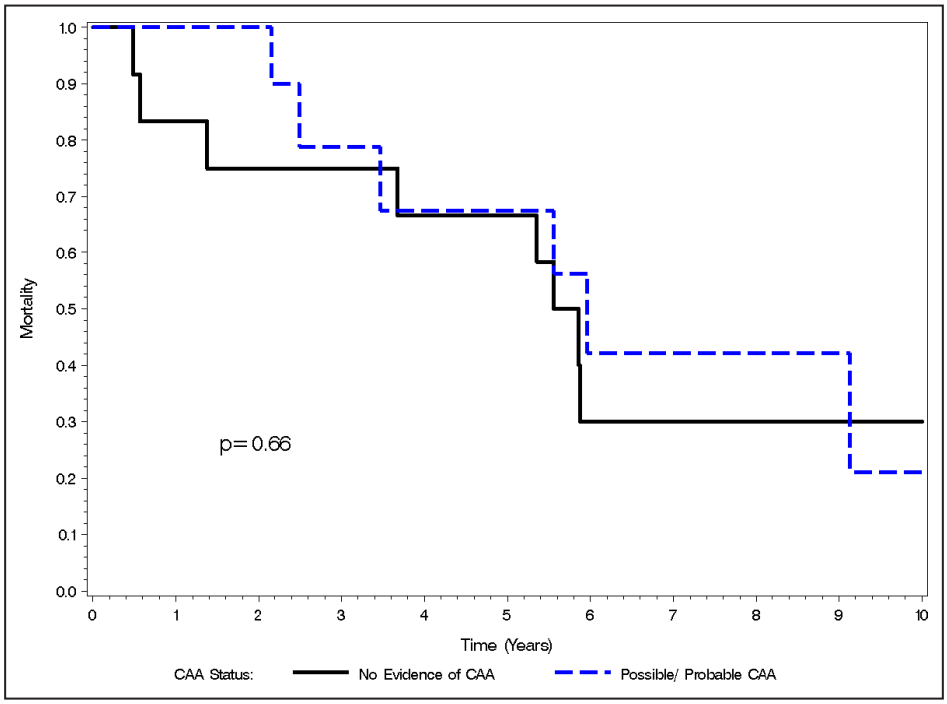

Figure 4. Kaplan–Meier curve for mortality for the 22 patients re-started on AP and not anticoagulation therapy, stratified by CAA status.
CAA indicates cerebral amyloid angiopathy.

Table 6. Recurrent ICH/Mortality by Anticoagulant/Antiplatelet Re-Start

Variable	None (n=7)		Anticoagulation only (n=10)		Antiplatelet Only (n=22)		Anticoagulation and Antiplatelet (n=9)		*P* value
Recurrent ICH/ mortality, # events (K-M)									0.21
1 y	1	(14%)	2	(20%)	2	(9%)	0	(0%)	
2 y	1	(14%)	3	(36%)	3	(14%)	1	(11%)	
5 y	5	(83%)	4	(57%)	7	(33%)	2	(22%)	
10 y	6	(%)	5	(79%)	14	(76%)	5	(%)	

ICH indicates intracerebral hemorrhage; and K-M, Kaplan–Meier.

Table 7. Time-Dependent Model for Recurrent ICH/Mortality Adjusted for AC/AP Restart and CAA Status For 48 Patients Who Survived 30 Days Post-ICH -Analysis of Maximum Likelihood Estimates

Variable	Chi-Square	Probability>Chi-Square	HR	95% HR CI	
*AC/AP restarted	2.92	0.09	0.70	0.46	1.05
CAA	1.48	0.22	0.63	0.30	1.32

*AC/AP indicates all 4 categories (AC, AP, AC + AP, none); AC, anticoagulation therapy; AP, antiplatelet therapy; CAA, cerebral amyloid angiopathy; and HR, hazard ratio.

our analysis. Selection bias could have influenced the analysis on ICH recurrence because restart of antithrombotics occurred at the discretion of the treating clinician, though this concern is assuaged by the fact that most survivors were restarted on antithrombotics and more patients were restarted on AC in the possible/probable CAA group than in the non-CAA group. CAA was diagnosed retrospectively after ICH and baseline CAA status at the time of starting antithrombotic therapy and before index ICH was unknown. Although data on pre-bleed international normalization ratios are presented, data

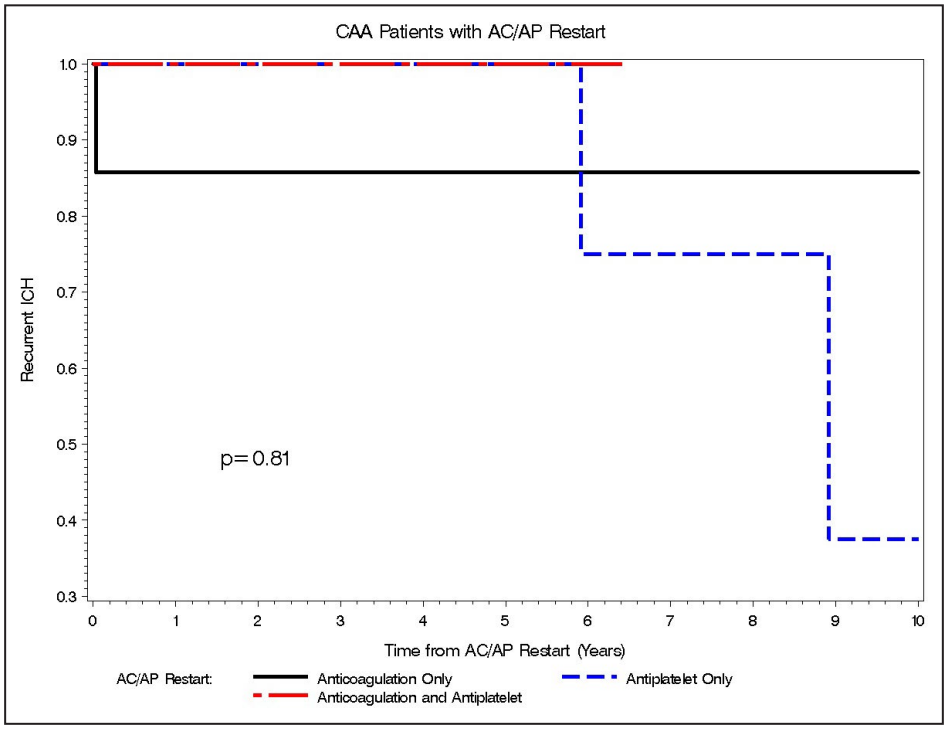

Figure 5. Kaplan–Meier curve for recurrent ICH for patients With CAA re-started on antiplatelet therapy or anticoagulation therapy.
AC indicates anticoagulation therapy; AP, antiplatelet therapy; and ICH, intracerebral hemorrhage (non-traumatic).

on AC compliance during follow-up are not available and there could be differences in the adherence rates among the 2 groups. The use of Modified Boston Criteria may have resulted in over-diagnosing of CAA in our cohort (sensitivity of 94.7% and specificity of 81.2%).[21] The findings of this study are not validated in the setting of patients using direct oral anticoagulants.

CONCLUSIONS

This study has important implications for elderly patients on AC with possible or probable CAA. Our study corroborates the findings of other studies with respect to increased incidence of non-traumatic ICH among elderly patients with AF on antithrombotics, but we report a higher percentage (51.4%) of patients with CAA at time of index non-traumatic ICH. Our study suggests that mortality after index ICH may not be different for patients with CAA and it is unclear if elderly patients with CAA are at increased risk of recurrent ICH when restarted on antithrombotic therapy after initial non-traumatic ICH. Large prospective cohort studies may be needed to evaluate the risk of recurrent ICH in patients with CAA when restarted on antithrombotic therapy. Until we have better data to assess risk of index/recurrent ICH and prevalence of CAA among elderly patients with AF, clinicians should cautiously weigh the risks and benefits when prescribing AC or AP treatment in elderly patients even if the HAS-BLED scores are low and consider the high possibility of underlying CAA in patients presenting with non-traumatic ICH.

ARTICLE INFORMATION

Received April 2, 2020; accepted June 9, 2020.

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Sources of Funding

This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG034676. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosures

None.

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