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ORIGINAL RESEARCH ARTICLE

# Arterial Thromboembolism in Patients With Atrial Fibrillation and CHA2DS2-VASc 1: A Nationwide Study

Lauge Østergaard, MD, PhD; Jonas Bjerring Olesen, MD, PhD; Jeppe Kofoed Petersen, MB; Lukas Schak Nielsen, MB; Søren Lund Kristensen, MD, PhD; Morten Schou, MD, PhD; Lars Køber, MD, DMSc; Emil Fosbøl, MD, PhD

**BACKGROUND:** Oral anticoagulation is suggested in patients with atrial fibrillation and a $CHA_2DS_2$-VASc score ≥1 (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65–74 years, and sex score). To assess granular differences within $CHA_2DS_2$-VASc 1, the incidence of arterial thromboembolism according to $CHA_2DS_2$-VASc 1 subgroups was examined.

**METHODS:** The Danish National Patient Registry and the Danish Prescription Registry linked nationally to identify patients with atrial fibrillation from 2000 to 2021 without oral anticoagulation and categorized according to $CHA_2DS_2$-VASc score: $CHA_2DS_2$-VASc 0 (male and female subjects); $CHA_2DS_2$-VASc 1 (hypertension, heart failure, diabetes, vascular disease, and age 65–74 years); or $CHA_2DS_2$-VASc 2 (age ≥75 years without other risk factors). Female sex was not considered a risk factor in any risk group. The outcome was arterial thromboembolism (ischemic stroke, embolism of extremity, or transient cerebral ischemia). Study groups were compared using Cox regression analysis.

**RESULTS:** We included 26 701 patients with a $CHA_2DS_2$-VASc 0 score; 22 915 with $CHA_2DS_2$-VASc 1 (1483 patients with heart failure, 9066 with hypertension, 843 with diabetes, 770 with vascular disease, and 10 753 who were 65 to 74 years of age); and 14 525 patients with $CHA_2DS_2$-VASc 2 (≥75 years of age without other risk factors). With a median of 1 year of observation time, the cumulative incidence of arterial thromboembolism was 0.6% (n=154 [95% CI, 0.6%–0.8%]), 1.4% (n=16 [95% CI, 0.8%–2.2%]), 1.9% (n=141 [95% CI, 1.6%–2.2%]), 1.7% (n=12 [95% CI, 0.9%–2.9%]), 2.0% (n=13 [95% CI, 1.1%–3.4%]), 2.3% (n=187 [95% CI, 2.0%–2.7%]), and 4.4% (n=533 [95% CI, 4.1%–4.8%]) for $CHA_2DS_2$-VASc 0, heart failure, hypertension, diabetes, vascular disease, age 65 to 74 years ($CHA_2DS_2$-VASc 1), and age ≥75 years ($CHA_2DS_2$-VASc 2), respectively. No statistically significant difference was identified among subgroups of $CHA_2DS_2$-VASc 1 ($P$=0.15 for difference).

**CONCLUSIONS:** For patients with atrial fibrillation, all subgroups of $CHA_2DS_2$-VASc 1 were associated with lower incidence of arterial thromboembolism compared with age ≥75 years without other risk factors (ie, $CHA_2DS_2$-VASc 2) and a higher incidence compared with $CHA_2DS_2$-VASc 0. No statistically significant difference was identified between the subgroups of $CHA_2DS_2$-VASc 1. These findings support current recommendations that patients within this intermediate risk group could be identified with a similar risk of arterial thromboembolism.

**Key Words:** arterial thromboembolism ■ atrial fibrillation ■ $CHA_2DS_2$-VASc ■ intermediate risk ■ ischemic stroke



Atrial fibrillation (AF) comes with an increased risk of arterial thromboembolism, especially ischemic stroke.[1] Several large randomized controlled trials have shown efficacy of oral anticoagulant (OAC) therapy for the prevention of arterial thromboembolism in patients with AF and risk factors for stroke.[2–6] European

Correspondence to: Lauge Østergaard, MD, PhD, Department of Cardiology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark.
Email laugeoestergaard@gmail.com or lauge.klement.molte.oestergaard.02@regionh.dk
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## Clinical Perspective

### What Is New?

- From Danish nationwide registries, we identified that patients with atrial fibrillation, not treated with oral anticoagulation, and $CHA_2DS_2$-VASc 1 had a higher associated rate of arterial thromboembolism than patients with $CHA_2DS_2$-VASc 0 and a lower associated rate of arterial thromboembolism compared with patients ≥75 years of age without other risk factors (ie, $CHA_2DS_2$-VASc 2).
- Within subgroups of $CHA_2DS_2$-VASc 1 (heart failure, diabetes, hypertension, vascular disease, and age 65 to 74 years), we found no statistically significant difference in the associated rate of arterial thromboembolism.

### What Are the Clinical Implications?

- European and American guidelines suggest, with a IIa recommendation, initiation of oral anticoagulation for patients with atrial fibrillation and $CHA_2DS_2$-VASc 1; however, clinicians have previously been provided with little data to differentiate in the associated rate of arterial thromboembolism between subgroups of $CHA_2DS_2$-VASc 1.
- Our findings suggest that there is no difference in the associated rate of arterial thromboembolism within subgroups of $CHA_2DS_2$-VASc 1, underlining guideline recommendations to individualize treatment based on net clinical benefit and patient preferences in the decision-making of initiation of oral anticoagulation for patients with atrial fibrillation and $CHA_2DS_2$-VASc 1.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AF** | atrial fibrillation |
| **HF** | heart failure |
| **HR** | hazard ratio |
| ***ICD-10*** | *International Classification of Diseases, Tenth Revision* |
| **OAC** | oral anticoagulant |
| **PPV** | positive predictive value |

guidelines recommend assessing risk of ischemic stroke in patients with AF using the $CHA_2DS_2$-VASc score, and OAC is recommended with a class I, level of evidence A for patients with a $CHA_2DS_2$-VASc score ≥2 for male subjects and ≥3 for female subjects.[1] However, guidelines on OAC are not definitive (and level of evidence is lower) with regard to patients with a $CHA_2DS_2$-VASc 1 score (male subjects) and a score of 2 (female subjects), for whom treatment should be considered (class IIa, level of evidence B).[1] Hence, the clinician is provided with a recommendation that is not optimal for patient guidance, and potentially shared decision-making. Therefore, more specific information is needed to granulate the risk of arterial thromboembolism according to which risk factor is present among patients in this intermediate $CHA_2DS_2$-VASc risk group, which constitutes a broad spectrum of patients <65 years of age with hypertension, diabetes, heart failure (HF), previous myocardial infarction, peripheral artery disease, or aortic plaque (vascular disease), and patients 65 to 74 years of age without other risk factors.[1] From Danish nationwide registries, we aimed to examine the incidence of arterial thromboembolism in nonanticoagulated patients with AF across the spectrum of $CHA_2DS_2$-VASc 1, also including the $CHA_2DS_2$-VASc 0 group and patients with $CHA_2DS_2$-VASc 2 (age ≥75 years) for comparison and reassurance of data validity.

## METHODS

### Data Availability

Data are owned by a third party, and the authors do not have the right to share data; however, upon request, the authors will help in applying to the third party for approval of data sharing.

### Data Sources

Danish nationwide registries are linkable because of a personal identifier that is given to all Danish citizens at birth.[7] For the purpose of this study, the Danish National Patient Registry, the Danish Prescription Registry, the Danish Population Registry, and the Danish Cause of Death Registry were used. The Danish National Patient Registry provides data on all patients admitted to a Danish hospital. A primary diagnosis (mandatory) and up to several secondary diagnosis codes are provided at discharge. Also, outpatient visits are recorded. The *International Classification of Diseases, Tenth Revision* (*ICD-10*), is used for disease categorization. The Danish Prescription Registry provides data on all filled prescriptions from Danish pharmacies. The type of drug is provided and classified according to the Anatomical Therapeutic Chemical classification. Date of prescription redemption and strength of tablets are provided. The Danish Population Registry provides information on date of birth and sex. The Danish Cause of Death Registry was used for identification of date of death. The registries were described in detail previously.[8–10]

### Study Sample

The study sample constituted all patients with a first-time AF diagnosis (*ICD-10* code I48) in the period from 2000 to 2021 from a hospital admission or an outpatient visit with a primary or secondary diagnosis code. The positive predictive value (PPV) of the AF diagnosis code is 95% in the Danish National Patient Registry.[11] We excluded patients with previous mechanical heart valve implantation, previous venous thromboembolism, previous stroke or transient cerebral ischemia, previous arterial thromboembolism, and patients who initiated OAC in relation to AF diagnosis (180 days before and up to 14 days after first outpatient visit or date of hospital discharge with AF). Patients who died before index (14 days after diagnosis) were excluded. The population was categorized into 7

study groups in which female sex was not calculated as part of the $CHA_2DS_2$-VASc score (this is established as a risk modifier rather than a risk factor): (1) $CHA_2DS_2$-VASc 0; (2) $CHA_2DS_2$-VASc 1: hypertension, defined from hospital admission or outpatient visit within the capture of the National Patient Registry or from 2 antihypertensive drugs filled within 180 days of AF diagnosis (as done previously),[12] without a previous HF diagnosis, as medication then was more likely to be associated with HF therapy; (3) $CHA_2DS_2$-VASc 1: diabetes, defined from hospital admission or outpatient visit within the capture of the National Patient Registry or from redemption of at least one antidiabetic drug within 180 days; (4) HF, defined from a hospital admission or outpatient visit within the capture of the National Patient Registry (PPV, 76%–81%; negative predictive value, 90%[11,13]); (5) vascular disease (myocardial infarction [PPV, 97%],[11] peripheral artery disease, or aortic plaque), defined from a hospital admission or outpatient visit within the capture of the National Patient Registry; (6) age 65 to 74 years without other risk factors; and (7) age ≥75 years without other $CHA_2DS_2$-VASc risk factors (ie, $CHA_2DS_2$-VASc 2). In a supplementary analysis, main results for $CHA_2DS_2$-VASc 0 and $CHA_2DS_2$-VASc 1 and for age ≥75 years were stratified according to sex. Table S1 provides diagnosis codes and codes for drug redemption for assessment of the study groups.

## Outcomes and Observational Period

The main outcome of the study was hospital admission with a primary or secondary code of arterial thromboembolism (ischemic or unspecified stroke [PPV, 79%–97%, and lower for unspecified stroke],[14,15] arterial embolism of the extremities (*ICD-10* codes I63, I64, and I74; Table S1). In an additional analysis, the outcome was narrowed down to ischemic or unspecified stroke (*ICD-10* codes I63 and I64). Data were collected from 14 days after first outpatient visit for AF or date of discharge after first hospital admission with AF. This 14-day grace period was provided for patients to fill an OAC prescription, which was an exclusion criterion. Patients were observed from index until date of arterial thromboembolism, date of death, maximum of 1 year of follow-up, date of increase in $CHA_2DS_2$-VASc score, date of initiation of OAC treatment, or December 31, 2021, whichever came first. The secondary outcome was all-cause mortality and hospital admission with bleeding using the same criteria for the observational period as explained above. Bleeding was defined as an inpatient primary or secondary diagnosis code as presented in Table S1. The observational period was restricted to a maximum of 1 year of follow-up, as the $CHA_2DS_2$-VASc model is built to predict the 1-year risk of arterial thromboembolism.

## Statistical Methods

Baseline characteristics were compared across study groups with categorical variables in counts and percentages and continuous variables with a median and 25th and 75th percentiles. The cumulative incidence of arterial thromboembolism was reported by study groups assessing death as a competing risk. The cumulative incidence function using the Aalen Johansen estimator was used to account for death as a competing risk. Crude difference in the cumulative incidence was reported using the Fine and Gray test examining differences between $CHA_2DS_2$-VASc 0 and $CHA_2DS_2$-VASc 1, and age ≥75 years without other risk factors (ie, $CHA_2DS_2$-VASc 2), and subgroups of $CHA_2DS_2$-VASc 1, restricting the observational period to a maximum of 1 year. All-cause mortality was reported using the reverse Kaplan-Meier estimator. For comparison of the incidence of arterial thromboembolism between study groups, a Cox regression analysis was computed with $CHA_2DS_2$-VASc 1, age 65 to 74 years as reference. In additional analyses, the reference group was varied across the spectrum of $CHA_2DS_2$-VASc 1 to identify differences with the $CHA_2DS_2$-VASc 0 and $CHA_2DS_2$-VASc 2 groups. The proportional hazard assumption was assessed using Martingale residuals without any violations. Results are reported with a hazard ratio (HR) and 95% CI. A $P$ value <0.05 was considered statistically significant. All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Inc, Cary, NC).

## Supplementary Analysis

As recommendations on the use of OAC were introduced in 2010,[16] we conducted a sensitivity analysis stratifying the total study sample according to calendar year (2000–2010; and 2011–2021), and calendar period was examined as an effect modifier.

## Ethics

In Denmark, registry-based studies that are not conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law.[17] However, the study is approved by the data-responsible institute (Capital Region of Denmark, approval No. P-2019-263) in accordance with the General Data Protection Regulation. All personal identifiers were anonymized, and subclassifications with ≤3 patients were not reported to assure anonymization as by rules of Statistics Denmark.



# RESULTS

## Study Sample

After applying the exclusion criteria (Figure 1), we included a total of 26701 patients with $CHA_2DS_2$-VASc 0 (62.6% male subjects), 22915 with $CHA_2DS_2$-VASc 1, and 14525 age ≥75 years without other risk factors (ie, $CHA_2DS_2$-VASc 2). For the $CHA_2DS_2$-VASc 1 group, the subsets were distributed as follows: 1483 patients with HF (6.5%), 9066 with hypertension (39.6%), 843 with diabetes (3.7%), 770 with vascular disease (3.4%), and 10753 who were 65 to 74 years of age (46.9%). Patients with hypertension and diabetes had the highest burden of chronic kidney failure, whereas chronic obstructive pulmonary disease and malignancy were most prevalent for the 2 age groups 65–74 years and ≥75 years (Table). Use of aspirin was highest among patients with $CHA_2DS_2$-VASc 1 (64.4%), whereas it was lowest for patients with $CHA_2DS_2$-VASc 0 (12.8%). We found significant differences in the use of aspirin across calendar periods (2000–2010 versus 2011–2021), with a higher use of aspirin in 2000 to 2010 for all study groups (Table S2). For patients with $CHA_2DS_2$-VASc 0

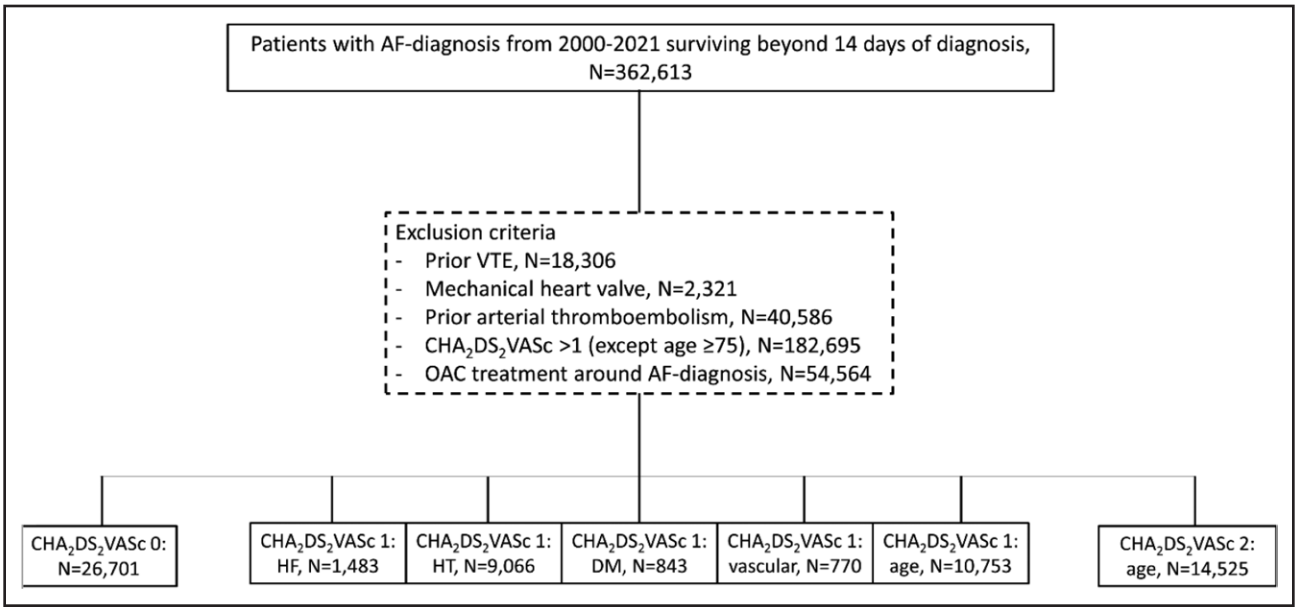


**Figure 1. Flow chart.**
Patient selection process. Female sex was not calculated as part of the $CHA_2DS_2$-VASc score. AF indicates atrial fibrillation; DM, diabetes; HF, heart failure; HT, hypertension; OAC, oral anticoagulation.

or $CHA_2DS_2$-VASc 1 because of age (65 to 74 years), diabetes, or hypertension, the index episode of AF was mainly diagnosed as primary in an inpatient setting (Table). For $CHA_2DS_2$-VASc 1 resulting from HF, vascular disease, and age ≥75 years, the index episode of AF was mainly diagnosed as secondary in an inpatient setting (Table).

## Incidence of Arterial Thromboembolism

The median observation time (the observational period was restricted at 1 year) for the overall study sample was 365 days (interquartile range, 161–365 days), with few differences among groups (Table S3). The crude cumulative incidence of arterial thromboembolism was 0.6% (95% CI, 0.6%–0.8%), 1.4% (95% CI, 0.8%–2.2%), 1.9% (95% CI, 1.6%–2.2%), 1.7% (95% CI, 0.9%–2.9%), 2.0% (95% CI, 1.1%–3.4%), 2.3% (95% CI, 2.0%–2.7%), and 4.4% (95% CI, 4.1%–4.8%) for $CHA_2DS_2$-VASc 0, $CHA_2DS_2$-VASc 1: HF (hypertension, diabetes, vascular disease, and age 65 to 74 years), and $CHA_2DS_2$-VASc 2 (age ≥75 years without other risk factors), respectively (Figure 2). The incidence of arterial thromboembolism for $CHA_2DS_2$-VASc 0 for female subjects was 0.6%, and for male subjects, it was 0.7% (Gray test *P* value=0.19 for difference; Figures S1 and S2). For $CHA_2DS_2$-VASc 1, this was 1.8% for female subjects and 2.2% for male subjects (Gray test *P* value=0.13 for difference; Figure S1). For age ≥75 years, the incidence was 4.6% for female subjects and 4.1% for male subjects (Gray test *P* value=0.21 for difference; Figure S1). Cumulative incidence of arterial thromboembolism was compared for $CHA_2DS_2$-VASc 0, $CHA_2DS_2$-VASc 1, and $CHA_2DS_2$-VASc 2 (age ≥75 years), and we found statistically significant differences among the 3 groups (Gray test $P<0.0001$ for difference between groups; Figure S3). When $CHA_2DS_2$-VASc 0 was compared with $CHA_2DS_2$-VASc 1, a statistically significant difference was identified between groups (Gray test $P<0.0001$ for difference between groups), and when $CHA_2DS_2$-VASc 1 was compared with $CHA_2DS_2$-VASc 2 (age ≥75 years), a statistically significant difference was identified (Gray test $P<0.0001$ for difference between groups).

## Incidence of Arterial Thromboembolism Among Subgroups of $CHA_2DS_2$-VASc 1

When examining differences within subgroups of $CHA_2DS_2$-VASc 1, we found no statistically significant difference ($P=0.15$ for difference between groups; Figure S4). In a comparative analysis of the incidence of arterial thromboembolism, compared with $CHA_2DS_2$-VASc 1 (age 65 to 74 years), we found HR=0.27 (95% CI, 0.22–0.34) for $CHA_2DS_2$-VASc 0, HR=0.60 (95% CI, 0.36–0.99) for $CHA_2DS_2$-VASc 1 HF, HR=0.80 (95% CI, 0.64–0.99) for $CHA_2DS_2$-VASc 1 hypertension, HR=0.73 (95% CI, 0.41–1.30) for $CHA_2DS_2$-VASc 1 diabetes, HR=0.83 (95% CI, 0.48–1.46) for $CHA_2DS_2$-VASc 1 vascular disease, and HR=2.05 (95% CI, 1.74–2.42) for age ≥75 years (ie, $CHA_2DS_2$-VASc 2; Figure 3). The reference group was varied for the comparative analysis of the incidence of arterial thromboembolism, and all 5 subgroups of $CHA_2DS_2$-VASc 1 were found to be associated with a lower incidence of arterial thromboembolism than in patients ≥75 years of age (ie, $CHA_2DS_2$-VASc 2) and a higher incidence

**Table. Baseline Characteristics**

| | $CHA_2DS_2$-VASc 0 | | $CHA_2DS_2$-VASc 1, age | | $CHA_2DS_2$-VASc 1, DM | | $CHA_2DS_2$-VASc 1, HF | | $CHA_2DS_2$-VASc 1, HT | | $CHA_2DS_2$-VASc 1, Vasc | | $CHA_2DS_2$-VASc 2, age | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| No. | 26701 | (100.0) | 10753 | (100.0) | 843 | (100.0) | 1483 | (100.0) | 9066 | (100.0) | 770 | (100.0) | 14525 | (100.0) |
| Male | 16722 | (62.6) | 5952 | (55.4) | 555 | (65.8) | 1086 | (73.2) | 5350 | (59.0) | 582 | (75.6) | 6355 | (43.8) |
| Age, median, y (IQR) | 53.5 (44.1–59.7) | | 69.8 (67.4–72.4) | | 56.8 (50.6–61.5) | | 56.3 (49.3–61.3) | | 58.8 (53.8–62.3) | | 58.6 (54.2–62.0) | | 83.1 (78.9–87.8) | |
| Medical history | | | | | | | | | | | | | | |
| Chronic kidney failure | 276 | (1.0) | 212 | (2.0) | 34 | (4.0) | 54 | (3.6) | 441 | (4.9) | 16 | (2.1) | 340 | (2.3) |
| COPD | 892 | (3.3) | 1150 | (10.7) | 74 | (8.8) | 218 | (14.7) | 572 | (6.3) | 53 | (6.9) | 1838 | (12.7) |
| Liver disease | 615 | (2.3) | 278 | (2.6) | 63 | (7.5) | 106 | (7.1) | 416 | (4.6) | 25 | (3.2) | 185 | (1.3) |
| Rheumatic disease | 848 | (3.2) | 758 | (7.0) | 30 | (3.6) | 76 | (5.1) | 449 | (5.0) | 54 | (7.0) | 1042 | (7.2) |
| Malignancy | 2040 | (7.6) | 2362 | (22.0) | 102 | (12.1) | 177 | (11.9) | 952 | (10.5) | 76 | (9.9) | 3252 | (22.4) |
| Pharmacotherapy | | | | | | | | | | | | | | |
| Aspirin | 3419 | (12.8) | 2825 | (26.3) | 192 | (22.8) | 457 | (30.8) | 3017 | (33.3) | 496 | (64.4) | 5545 | (38.2) |
| 4 ADPi | 281 | (1.1) | 275 | (2.6) | 19 | (2.3) | 32 | (2.2) | 254 | (2.8) | 227 | (29.5) | 372 | (2.6) |
| β-Blockade | 8595 | (32.2) | 3207 | (29.8) | 231 | (27.4) | 792 | (53.4) | 5771 | (63.7) | 433 | (56.2) | 2872 | (19.8) |
| RASi | 420 | (1.6) | 341 | (3.2) | 86 | (10.2) | 683 | (46.1) | 4780 | (52.7) | 31 | (4.0) | 440 | (3.0) |
| Loop diuretics | 346 | (1.3) | 487 | (4.5) | 45 | (5.3) | 657 | (44.3) | 1353 | (14.9) | 12 | (1.6) | 2032 | (14.0) |
| Statin | 1828 | (6.8) | 1523 | (14.2) | 257 | (30.5) | 211 | (14.2) | 2169 | (23.9) | 446 | (57.9) | 1020 | (7.0) |
| Antiplatelet therapy | | | | | | | | | | | | | | |
| None | 23108 | (86.5) | 7754 | (72.1) | 641 | (76.0) | 1013 | (68.3) | 5908 | (65.2) | 247 | (32.1) | 8713 | (60.0) |
| Aspirin | 3312 | (12.4) | 2724 | (25.3) | 183 | (21.7) | 438 | (29.5) | 2904 | (32.0) | 296 | (38.4) | 5440 | (37.5) |
| ADPi | 174 | (0.7) | 174 | (1.6) | 10 | (1.2) | 13 | (0.9) | 141 | (1.6) | 27 | (3.5) | 267 | (1.8) |
| Aspirin + ADPi | 107 | (0.4) | 101 | (0.9) | 9 | (1.1) | 19 | (1.3) | 113 | (1.3) | 200 | (26.0) | 105 | (0.7) |
| Diagnosis of index AF | | | | | | | | | | | | | | |
| Inpatient primary | 13688 | (51.3) | 3928 | (36.5) | 350 | (41.5) | 489 | (33.0) | 4010 | (44.2) | 285 | (37.0) | 4403 | (30.3) |
| Inpatient secondary | 3356 | (12.6) | 2803 | (26.1) | 220 | (26.1) | 562 | (37.9) | 1796 | (19.8) | 289 | (37.5) | 6694 | (46.1) |
| Outpatient primary | 8795 | (32.9) | 3341 | (31.1) | 232 | (27.5) | 247 | (16.7) | 2665 | (29.4) | 156 | (20.3) | 2501 | (17.2) |
| Outpatient secondary | 862 | (3.2) | 681 | (6.3) | 41 | (4.9) | 185 | (12.5) | 595 | (6.6) | 40 | (5.2) | 927 | (6.4) |

ADPi indicates adenosine diphosphate inhibitor; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; and RASi, renin angiotensin system inhibitor.



of arterial thromboembolism than in the $CHA_2DS_2$-VASc 0 group (Table S4). When the outcome was narrowed down to ischemic or unspecified stroke, the cumulative incidence was 0.6%, 0.9%, 1.5%, 1.4%, 1.4%, 1.7%, and 3.6% for $CHA_2DS_2$-VASc 0, $CHA_2DS_2$-VASc 1: HF, hypertension, diabetes, vascular disease, age 65 to 74 years, and age ≥75 years (ie, $CHA_2DS_2$-VASc 2), respectively.

Table S5 shows reasons for censoring for the study groups.

## Supplementary Analyses

We found differences in the incidence of arterial thromboembolism when data were stratified according to calendar period (2000–2010 and 2011–2021; *P* value for interaction <0.0001; Figure S5). No difference was found in the direction across $CHA_2DS_2$-VASc groups and subgroups of $CHA_2DS_2$-VASc 1 according to calendar period (Table S6).

## Mortality

The 1-year cumulative incidence of all-cause mortality was 2.6%, 8.3%, 4.4%, 7.9%, 4.6%, 8.8%, and 21.1% for $CHA_2DS_2$-VASc 0, $CHA_2DS_2$-VASc 1: HF (hypertension, diabetes, vascular disease, age 65 to 74 years), and age ≥75 years (ie, $CHA_2DS_2$-VASc 2), respectively (Figure 4). In a comparative analysis, compared with $CHA_2DS_2$-VASc 1 age 65 to 74 years, we found HR=0.29 (95% CI, 0.26–0.32) for $CHA_2DS_2$-VASc 0, HR=0.94 (95% CI, 0.78–1.14) for $CHA_2DS_2$-VASc 1 HF, HR=0.49 (95% CI, 0.44–0.56) for hypertension, HR=0.90 (95% CI, 0.70–1.15) for diabetes, HR=0.51 (95% CI, 0.37–0.72)

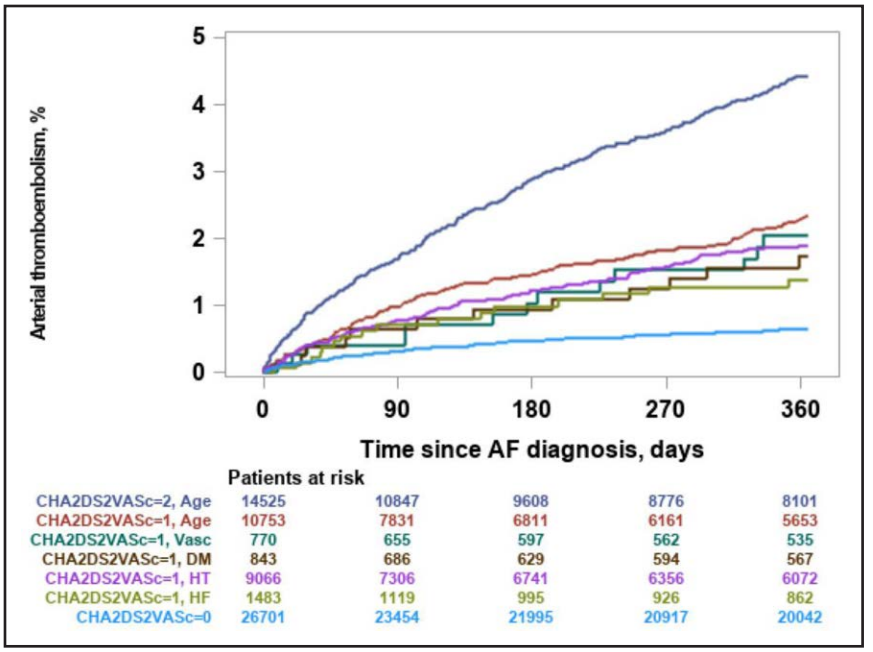


**Figure 2. Cumulative incidence of arterial thromboembolism.**
Female sex was not calculated as part of the $CHA_2DS_2$-VASc score. AF indicates atrial fibrillation; DM, diabetes; HF, heart failure; HT, hypertension; and Vasc, vascular disease.

for vascular disease, and HR=2.58 (95% CI, 2.40–2.78) for age ≥75 (ie, $CHA_2DS_2$-VASc 2).

## Bleeding

The 1-year cumulative incidence of hospital admission with bleeding was 0.4%, 1.2%, 1.1%, 1.2%, 1.8%, 1.2%, and 2.2% for $CHA_2DS_2$-VASc 0, $CHA_2DS_2$-VASc 1: HF (hypertension, diabetes, vascular disease, age 65 to 74 years), and age ≥75 years, respectively (Figure 5). Compared with $CHA_2DS_2$-VASc 1 age 65 to 74 years, we found HR=0.29 (95% CI, 0.21–0.38) for $CHA_2DS_2$-VASc 0, HR=1.08 (95% CI, 0.54–2.13) for $CHA_2DS_2$-VASC 1 HF, HR=0.96 (95% CI, 0.54–1.71) for hypertension,

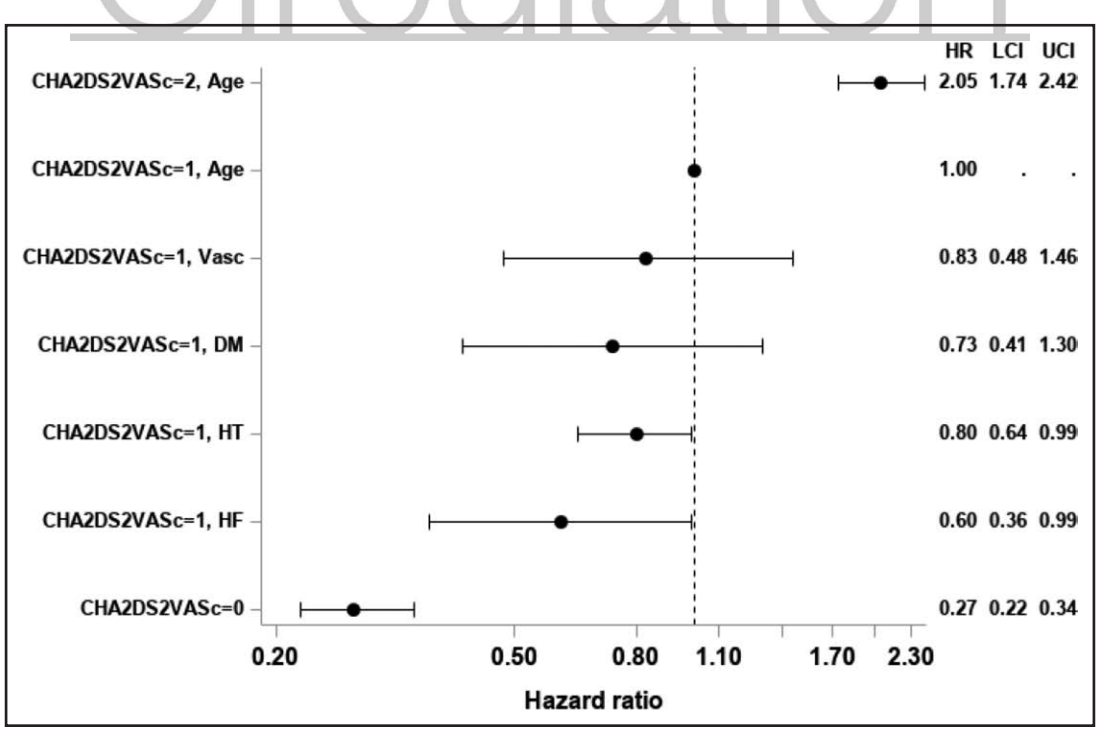


**Figure 3. Comparative analysis of arterial thromboembolism.**
Associated HR of arterial thromboembolism with a median of 1 year of observation time with $CHA_2DS_2$-VASc 1 (age 65–74 years) as reference. Female sex was not calculated as part of the $CHA_2DS_2$-VASc score. DM indicates diabetes; HF, heart failure; HR, hazard ratio; HT, hypertension; LCI, lower CI; UCI, upper CI; and Vasc, vascular disease.

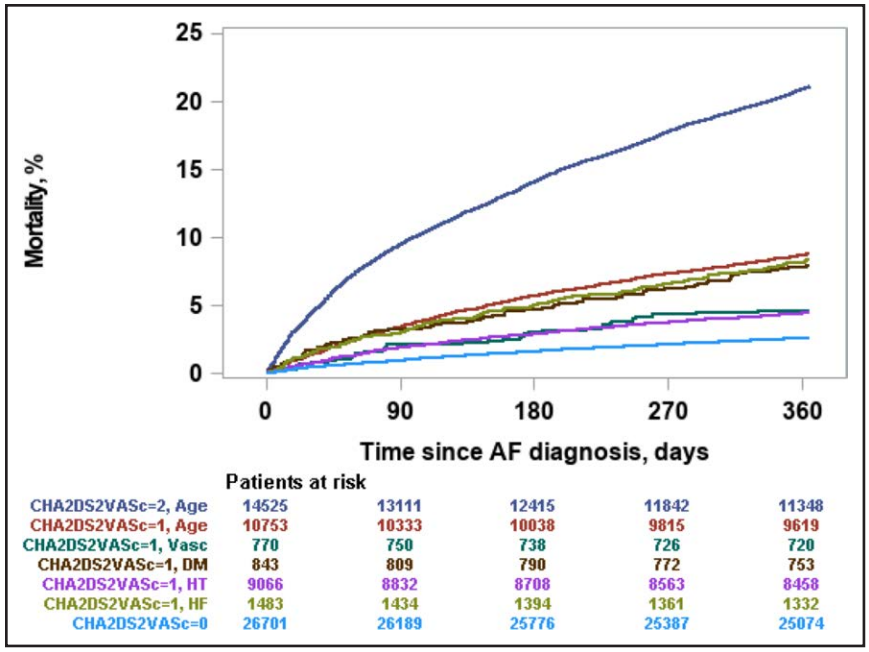


**Figure 4. All-cause mortality.** Mortality with a median of 1 year of observation time. Female sex was not calculated as part of the $CHA_2DS_2$-VASc score. AF indicates atrial fibrillation; DM, diabetes; HF, heart failure; HT, hypertension; and Vasc, vascular disease.

HR=0.86 (95% CI, 0.63–1.16) for diabetes, HR=1.52 (95% CI, 0.84–2.78) for vascular disease, and HR=2.02 (95% CI, 1.60–2.55) for age ≥75 years (ie, $CHA_2DS_2$-VASc 2).

## DISCUSSION

In this nationwide study during a calendar period of 20 years, we examined the incidence of arterial thromboembolism with a median observation time of 1 year across the spectrum of patients with AF and $CHA_2DS_2$-VASc 1 not treated with OACs. The study had 3 major findings. First, no statistically significant difference was observed among the 5 subgroups of $CHA_2DS_2$-VASc 1. Second, when compared with patients ≥75 years of age without other risk factors (ie, $CHA_2DS_2$-VASc 2), all 5 subgroups of $CHA_2DS_2$-VASc 1 were associated with a lower incidence of arterial thromboembolism; and when compared with a $CHA_2DS_2$-VASc 0 group (including female subjects), all 5 subgroups were associated with a higher incidence of arterial thromboembolism. Third, differences in all-cause mortality were identified across the spectrum of $CHA_2DS_2$-VASc 1, in which patients 65 to 74 years of age had the highest associated mortality, followed by HF, diabetes, vascular disease, and hypertension.

European guidelines are very clear with regard to to OAC initiation in patients with AF and $CHA_2DS_2$-VASc ≥2 (start OAC, class Ia); however, for patients with $CHA_2DS_2$-VASc 1, treatment initiation "… should be individualized based on net clinical benefit and consideration of patient values and preferences."[1] As the $CHA_2DS_2$-VASc 1 group constitutes 5 distinct subgroups, we hypothesized that the risk of arterial thromboembolism may differ within this group, which could help the clinician in patient guidance about OAC initiation. A study by Eckman et al identified a tipping point in terms of achieving treatment efficacy of 0.9% risk of ischemic stroke per year for the initiation of dabigatran, whereas this was 1.7% per year for warfarin.[18] Our analyses identify that the $CHA_2DS_2$-VASc 1 group lies within this spectrum of risk of arterial thromboembolism, which underlines the current recommendations that initiation of OAC should be based on several factors, including patient values and preferences. From our analyses, we found that among patients with $CHA_2DS_2$-VASc 1, HF and hypertension were associated with a statistically significant lower incidence of arterial thromboembolism compared with patients age 65 to 74 years. As our main analysis found no overall difference between subgroups of $CHA_2DS_2$-VASc 1, we see this finding as hypothesis-generating, and more data on this area are needed for such a finding to translate into clinical practice of OAC treatment. Some studies have previously assessed the incidence of ischemic stroke in patients with $CHA_2DS_2$-VASc 1 (not counting female sex as a score point). A meta-analysis of 10 studies (up until 2015) identified an annual stroke risk of 1.6% in nonanticoagulated patients with $CHA_2DS_2$-VASc 1; however, the studies included had considerable heterogeneity, and differences within the spectrum of $CHA_2DS_2$-VASc 1 were not assessed.[19] Our study reports similar incidences between 1.1% and 1.7%, with a median observational period of 1 year of follow-up across the spectrum of $CHA_2DS_2$-VASc 1 when only stroke was assessed as an end point. A Swedish population-based study examining patients from 2005 to 2010 identified event rates from 0.5% to 0.9% per year.[20] The authors identified all patients on warfarin during the study period and excluded these

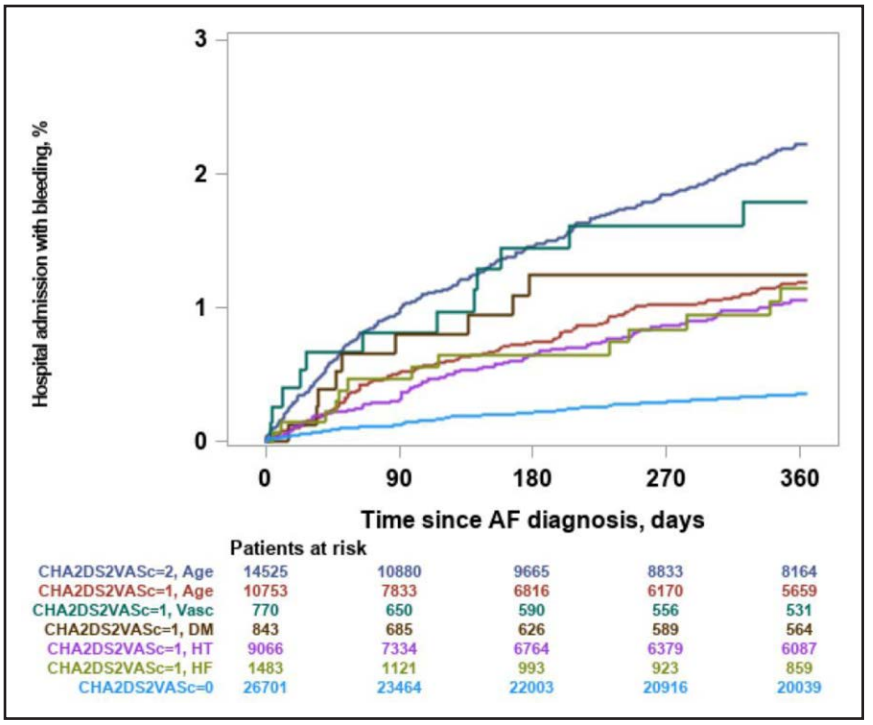


**Figure 5. Cumulative incidence of hospital admission with bleeding.** Female sex was not calculated as part of the $CHA_2DS_2$-VASc score. AF indicates atrial fibrillation; DM, diabetes; HF, heart failure; HT, hypertension; and Vasc, vascular disease.



patients; however, these patients could have contributed with risk time (and events) in the period from index and up until OAC initiation, which may have skewed the results toward lower estimates.[20] Further, comparison across the spectrum of $CHA_2DS_2$-VASc 1 was not analyzed.[20] A previous Danish study identified OAC-naïve patients with AF and $CHA_2DS_2$-VASc 1 from 1997 to 2006 and found that all subgroups were associated with a statistically significant higher incidence of thromboembolism compared with $CHA_2DS_2$-VASc 0, with a maximum of 10 years of follow-up.[12] In our analysis, we provide updated estimates of this study sample, ensuring that patients remain OAC-naïve during the observational period and within the $CHA_2DS_2$-VASc 1 risk group by censoring patients during the observational period, avoiding case mixing.

We found that all $CHA_2DS_2$-VASc 1 subgroups had a higher incidence of arterial thromboembolism compared with the $CHA_2DS_2$-VASc 0 group, and a lower incidence compared with the patients ≥75 years of age without other risk factors (ie, $CHA_2DS_2$-VASc 2). Further, we found no statistically significant difference when data were stratified according to sex, which supports recommendations of not including sex as a risk factor to the $CHA_2DS_2$-VASc score for low-risk patient groups.[21] These findings are in accordance with guidelines and previously published literature and reassure that our study provides clinically valid estimates.[1,12,19,22,23]

We found differences in mortality estimates within the spectrum of $CHA_2DS_2$-VASC 1 with patients 65 to 74 years of age with HF having the highest associated mortality estimates. Mortality is a competing risk of arterial thromboembolism, and despite the differences in mortality among subgroups of $CHA_2DS_2$-VASc 1, we found no associated difference in the incidence of arterial thromboembolism across the spectrum of $CHA_2DS_2$-VASc 1. It should be noted that mortality was, in absolute terms, a more common event than arterial thromboembolism and should be remembered in the interpretation of our findings and how competing factors relate to mortality. Also, incidence of bleeding was similar to that of arterial thromboembolism, and in this context, for a patient with $CHA_2DS_2$-VASc 1, the incidence of adverse events should not be considered low.

Significant guideline alterations occurred during the study period, investigating when aspirin was left out of treatment for stroke prophylaxis in 2010.[16] We observed a significant difference in the clinical practice patterns after this alteration, with a substantial decrease in the use of aspirin from 2011 and onward compared with 2000 to 2010. However, because aspirin has been shown to have little effect in stroke prevention, we are convinced that this finding plays little role in the estimates presented in this study.[24] Further, we found an interaction with the outcome and calendar period; however, no difference in the direction of the results was identified across subgroups of $CHA_2DS_2$-VASc 1.

Patients ≥75 years of age without other risk factors (ie, $CHA_2DS_2$-VASc 2) were associated with the highest incidence of hospital admission with bleeding followed by patients with vascular disease. Patients with vascular disease were more often treated with aspirin or adenosine diphosphate inhibitor at baseline, an independent risk factor for bleeding. Aspirin and adenosine diphosphate

inhibitor in combination have shown to be efficient in the reduction of ischemic stroke, although with an increased risk of major hemorrhage.[25] This is in accordance with our observational findings for patients with vascular disease, who had a high baseline use of aspirin and adenosine diphosphate inhibitor.

## Limitations

Our study has some limitations. First, exposure variables were defined from *ICD-10* codes derived from nationwide registries, and although most of the codes used have been validated with high reliability previously, no codes are without misclassification. Moreover, although the PPVs have been validated for most of the codes used, the negative predictive value has been studied less extensively. The nationwide nature of the study increases the generalizability of our findings; however, if systematic misclassification exists in patients not receiving the code, yet having the disease, the validity of the study will decrease. Our study has little generalizability to other ethnic groups. The Asian population is of particular interest, as several studies have indicated that AF among this patient group has a higher risk of ischemic stroke as well as bleeding compared with non-Asians. Our results should be reproduced in this population to gain generalizable recommendations across ethnic populations.[26,27] Second, the observational nature of the study necessitates that the conclusions only relate to associations and no causal relations. In relation to this limitation, efficacy of anticoagulant therapy cannot be assessed from an observational study design. Third, several variables of interest to the study were not available from the registries used: ECGs, left ventricular ejection fraction, pathogenesis of arterial thromboembolism, or type of AF (paroxysmal, persistent, or permanent). Fourth, the study sample was assessed from hospital coding and pharmacy prescriptions; however, diabetes and hypertension treated by lifestyle interventions could not be identified from this method, and our results could therefore only be translated into patient groups similar to the ones included in this study. Fifth, it should be noted that in some subgroups of $CHA_2DS_2$-VASc 1, numbers and events are small, limiting the power to detect potential differences between groups. Cohort studies of larger character could help address this issue.

## CONCLUSIONS

In this >20-year nationwide study on patients with AF and $CHA_2DS_2$-VASc 1 not treated with OAC, we found that all subgroups of $CHA_2DS_2$-VASc 1 were associated with a higher incidence of arterial thromboembolism compared with $CHA_2DS_2$-VASc 0 and a lower incidence compared with age ≥75 years without other risk factors (ie, $CHA_2DS_2$-VASc 2). No statistically significant difference was identified between subgroups of $CHA_2DS_2$-VASc 1. Our findings suggest that there is no difference in the associated rate of arterial thromboembolism within subgroups of $CHA_2DS_2$-VASc 1, underlining guideline recommendations to individualize treatment on the basis of net clinical benefit and patient preferences in the decision-making of OAC initiation for patients with AF and $CHA_2DS_2$-VASc 1.

## ARTICLE INFORMATION

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### Affiliations

The Heart Center, Rigshospitalet (L.Ø., J.K.P., L.S.N., S.L.K., L.K., E.F.), Department of Cardiology, Herlev-Gentofte Hospital (J.B.O., M.S.), University of Copenhagen, Denmark.

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### Supplemental Material

Figures S1–S5
Tables S1–S6

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