Relationship of Preexisting Cardiovascular Comorbidities to Newly Diagnosed Atrial Fibrillation After Ischemic Stroke

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Background and Purpose—There remains uncertainty as whether newly diagnosed atrial fibrillation (AF) after ischemic stroke reflects underlying heart disease and represents an increased risk of cardioembolic stroke, or whether it is triggered by neurogenic mechanisms. We aimed to determine whether cardiovascular comorbidities in patients with new AF after ischemic stroke differ from patients with previous known AF or without AF.

Methods—This French longitudinal cohort study was based on the database covering hospital care from 2009 to 2012 for the entire population.

Results—Of 336 291 patients with ischemic stroke, 240 459 (71.5%) had no AF and 95 832 (28.5%) had previously known AF at baseline. Patients without previous AF had a mean CHA_2DS_2-VASc score of 4.98±1.63 SD. During a mean follow-up of 7.9±11.5 months, 14 095 (5.9%) of these patients had incident AF, representing an annual incidence of AF after ischemic stroke of 8.9 per 100 person-years (95% confidence interval, 8.8–9.0). New AF patients had higher CHA_2DS_2-VASc score, more likely comorbidities, and more frequent history of previous transient ischemic attack than patients with previous known AF or without AF.

Conclusions—Preexisting cardiovascular comorbidities underlie AF newly diagnosed after stroke. Consequently, these high-risk patients should be closely monitored for incident AF to facilitate an earlier diagnosis of AF and avoid stroke with appropriate thromboprophylaxis. **(*Stroke*. 2017;48:2878-2880. DOI: 10.1161/STROKEAHA.117.018251.)**

Key Words: atrial fibrillation ■ incidence ■ risk factors ■ stroke ■ uncertainty

Atrial fibrillation (AF) is a major cause of ischemic stroke (IS), and 20% of all strokes can be attributed to AF.[1] The use of oral anticoagulation reduces this risk by 64% and all-cause mortality by 26%, when compared with control or placebo.[2] oral anticoagulation initiation is generally required for secondary prevention after IS and evidence of AF. In the absence of documented AF, antiplatelet agents are usually recommended.

New AF after IS possibly reflects underlying cardiovascular comorbidities but might also be triggered by neurogenic mechanisms involving the autonomic nervous system.[3–5] We assessed whether cardiovascular risk factors in patients with new AF after IS during follow-up differed from patients with (previous) known AF and patients without AF.

Methods

This French longitudinal cohort study was based on the national hospitalization database covering hospital care from for the entire population. Data for all patients admitted with IS in France from January 2008 to December 2012 were collected from the national administrative database, the Program de Médicalisation des Systèmes d'Information. These data are rendered anonymous, which makes it possible to link discharge abstracts related to a given patient. Diagnoses identified are coded according to the *International Classification of Diseases*, Tenth Revision. The reliability of Program de Médicalisation des Systèmes d'Information data has already been assessed and has previously been used to study patients with stroke and AF.[6]

This study was approved by the local institutional review board, on December 1, 2015, and registered as a clinical audit. Ethical review was therefore not required. Procedures for data collection and management were approved by the Conseil National de l'Informatique et des Libertés (authorization number 1749007).

Study Population

The study included adults (≥18 years) with a diagnosis of acute IS (I63 and subsections using *International Classification of Diseases, Tenth Revision* codes) coded as a principal or related diagnosis who were hospitalized from January 1, 2009, to December 31, 2012. All patients had at least 1 year where previous events were recorded to establish history of previous AF and comorbidities. Patient information (demographics, comorbid conditions, medical history, vital status, and events during follow-up) was described using data collected in the hospital records. AF recorded during medical history or hospital stay until the first 30 days was considered as AF at baseline. Information on emigration status was not available in this database.

Statistical Analysis

The Mann–Whitney and Kruskal–Wallis tests were used for comparing values between 2 independent groups and the χ^2 test for comparing

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categorical data. A proportional hazard model was used to identify independent characteristics associated with the occurrence of AF during follow-up. Discrimination and calibration were, respectively, evaluated using Harrell C statistic and Groennesby and Borgan test.

Results

In 336 291 patients with IS from 2009 to 2012, rhythm status was established before and after IS. We identified 240 459 (71.5%) as not having AF at baseline and 95 832 (28.5%) with previously known AF based on their clinical history or during their hospital stay with diagnosis of stroke (Figure).

After a follow-up of 7.9±11.5 months, 14 095 (5.9%) of these patients without AF at baseline were diagnosed as having incident AF during a subsequent hospitalization (Table). The yearly incidence rate for AF for participants with IS was 8.9 per 100 person-years (95% confidence interval, 8.8–9.0; Figure I in the online-only Data Supplement). Cardiovascular risk factors and comorbidities seen in patients with IS were more prevalent among patients with known AF than in patients with no AF. These risk factors and comorbidities were even more prevalent among patients with new AF after IS (Table). Mean CHA_2DS_2-VASc score was lowest for patients with no AF and higher for patients with new AF compared with those with known AF at baseline. Patients with newly diagnosed AF more frequently had history of previous transient ischemic attack than those with known AF and those with no AF.

Most powerful predictors of incident AF were older age, hypertension, heart failure, systemic embolism, coronary artery disease, abnormal renal function, anemia, lung disease, pacemaker/implantable cardioverter defibrillator implantation, and valvular disease (Table I in the online-only Data Supplement).

Discussion

Our results confirm that preexisting cardiovascular comorbidities clearly underlie newly diagnosed AF after acute IS. In this cohort of patients with IS, those with new AF tended to have more comorbidities than patients without AF and had higher CHA2DS2-VASc scores (1 point for heart failure, hypertension, diabetes, vascular disease, age 65-74, and female gender; 2 points for prior stroke or thromboembolism and age ≥75).

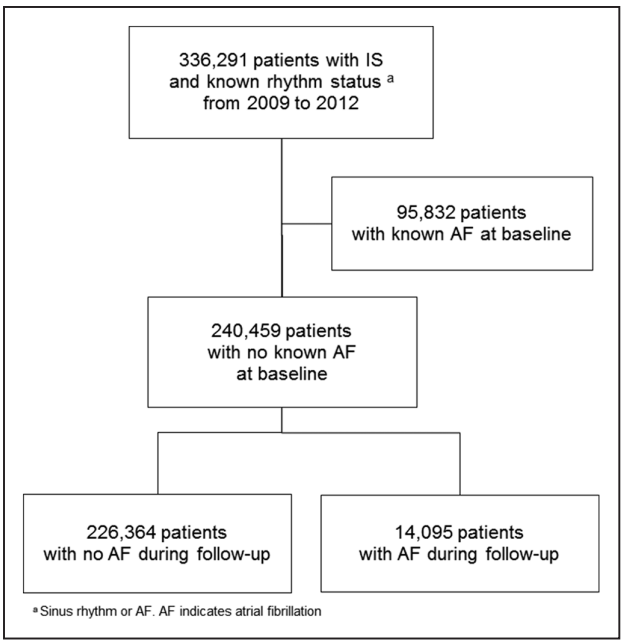

Figure. Flow chart of the study patients. AF indicates atrial fibrillation; and IS, ischemic stroke.

There has been speculation that new AF after IS may represent the consequence of the brain damage that is induced by the IS rather than its cause[3] perhaps related to imbalances of sympathetic and parasympathetic activity with resulting myocardial changes, particularly as a result of insular ischemic lesions.[7] However, it is unknown whether insular infarction is only a frequent destination of cardiogenic emboli or truly triggers neurogenic AF. We clearly show that patients with new AF more frequently had cardiovascular risk factors and comorbidities than patients with known AF or no AF. Left atrial enlargement, previously reported in new AF patients, may not be because of IS and would more likely be the consequence of long-term comorbidities.[4]

Our results strongly suggest that preexisting comorbidities are the major cause of AF that is newly diagnosed after stroke because they were even more prevalent that in patients with known AF. These are new findings extending those obtained in the recent analysis by Rizos et al[4] with a smaller number of patients. The fact that patients with so-called new AF more often had a history of transient ischemic attack suggests that AF was previously unknown rather than being true new-onset AF.

Consistently reported risk indicators of incident AF in the general population or after IS were sex, advancing age, body mass index, hypertension, heart failure, myocardial infarction, and valvular heart disease as in our study.[6,8] We found that other factors, less well described in studies, such as abnormal renal function, anemia, lung disease, pacemaker/implantable cardioverter defibrillator implantation, could be independently involved in AF genesis.

Of note, patients with new AF are significantly less likely to get anticoagulated than patients with prior known AF despite the presence of stroke risk factors,[9] although they seem to be those getting the highest benefits from anticoagulation because of their high CHA_2DS_2-VASc scores. One should therefore target patients in sinus rhythm at time of IS with such cardiovascular risk factors at risk to have more intense monitoring strategies for so-called incident AF during following months. Diagnosing earlier AF in these high-risk patients would allow oral anticoagulants initiation for better stroke recurrences prevention.

Study Limitations

Even though the reliability of Program de Médicalisation des Systèmes d'Information data has been verified previously and used for epidemiological purposes in AF,[6] the analysis presents inherent potential information bias of its retrospective observational nature. Diagnoses during outpatient visits were not included in our analysis and this possibly underestimated the true incidence of AF. Some echocardiographic parameters may help to identify a higher risk of AF,[10] and these parameters were lacking in the present study performed on a nationwide basis. Given the often paroxysmal and asymptomatic nature of AF, this arrhythmia may not be detected very early with the use of traditional monitoring techniques.[11]

Table. Baseline Characteristics of the Patients With Ischemic Stroke

Variables	No AF (n=226 364)	Known AF (n=95 832)	New AF (n=14 095)	Known vs New AF
Age, y	70.7±15.7	80.4±9.8*	77.6±10.6*	<0.0001
Sex (female)	107 266 (47.4%)	52 998 (55.3%)*	7082 (50.3%)*	<0.0001
Underlying diseases				
Hypertension	141 045 (62.3%)	71 078 (74.2%)*	11 745 (83.3%)*	<0.0001
Diabetes mellitus	50 977 (22.5%)	23 038 (24%)*	4083 (29%)*	<0.0001
Heart failure	33 162 (14.7%)	39 935 (41.7%)*	6261 (44.4%)*	<0.0001
Vascular disease	70 636 (31.2%)	37 892 (39.5%)*	6907 (49%)*	<0.0001
CHA_2DS_2-VASc score	4.98±1.63	6.02±1.43	6.09±1.44	<0.0001
Comorbidities				
Systemic embolism	6261 (2.8%)	4758 (5%)*	807 (5.7%)*	0.0001
Coronary artery disease	39 652 (17.5%)	27 315 (28.5%)*	4969 (35.3%)*	<0.0001
Transient ischemic attack	22 853 (10.1%)	9508 (9.9%)†	2075 (14.7%)*	<0.0001
Obesity	22 901 (10.1%)	10 795 (11.3%)*	2071 (14.7%)*	<0.0001
Abnormal renal function	38 618 (17.1%)	31 783 (33.2%)*	5393 (38.3%)*	<0.0001
Lung disease	35 320 (15.6%)	23 046 (24.1%)*	3661 (26%)*	<0.0001
Alcohol-related diagnoses	17 680 (7.8%)	4764 (5%)*	954 (6.8%)*	<0.0001
Thyroid disease	68 247 (30.2%)	35 274 (36.8%)*	6040 (42.9%)*	<0.0001
Dyslipidemia	69 428 (30.7%)	26 516 (27.7%)*	5793 (41.1%)*	<0.0001
PM-ICD	7201 (3.2%)	11 015 (11.5%)*	1643 (11.7%)*	0.5724
Valvular disease	15 121 (6.7%)	17 280 (18%)*	2780 (19.7%)*	<0.0001
Tobacco smoking	28 840 (12.7%)	5484 (5.7%)*	1415 (10%)*	<0.0001

AF indicates atrial fibrillation; and PM-ICD, pacemaker/implantable cardioverter defibrillator.
*P<0.0001 vs no AF.
†P=0.13 vs no AF.

Conclusions

Our results suggest that preexisting cardiovascular comorbidities are the major determinants of incident AF that is newly diagnosed after IS. Risk factors of developing incident AF after IS are similar to risk factors of thromboembolic events in AF patients. Such high-risk patients should be closely monitored for incident AF to facilitate an earlier diagnosis of AF (with optimal modalities still to be determined[6]) and this might avoid stroke with appropriate thromboprophylaxis.

Disclosures

Dr Fauchier has served as a consultant or speaker for Bayer, Boehringer Ingelheim, BMS/Pfizer, and Medtronic. Dr Angoulvant has received funding for conference travel and educational symposia from AstraZeneca, Eli-Lilly, Novartis, Bayer, Merck Sharp & Dohme, Amgen, Pfizer. Dr Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. The other authors report no conflicts.

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