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Full Length Article

Ischemic stroke rates decline in patients with atrial fibrillation as anticoagulants uptake improves: A Swedish cohort study

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ABSTRACT

Introduction: The impact of the increased anticoagulants uptake on incidence rate of ischemic stroke is largely unknown. We assessed time trends in rates of ischemic stroke in patients with incident atrial fibrillation (AF) diagnosed between 2011 and 2013.

Materials and methods: Population-based retrospective registry study of all 11,500 adults diagnosed with incident non-valvular atrial fibrillation in 2011–2013 in primary and secondary care and receiving oral anticoagulants (n = 4847), aspirin (n = 2850) or no treatment (n = 3766) in Skåne County, Sweden. The primary outcome was the rate of ischemic stroke within 365 days after AF diagnosis.

Results and conclusion: Cumulative incidence of ischemic stroke decreased from 2.87% (95% confidence interval (CI) 2.37–3.45%) to 1.93% (95% CI 1.54–2.41%) while the uptake of oral anticoagulants increased from 36.6% to 48.4% between 2011 and 2013 (regression coefficient − 0.08; 95% CI, − 0.09 to − 0.07, p < 0.001). The increased uptake of oral anticoagulants in the community is associated with decreased incidence of ischemic stroke in AF patients.

1. Introduction

Stroke prevention is crucial in the management of patients with atrial fibrillation (AF), since non-valvular AF increases the risk of ischemic stroke five-fold [1]. AF related strokes are associated with greater mortality, disability and recurrence [2].

Oral anticoagulation (OAC) with direct oral anticoagulants (DOAC) or warfarin is recommended in European Society of Cardiology (ESC) guidelines [3] for all patients with AF, except in those patients who are at low risk (aged < 65 years and lone AF), or with contraindications. Aspirin is not effective in ischemic stroke prevention in AF and the risk of major bleeding is comparable to that of OAC [4]. ESC guidelines adherence increased from 47.6% in 2011 to 66.1% in 2014 in Southern Sweden [5], where the present study was carried out. The impact of increased oral anticoagulants (warfarin or DOAC) uptake on incidence rate of ischemic stroke is largely unknown. We aimed to assess time trends in OAC uptake and ischemic stroke rates among patients diagnosed with incident AF in Southern Sweden between 2011 and 2013.

2. Methods

2.1. Study population

All adult patients (> 18 years old) diagnosed with their first episode of non-valvular atrial fibrillation or flutter between the 1st of January 2011 and the 31st of December 2013 were identified in the Skåne Healthcare register (SHR) by the International Classification of Diseases (ICD 10) code I48 and included in the study. The register contains detailed information about ambulatory health care visits and hospital admissions from all health care providers in the Skåne Region (total population 2010, n = 1,243,329). Previous studies have confirmed validity of diagnoses in the register [6,7].

We excluded all patients with valvular heart disease (identified by

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ICD code I05-09 or I33-39) and those who had not been a resident of the Skåne County the entire 10 years preceding the AF diagnosis (to ensure correct assessment of baseline comorbidities).

The present study complies with the Declaration of Helsinki and was approved by the Ethics Committee at the Lund University, Sweden (EPN 2015/308).

2.2. Assessment of risk factors

CHA_2DS_2-VASc score [8] was calculated to assess ischemic stroke risk. Points were given for congestive heart failure, hypertension, age over 65 or 75 years, diabetes mellitus, history of a thromboembolic event (ischemic stroke, unspecified stroke, transient ischemic attack (TIA) or peripheral arterial embolism), vascular disease (prior myocardial infarction or peripheral arterial disease) and female sex. Comorbidities relevant for the calculation of CHA_2DS2-VASc score were assessed during the 10 years preceding the AF-diagnosis, using the ICD-10 codes in positions 1 through 8 listed in Supplement Table A.1.

2.3. Baseline medication

The Skåne Region's Prescribed Drug Database contains detailed information of every dispensed prescription linked to the individual patient for all inhabitants in the Skåne County. The information is automatically collected from all pharmacies. Baseline medication was defined as warfarin, DOAC (direct oral anticoagulants) or aspirin collected at a pharmacy within 3 months from the AF diagnosis and prior to the outcome. OAC treatment was defined as treatment with warfarin or DOAC. Patients receiving combined therapy with OAC and aspirin were classified as treated with OAC, since aspirin was likely prescribed for some other indications than atrial fibrillation.

2.4. Outcome

The endpoint was ischemic stroke (ICD-10 code I63 in the first position) within 365 days from AF diagnosis. Diagnoses of ischemic stroke registered under the same admission as the first AF diagnosis were considered as comorbidities and not as new events.

2.5. Statistical analysis

The study population was divided into three cohorts (2011, 2012 and 2013) according to the year of AF diagnosis. The uptake of aspirin, warfarin and DOAC was assessed in each of the three cohorts.

Cumulative incidence rate of ischemic stroke within 365 days from AF diagnosis was calculated. We have also assessed stroke rates in patients with CHA_2DS_2-VASc score ≥ 2 receiving OAC, aspirin or no treatment. Incidence trend of ischemic stroke was assessed in the whole population, then in male and female patients and finally in different risk groups (CHA_2DS_2-VASc score 0 through 1; 2 through 4 and 5 through 9).

Correlation between OAC uptake and stroke incidence was assessed by linear regression.

All data analyses were performed using IBM SPSS Statistics for Macintosh, Version 22.0.

3. Results

Overall, 13,219 patients were newly diagnosed with AF between the 1st of January 2011 and the 31st of December 2013. Patients with valvular heart disease ($n = 1118$) or moving out of the Skåne County during 2001–2013 ($n = 655$) were excluded. The final study population consisted of 11,500 patients, since 64 patients fulfilled both exclusion criteria. The mean age was 77 ± 11 years and 51.5% were men. Mean observation time was 321 days and total observation time was 10,116 patient-years.

Table 1
Baseline characteristics of the study population.

	2011 ($n = 3700$)	2012 ($n = 3907$)	2013 ($n = 3893$)	Total ($n = 11,500$)
Age, mean ± SD	77 ± 11	77 ± 11	77 ± 11.	77 ± 11
Male, n (%)	1868 (50.5)	2024 (51.8)	2032 (52.2)	5924 (51.5)
CHA_2DS_2-VASc score				
0–1	357 (9.6)	376 (9.6)	362 (9.3)	1095 (9.5)
2–4	2143 (57.9)	2270 (58.1)	2235 (57.4)	6648 (57.8)
5–9	1200 (32.4)	1261 (32.2)	1296 (33.3)	3757 (32.7)
Heart failure, n (%)	888 (24.0)	928 (23.8)	896 (23.0)	2712 (23.6)
Hypertension, n (%)	2484 (67.1)	2615 (66.9)	2738 (70.3)	7837 (68.1)
Diabetes, n (%)	743 (20.1)	825 (21.5)	794 (20.4)	2362 (20.5)
Ischemic stroke, n (%)	435 (11.8)	457 (11.7)	500 (12.8)	1392 (12.1)
Unspecified stroke, n (%)	158 (4.3)	160 (4.1)	149 (3.8)	467 (3.8)
TIA, n (%)	249 (6.7)	271 (6.9)	301 (7.7)	821 (7.1)
Myocardial infarction, n (%)	687 (18.6)	720 (18.4)	749 (19.2)	2156 (18.7)

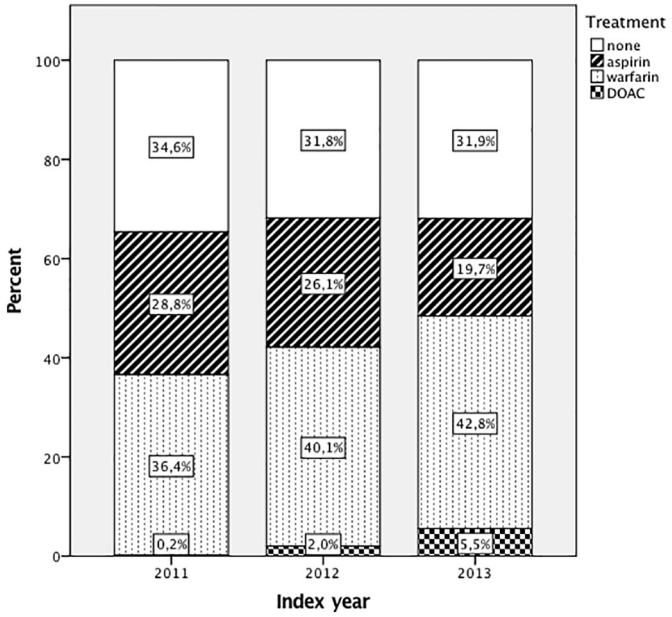

Fig. 1. Treatment trends.

Baseline characteristics of the study patients are outlined in Table 1.

The proportion of newly diagnosed patients receiving OAC increased from 36.6% during the first year to 48.4% the third year, while uptake of aspirin decreased from 28,8% to 19,7% (Fig. 1). Overall, aspirin uptake increased with increasing CHA_2DS_2-VASc score, while OAC uptake was highest among patients with CHA_2DS_2-VASc score 2 through 3 (Fig. 2).

OAC uptake increased in both sexes, all age subgroups and in all CHA_2DS_2-VASc score subgroups (Table 2).

Cumulative incidence of ischemic stroke among patients with CHA_2DS_2-VASc score ≥ 2 receiving different treatments (none, aspirin or OAC) was 3.02% (95% confidence interval (CI) 2.49–3.66%), 3.43% (95% CI 2.81–4.19%) and 1.54% (95% CI 1.22–1.95%).

Cumulative incidence of ischemic stroke decreased from 2.87% (95% CI 2.37–3.45%) in 2011 to 2.33% (95% CI 1.90–2.85%) in 2012 and 1.93% (95% CI 1.54–2.41%) (Fig. 3). The stroke rate reduction was more pronounced in patients with CHA_2DS_2-VASc score 5 through 9 compared with those with CHA_2DS_2-VASc score 0 through 1 (Fig. 4).

Ischemic stroke incidence decreased in both sexes, but women had higher ischemic stroke rates compared to men (Fig. 5). Women in our population were older than men (mean age ± SD 79 ± 11 years vs. 75 ± 11 years) and 43.1% of women had CHA_2DS_2-VASc score 5