**Age-Dependent Risk of Stroke and Death in Young Patients with Atrial Fibrillation: A Nationwide Cohort Study.**

Line Melgaard, BSc1

Lars Hvilsted Rasmussen, MD, PhD2

Flemming Skjøth, MSc, PhD3

Gregory Y.H. Lip, MD2,4

Torben Bjerregaard Larsen, MD, PhD1,2,3

1 Department of Health Science and Technology, Aalborg University, Denmark. 2 Aalborg Thrombosis Research Unit, Aalborg University, Aalborg, Denmark. 3 Department of Cardiology, Cardiovascular Research Centre, Aalborg University Hospital, Denmark. 4 University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom

**Abstract**

**Importance:** The risk of stroke and death in patients with atrial fibrillation is strongly associated with age and concomitant comorbidities.

**Objective:** To examine the age-dependent risk of stroke, mortality and composite stroke and mortality in young patients with atrial fibrillation.

**Design, Settings and Participants:** Population based cohort study of patients with AF age<65 years, identified by record linkage between nationwide registries. Registry data for 139,071 non-valvular AF patients diagnosed during 2000-2011 and followed in a period of 5 years, giving at least 1 year of full follow-up.

**Main Outcome and Measure:** Cox regression models used to estimate risk of stroke and mortality according to risk factors.

**Results:** We identified 139,071non-valvular atrial fibrillation patients, of which 39,496 (28.4%) were aged <65 (mean age 54.9). Higher CHA2DS2-VASc scores were associated with decreased survival probability in all age groups. Increasing age was associated with the presence of more stroke risk factors and higher CHA2DS2-VASc score. The incidence of stroke per year in patients aged <65 was 0.1%, 0.5%, and 1.1% in respectively the age groups 20-35, 35-50, and 50-65 years. Overall, risk factors such as prior stroke, heart failure, vascular disease, diabetes and hypertension remained independent predictors of stroke and death in non-valvular atrial fibrillation patients aged <65.

**Conclusions and Relevance:** The CHA2DS2-VASc score is an applicable tool for all age groups and in non-valvular atrial fibrillation patients aged <65, the same risk factors apply to these patients. The weight of some risk factors was higher with regard to the risk of stroke and death, especially prior stroke, vascular disease and diabetes mellitus. Younger non-valvular atrial fibrillation patients with these risk factors should be offered oral anticoagulant therapy.

**Keywords**: atrial fibrillation, atrial arrhythmia, risk factors, adverse events, stroke, death, CHADS2, CHA2DS2-VASc, Danish registers, prospective cohort study.

**Introduction**

The risk of stroke and death in patients with atrial fibrillation (AF) is strongly associated with age and concomitant comorbidities. The prevalence of AF doubles with each decade of age, reaching almost 9% at ages 80 to 89 years1; thus, age is an independent risk factor for the development of AF2.

The risk of stroke and thromboembolism is increased in AF, but this risk is not homogeneous in all patients3 and is dependent upon the presence of various stroke risk factors in the individual patient4.

The most common stroke risk prediction score in clinical use is the classic CHADS2 (congestive heart

failure, hypertension, age ≥75 years, diabetes, stroke/transient cerebral ischemia/thrombo-embolism (doubled)) score5. Given its various limitations6,7,the CHADS2 score has been refined by use of the CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke/transient cerebral ischemia/thrombo-embolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or

aortic plaque), age 65–74 years, sex category (female)) score 8. The CHA2DS2-VASc score includes additional common stroke risk factors9–11. The CHA2DS2-VASc score better identifies the ‘truly low-risk’ AF patients who do not require any antithrombotic therapy, so that those with one or more stroke risk factors can be offered effective antithrombotic treatment8.

Risk stratification scores for AF have been primarily evaluated in older AF patients, usually above the age of 65 and no study has adequately investigated if the risk factors have similar impact amongst younger patients with AF. Second, whether the increasing number of CHA2DS2-VASc risk factors associate with comparable increases in stroke risk in all age groups remains unknown. Using data from nationwide Danish registries, we assessed the rate and risk of stroke and mortality in a cohort of AF patients, and furthermore, identified which independent CHA2DS2-VASc risk factors that increased the risk of stroke, death and the composite of ‘stroke and death’ in young patients with AF.

**Methods**

*Registry Data Sources*

Using nationwide cohort registers, we identified patients discharged with non-valvular AF (1 January 2000 - 31 December 2011) and followed them in a period of 5 years, giving at least 1 year of full follow-up, at least 3 years pre-baseline hospital history (start ICD-10) and 5 years of medical history.

Independent risk factors were identified using the Danish National Patient Registry which has registered all hospital admissions along with diagnoses since 1978 coding all diagnoses according to the 10th revision of the International Classification of Diseases since 1994, and further using the Danish Registry of Medicinal Product Statistics which keeps data on all prescriptions dispensed from Danish pharmacies, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System. To identify the events of interest we used the abovementioned Danish National Patient Registry, and further used the National Civil Registration System that holds information on date of birth, vital status, date of death and sex of all citizens12. Data from the Danish National Prescription Registry was used to ascertain the antithrombotic treatment status of each patient. Data were linked using a unique person identification number (CPR number) which is used through all Danish national registries. These registries have previously been validated13,14 and the predictive value of AF diagnosis was found to be high (99%) with a sensitivity of 88% and a specificity of 88-99% in these registries15.

***Figure 1:*** *Flowchart of Patients Included in the Final Study Population*



*Study Population*

The study population consisted of patients with non-valvular AF aged 20-90 years. Non-valvular AF was defined by a discharge diagnosis of AF or atrial flutter, but without an ICD-10 code of valvular disease or mechanical cardiac valve. This is consistent with the definition used in similar cohort studies9,12. The cohort consisted of patients both treated with anticoagulation and untreated. However, patients with a diagnosis of cancer (according to ICD-10) or HIV/AIDS (according to Charlson’s AIDS definition; ICD-10: B20-B24) were excluded. Similarly, patients with an invalid CPR number (personal identification number), inconsistent death information (death before AF diagnosis), a date of death equal to the date of AF diagnosis, and immigration within 1 year prior to AF diagnosis were also excluded [Figure 1].

Comorbidities were assessed by the components of the CHA2DS2-VASc score at time of AF diagnosis. Patients with congestive heart failure were identified from the combination of a diagnosis of previous heart failure or left ventricular dysfunction and treatment with loop diuretics. Patients with hypertension were identified from a diagnosis of hypertension and a combination therapy with at least two of the following antihypertensive medications: adrenergic antagonist, beta-blockers, calcium channel blockers, non-loop diuretics, renin–angiotensin system inhibitors, and vasodilators. Patients with diabetes mellitus were identified as those who had any diagnosis of diabetes and claimed prescriptions for glucose-lowering medication. To identify patients who had suffered a previous stroke, we searched for patients diagnosed with ischemic stroke, hemorrhagic stroke, and transient cerebral ischemia. Information on vascular disease, such as myocardial infarction and peripheral artery disease, was also retrieved from the National Patient Registry (see web-only Table for ICD and ATC codes).

Treatment of warfarin was defined by first prescription and assumed to last until the package was assumed used with a standard daily dosage (5 mg per day). With repeated prescriptions, dosage was estimated based on time between prescriptions. Treatment was assumed terminated if there were more than 180 days between end of treatment and next new prescription. If treatment was initiated less than 30 days after diagnosis of AF, treatment was assumed to start at the date of the AF diagnosis, assuming that warfarin was handed out from the hospital.

According to the CHA2DS2-VASc scheme, patients are given one point for congestive heart failure, hypertension, diabetes mellitus, vascular disease, and two points for previous thromboembolism16. Age group was handled separately in the analysis and therefore not included. Female sex count for one point in the CHA2DS2-VASc scheme, but was not included this analysis to avoid a score of 1 to consist of males only. This modified CHA2DS2-VASc score is hereafter denoted mCHA2DS2-VASc. According to ESC guidelines per 2012, a score of 0 (or a CHA2DS2-VASc score=1 in females) is considered as “truly low risk” and no antithrombotic therapy needed.

*Outcomes*

We defined our primary outcome as the composite of stroke or death resulting in an ICD-10 code of stroke or a date of death. Information on emigration or death was available from the National Civil Registration System, and incident cases of stroke after AF using ICD-10 (I60, I61, I62, I63, and I64) were found in the National Patient Register.

*Statistical Methods*

The study population was stratified into five groups according to age at non-valvular AF diagnosis; age 20-35, 35-50, 50-65, 65-75, and 75-90 years. Baseline characteristics and independent risk factors were described separately for each of the five age strata with means and standard deviation for continuous measures and proportions for categorical measures.

In each of the five age categories, estimates for remaining event free up to 5 years after non-valvular AF were calculated for all patients and stratified on mCHA2DS2-VASc score of 0, 1, 2, and ≥3. Stroke event probabilities were obtained as cumulative incidence rates assuming death as a competing event, whereas risk for death and the composite of stroke and death were based on the Kaplan-Meier estimator. The effect of an increasing mCHA2DS2-VASc score was assessed by a Cox proportional-hazards model stratified by separate analyses on age group with no risk factors as reference. The analyses were adjusted for VKA-treatment, by including an indicator for treatment, as a time-varying covariate.

The analyses were performed using SAS/STAT software, Version 9.2 for Windows (SAS Institute Inc. (2008), Cary, NC, USA) and Stata version 11 (Stata Corporation, College Station, TX, USA). A two-sided p-value of <0.05 was considered statistically significant.

*Ethical Considerations*

No ethical approval is required for anonymous register studies in Denmark. The study was approved by the Danish Data Protection Agency (J. No. 2012-41-063).

**Results**

The study population comprised 139,071 non-valvular AF patients aged 20-90 years (mean age 71.2 years; 45.1% female; mean CHA2DS2-VASc score 2.0 ±1.5). Of this, 39,496 (28.4%) were aged <65 (mean age 54.9 years) and used for our main analyses [Figure 1]. For the 5-years follow-up analyses, the median follow-up period were 1405 days overall (IQR 602-2515). We had at least one year of follow-up data on all patients for the entire study period. During follow-up, 76,589 (57%) initiated anticoagulant treatment and of these, 66,973 (48%) were initiated within the first year of follow-up.

Baseline characteristics of the study population are shown in Table 1. As expected, we found increased comorbidity with increasing age, and correspondingly higher CHA2DS2-VASc score with increasing age strata. In all five age categories, except the age group 20-35 years, the most frequent comorbidities were vascular disease, heart failure and diabetes. In the age category 20-35 years, heart failure and renal disease were most common comorbidities at baseline.

**Table 1**: *Baseline Characteristics of Study Population According to Age.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
|  | ***All (Age 20-90 years)*** | ***Age 20-35 years*** | ***Age 35-50 years*** | ***Age 50-65 years*** | ***Age 65-75 years*** | ***Age 75-90 years*** |
|  |  |  |  |  |  |  |
| *N* | 139071 | 1784 | 7253 | 30474 | 36937 | 62623 |
| *Average Age (years)* | 71.2 | 29.1 | 44.1 | 59.0 | 70.3 | 82.0 |
| *Sex (Female), No. (%)* | 62704 (45.1) | 568 (31.8) | 2130 (29.4) | 9448 (31.0) | 14978 (40.6) | 35580 (56.8) |
| *Previous Ischemic Stroke, No. (%)* | 15980 (11.5) | 16 (0.1) | 187 (2.6) | 1847 (6.1) | 4002 (10.8) | 9928 (15.9) |
| *Previous Hemorrhagic Stroke, No. (%)* | 1421 (1.0) | 6 (0.3) | 39 (0.5) | 249 (0.8) | 383 (1.0) | 744 (1.2) |
| *Systemic Embolism, No. (%)* | 936 (0.7) | 1 (0.1) | 25 (0.3) | 141 (0.5) | 219 (0.6) | 550 (0.9) |
| *Previous Transient Cerebral Ischemia, No. (%)* | 5841 (4.2) | 9 (0.5) | 77 (1.1) | 780 (2.6) | 1523 (4.1) | 3452 (5.5) |
| *Previous Stroke\*, No. (%)* | 20814 (15.0) | 29 (1.6) | 267 (3.7) | 2557 (8.4) | 5285 (14.3) | 12676 (20.2) |
| *Heart Failure, No. (%)* | 23359 (16.8) | 50 (2.8) | 461 (6.4) | 3406 (11.2) | 5849 (15.8) | 13593 (21.7) |
| *Prior Myocardial Infarction, No. (%)* | 14342 (10.3) | 12 (0.7) | 235 (3.2) | 2355 (7.7) | 4159 (11.3) | 7581 (12.1) |
| *Periphery Ischemic Disease, No. (%)* | 10813 (7.8) | 14 (0.8) | 131 (1.8) | 1410 (4.6) | 3133 (8.5) | 6125 (9.8) |
| *Vascular Disease, No. (%)* | 22929 (16.5) | 26 (1.5) | 342 (4.7) | 3491 (11.5) | 6617 (17.9) | 12453 (19.9) |
| *Diabetes, No. (%)* | 15312 (11.0) | 24 (1.3) | 346 (4.8) | 3231 (10.6) | 4855 (13.1) | 6856 (10.9) |
| *Hypertension, No. (%)* | 16083 (11.6) | 9 (0.5) | 281 (3.9) | 3256 (10.7) | 4928 (13.3) | 7609 (12.2) |
| *Renal Disease, No. (%)* | 5687 (4.1) | 34 (1.9) | 188 (2.6) | 1000 (3.3) | 1554 (4.2) | 2911 (4.6) |
| *Liver Disease, No. (%)* | 509 (0.4) | 1 (0.1) | 36 (0.5) | 220 (0.7) | 154 (0.4) | 98 (0.2) |
|  |  |  |  |  |  |  |
| *CHA2DS2-VASc score, No. (%)* |  |  |  |  |  |  |
| *Score = 0* | 26674 (19.2) | 1664 (93.3) | 5913 (81.5) | 19097 (62.7) | 0 (0.0) | 0 (0.0) |
| *Score = 1* | 25882 (18.6) | 79 (4.4) | 875 (12.1) | 6461 (21.2) | 18467 (50.0) | 0 (0.0) |
| *Score = 2* | 39390 (28.3) | 35 (2.0) | 342 (4.7) | 3341 (11.0) | 9046 (24.5) | 26626 (42.5) |
| *Score ≥ 3* | 47125 (33.9) | 6 (0.3) | 123 (1.7) | 1205 (5.2) | 9424 (25.5) | 35997 (57.5) |
|  |  |  |  |  |  |  |
| *Mean CHA2DS2-VASc score (Standard deviation)* | 2.0 (1.5) | 0.1 (0.4) | 0.3 (0.7) | 0.6 (1.0) | 1.9 (1.1) | 3.1 (1.2) |
|  |  |  |  |  |  |  |
| CHA2DS2 VASc (congestive heart failure, age ≥ 75, diabetes, previous stroke, vascular disease, age 65-74, sex category (female)) | | | |  |  |  |
| \*Combined Previous Ischemic-, Hemorrhagic Stroke and Transient Cerebal Ischemia, | | |  |  |  |  |

The overall incidence of stroke per year was 0.1% (95% CI 0.0%-0.2%), 0.5% (95% CI 0.4%-0.6%), and 1.1% (95% CI 0.0%-1.1%) for the age groups 20-35, 35-50, and 50-65 respectively.

The incidence rate of stroke per year was significantly associated with higher CHA2DS2-VASc score [Table 2]. A similar association existed between event rate of death and higher CHA2DS2-VASc score, and likewise between event rate of ‘combined stroke and death’ and higher CHA2DS2-VASc score. The incidence rate of stroke in the age group 20-35 had a similar association with the CHA2DS2-VASc score, though, most of these incidence rates of stroke had wide confidence intervals and no stroke events occurred in patients in this age group with a CHA2DS2-VASc score of 1.

**Table 2**: *Event Rates of Stroke, Death and ‘Composite Stroke and Death’. The table illustrates the event rates of stroke, death and ‘composite Stroke and Death’ in each age group and for each CHA2DS2-VASc score (excl. age and sex) divided into scores of 0 (no risk factors present), 1, 2, and 3+.*

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Stroke** |  |  |  | **Death** |  |  |  | **Composite Stroke and Death** | | |
| **Age Group** | **Score** | **Event No.** | **Rate** | **(95% CI)** |  | **Event No.** | **Rate** | **(95% CI)** |  | **Event No.** | **Rate** | **(95% CI)** |
| 20-35 | 0 | 4 | 0.38 | (0.14-1.01) |  | 27 | 2.56 | (1.75-3.73) |  | 31 | 2.94 | (2.07-4.18) |
| 20-35 | 1 | 0 | 0.00 | - |  | 15 | 40.58 | (24.47-67-32) |  | 15 | 40.58 | (24.47-67.32) |
| 20-35 | 2 | 4 | 23.34 | (8.76-62.19) |  | 2 | 10.44 | (2.61-41-73) |  | 6 | 35.01 | (15.73-77.93) |
| 20-35 | 3+ | 1 | 53.00 | (7.47-380.00) |  | 1 | 52.22 | (7.36-370.71) |  | 2 | 105.99 | (26.51-423.80) |
| 35-50 | 0 | 112 | 3.04 | (2.53-3.66) |  | 294 | 7.89 | (7.04-8.84) |  | 389 | 10.56 | (9.56-11.66) |
| 35-50 | 1 | 37 | 7.79 | (5.64-10.74) |  | 118 | 24.02 | (20.05-28.77) |  | 151 | 31.77 | (27.09-37.27) |
| 35-50 | 2 | 70 | 47.71 | (37.75-60.31) |  | 66 | 37.76 | (29.66-48.06) |  | 123 | 83.84 | (70.26-100.05) |
| 35-50 | 3+ | 30 | 67.06 | (46.89-95.91) |  | 34 | 60.61 | (43.31-84.83) |  | 59 | 131.88 | (102.18-170.22) |
| 50-65 | 0 | 959 | 8.51 | (7.99-9.07) |  | 2289 | 19.69 | (18.90-20.52) |  | 3007 | 26.69 | (25.76-27.66) |
| 50-65 | 1 | 402 | 11.98 | (10.87-13.21) |  | 1410 | 40.34 | (38.29-42.50) |  | 1654 | 49.30 | (46.98-51.74) |
| 50-65 | 2 | 636 | 44.52 | (41.19-48.12) |  | 919 | 53.68 | (50.32-57.26) |  | 1377 | 96.40 | (91.44-101.63) |
| 50-65 | 3+ | 389 | 74.59 | (67.53-82.38) |  | 597 | 88.80 | (81.95-96.21) |  | 821 | 157.42 | (147.01-168.57) |
| 65-75 | 0 | 1523 | 15.88 | (15.10-16.70) |  | 5001 | 49.67 | (48.32-51.07) |  | 5838 | 60.88 | (59.33-62.46) |
| 65-75 | 1 | 802 | 19.84 | (18.52-21.27) |  | 3485 | 82.02 | (79.34-84.79) |  | 3857 | 95.43 | (92.47-98.49) |
| 65-75 | 2 | 1202 | 56.35 | (53.26-59.63) |  | 2608 | 101.65 | (97.82-105.62) |  | 3212 | 150.59 | (145.47-155.88) |
| 65-75 | 3+ | 828 | 82.21 | (76.80-88.00) |  | 1829 | 146.10 | (139.55-152.95) |  | 2178 | 216.24 | (207.35-225.52) |
| 75-90 | 0 | 3223 | 31.98 | (30.90-33.11) |  | 15935 | 148.79 | (146.50-151.12) |  | 16768 | 166.39 | (163.89-168.93) |
| 75-90 | 1 | 1854 | 37.12 | (35.47-38.85) |  | 11049 | 206.98 | (203.16-210.88) |  | 11445 | 229.17 | (225.01-233.41) |
| 75-90 | 2 | 2747 | 93.01 | (89.60-96.55) |  | 8598 | 237.10 | (232.14-242.16) |  | 9318 | 315.50 | (309.16-321.97) |
| 75-90 | 3+ | 1833 | 130.00 | (120.00-130.00) |  | 5542 | 303.80 | (295.91-311.91) |  | 6000 | 415.36 | (404.98-426.01) |

Figure 2 shows age-dependent 5-years cumulative incidence rates of death, and combined endpoint death or stroke in each age interval according to mCHA2DS2-VASc scores of 0 (no risk factors present, including females), 1, 2 and ≥3. The survival probability of stroke or death significantly decreased in patients with a higher CHA2DS2-VASc score in each age group, with a score of ≥3 being the

most hazardous score associated with a lower survival. In the age group 20-35, the association was more diffuse and small numbers were seen. In terms of hazard ratios, the presence of one risk factor increased the risk significantly in all age groups.

**Figure 2**: *5-Year Survival probability According to CHA2DS2-VASc* *Score. The figure is composed of two graphs that illustrate the survival probability of combined stroke and death and the survival probability of death alone. The CHA2DS2-VASc* *score, without age and sex as a risk factor, is divided into scores of 0 (no risk factors present), 1, 2, and 3+ and is separated into age groups. ES is an abbreviation for effect size and 95% CI is the 95% confidence interval.*



The independent risk factors for stroke, death and ‘composite stroke and death’ in each age strata are shown in Figure 3. The figure shows hazard ratios of stroke, death and ‘composite stroke and death’ in the presence of heart failure, hypertension, diabetes, prior stroke, vascular disease, and female sex.

The endpoint of stroke was strongly associated with the presence of prior stroke (hazard ratio HR, 24.3, 95% CI, 6.1-97.0), vascular disease (HR, 5.2, 95% CI, 0.6-42.4) and female sex (HR, 4.0, 95% CI, 1.1-14.9) in the age group of 20-35 [Figure 3]. Wide confidence intervals existed in the latter age group. In the age group of 35-50, the strongest associations with stroke were with prior stroke (HR, 16.0, 95% CI, 11.5-22.4), vascular disease (HR, 2.8, 95% CI, 1.7-4.5), and diabetes (HR, 1.8, 95% CI, 1.0-3.1). In the age group of 50-65, the strongest associations with stroke were with prior stroke (HR, 8.2, 95% CI, 7.4-9.0), vascular disease (HR, 1.8, 95% CI, 1.6-4.5), and diabetes (HR, 1.4, 95% CI, 1.2-1.6).

The endpoint of death in the age group of 20-35 was strongly associated with diabetes, heart failure, and prior stroke [Figure 3]. In the age groups of 35-50 and 50-65 the strongest associations with death were with heart failure, diabetes and vascular disease. As expected, female sex had a lower HR when associated with death in the age groups of 50-65, 65-75, and 75-90.

The composite endpoint of ‘stroke and death’ in the age group of 20-35 was strongly associated with prior stroke, diabetes mellitus and heart failure [Figure 3]. In the age group of 35-50 and 50-65 the strongest associations with ‘stroke and death’ were with prior stroke, heart failure, and vascular disease.

**Discussion**

In this real-world cohort study, we confirmed a low risk of stroke in patients aged <65, but demonstrated that the risk is different in each age strata. The risk of stroke increased by the risk factors of prior stroke, heart failure, vascular disease, diabetes, and hypertension in most age categories. Event rates for ‘stroke and death’ were significantly increased in all non-valvular AF patients by the presence of these risk factors. Indeed, higher CHA2DS2-VASc scores were associated with decreased survival probability in all age groups.

Patients with AF age <65 are considered to have a low annual risk of thromboembolic events8, as supported by the results of this study. In current guidelines, no antithrombotic treatment is recommended for most of these patients, if age <65 and lone AF16. The influence of independent risk factors, as used in the CHA2DS2-VASc score, have essentially been evaluated in AF patients age <65 as a homogenous group17. One study found an Nonetheless, when applying the CHA2DS2-VASc score on the young non-valvular AF patients, it is still preferable to score these patients and apply the CHA2DS2-VASc score in clinical practice, as recommended in the international guidelines by the European Society of Cardiology16.

Overall, risk factors such as prior stroke, heart

**Figure 3:** *Independent Risk Factors of Stroke, Death and Composite Stroke and Death in each Age Group. The figure illustrates the hazard rate ratio for the presence of each CHA2DS2-VASc risk factor (excl. age) in each age group. In the age group of 20-35 no data on diabetes was observed in the event of stroke.*





failure, vascular disease, and diabetes remained independent predictors of stroke and death in non-valvular AF patients aged <65.

Given that guidelines should be applicable for most of the time and for majority of the patients, the European Society of Cardiology guidelines and the CHA2DS2-VASc stroke risk assessment approach would cover most of the patients who is commonly seen in everyday clinical practice, and consider the common stroke risk factors in such patients. However, patient values and preferences should also be considered12,18. Currently, every non-valvular AF patient is recommended antithrombotic treatment with a CHA2DS2-VASc score of ≥1. This broad biphasic decision-making may be too simplistic, since not every risk factor is equally important when estimating the risk of stroke as shown in Figure 3. In our study, the risk of stroke was not increased considerably by every risk factor. In particular, heart failure and female sex did not increase this risk noticeably in some age groups, although in the age group 20-35 years, these risk factors did increase the hazard ratio. However, these results support the score of 2 points for prior stroke in the CHA2DS2-VASc score. Interestingly, our results indicate that in the older age groups, 65-75 and 75-90, the risk of stroke was not considerably higher with the presence of the investigated risk factors, except prior stroke, but the risk increased with age, supporting the focus on age in the CHA2DS2-VASc score.

By illustrating the probability of survival according to different CHA2DS2-VASc scores, it is possible to see how much each score influence the survival rate. According to our results, the 5-year survival rate decreased noticeably with a CHA2DS2-VASc score of >1 and with a score of ≥3 being the most hazardous score associated with a lower survival. This indicates that it is reasonable to manage patients with a CHA2DS2-VASc score of ≥1 with antithrombotic therapy, as currently suggested in guidelines. Today, many non-valvular AF patients aged <65 are not necessarily on antithrombotic therapy, but with presence of the risk factors of prior stroke or vascular disease, this patient group has an increased risk of stroke, and would probably benefit from thromboprophylaxis17,19. However, for patients aged <65 with only female sex or well-treated hypertension as a risk factor, anticoagulant treatment will most likely not be a clinical beneficial or socio-economic choice20. Additionally, the development over time of risk factors such as hypertension, diabetes mellitus and cardiovascular disease have been associated with an increased risk of stroke8,11,16,17, again emphasizing the importance of reassessment of risk factors for stroke over time. However, the influence and importance of hyper-tension and female sex as independent risk factors have been discussed 21,22.

The age group of 20-35 years had a low rate of events and a more diffuse association with the CHA2DS2-VASc score. As shown in Figures 2 and 3, this age group had a low number of patients with the events of interest. Therefore, the results in this age group should be interpreted carefully. Further investigations are necessary in these younger age groups, especially since AF could be related to an electrophysiological abnormality (e.g. pre-excitation) or structural heart disease (e.g. congenital heart disease).

The threshold for anticoagulant treatment has been in focus and debated in research. The threshold has previously been proposed at a stroke rate of 1.7% per year23. However, studies of anticoagulation with newer and safer agents have suggested a lowering of the threshold for anticoagulant therapy to a stroke rate of 0.9% per year23. With the development of new and safer agents, the discussion of whether to give antithrombotic therapy may be simpler in the future as the risk of bleeding and other adverse reactions decrease.

*Limitations*

Due to the nature of our nationwide registry study, several limitations are present. Some results should be interpreted with caution due to the small number of strokes, especially in the younger age groups, given the generally low incidence rate of stroke in young non-valvular AF patients. We used an endpoint of stroke and death, and our follow-up was dependent upon the National Civil Registration System, where some deaths could be due to undiagnosed stroke. The incidence of stroke was defined by the Danish Hospital Discharge Register, and not all stroke endpoints have been defined by cerebral imaging. Furthermore, we only included ischemic stroke and systemic embolism and not hemorrhagic stroke.

We only included risk factors commonly used when assessing risk of stroke in non-valvular AF patients. Due to the biological nature of the younger group of patients, it could be relevant to look at several other risk factors such as smoking, dyslipidemia, body mass index, family history of stroke, echo-cardiographic or electrocardiographic findings. This aspect was beyond the scope of this study and has somewhat been evaluated in a previous study by Ruigomez et al., although in an older study population24. Thus, residual confounding may still be evident, even though we attempted to adjust for baseline clinical characteristics in the statistical analysis. As this was an observational study, it is not possible to draw direct conclusions on causal relationships of the findings. The frequencies of risk factors in the study population may also be underestimated because patients with heart failure, hypertension and diabetes were identified from prescription claims, and thus, we were not able to detect patients treated non-pharmaceutical with diet control and lifestyle interventions alone. In addition, oral anticoagulation could influence the rate of stroke during follow-up but all analyses were adjusted for the use of oral anticoagulation in the statistical analysis.

Due to the low number of patients in some age intervals, analyses in some of these age groups were conducted with reduced power resulting in wide confidence intervals. However, this study investigated a “real world” and contemporary population of non-valvular AF patients followed in nationwide registers which has very limited loss to follow-up, and therefore, the study is unlikely to be subject to selection bias. The major strengths of this study remain the well-validated outcomes and large sample size uniquely possible with this type of cohort study, and almost no patients were lost for follow up.

In conclusion, the CHA2DS2-VASc score is an applicable tool for all age groups and in non-valvular AF patients aged <65 years, the same risk factors apply to these patients. The weight of some risk factors was higher with regard to the risk of stroke and death, especially prior stroke, vascular disease and diabetes mellitus. Younger non-valvular AF patients with these risk factors should be offered oral anticoagulant therapy.

**Disclosure of Conflict of Interests**

The authors state that they have no conflict of interest.

**References**

1. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol.* 1998;Oct 16(82):2-9.

2. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke; a journal of cerebral circulation*. 2009;40(4):1410-1416.

3. Wolf P a., Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-988.

4. Avenue G. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. *Stroke; a journal of cerebral circulation*. 2008;39(6):1901-1910.

5. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA : the journal of the American Medical Association*. 2001;285(22):2864-2870.

6. Karthikeyan G, Eikelboom JW. The CHADS2 score for stroke risk stratification in atrial fibrillation - friend or foe? *Thrombosis and haemostasis*. 2010;104(1):45-48.

7. Keogh C, Wallace E, Dillon C, Dimitrov BD, Fahey T. Validation of the CHADS2 clinical prediction rule to predict ischaemic stroke. A systematic review and meta-analysis. *Thrombosis and haemostasis*. 2011;106(3):528-538.

8. Lip GYH, Nieuwlaat R, Pisters R, Lane D a, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-272.

9. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342(jan31):124-124.

10. Van Staa TP, Setakis E, Di Tanna GL, Lane D a, Lip GYH. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. *Journal of thrombosis and haemostasis : JTH*. 2011;9(1):39-48.

11. Lip GYH, Frison L, Halperin JL, Lane D a. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke; a journal of cerebral circulation*. 2010;41(12):2731-2738.

12. Mikkelsen a, Lindhardsen J, Lip G, Gislason GH, Torp-Pedersen C, Olesen JB. Female sex asa risk factor for stroke in atrial fibrillation: A nationwide cohort study. *Journal of thrombosis and haemostasis : JTH*. 2012;(July):1745-1751.

13. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scandinavian journal of public health*. 2011;39(7 Suppl):38-41.

14. Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28(3):150-154.

15. Frost L, Andersen LV, Vestergaard P, Husted S, Mortensen LS. Trend in mortality after stroke with atrial fibrillation. *The American journal of medicine*. 2007;120(1):47-53.

16. Camm a J, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2010;12(10):1360-1420.

17. Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GYH. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest*. 2012;141(1):147-153.

18. Lahaye SA, Gibbens SL, Ball DGA, Day AG, Olesen JB, Skanes AC. A clinical decision aid for the selection of antithrombotic therapy for the prevention of stroke due to atrial fibrillation. *European heart journal*. 2012:2163-2171.

19. Jahangir A, Lee V, Friedman P a, et al. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation*. 2007;115(24):3050-3056.

20. Hughes M, Lip GYH. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thrombosis and haemostasis*. 2008;99(2):295-304.

21. Healey JS, Connolly SJ. Atrial fibrillation: hypertension as a causative agent, risk factor for complications, and potential therapeutic target. *The American journal of cardiology*. 2003;91(10A):9G-14G.

22. Prescott E, Sørensen R. Female sex as a risk factor for stroke in atrial fibrillation. *BMJ (Clinical research ed.)*. 2012;344:e3789.

23. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circulation. Cardiovascular quality and outcomes*. 2011;4(1):14-21.

24. Ruigómez A, Johansson S, Wallander M-A, Edvardsson N, García Rodríguez LA. Risk of cardiovascular and cerebrovascular events after atrial fibrillation diagnosis. *International journal of cardiology*. 2009;136(2):186-192.