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
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 \(\geq 7.8 \text{ mmol/L} \)) reported in the medical record or patients taking insulin or oral hypoglycemic agents), hypercholesterolemia (total cholesterol level \(\geq 5.7 \text{ mmol/L} \)) 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 \(\geq 3 \text{ units a day in men and } \geq 2 \text{ in women} \)). 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\(_2\)DS\(_2\)-VASc 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 \(\chi^2\) 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 χ² 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 outcomes13–22 (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 AF23,24 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’Évaluation 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 (52.3) | 86 (48.3) | 0.506 | 232 (52.2) | 56 (57.7) | 176 (50.7) | 0.222 |
| AF, n (%) | 35 (17.2) | 35 (100) | 0 | | 62 (25.8) | 62 (100) | 0 | | 97 (21.9) | 97 (100) | 0 | |
| Known AF, n (%) | 32 (15.7) | 32 (91.4) | 0 | | 52 (21.7) | 52 (83.9) | 0 | | 84 (18.9) | 84 (86.6) | 0 | |
| Known AF treated with OAC, n(%) | 23 (11.3) | 23 (65.7) | 0 | | 42 (17.5) | 42 (67.7) | 0 | | 65 (14.6) | 65 (87.0) | 0 | |
| Newly diagnosed AF, n (%) | 3 (1.5) | 3 (8.6) | 0 | | 10 (4.2) | 10 (16.1) | 0 | | 13 (2.9) | 13 (13.4) | 0 | |
| ICH location, n (%) | | | | | | | | | | | | |
| 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) | 75 (58.8) | 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 (65.6) | 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 | 36 (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 (28.3) | 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) | 21 (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 |
**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          |       |
| CHA²DS₂VaSc 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 | 0.034 |       | 0.0003 | 0.034 |       |       |       |       |       |       |
| 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) | 0.666 | 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).
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

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.
### 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

| Effects                      | Modified Rankin scale scores (ordinal) | In-hospital death |
|------------------------------|----------------------------------------|-------------------|
|                              | Univariate Model 1 | Multivariate Model 2 | Multivariate Model 3 | Univariate Model 1 | Multivariate Model 2 | Multivariate Model 3 |
| AF (yes vs no)               |                          |                    |                        |                    |                  |                  |
|                              | 2.40 [1.58–3.64]*       | 1.93 [1.23–3.05]*  | 1.44 [1.06–2.96]*    | 1.29 [0.69–2.42]  | 2.11 [1.33–3.34]* | 1.69 [1.00–2.84]* |
| Severity                     |                          |                    |                        |                    |                  |                  |
| NIHSS (for 1-point increase) | 1.21 [1.17–1.24]*       | ...                | 1.22 [1.19–1.26]*    | 1.16 [1.13–1.20]* | ...               | 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                 |
| 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] |
| Sex                          |                          |                    |                        |                    |                  |                  |
| Men (reference)              | 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] |
| Age group, y                 |                          |                    |                        |                    |                  |                  |
| <65 (reference)              | 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] |
| 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]*|
| ≥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]* |
| 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] |
| 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] |
| 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] |
| 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]* |
| 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]*|
| 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] |
| 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] |
| 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] |
| 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] |
| ICH location                 |                          |                    |                        |                    |                  |                  |
| Lobar (reference)            | 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]*|
| 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] |
| Undetermined                 | 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] |

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.
stroke incidence in both lobar and deep ICH, 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 Antiplatelet Drugs after Anticoagulation-Associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation], STATICH [Study of Antithrombotic Treatment after Intracerebral Hemorrhage], NASPAsf-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]). 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, which suggests a pivotal role of OAC on poor prognosis after ICH, as suspected in other works. Several studies demonstrated larger ICH volumes among patients with premorbid anticoagulation compared with patients without 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, which is associated with a worse neurological outcome in turn. 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

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.
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 elderly patients with ICH and AF outcomes. With the ongoing aging population, and the expected increase 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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