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Prediction of Incident Atrial Fibrillation According to Gender in Patients with Ischemic Stroke From a Nationwide Cohort

Arnaud Bisson, MD[1], Alexandre Bodin, MD[1], Nicolas Clementy, MD[1], Dominique Babuty, MD[1], Gregory Y. H. Lip, MD[2], Laurent Fauchier, MD[1].

Affiliations:

[1] Service de Cardiologie, Pôle Cœur Thorax Vasculaire, Centre Hospitalier Universitaire Trousseau et Faculté de Médecine, Université François Rabelais, Tours, France.

[2] University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom

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Corresponding author:

Professor Laurent Fauchier

Service de Cardiologie et Laboratoire d'Electrophysiologie Cardiaque

Centre Hospitalier Universitaire Trousseau

37044 TOURS, FRANCE

Phone: 33247474650 ; Fax: 33247475919 lfau@med.univ-tours.fr

Abstract

The CHA_2DS_2-VASc score may identify patients at higher risk of atrial fibrillation (AF) following ischemic stroke (IS) among patients without known AF. We compared gender-related differences in items from CHA_2DS_2-VASc score and their relationship with AF occurrence after IS. This French cohort study was based on the database covering hospital care from 2009 to 2012 for the entire population. Of 336,291 patients with IS, 240,459 (71.5%) had no AF at baseline. Women were older, more frequently had hypertension, heart failure, and had a higher CHA_2DS_2-VASc score than men (4.63 vs 4.39, $p<0.0001$, after excluding the female gender component). The annual incidence of AF after IS was higher in women than in men (9.8 vs 8.2%/year, $p<0.0001$). CHA_2DS_2-VASc score items were independent predictors of incident AF, except diabetes and vascular disease. Results were similar in men and women when one analyzed separately these predictors except for vascular disease (associated with a lower risk of AF in women but not in men). Predictive value of the CHA_2DS_2-VASc score for identifying patients at higher risk of incident AF was somewhat higher in men (C statistic 0.720, 95%CI 0.717-0.722) than in women (0.702, 95%CI 0.699-0.704). Coronary artery disease, valvular disease and history of pacemaker/defibrillator implantation were also independent predictors of incident AF. In conclusion, there were significant differences in comorbidities, possible mechanisms, incidence and predictors of AF between men and women after IS. However, a strategy using CHA_2DS_2-VASc score for identifying a higher risk of incident AF following IS was useful in both genders.

Key words: atrial fibrillation, ischemic stroke, risk prediction

Introduction

One in five of all ischemic strokes (IS) can be attributed to atrial Fibrillation (AF) [1]. The risk of recurrence is 22% in cases of cardio embolic stroke [2] and oral anticoagulation would be needed for patients with AF. Documentation of AF by electrocardiogram is generally required to initiate oral anticoagulation for secondary prevention after IS, but in the absence of documented AF, antiplatelet agents are usually recommended [3]. A simple way to 'flag up' patients with a high risk of developing incident AF after IS for more intense monitoring strategies or follow-up would help management. The CHA_2DS_2-VASc score has been widely used to estimate the risk of stroke in patients with AF [4] and for adverse outcomes even in patients without known AF [5,6]. Its usefulness for prediction of new AF in patients after IS has also been observed in a French Nationwide Cohort Study [7]. AF has been associated with a stronger relative risk of IS in women than in men [8,9]. Importantly, mechanisms and comorbidities associated with AF incidence may differ between men and women [10]. We aimed to compare gender-related differences in items from CHA_2DS_2-VASc score and their relationship with differences in AF occurrence between men and women after IS.

METHODS

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. 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 for

inpatients in the 1,546 French healthcare facilities. The reliability of PMSI data has already been assessed [11] and has previously been used to study patients with stroke and AF [7,12,13].

This 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).

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. Patients with no diagnosis of AF were considered as having sinus rhythm. 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 CHA_2DS_2-VASc score as previously described [4].

Qualitative variables are described using counts and percentages, and continuous

quantitative variables as means ± standard deviation or median (IQR, interquartile range). Comparisons were made using parametric or 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. Receiver operating characteristic (ROC) curves were constructed and the Harrell's c statistics were calculated as a measure of model performance and compared using the DeLong test. In all analyses, a p value <0.05 was considered statistically significant. 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 rhythm status 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 1). Baseline characteristics of patients without AF at baseline indicated that more than half were aged ≥75 years with significant differences in associated comorbidities between men and women (Table 1). Women were significantly older, more frequently had hypertension, congestive heart failure, and had a higher CHA_2DS_2-VASc score. 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). Women also more frequently had valvular disease and anaemia. By contrast, they less frequently had dyslipidaemia,

tobacco smoking, coronary artery or vascular disease, pacemaker or defibrillator implantation, renal failure, lung disease or history of cancer.

Of these patients, a total of 14,095 (5.9%) without AF at baseline, were diagnosed as having incident AF during a subsequent hospitalization over a mean follow-up of 7.9±11.5 months (Table 2). The total yearly incidence rate for AF for participants with IS was 8.9 per 100 person-years (95% confidence interval [CI] 8.8-9.0-7.9). Patients with AF during follow-up were significantly older, including a higher proportion of women, and more prevalent items of the CHA_2DS_2-VASc score than patient without AF during follow-up.

Predictors of incident AF are shown in Table 3 for the whole population, and in Table 4 for men and for women. In the whole population, most powerful predictors of incident AF (hazard ratio [HR] $\geq$1.20) were older age, hypertension, heart failure (among items of the CHA_2DS_2-VASc score), coronary artery disease, valvular disease and history of pacemaker/defibrillator implantation. The association between vascular disease and AF occurrence was weaker and borderline to significance for female gender after adjusting for other items. Diabetes mellitus was associated with a higher incidence of AF in univariate analysis but was independently associated with a lower rate of incident AF on multivariable analysis. Results were broadly similar when one analysed separately men and women, except for obesity, abnormal renal function and anaemia (predictor of incident AF in men whilst not significant predictors of AF in women).

The 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. Increasing CHA_2DS_2-VASc score was associated with higher 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 highest CHA_2DS_2-VASc score =9

(only women) and 20.1% for men with CHA_2DS_2-VASc score =8 (Figure 3). In patients with no other CHA_2DS_2-VASc score item, women with IS (thus, CHA_2DS_2-VASc score =3) had a lower incidence of AF during follow-up than men with IS (CHA_2DS_2-VASc score =2) (1.3% vs 2.0%) but the total incidence in women was higher when considering the whole population of the study (9.8% for women vs 8.2% for men).

ROC curve analysis for prediction of AF by the CHA_2DS_2-VASc score showed an area under the curve at 0.7025 (95%CI 0.7007-0.7043), 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 score ≥6. Predictive value of the CHA_2DS_2-VASc score for identifying patients at higher risk of incident AF was somewhat higher in men (C statistics 0.720, 95%CI 0.717-0.722) than in women (0.702, 95%CI 0.699-0.704; De Long test, $p<0.0001$).

DISCUSSION

Our results confirm that IS was associated with substantially increased risk of AF among individuals with higher CHA_2DS_2-VASc score, as previously reported [16]. However, we extend prior observations by showing significant differences in comorbidities and incidence of AF in men and women after IS. Furthermore, CHA_2DS_2-VASc had a slightly better ability to predict incident AF diagnosed in men than in women after IS. Thus, this score would be a simple way to 'flag up' high risk patients for more intense monitoring strategies or follow-up (even in primary care) would help the holistic management of such patients.

Women and men may have different sequelae to various risk factors for cardiovascular disease [9,14]. Previous analyses have shown that smoking and diabetes are associated with greater proportional risks of coronary heart disease in women than in men [15,16]. It is currently unclear, however, whether such sex differences exist for incident AF, whilst conversely AF is a stronger risk factor for cardiovascular disease and death in women compared with men [9,17].

The CHA_2DS_2-VASc score is a validated tool to estimate the risk of stroke in patients with documented AF. The pre-stroke CHA_2DS_2-VASc score has also been associated with neurological outcomes following IS in patients with AF [18,19]. It has also been linked to long-term mortality, stroke recurrence and cardiovascular events in IS patients without AF [20]. The CHA_2DS_2-VASc score has also been useful in predicting the risk of incident AF in a large population [21] and in patients after IS [7]. Whether this simple score works similarly in men and women has not been previously established.

We found marked differences in baseline characteristics of men and women experiencing IS, whereby women were older and had more hypertension, heart failure and accordingly a higher CHA_2DS_2-VASc score. By contrast, they less frequently had coronary or vascular disease, lung disease or renal failure, which may be due to their lower prevalence of dyslipidaemia and tobacco smoking at baseline. The incidence of new incident AF was high, and this rises the possibility that IS was cardioembolic in a vast part of this population, although we were not able to identify the subtypes of IS. The annual incidence of AF after IS was greater in women than in men. The older age, more frequent comorbidities and higher CHA_2DS_2-VASc score at baseline in women may explain these results. An easier and earlier diagnosis of AF might be possible in women because asymptomatic AF is less common in females[22], which may be related to their older age and more frequent comorbidities.

There are 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 [23–25]. Many components of the CHA_2DS_2-VASc scores are associated with higher prevalence of AF. Consistently reported risk indicators of incident AF in the general population or after IS were sex, older age, body mass index, hypertension, heart failure, myocardial infarction and valvular heart disease [7,23,25].

We found that diabetes mellitus was independently associated with a lower risk of AF after IS. Previous epidemiological studies have reported on the association between diabetes mellitus and subsequent risk of AF, with inconsistent results [26]. Diabetes seems less strongly associated with AF than with other cardiovascular diseases and the causality link between diabetes and AF has been debated because of the frequent association with hypertension and obesity. In several cohort analyses, diabetes was less frequent in patients with cardioembolic stroke than in patients with other causes of IS [2,27,28]. Patients with diabetes could also be exposed to more silent AF and our study did not evaluate this issue.

Similarly, vascular disease (as defined in the CHA_2DS_2-VASc score) was associated with a lower AF incidence in women. We may hypothesize that vascular disease is more likely to be associated with large artery or small vessel pathology in women with IS (and less likely to be associated with IS of thromboembolic origin), which may explain the lower association with incident AF occurrence in spite of females being older than males at baseline. This might also explain why the CHA_2DS_2-VASc score had a lower predictive ability to identify the risk of incident AF in women compared to men in our analysis. However, coronary artery disease *per se* was associated with a higher incidence of AF in both genders.

In spite of these differences, the CHA_2DS_2-VASc score was able to predict subsequent AF in those patients with IS in both genders similarly, although the diagnostic value of the CHA_2DS_2-VASc score was slightly higher in men. Higher scores identified patients more likely to develop incident AF, and our findings help targeting patients at highest risk of AF in both groups of male and female patients. Some other characteristics not included in the CHA_2DS_2-VASc score may also help to identify a higher risk of subsequent AF, particularly a history of coronary artery disease or valvular disease. In males with IS, obesity (which may be related to a critical size of the atrium) and anaemia (for unclear reasons) may also marginally identify a higher risk of AF. Patients with a CHA_2DS_2-VASc score of 6 (as per and above

who have sustained an ischemic stroke might have the likelihood of AF high enough to warrant oral anticoagulation before the arrhythmia is formally documented or, more in common with the current opinion, encourage enhanced screening for AF. However, the intensity of such a screening procedure and the duration of clinical/monitoring follow-up have not yet been established and are beyond the scope of this analysis.

A limitation of this study is inherent to its retrospective observational nature. Even though the reliability of PMSI data has been verified previously [11] and used for epidemiological purposes in AF [7,13], 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. Besides, some echocardiographic parameters may help to identify risk of AF [27], and these parameters were lacking in the present study. However, the goal of the present study was to use a simple clinical risk score for predicting the risk of new-onset AF in patients without performing further examinations. Considering its often paroxysmal and asymptomatic nature, AF may not be detected very early with the use of traditional monitoring techniques [29,30]. The analysis also presents inherent potential for information bias, given that no information was available for medications, drug misuse, and international normalized ratios.

In conclusion, among IS patients without known AF, the CHA_2DS_2-VASc score is simple risk tool for identifying patients at higher risk of developing incident AF following IS. Whilst there were significant differences in comorbidities, possible mechanisms and incidence of AF between men and women after IS, a strategy using CHA_2DS_2-VASc score for identifying a higher risk of incident AF was similarly useful in both genders.

Disclosures

NC has received consulting honoraria and travel support from Boston Scientific, Medtronic, St. Jude Medical, and Sorin-LivaNova. DB has received travel support and clinical study support from Biotronik, Boston Scientific, Medtronic, St. Jude Medical, and Sorin-LivaNova and served as a speaker for BMS/Pfizer and Medtronic. GYHL has served as a consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. LF has served as a consultant for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic and Novartis and as a speaker for Bayer, BMS/Pfizer, and Boehringher Ingelheim. Other authors - no conflicts of interest.

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Figure legends

Figure 1. Flow chart of the study patients.

[a] Sinus rhythm or AF. 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.

Figure 2. The Kaplan–Meier curves indicate that patients with ischemic stroke and higher CHA_2DS_2-VASc scores had higher rates of new-onset atrial fibrillation (AF) during the follow-up period in men (**Upper panel**) and in women (**Lower panel**). 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. Hazard ratio of new onset atrial fibrillation in patients with ischemic stroke with different CHA2DS2-VASc scores (in comparison to the patients with score of two) in men and (in comparison to the patients with score of two) in women.

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

Variable	Study population, (n=240,459)	Men (n=126,111)	Women (n=114,348)	p value
Age (years)	71.2±15.5	68.3±14.5	74.2±16	<0.0001
Age ≥75 years old	120,537(50.2%)	49,493(39.3%)	71,044(62.2%)	<0.0001
Underlying diseases				
Hypertension	152,790(63.5%)	78,917(62.6%)	73,873(64.6%)	<0.0001
Diabetes mellitus	55,060(22.9%)	31,558(25.0%)	23,502(20.6%)	<0.0001
Congestive heart failure	39,423(16.4%)	20,129(16.0%)	19,294(16.9%)	<0.0001
Vascular disease	77,543(32.3%)	48,252(38.3%)	29,291(25.6%)	<0.0001
CHA_2DS_2-VASc score	4.98±1.63	4.38±1.53	5.63±1.47	0.0001
Coronary artery disease	44,621(18.6%)	27,803(22.1%)	16,818(14.7%)	<0.0001
Obesity *	24,972(10.4%)	13,013(10.3%)	11.959(10.5%)	0.26
Abnormal renal function	44,011(18.3%)	23,625(18.7%)	20,386(17.8%)	<0.0001
Liver disease	7,298(3.0%)	4,644(3.7%)	2,654(2.3%)	<0.0001
Anemia *	35,145(14.6%)	16,217(12.9%)	18,928(16.6%)	<0.0001
Lung disease	38,981(16.2%)	23,094(18.3%)	15,887(13.9%)	<0.0001
Cancer within preceding 5 years	40,456(16.8%)	24,364(19.3%)	16,092(14.1%)	<0.0001
Inflammatory diseases	15,656(6.5%)	8,127(6.4%)	7,529(6.6%)	0.17
Alcohol-related diagnoses	18,634(7.8%)	14,895(11.8%)	3,739(3.3%)	<0.0001
Thyroid disease	74,287(30.9%)	39,228(31.1%)	35,059(30.7%)	0.02
Dyslipidemia *	75,221(31.3%)	43,535(34.5%)	31,686(27.7%)	<0.0001
Pacemaker-cardioverter defibrillator implantation	8,844(3.7%)	5,377(4.3%)	3,467(3.0%)	<0.0001
Valvular heart disease	17,901(7.4%)	9,203(7.3%)	8,698(7.6%)	0.004
Tobacco smoker	30,255(12.6%)	22,794(18.1%)	7,461(6.5%)	<0.0001

* Obesity defined as International Classification of Disease 10 (ICD-10) codes E65–E66; Anemia defined as ICD codes D50–D64; Dyslipidemia defined as ICD code E78

Table 2 Baseline characteristics of the patients with ischemic stroke and no known atrial fibrillation at baseline according to atrial fibrillation occurrence during follow-up.

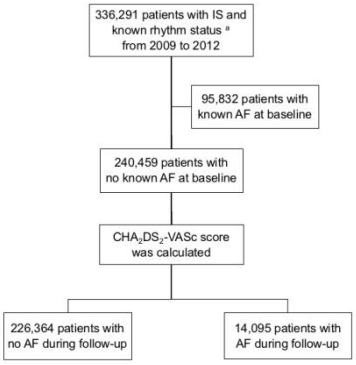
Variables	AF during follow-up (n=14,095)	No AF during follow-up (n=226,364)	p value
Age (years)	77.6±10.6	70.8±15.7	<0.0001
Age ≥75-year old	9,755(69.2%)	110,782(49%)	<0.0001
Women	7,082(50.3%)	107,266(47.4%)	<0.0001
Hypertension	11,745(83.3%)	141,045(62.3%)	
Diabetes mellitus	4,083(29%)	50,977(22.5%)	<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	6.08±1.44	4.91±1.61	<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%)	<0.0001
Anemia	3,980(28.2%)	31,165(13.8%)	<0.0001
Lung disease	3,661(26.0%)	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
Dyslipidemia	5,793(41.1%)	69,428(30.7%)	<0.0001
Pacemaker-cardioverter defibrillator implantation	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(10.0%)	28,840(12.7%)	<0.0001

Table 3. 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 the overall population.

	Univariate analysis (overall population)		Multivariable analysis (overall population)	
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
Vascular disease	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
Dyslipidemia	1.06 (1.03-1.10)	0.0005	0.97 (0.93-1.00)	0.0773
Pacemaker-cardioverter defibrillator implantation	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 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 in men and in women.

	Multivariable analysis (in men)		**Multivariable analysis (in women)**	
Covariate	**HR(95%CI)**	**P-value**	**HR(95%CI)**	**P-value**
Age 65–74 years	1.79 (1.66-1.94)	<0.0001	2.40 (2.15-2.68)	<0.0001
Age ≥75 years	2.58 (2.40-2.77)	<0.0001	3.32 (3.02-3.67)	<0.0001
Female gender	-	-	-	-
Hypertension	1.17 (1.10-1.25)	<0.0001	1.30 (1.21-1.39)	<0.0001
Diabetes	0.93 (0.88-0.98)	0.0039	0.85 (0.80-0.90)	<0.0001
Heart failure	1.99 (1.88-2.10)	<0.0001	2.11 (2.00-2.22)	<0.0001
Vascular disease	0.94 (0.87-1.01)	0.0804	0.86 (0.80-0.93)	<0.0001
Systemic embolism	1.09 (0.98-1.19)	0.1021	1.36 (1.21-1.52)	<0.0001
Coronary artery disease	1.21 (1.13-1.30)	<0.0001	1.22 (1.12-1.32)	<0.0001
Obesity	1.10 (1.03-1.18)	0.0073	1.03 (0.96-1.10)	0.4737
Abnormal renal function	1.18 (1.11-1.25)	<0.0001	1.06 (0.99-1.13)	0.0722
Liver disease	1.06 (0.95-1.19)	0.2855	1.03 (0.90-1.18)	0.6568
Anaemia	1.21 (1.15-1.28)	<0.0001	1.01 (0.96-1.07)	0.7463
Lung disease	1.17 (1.11-1.24)	<0.0001	1.10 (1.04-1.17)	0.0015
Cancer within preceding 5 years	0.94 (0.89-0.99)	0.0165	0.91 (0.86-0.97)	0.0044
Inflammatory diseases	0.97 (0.89-1.04)	0.3915	0.93 (0.86-1.00)	0.0641
Alcohol-related diagnoses	0.96 (0.88-1.04)	0.2841	0.88 (0.75-1.02)	0.0968
Thyroid disease	0.96 (0.91-1.10)	0.0758	0.98 (0.94-1.03)	0.4740
Dyslipidemia	0.95 (0.90-0.99)	0.0483	0.98 (0.93-1.03)	0.4215
Pacemaker-cardioverter defibrillator implantation	1.58 (1.47-1.69)	<0.0001	1.54 (1.41-1.67)	<0.0001
Valvular disease	1.35 (1.26-1.45)	<0.0001	1.54 (1.43-1.65)	<0.0001
Tobacco smoking	0.93 (0.87-0.99)	0.0446	0.86 (0.75-0.97)	0.0164



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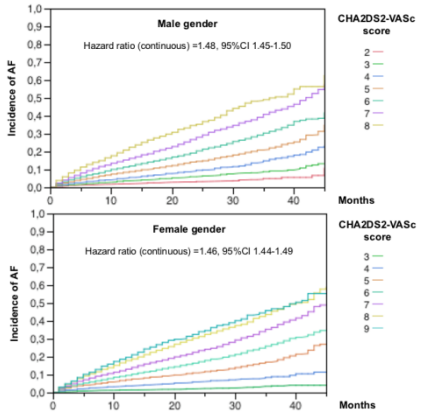
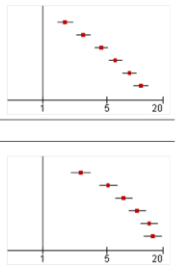


Figure 2_bestsetConverted.png

CHA_2DS_2-VASc score	Number of Patients	Number of new onset AF	Incidence[a]	Hazard ratio	p Value	Forest plots for Hazard Ratios vs Reference
Male gender						
2	17,153	161	2.0	(reference)	-	
3	21,313	429	3.5	1.76 (1.46-2.10)	<0.0001	
4	28,068	935	5.4	2.77 (2.34-3.28)	<0.0001	
5	28,281	1,717	8.3	4.33 (3.68-5.09)	<0.0001	
6	19,919	1,940	11.5	6.13 (5.22-7.20)	<0.0001	
7	9,123	1,368	16.0	8.74 (7.42-10.29)	<0.0001	
8	2,166	463	20.1	11.70 (9.78-14.00)	<0.0001	
Total	126,023 [b]	7,013	8.2	-	-	
Female gender						
3	12,476	94	1.3	(reference)	-	
4	12,424	257	3.5	2.63 (2.07-3.33)	<0.0001	
5	24,900	879	6.8	5.26 (4.25-6.51)	<0.0001	
6	32,427	1,963	9.9	7.71 (6.27-9.49)	<0.0001	
7	20,952	2,073	13.7	10.90 (8.87-13.41)	<0.0001	
8	8,929	1,418	17.6	14.73 (11.96-18.15)	<0.0001	
9	2,175	398	18.8	16.05(12.82-20.10	<0.0001	
Total	114,283 [c]	7,082	9.8	-	-	



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

Figure 3 v2_bestsetConverted.png