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TITRE

Facteurs prédictifs de fibrillation atriale après un accident vasculaire cérébral ischémique selon le sexe : Une étude de cohorte nationale

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
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Table des matières

Résumé

Introduction : La fibrillation atriale (FA) est une cause importante d'accidents vasculaires cérébraux ischémiques (AVCi). Certains scores comme le CHA_2DS_2-VASc permettent d'identifier les patients à risque de faire de la FA dans les suites d'un AVCi chez les patients sans FA connue. Nous avons cherché d'autres facteurs prédictifs indépendants de survenue de FA et comparé ces caractéristiques selon le sexe.

Méthodes : Cette étude de cohorte longitudinale française a été fondée à partir d'une base de données nationale couvrant les soins hospitaliers de 2009 à 2012 pour l'ensemble de la population.

Résultats : Sur les 336 291 patients ayant un AVCi de 2009 à 2012, 240 459 (71,5%) n'avaient pas de FA initialement. 14 095 (5,9%) de ces patients ont développé de la FA au cours d'un suivi moyen de 7,9 ± 11,5 mois (incidence de 8,9% pour 100 personnes-années). La plupart des items constituants le score CHA_2DS_2-VASc étaient des facteurs prédictifs indépendants de diagnostic ultérieur de FA. Les principaux nouveaux prédicteurs étaient l'implantation de pacemaker/défibrillateur (OR 1,56, IC 95% 1,48-1,64), les valvulopathies (OR 1,44, IC 95% 1,37-1,51), les coronaropathies (OR 1,22, IC 95% 1,15-1,28), les maladies pulmonaires chroniques (OR 1,14, IC 95% de 1,09-1,18), l'insuffisance rénale (OR 1,12, IC 95% 1,07-1,17) et l'anémie (OR 1,10, IC 95% 1,06-1,15) sans grande différence entre les hommes et les femmes. A partir de ces résultats, nous avons développé un nouveau score ayant une meilleure capacité diagnostic que le score CHA_2DS_2-VASc dans l'identification des patients à haut risque de FA dans les suites d'un AVCi.

Conclusion : De nouveaux facteurs prédictifs, cardiaques et extracardiaques, étaient associés à l'apparition de FA dans les suites d'un AVCi, sans différence entre les hommes et les femmes. Nous avons, à partir de ces conclusions, établi un nouveau score de risque identifiant les patients à risque de survenue de FA après un AVCi avec une meilleure capacité diagnostic que les scores décrits précédemment.

Mots-clés : fibrillation atriale, accident vasculaire cérébral, facteur prédictif

Abstract

Background and Purpose: Atrial Fibrillation (AF) is a cause of a substantial part of ischemic strokes (IS). Preexisting scores like CHA_2DS_2-VASc score may identify patients at higher risk of AF following IS among patients without known AF. We aimed to find other independent predictive factors and also compared gender-related characteristics and their relationship with AF occurrence differences.

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

Results: Of 336,291 patients with IS from 2009 to 2012, 240,459 (71.5%) did not have AF at baseline. A total of 14,095 (5.9%) of these patients were diagnosed as having AF during a mean follow-up of 7.9 ± 11.5 months (incidence rate 8.9% per 100 person-years). Most of the CHA_2DS_2-VASc score items were independent predictors of subsequent diagnosis of AF. Main newly found predictors were pacemaker/defibrillator implantation (HR 1.56, 95% CI 1.48-1.64), valvular disease (HR 1.44, 95% CI 1.37-1.51), coronary artery disease (HR 1.22, 95% CI 1.15-1.28), lung disease (HR 1.14, 95% CI 1.09-1.18), abnormal renal function (HR 1.12, 95% CI 1.07-1.17) and anemia (HR 1.10, 95% CI 1.06-1.15) without major difference between men and women. From these results, we developed a new score with better diagnostic ability than CHA_2DS_2-VASc score for identifying patients at higher risk of incident AF following IS.

Conclusion: Beyond items used in CHA_2DS_2-VASc score, we found new predictive factors, cardiac and extra cardiac, of AF onset after IS without difference between men and women. These findings helped us to establish a new risk score to identify patients at higher risk of incident AF following IS with better diagnostic ability than previously describes scores.

Key words: atrial fibrillation, ischemic stroke, risk prediction

Abbreviations

AF: Atrial fibrillation

AUC: Area under the curve

CI: Confidence interval

HR: Hazard ratio

IS: Ischemic stroke

NS: Non significant

PM-ICD: pacemaker or implantable cardioverter defibrillator

ROC curves: Receiver operating characteristic curves

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac rhythm disorder and affects 1 – 2% of the population. Its prevalence will at least double in the next 50 years because of an aging population [1]. A substantial part of ischemic strokes (IS) occurs in patients with AF and one in five of all strokes can be attributed to AF [2,3]. The use of oral anticoagulant treatments reduces this risk by 64% [4].

Ischemic stroke is a heterogeneous disease whose mechanisms and causes may be described using the TOAST classification [4] (including large artery atherosclerosis, small-vessel occlusion, cardioembolism, other determined aetiology, stroke of undetermined aetiology). Its cause may however remain unexplained even after routine evaluation in 20 to 40% of cases [6,7]. Documentation of AF is required to initiate anticoagulant therapy after IS for secondary prevention [2]. Given the often paroxysmal and asymptomatic nature of AF [8], this arrhythmia may not be detected easily or very early with the use of traditional monitoring techniques [9-12]. In the absence of documented AF, antiplatelet agents are usually recommended [7] despite the risk of recurrence of 22% in case of cardioembolic stroke [6] whilst oral anticoagulation would be needed for patients with AF. That is why a better identification of the risk of incident AF in patients with IS is currently a challenge.

The $CHADS_2$ and CHA_2DS_2-VASc scores have initially emerged as the dominant prediction scores to estimate the risk of stroke or systemic thromboembolism in patients with AF [13,14]. Moreover these clinical tools have also the capacity to predict adverse events in selected patients without known AF [15-20]. Their usefulness for prediction of new (or previously

unknown) incident AF in patients discharged after an IS has also been observed in a large French Nationwide Cohort Study [21].

In CHA_2DS_2-VASc score female sex is considered as a cofactor of AF and can influence the management of IS [22,23].

We aimed to confirm the ability of CHA_2DS_2-VASc score to identify patients at higher risk of AF following IS with a larger unselected study population of IS, and try to find other independent predictive factors. We also compared gender-related characteristics and their relationship with AF occurrence differences.

METHODS

Data source

This French longitudinal cohort study was based on the national hospitalization database covering hospital care from for the entire population. The main outcome measure was rate of incident AF. The data for all patients admitted with IS in France from January 2008 to December 2012 were collected from the national administrative database, the PMSI (Programme de Médicalisation des Systèmes d'Information), inspired by the US Medicare system. Since 2004, each hospital's budget has been linked to the medical activity described in this specific program, which compiles discharge abstracts related to all admissions in the 1,546 French healthcare facilities. These data are rendered anonymous, which makes it possible to link discharge abstracts related to a given patient. Routinely collected medical information includes the principal diagnosis, secondary diagnoses, and procedures performed. Diagnoses identified are coded according to the International Classification of Diseases,

Tenth Revision (ICD-10). The reliability of PMSI data has already been assessed [24,25] and PMSI has previously been used to study patients with stroke, myocardial infarction, and AF [21,26-28]. This type of study was approved by the institutional review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital, on December 1, 2015 and registered as a clinical audit. Ethical review was therefore not required. Patient consent was not sought. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care. Procedures for data collection and management were approved by the Conseil National de l'Informatique et des Libertés, the independent National ethical committee protecting human rights in France which ensures that all information is kept confidential and anonymous (authorization number 1749007).

Study population

The study included adults (≥18 years) with a diagnosis of acute IS (I63 and its subsections using ICD10 codes) coded in the principal diagnosis (i.e. the health problem that justified admission to hospital), the related diagnosis (i.e. potential chronic disease or health state during hospital stay) or the significantly associated diagnosis (i.e. comorbidity or associated complication) who were hospitalized from January 1, 2008 to December 31, 2012. We made an analysis restricted to the patients seen after 2009, meaning that all patients had at least 1 year where previous events were recorded to establish history of previous AF and comorbidities. Of note, asymptomatic cerebrovascular diseases and sequelae of stroke have different codes (I65-I66 and I69 with subdivisions) to be distinguished from acute strokes in the patients of our analysis. Patient information (demographics, comorbid conditions, medical history, and events during follow-up or during hospitalization) was described using data collected in the hospital records. For each hospital stay, all diagnoses were obtained together

at discharge. We calculated the $CHADS_2$ score and CHA_2DS_2-VASc score as previously described [13,14].

Statistical analysis

Qualitative variables are described using counts and percentages and continuous quantitative variables as means ± standard deviation. Comparisons were made using non-parametric tests as appropriate: The Wilcoxon W and Kruskal – Wallis tests were used for comparing values between two independent groups and the X^2 test for comparing categorical data. The population of individuals seen with IS without prior AF was analysed by calculating incidence rates of new onset AF and by multivariable Cox regression models. A proportional hazard model was used to identify independent characteristics associated with the occurrence of AF during follow-up. The proportional hazard assumption was checked by plotting the log-rank Kaplan Meier curves. The results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). In all analyses, a p value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were constructed to compare the predictive performance of each score, and areas under the curve (c-indexes) were calculated. A c-statistic of 0.5 was taken to represent a chance discrimination, and a value of 1 to correspond to perfect discrimination. The Harrell's c statistics with 95% confidence intervals were calculated as a measure of model performance and compared using the DeLong test. All analyses were performed using JMP ® 9.0.1 (SAS Institute, Cary, NC, USA) and Statview 5.0 (Abacus, Berkeley CA, USA).

RESULTS

Of 336,291patients with IS from 2009 to 2012 with a known rhythmic status before and after IS, 240,459 (71.5%) were identified as not having AF at baseline and 95,832 (28.5%) had previous known AF (i.e. in their history or during hospital stay with diagnosis of stroke) (figure 1). The baseline characteristics of patients without AF indicated that more than half was aged ≥75 years (table 1) with differences between men and women (Table 2). Indeed, women were significantly older and more frequently had hypertension, congestive heart failure, had a higher CHA_2DS_2-VASc score, and more frequent anaemia, and valvular disease a than men. CHA_2DS_2-VASc score after excluding the female gender component (1 point) remained higher in women than men (4.63 vs 4.39, $p<0.0001$).

A total of 14,095 (5.9%) of these patients, without AF at baseline, were diagnosed as having incident AF during a subsequent hospitalization over a follow-up of 7.9±11.5 months (Table 3). Patients with AF during follow-up were significantly older, had a higher proportion of women, they had more CHA_2DS_2-VASc score items and comorbidities than patient without AF during follow-up, except for alcohol-related diagnoses and tobacco smoking witch were more prevalent in the group without AF.

Univariate and independent predictors of incident AF are shown in Table 4 for the whole population, in Table 5 for men and Table 6 for women. In the total population, most powerful predictors of incident AF (HR ≥1.10) were older age, hypertension, heart failure, systemic embolism, coronary artery disease, abnormal renal function, anaemia, lung disease, PM-ICD implantation and valvular disease. Diabetes, vascular disease (composed of peripheral vascular disease and myocardial infarction), cancer within the preceding 5 years,

inflammatory disease and tobacco were associated significantly with a lower rate of AF occurrence during follow-up. Results were similar when one analysed separately men and women except for vascular disease (NS), systemic embolism (NS) and dyslipidaemia (HR 0.095, p=0.0483) in men and obesity (NS), abnormal renal function (NS) and anaemia (NS) in women.

CHA_2DS_2-VASc score predicted subsequent hospital discharge with a new diagnosis of AF in those patients with IS, without pre-existing AF at baseline (Tables 7, 8 and 9). Thus, the total yearly incidence rate for AF for participants with IS was 8.9 per 100 person-years (figure 10). Multivariable analysis indicated that increasing CHA_2DS_2-VASc score was associated with the risk of new onset (or previously undiagnosed) incident AF during follow-up (HR 1.43 CI 1.41-1.45, HR 1.48 CI 1.45-1.50 in men and HR 1.46 CI 1.44-1.49 in women) (Figure 2).

The annual incidence of AF increased in a stepwise fashion and reached 18.8% in patients with CHA_2DS_2-VASc =9 (only women) and 20.1% for men (with CHA_2DS_2-VASc =8) (Table 10, 11 and 12). The total incidence was superior in women (9.8%) than in men (8.2%).

Receiver operating characteristic (ROC) curve analysis for prediction of AF by the CHA_2DS_2-VASc score, showed an area under the curve (AUC) at 0.7025, with a sensibility of 68.3%, a specificity of 62%, a positive predictive value of 10.1% and a negative predictive value of 96.9% for a cut off ≥ 6. Diagnostic values were significantly similar between men and women (Figure 3).

$CHADS_2$ score could also predict AF occurrence with a non-significantly lower diagnosis capacity than CHA_2DS_2-VASc score ($p = 0.5996$) (Figure 4).

Schnabel et al. built a risk-prediction tool for incident AF in the Framingham heart study [29] with a good model fit. Based on the "Framingham risk score of AF" items, we have calculated a similar score. Some information was not available in our database as PR interval, age at which significant cardiac murmur developed and age of heart failure. They were respectively replaced by PM-ICD implantation, valvular disease and heart failure at the age of IS. ROC curve for prediction capacity of AF after IS of this model-like shown an AUC = 0.69829, 95% CI 0.6965-0.7001, p<0.0001 without significant difference with CHA_2DS_2-VASc score (p = 0.5451).

Based on these considerations, we developed a new score integrating these new predictive factors of AF after stroke. The weight of each item was determined according to the HR of the multivariate analysis. Here is the detail of this score: congestive heart failure and age ≥75 years = 2 points; valvular disease and PM-ICD implantation = 1.5 points; age 65–74 years, hypertension and coronary artery disease =1 point; female gender, obesity, abnormal renal function, anaemia, lung disease and systemic embolism = 0.5 point (Table 13). The annual incidence of AF according to our score is shown table 14. Comparison of ROC curves analysis showed a significantly better ability than CHA_2DS_2-VASc score (p < 0.0001) and "Framingham-like" score (p < 0.0001) to predict AF after IS (AUC: 0.7557, 95% CI 0.7540-0.7574, p<0.0001) (figure 5). Predictive ability of the score was significantly higher in men than in women (AUC: 0.76557 VS 0.74742, p=0.0230).

Moreover, of the 336,291 patients with a known rhythmic status before and after IS, 226,364 (67.3%) had no AF, 95,832 (28.5%) had known AF and 14,095 (4.2%) had new AF (Table

15). Patients with newly diagnosed AF during follow-up were significantly older, more often women, had more CHA_2DS_2-VASc items, and more comorbidities except for alcohol-related diagnoses and tobacco smoking. They also had more frequent history of previous TIA.

DISCUSSION

Our results confirm that IS was associated with substantially increased risk of AF among individuals with higher $CHADS_2$ and/or CHA_2DS_2-VASc scores, as previously found [21]. $CHADS_2$ and CHA_2DS_2-VASc scores had no significant difference in the ability to predict AF diagnosed after IS, after comparison of C statistics. Using these simple risk stratification tools, assessed in primary care, might be relevant to define exploration strategies for AF screening and subsequent patient management.

The $CHADS_2$ and CHA_2DS_2-VASc scores are validated tools to estimate the risk of stroke or systemic thromboembolism in patients with documented AF. These scores have been shown interesting in other applications. Indeed, pre-stroke $CHADS_2$ and CHA_2DS_2-VASc scores are also associated with neurological outcomes, long-term mortality, stroke recurrence and cardiovascular events in IS patients with and without AF [15,30-32]. Previously, $CHADS_2$ and CHA_2DS_2-VASc scores were useful in predicting the risk of incident AF in a large population without [33] and after IS [21]. However, there are only few tools integrating multiple risk factors to establish an individual's absolute risk of incident AF post-stroke while risk factors such as ageing, diabetes mellitus, hypertension, obesity, and cardiovascular disease, including alterations in cardiac structure and function consistently predispose individuals to AF [34-36]. These considerations may help us for the post-stroke antithrombotic management in secondary prevention by targeting patients at highest risk of AF.

Many components of the $CHADS_2$ and CHA_2DS_2-VASc scores are associated with higher prevalence of AF. Consistently reported risk indicators of AF in previous studies were sex, advancing age, body mass index, hypertension, heart failure, myocardial infarction and valvular heart disease [21,34,36].

Conversely, some characteristics are risk indicators of the other causes of IS defined in the TOAST Classification [5]. Indeed, smoking and diabetes, though consistently related to incident AF [37] are less strongly associated with AF than with other cardiovascular diseases. It is relatively well established that patients with diabetes more frequently have AF [37,38-40], but the causality link between diabetes and AF has been debated because of the frequent association with hypertension and obesity. Incident AF in diabetic patients would be mediated by insulin resistance which is also responsible for hypertension and obesity [41,42]. In several cohort analyses, diabetes and active smoking were less frequent in patients with cardioembolic stroke than in patients with other causes of IS [29,43-45]. This suggests that IS in patients with diabetes or smoking could rather be caused by other mechanism such as large artery or small vessel pathology. Vascular disease was associated with a lower AF incidence, which might be explained by the composite nature of the criterion. We may hypothesize that peripheral vascular disease is more likely to be associated with large artery pathology, that coronary artery disease including myocardial infarction have a higher association with cardioembolic IS [43], and that pooling both makes a lower association with AF occurrence. Active or recent cancer was also significantly associated with no AF during follow-up after IS. Some authors suggest that cancer could be an aetiology of IS because of hypercoagulable state (high D-dimer levels) and vascular lesions dues to radiation and chemotherapy explaining the high rate of cryptogenic stroke in this population [46-48]. About inflammatory diseases, they were

significantly associated with no AF occurrence possibly by the involvement of hypercoagulable state or increased atherothrombosis [49,50].

We found that PM-ICD implantation was an important and independent predictor of AF after IS. Right ventricular pacing, in patients implanted for sinus node diseases or atrio-ventricular block, adversely affects left atrial structure and function that may trigger AF [51-58]. The mechanisms are not fully understood but are thought to relate to induced dyssynchrony, mitral regurgitation secondary to papillary muscle dysfunction, and increased atrial pressure and size which may be pro-arrhythmic [59-62]. We were not able to analyse details in programming mode for patients with PM or ICD in our study. However, one may suggest that sub-optimal dual-chamber programming can result in non-physiological atrio-ventricular intervals and subsequent dyssynchrony causing atrial and pulmonary vein distension similar to VVI pacing [63]. Consequently, modern pacemaker algorithms witch significantly reduce ventricular pacing when compared with conventional dual chamber pacing, reduces the incidence of progression to persistent AF in patients with paroxysmal AF [64]. Moreover, the site of right ventricular pacing may affect the risk of AF [65]. However, prevalence of subclinical atrial tachyarrhythmia may be higher in patients with pace-makers because sinus-node dysfunction is associated with an increased risk of atrial fibrillation [52,66]. Furthermore, patients with atrioventricular-node disease may be more likely to be asymptomatic when atrial tachyarrhythmia occurs, owing to reduced atrio-ventricular conduction. PM and ICD also represent a useful tool in the screening of AF by their detection of episodes of rapid atrial rate which are well correlates with electrocardiographic documentation of AF, and this may be another explanation for these results in our analysis [9].

Regarding gender differences, women were older and had more hypertension, congestive heart failure, a higher CHA_2DS_2-VASc score, more anaemia, and valvular disease than men. These characteristics are especially known as triggers of supra-ventricular arrhythmias, that can explain why women were more prone to have known or newly diagnosed AF. Despite these differences, many predictive criterions of AF were significant predictors in both groups. AF occurs more often in women and the rate reached 55% in the group with known AF possibly because women are more symptomatic allowing an earlier diagnosis of the arrhythmia even if they have more paroxysmal AF [67,68].

Some authors suggested that newly diagnosed AF, after IS, may represent the consequence of the brain damage that is induced by the IS rather than its cause [69] and it has been speculated that it may be related to imbalances of sympathetic and para- sympathetic activity with resulting myocardial changes that have been observed particularly as a result of insular ischemic lesions [70]. However, it is not known whether insular infarction is only a frequent destination of cardiogenic emboli or truly triggers neurogenic AF. Patients with new AF have more cardiovascular risk factors and comorbidities than patients with known AF or no AF. It has already been found that pre-existing heart disease is a major cause of AF newly diagnosed after IS [71]. Our results suggest that pre-existing comorbidities are the major cause of AF that is newly diagnosed after stroke. 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. An earlier diagnosis of AF may be relevant for stroke prevention in these high risk patients. Intermittent ECG recordings for mass screening in the STROKESTOP study [72] revealed that 3% of patients aged of 75 to 76 years-old had unknown AF and 5.1% untreated AF. The more they had cardiovascular risk factors as described above,

the more they were prone to have AF. Making the diagnosis allowed to start oral anticoagulant treatment in 3.7% of the screened population.

The CRYSTAL AF and EMBRACE with continuous monitoring indicated that AF was relatively often detected early after stroke onset [12,73]. There was seemingly a higher rate of AF detection in the 3 first months in the CRYSTAL-AF study and detection curve was quite flat between the third and the sixth month. However, the longer term curve over 36 months was not flat but actually linear, and not that dissimilar from our curves with incidence of AF over 45 months. However, unexpected low prevalence of AF after cryptogenic stroke has already been reported [74], but it was in a younger population with a lower $CHADS_2$ score.

Concerning the risk prediction score of incident AF built by Schnabel et al. in the Framingham heart study [29], echocardiographic information on cardiac structure and function interestingly did not improve the risk function to a relevant extent. Prediction capacity of AF after IS of our "Framingham-like" model was similar to CHA_2DS_2-VASc score. Adding new predictive factors of AF after stroke helped us to build our post IS French score of AF, which has shown a significantly better predictive ability than the already existing scores, with significant differences between men and women (AUC: 0.766 VS 0.747, p=0.02). This may be a non-negligible improvement compared to the CHA_2DS_2-VASc score, which however has the advantage to be easily calculated and widely known in the cardiology community.

Potential clinical applications and perspectives

In agreement with previous findings [21], we confirm that the $CHADS_2$ and the CHA_2DS_2-VASc scores were significant predictors of AF after IS. Thus, it seems clear that we should

actively track the diagnosis of AF when patients with IS and a high score exhibit symptoms of cardiac arrhythmias.

We also found other clinical independent predictors of AF after IS that helped us to create a new score with improved diagnostic ability than CHA_2DS_2-VASc score. Higher scores identify patients more likely to develop incident AF after IS, which may be asymptomatic. When patients who have a high score and no previously documented AF exhibit acute stroke/TIA, we may have to search silent AF more aggressively to reduce the risk of recurrent ischemic events through appropriate and as early as possible anticoagulant therapies. Several randomized controlled trials have shown the effectiveness of longer monitoring durations in the detection of AF after cryptogenic IS [12,73,75]. Consequently, it has been proposed that prolonged monitoring of heart rhythm becomes part of the standard care of patients with cryptogenic stroke [12,73]. Our score may help to target the population likely to benefit of such monitoring with an insertable device or to propose early oral anticoagulation in patients with IS of undetermined source with a high risk of AF, before AF itself is documented [7]. Knowing that only 35% of patient with diagnosed AF during IS have anticoagulant treatment after hospital discharge [76]. Another strategy is to treat and control the underlying diseases, such as hypertension, coronary artery disease and heart failure, by statins or renin–angiotensin system blockers, to prevent the occurrence of AF. This AF prevention by upstream therapy could decrease the incidence of AF but its clinical relevance still deserves confirmation in prospective trials. Whilst there are significant differences in comorbidities and possible mechanisms of AF in men and women, the different strategies mentioned above would probably need to be similarly proposed in both genders because most of our results were very similar in both groups and because sex ratio of new AF after stroke was close to one.

Otherwise, the national administrative database, the PMSI, is now integrated in the new medical and administrative database called SNIIRAM (Système national d'information interrégimes de l'Assurance Maladie) whose data would be more widely available now. This will provide new information on outpatient care such as medications, medical procedures (electrocardiogram, 24-hour Holter monitor), and some diagnoses (Affections Longue Durée). It should be possible, with this new tool, to include AF diagnoses in outpatients and follow the prescriptions of anticoagulation.

Study limitations

A main limitation of this study was inherent to its retrospective observational nature. Even though the reliability of PMSI data has been verified previously [24,25] and used for epidemiological purposes [21], the analysis presents inherent potential information bias. The study methodology possibly underestimated the true incidence of AF in this population and may overestimate the importance of the components of the CHA_2DS_2-VASc score and comorbidities, which might predispose to hospitalization. Whether it indicates any potential for modifying risk of developing AF is still speculative and should be confirmed prospectively. Besides, the echocardiographic parameters were lacking in the present study because they are not available in such a database. However, the goal of this study was to confirm, with a larger population, whether simple risk tools were useful in predicting the risk of new-onset AF in patients without obtaining more detailed information or performing further examinations. In view of costs, use of echocardiography to predict risk of AF is unlikely to be justifiable for screening in a large population. The occurrence of incident AF was based on the diagnostic code registered by a responsible physician and was not further checked externally. However, this was a common limitation also noted in most previous studies. The analysis presents inherent potential for information bias. In particular, no

information was available for medications, drug misuse, and international normalized ratios. AF diagnoses in outpatients were not included that which could be corrected in the next studies by using the national database SNIIRAM. Finally, arrhythmia monitoring such as 24-hour Holter monitor or cardiac event recording was not routinely performed for every patient to detect asymptomatic AF, and it may underestimate the true incidence of new-onset AF.

CONCLUSION

$CHADS_2$ and/or CHA_2DS_2-VASc scores are simple risk tools for identifying patients at higher risk of AF following IS among patients without known AF. Other risk factors, particularly a history of pacemaker/defibrillator implantation, valvular disease, coronary artery disease and lung disease, kidney disease or anaemia are associated with AF onset after IS. From these results, we developed a new score with better diagnostic ability than previously describes tools. Importantly, women were more prone to have a history of previous known AF than men but the incidence of new AF and its predictors were not gender related. Strategies aimed at preventing AF early during the course after IS or at better diagnosing incident AF in prevention of IS should be based on these simple predictive tools.

REFERENCES

1. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ. Cardiovasc. Qual. Outcomes*. 2012;5:85–93.

2. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D et al; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation * Developed with the special contribution of the European Heart Rhythm Association. *Eur. Heart J.* 2012;33:2719–2747.

3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). Eur Heart J. 2016 Aug 27.

4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007 Jun 19;146(12):857–67.

5. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993 Jan 1;24(1):35–41.

6. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke J. Cereb. Circ.* 2001;32:2735–2740.

7. Hart RG, Diener H-C, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al., Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol.* 2014;13:429–438.

8. A.V.Ganapathy,S.Monjazeb,K.S.Ganapathy,F.Shanoon,M.Razavi,"Asymptomat- ic" persistent or permanent atrial fibrillation: a misnomer in selected patients, Int. J. Cardiol. 185 (2015) 112–113.

9. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al., ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N. Engl. J. Med.* 2012;366:120–129.

10. Ziegler PD, Glotzer TV, Daoud EG, Singer DE, Ezekowitz MD, Hoyt RH, et al. Detection of previously undiagnosed atrial fibrillation in patients with stroke risk factors

and usefulness of continuous monitoring in primary stroke prevention. *Am. J. Cardiol.* 2012;110:1309–1314.

11. Seet RCS, Friedman PA, Rabinstein AA. Prolonged rhythm monitoring for the detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause. *Circulation*. 2011;124:477–486.

12. Sanna T, Diener H-C, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al., CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N. Engl. J. Med.* 2014;370:2478–2486.

13. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.

14. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.

15. Henriksson KM, Farahmand B, Johansson S, Asberg S, Terént A, Edvardsson N. Survival after stroke--the impact of CHADS2 score and atrial fibrillation. *Int. J. Cardiol.* 2010;141:18–23.

16. Chao T-F, Liu C-J, Chen S-J, Wang K-L, Lin Y-J, Chang S-L, et al. CHADS2 score and risk of new-onset atrial fibrillation: a nationwide cohort study in Taiwan. *Int. J. Cardiol.* 2013;168:1360–1363.

17. Lip GYH, Lin H-J, Chien K-L, Hsu H-C, Su T-C, Chen M-F, et al. Comparative assessment of published atrial fibrillation stroke risk stratification schemes for predicting stroke, in a non-atrial fibrillation population: the Chin-Shan Community Cohort Study. *Int. J. Cardiol.* 2013;168:414–419.

18. Welles CC, Whooley MA, Na B, Ganz P, Schiller NB, Turakhia MP. The CHADS2 score predicts ischemic stroke in the absence of atrial fibrillation among subjects with coronary heart disease: data from the Heart and Soul Study. *Am. Heart J.* 2011;162:555–561.

19. Poçi D, Hartford M, Karlsson T, Herlitz J, Edvardsson N, Caidahl K. Role of the CHADS2 score in acute coronary syndromes: risk of subsequent death or stroke in patients with and without atrial fibrillation. *Chest*. 2012;141:1431–1440.

20. Mitchell LB, Southern DA, Galbraith D, Ghali WA, Knudtson M, et al; APPROACH investigators. Prediction of stroke or TIA in patients without atrial fibrillation using CHADS2 and CHA2DS2-VASc scores. *Heart Br. Card. Soc.* 2014;100:1524–1530.

21. Fauchier L, Clementy N, Pelade C, Collignon C, Nicolle E, Lip GYH. Patients With Ischemic Stroke and Incident Atrial Fibrillation: A Nationwide Cohort Study. Stroke. 2015 Sep;46(9):2432–7.

22. Wagstaff AJ, Overvad TF, Lip GYH, Lane DA. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. QJM. 2014 Dec;107(12):955–67.

23. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ. 2016;532:h7013.

24. Couris CM, Polazzi S, Olive F, Remontet L, Bossard N, Gomez F, et al. Breast cancer incidence using administrative data: correction with sensitivity and specificity. *J. Clin. Epidemiol.* 2009;62:660–666.

25. Chantry AA, Deneux-Tharaux C, Cans C, Ego A, Quantin C, et al; GRACE study group. Hospital discharge data can be used for monitoring procedures and intensive care related to severe maternal morbidity. *J. Clin. Epidemiol.* 2011;64:1014–1022.

26. Charlemagne A, Blacher J, Cohen A, Collet J-P, Diévart F, de Groote P, et al. Epidemiology of atrial fibrillation in France: extrapolation of international epidemiological data to France and analysis of French hospitalization data. *Arch. Cardiovasc. Dis.* 2011;104:115–124.

27. Chevreul K, Durand-Zaleski I, Gouépo A, Fery-Lemonnier E, Hommel M, Woimant F. Cost of stroke in France. *Eur. J. Neurol. Off. J. Eur. Fed. Neurol. Soc.* 2013;20:1094–1100.

28. Lorgis L, Cottenet J, Molins G, Benzenine E, Zeller M, Aube H, et al. Outcomes after acute myocardial infarction in HIV-infected patients: analysis of data from a French nationwide hospital medical information database. *Circulation*. 2013;127:1767–1774.

29. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373:739–745.

30. Tu HTH, Campbell BCV, Meretoja A, Churilov L, Lees KR, Donnan GA, et al. Pre-stroke CHADS2 and CHA2DS2-VASc scores are useful in stratifying three-month outcomes in patients with and without atrial fibrillation. *Cerebrovasc. Dis. Basel Switz.* 2013;36:273–280.

31. Kim YD, Cha MJ, Kim J, Lee DH, Lee HS, Nam CM, et al. Ischaemic cardiovascular mortality in patients with non-valvular atrial fibrillation according to $CHADS_2$ score. *Thromb. Haemost.* 2011;105:712–720.

32. Ntaios G, Lip GYH, Makaritsis K, Papavasileiou V, Vemmou A, Koroboki E, et al. CHADS2, CHA2DS2-VASc, and long-term stroke outcome in patients without atrial fibrillation. *Neurology*. 2013;80:1009–1017.

33. Guo Y, Tian Y, Wang H, Si Q, Wang Y, Lip GYH. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. *Chest*. 2015;147:109–119.

34. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271:840–844.

35. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am. J. Med.* 1995;98:476–484.

36. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455–2461.

37. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. *Am. J. Cardiol.* 2011;108:56–62.

38. Schoen T, Pradhan AD, Albert CM, Conen D. Type 2 diabetes mellitus and risk of incident atrial fibrillation in women. J Am Coll Cardiol. 2012 Oct 9;60(15):1421–8.

39. Sun Y, Hu D. The link between diabetes and atrial fibrillation: cause or correlation? J Cardiovasc Dis Res. 2010 Jan;1(1):10–1.

40. Staszewsky L, Cortesi L, Baviera M, Tettamanti M, Marzona I, Nobili A, et al. Diabetes mellitus as risk factor for atrial fibrillation hospitalization: Incidence and outcomes over nine years in a region of Northern Italy. Diabetes Res Clin Pract. 2015 Sep;109(3):476–84.

41. Huxley RR, Alonso A, Lopez FL, Filion KB, Agarwal SK, Loehr LR, et al. Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: the Atherosclerosis Risk in Communities study. Heart. 2012 Jan;98(2):133–8.

42. Ostgren CJ, Merlo J, Råstam L, Lindblad U. Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community. Diabetes Obes Metab. 2004 Sep;6(5):367–74.

43. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurol. 2015 Sep;14(9):903–13.

44. Grau AJ, Weimar C, Buggle F, Heinrich A, Goertler M, Neumaier S, et al. Risk Factors, Outcome, and Treatment in Subtypes of Ischemic Stroke The German Stroke Data Bank. Stroke. 2001 Nov 1;32(11):2559–66.

45. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of Ischemic Stroke Subtypes According to TOAST Criteria Incidence, Recurrence, and Long-Term Survival in Ischemic Stroke Subtypes: A Population-Based Study. Stroke. 2001 Dec 1;32(12):2735–40.

46. Kim SG, Hong JM, Kim HY, Lee J, Chung P-W, Park K-Y, et al. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. Stroke. 2010 Apr;41(4):798–801.

47. Schwarzbach CJ, Schaefer A, Ebert A, Held V, Bolognese M, Kablau M, et al. Stroke and cancer: the importance of cancer-associated hypercoagulation as a possible stroke etiology. Stroke. 2012 Nov;43(11):3029–34.

48. Gon Y, Okazaki S, Terasaki Y, Sasaki T, Yoshimine T, Sakaguchi M, et al. Characteristics of cryptogenic stroke in cancer patients. Ann Clin Transl Neurol. 2016 Apr;3(4):280–7.

49. Kucharz EJ. Chronic inflammation-enhanced atherosclerosis: can we consider it as a new clinical syndrome? Med Hypotheses. 2012 Mar;78(3):396–7.

50. McColl BW, Allan SM, Rothwell NJ. Systemic inflammation and stroke: aetiology, pathology and targets for therapy. Biochem Soc Trans. 2007 Nov;35(Pt 5):1163–5.

51. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet. 1997 Oct 25;350(9086):1210–6.

52. Kerr CR, Connolly SJ, Abdollah H, Roberts RS, Gent M, Yusuf S, et al. Canadian Trial of Physiological Pacing: Effects of physiological pacing during long-term follow-up. Circulation. 2004 Jan 27;109(3):357–62.

53. Kristensen L, Nielsen JC, Mortensen PT, Pedersen OL, Pedersen AK, Andersen HR. Incidence of atrial fibrillation and thromboembolism in a randomised trial of atrial versus dual chamber pacing in 177 patients with sick sinus syndrome. Heart. 2004 Jun;90(6):661–6.

54. Lamas GA, Orav EJ, Stambler BS, Ellenbogen KA, Sgarbossa EB, Huang SK, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. Pacemaker Selection in the Elderly Investigators. N Engl J Med. 1998 Apr 16;338(16):1097–104.

55. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med. 2002 Jun 13;346(24):1854–62.

56. Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol. 2003 Aug 20;42(4):614–23.

57. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation. 2003 Jun 17;107(23):2932–7.

58. Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. N Engl J Med. 2007 Sep 6;357(10):1000–8.

59. Calkins H, el-Atassi R, Kalbfleisch S, Langberg J, Morady F. Effects of an acute increase in atrial pressure on atrial refractoriness in humans. Pacing Clin Electrophysiol. 1992 Nov;15(11 Pt 1):1674–80.

60. Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorcsan I John. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapyInsights from mechanical activation strain mapping. J Am Coll Cardiol. 2004 Oct 19;44(8):1619–25.

61. Klein LS, Miles WM, Zipes DP. Effect of atrioventricular interval during pacing or reciprocating tachycardia on atrial size, pressure, and refractory period. Contraction-excitation feedback in human atrium. Circulation. 1990 Jul;82(1):60–8.

62. Prinzen FW, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. Pacing Clin Electrophysiol. 2002 Apr;25(4 Pt 1):484–98.

63. Israel CW. The role of pacing mode in the development of atrial fibrillation. Europace. 2006 Feb;8(2):89–95.

64. Veasey RA, Arya A, Silberbauer J, Sharma V, Lloyd GW, Patel NR, et al. The relationship between right ventricular pacing and atrial fibrillation burden and disease progression in patients with paroxysmal atrial fibrillation: the long-MinVPACE study. Europace. 2011 Jun;13(6):815–20.

65. Skanes AC, Krahn AD, Yee R, Klein GJ, Connolly SJ, Kerr CR, et al. Progression to chronic atrial fibrillation after pacing: the Canadian Trial of Physiologic Pacing. CTOPP Investigators. J Am Coll Cardiol. 2001 Jul;38(1):167–72.

66. Pastore G, Zanon F, Baracca E, Aggio S, Corbucci G, Boaretto G, et al. The risk of atrial fibrillation during right ventricular pacing. Europace. 2016 Mar;18(3):353–8.

67. Potpara TS, Marinkovic JM, Polovina MM, Stankovic GR, Seferovic PM, Ostojic MC, et al. Gender-related differences in presentation, treatment and long-term outcome in patients with first-diagnosed atrial fibrillation and structurally normal heart: the Belgrade atrial fibrillation study. Int J Cardiol. 2012 Nov 1;161(1):39–44.

68. Xiong Q, Proietti M, Senoo K, Lip GYH. Asymptomatic versus symptomatic atrial fibrillation: A systematic review of age/gender differences and cardiovascular outcomes. Int J Cardiol. 2015 Jul 15;191:172–7.

69. González Toledo ME, Klein FR, Riccio PM, Cassará FP, Muñoz Giacomelli F, Racosta JM, et al. Atrial fibrillation detected after acute ischemic stroke: evidence supporting the neurogenic hypothesis. J Stroke Cerebrovasc Dis. 2013 Nov;22(8):e486–91.

70. Cechetto DF, Wilson JX, Smith KE, Wolski D, Silver MD, Hachinski VC. Autonomic and myocardial changes in middle cerebral artery occlusion: stroke models in the rat. Brain Res. 1989 Nov 20;502(2):296–305.

71. Rizos T, Horstmann S, Dittgen F, Täger T, Jenetzky E, Heuschmann P, et al. Preexisting Heart Disease Underlies Newly Diagnosed Atrial Fibrillation After Acute Ischemic Stroke. Stroke. 2016 Feb;47(2):336–41.

72. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. Circulation. 2015 Jun 23;131(25):2176–84.

73. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, et al; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N. Engl. J. Med.* 2014;370:2467–2477.

74. Dion F, Saudeau D, Bonnaud I, Friocourt P, Bonneau A, Poret P, et al. Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: a prospective study. J Interv Card Electrophysiol. 2010 Aug;28(2):101–7.

75. Higgins P, MacFarlane PW, Dawson J, McInnes GT, Langhorne P, Lees KR. Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial. Stroke. 2013 Sep;44(9):2525–31.

76. Friberg L, Rosenqvist M, Lindgren A, Terént A, Norrving B, Asplund K. High prevalence of atrial fibrillation among patients with ischemic stroke. Stroke. 2014 Sep;45(9):2599–605.

Table 1. Baseline characteristics of the patients with ischemic stroke and no known AF at baseline.

Variables	Study population, n=240,459
Age, years	71.2±15.5
Age ≥75 years old, n (%)	120,537(50.2%)
Gender (female), n (%)	114,348(47.6%)
Underlying diseases, n (%)	
Hypertension	152,790(63.5%)
Diabetes mellitus	55,060(22.9%)
Congestive heart failure	39,423(16.4%)
Vascular disease	77,543(32.3%)
CHA_2DS_2-VASc score, n (%)	
Score=2	17,153(7.1%)
Score=3	33,789(14.1%)
Score=4	40,492(16.9%)
Score=5	53,181(22.1%)
Score=6	52,346(21.8%)
Score=7	30,075(12.5%)
Score=8	11,095(4.6%)
Score=9	2,175(0.9%)
Comorbidities	
Systemic embolism	7,068(2.9%)
Coronary artery disease	44,621(18.6%)
Obesity	24,972(10.4%)
Abnormal renal function	44,011(18.3%)
Liver disease	7,298(3%)
Anaemia	35,145(14.6%)
Lung disease	38,981(16.2%)
Cancer within preceding 5 years	40,456(16.8%)
Inflammatory diseases	15,656(6.5%)
Alcohol-related diagnoses	18,634(7.8%)
Thyroid disease	74,287(30.9%)
Dyslipidaemia	75,221(31.3%)
PM-ICD	8,844(3.7%)
Valvular disease	17,901(7.5%)
Tobacco smoking	30,255(12.6%)

Table 2. Baseline characteristics of the patients with ischemic stroke and no known AF at baseline in men and women.

Variables	Men n=126,111	Women n=114,348	p value
Age, years	68.3±14.5	74,2±16	<0.0001
Age ≥75 years old, n (%)	49,493(39.3%)	71,044(62.2%)	<0.0001
Underlying diseases, n (%)			
Hypertension	78,917(62.6%)	73,873(64.6%)	<0.0001
Diabetes mellitus	31,558(25%)	23,502(20,6%)	<0.0001
Congestive heart failure	20,129(16%)	19,294(16.9%)	<0.0001
Vascular disease	48,252(38.3%)	29,291(25.6%)	<0.0001
CHA_2DS_2-VASc score, n (%)			
Score=2	17,153(13.6%)	0	
Score=3	21,313(16.9%)	12,476(10.9%)	
Score=4	28,068(22.3%)	12,424(10.9%)	
Score=5	28,281(22.4%)	24,900(21.8%)	0.0001
Score=6	19,919(15.8%)	32,427(28.4%)	
Score=7	9,123(7.2%)	20,952(18.3%)	
Score=8	2,166(1.7%)	8,929(7.8%)	
Score=9	0	2,175(1.9%)	
Comorbidities			
Systemic embolism	4,569(3.6%)	2,499(2.2%)	<0.0001
Coronary artery disease	27,803(22.1%)	16,818(14.7%)	<0.0001
Obesity	13,013(10.3%)	11,959(10.5%)	0.2620
Abnormal renal function	23,625(18.7%)	20,386(17.8%)	<0.0001
Liver disease	4,644(3.7%)	2,654(2.3%)	<0.0001
Anaemia	16,217(12,9%)	18,928(16.6%)	<0.0001
Lung disease	23,094(18.3%)	15,887(13.9%)	<0.0001
Cancer within preceding 5 years	24,364(19.3%)	16,092(14.1%)	<0.0001
Inflammatory diseases	8,127(6.4%)	7,529(6.6%)	0.1648
Alcohol-related diagnoses	14,895(11.8%)	3,739(3.3%)	<0.0001
Thyroid disease	39,228(31.1%)	35,059(30.7%)	0.0181
Dyslipidaemia	43,535(34.5%)	31,686(27.7%)	<0.0001
PM-ICD	5,377(4.3%)	3,467(3%)	<0.0001
Valvular disease	9,203(7.3%)	8,698(7.6%)	0.0039
Tobacco smoking	22,794(18.1%)	7,461(6.5%)	<0.0001

Table 3. Baseline characteristics of the patients with ischemic stroke and no known AF at baseline according to AF occurrence during follow-up.

Variables	AF during follow-up n=14,095	No AF during follow-up n=226,364	p value
Age, years	77.6±10.6	70.8±15.7	<0.0001
Age ≥75 years old, n (%)	9,755(69,2%)	110,782(49%)	<0.0001
Gender (female), n (%)	7,082(50.3%)	107,266(47.4%)	<0.0001
Underlying diseases, n (%)			
Hypertension	11,745(83.3%)	141,045(62.3%)	<0.0001
Diabetes mellitus	4,083(29%)	50,977(22.5%)	<0.0001
Congestive heart failure	6,261(44.4%)	33,162(14.7%)	<0.0001
Vascular disease	6,907(49%)	70,636(31.2%)	<0.0001
CHA_2DS_2-VASc score, n (%)			
Score=2	161(1.1%)	16,992(7.5%)	<0.0001
Score=3	523(3.7%)	33,266(14.7%)	<0.0001
Score=4	1,192(8.5%)	39,300(17.4%)	<0.0001
Score=5	2,596(18.4%)	50,585(22.4%)	<0.0001
Score=6	3,903(27.7%)	48,443(21.4%)	<0.0001
Score=7	3,441(24.4%)	26,634(11.8%)	<0.0001
Score=8	1,881(13.4%)	9,214(4.1%)	<0.0001
Score=9	398(2.8%)	1,777(0.8%)	<0.0001
Comorbidities			
Systemic embolism	807(5.7%)	6,261(2.8%)	<0.0001
Coronary artery disease	4,969(35.3%)	39,652(17.5%)	<0.0001
Obesity	2,071(14.7%)	22,901(10.1%)	<0.0001
Abnormal renal function	5,393(38.3%)	38,618(17.1%)	<0.0001
Liver disease	593(4.2%)	6,705(3%)	<0.0001
Anaemia	3,980(28.2%)	31,165(13.8%)	<0.0001
Lung disease	3,661(26%)	35,320(15.6%)	<0.0001
Cancer within preceding 5 years	3,056(21.7%)	37,400(16.5%)	<0.0001
Inflammatory diseases	1,470(10.4%)	14,186(6.3%)	<0.0001
Alcohol-related diagnoses	954(6.8%)	17,680(7.8%)	<0.0001
Thyroid disease	6,040(42.9%)	68,247(30.2%)	<0.0001
Dyslipidaemia	5,793(41.1%)	69,428(30.7%)	<0.0001
PM-ICD	1,643(11.7%)	7,201(3.2%)	<0.0001
Valvular disease	2,780(19.7%)	15,121(6.7%)	<0.0001
Tobacco smoking	1,415(10%)	28,840(12.7%)	<0.0001

Table 4. Cox regression analysis for prediction of atrial fibrillation after ischemic stroke for items constituting the CHA_2DS_2-VASc score and other baseline characteristics.

	Univariate analysis		Multivariable analysis	
Covariate	**HR(95%CI)**	**P-value**	**HR(95%CI)**	**P-value**
Age 65–74 years	0.85 (0.82-0.89)	<0.0001	1.99 (1.87-2.12)	<0.0001
Age ≥75 years	2.54 (2.45-2.63)	<0.0001	2.86 (2.70-3.02)	<0.0001
Female gender	1.21 (1.17-1.25)	<0.0001	1.05 (1.01-1.09)	0.0095
Hypertension	1.90 (1.81-1.98)	<0.0001	1.24 (1.18-1.30)	<0.0001
Diabetes	1.07 (1.04-1.11)	<0.0001	0.89 (0.85-0.92)	<0.0001
Heart failure	2.99 (2.89-3.09)	<0.0001	2.05 (1.97-2.13)	<0.0001
Peripheral vascular disease or myocardial infarction	1.42 (1.37-1.46)	<0.0001	0.90 (0.85-0.94)	<0.0001
Systemic embolism	1.37 (1.28-1.47)	<0.0001	1.20 (1.11-1.29)	<0.0001
Coronary artery disease	1.70 (1.64-1.76)	<0.0001	1.22 (1.15-1.28)	<0.0001
Obesity	1.07 (1.02-1.12)	0.0064	1.05 (1.00-1.11)	0.0460
Abnormal renal function	2.02 (1.96-2.09)	<0.0001	1.12 (1.07-1.17)	<0.0001
Liver disease	1.01 (0.93-1.10)	0.7536	1.05 (0.97-1.15)	0.2440
Anaemia	1.53 (1.47-1.58)	<0.0001	1.10 (1.06-1.15)	<0.0001
Lung disease	1.42 (1.36-1.47)	<0.0001	1.14 (1.09-1.18)	<0.0001
Cancer within preceding 5 years	0.95 (0.91-0.99)	0.007	0.92 (0.89-0.96)	0.0002
Inflammatory diseases	1.13 (1.07-1.20)	<0.0001	0.95 (0.90-0.99)	0.0485
Alcohol-related diagnoses	0.66 (0.62-0.71)	<0.0001	0.96 (0.89-1.03)	0.2126
Thyroid disease	1.02 (0.99-1.06)	0.2086	0.97 (0.93-1.00)	0.0670
Dyslipidaemia	1.06 (1.03-1.10)	0.0005	0.97 (0.93-1.00)	0.0773
PM-ICD	2.67 (2.53-2.81)	<0.0001	1.56 (1.48-1.64)	<0.0001
Valvular disease	2.41 (2.31-2.51)	<0.0001	1.44 (1.37-1.51)	<0.0001
Tobacco smoking	0.63 (0.59-0.66)	<0.0001	0.92 (0.86-0.98)	0.0055

Table 5. Cox regression analysis for prediction of atrial fibrillation after ischemic stroke for items constituting the CHA_2DS_2-VASc score and other baseline characteristics in men.

	Univariate analysis		Multivariable analysis	
Covariate	**HR(95%CI)**	**P-value**	**HR(95%CI)**	**P-value**
Age 65–74 years	0.92 (0.87-0.98)	0.0043	1.79 (1.66-1.94)	<0.0001
Age ≥75 years	2.42 (2.31-2.54)	<0.0001	2.58 (2.40-2.77)	<0.0001
Hypertension	1.74 (1.63-1.84)	<0.0001	1.17 (1.10-1.25)	<0.0001
Diabetes	1.15 (1.09-1.21)	<0.0001	0.93 (0.88-0.98)	0.0039
Heart failure	2.99 (2.85-3.14)	<0.0001	1.99 (1.88-2.10)	<0.0001
Peripheral vascular disease or myocardial infarction	1.54 (1.47-1.61)	<0.0001	0.94 (0.87-1.01)	0.0804
Systemic embolism	1.32 (1.20-1.44)	<0.0001	1.09 (0.98-1.19)	0.1021
Coronary artery disease	1.82 (1.73-1.91)	<0.0001	1.21 (1.13-1.30)	<0.0001
Obesity	1.17 (1.09-1.25)	<0.0001	1.10 (1.03-1.18)	0.0073
Abnormal renal function	2.17 (2.06-2.27)	<0.0001	1.18 (1.11-1.25)	<0.0001
Liver disease	1.06 (0.96-1.18)	0.2503	1.06 (0.95-1.19)	0.2855
Anaemia	1.70 (1.62-1.79)	<0.0001	1.21 (1.15-1.28)	<0.0001
Lung disease	1.51 (1.43-1.59)	<0.0001	1.17 (1.11-1.24)	<0.0001
Cancer within preceding 5 years	1.05 (0.99-1.10)	0.0884	0.94 (0.89-0.99)	0.0165
Inflammatory diseases	1.18 (1.09-1.27)	<0.0001	0.97 (0.89-1.04)	0.3915
Alcohol-related diagnoses	0.73 (0.68-0.79)	<0.0001	0.96 (0.88-1.04)	0.2841
Thyroid disease	1.07 (1.02-1.12)	0.0091	0.96 (0.91-1.10)	0.0758
Dyslipidaemia	1.07 (1.02-1.13)	0.0034	0.95 (0.90-0.99)	0.0483
PM-ICD	2.85 (2.67-3.05)	<0.0001	1.58 (1.47-1.69)	<0.0001
Valvular disease	2.42 (2.28-2.57)	<0.0001	1.35 (1.26-1.45)	<0.0001
Tobacco smoking	0.73 (0.69-0.78)	<0.0001	0.93 (0.87-0.99)	0.0446

Table 6. Cox regression analysis for prediction of atrial fibrillation after ischemic stroke for items constituting the CHA_2DS_2-VASc score and other baseline characteristics in women.

	Univariate analysis		Multivariable analysis	
Covariate	**HR(95%CI)**	**P-value**	**HR(95%CI)**	**P-value**
Age 65–74 years	0.80 (0.75-0.86)	<0.0001	2.40 (2.15-2.68)	<0.0001
Age ≥75 years	2.70 (2.55-2.85)	<0.0001	3.32 (3.02-3.67)	<0.0001
Hypertension	2.08 (1.95-2.22)	<0.0001	1.30 (1.21-1.39)	<0.0001
Diabetes	1.02 (0.97-1.08)	0.4252	0.85 (0.80-0.90)	<0.0001
Heart failure	2.97 (2.84-3.11)	<0.0001	2.11 (2.00-2.22)	<0.0001
Peripheral vascular disease or myocardial infarction	1.41 (1.34-1.48)	<0.0001	0.86 (0.80-0.93)	<0.0001
Systemic embolism	1.56 (1.40-1.74)	<0.0001	1.36 (1.21-1.52)	<0.0001
Coronary artery disease	1.70 (1.61-1.79)	<0.0001	1.22 (1.12-1.32)	<0.0001
Obesity	0.97 (0.91-1.04)	0.3486	1.03 (0.96-1.10)	0.4737
Abnormal renal function	1.91 (1.82-2.00)	<0.0001	1.06 (0.99-1.13)	0.0722
Liver disease	0.99 (0.86-1.13)	0.8772	1.03 (0.90-1.18)	0.6568
Anaemia	1.35 (1.28-1.42)	<0.0001	1.01 (0.96-1.07)	0.7463
Lung disease	1.37 (1.29-1.45)	<0.0001	1.10 (1.04-1.17)	0.0015
Cancer within preceding 5 years	0.87 (0.81-0.92)	<0.0001	0.91 (0.86-0.97)	0.0044
Inflammatory diseases	1.08 (1.00-1.17)	0.0440	0.93 (0.86-1.00)	0.0641
Alcohol-related diagnoses	0.58 (0.50-0.68)	<0.0001	0.88 (0.75-1.02)	0.0968
Thyroid disease	0.98 (0.94-1.03)	0.5147	0.98 (0.94-1.03)	0.4740
Dyslipidaemia	1.08 (1.03-1.14)	0.001	0.98 (0.93-1.03)	0.4215
PM-ICD	2.55 (2.35-2.77)	<0.0001	1.54 (1.41-1.67)	<0.0001
Valvular disease	2.39 (2.26-2.54)	<0.0001	1.54 (1.43-1.65)	<0.0001
Tobacco smoking	0.46 (0.41-0.52)	<0.0001	0.86 (0.75-0.97)	0.0164

Table 7. Hazard ratio of new onset atrial fibrillation in patients with ischemic stroke with different CHA_2DS_2-VASc scores (in comparison to the patients with score of two).

	Number of Patients [a] (N=240,306)	Number of new onset AF (N=14,095)	Hazard ratio	95 CI	p Value
CHA_2DS_2-VASc score					
2 (reference)	17,153	161	-	-	-
3	33,789	523	1.36	1.14-1.62	0.001
4	40,492	1,192	2.47	2.09-2.91	<0.0001
5	53,181	2,596	4.02	3.43-4.71	<0.0001
6	52,346	3,903	5.61	4.79-6.57	<0.0001
7	30,075	3,441	7.82	6.68-9.16	<0.0001
8	11,095	1,881	10.27	8.74-12.06	<0.0001
9	2,175	398	10.75	8.95-12.91	<0.0001

[a] Calculation of CHA_2DS_2-VASc score was impossible in 153 patients because age was missing.

Table 8. Hazard ratio of new onset atrial fibrillation in patients with ischemic stroke with different CHA_2DS_2-VASc scores (in comparison to the patients with score of two) in men.

	Number of Patients [a] (N=126,023)	Number of new onset AF (N=7,013)	Hazard ratio	95 CI	p Value
CHA_2DS_2-VASc score					
2 (reference)	17,153	161	-	-	-
3	21,313	429	1.76	1.46-2.1	<0.0001
4	28,068	935	2.77	2.34-3.28	<0.0001
5	28,281	1,717	4.33	3.68-5.09	<0.0001
6	19,919	1,940	6.13	5.22-7.2	<0.0001
7	9,123	1,368	8.74	7.42-10.29	<0.0001
8	2,166	463	11.7	9.78-14	<0.0001

[a] Calculation of CHA_2DS_2-VASc score was impossible in 88 patients because age was missing.

Table 9. Hazard ratio of new onset atrial fibrillation in patients with ischemic stroke with different CHA_2DS_2-VASc scores (in comparison to the patients with score of three) in women.

	Number of Patients [a] (N=114,283)	Number of new onset AF (N=7,082)	Hazard ratio	95 CI	p Value
CHA_2DS_2-VASc score					
3 (reference)	12,476	94	-	-	-
4	12,424	257	2.63	2.07-3.33	<0.0001
5	24,900	879	5.26	4.25-6.51	<0.0001
6	32,427	1,963	7.71	6.27-9.49	<0.0001
7	20,952	2,073	10.9	8.87-13.41	<0.0001
8	8,929	1,418	14.73	11.96-18.15	<0.0001
9	2,175	398	16.05	12.82-20.10	<0.0001

[a] Calculation of CHA_2DS_2-VASc score was impossible in 65 patients because age was missing.

Table 10. Incidence (per 100 person-years) of atrial fibrillation in patients with different CHA_2DS_2-VASc scores.

	Number of new onset AF	Number of patients	Person-years	Incidence [a]
CHA_2DS_2-VASc score				
2	161	17,153	8,076	2
3	523	33,789	19,401	2.7
4	1,192	40,492	24,633	4.8
5	2,596	53,181	33,460	7.8
6	3,903	52,346	36,642	10.7
7	3,441	30,075	23,709	14.5
8	1,881	11,095	10,383	18.1
9	398	2,175	2,120	18.8
Total	14,095	240,306 [b]	158,401 [b]	8.9

[a] AF cases per 100 person-years of follow-up.

[b] Calculation of CHA_2DS_2-VASc score was impossible in 153 patients because age was missing.

Table 11. Incidence (per 100 person-years) of atrial fibrillation in patients with different CHA_2DS_2-VASc scores in men.

	Number of new onset AF	Number of patients	Person-years	Incidence [a]
CHA_2DS_2-VASc score				
2	161	17,153	8,076	2
3	429	21,313	12,362	3.5
4	935	28,068	17,215	5.4
5	1,717	28,281	20,622	8.3
6	1,940	19,919	16,881	11.5
7	1,368	9,123	8,538	16
8	463	2,166	2,303	20.1
Total	7,013	126,023 [b]	85,997 [b]	8.2

[a] AF cases per 100 person-years of follow-up.

[b] Calculation of CHA_2DS_2-VASc score was impossible in 88 patients because age was missing.

Table 12. Incidence (per 100 person-years) of atrial fibrillation in patients with different CHA_2DS_2-VASc scores in women.

	Number of new onset AF	Number of patients	Person-years	Incidence [a]
CHA_2DS_2-VASc score				
3	94	12,476	7,049	1.3
4	257	12,424	7,423	3.5
5	879	24,900	12,844	6.8
6	1,963	32,427	19,754	9.9
7	2,073	20,952	15,155	13.7
8	1,418	8,929	8,081	17.6
9	398	2,175	2,121	18.8
Total	7,082	114,283[b]	72,427 [b]	9.8

[a] AF cases per 100 person-years of follow-up.

[b] Calculation of CHA2DS2VASc score was impossible in 65 patients because age was missing.

Table 13. Details of items constituting our post IS French score

New score risk factors	Points
- Congestive heart failure - Age ≥75 years	+2
- Valvular disease - PM/ICD implantation	+1.5
- Age 65–74 years - Hypertension - Coronary artery disease	+1
- Female gender - Obesity - Abnormal renal function - Anaemia - Lung disease - Systemic embolism	+0.5

Table 14. Incidence (per 100 person-years) of atrial fibrillation in patients with different post IS French scores.

	Number of new onset AF	Number of patients	Person-years	Incidence [a]
Post IS French score				
<3	2,272	116,921	65,169	3.5
≥3 - <6	6,880	98,194	68,625	10
≥6 - <9	4,348	23,107	22,169	19.6
≥9	595	2,084	2,445	24.3
Total	14,095	240,306 [b]	158,401 [b]	8.9

[a] AF cases per 100 person-years of follow-up.

[b] Calculation of our post IS French score was impossible in 153 patients because age was missing.

Table 15. Baseline characteristics of the patients with ischemic stroke and known AF at baseline according and new AF during follow-up.

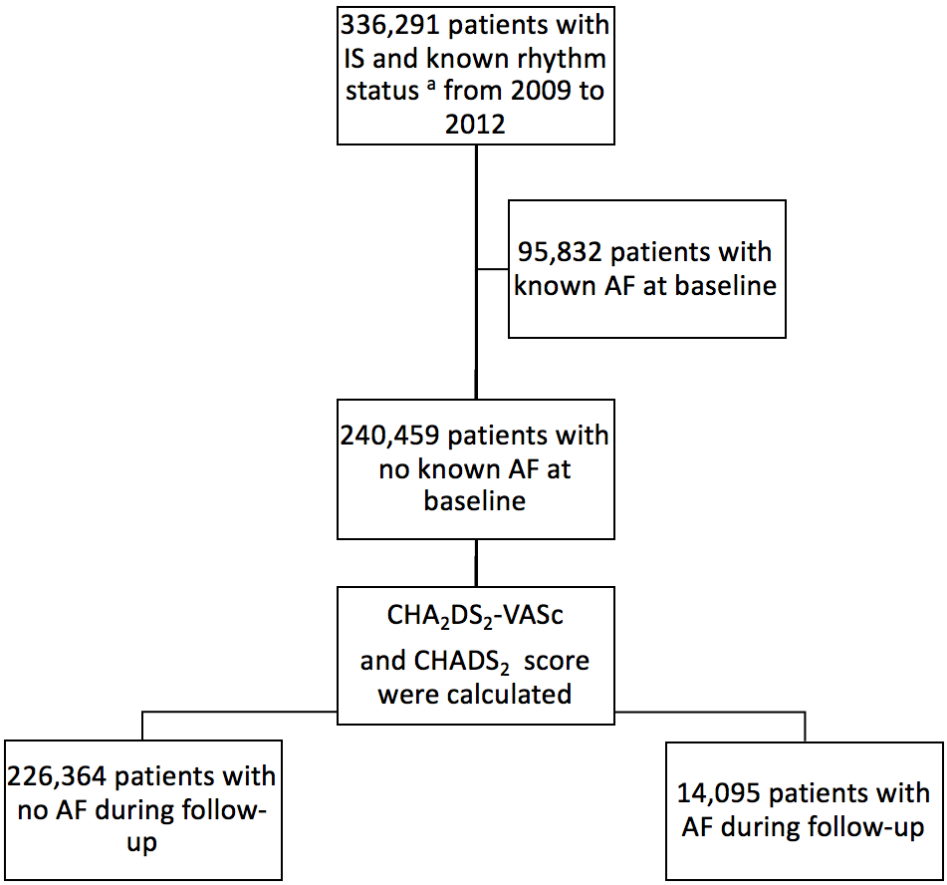
Variables	No AF n=226,364	Known AF n=95,832	New AF n=14,095	Known VS New AF P Value
Age, years	70.7±15.7	80.4±9.8*	77.6±10.6*	<0.0001
Age ≥75 years old, n (%)	110,782(49%)	74,588(77.8%)*	9,755(69.2%)*	<0.0001
Gender (female), n (%)	107,266(47.4%)	52,998(55.3%)*	7,082(50.3%)*	<0.0001
Underlying diseases, n (%)				
Hypertension	141,045(62.3%)	71,078(74.2%)*	11,745(83.3%)*	<0.0001
Diabetes mellitus	50,977(22.5%)	23,038(24%)*	4,083(29%)*	<0.0001
Congestive heart failure	33,162(14.7%)	39,935(41.7%)*	6,261(44.4%)*	<0.0001
Vascular disease	70,636(31.2%)	37,892(39.5%)*	6,907(49%)*	<0.0001
CHA_2DS_2-VASc score, n (%)				
Score=2	16,992(7.5%)	1,174(1.2%)*	161(1.1%)*	<0.0001
Score=3	33,266(14.7%)	3,337(3.5%)*	523(3.7%)*	<0.0001
Score=4	39,300(17.4%)	9,039(9.4%)*	1,192(8.5%)*	<0.0001
Score=5	50,585(22.4%)	19,046(19.9%)*	2,596(18.4%)*	<0.0001
Score=6	48,443(21.4%)	26,519(27.8%)*	3,903(27.7%)*	<0.0001
Score=7	26,634(11.8%)	22,632(23.6%)*	3,441(24.4%)*	<0.0001
Score=8	9,214(4.1%)	11,532(12%)*	1,881(13.4%)*	<0.0001
Score=9	1,777(0.8%)	2,553(2.7%)*	398(2.8%)*	<0.0001
Comorbidities				
Systemic embolism	6,261(2.8%)	4,758(5%)*	807(5.7%)*	0.0001
Coronary artery disease	39,652(17.5%)	27,315(28.5%)*	4,969(35.3%)*	<0.0001
Transient ischaemic attack	22,853(10.1%)	9,508(9.9%)†	2,075(14.7%)*	<0.0001
Obesity	22,901(10.1%)	10,795(11.3%)*	2,071(14.7%)*	<0.0001
Abnormal renal function	38,618(17.1%)	31,783(33.2%)*	5,393(38.3%)*	<0.0001
Liver disease	6,705(3%)	3,339(3.5%)*	593(4.2%)*	<0.0001
Anaemia	31,165(13.8%)	20,908(21.8%)*	3,980(28.2%)*	<0.0001
Lung disease	35,320(15.6%)	23,046(24.1%)*	3,661(26%)*	<0.0001
Cancer within preceding 5 years	37,400(16.5%)	16,401(17.1%)*	3,056(21.7%)*	<0.0001
Inflammatory diseases	14,186(6.3%)	8,450(8.8%)*	1,470(10.4%)*	<0.0001
Alcohol-related diagnoses	17,680(7.8%)	4,764(5%)*	954(6.8%)*	<0.0001
Thyroid disease	68,247(30.2%)	35,274(36.8%)*	6,040(42.9%)*	<0.0001
Dyslipidaemia	69,428(30.7%)	26,516(27.7%)*	5,793(41.1%)*	<0.0001
PM-ICD	7,201(3.2%)	11,015(11.5%)*	1,643(11.7%)*	0.5724
Valvular disease	15,121(6.7%)	17,280(18%)*	2,780(19.7%)*	<0.0001
Tobacco smoking	28,840(12.7%)	5,484(5.7%)*	1,415(10%)*	<0.0001

* p<0.0001 VS No AF

† p=0,1323 VS No AF

Supplemental Table. Baseline characteristics of the patients with ischemic stroke from 2008 to 2012.

Variables	Study population, n=418,601
Age, years	72.9±14.6
Age ≥75 years old, n (%)	242,957(58.1%)
Gender (female), n (%)	207,929(49.7%)
Atrial fibrillation	136,130(32.5%)
Underlying diseases, n (%)	276,414(66%)
Hypertension	97,188(23.2%)
Diabetes mellitus	99,835(23.9%)
Congestive heart failure	143,740(34.3%)
Vascular disease	
CHA_2DS_2-VASc score, n (%)	22,460(5.4%)
Score=2	45,884(11%)
Score=3	62,138(14.9%)
Score=4	91,167(21.8%)
Score=5	97,965(23.4%)
Score=6	65,188(15.6%)
Score=7	27,874(6.7%)
Score=8	5,748(1.4%)
Score=9	
Comorbidities	
Systemic embolism	14,627(3.5%)
Coronary artery disease	90,209(21.6%)
Obesity	43,217(10.3%)
Abnormal renal function	94,545(22.6%)
Liver disease	13,030(3.1%)
Anaemia	68,708(16.4%)
Lung disease	77,473(18.5%)
Cancer within preceding 5 years	70,680(16.9%)
Inflammatory diseases	29,057(6.9%)
Alcohol-related diagnoses	28,658(6.9%)
Thyroid disease	132,584(31.7%)
PM-ICD	24,837(5.9%)
Valvular disease	42,955(10.3%)
Tobacco smoking	43,300(10.3%)



[a] Sinus rhythm or AF

Figure 1. Flow chart of the study patients. AF indicates atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke/transient ischemic attack (doubled), vascular disease, age 65-74 years, and sex category (female); and IS, ischemic stroke; CHADS2 indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (doubled).

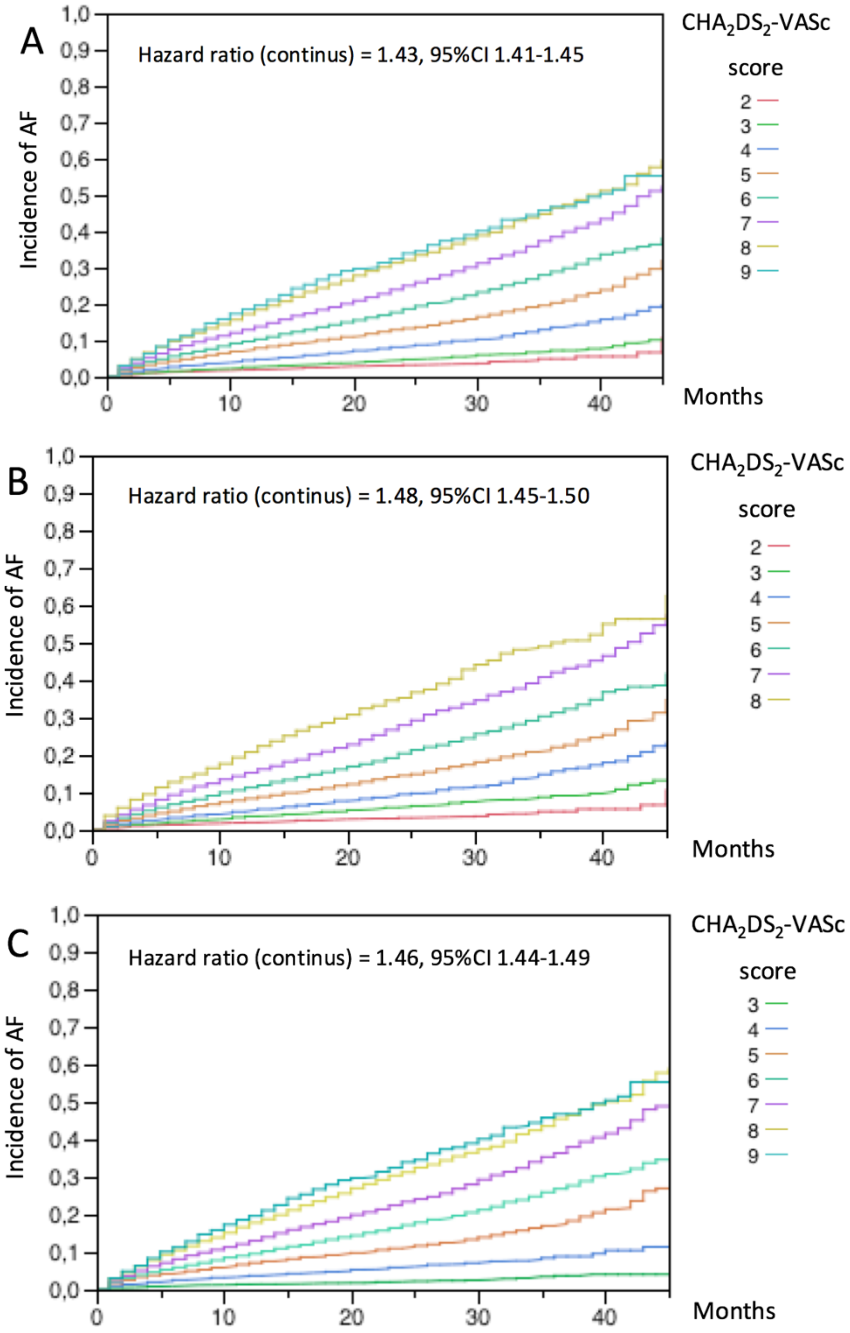


Figure 2. The Kaplan–Meier curves demonstrated that patients with ischemic stroke and higher CHA_2DS_2-VASc scores were associated with a higher rate of new-onset atrial fibrillation (AF) during the follow-up period in all patients (**A**), in men (**B**) and women (**C**). CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke/transient ischemic attack (doubled), vascular disease, age 65–74 years, and sex category (female); and CI, confidence interval.

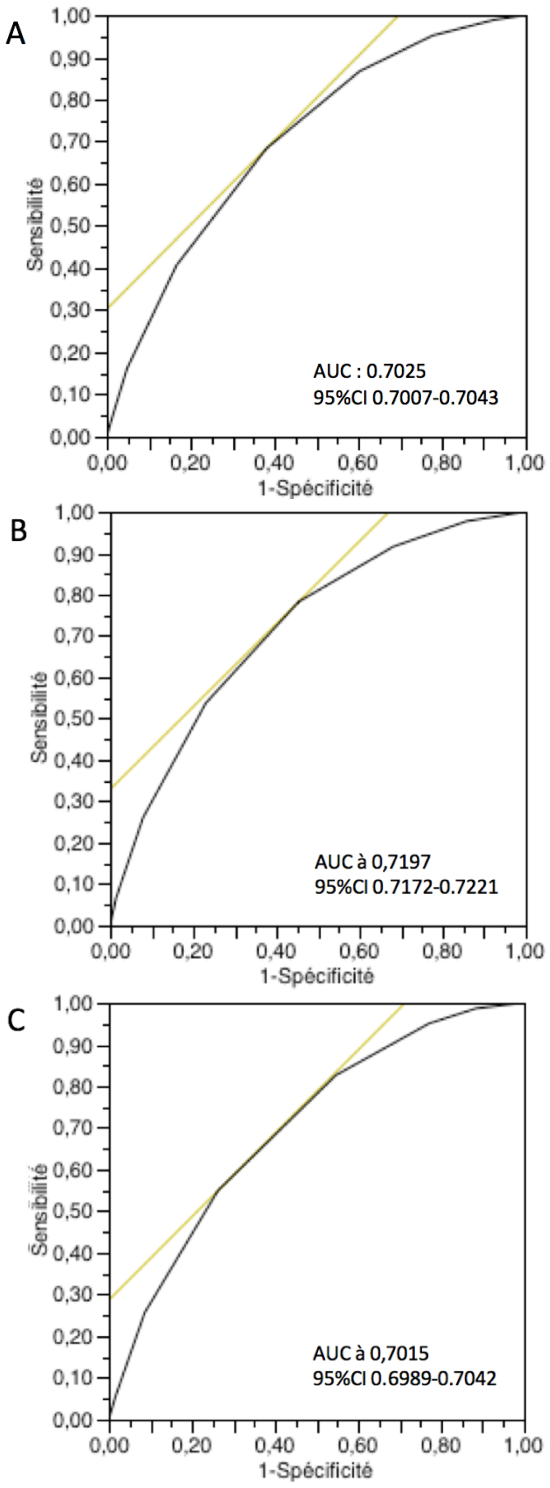


Figure 3. ROC Curves of CHA_2DS_2-VASc score in prediction of new onset of AF after stroke in all patients (**A**), in men (**B**) and women (**C**). CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke/transient ischemic attack (doubled), vascular disease, age 65–74 years, and sex category (female); AUC, area under curve and CI, confidence interval.

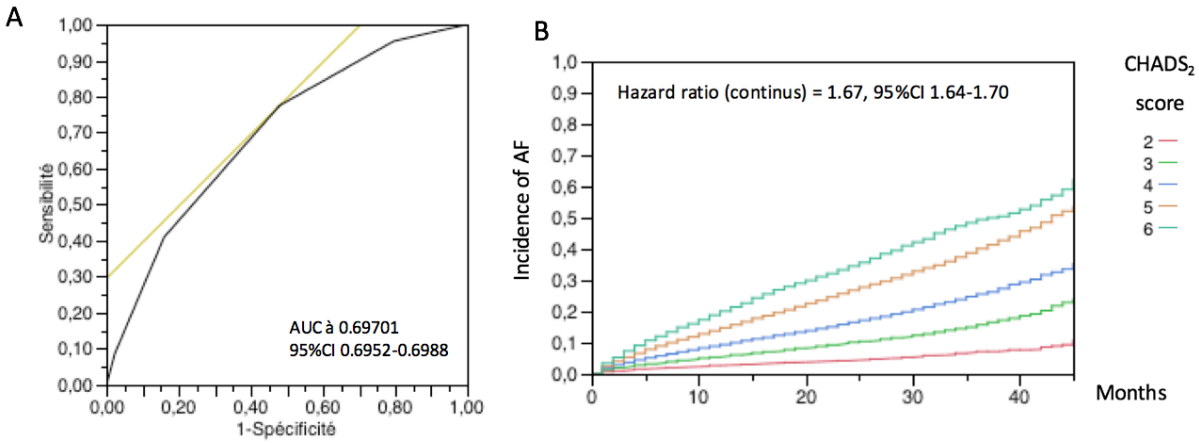


Figure 4. ROC Curve (**A**) and Kaplan–Meier curves (**B**) of $CHADS_2$ score in prediction of new onset of AF after stroke in all patients. $CHADS_2$ indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (doubled); AUC, area under curve and CI, confidence interval.

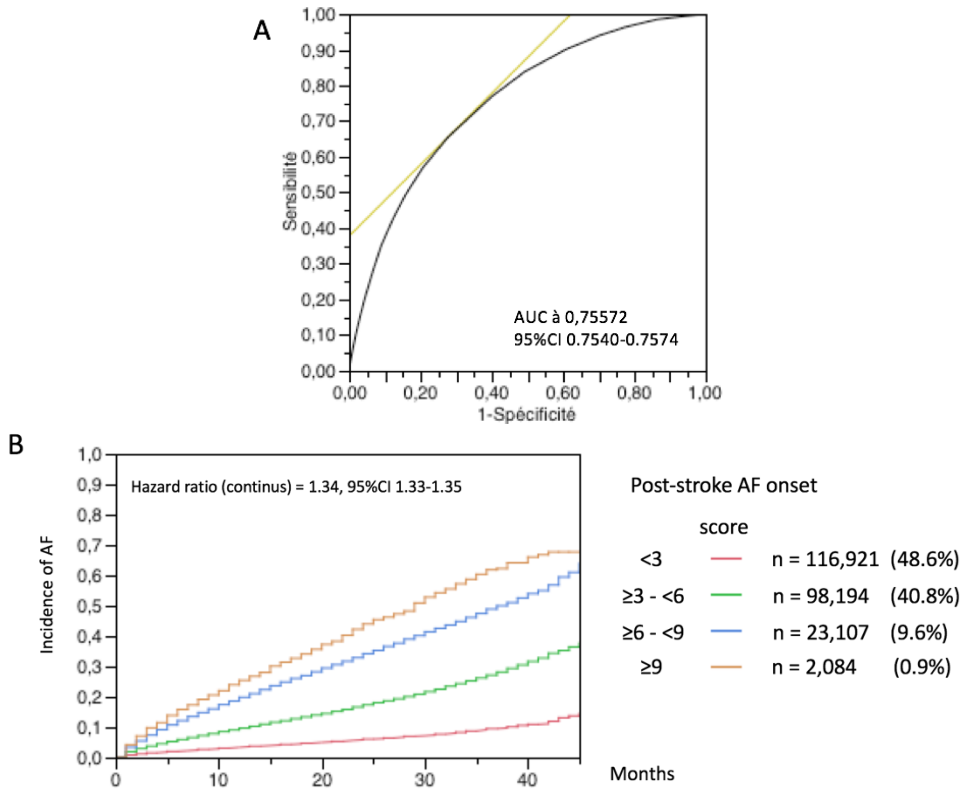


Figure 5. ROC Curve (**A**) and Kaplan–Meier curves [a] (**B**) of our post IS French score in all patients.

[a] Calculation of our post IS French score score was impossible in 153 patients because age was missing.

Vu, le Directeur de Thèse

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BISSON Arnaud
59 pages – 15 tableaux – 5 figures

Résumé :

Introduction *:* La fibrillation atriale (FA) est une cause importante d'accidents vasculaires cérébraux ischémiques (AVCi). Certains scores comme le CHA_2DS_2-VASc permettent d'identifier les patients à risque de faire de la FA dans les suites d'un AVCi chez les patients sans FA connue. Nous avons cherché d'autres facteurs prédictifs indépendants de survenue de FA et comparé ces caractéristiques selon le sexe.

Méthodes : Cette étude de cohorte longitudinale française a été fondée à partir d'une base de données nationale couvrant les soins hospitaliers de 2009 à 2012 pour l'ensemble de la population.

Résultats *:* Sur les 336 291 patients ayant un AVCi de 2009 à 2012, 240 459 (71,5%) n'avaient pas de FA initialement. 14 095 (5,9%) de ces patients ont développé de la FA au cours d'un suivi moyen de 7,9 ± 11,5 mois (incidence de 8,9% pour 100 personnes-années). La plupart des items constituants le score CHA_2DS_2-VASc étaient des facteurs prédictifs indépendants de diagnostic ultérieur de FA. Les principaux nouveaux prédicteurs étaient l'implantation de pacemaker/défibrillateur (OR 1,56, IC 95% 1,48-1,64), les valvulopathies (OR 1,44, IC 95% 1,37-1,51), les coronaropathies (OR 1,22, IC 95% 1,15-1,28), les maladies pulmonaires chroniques (OR 1,14, IC 95% de 1,09-1,18), l'insuffisance rénale (OR 1,12, IC 95% 1,07-1,17) et l'anémie (OR 1,10, IC 95% 1,06-1,15) sans grande différence entre les hommes et les femmes. A partir de ces résultats, nous avons développé un nouveau score ayant une meilleure capacité diagnostic que le score CHA_2DS_2-VASc dans l'identification des patients à haut risque de FA dans les suites d'un AVCi.

Conclusion *:* De nouveaux facteurs prédictifs, cardiaques et extracardiaques, étaient associés à l'apparition de FA dans les suites d'un AVCi, sans différence entre les hommes et les femmes. Nous avons, à partir de ces conclusions, établi un nouveau score de risque identifiant les patients à risque de survenue de FA après un AVCi avec une meilleure capacité diagnostic que les scores décrits précédemment.

Mots clés : fibrillation atriale, accident vasculaire cérébral, facteur prédictif

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