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Alexandre BODIN

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Président du Jury : Professeur Dominique BABUTY, Cardiologie, Faculté de Médecine - Tours

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

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ma langue taira les secrets qui me seront confiés
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je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

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RÉSUMÉ

Introduction : Fibrillation atriale (FA) et dysfonction sinusale (DS) sont souvent associées dans le cadre de la maladie rythmique atriale (MRA). MRA et FA ont un risque embolique assez bien estimé par le score de CHA_2DS_2-VASc mais ce risque est incertain concernant la DS. Notre objectif était de décrire l'épidémiologie et l'histoire naturelle de ces entités ainsi que leurs complications.

Méthodes : Cette étude de cohorte longitudinale française a été réalisée à partir d'une base de données nationale couvrant les soins hospitaliers de 2008 à 2015, pour l'ensemble de la population.

Résultats : 1 732 412 patients ont été inclus dans la cohorte : 1 601 435 avec FA, 102 849 avec DS et 28 128 avec MRA. Les patients avec DS à l'inclusion évoluaient plus vers la MRA que les patients avec FA : 14,35% vs. 2,24% ($p<0,0001$). Le risque de mortalité totale était plus élevé dans le groupe FA que dans le groupe DS ou MRA (respectivement, 21,09%/an, 8,65%/an et 10,32%/an). L'évolution vers la MRA via la FA ou la DS était à risque plus élevé d'insuffisance cardiaque que la FA ou la DS isolée (respectivement 12,73%/an vs. 7,41%/an et 15,81%/an vs. 5,28%/an). Nous avons créé le score SEARCH-AF pour prédire le risque de FA dans une population cardiologique où 950 782 patients ont été inclus. L'aire sous la courbe ROC était de 0,7562 alors qu'elle était de 0,6722 pour le score de CHA_2DS_2-VASc et de 0.6894 pour le score Mayo. 479 108 patients ont été inclus dans une population contrôle, l'incidence d'AVC ischémique y était moins importante que dans la DS et la FA (respectivement 0,67%/an, 1,93%/an et 6,72%/an).

Conclusion : La DS évolue plus vers la MRA que la FA. À partir d'une population cardiologique, nous avons développé le score SEARCH-AF pour prédire la FA, un score ≥ 2 pourrait justifier une stratégie de dépistage intensif de la FA. La mortalité toute cause était plus importante au sein de la population de FA par rapport aux patients avec DS ou MRA. L'évolution vers la MRA, via la FA ou la DS, est à risque d'insuffisance cardiaque. Dans les FA et les DS, un score de CHA_2DS_2-VASc ≥ 2 était associé à un risque supérieur d'AVC ischemique et d'insuffisance cardiaque. Le risque embolique des patients avec DS était moins important que celui des FA et MRA mais restait plus supérieur à celui d'une population contrôle. L'incidence de l'AVC ischémique au sein des patients avec DS doit être considérée (1,95%/an et 1,85%/an dans la population de DS sans FA dans le suivi). Une anticoagulation orale pour la prévention de l'AVC ischémique chez des patients selectionnés (par exemple, un score de CHA_2DS_2-VASc ≥ 3) pourrait être envisagée. Une étude prospective pour évaluer le rapport bénéfice-risque d'une telle stratégie est nécessaire.

Epidemiology of atrial fibrillation, sinus node disease and their clinical outcomes: a French nationwide cohort study

ABSTRACT

Introduction: The association between atrial fibrillation (AF) and sinus node disease (SND) is recognized through bradycardia-tachycardia syndrome (BTS). BTS and AF are known to have a risk of ischemic stroke (IS) but the risk of IS in SND population is unclear. Our objective was to describe the epidemiology of AF, SND and BTS, and to compare their different clinical outcomes.

Methods: This French longitudinal cohort study was based on the national hospitalisation database covering hospital care from the entire population from 2008 to 2015.

Results: Of 1,732,412 patients included in the cohort, 1,601,435 had isolated AF, 102,849 had isolated SND and 28,128 had BTS. Patients with SND at baseline had more evolution to BTS than patients with AF at baseline: 14.35% vs. 2.24% ($p < 0.0001$). Incidence of all-cause death was significantly higher in AF compared to SND and BTS (yearly rate of 21.09%, 8.65% and 10.32% respectively). Evolution toward BTS, whether via AF or SND, was associated with a higher risk of heart failure during follow-up compared to isolated AF or SND (Respectively, yearly rate of 12.73% vs. 7.41% and 15.81% vs. 5.28%).

We created the SEARCH-AF score integrating predictors of AF in a cardiologic population where 950,782 patients were included. ROC curve analysis showed an AUC of 0.7562 for SEARCH-AF which was better than pre-existing simple clinical scores: 0.6722 for the CHA_2DS_2-VASc score and 0.6894 for Mayo score. 479,108 patients were included in a control population where the incidence of IS was lower compared to SND and AF patients (respectively 0.67%/year, 1.93%/year and 6.72%/year).

Conclusion: Patients with SND more frequently had evolution to BTS than patients with AF.

From a cardiologic population, we developed the SEARCH-AF score to predict AF, and a SEARCH-AF score ≥ 2 might justify a more systematic intensive screening for AF. AF patients had a worse prognosis compared to other patients evaluated in this study. Evolution toward BTS, whether via AF or SND, was associated with a higher risk of heart failure during follow-up compared to isolated AF or SND. In SND as in AF patients, CHA_2DS_2-VASc score ≥ 2 was associated with a higher risk of ischemic stroke and heart failure. SND patients had a lower risk of thromboembolic events than AF or BTS patients but a higher risk than a control population. The incidence of ischemic stroke in patients with SND was 1.95% yearly (and 1.85% in the SND population without AF during follow-up), which deserves to be considered. Oral anticoagulation for appropriate stroke prevention might be considered in selected patients (for example, those with a CHA2DS2-VASc score ≥ 3). A prospective randomized trial evaluating the risk/benefit ratio of such a strategy is thus needed.

ABBREVIATIONS

AF: Atrial fibrillation

AUC: Area under the curve

BTS: bradycardia-tachycardia syndrome

CCAM: Classification commune des actes médicaux

CI: Confidence interval

HF: Heart failure

HR: Hazard Ratio

ICD: intracardiac defibrillator

ICD-10: International Classification of Disease - 10th revision

IS: ischemic stroke

PM: pacemaker

PMSI: Programme de médicalisation des systèmes d'information

ROC curves: Receiver operating characteristic curves

SND: sinus node disease

INTRODUCTION

Atrial fibrillation (AF) is the most frequent arrhythmia affecting 3% of the population[1,2,3] and is associated with a reduced quality of life.

Sinus node disease (SND) is among the commonest indication for pacemaker implantation worldwide.[4] However, epidemiological information is limited.[5] Historically, SND physiopathology may result from the same organic substrate as AF but is still not clearly understood.[6,7,8,9,10] The association between AF and SND is recognized through bradycardia-tachycardia syndrome (BTS).[11] SND is present in one out of six patients with AF.[12]

BTS and AF are known for decades to have a substantial risk of fatal and disabling stroke. Stroke prevention therapy in AF patients is based on use of oral anticoagulation[13] according to CHA_2DS_2-VASc score[14], with a reduction of this risk up to 64%.[15]

It remains unclear whether the risk of ischemic stroke (IS) is higher in patients with SND and how it could be stratified.

Approximately 10% of ischemic strokes are associated with AF first diagnosed at the time of stroke[16]. Detecting asymptomatic AF would provide an opportunity to prevent these strokes by instituting appropriate anticoagulation[17]. Current European Society of Cardiology guidelines recommend an opportunistic screening for patients >65 years of age or with transient ischemic attack or IS and consider a systematic screening in patients ≥75 years of age or those at high stroke risk.[18] The American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines make no recommendation on the topic of screening but do state that early detection and treatment of asymptomatic AF before the first complications occur is a recognized priority for the prevention of stroke.[19]

Our objective was to describe the epidemiology of AF, SND and BTS, to compare different clinical outcomes (death, ischemic stroke and heart failure) and their potential markers such as CHA_2DS_2-VASc score. We also created the new SEARCH-AF score to predict AF toward general population.

METHODS

Data sources

This French longitudinal cohort study was based on the national hospitalisation database covering hospital care from the entire population. The data for all patients admitted with AF or SND in France from January 2008 to December 2015 were collected from the national administrative database, the PMSI (*Programme de Médicalisation des Systèmes d'Information*), inspired by the US Medicare system. Thanks to this program implemented in 2004, medical activity is recorded in a database, computed, and rendered anonymous. This process allows the determination of each hospital's budget, in the 1,546 French healthcare facilities. Routinely collected medical information includes the principal diagnosis and secondary diagnoses. Diagnoses identified are coded according to the International Classification of Diseases, Tenth Revision (ICD-10). Data for implantation of pacemaker (PM) or implantable cardioverter defibrillator (ICD) were collected with the CCAM (CCAM = *classification commune des actes médicaux)* which is the French medical reimbursement classification for clinical procedures.

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 Commission Nationale de l'Informatique et des Libertés (CNIL), the independent National ethical committee protecting human rights in France which ensures that all information is kept confidential and anonymous, in compliance with the Helsinki Declaration (authorization number 1897139).

Study population.

AF, SND and BTS population

We included all patients over 18 y.o from January 1, 2010 to December 31, 2015 who were hospitalised with a main or related diagnosis of AF or flutter (I48 and its subsections using ICD10 codes) or SND (I45.5 and I49.5 codes). Patients with atrial flutter and prior PM or ICD were excluded. BTS was defined as the presence of both AF and SND codes in the database.

"Cardiologic" population

We included all patients over 18 y.o who were hospitalised from January 1, 2010 to December 31, 2010 (before the beginning of ESC recommendation on anticoagulation) with a main diagnosis of a disease of the circulatory system (I and its subsections using ICD10 codes). Risk factors of AF were calculated in order to establish a new score for prediction of

AF and to compare it to CHA_2DS_2-VASc score and Mayo AF risk score which are known to be predictive for AF[20, 21].
To compare ischemic stroke incidence in the different groups, we created a "control" population based on the "cardiologic" population by excluding patients with AF, SND and valvular disease (including mechanical valve and mitral stenosis) during all the study period and ischemic stroke at inclusion (patients with prior IS were not excluded in order to be either in primary or secondary prevention).

Patients' information was collected from January 1, 2008 to December 31, 2015. Every hospital stay was linked to the patient by an anonymised number, resulting in the patient care pathway. This study database was constructed using the encrypted anonymised number. 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 for every patient.

Statistical analyses.
Qualitative variables are described using counts and percentages and continuous quantitative variables as means ± standard deviation. Comparisons between groups were made using chi-square tests for comparing categorical variables and the Student t test or non-parametric Kruskal Wallis test where appropriate for continuous variables.
To identify independent characteristics associated with death, stroke, heart failure or evolution toward BTS during follow-up, a proportional hazard model was used. CHA_2DS_2-VASc score and other baseline characteristics were pooled into a multivariate Cox model. The results were expressed as hazard ratios risk (HR) and 95% confidence intervals (CI). The proportional hazard assumption was checked by plotting the log-rank Kaplan Meier curves. 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 *Enterprise Guide® 7.1, © SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA.*

RESULTS

AF, SND and BTS at baseline (Tables 1 and 2, and Figures 1, 2, 3 and 4)

Of 1,732,412 patients included in the cohort after exclusion of pacemaker or implantable cardiac defibrillator patients (PM/ICD), 1,601,435 (92.44%) had isolated AF, 102,849 (5.94%) had isolated SND and 28,128 (1.62%) had BTS. (Figure 1)

AF patients were 77.0±11.9 y.o, 48.06% were female, and more frequently had diabetes mellitus, anemia, lung disease, cancer and inflammatory disease compared to SND and BTS patients.
SND patients were younger and had less comorbidities. Though, they more frequently had heart failure, vascular disease and tobacco smoking compared to AF and BTS patients.
BTS patients were older, more frequently had hypertension, coronary heart disease and cardiomyopathy. Their CHA_2DS_2-VASc score was higher than in AF and SND patients (Respectively 3.42, 3.27 and 3.18, $p < 0.0001$). BTS also had more often a HAS BLED score ≥ 3.
Rate of prior ischemic stroke was not significantly different between the 3 groups. (Table 1)

Mean follow-up was 467.3±552.8 days for AF (median: 210 days, first quartile: 15 days and third quartile: 832 days), 509.1±580.5 days for SND (median: 266 days, first quartile: 9 days and third quartile: 895 days) and 530.7±579.0 days for BTS (median: 311 days, first quartile: 18 days and third quartile: 920 days).

Patients with SND at baseline had more evolution to BTS than patients with AF at baseline: 14.35% (14,759) vs. 2.24% (35,891) ($p < 0.0001$), and mean delays to BTS were respectively 518.5±497.8 days and 485.2±487.4 days.

Incidence of all-cause death was significantly higher in AF compared to SND and BTS (yearly rate of 21.09%, 8.65% and 10.32% respectively).
Incidence of heart failure was higher in BTS patients than in AF patients and higher in AF patients than in SND patients (yearly rate 8.21%, 7.50% and 6.76% during follow-up respectively).
Incidence of IS stroke during follow-up was higher in isolated AF patients than in BTS patients (yearly rate 5.48% vs 3.03%) and in isolated AF patients than in isolated SND

patients (yearly rate 5.48% vs 1.95%). The survival free of IS was worsened as the CHA_2DS_2-VASc score was higher for AF, BTS and SND patients. (Figure 3)
Rate of major bleeding was higher in AF and BTS groups compared to SND patients.
PM or ICD was implanted in 64.05% of BTS patients, 48.64% of SND patients and in 8.30% of AF patients. (Table 2 and Figure 2).

Receiver operating characteristic (ROC) curve analysis for prediction of IS by the CHA_2DS_2-VASc score showed an area under the curve (AUC) at 0.5867 (95% CI: 0.5859 – 0.5875) in the AF and BTS population and 0.6246 (95% CI: 0.6216 – 0.6276) in the SND population. (Figure 4) Surprisingly, the CHA_2DS_2-VASc score was more efficient to predict IS in the SND population than in the AF population ($p<0.0001$).

In AF and BTS population, a CHA_2DS_2-VASc score with a cut-off ≥ 1 had a sensitivity of 98.62%, a specificity of 4.47%, a positive predictive value of 8.23% and a negative predictive value of 97.39%. A CHA_2DS_2-VASc score with a cut-off ≥ 2 had a sensitivity of 94.61%, a specificity of 12.71%, a positive predictive value of 8.61% and a negative predictive value of 96.44%.
Concerning SND population, a CHA_2DS_2-VASc score with a cut-off ≥ 2 had a sensitivity of 93.09%, a specificity of 16.73%, a positive predictive value of 4.27% and a negative predictive value of 98.39%. A CHA_2DS_2-VASc score with a cut-off ≥ 3 had a sensitivity of 82.97%, a specificity of 32.96%, a positive predictive value of 4.70% and a negative predictive value of 97.98%.

AF at baseline (Tables 3, 4 and 5, figure 5)
We compared patients with AF at baseline without SND during follow-up (Isolated AF, n = 1,565,026) and with SND during follow-up (BTS via AF, n= 36,409).

When considering differences in prevalence ≥10%, BTS via AF compared to isolated AF had more comorbidities such as hypertension, coronary artery disease, valvular disease, dyslipidaemia and renal disease. CHA_2DS_2-VASc score was significantly higher in patients with SND during follow-up and these patients more frequently had HAS BLED score ≥ 3 (Table 3).

BTS via AF compared to isolated AF patients more often had heart failure (yearly rate of 12.73% vs. 7.41%) but lower risk of ischemic stroke (yearly rate of 3.46% vs. 5.58%) and all-cause death (yearly rate of 7.36% vs. 21.67%) during follow-up (Table 4).

Most powerful predictors (HR ≥ 1.20) of SND occurrence (and consequently evolution to BTS) in the total population of AF patients were age 65-74 years old and over 75 y.o, hypertension, heart failure, coronary artery disease, cardiomyopathy, valvular disease, dyslipidaemia, renal disease and thyroid disease. (Table 5)

In all patients with AF at baseline, ischemic stroke and heart failure risk increased according to the CHA_2DS_2-VASc score. This was also significant (although less obvious) for evolution to BTS (Figure 5).

SND at baseline (Tables 6, 7 and 8, Figure 6)

We compared patients with SND at baseline with no AF during follow-up (isolated SND, n = 87,650) and those with AF during follow-up (BTS via SND, n=15,199).

Patients with BTS via initial SND were older than those with isolated BTS. When considering differences in prevalence ≥10% versus isolated SND patients, they more frequently had hypertension, coronary artery disease, valvular disease, renal disease, anaemia and lung disease.

CHA_2DS_2-VASc score was significantly higher in patients with AF during follow-up and their HAS-BLED score was more often ≥ 3 (Table 6).

Compared to patients with isolated SND, patients with BTS via SND were more prone to develop heart failure (yearly rate of 15.81% vs. 5.28%), to have ischemic stroke (yearly rate of 3.11% vs. 1.85%) and had a higher rate of all-cause death (yearly rate of 9.48% vs. 9.35%) during follow-up. Patients with BTS via SND were more frequently treated with cardiac pacing (65.98% vs. 45.63% during follow-up) compared to patients with isolated SND (Table 7).

In the total SND population, most powerful predictors (HR ≥ 1.20) of evolution to BTS in multivariate analysis were age 65-74 years old, age ≥ 75 y.o, hypertension, cardiomyopathy,

valvular disease, renal disease and thyroid disease. HR for prediction of AF in univariate analysis for CHA_2DS_2-VASc score ≥ 2 was 3.515 (95%CI: 3.326-3.71, p < 0.0001) (Table 8).

Most powerful predictors (HR ≥ 1.20) for ischemic stroke occurrence in the total SND population were age 65-74 years old, age ≥ 75 yo, hypertension, vascular disease, alcohol-related diagnoses and lung disease. HR for prediction of ischemic stroke in univariate analysis for CHA_2DS_2-VASc score ≥ 2 was 2.665 (95%CI: 2.391-2.969, p < 0.0001).

A CHA_2DS_2-VASc score ≥ 2 was associated with a higher risk of evolution to BTS, ischemic stroke and heart failure (Figure 6).

BTS at baseline (Tables 10 and 11, Figure 7)

We compared patients with BTS during follow-up via initial SND (n=15,199) versus BTS during follow-up via initial AF (n=36,409).

There was no relevant difference (≥ 10%) between these two groups (Table 10).

There was also no significant difference for of ischemic stroke occurrence between these two groups.

However, BTS via AF patients less frequently had heart failure than those with BTS via SND (yearly rate of 12.73% vs. 15.81%) and had lower mortality during follow-up (yearly rate of 7.36% vs. 9.48%). (Table 11 and Figure 7)

"Cardiologic" population (Tables 12, 13, 14 and 15, Figures 8, 9 and 10)

950,782 patients were included in this "cardiologic" population. Mean age was 69.6±15.2 y.o., 44.33% were ≥75 y.o and 43.19% were female. Main diagnoses at inclusion were heart failure (14.26%), coronary artery disease (13.89%), atrial fibrillation (8.13%), stroke (5.69%) and peripheral arterial disease (5.43%). (Table 12)

Of those, 263,887 (27.75%) had AF during follow-up with a yearly incidence of 8.65%.

Most powerful predictors (HR ≥ 1.20) of AF in this "cardiologic" population were age 65-74 years old, age ≥ 75 y.o, heart failure, prior ischemic stroke, SND, Cardiomyopathy, valvular disease, renal disease and thyroid disease. (Table 13)

AF was significantly more prevalent among patients with SND. (Figure 8)

Based on these findings, we created a new SEARCH-AF score integrating these predictors of AF in the "cardiologic" population. The weight of each item was determined according to the HR in the multivariate analysis. Here is the detail of this score: Age ≥ 75y.o and congestive

heart failure = 2 points; Age 65-74y.o, hypertension, prior stroke, SND, PM or ICD, cardiomyopathy, valvular disease, renal disease and thyroid disease = 1 point. (Table 14)
ROC curve analysis for our SEARCH-AF score showed a better ability to predict AF occurrence with an AUC = 0. 7562 (95% CI: 0.7553 – 0.7571) for SEARCH-AF which was better than two others simple pre-existing clinical scores: 0.6722 (95% CI: 0.6713 – 0.6731) for the CHA_2DS_2-VASc score and 0. 6894 (95% CI: 0.6885 – 0.6903) for Mayo score. (Figure 9) Incidence of AF increased gradually according to the SEARCH-AF score on Kaplan Meier curves showing a good correlation. (Table 15 and Figure 10)
A SEARCH-AF score with a cut-off ≥ 2 had a sensitivity of 91.18%, a specificity of 38.76%, a positive predictive value of 36.39% and a negative predictive value of 91.97%. While a cut-off ≥ 3 had a sensitivity of 79.47%, a specificity of 58.76%, a positive predictive value of 42.54% and a negative predictive value of 88.16%.

"Control" population and incidence of IS in the different study populations (Table 16 and Figure 11)

479,108 patients were included in this cohort. (Figure 11) Incidence of IS was lower in the "control" population compared to SND and AF patients (respectively 0.67%/year, 1.93%/year and 6.72%/year).
SND patients with a CHA_2DS_2-VASc score ≥ 3 had a yearly incidence of IS > 2%, comparable to AF population with a CHA_2DS_2-VASc score ≥ 1. In the "control" population, a similar incidence was found in patients with a CHA_2DS_2-VASc score ≥ 6 for men and ≥ 7 for women. (Table 16)

DISCUSSION

Using a French nationwide database, we performed an overview of epidemiology of AF, SND and their outcomes. We obtained population where mean age and percentage of women were similar to those from several previous studies[22,23,24] highlighting the clinical consistency of our dataset. Our study included the largest cohort of SND patients to our knowledge describing the natural history of the disease and the risk of clinical events during follow-up.

Population characteristics

AF patients more frequently had diabetes mellitus, anaemia, lung disease and inflammatory disease than SND and BTS patients. Cancer was also more frequently reported for these patients, which may be explained by a better or earlier diagnosis because of bleeding promoted by anticoagulation.

Patients with SND had more frequent history of heart failure, and use of beta-blocker in heart failure may in part contribute to SND for some patients. In our study, they also were more frequent tobacco smoker or more frequently had vascular disease compared to AF and BTS patients.

BTS patients were older and had more comorbidities than AF and SND patients.

Natural history

Patients with SND at baseline had more frequent evolution to BTS than patients with AF at baseline.

In our study, most powerful predictors of evolution toward BTS either for AF or SND were: older age, hypertension and cardiomyopathy (which are items of the CHA_2DS_2-VASc score) but also valvular disease, renal disease and thyroid disease.

A CHA_2DS_2-VASc score ≥ 2 was associated with a higher risk of evolution toward BTS in SND patients but was not predictive of evolution toward BTS in the AF population.

This highlights that patients with SND are at very high risk of AF during follow-up, while the opposite is less common.

SEARCH-AF score

Asymptomatic screen-detected AF have a worse prognosis than symptomatic AF and may benefit from anticoagulation in term of stroke and mortality[25, 26, 27, 28]. AF screening is challenging, and technology improvement such as Handheld single-lead ECG might be helpful in the future.

However, we need to focus on a specific at-risk population in order to increase cost-effectiveness of AF screening. Single-timepoint screening of a general population ≥65y.o detects undiagnosed AF in 1.4%[29]. A more intensive screening in individuals 75 to 76 years of age identified AF in 3.0% (0.5% on the initial ECG) and if one or more additional stroke risk factor (according to CHA_2DS_2-VASc score) was added, 7.4% of patients had silent AF[30, 31].

We thus developed a tool to predict AF in a cardiologic population, including patient with ischemic stroke, called SEARCH-AF score.

Linker et al. recently developed a risk model to identify subject at risk of AF called SAAFE (Screening for Asymptomatic Atrial Fibrillation Events) and made a comparison to other known scores (CHARGE-AF, ARIC, Framingham, Mayo, HATCH).[32] Risk factors of AF were similar except for coronary artery disease and diabetes that were not identified in our cohort as a predictive factor for AF.

We were not able to compare most of the scores because of the lack for some data which were not reported, underlining their complexity or inability for a very wide use. CHA_2DS_2-VASc score and Brunner's Mayo AF risk score are known to be predictive of AF[33, 34] and were the 2 better simple clinical scores in the study by Linker where such a comparison could be made. Our results indicate that AUC of SEARCH-AF score was higher than CHA_2DS_2-VASc and Mayo scores (0.756, 0.672 and 0.689 respectively) and was close to that reported for SAAFE although a direct comparison could not be made (0.756 vs. 0.766, respectively). A validation analysis for prediction of AF in other cohorts would be of interest.

Our score only uses simple clinical features, which is the best way in our belief to extend its clinical use. It is also the first considering SND as a major risk factor of AF.

In order to have a good sensitivity and the highest negative predictive value, our results suggest that a systematic intensive screening for AF might be made in patients with a SEARCH AF score ≥ 2.

Outcomes

AF patients had a worse prognosis with a higher all-cause yearly death rate and a shorter delay to death than SND and BTS patients. No causality link can be made with this observational study.

Regarding yearly rates of outcomes, an evolution to BTS whether via initial AF or initial SND was at a higher risk of heart failure compared to isolated AF or SND. A closer follow-up and

maybe an earlier management of heart failure might be considered in these patients in order to possibly improve prognosis.

Rate of prior ischemic stroke was not significantly different between the AF, BTS and SND groups. However, yearly incidence of ischemic stroke was significantly different in the 3 groups. These findings may emphasize the role of atrial conditions (or a so-called atrial cardiomyopathy[35]) in the thrombotic pathway and the subsequent risk of stroke.
There was no significant difference for IS for BTS via AF or via SND. This has not been reported earlier to our knowledge. This may once again emphasize that patients with SND should probably be closely monitored for an early diagnosis of AF and an optimal antithrombotic management, particularly in patients at high risk of AF during follow-up (those with a SEARCH-AF score of 2 and above), This might be a perspective for improving prognosis and reducing the risk of stroke at a population level.

Incidence of major bleeding was higher in AF and BTS groups than in SND patients. There was not significant difference for bleeding events in these 2 groups and this may result from oral anticoagulation for stroke prevention (indicated for most of these patients in the guidelines based on the CHA_2DS_2-VASc score) although we were not able to analyse this item in our database.

In SND as in AF patients, CHA_2DS_2-VASc score ≥ 2 was associated with a higher risk of ischemic stroke and heart failure.

Ischemic stroke and SND

SND patients had a lower risk of thromboembolic events than AF or BTS patients. This underlies the importance of AF in the genesis of thrombi and the risk of stroke. However, in this unselected French population of patients seen in hospital, SND patients had a non-neglectable risk of IS during follow-up which was higher than in our "control" population (1.95% and 0.67% yearly, respectively).
Oral anticoagulation is generally recommended when the yearly rate of thromboembolic events is expected to be above 1% for patients with a so-called « non-valvular » AF based on the CHA_2DS_2-VASc score.[36] Ischemic stroke incidence in SND patients was lower than in AF and BTS population but was still 1.95% of IS yearly (and 1.85% in the SND population without AF during follow-up). A CHA_2DS_2-VASc score ≥ 3 in the SND population was

associated with a yearly incidence of IS ≥2% and had relatively good specificity and sensitivity for identifying the risk of IS. Anticoagulation might be considered in these patients since it had a quite similar sensitivity but a little better specificity than those of CHA_2DS_2-VASc score ≥ 2 in AF and BTS patients. Of note, AUC of CHA_2DS_2-VASc score for prediction of IS in AF and BTS population may have been weakened by the generalization of anticoagulation during our study in 2012.

The CHA_2DS_2-VASc score is known to be predictive of thrombo-embolic risk in the absence of any AF history in patients with heart failure.[37,38] In a relatively small series of patients with SND and pacemaker implantation in China, the CHA_2DS_2-VASc score was found to be predictive of stroke and had an improved predictive value when adding an evaluation of the left atrial size[39], which we were not able to obtain at a national level in our analysis.

Atrial cardiomyopathy was recently redefined[40] and is described as an independent factor of stroke even without AF. It can actually precede the occurrence of AF.[41] A recent study by Fonseca et al. found that patients with undetermined stroke have increased atrial fibrosis.[42] Persistent or permanent AF are well-known to be associated with atrial remodelling. Patients with paroxysmal AF, remote from arrhythmia, may have bi-atrial structural changes and sinus node dysfunction.[43] SND is also associated with diffuse atrial remodelling.[44,45] SND is a wide and complex spectrum with different aetiologies. However, we may consider AF and SND as two clinical phenotypes of atrial fibrosis in a specific context (such as a high CHA_2DS_2-VASc score). This could partially explain the risk of embolic events found in SND patients in our study, which is a new result with possibly important clinical implications. This approach would also be easier than TTE or MRI for an early screening and diagnosis of atrial cardiomyopathy.

Limitation

A main limitation of this study was inherent to its retrospective observational nature. Identifying AF, SND and comorbidities is challenging and stroke lack of adjudication as cardioembolic. However, ICD-10 is considered reliable in AF, stroke and stroke risk factors constituting the CHA_2DS_2-VASc score with a relatively low proportion of false positives and negatives.[46,47,48] The PMSI was previously verified[49,50] and used for epidemiologic purpose in patients with AF or ischemic stroke.[51,52,53,54] However, SND prevalence and incidence may have been underestimated as its code is not used as often as AF.

Events included were only in-hospital, we had no data on extra-hospital diagnoses. However, ischemic stroke is most often managed in hospital in our (as in most other) health system. Data were based on the diagnostic codes registered for reimbursement purposes by a responsible physician and were not checked externally with a potential information bias. Echocardiographic and electrographic parameters were lacking because they are not available in the database. However, the goal of this study was to provide a simple clinical approach and a global picture at a national level not limited to tertiary referral centers.

Drug therapies were not included in the analysis, which may be corrected in next studies by using the national database SNIIRAM (Système National d'Information Interrégimes de l'Assurance Maladie). Another potential information bias is the lack of available information concerning drug misuse, international normalized ratios and time in therapeutic range.

However, the size of the study population including every hospitalization in France with a neglectable risk of follow-up loss may compensate some of these biases.

CONCLUSION

Using a French nationwide database, we performed an overview of epidemiology of AF and SND over the last years. Our main findings were that:

- Patients with SND more frequently had evolution to BTS than patients with AF.
- From a cardiologic population, we developed the SEARCH-AF score to predict AF, and a SEARCH-AF score ≥ 2 might justify a more systematic intensive screening for AF.
- AF patients had a worse prognosis with a higher yearly rate of all-cause death compared to other patients evaluated in this study.
- Evolution toward BTS, whether via AF or SND, was associated with a higher risk of heart failure during follow-up compared to isolated AF or SND.
- In SND as in AF patients, CHA_2DS_2-VASc score ≥ 2 was associated with a higher risk of ischemic stroke and heart failure.
- SND patients had a lower risk of thromboembolic events than AF or BTS patients but a higher risk than a control population. The incidence of ischemic stroke in patients with SND was 1.95% yearly (and 1.85% in the SND population without AF during follow-up), which deserves to be considered. Oral anticoagulation for appropriate stroke prevention is thus an option which might be considered in selected patients (for example, those with a CHA_2DS_2-VASc score ≥ 3). A prospective randomized trial evaluating the risk/benefit ratio of such a strategy is thus needed.

Table 1 - Baseline characteristics of patients with AF at baseline, SND at baseline and BTS at baseline.

Variables	AF n=1,601,435	Sinus node disease (SND) n=102,849	Bradycardia-tachycardia syndrome (BTS) n=28,128	BTS vs. AF p Value
Age, years	77.0±11.9	73.9±13.7*	78.3±10.1	<0.0001
Age ≥75 years old, n (%)	1,045,781(65.3%)	59,853(58.20%)*	19,962 (70.97%)	<0.0001
Gender (female), n (%)	769,575 (48.06%)	46,052 (44.78%)*	13,820 (49.13%)	0.0003
Underlying diseases, n (%)				
Hypertension	1,108,284 (69.21%)	69,241 (67.32%)*	20,778 (73.87%)	<0.0001
Diabetes mellitus	370,840 (23.16%)	23,674 (23.02%)*	6,096 (21.67%)	<0.0001
Heart failure	229,265 (14.32%)	15,691 (15.26%)*	3,879 (13.79%)	0.0126
Vascular disease	364,370 (22.75%)	26,877 (26.13%)*	6,795 (24.16%)	<0.0001
CHA_2DS_2-VASc score	3.27±1.47	3.18±1.60*	3.42±1.36	<0.0001
HAS BLED ≥ 3	422,589 (26.39%)	24,097 (23.43%)*	7,772 (27.63%)	<0.0001
Comorbidities				
Prior ischemic stroke	37,165 (2.32%)	2,483 (2.41%)†	607 (2.16%)	0.2432
Coronary artery disease	473,134 (29.54%)	35,889 (34.89%)*	14,520 (35.53%)	<0.0001
Cardiomyopathy	163,585 (10.21%)	9,219 (8.96%)*	3,489 (12.40%)	<0.0001
Valvular disease	294,446 (18.39%)	15,557 (15.13%)*	6,726 (23.91%)	<0.0001
Obesity	283,718 (17.72%)	17,883 (17.39%)††	4,863 (17.29%)	0.0625
Dyslipidaemia	433,933 (27.10%)	34,820 (33.86%)*	9,166 (32.59%)	<0.0001
Liver disease	88,979 (5.56%)	4,999 (4.86%)*	1,312 (4.66%)	<0.0001
Renal disease	389,290 (24.31%)	21,045 (20.46%)*	7,267 (25.84%)	<0.0001
Anaemia	372,233 (23.24%)	18,991 (18.46%)*	5,709 (20.30%)	<0.0001
Lung disease	375,466 (23.45%)	18,059 (17.56%)*	5,029 (17.88%)	<0.0001
Obstructive sleep apnea	110,050 (6.87%)	7,725 (7.51%)*	1,995 (7.09%)	0.1472
Cancer within preceding 5 years	363,371 (22.69%)	19,685 (19.14%)*	5,152 (18.32%)	<0.0001
Inflammatory diseases	138,775 (8.67%)	8,090 (7.87%)*	2,242 (7.97%)	<0.0001
Alcohol-related diagnoses	103,407 (6.46%)	6,422 (6.24%)†††	1,204 (4.28%)	<0.0001
Tobacco smoking	121,478 (7.59%)	10,284 (10.00%)*	1,782 (6.34%)	<0.0001
Thyroid disease	202,559 (12.65%)	10,731 (10.43%)*	4,175 (14.84%)	<0.0001

* p<0.0001 vs. AF, † p=0.0539 vs. AF, †† p=0.0074 vs. AF, ††† p=0.0070

Table 2 - Outcomes during follow-up for patients with AF at baseline, SND at baseline and BTS at baseline.

	AF n=1,601,435	SND n=102,849	BTS n=28,128	BTS vs. AF P value
Mean duration of follow-up (days)	467.3±552.8	509.1±580.5*	530.7±579.0	<0.0001
All-cause death	341,255 (21.31%)	12,141 (11.80%)*	4,183 (14.87%)	<0.0001
Mean delay to death (days)	369.1±473.5	496.7±521.3*	525.2±524.4	<0.0001
Evolution to BTS	35,891 (2.24%)	14,759 (14.35%)*	-	
Mean delay to BTS (days)	485.2±487.4	518.5±497.8*	-	
Heart failure	266,339 (16.63%)	16,602 (16.14%)*	5,500 (19.55%)	<0.0001
Mean delay to heart failure (days)	293.1±473.1	375.8±524.8*	332.6±500.8	<0.0001
Ischemic stroke	128,641 (8.03%)	3,939 (3.83%)*	1,616 (5.75%)	<0.0001
Mean delay to ischemic stroke (days)	204.8±405.1	382.8±506.4*	343.1±504.5	<0.0001
Major bleeding	123,097 (7.69%)	5,197 (5.05%)*	2,076 (7.38%)	0.0560
Intracranial bleeding	48,510 (3.03%)	1,927 (1.87%)*	683 (2.43%)	<0.0001
Pacemaker/ICD	132,843 (8.30%)	50,024 (48.64%)*	18,016 (64.05%)	<0.0001

*p<0.0001 vs AF

Table 3 - Baseline characteristics of AF without SND during follow-up and AF with SND during follow-up.

Variables	*AF at baseline n=1,601,435*	AF without SND during follow-up n=1,565,026	AF with SND during follow-up n=36,409	p Value
Age, years	*77.0±11.9*	77.05±11.99	77.84±9.59	<0.0001
Age ≥75 years old, n (%)	*1,045,781(65.3%)*	1,020,427 (65.20%)	25,354 (69.64%)	<0.0001
Gender (female), n (%)	*769,575 (48.06%)*	751,562 (48.02%)	18,013 (49.47%)	<0.0001
Underlying diseases, n (%)				
Hypertension	*1,108,284 (69.21%)*	1,077,810 (68.87%)	30,474 (83.70%)	<0.0001
Diabetes mellitus	*370,840 (23.16%)*	360,865 (23.06%)	9,975 (27.40%)	<0.0001
Heart failure	*229,265 (14.32%)*	223,875 (14.30%)	5,390 (14.80%)	0.0072
Vascular disease	*364,370 (22.75%)*	352,741 (22.54%)	11,629 (31.94%)	<0.0001
CHA_2DS_2-VASc score	*3.27±1.47*	3.31±1.50	3.71±1.37	<0.0001
HAS BLED ≥ 3	*422,589 (26.39%)*	408,475 (26.10%)	14,114 (38.77%)	<0.0001
Comorbidities				
Prior ischemic stroke	*37,165 (2.32%)*	36,414 (2.33%)	751 (2.06%)	0.0009
Coronary artery disease	*473,134 (29.54%)*	457,184 (29.21%)	15,950 (43.81%)	<0.0001
Cardiomyopathy	*163,585 (10.21%)*	156,374 (9.99%)	7,211 (19.81%)	<0.0001
Valvular disease	*294,446 (18.39%)*	282,759 (18.07%)	11,687 (32.10%)	<0.0001
Obesity	*283,718 (17.72%)*	275,119 (17.58%)	8,599 (23.62%)	<0.0001
Dyslipidaemia	*433,933 (27.10%)*	418,868 (26.76%)	15,065 (41.38%)	<0.0001
Liver disease	*88,979 (5.56%)*	86,530 (5.53%)	2,449 (6.73%)	<0.0001
Renal disease	*389,290 (24.31%)*	375,996 (24.02%)	13,294 (36.51%)	<0.0001
Anaemia	*372,233 (23.24%)*	361,553 (23.10%)	10,680 (29.33%)	<0.0001
Lung disease	*375,466 (23.45%)*	366,126 (23.39%)	9,340 (25.65%)	<0.0001
Obstructive sleep apnea	*110,050 (6.87%)*	106,275 (6.79%)	3,775 (10.37%)	<0.0001
Cancer within preceding 5 years	*363,371 (22.69%)*	355,777 (22.73%)	7,594 (20.86%)	<0.0001
Inflammatory diseases	*138,775 (8.67%)*	134,692 (8.61%)	4,083 (11.21%)	<0.0001
Alcohol-related diagnoses	*103,407 (6.46%)*	101,074 (6.46%)	2,333 (6.41%)	0.6981
Tobacco smoking	*121,478 (7.59%)*	118,350 (7.56%)	3,128 (8.59%)	<0.0001
Thyroid disease	*202,559 (12.65%)*	194,884 (12.45%)	7,675 (21.08%)	<0.0001

Table 4 - Outcomes during follow-up of AF without SND during follow-up and AF with SND during follow-up.

	AF at baseline n=1,601,435	AF without SND during follow-up n=1,565,026	AF with SND during follow-up n=36,409	p value
Mean duration of follow-up (days)	*467.3±552.8*	457.3±548.0	898.3±585.3	<0.0001
All-cause death	*341,255 (21.31%)*	335,152 (21.42%)	6,103 (16.76%)	<0.0001
Mean delay to death (days)	*369.1±473.5*	360.7±467.7	831.1±538.8	<0.0001
Heart failure	*266,339 (16.63%)*	253,202 (16.18%)	13,137 (36.08%)	<0.0001
Mean delay to heart failure (days)	*293.1±473.1*	289±469.9	470.8±563.6	<0.0001
Ischemic stroke	*128,641 (8.03%)*	125,309 (8.01%)	3,332 (9.15%)	<0.0001
Mean delay to ischemic stroke (days)	*204.8±405.1*	200.2±400.9	378.5±509.6	<0.0001
Major bleeding	*123,097 (7.69%)*	118,976 (7.60%)	4,121 (11.32%)	<0.0001
Intracranial bleeding	*48,510 (3.03%)*	47,205 (3.02%)	1,305 (3.58%)	<0.0001
Pacemaker/ICD	*132,843 (8.30%)*	108,900 (6.96%)	23,943 (65.76%)	<0.0001

Table 5 - Cox regression analysis for prediction of SND in patients with AF at baseline.

n = 1,601,435

	Univariate analysis		Multivariable analysis	
Covariate	**HR (95%CI)**	**P-Value**	**HR (95%CI)**	**P-Value**
CHA_2DS_2-VASc score = 0	0.434 (0.399-0.472)	<0.0001		
CHA_2DS_2-VASc score = 1	0.593 (0.564-0.622)	<0.0001		
CHA_2DS_2-VASc score ≥2	1.891 (1.812-1.974)	<0.0001		
Age ≥75 years old	1.410 (1.378-1.442)	<0.0001	1.845 (1.775-1.917)	<0.0001
Age 65-74 years old	0.950 (0.926-0.975)	<0.0001	1.589 (1.525-1.656)	<0.0001
Gender (female)	1.129 (1.106-1.153)	<0.0001	1.030 (1.007-1.054)	0.0099
Hypertension	1.566 (1.522-1.610)	<0.0001	1.240 (1.204-1.277)	<0.0001
Diabetes mellitus	1.056 (1.032-1.081)	<0.0001	0.913 (0.891-0.936)	<0.0001
Heart failure	1.171 (1.137-1.205)	<0.0001	0.890 (0.862-0.918)	<0.0001
Vascular disease	1.278 (1.250-1.307)	<0.0001	1.002 (0.977-1.027)	0.9029
Ischemic stroke	1.062 (0.987-1.142)	0.1050	0.982 (0.913-1.057)	0.6358
Coronary artery disease	1.460 (1.430-1.491)	<0.0001	1.240 (1.210-1.270)	<0.0001
Cardiomyopathy	1.637 (1.595-1.680)	<0.0001	1.450 (1.411-1.490)	<0.0001
Valvular disease	1.665 (1.629-1.703)	<0.0001	1.398 (1.366-1.431)	<0.0001
Obesity	1.076 (1.050-1.102)	<0.0001	1.016 (0.989-1.044)	0.2451
Dyslipidaemia	1.412 (1.382-1.442)	<0.0001	1.247 (1.219-1.276)	<0.0001
Alcohol-related diagnoses	0.831 (0.796-0.866)	<0.0001	0.932 (0.890-0.975)	0.0025
Tobacco smoking	0.962 (0.927-0.998)	0.0402	1.087 (1.044-1.131)	<0.0001
Liver disease	1.036 (0.995-1.080)	0.0892	1.037 (0.993-1.083)	0.1020
Renal disease	1.451 (1.420-1.483)	<0.0001	1.248 (1.219-1.278)	<0.0001
Anaemia	1.062 (1.038-1.086)	<0.0001	0.928 (0.906-0.951)	<0.0001
Lung disease	0.911 (0.890-0.933)	<0.0001	0.819 (0.799-0.840)	<0.0001
Obstructive sleep apnea	1.078 (1.042-1.115)	<0.0001	1.112 (1.072-1.154)	<0.0001
Cancer within preceding 5 years	0.770 (0.751-0.790)	<0.0001	0.778 (0.758-0.798)	<0.0001
Inflammatory diseases	1.005 (0.972-1.038)	0.7853	0.900 (0.871-0.931)	<0.0001
Thyroid disease	1.403 (1.368-1.440)	<0.0001	1.265 (1.233-1.299)	<0.0001

Table 6 - Baseline characteristics of SND without AF during follow-up and SND with AF during follow-up.

Variables	*Sinus node disease (SND) n=102,849*	SND without AF during follow-up n=87,650	SND with AF during follow-up n=15,199	p Value
Age, years	*73.9±13.7*	73.04±14.10	79.03±9.50	<0.0001
Age ≥75 years old, n (%)	*59,853(58.20%)*	48,527 (55.36%)	11,326 (74.52%)	<0.0001
Gender (female), n (%)	*46,052 (44.78%)*	39,159 (44.68%)	6,893 (45.35%)	0.1223
Underlying diseases, n (%)				
Hypertension	*69,241 (67.32%)*	56,610 (64.59%)	12,631 (83.10%)	<0.0001
Diabetes mellitus	*23,674 (23.02%)*	19,361 (22.09%)	4,313 (28.38%)	<0.0001
Heart failure	*15,691 (15.26%)*	112,884 (14.65%)	2,847 (18.73%)	<0.0001
Vascular disease	*26,877 (26.13%)*	21,662 (24.71%)	5,215 (34.31%)	<0.0001
CHA_2DS_2-VASc score	*3.18±1.60*	3.07±3.06	3.82±3.80	<0.0001
HAS BLED ≥ 3	*24,097 (23.43%)*	18,071 (20.62%)	6,026 (39.65%)	<0.0001
Comorbidities				
Prior ischemic stroke	*2,483 (2.41%)*	2,066 (2.36%)	417 (2.74%)	0.0042
Coronary artery disease	*35,889 (34.89%)*	29,060 (33.15%)	6,829 (44.93%)	<0.0001
Cardiomyopathy	*9,219 (8.96%)*	6,640 (7.58%)	2,579 (16.97%)	<0.0001
Valvular disease	*15,557 (15.13%)*	11,432 (13.04%)	4,125 (27.14%)	<0.0001
Obesity	*17,883 (17.39%)*	14,558 (16.61%)	3,325 (21.88%)	<0.0001
Dyslipidaemia	*34,820 (33.86%)*	28,601 (32.63%)	6,219 (40.92%)	<0.0001
Liver disease	*4,999 (4.86%)*	4,037 (4.61%)	962 (6.33%)	<0.0001
Renal disease	*21,045 (20.46%)*	15,416 (17.59%)	5,629 (37.04%)	<0.0001
Anaemia	*18,991 (18.46%)*	14,423 (16.46%)	4,568 (30.05%)	<0.0001
Lung disease	*18,059 (17.56%)*	14,041 (16.02%)	4,018 (26.44%)	<0.0001
Obstructive sleep apnea	*7,725 (7.51%)*	6,164 (7.03%)	1,561 (10.27%)	<0.0001
Cancer within preceding 5 years	*19,685 (19.14%)*	16,155 (18.43%)	3,530 (23.23%)	<0.0001
Inflammatory diseases	*8,090 (7.87%)*	6,334 (7.23%)	1,756 (11.55%)	<0.0001
Alcohol-related diagnoses	*6,422 (6.24%)*	5,511 (6.29%)	911 (5.99%)	0.1671
Tobacco smoking	*10,284 (10.00%)*	9,025 (10.30%)	1,259 (8.28%)	<0.0001
Thyroid disease	*10,731 (10.43%)*	8,034 (9.17%)	2,697 (17.74%)	<0.0001

Table 7 - Outcomes during follow-up of SND at baseline without AF during follow-up and SND with AF during follow-up.

	SND at baseline n=102,849	SND without AF during follow-up n=87,650	SND with AF during follow-up n=15,199	p value
Mean duration of follow-up (days)	*509.1±580.5*	441.3±553.1	899.5±581.1	<0.0001
All-cause death	*12,141 (11.80%)*	9,071 (10.35%)	3,070 (20.20%)	<0.0001
Mean delay to death (days)	*496.7±521.3*	401.8±482.9	777.3±529.5	<0.0001
Heart failure	*16,602 (16.14%)*	10,074 (11.49%)	6,528 (42.95%)	<0.0001
Mean delay to heart failure (days)	*375.8±524.8*	341.2±507.6	575.4±575.6	<0.0001
Ischemic stroke	*3,939 (3.83%)*	2,694 (3.07%)	1,245 (8.19%)	<0.0001
Mean delay to ischemic stroke (days)	*382.8±506.4*	305.5±464.3	550.2±551.4	<0.0001
Major bleeding	*5,197 (5.05%)*	3,578 (4.08%)	1,619 (10.65%)	<0.0001
Intracranial bleeding	*1,927 (1.87%)*	1,448 (1.65%)	479 (3.15%)	<0.0001
Pacemaker/ICD	*50,024 (48.64%)*	39,995 (45.63%)	10,029 (65.98%)	<0.0001

Table 8 - Cox regression analysis for prediction of AF in patients with SND at baseline.
n = 102,849

	Univariate analysis		Multivariable analysis	
Covariate	**HR (95%CI)**	**P-Value**	**HR (95%CI)**	**P-Value**
CHA_2DS_2-VASc score = 0	0.285 (0.247-0.330)	<0.0001		
CHA_2DS_2-VASc score = 1	0.338 (0.310-0.364)	<0.0001		
CHA_2DS_2-VASc score ≥2	3.247 (3.013-3.500)	<0.0001		
Age ≥75 years old	2.179 (2.100-2.261)	<0.0001	2.998 (2.813-3.196)	<0.0001
Age 65-74 years old	0.777 (0.744-0.810)	<0.0001	2.001 (1.866-2.146)	<0.0001
Gender (female)	1.053 (1.019-1.087)	0.0019	0.916 (0.884-0.949)	<0.0001
Hypertension	1.802 (1.726-1.881)	<0.0001	1.266 (1.209-1.326)	<0.0001
Diabetes mellitus	1.142 (1.102-1.184)	<0.0001	0.947 (0.911-0.984)	0.0057
Heart failure	1.324 (1.270-1.380)	<0.0001	0.922 (0.881-0.966)	0.0006
Vascular disease	1.205 (1.165-1.247)	<0.0001	0.966 (0.929-1.006)	0.0933
Ischemic stroke	1.234 (1.117-1.362)	<0.0001	1.077 (0.975-1.190)	0.1446
Coronary artery disease	1.244 (1.204-1.285)	<0.0001	1.036 (0.996-1.077)	0.0753
Cardiomyopathy	1.711 (1.639-1.786)	<0.0001	1.402 (1.339-1.468)	<0.0001
Valvular disease	1.814 (1.749-1.881)	<0.0001	1.481 (1.425-1.539)	<0.0001
Obesity	1.108 (1.065-1.152)	<0.0001	1.081 (1.035-1.129)	0.0004
Dyslipidaemia	1.079 (1.044-1.115)	<0.0001	0.916 (0.883-0.949)	<0.0001
Alcohol-related diagnoses	0.847 (0.791-0.906)	<0.0001	0.972 (0.903-1.047)	0.4551
Tobacco smoking	0.753 (0.710-0.798)	<0.0001	0.958 (0.899-1.021)	0.1874
Liver disease	1.141 (1.068-1.220)	<0.0001	1.127 (1.051-1.209)	0.0008
Renal disease	1.866 (1.804-1.929)	<0.0001	1.366 (1.316-1.418)	<0.0001
Anaemia	1.486 (1.435-1.540)	<0.0001	1.152 (1.109-1.197)	<0.0001
Lung disease	1.357 (1.308-1.408)	<0.0001	1.171 (1.127-1.218)	<0.0001
Obstructive sleep apnea	1.093 (1.036-1.152)	0.0011	1.073 (1.014-1.135)	0.0150
Cancer within preceding 5 years	1.009 (0.971-1.048)	0.6453	0.908 (0.873-0.944)	<0.0001
Inflammatory diseases	1.196 (1.137-1.258)	<0.0001	0.990 (0.940-1.042)	0.6936
Thyroid disease	1.563 (1.498-1.631)	<0.0001	1.368 (1.309-1.429)	<0.0001

Table 9 – Cox regression analysis for prediction of ischemic stroke in patients with SND at baseline.
n = 102,849

	Univariate analysis		Multivariable analysis	
Covariate	**HR (95%CI)**	**P-Value**	**HR (95%CI)**	**P-Value**
CHA_2DS_2-VASc score = 0	0.413 (0.329-0.519)	<0.0001		
CHA_2DS_2-VASc score = 1	0.468 (0.405-0.540)	<0.0001		
CHA_2DS_2-VASc score ≥2	2.307 (2.040-2.610)	<0.0001		
Age ≥75 years old	1.608 (1.503-1.721)	<0.0001	1.729 (1.559-1.918)	<0.0001
Age 65-74 years old	0.816 (0.752-0.885)	<0.0001	1.253 (1.114-1.409)	0.0002
Gender (female)	1.016 (0.954-1.081)	0.6306	0.983 (0.918-1.051)	0.6103
Hypertension	1.875 (1.726-2.035)	<0.0001	1.528 (1.397-1.672)	<0.0001
Diabetes mellitus	1.269 (1.185-1.359)	<0.0001	1.125 (1.045-1.211)	0.0017
Heart failure	1.094 (1.005-1.191)	0.0380	0.920 (0.838-1.010)	0.0796
Vascular disease	1.630 (1.529-1.737)	<0.0001	1.662 (1.539-1.795)	<0.0001
Coronary artery disease	1.031 (0.967-1.099)	0.3510	0.693 (0.642-0.749)	<0.0001
Cardiomyopathy	1.030 (0.931-1.138)	0.5703	0.937 (0.843-1.042)	0.2289
Valvular disease	1.258 (1.165-1.359)	<0.0001	1.134 (1.046-1.229)	0.0023
Obesity	0.971 (0.896-1.051)	0.4653	0.908 (0.833-0.991)	0.0296
Dyslipidaemia	1.353 (1.271-1.441)	<0.0001	1.178 (1.099-1.262)	<0.0001
Alcohol-related diagnoses	1.198 (1.067-1.345)	0.0022	1.327 (1.168-1.507)	<0.0001
Tobacco smoking	1.140 (1.034-1.257)	0.0086	1.198 (1.075-1.336)	0.0011
Liver disease	0.855 (0.737-0.992)	0.0384	0.789 (0.675-0.922)	0.0029
Renal disease	1.344 (1.255-1.440)	<0.0001	1.095 (1.014-1.181)	0.0199
Anaemia	1.066 (0.989-1.149)	0.0935	0.915 (0.845-0.992)	0.0308
Lung disease	1.316 (1.224-1.414)	<0.0001	1.230 (1.139-1.327)	<0.0001
Obstructive sleep apnea	0.801 (0.711-0.903)	0.0003	0.765 (0.674-0.867)	<0.0001
Cancer within preceding 5 years	0.788 (0.726-0.855)	<0.0001	0.730 (0.672-0.793)	<0.0001
Inflammatory diseases	1.076 (0.970-1.195)	0.1665	0.979 (0.881-1.089)	0.6973
Thyroid disease	1.045 (0.951-1.149)	0.3583	0.959 (0.871-1.057)	0.3998

Table 10 - Baseline characteristics of BTS during follow-up via SND and BTS during follow-up via AF.

Variables	*Bradycardia-tachycardia syndrome (BTS) at baseline n=28,128*	BTS via SND during follow-up n=15,199	BTS via AF during follow-up n=36,409	BTS via AF vs. BTS via SND p Value
Age, years	*78.3±10.1*	79.03±9.50	77.84±9.59	<0.0001
Age ≥75 years old, n (%)	*19,962 (70.97%)*	11,326 (74.52%)	25,354 (69.64%)	<0.0001
Gender (female), n (%)	*13,820 (49.13%)*	6,893 (45.35%)	18,013 (49.47%)	<0.0001
Underlying diseases, n (%)				
Hypertension	*20,778 (73.87%)*	12,631 (83.10%)	30,474 (83.70%)	0.0968
Diabetes mellitus	*6,096 (21.67%)*	4,313 (28.38%)	9,975 (27.40%)	0.0234
Heart failure	*3,879 (13.79%)*	2,847 (18.73%)	5,390 (14.80%)	<0.0001
Vascular disease	*6,795 (24.16%)*	5,215 (34.31%)	11,629 (31.94%)	<0.0001
CHA_2DS_2-VASc score	*3.42±1.36*	3.82±1.36	3.72±1.37	<0.0001
HAS BLED ≥ 3	*7,772 (27.63%)*	6,026 (39.65%)	14,114 (38.77%)	0.0611
Comorbidities				
Prior ischemic stroke	*607 (2.16%)*	417 (2.74%)	751 (2.06%)	<0.0001
Coronary artery disease	*14,520 (35.53%)*	6,829 (44.93%)	15,950 (43.81%)	0.0192
Cardiomyopathy	*3,489 (12.40%)*	2,579 (16.97%)	7,211 (19.81%)	<0.0001
Valvular disease	*6,726 (23.91%)*	4,125 (27.14%)	11,687 (32.10%)	<0.0001
Obesity	*4,863 (17.29%)*	3,325 (21.88%)	8,599 (23.62%)	<0.0001
Dyslipidaemia	*9,166 (32.59%)*	6,219 (40.92%)	15,065 (41.38%)	0.3333
Liver disease	*1,312 (4.66%)*	962 (6.33%)	2,449 (6.73%)	0.0980
Renal disease	*7,267 (25.84%)*	5,629 (37.04%)	13,294 (36.51%)	0.2616
Anaemia	*5,709 (20.30%)*	4,568 (30.05%)	10,680 (29.33%)	0.1017
Lung disease	*5,029 (17.88%)*	4,018 (26.44%)	9,340 (25.65%)	0.0642
Obstructive sleep apnea	*1,995 (7.09%)*	1,561 (10.27%)	3,775 (10.37%)	0.7392
Cancer within preceding 5 years	*5,152 (18.32%)*	3,530 (23.23%)	7,594 (20.86%)	<0.0001
Inflammatory diseases	*2,242 (7.97%)*	1,756 (11.55%)	4,083 (11.21%)	0.2676
Alcohol-related diagnoses	*1,204 (4.28%)*	911 (5.99%)	2,333 (6.41%)	0.0774
Tobacco smoking	*1,782 (6.34%)*	1,259 (8.28%)	3,128 (8.59%)	0.2530
Thyroid disease	*4,175 (14.84%)*	2,697 (17.74%)	7,675 (21.08%)	<0.0001

Table 11 - Outcomes during follow-up for BTS via SND and BTS via AF.

	BTS at presentation n=28,128	BTS via SND during follow-up n=15,199	BTS via AF during follow-up n=36,409	p value
Mean duration of follow-up (days)	*530.7±579.0*	899.5±581.1	898.3±585.3	0.8282
All-cause death	*4,183 (14.87%)*	3,070 (20.20%)	6,103(16.76%)	<0.0001
Mean delay to death (days)	*525.2±524.4*	777.3±529.5	831.1±538.8	<0.0001
Heart failure	*5,500 (19.55%)*	6,528 (42.95%)	13,137 (36.08%)	<0.0001
Mean delay to heart failure (days)	*332.6±500.8*	575.4±575.6	470.8±563.6	<0.0001
Ischemic stroke	*1,616 (5.75%)*	1,245 (8.19%)	3,332 (9.15%)	0.0005
Mean delay to ischemic stroke (days)	*343.1±504.5*	550.2±551.4	378.5±361.2	<0.0001
Major bleeding	*2,076 (7.38%)*	1,619 (10.65%)	4,121 (11.32%)	0.0281
Intracranial bleeding	*683 (2.43%)*	479 (3.15%)	1,305 (3.58%)	0.0142
Pacemaker/ICD	*18,016 (64.05%)*	10,029 (65.98%)	23,943 (65.76%)	0.6257

Table 12 - Baseline characteristics of "cardiologic" population.

Variables	"Cardiologic" population n=950,782
Age, years	69.6±15.2
Age ≥75 years old, n (%)	421,494 (44.33%)
Gender (female), n (%)	410,598 (43.19%)
Underlying diseases, n (%)	
Hypertension	647,878 (68.14%)
Diabetes mellitus	246,801 (25.96%)
Heart failure	459,025 (48.28%)
Vascular disease	358,900 (37.75%)
Prior ischemic stroke	15,153 (1.59%%)
CHA_2DS_2-VASc score, n (%)	2.99±1.65
HAS BLED ≥ 3, n (%)	230,672 (24.26%)
Principal diagnosis of inclusion	
Heart failure, n (%)	135,650 (14.26%)
Coronary artery disease, n (%)	132,028 (13.89%)
Atrial fibrillation, n (%)	77,248 (8.13%)
Stroke, n (%)	54,095 (5.69%)
Peripheral arterial disease, n (%)	51,540 (5.43%)
Varicose, n (%)	42,489 (4.47%)
Hypertension, n (%)	26,629 (2.59%)
Pulmonary embolism, n (%)	23,820 (2.51%)
Hemorroids, n (%)	13,124 (1.38%)
Aortic stenosis, n (%)	12,410 (1.31%)
Complete AV block, n (%)	12,092 (1.27%)
Supraventricular tachycardia, n(%)	10,874 (1.14%)
SND, n (%)	9,956 (1.05%)

Table 13 - Cox regression analysis for prediction of AF in the "cardiologic" population. n = 950,782

	Univariate analysis		Multivariable analysis	
Covariate	**HR (95%CI)**	**P-Value**	**HR (95%CI)**	**P-Value**
CHA_2DS_2-VASc score = 0	0.409 (0.399-0.419)	<0.0001		
CHA_2DS_2-VASc score = 1	0.344 (0.339-0.350)	<0.0001		
CHA_2DS_2-VASc score ≥ 2	2.956 (2.916-2.997)	<0.0001		
Age ≥75 years old	2.815 (2.793-2.838)	<0.0001	2.630 (2.599-2.662)	<0.0001
Age 65-74 years old	0.905 (0.896-0.913)	<0.0001	1.813 (1.790-1.837)	<0.0001
Gender (female)	1.074 (1.066-1.083)	<0.0001	0.842 (0.835-0.849)	<0.0001
Hypertension	1.937 (1.918-1.957)	<0.0001	1.171 (1.158-1.184)	<0.0001
Diabetes mellitus	1.175 (1.165-1.185)	<0.0001	0.943 (0.935-0.951)	<0.0001
Heart failure	3.506 (3.475-3.537)	<0.0001	2.234 (2.211-2.257)	<0.0001
Vascular disease	1.027 (1.019-1.035)	<0.0001	0.849 (0.841-0.856)	<0.0001
Prior ischemic stroke	1.534 (1.494-1.576)	<0.0001	1.265 (1.232-1.300)	<0.0001
SND	2.203 (2.176-2.230)	<0.0001	1.296 (1.279-1.314)	<0.0001
PM/ICD	2.156 (2.136-1.176)	<0.0001	1.172 (1.160-1.184)	<0.0001
Coronary artery disease	1.161 (1.152-1.169)	<0.0001	0.820 (0.813-0.827)	<0.0001
Cardiomyopathy	2.327 (2.306-2.349)	<0.0001	1.230 (1.218-1.242)	<0.0001
Valvular disease	2.646 (2.625-2.668)	<0.0001	1.571 (1.558-1.585)	<0.0001
Obesity	1.120 (1.110-1.130)	<0.0001	1.085 (1.075-1.096)	<0.0001
Dyslipidaemia	0.959 (0.952-0.967)	<0.0001	0.862 (0.855-0.869)	<0.0001
Alcohol-related diagnoses	0.867 (0.855-0.880)	<0.0001	1.069 (1.053-1.085)	<0.0001
Tobacco smoking	0.608 (0.601-0.616)	<0.0001	0.846 (0.835-0.857)	<0.0001
Liver disease	1.188 (1.171-1.204)	<0.0001	1.088 (1.072-1.105)	<0.0001
Renal disease	2.268 (2.250-2.286)	<0.0001	1.251 (1.240-1.262)	<0.0001
Anaemia	1.648 (1.635-1.662)	<0.0001	1.105 (1.095-1.114)	<0.0001
Lung disease	1.622 (1.609-1.635)	<0.0001	1.150 (1.140-1.160)	<0.0001
Obstructive sleep apnea	1.221 (1.206-1.236)	<0.0001	1.099 (1.085-1.114)	<0.0001
Cancer within preceding 5 years	1.095 (1.085-1.105)	<0.0001	0.949 (0.940-0.957)	<0.0001
Inflammatory diseases	1.349 (1.333-1.364)	<0.0001	1.004 (0.992-1.016)	0.5151
Thyroid disease	2.003 (1.984-2.023)	<0.0001	1.460 (1.446-1.475)	<0.0001

Table 14 - SEARCH-AF score to predict AF in the "cardiologic" population. n = 950,782

SEARCH-AF risk factors	**Points**
- Age ≥75 years - Congestive heart failure	+2
- Age 65–74 years - Hypertension - Prior stroke - SND - PM or ICD - Cardiomyopathy - Valvular disease - Renal disease - Thyroid disease	+1

Table 15 – SEARCH-AF score validation summary. n = 950,782

SEARCH-AF score	No. (%) of patients with AF by SEARCH-AF score	Annual incidence of AF (%)	Univariable odds (95% CI) (vs. a score of 0)	p value
0	6,725 (5.23%)	1.66%	1.0 (reference)	1.0 (reference)
1	16,533 (10.27%)	2.95%	1.74 (1.70-1.79)	<0.0001
2	30,925 (18.38%)	5.40%	3.34 (3.26-3.43)	<0.0001
3	52,582 (28.42%)	8.75%	5.55 (5.41-5.70)	<0.0001
4	52,524 (41.86%)	12.87%	8.36 (8.15-8.58)	<0.0001
5	40,130 (51.96%)	16.11%	11.32 (11.03-11.62)	<0.0001
6	28,975 (56.51%)	18.51%	14.19 (13.81-14.57)	<0.0001
≥7	35,493 (65.76%)	22.55%	18.47 (17.99-18.96)	<0.0001

Table 16 – Yearly incidence of ischemic stroke in the different study populations.

	Incidence of IS (%/year) in AF population (n =1,601,435)			Incidence of IS (%/year) in SND population (n=102,849)			Incidence of IS (%/year) in "control" population (n=479,108)		
CHA_2DS_2-VASc	Overall	Women	Men	Overall	Women	Men	Overall	Women	Men
All scores	5.48%	6.72%	4.37%	1.95%	1.93%	1.96%	0.67%	0.67%	0.68%
Score = 0	1.960%	-	1.960%	1.211%	-	1.211%	0.217%	-	0.217%
Score = 1	2.875%	2.337%	3.046%	1.117%	0.538%	1.486%	0.274%	0.166%	0.345%
Score = 2	4.373%	3.917%	4 .499%	1.365%	0.879%	1.541%	0.478%	0.298%	0.580%
Score = 3	5.677%	7.572%	4.733%	1.795%	2.207%	2.084%	0.756%	0.541%	0.907%
Score = 4	6.183%	7.016%	4.820%	2.314%	2.363%	2.305%	1.075%	0.930%	1.278%
Score = 5	6.307%	6.725%	5.345%	2.533%	2.845%	2.849%	1.340%	1.249%	1.553%
Score = 6	7.614%	7.637%	7.543%	3.548%	3.319%	4.109%	1.790%	1.737%	2.031%
Score = 7	10.807%	10.196%	13.927%	6.356%	4.663%	7.708%	2.611%	2.346%	4.089%
Score = 8	16.416%	17.654%	12.607%	9.371%	8.519%	11.904%	2.413%	2.446%	2.355%
Score = 9	17.605%	17.605%	-	5.721%	5.721%	-	3.198%	3.198%	-

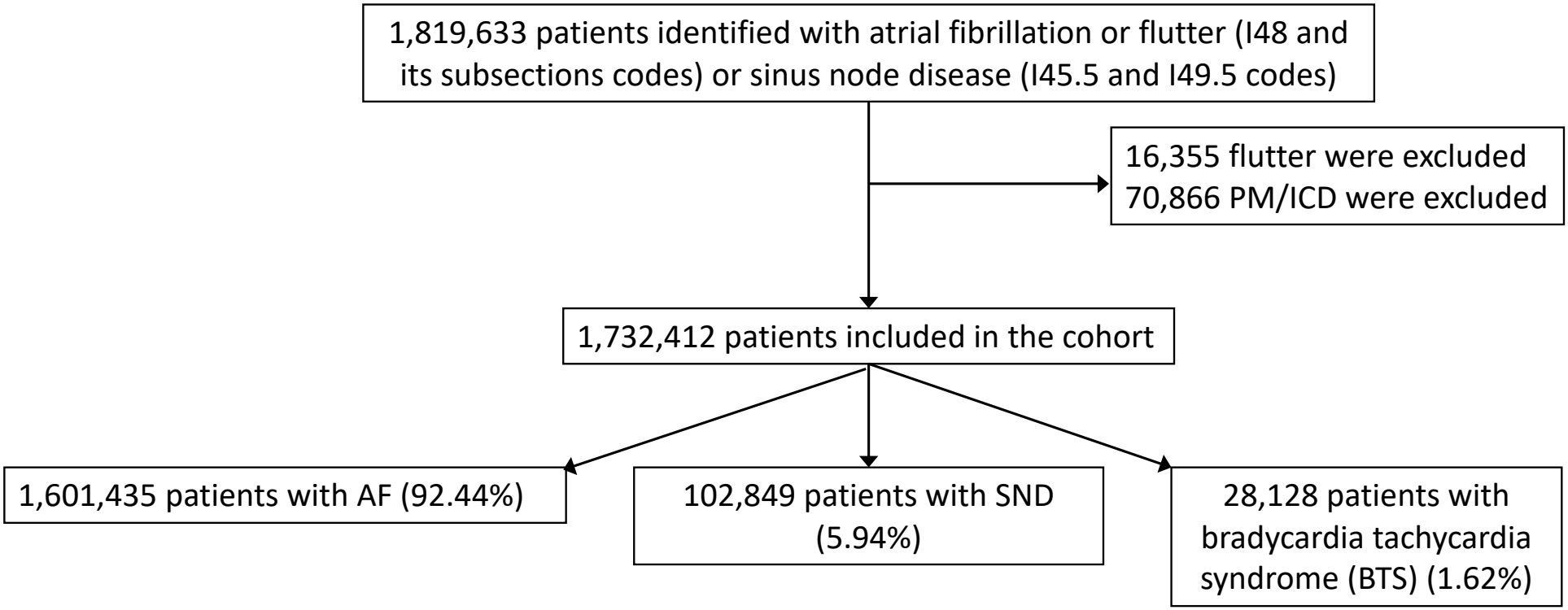
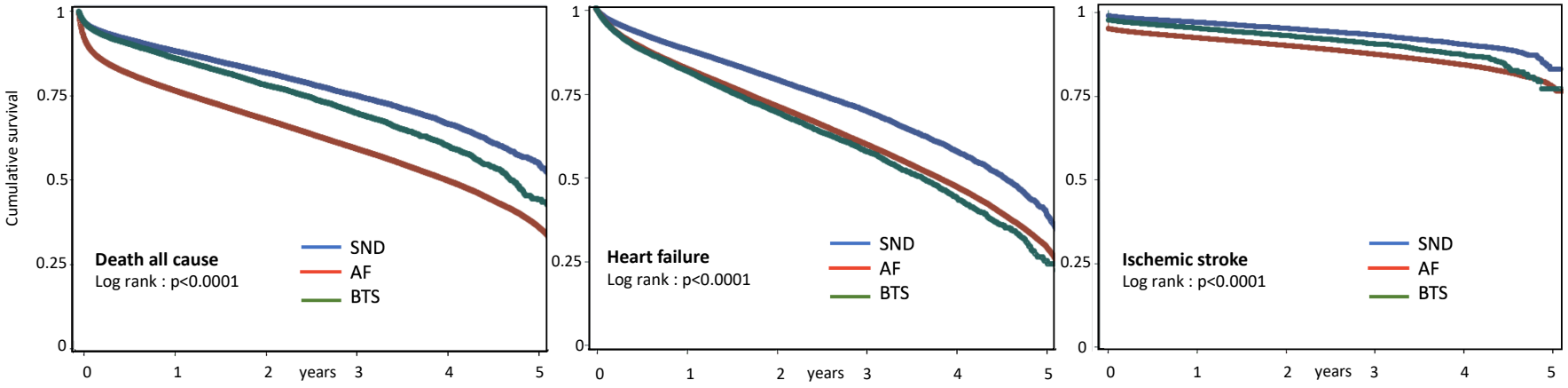
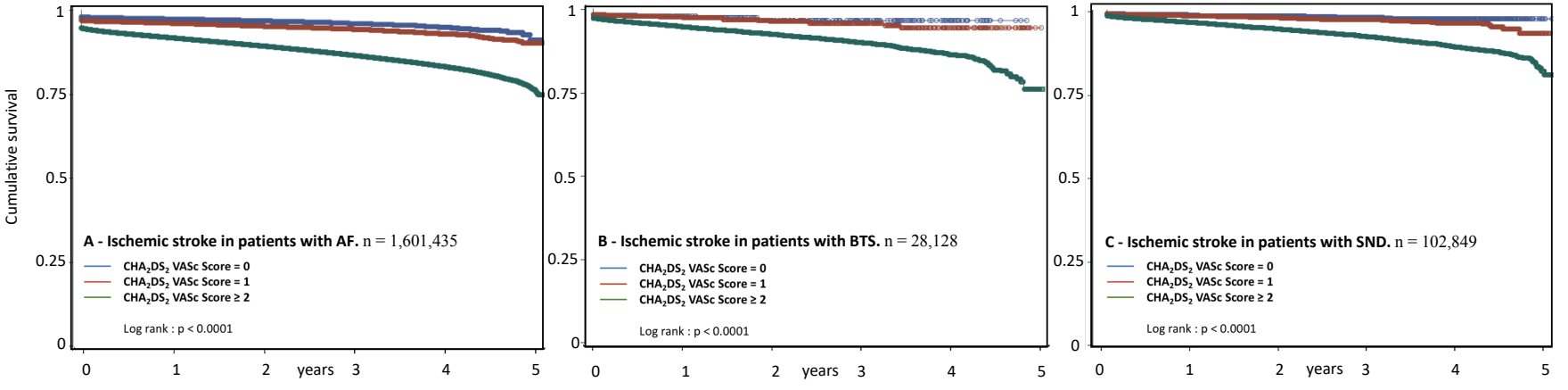


Figure 1 - Flow chart of the study patients.



	No. of patients at risk																	
SND	102,849	46,567	31,413	19,620	10,064	3,207	102,849	35,264	22,673	13,422	6,303	1,877	102,849	45,574	30,507	19,004	9,499	3,939
AF	1,601,435	671,422	439,465	261,923	129,363	39,858	1,601,435	431,873	267,821	150,662	69,694	18,950	1,601,435	632,108	411,744	242,919	119,813	116,623
BTS	28,128	13,359	8,977	5,485	2,714	848	28,128	8,638	5,450	3,148	1,484	405	28,128	12,852	8,593	5,236	2,644	821

Figure 2 - Kaplan-Meier of event free curves for all-cause death, ischemic stroke and heart failure in patients with AF, SND or BTS at baseline. n = 1,732,412



	No. of patients at risk																	
CV = 0	68,112	22,437	14,841	8,957	4,316	1,353	637	235	154	102	56	13	5,603	1,780	1,198	753	365	109
CV = 1	127,096	48,128	32,283	19,957	9,984	3,079	1,671	662	447	279	143	49	11,321	4,190	2,762	1,834	944	269
CV ≥ 2	1,406,227	564,360	365,628	215,566	103,367	32,150	25,820	12,007	7,990	4,855	2,450	762	85,925	39,533	26,402	16,390	8,341	2,625

Figure 3 – Kaplan-Meier event free curves for ischemic stroke in patients with AF, BTS or SND at baseline.

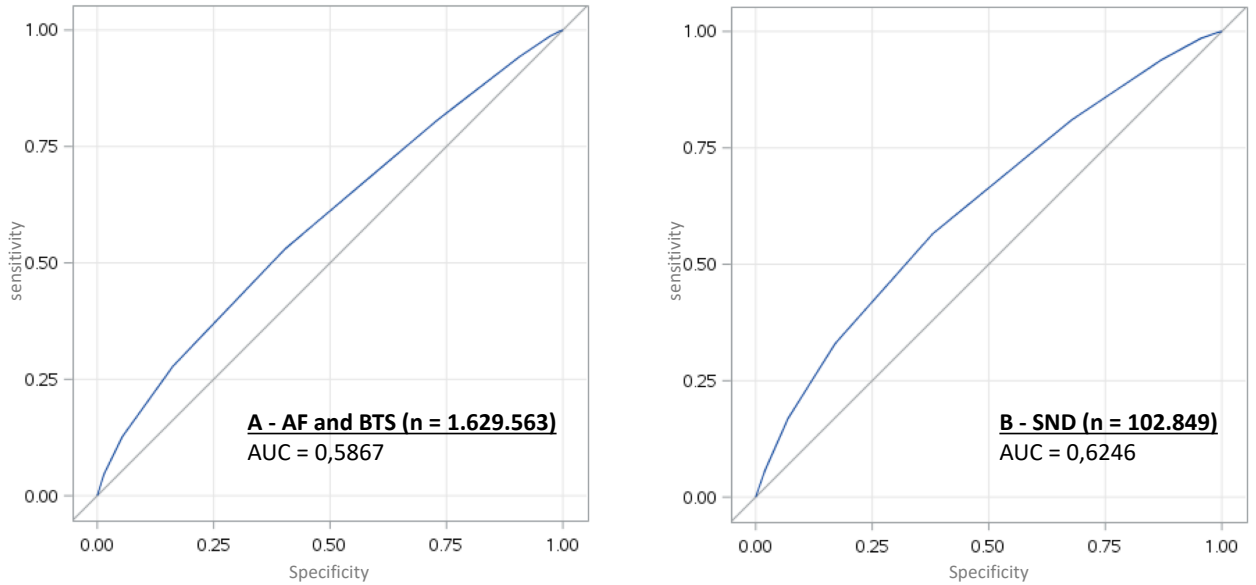
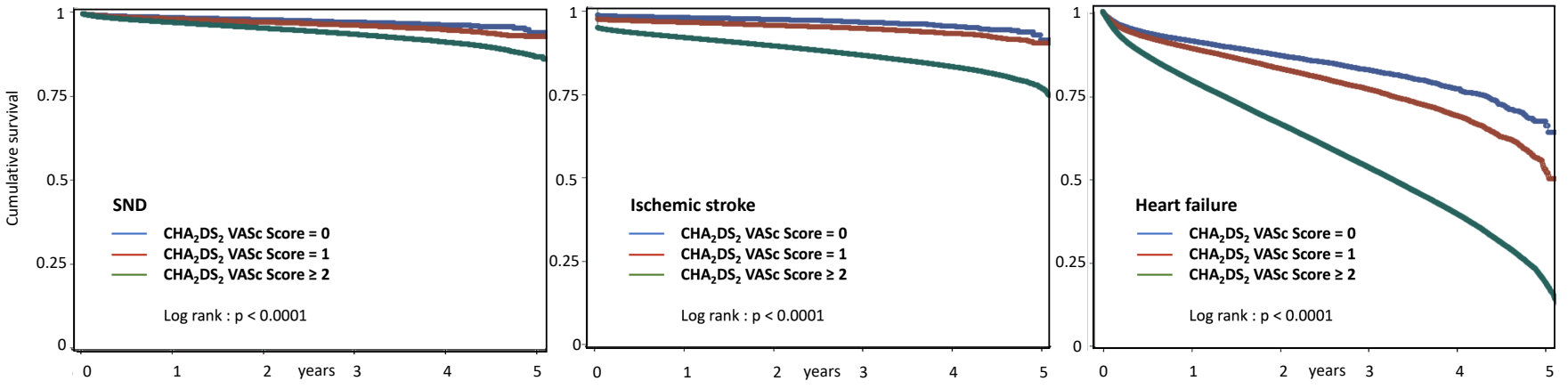


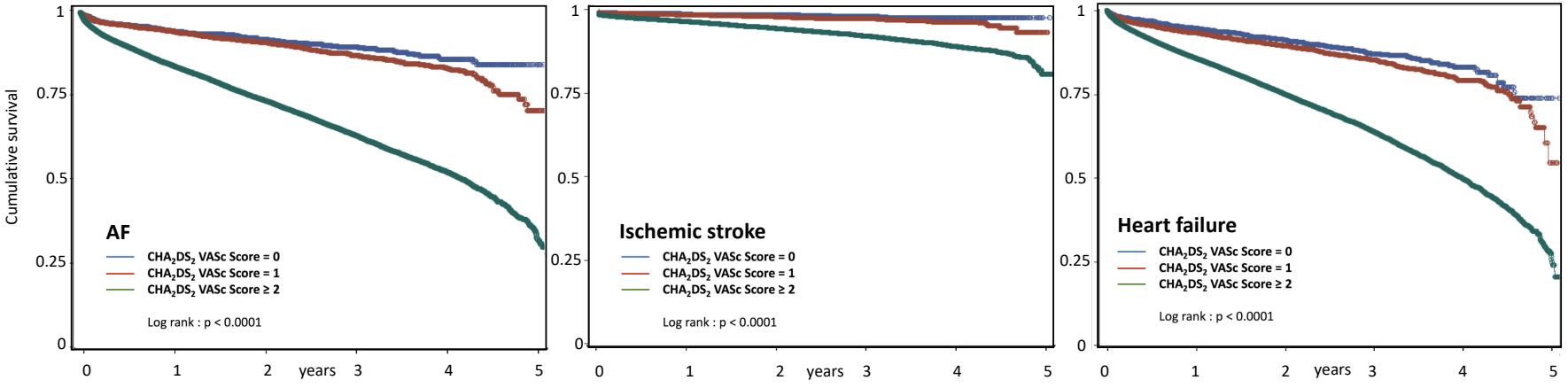
Figure 4 - ROC Curves of CHA_2DS_2-VASc score in prediction of ischemic stroke and AF and BTS patients (A) and SND patients (B). CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke/transient ischemic attack (doubled), vascular disease, age 65–74 years, and sex category (female); AUC, area under curve.



No. of patients at risk

CV = 0	68,112	22,437	14,841	8,957	4,316	1,353	68,112	22,437	14,841	8,957	4,316	1,353	68,112	22,437	14,841	8,957	4,316	1,353
CV = 1	127,096	48,128	32,283	19,957	9,984	3,079	127,096	48,128	32,283	19,957	9,984	3,079	127,096	48,128	32,283	19,957	9,984	3,079
CV ≥ 2	1,406,227	564,360	365,628	215,566	103,367	32,150	1,406,227	564,360	365,628	215,566	103,367	32,150	1,406,227	564,360	365,628	215,566	103,367	32,150

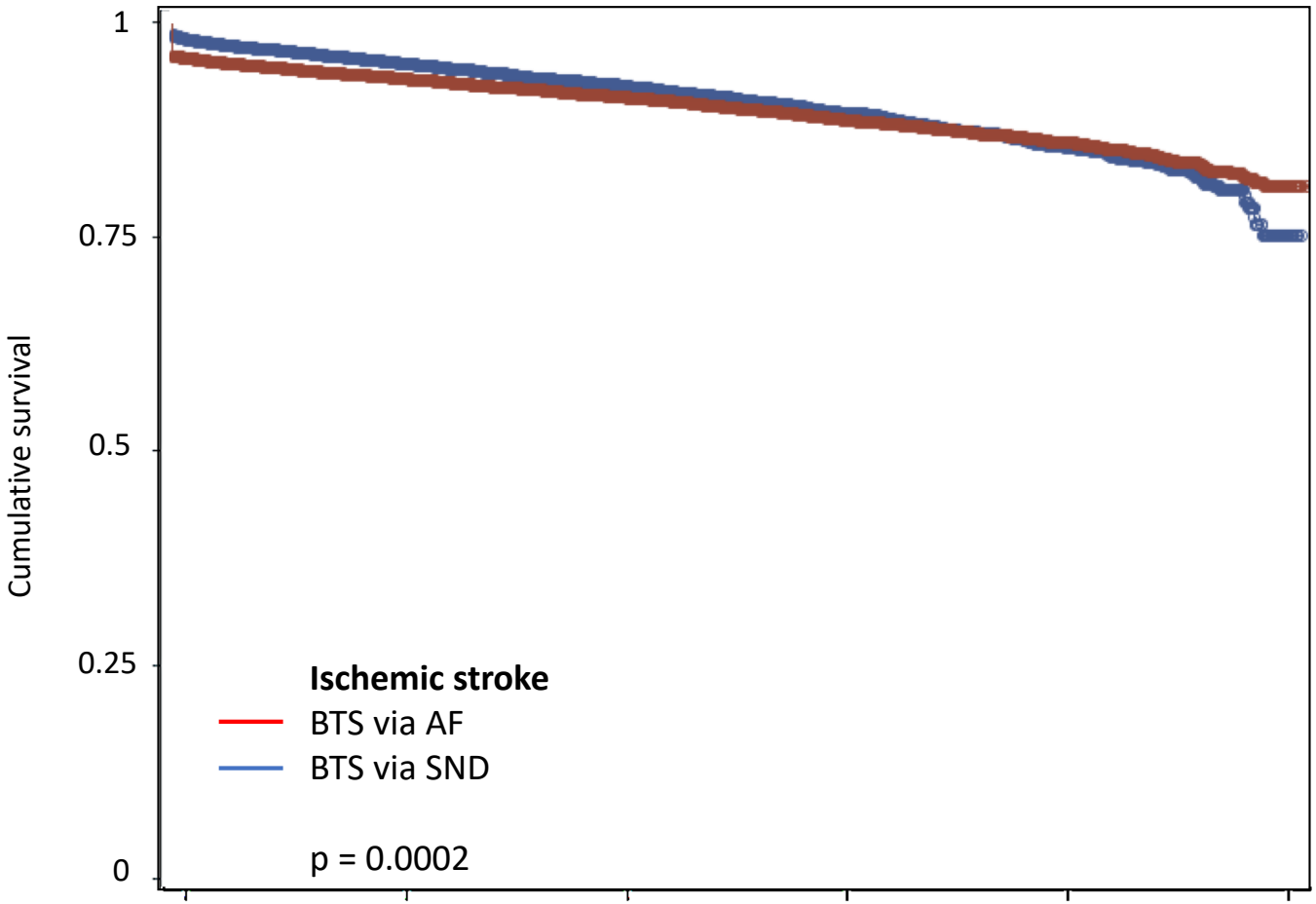
Figure 5 - Kaplan-Meier of event free curves for SND, ischemic stroke and heart failure according to nominal CHA_2DS_2-VASc score in patients with AF at baseline.
n = 1,601,435



No. of patients at risk

CV = 0	5,603	1,780	1,198	753	365	109	5,603	1,780	1,198	753	365	109	5,603	1,780	1,198	753	365	109
CV = 1	11,321	4,190	2,762	1,834	944	269	11,321	4,190	2,762	1,834	944	269	11,321	4,190	2,762	1,834	944	269
CV ≥ 2	85,925	39,533	26,402	16,390	8,341	2,625	85,925	39,533	26,402	16,390	8,341	2,625	85,925	39,533	26,402	16,390	8,341	2,625

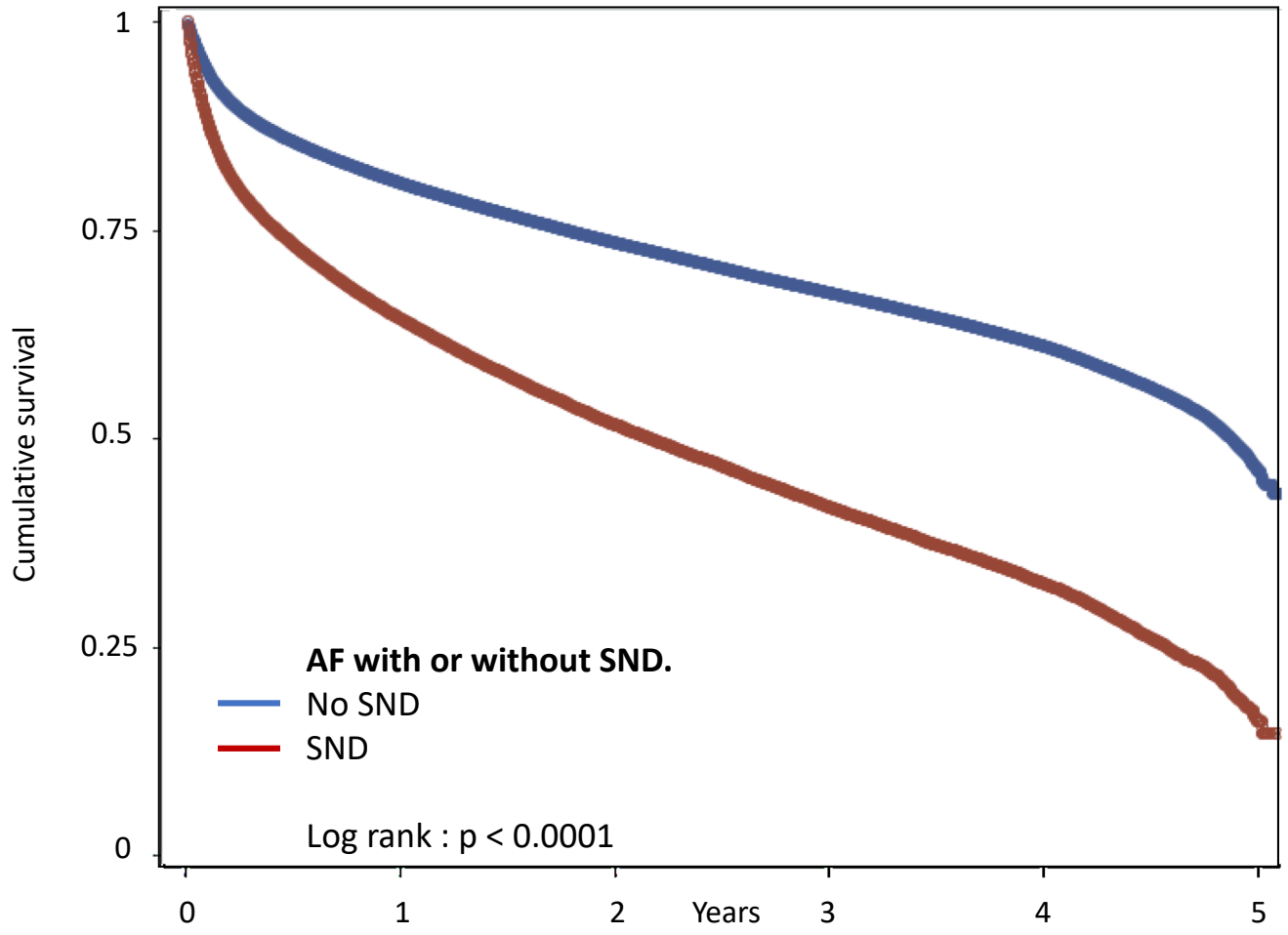
Figure 6 - Kaplan-Meier event free curves forAF, ischemic stroke and heart failure according to CHA_2DS_2-VASc score in patients with SND at presentation.
n=102,849



No. of patients at risk

BTS via AF	36,409	26,247	19,384	12,789	6,921	2,381
BTS via SND	15,199	11,258	8,297	5,525	2,950	973

Figure 7 - Kaplan-Meier event free curves for ischemic stroke in patients with BTS via initial AF or BTS via initial SND. n=51,608



No. Of patients at risk

No SND	900,652	516,556	418,663	328,959	323,160	105,999
SND	50,130	28,119	21,129	15,662	10,511	4,595

Figure 8 - Kaplan-Meier of event free curves for atrial fibrillation in patients with or without SND in the "cardiologic population". n = 950,782

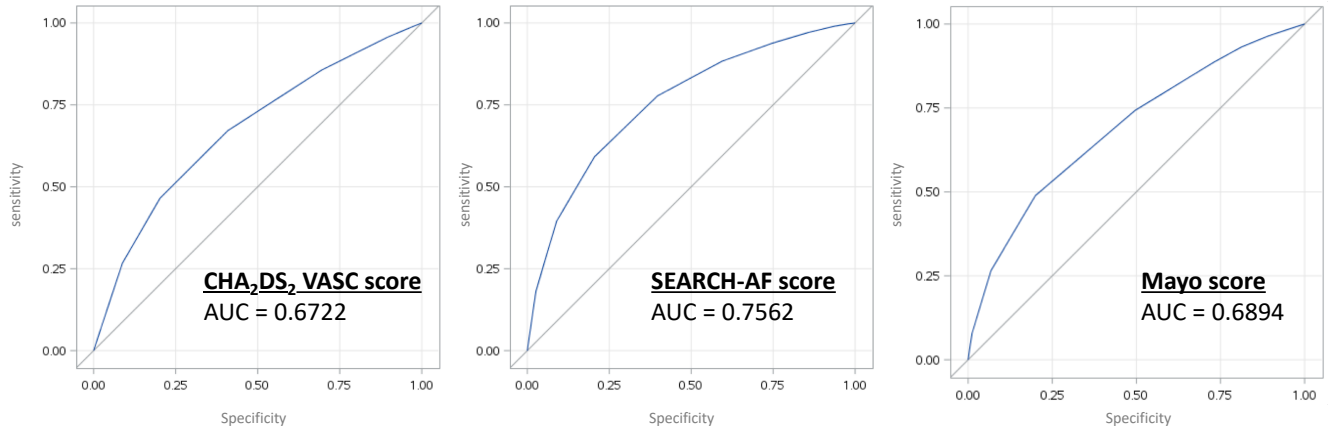
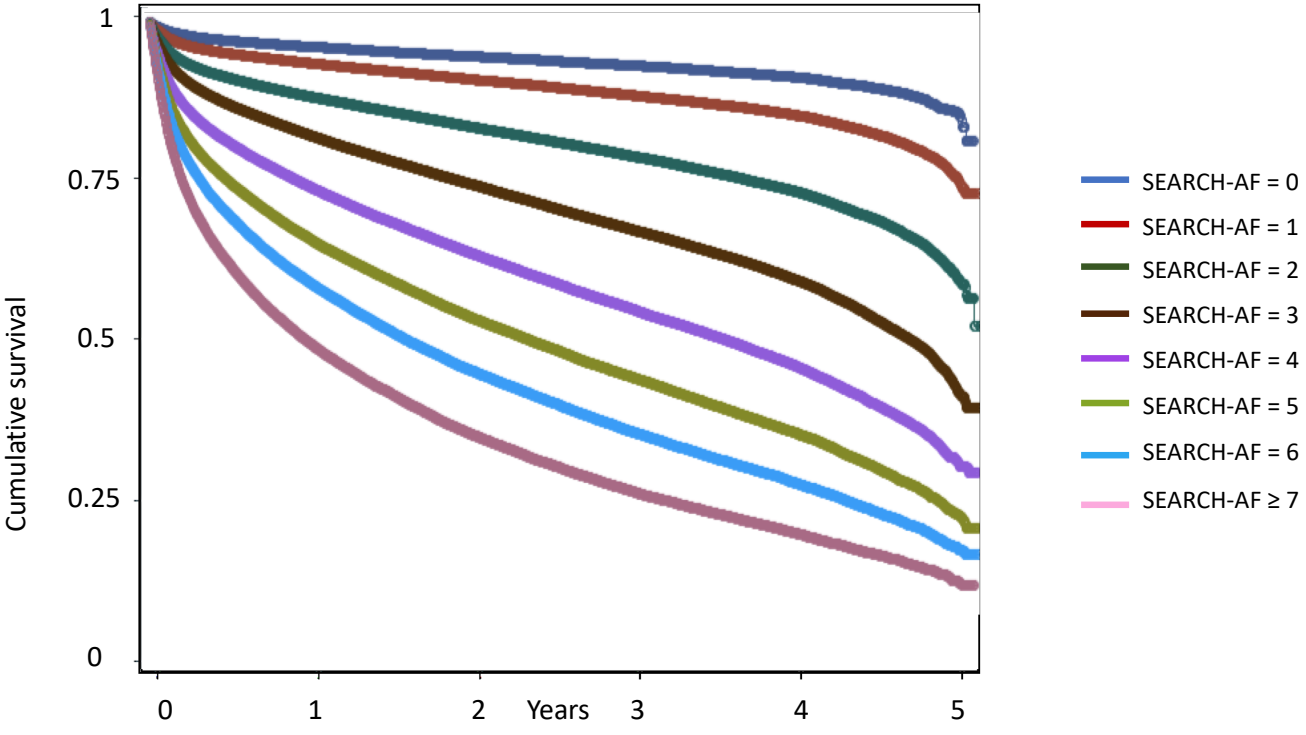


Figure 9 - ROC Curves of CHA_2DS_2-VASc, SEARCH-AF and Mayo scores in prediction of AF in "cardiologic" population. n = 950,782

Mayo scor includes heart failur (tripled), valvular disease (doubled), coronary artery disease (doubled), age >75y.o (doubled), age 65-75y.o, Hypertension, diabetes mellitus and sex (male).

AUC, area under curve.



No. Of patients at risk						*Risk score*
128,267	75,362	64,004	52,137	37,014	17,510	0
160,990	105,204	90,819	74,898	59,949	23,659	1
168,295	101,654	85,692	69,695	50,194	23,465	2
185,039	107,169	85,988	66,379	46,105	20,673	3
125,484	71,568	54,993	41,123	27,921	12,351	4
77,247	39,992	29,392	21,274	13,931	6,422	5
51,278	22,271	15,441	10,587	6,762	3,049	6
53,982	20,922	12,847	8,333	5,009	2,207	≥ 7

Figure 10 - Kaplan-Meier event free curves for AF in patients according to SEARCH-AF score in the "cardiologic" population. n = 950,782

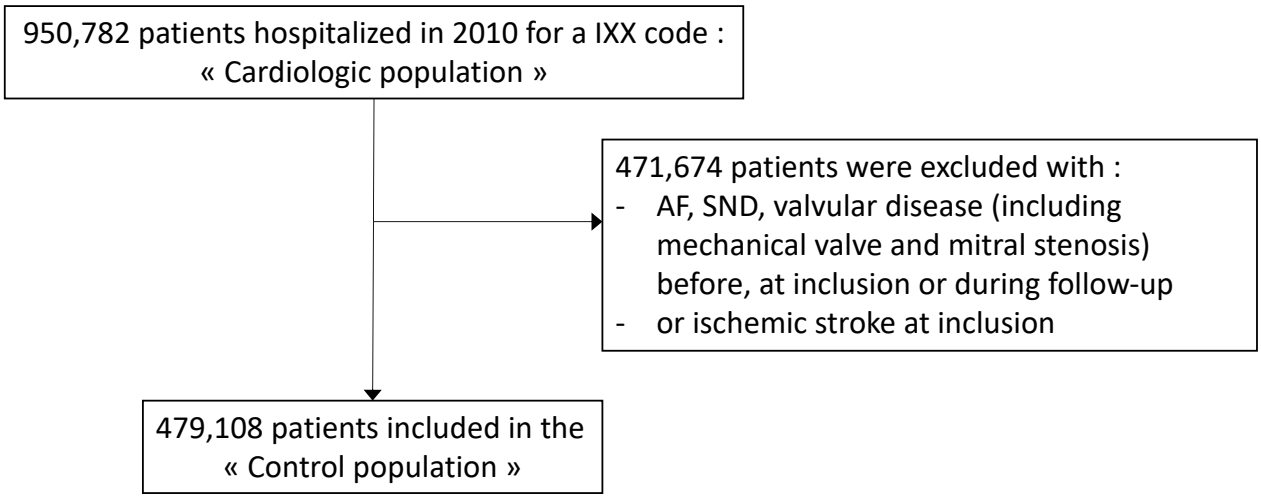


Figure 11 - Flow chart of the "cardiologic" and "control" population.

Supplemental table 1 – International Classification of Disease 10 (ICD-10) codes and classification commune des actes médicaux (CCAM) codes

AF	I48.0, I48.1, I48.2
SND	I45.5, I49.5
BTS	AF codes and SND codes
Flutter	I48.3, I48.4
Hypertension	I10–I15
Diabetes mellitus	E10–E14
Heart failure	I50, I11.0, I13.0, I13.2, I25.5, I42, I43, R06.0
Vascular disease	I21, I25.2, I65, I70, I71, I72, I73
Ischemic stroke	I63
Coronary artery disease	I20, I21, I22, I23, I24, I25
Cardiomyopathy	I42, I43, O99.4
Valvular disease	I05, I06, I07, I08, I34, I35, I36, I37, Q22, Q23
Obesity (BMI > 30)	E65, E66
Dyslipidaemia	E78
Liver disease	K70-K77
Renal disease	N17, N18, N19, T86.1, Z49, Z94, Z99.2
Anaemia	D50-D64
Lung disease	J40-J70, J96.1
Obstructive sleep apnea	G47.3
Cancer within preceding 5 years	Entire C-series
Inflammatory diseases	M05-M14, M45, M46, K50, K51, K52
Alcohol-related diagnoses	E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, P04.3, Q86.0, T51, Y90, Y91, Z50.2, Z71.4, Z72.1
Tobacco smoking	Z72.0, F17.2
Thyroid disease	E00, E01, E02, E03, E05, E89.0
Major bleeding	I85.0, I98.3, K25, K26, K27, K28, K62.5, K92.2, D62
Intracranial bleeding	I60, I61, I62, S06.4, S06.5, S06.6

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Vu, le Directeur de Thèse

Vu, le Doyen
De la Faculté de Médecine de Tours
Tours, le

RESUME

Introduction : Fibrillation atriale (FA) et dysfonction sinusale (DS) sont souvent associées dans le cadre de la maladie rythmique atriale (MRA). MRA et FA ont un risque embolique assez bien estimé par le score de CHA_2DS_2-VASc mais ce risque est incertain concernant la DS. Notre objectif était de décrire l'épidémiologie et l'histoire naturelle de ces entités ainsi que leurs complications.

Méthodes : Cette étude de cohorte longitudinale française a été réalisée à partir d'une base de données nationale couvrant les soins hospitaliers de 2010 à 2015, pour l'ensemble de la population.

Résultats : 1 732 412 patients ont été inclus dans la cohorte : 1 601 435 avec FA, 102 849 avec DS et 28 128 avec MRA. Les patients avec DS à l'inclusion évoluaient plus vers la MRA que les patients avec FA : 14,35% vs. 2,24% ($p<0,0001$). Le risque de mortalité totale était plus élevé dans le groupe FA que dans le groupe DS ou MRA (respectivement, 16,66%/an, 8,47%/an et 10,23%/an).

L'évolution vers la MRA était à risque plus élevé d'insuffisance cardiaque que la FA ou la DS isolée (respectivement 14,67%/an vs. 12,92%/an et 17,44%/an vs. 9,50%/an).

L'incidence d'accident ischémique cérébral (AIC) était plus élevée dans la FA que dans la MRA et la DS (respectivement 7,27/an, 3,95%/an et 2,75%/an). Ce risque reste élevé même dans la DS isolée sans FA durant le suivi (2,54%/an). L'aire sous la courbe ROC pour la prédiction de l'AIC dans la DS avec le score CHA_2DS_2-VASc était de 0,6246, alors qu'elle était de 0,5867 dans la FA.

Conclusion : La DS évolue plus vers la MRA que la FA. L'évolution vers la MRA est à risque d'insuffisance cardiaque. Un score de CHA_2DS_2-VASc ≥ 2 est associé à une augmentation du risque d'évolution de la DS vers la MRA. Il est aussi associé à une augmentation du risque d'AIC et d'insuffisance cardiaque aussi bien dans la FA que dans la DS. Nous montrons pour la première fois que le risque embolique propre de la DS n'est pas négligeable. Une anticoagulation afin de prévenir le risque embolique en cas de DS pourrait être envisagée en fonction du risque individuel (par exemple score de CHA_2DS_2-VASc ≥ 2). Une étude prospective randomisée est nécessaire pour évaluer le bénéfice potentiel de cette stratégie.

académie d'Orléans-Tours

université de TOURS | Faculté de médecine

BODIN Alexandre

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Résumé :
La DS évolue plus vers la MRA que la FA.
À partir d'une population cardiologique, nous avons développé le score SEARCH-AF pour prédire la FA, un score ≥ 2 pourrait justifier une stratégie de dépistage intensif de la FA.
La mortalité toute cause était plus importante au sein de la population de FA par rapport aux patients avec DS ou MRA.
L'évolution vers la MRA, via la FA ou la DS, est à risque d'insuffisance cardiaque.
Dans les FA et les DS, un score de CHA_2DS_2-VASc ≥ 2 était associé à un risque supérieur d'AVC ischemique et d'insuffisance cardiaque.
Le risque embolique des patients avec DS était moins important que celui des FA et MRA mais restait plus supérieur à celui d'une population contrôle. L'incidence de l'AVC ischémique au sein des patients avec DS doit être considérée (1,95%/an et 1,85%/an dans la population de DS sans FA dans le suivi). Une anticoagulation orale pour la prévention de l'AVC ischémique chez des patients selectionnés (par exemple, un score de CHA_2DS_2-VASc ≥ 3) pourrait être envisagée.
Une étude prospective pour évaluer le rapport bénéfice-risque d'une telle stratégie est nécessaire.

Mots clés : Fibrillation atriale ; dysfonction sinusale ; maladie rythmique atriale ; AVC ischémique

Jury :

Président du Jury : Professeur Dominique BABUTY, Cardiologie, Faculté de Médecine - Tours

Membres du Jury :

- Professeur Laurent FAUCHIER, Cardiologie, Faculté de Médecine - Tours
- Professeur Denis ANGOULVANT, Cardiologie, Faculté de Médecine - Tours
- Docteur Arnaud BISSON, Cardiologie - Tours
- Docteur Nicolas CLEMENTY, Cardiologie - Tours
- Docteur Bertrand PIERRE, cardiologie – Tours

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