Journal of the American Heart Association

ORIGINAL RESEARCH

Atrial Fibrillation in Spontaneous Intracerebral Hemorrhage, Dijon Stroke Registry (2006–2017)

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BACKGROUND: Atrial fibrillation (AF) represents a major indication for oral anticoagulants (OAC) that contribute to spontaneous intracerebral hemorrhage (ICH). This study evaluated AF prevalence among patients with ICH, temporal trends, and early functional outcomes and death of patients.

METHODS AND RESULTS: Patients with first-ever ICH were prospectively recorded in the population-based stroke registry of Dijon, France, (2006–2017). Association between AF and early outcome of patients with ICH (ordinal modified Rankin Scale score and death at discharge) were analyzed using ordinal and logistic regressions. Among 444 patients with ICH, 97 (21.9%) had AF, including 65 (14.6%) with previously known AF treated with OAC, and 13 (2.9%) with newly diagnosed AF. AF prevalence rose from 17.2% (2006–2011) to 25.8% (2012–2017) (*P*-trend=0.05). An increase in the proportion of AF treated with OAC (11.3% to 17.5%, *P*-trend=0.09) and newly diagnosed AF (1.5% to 4.2%, *P*-trend=0.11) was observed. In multivariable analyses, after adjustment for premorbid OAC, AF was not significantly associated with ordinal modified Rankin Scale score (odds ratio [OR], 1.29; 95% CI, 0.69–2.42) or death (OR, 0.89; 95% CI, 0.40–1.96) in patients with ICH. Nevertheless, adjusted premorbid OAC use remained highly associated with a higher probability of death (OR, 2.53; 95% CI, 1.11–5.78).

CONCLUSIONS: AF prevalence and use of OAC among patients with ICH increased over time. Premorbid use of OAC was associated with poor outcome after ICH, thus suggesting a need to better identify ICH risk before initiating or pursuing OAC therapy in patients with AF, and to develop acute treatment and secondary prevention strategies after ICH in patients with AF.

Key Words: anticoagulants ■ atrial fibrillation ■ epidemiology ■ intracerebral hemorrhage ■ outcomes

Although spontaneous (non-traumatic) intracerebral hemorrhage (ICH) accounts for only 15% of overall strokes, it is associated with half of stroke-related deaths, and 42% of stroke related disability-adjusted life-years lost worldwide.[1] Because of the absence of major change in the acute treatment of ICH, early mortality of patients with ICH did not improve over the last 3 decades.[2] Oral anticoagulants (OAC) are important contributors of ICH, and since the main indication for their prescription is atrial fibrillation (AF), patients with ICH have frequently associated AF. Given the ongoing aging population, the burden of AF is increasing worldwide,[3] and this trend could lead to a rise in the incidence of OAC-related ICH, as demonstrated in previous studies.[2,4]

Therefore, using a stroke population-based registry, this study aimed to assess the overall prevalence of AF among patients with ICH, time trends between 2006 and 2017, and to analyze associations between AF and early functional outcomes and death at discharge among patients with ICH, including the role of premorbid OAC use on these associations.

METHODS

Data Source

Non-traumatic non-tumor–related patients with ICH were retrieved from the Dijon Stroke Registry, a prospective population-based study that complies with the defined criteria for conducting "ideal" incidence

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CLINICAL PERSPECTIVE

What Is New?

- The prevalence of atrial fibrillation (AF) reached 1 in 4 patients with intracerebral hemorrhage in the Dijon Stroke Registry for the 2012 to 2017 period.
- The observed increase in AF prevalence among patients with intracerebral hemorrhage over time partly reflected a rise in the prevalence of previously anticoagulated patients with AF.

What Are the Clinical Implications?

- With the ongoing aging population, and the expected increase in the burden of AF, our results highlight the urgent need for defining acute treatment and secondary prevention strategies after intracerebral hemorrhage in patients with AF.

Nonstandard Abbreviations and Acronyms

ICH	intracerebral hemorrhage
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OAC	oral anticoagulants

stroke studies,[5] and the guidelines for the reporting of incidence and prevalence studies in neuroepidemiology according to Standards of Reporting of Neurological Disorders.[6] The registry collects all cases of acute stroke and transient ischemic attack among residents of the city of Dijon (Burgundy, France, currently 156 000 inhabitants). The methodology of the Dijon Stroke Registry has been detailed in previous studies.[7,8] Briefly, case-collection relies on multiple overlapping sources of information to identify hospitalized and not hospitalized cases of stroke. The final adjudication of cases is systematically made by senior neurologists trained in stroke ascertainment according to the World Health Organization diagnostic criteria[9] based on all information available. ICH location was determined through brain imaging as follows: lobar (frontal, temporal, parietal, and occipital); deep, when it originated from the lenticular or caudate nuclei, thalamus, or internal or external capsule; and infratentorial, when it originated from the brainstem or cerebellum.[2,10] ICH was classified as undetermined when the origin could not be reliably identified, as was the case in hemorrhages that overlapped 2 territories, or when data were missing.

Among the 2772 patients registered in the Dijon Stroke Registry between January 1, 2006 and December 31, 2017 (n=1373 for 2006–2011 and n=1399 for 2012–2017), only first-ever ICH were included in the present study.

Data Collected

At registration, the following vascular risk factors and past medical history were collected[7,8]: hypertension (high blood pressure recorded in a patient's medical history or patients under antihypertensive treatment), diabetes mellitus (glucose level ≥7.8 mmol/L reported in the medical record or patients taking insulin or oral hypoglycemic agents), hypercholesterolemia (total cholesterol level ≥5.7 mmol/L reported in the medical history or patients treated with lipid-lowering therapy), smoking status (current smoker or past smoker), history of coronary heart disease, history of stroke or transient ischemic attack, chronic heart failure, and excessive alcohol consumption (defined as alcohol intake ≥3 units a day in men and ≥2 in women). AF (including atrial flutter) was defined as "known AF" if it was mentioned in the medical file of the patient before ICH, and "newly diagnosed AF" if it was diagnosed during the diagnostic work-up of the ICH by ECG monitoring or further examinations. AF was registered whatever the ICH location. Prior-to-stroke treatment with oral anticoagulant treatments (vitamin K antagonists or direct oral anticoagulants) were recorded. Other premorbid therapies including antiplatelet agents and antihypertensive treatment were collected. The CHA_2DS_2VaSc score was calculated for each patient.[11]

Severity at onset was quantified using the National Institutes of Health Stroke Scale (NIHSS) score either obtained at the first clinical examination, or retrospectively estimated on the basis of medical records and charts, as previously validated in the literature.[12] Post-stroke outcome of patients was evaluated using the ordinal modified Rankin Scale (mRS) score at discharge from the acute care ward for hospitalized patients or at last clinical examination for non-hospitalized patients.

Statistical Analysis

Characteristics were described according to the presence or absence of AF in participants with the first occurrence of ICH in 2006 to 2011, 2012 to 2017, and the overall 2006 to 2017 period. Prevalence of AF among patients with ICH was given through percentage for these periods. We assumed Poisson distribution for AF prevalence to calculate 95% CI. Time trends in AF prevalence was assessed using Poisson regression, treating time as a categorical variable (2012–2017 versus 2006–2011). Comparisons between categorical variables were performed using χ^2 or Fisher tests and using Wilcoxon-Mann-Whitney test for quantitative

variables. The association between AF and respectively mRS scores (using ordinal logistic regression, whom proportional odds assumptions were verified using score χ^2 test) and death was studied using logistic regressions in a 3-step modeling: a first model was adjusted for confounding factors described in the literature focusing on ICH outcomes[13–22] (age, sex, ICH location, time period of occurrence, vascular risk factors including hypertension, hypercholesterolemia, diabetes, smoking, excessive alcohol intake, and history of heart failure, stroke (other than ICH), transient ischemic attack, and coronary heart disease), and that were previously found to be associated with AF[23,24] or ICH outcomes but might not be along the causal pathway from AF to outcomes; 2 additional models, also adjusted for the above-mentioned factors, were implemented to precise the role of severity, assessed by the NIHSS score (model 2), and premorbid use of OAC (model 3) on ICH outcomes as they both act as mediators, meaning these factors might be along the causal pathway from AF to ICH outcomes. ICH location was introduced in the models as it was found to be associated with ICH outcomes in several studies including among OAC-related ICH.[25–27] Patients with missing data were excluded from logistic regressions. Statistical analyses were performed using SAS Guide version 9.4 software.

Ethics Approval

The Dijon Stroke Registry was approved by following national ethics boards: the Comité d'Evaluation des Registres (French National Committee of Registers), Santé Publique France (French Institute for Public Health Surveillance), and the Commission Nationale Informatique et Liberté (French data protection authority). In accordance with the French legislation, boards waived the need for written patient consent.

DATA AVAILABILITY STATEMENT

Anonymized grouped data can be shared by request from a qualified investigator.

RESULTS

Over the whole study period (2006–2017), 445 patients with a first-ever acute ICH were recorded in the Dijon Stroke Registry. After excluding 1 patient in whom no information about AF was available, data of 444 patients with ICH were analyzed for this study, including 204 patients over period 2006 to 2011, and 240 patients over period 2012 to 2017.

Characteristics of patients are shown in Table 1. Over the whole study period (2006–2017), mean age at onset was 73.8±17 years, and women accounted for 52.2% of patients with ICH. A total of 97 (22%) patients with ICH had AF. AF was known before stroke in the majority of these cases (n=84, 87%). Among patients with previously known AF, 67% were receiving OAC. Compared with patients with ICH without AF, patients with AF were older (aged, 83.3 versus 71.8 years, $P<0.0001$), had higher prevalence of hypertension (78.3% versus 62.2%, $P=0.003$), hypercholesterolemia (37.1% versus 22.2%, $P=0.003$), chronic heart failure (17.5% versus 7.5%, $P=0.003$), and coronary heart disease (16.7% versus 6.3%, $P=0.001$) (Table 1). ICH location was similarly distributed among patients with ICH with or without AF ($P=0.41$). OAC were more frequently reported in patients with ICH with AF (72.2% versus 10.1%, $P<0.0001$). Patients with AF had a greater severity at ICH onset (median NIHSS 14 versus 8, $P=0.03$) as well as a poorer functional outcome: 81.5% of them had mRS ≥4 compared with 64.9% in patients without AF (Figure 1). In addition, mortality at discharge was higher in patients with ICH with AF (47.4% versus 30%, $P<0.0001$, Table 1).

The prevalence of AF in patients with first-ever ICH increased over time from 17.2% (95% CI, 12.3–23.9) for years 2006 to 2011 to 25.8% (95% CI, 20.1–33.1) in 2012 to 2017 (P-trend=0.05). Concomitantly, the prevalence of patients with AF treated with OAC rose from 11.3% (95% CI, 7.5–17.0) to 17.5% (95% CI, 12.9–23.7) (P-trend=0.09). Similarly, we observed a non-significant increase in newly diagnosed AF in patients with ICH (1.5% [95% CI, 0.5–4.6] in 2006 to 2011 to 4.2 [95% CI, 2.2–7.7] in 2012 to 2017, P-trend=0.11).

With regard to post-stroke outcomes, AF was associated with higher mRS scores (univariate odds ratio [OR], 2.40; 95% CI, 1.58–3.64, $P<0.0001$), even after adjusting for confounding factors and NIHSS score (model 2: OR, 1.77; 95% CI, 1.06–2.96, $P=0.03$) (Table 2 and Figure 2). However, AF was no longer independently associated with mRS after adjusting for premorbid anticoagulants (model 3: OR, 1.29; 95% CI, 0.69–2.42, $P=0.42$). Finally, no significant association between AF and death were observed in multivariable analyses adjusted for NIHSS (model 2: OR, 1.41; 95% CI, 0.73–2.73, $P=0.30$; model 3: OR, 0.89; 95% CI, 0.40–1.96, $P=0.76$). According to interaction analyses, no significant interaction was found between AF and age for mRS, nor for death, and no interaction was found between AF and age according to OAC status for all outcomes.

DISCUSSION

This population-based study demonstrated that AF is a frequent condition in patients with ICH and had been increasing over time. Hence, more than 1 in 6 patients with ICH during period 2006–2011, and 1 in 4 during period 2012–2017 had AF. Although AF was

Table 1. Characteristics of Patients With ICH According to AF Prevalence and Prior AF, 2006 to 2017

	Time period											
	2006–2011				2012–2017				Overall period (2006–2017)			
	All ICH	ICH with AF‡	ICH without AF	*P* value*	All ICH	ICH with AF‡	ICH without AF	*P* value*	All ICH	ICH with AF‡	ICH without AF	*P* value*
n	204	35	169		240	62	178		444	97	347	
Mean age, y (SD)	75.0 (16)	82.3 (9)	73.8 (17)	0.022	72.7 (18)	83.6 (11)	69.9 (20)	<0.0001	73.8 (17)	83.3 (10)	71.8 (18)	<0.0001
Age <65 y, n (%)	39 (19.1)	2 (5.7)	37 (21.9)	0.027	67 (27.9)	6 (9.7)	61 (34.3)	0.0002	106 (23.9)	8 (8.2)	98 (28.2)	<0.0001
Women, n (%)	113 (55.4)	23 (65.7)	90 (53.3)	0.178	119 (49.6)	33 (53.2)	86 (48.3)	0.506	232 (52.2)	56 (57.7)	176 (50.7)	0.222
AF, n (%)	35 (17.2)	35 (100)	0	0	62 (25.8)	62 (100)	0	0	97 (21.9)	97 (100)	0	0
Known AF, n (%)	32 (15.7)	32 (91.4)	0	0	52 (21.7)	52 (83.9)	0	0	84 (18.9)	84 (86.6)	0	0
Known AF treated with OAC, n(%)	23 (11.3)	23 (65.7)	0	0	42 (17.5)	42 (67.7)	0	0	65 (14.6)	65 (67.0)	0	0
Newly diagnosed AF, n (%)	3 (1.5)	3 (8.6)	0	0	10 (4.2)	10 (16.1)	0	0	13 (2.9)	13 (13.4)	0	0
ICH location, n (%)				0.509				0.449				0.407
Lobar	96 (48.7)	15 (42.9)	81 (50.0)		121 (50.4)	26 (41.9)	95 (53.4)		217 (49.7)	41 (42.3)	176 (51.8)	
Deep	77 (39.1)	15 (42.9)	62 (38.3)		77 (32.1)	23 (37.1)	54 (30.3)		154 (35.2)	38 (39.2)	116 (34.1)	
Infratentorial	18 (9.1)	4 (11.4)	14 (8.6)		25 (10.4)	7 (11.3)	18 (10.1)		43 (9.8)	11 (11.3)	32 (9.4)	
Undetermined	6 (3.1)	1 (2.9)	5 (3.1)		17 (7.1)	6 (9.7)	11 (6.2)		23 (5.3)	7 (7.2)	16 (4.7)	
Missing	7 (3.4)	0	7 (4.1)		0	0	0		7 (1.6)	0	7 (2.0)	
Premorbid treatment, n (%)												
Anticoagulants	40 (19.6)	24 (68.6)	16 (9.5)	<0.0001	65 (27.1)	46 (74.2)	19 (10.7)	<0.0001	105 (23.6)	70 (72.2)	35 (10.1)	<0.0001
Antiplatelet agents	37 (18.1)	4 (11.4)	33 (19.5)	0.259	44 (18.3)	14 (22.6)	30 (16.8)	0.317	81 (18.2)	18 (18.6)	63 (18.2)	0.928
Antihypertensive treatments	83 (40.7)	15 (42.9)	68 (40.2)	0.774	115 (47.9)	47 (75.8)	68 (38.2)	<0.0001	198 (44.6)	62 (63.9)	136 (39.2)	<0.0001
Medical history, n (%)												
Hypertension§	146 (71.6)	23 (65.7)	123 (72.8)	0.401	146 (60.8)	53 (85.5)	93 (52.2)	<0.0001	292 (65.8)	76 (78.3)	216 (62.2)	0.003
Hypercholesterolemia§	49 (24.0)	9 (25.7)	40 (23..7)	0.797	64 (26.7)	27 (43.5)	37 (20.8)	0.0005	113 (25.4)	36 (37.1)	77 (22.2)	0.003
Diabetes§	33 (16.3)	5 (14.3)	28 (16.7)	0.729	26 (10.8)	10 (16.1)	16 (9.0)	0.120	59 (13.3)	15 (15.5)	44 (12.7)	0.482
Missing	1 (0.5)	0	1 (0.6)		0	0	0		1 (0.2)	0	1 (0.3)	
Smoking (current or former smoker)	58 (29.3)	7 (21.2)	51 (30.9)	0.265	66 (29.7)	16 (28.6)	50 (30.1)	0.827	124 (29.5)	23 (25.8)	101 (30.5)	0.392
Missing	6 (2.9)	2 (5.7)	4 (2.4)		18 (7.5)	6 (9.7)	12 (6.7)		24 (5.4)	8 (8.2)	16 (4.6)	
Alcohol intake	21 (10.4)	2 (5.9)	2 (11.4)	0.341	28 (12.4)	7 (12.5)	21 (12.4)	0.988	49 (11.5)	9 (10.0)	40 (11.9)	0.615
Missing	3 (1.5)	1 (2.9)	2 (1.2)		15 (6.3)	6 (9.7)	9 (5.1)		18 (4.0)	7 (7.2)	11 (3.2)	
Chronic heart failure	25 (12.2)	7 (20.0)	18 (10.6)	0.126	18 (7.5)	10 (16.1)	8 (4.5)	0.003	43 (9.7)	17 (17.5)	26 (7.5)	0.003
Previous stroke	43 (21.1)	6 (17.1)	37 (21.9)	0.531	55 (22.9)	17 (27.4)	38 (21.4)	0.328	98 (22.1)	23 (23.7)	75 (21.6)	0.660
Previous TIA	7 (3.4)	1 (2.9)	6 (3.5)	0.838	16 (6.7)	7 (11.3)	9 (5.1)	0.134	23 (5.2)	8 (8.2)	15 (4.3)	0.123

(*Continued*)

Table 1. Continued

	Time period											
	2006–2011				2012–2017				Overall period (2006–2017)			
	All ICH	ICH with AF‡	ICH without AF	*P* value*	All ICH	ICH with AF‡	ICH without AF	*P* value*	All ICH	ICH with AF‡	ICH without AF	*P* value*
Coronary heart diseases	19 (9.3)	6 (17.1)	13 (7.7)	0.080	19 (7.9)	10 (16.4)	9 (5.1)	0.011	38 (8.6)	16 (16.7)	22 (6.3)	0.001
Missing	0	0	0		1 (0.4)	1 (1.6)	0		1 (0.2)	1 ()	0	
CHA_2DS_2VaSc score ≥2, %	132 (84.2)	24 (91.4)	108 (82.3)	0.199	139 (80.0)	52 (96.8)	87 (74.2)	<0.0001	271 (81.8)	76 (94.9)	195 (78.1)	<0.0001
Missing	1 (0.5)	0	1 (0.6)		0	0	0		1 (1.0)	0	1 (0.3)	
NIHSS score on admission, median (IQR)	8.5 (4–21)	11 (4–24)	8 (4–19)	0.243	11 (3–21)	14 (5–23)	8.5 (3.0–20)	0.077	10 (4–21)	14 (5–23)	8 (4–20)	0.031
Modified Rankin Scale score at discharge, n (%)				0.034				0.0003				<0.0001
mRS 0	8 (3.9)	0	8 (4.7)		15 (6.2)	0	15 (8.4)		5.2 (23)	0	23 (6.6)	
mRS 1	19 (9.3)	2 (5.7)	17 (10.1)		24 (10.0)	2 (3.2)	22 (12.4)		43 (9.7)	4 (4.1)	39 (11.2)	
mRS 2	26 (12.7)	3 (8.6)	23 (13.6)		10 (4.2)	3 (4.8)	7 (3.9)		36 (8.1)	6 (6.2)	30 (8.6)	
mRS 3	14 (6.9)	1 (2.9)	13 (7.7)		24 (10.0)	7 (11.3)	17 (9.6)		38 (8.6)	8 (8.2)	30 (8.7)	
mRS 4	58 (28.4)	11 (31.4)	47 (27.8)		34 (14.2)	4 (6.5)	30 (16.9)		92 (20.7)	15 (15.5)	77 (22.2)	
mRS 5	15 (7.4)	4 (11.4)	11 (6.5)		47 (19.6)	14 (22.6)	33 (18.5)		62 (14.0)	18 (18.6)	44 (12.7)	
mRS 6	64 (31.4)	14 (40.0)	50 (29.6)		86 (35.8)	32 (51.6)	54 (30.3)		150 (33.8)	46 (47.4)	104 (30.0)	
Length of hospital stay‖, d (sd)	19 (26)	24 (37)	19 (24)	0.665	14 (15)	16 (16)	14 (15)	0.268	17 (21)	19 (25)	16 (20)	

Abbreviations: AF, atrial fibrillation; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified rankin score; TIA, transient ischemic attack; OAC, oral anticoagulants.
* Between stroke with atrial fibrillation and stroke without atrial fibrillation.
†Between stroke with known atrial fibrillation and stroke with newly diagnosed atrial fibrillation.
‡Refers to patients with both previously known atrial fibrillation and those with newly diagnosed atrial fibrillation.
§Treated or not.
‖Among patients with intracerebral hemorrhage; hospitalized (436 of the 444 intracerebral hemorrhage).

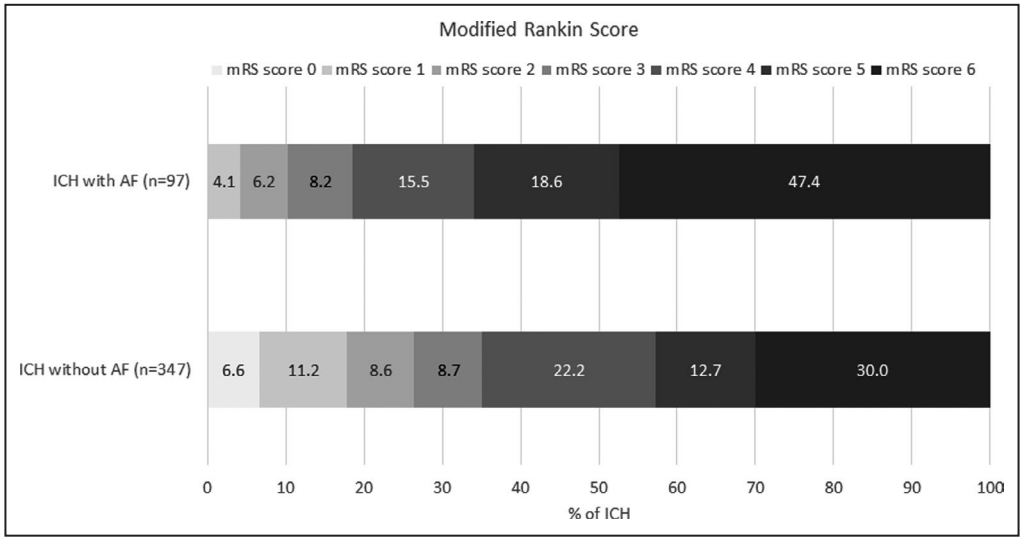

Figure 1. Unadjusted distribution of modified Rankin Scores in intracerebral hemorrhage with and without atrial fibrillation for the period 2006 to 2017.
AF indicates atrial fibrillation; ICH, intracerebral hemorrhage; and mRS, modified Rankin Scale.

known before ICH in the large majority of patients with ICH with AF (86.6%), the proportion of newly diagnosed AF among patients with ICH with AF almost doubled between these 2 time periods (from 8.6% to 16.1%). There was a trend toward an increase in the proportion of patients with ICH with previously known AF treated with OAC, who accounted for two third of cases. Despite an apparent deleterious impact of AF on post-ICH prognosis in univariate analyses, AF was not significantly associated with early poor functional outcome or death after considering confounding factors and the premorbid use of OAC.

In our study, the prevalence of AF in patients with ICH was consistent with that reported in population-based and hospital-based studies for the same time period, with numbers ranging from 16% to 31%.[28–31] Over the 2012 to 2017 period, 17.5% of ICH were previously anticoagulated for AF and 11% over the 2006 to 2011 period. A similar proportion was found in the PITCH (Prognosis of Intra-Cerebral Hemorrhage) cohort study (10%) over the same time period (2004–2009).[32]

The proportion of ICH with prior anticoagulation for AF rose between 2006 and 2017. Previous studies reported an increase in the incidence of overall ICH associated with antithrombotic use, irrespective of the indication for this therapy.[2,4] Of note, in a previous analysis of the Dijon Stroke Registry, we observed a 75% increase in the incidence of ICH in people aged >75 years between 1985 and 2008, mainly because of a rise in the incidence of lobar ICH.[2] Concomitantly, the prevalence of prior-to-ICH use of anticoagulants quadrupled among patients with ICH aged >75 years, thus indicating the continued importance of studying the optimal treatment strategies for this group of older individuals at risk for bleeding-prone vasculopathies such as cerebral amyloid angiopathy. Our present findings highlight the fact that the increase in prior use of OAC in overall patients with ICH could be associated with the rise in the number of patients with AF receiving OAC. This result raises an important issue on a clinical point of view with regard to secondary prevention strategies. Indeed, a large majority of patients with ICH with AF were eligible to have an OAC prescription according to the CHA_2DS_2VaSc score that was ≥2 in 91.4% of them during period 2006 to 2011 and 96.8% during period 2012 to 2017. In the absence of current strong evidence-based guidelines, there are therapeutic dilemmas around the net benefit of anticoagulation in this setting.

Although ICH has been longstanding regarded as a contraindication for OAC, a recent analysis from the PITCH cohort pointed out a high risk of long-term occurrence of major ischemic events in ICH survivors.[33] At 5 years, the incidence of ischemic stroke was 9% whereas that of ICH recurrence was 4.9%. Interestingly, deep index ICH was associated with greater ischemic stroke events than ICH recurrences during follow-up, whereas an inverse association was observed for lobar location. Anticoagulation during follow-up was neither associated with hemorrhagic events nor with ischemic events. Patients with AF accounted for 11% of this cohort enrolled between 2004 and 2009 versus 26% in our study during 2012 to 2017 period, thus suggesting that this issue is getting greater in contemporary clinical practice. Although a recent meta-analysis showed that OAC resumption after ICH was associated with decreased mortality, improved functional outcome, and decreased all-cause

Table 2. Association Between AF and Respectively Higher Modified Rankin Scores and Death in Patients With ICH From the Dijon Stroke Registry, 2006 to 2017

	Modified Rankin scale scores (ordinal)				In-hospital death			
		Multivariate			Univariate	Multivariate		
Effects	Univariate	Model 1	Model 2	Model 3		Model 1	Model 2	Model 3
AF (yes vs no)	2.40 [1.58–3.64]*	1.93 [1.23–3.05]*	1.44 [1.0.6–2.96]*	1.29 [0.69–2.42]	2.11 [1.33–3.34]*	1.69 [1.00–2.84]*	1.41 [0.73–2.73]	0.89 [0.40–1.96]
Severity								
NIHSS (for 1-point increase)	1.21 [1.17–1.24]*	…	1.22 [1.19–1.26]*	1.22 [1.19–1.26]*	1.16 [1.13–1.20]*	…	1.18 [1.14–1.22]*	1.18 [1.14–1.22]*
Premorbid anticoagulant treatment	2.35 [1.57–3.52]*	…	…	1.74 [0.93–3.26]	2.41 [1.54–3.78]*	…	…	2.53 [1.11–5.78]*
Time period								
2006–2011	1	1	1	1	1	1	1	1
2012–2017	1.32 [0.94–1.84]	1.31 [0.90–1.89]	1.06 [0.71–1.57]	1.03 [0.69–1.54]	1.22 [0.82–1.82]	1.20 [0.75–1.90]	0.86 [0.48–1.54]	0.85 [0.47–1.55]
Sex								
Men (reference)	1	1	1	1	1	1	1	1
Women	1.10 [0.79–1.54]	0.71 [0.48–1.05]	0.73 [0.47–1.12]	0.73 [0.47–1.12]	1.26 [0.85–1.86]	0.85 [0.51–1.40]	0.84 [0.44–1.61]	0.82 [0.42–1.58]
Age group, y								
<65 (reference)	1	1	1	1	1	1	1	1
65–74	1.75 [1.03–2.99]*	1.81 [1.02–3.22]*	1.13 [0.61–2.11]	1.12 [0.60–2.07]	1.95 [0.93–4.09]	2.04 [0.90–4.63]	1.38 [0.50–3.83]	1.33 [0.47–3.73]
75–84	2.95 [1.88–4.64]*	3.00 [1.78–5.06]*	2.27 [1.28–4.01]*	2.05 [1.16–3.65]*	3.88 [2.10–7.16]*	3.99 [1.94–8.19]*	2.90 [1.16–7.26]*	2.55 [1.00–6.46]
≥85	3.70 [2.30–5.97]*	3.88 [2.22–6.77]*	4.45 [2.41–8.21]*	4.23 [2.29–7.84]*	3.87 [2.06–7.28]*	4.00 [1.89–8.43]*	3.42 [1.31–8.95]*	3.18 [1.20–8.46]*
Vascular risk factors								
Hypertension (yes vs no)	1.36 [0.96–1.92]	0.94 [0.62–1.42]	1.02 [0.65–1.60]	1.01 [0.64–1.58]	1.27 [0.84–1.94]	0.96 [0.57–1.61]	1.05 [0.54–2.03]	1.00 [0.51–1.96]
Hypercholesterolemia (yes vs no)	1.04 [0.71–1.53]	0.92 [0.58–1.46]	0.80 [0.48–1.33]	0.82 [0.49–1.37]	1.04 [0.67–1.64]	1.05 [0.59–1.87]	1.26 [0.58–2.73]	1.37 [0.63–2.99]
Diabetes mellitus (yes vs no)	0.84 [0.52–1.37]	0.79 [0.45–1.38]	0.53 [0.29–0.96]*	0.52 [0.28–0.94]*	0.77 [0.42–1.41]	0.66 [0.32–1.39]	0.50 [0.19–1.31]	0.45 [0.17–1.19]
Smoking	0.61 [0.42–0.88]*	0.61 [0.39–0.95]*	0.72 [0.44–1.17]	0.70 [0.43–1.14]	0.53 [0.33–0.86]*	0.50 [0.27–0.95]*	0.37 [0.16–0.86]	0.36 [0.16–0.85]
Alcohol intake	1.43 [0.84–2.45]	2.09 [1.11–3.95]*	2.00 [1.01–3.98]*	2.13 [1.07–4.24]*	1.46 [0.79–2.68]	2.43 [1.09–5.41]*	2.78 [0.99–7.77]	3.20 [1.13–9.07]*
Heart failure (yes vs no)	1.31 [0.74–2.31]	1.33 [0.68–2.58]	1.73 [0.84–3.56]	1.64 [0.80–3.38]	0.94 [0.48–1.84]	0.93 [0.40–2.15]	1.15 [0.41–3.24]	1.11 [0.39–3.14]
Stroke (yes vs no)	1.16 [0.78–1.73]	1.35 [0.87–2.11]	1.43 [0.86–2.35]	1.40 [0.84–2.31]	0.83 [0.51–1.35]	0.86 [0.49–1.50]	0.54 [0.25–1.17]	0.50 [0.23–1.10]
TIA (yes vs no)	0.89 [0.42–1.87]	0.67 [0.30–1.50]	1.03 [0.41–2.54]	0.96 [0.39–2.38]	1.05 [0.43–2.53]	1.17 [0.43–3.15]	1.92 [0.45–8.15]	1.84 [0.45–7.54]
Coronary heart disease (yes vs no)	0.95 [0.53–1.71]	0.63 [0.32–1.26]	0.76 [0.36–1.61]	0.76 [0.36–1.61]	0.79 [0.38–1.64]	0.54 [0.22–1.35]	0.56 [0.16–1.96]	0.61 [0.17–2.12]
ICH location								
Lobar (reference)	1	1	1	1	1	1	1	1
Deep	1.56 [1.07–2.26]*	1.58 [1.05–2.36]*	1.04 [0.67–1.62]	1.03 [0.66–1.61]	1.66 [1.08–2.56]*	1.89 [1.15–3.10]*	1.83 [0.98–3.44]	1.78 [0.94–3.36]
Infratentorial	0.86 [0.48–1.53]	0.85 [0.45–1.60]	0.96 [0.49–1.87]	0.96 [0.49–1.89]	1.01 [0.50–2.07]	1.09 [0.48–2.49]	1.61 [0.55–4.78]	1.58 [0.52–4.78]
Undertermined	0.93 [0.44–1.99]	0.89 [0.41–1.95]	1.30 [0.53–3.22]	1.30 [0.52–3.21]	1.25 [0.50–3.09]	1.45 [0.54–3.91]	2.52 [0.60–10.5]	2.34 [0.54–10.1]

Model 1: adjusted for age, sex, intracerebral hemorrhage location, vascular risk factors, comorbidities; Model 2: model 1 adjusted for National Institutes of Health Stroke Scale; Model 3: model 2 adjusted for premorbid anticoagulants. Abbreviations: AF, atrial fibrillation; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

* P value < 0.05.

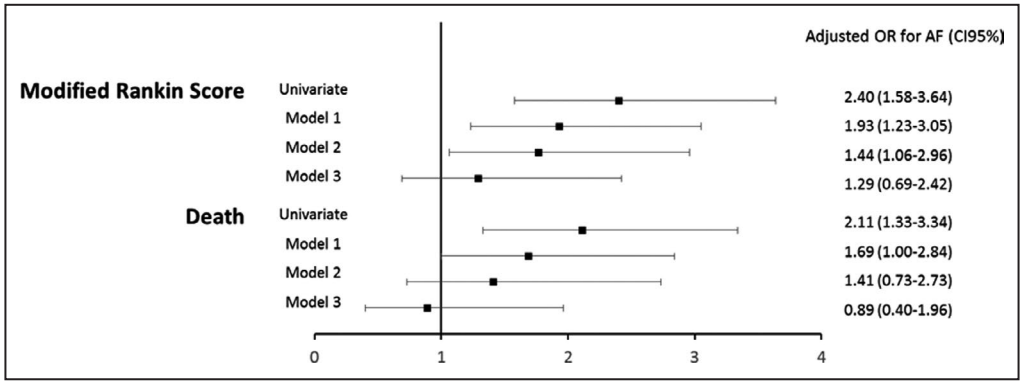

Figure 2. Association between atrial fibrillation and respectively higher modified Rankin scores and death in patients with intracerebral hemorrhage from the Dijon Stroke Registry, 2006 to 2017. Model 1: adjusted for age, sex, intracerebral hemorrhage location, vascular risk factors, comorbidities. Model 2: Model 1 adjusted for National Institutes of Health Stroke Scale. Model 3: Model 2 adjusted for premorbid anticoagulants. AF indicates atrial fibrillation; and OR, odds ratio.

stroke incidence in both lobar and deep ICH,[34] results of ongoing randomized clinical trials conducted on patients with ICH with AF are to be expected before drawing any definite conclusion (APACHE-AF [Apixaban Versus Antiplatelet Drugs or No Antithrombotic Drugs after Anticoagulation-Associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation],[35] STATICH [Study of Antithrombotic Treatment after Intracerebral Hemorrhage], NASPAF-ICH [Non-VKA Anticoagulants for Stroke Prevention in Patients with AF and Previous Intracerebral Hemorrhage], SoSTART [Start or Stop Anticoagulants Randomised Trial] After Spontaneous Intracranial Haemorrhage, ASPIRE [Anticoagulation in ICH Survivors for Stroke Prevention and Recovery], ENRICH-AF [Edoxaban for Intracranial Hemorrhage Survivors With Atrial Fibrillation], PRESTIGE-AF [Prevention of Stroke in Intracerebral HaemorrhagE Survivors With Atrial Fibrillation]).[36] These results would probably also apply to patients with ICH with newly diagnosed AF who accounted for 4% of overall ICH cases in our study over the more recent time period.

Patients with ICH and AF had worse functional and vital outcomes compared with patients with ICH without AF. This observation remained significant for both outcomes after adjustments for confounding factors age, sex, ICH location, time period of occurrence, vascular risk factors, and comorbidities. The apparent increased probability of death and higher mRS score associated with AF was no longer observed after a further adjustment for severity through NIHSS score about death outcome but OR for AF remained high even non-significant. It was only after adjustment for premorbid OAC that association between AF and mRS score was no more significant. A similar result was observed in a hospital-based stroke registry,[37] which suggests a pivotal role of OAC on poor prognosis after ICH, as suspected in other works.[19,23–27] Several studies demonstrated larger ICH volumes among patients with premorbid anticoagulation compared with patients without[32,38,39] supporting the causal impact of premorbid OAC use on ICH outcomes among patients with AF but not AF itself. Although we did not evaluate ICH volume in our study, the observed greater severity at onset in patients with ICH and AF could reflect such an association. Nevertheless, the fact that the NIHSS score was added to our multivariable models indicated that the deleterious effect of OAC on post-ICH prognosis could be mediated by other factors. Among these, OAC therapy has been shown to represent an important contributor of hematoma expansion in patients with ICH,[40] which is associated with a worse neurological outcome in turn.[41] Taken together, these results underline the increasing need for developing therapeutic strategies aiming at reducing such a complication in anticoagulated patients with AF and ICH so as to improve their prognosis.

Our study has several strengths. The Dijon Stroke Registry exhaustively recorded all stroke cases, including ICH, in a population-based setting, thus ruling out the bias of hospital-based collection of cases, and with few missing data. Although the epidemiology of ICH in Dijon could differ from that observed in other areas, our study came from real life experience and findings could be useful for stroke clinicians by underlying potential targets so as to improve ICH management. In addition, the population-based methodology makes it possible for future comparisons with other similar studies. The long duration of the study with constant procedures for case-collection allowed analyzing temporal trends. Several limitations should be acknowledged. Despite a large sample size given the population-based methodology, study power was not sufficient to perform stratified analyses according to ICH locations or types of

OAC. This could be of interest considering the debate about potential differential outcomes in patients with ICH according to the type of OAC therapy. Indeed, several studies compared characteristics of patients with ICH receiving vitamin K antagonists to those on direct oral anticoagulants with conflicting findings.[26,27,42,43] A recent collaborative multicenter pooled analysis did not conclude to differences between patients with ICH on vitamin K antagonists and patients with ICH on direct oral anticoagulants with regard to baseline ICH volume, hematoma expansion, 90-day mortality, and functional outcome.[27] Finally, the cross-sectional design did not allow us to investigate causality between AF and ICH outcomes.

To conclude, the prevalence of AF reached 1 in 4 patients with ICH in the Dijon Stroke Registry for the 2012 to 2017 period. The observed increase in AF prevalence among patients with ICH over time partly reflected a rise in the prevalence of previously anticoagulated patients with AF. Premorbid use of anticoagulants was a major contributor of the poor outcome observed in patients with ICH and AF. With the ongoing aging population, and the expected increase in the burden of AF, our results highlight the urgent need for defining acute treatment and secondary prevention strategies after ICH in patients with AF.

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Received November 24, 2020; accepted July 13, 2021.

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Sources of Funding

This work was supported by the Santé Publique France (French Institute for Public Health Surveillance), Institut National de la Santé et de la Recherche Médicale, and University Hospital of Dijon.

Disclosures

Yannick Béjot reports personal fees from BMS, Pfizer, Medtronic, Amgen, Servier, and Boehringer-Ingelheim, outside the submitted work. The remaining authors have no disclosures to report.

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