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Full Length Article

Antithrombotic therapy in patients with non-valvular atrial fibrillation in Southern Sweden: A population-based cohort study

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ABSTRACT

Introduction: Oral anticoagulants in patients with atrial fibrillation (AF) with moderate-to-high stroke risk are strongly recommended by the current guidelines.
Materials and methods: Population-based register study of all 13,837 patients with incident non-valvular AF diagnosed during 2011–2014 in primary and secondary care (including all in- and outpatient visits) in Skåne County, Sweden. The outcome was the prescription of direct-acting oral anticoagulants (DOAC), warfarin or acetylsalicylic acid (ASA).
Results and conclusion: Guideline adherence increased from 47.6% in 2011 to 66.1% in 2014, mostly due to decrease in undertreatment. In patients with CHA_2DS_2-VASc score ≥ 2, ASA uptake decreased from 29.9% to 14.7% and DOAC uptake increased from 2.1% to 25.1%. The use of ASA was more common among elderly and with increasing stroke- and bleeding risk. Overall, 47.4% of patients with CHA_2DS_2-VASc score ≥ 2 did not receive oral anticoagulants. Undertreatment was particularly common in women < 65 years (55.8%) and in patients > 84 years (65.3% in women and 62% in men). Overtreatment of patients at low stroke risk was 35.9% in men and 36.4% in women. Provider speciality affected the choice of treatment only to a minor degree. Despite increasing guideline adherence, there is a suboptimal use of antithrombotic therapy in a large proportion of AF patients diagnosed in different clinical settings. Efforts to further improve guideline adherence should particularly be targeted on women < 65 years, elderly > 84 years and patients at low stroke risk.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with increased morbidity and mortality from stroke and systemic thromboembolism [1].

The overall burden, prevalence, incidence and AF-associated mortality are progressively increasing worldwide [2]. Twenty-five per cent of all adults over 40 years of age will develop AF during their life-time [3] with a five-fold increased risk of stroke compared to a non-AF population [4]. Atrial fibrillation accounts for at least 15% of all strokes and as many as 36% of strokes in patients over 80 years of age [5]. Strokes associated with AF are generally more severe with increased risk of death, disability, complications and recurrence compared to non-AF strokes [6].

Warfarin reduces stroke risk in patients with non-valvular AF by 64% [7]. Direct-acting oral anticoagulants (DOAC), such as rivaroxaban, dabigatran and apixaban, are non-inferior to warfarin in stroke prevention without increasing the risk of major bleeding [8].

CHA_2DS_2-VASc score [9] is used as risk stratification criteria and has been validated in multiple cohorts [10,11]. Oral anticoagulation (OAC) (warfarin or DOAC) is recommended by European Society of cardiologists (ESC) guidelines from 2010 [12] and 2012 [13] for prevention of thromboembolism for patients with CHA_2DS_2-VASc score ≥ 2 and should be considered for patients with CHA_2DS_2-VASc score of 1 [13]. For women under 65 with lone atrial fibrillation no anticoagulation should be considered [13]. The ESC 2010 guidelines recommended use of ASA or OAC in patients with CHA_2DS_2-VASc score of 1 (with OAC as preferred option) and ASA or no antithrombotic treatment in patients

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with CHA_2DS_2-VASc score of 0 (with no antithrombotic treatment as preferred option) [12]. The role of ASA was de-emphasized in the 2012 focused update of the ESC guidelines, since the evidence for stroke prevention in AF with acetylsalicylic acid (ASA) is weak and the risk of bleeding is similar to warfarin [13].

Patients with a high bleeding risk according to HAS-BLED score [14] had even better net clinical benefits with warfarin [10] and therefore HAS-BLED score *per se* should not be used to exclude patients from anticoagulation therapy [13]. Contraindications to anticoagulants are present in about 15–20% of AF patients [15,16].

Current treatment practice does not seem to follow the guidelines. Underuse of anticoagulants in high risk patients was reported in multiple observational studies with treatment levels below 60% (range: 19–81.3%) for patients with previous stroke and below 70% (range: 39–92.3%) for patients with CHADS score ≥ 2 [17]. Recent data from 17,000 patients enrolled in Global Anticoagulant registry in the Field – Atrial Fibrillation (GARFIELD-AF) reports that over 35% of patients with CHA_2DS_2-VASc score ≥ 2 did not receive OAC, while over 41% of patients at low stroke risk were treated [18].

According to Swedish Council on Health Technology Assessment (SBU) report from 2013 only 42% of AF patients in Sweden were treated with anticoagulants and undertreatment was more common in women and patients over 80 years of age [19]. The proportion of patients with CHA_2DS_2-VASc score ≥ 2 receiving OAC varies between 56 and 71% in different county councils of Sweden [20].

The present study aims to provide a detailed description of current clinical practice of anticoagulation therapy in newly diagnosed non-valvular atrial fibrillation in Skåne County of Southern Sweden and assess the impact of the components of CHA_2DS_2-VASc score on the treatment choice.

2. Methods

2.1. Study population

All adult patients (>18 years old) diagnosed with their first non-valvular atrial fibrillation or flutter between the 1st of January 2011 and the 31st of December 2014 were identified in the Skåne Healthcare register (SHR) by the International Classification of Diseases (ICD 10) code I48 and included in the study. The SHR contains detailed information (including date of visit and ICD-10 diagnostic codes) about hospital admissions and ambulatory health care visits from all health care providers (cardiology, emergency medicine, internal medicine, other secondary care and primary care) in Skåne Region (total population 2010, n = 1,243,329). Validity of diagnoses in SHR has been confirmed in previous studies [21,22].

Valvular heart disease (identified by ICD code I05-09 or I33-39), death before the study's end-point, or not being a resident of the Skåne County the entire 10 years preceding the AF diagnosis (for assessing comorbidities) were cause for exclusion.

2.2. Assessment of risk factors

CHA_2DS_2-VASc score [9] (congestive heart failure, hypertension, age over 65 or 75 years, diabetes mellitus, 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 gender) and HAS-BLED score [14] (hypertension, renal disease, liver disease, prior stroke, prior major bleeding (intracranial, gastro-duodenal or other) or predisposition to bleeding (anaemia, platelet or coagulation defect), age over 65 years, alcoholism) were calculated to assess the risk of ischemic stroke and bleeding respectively. Since we did not have any information on NSAID use or history of labile INR (international normalised ratio), no points were given for these components of HAS-BLED. Comorbidities relevant for the calculation of CHA_2DS_2-VASc and HAS-BLED scores were assessed during the 10 years (for cancer; 3 years) preceding the AF-diagnosis, using the ICD-10 codes listed in Table A.1 in the Appendix.

2.3. Outcome

Potential undertreatment was defined as ASA or no treatment in patients with CHA_2DS_2-VASc score ≥ 2. Overtreatment was defined as treatment with ASA or OAC in patients with CHA_2DS_2-VASc score = 0 without any other indications to OAC (cardioversion within 3 months from the AF diagnosis date, venous thromboembolism (VTE) 6 months backwards and 3 months forward from the AF diagnosis date or recurrent VTE (defined as ≥2 VTE diagnoses 10 years backwards from the AF diagnosis date). Treatment with OAC in patients with CHA_2DS_2-VASc ≥ 2, OAC or no treatment in patients with CHA_2DS_2-VASc score 1 and no treatment of patients with CHA_2DS_2-VASc score 0 was considered guideline adherent treatment.

The ESC guidelines update from 2012 recommends that no anticoagulant treatment should be considered to women < 65 years with lone AF. Therefore, the proportion of women diagnosed with AF 2012–2014 with CHA_2DS_2-VASc score = 1 receiving treatment with OAC or ASA (without other indications for OAC) was also assessed.

The outcome of this study was ASA, DOAC or warfarin dispensed within 3 months after the index date and identified in Skåne Region's Prescribed Drug Database. Detailed information of every dispensed prescription linked to the individual patient is automatically collected from all pharmacies. The database in Skåne receives information for all inhabitants in Skåne. Patients receiving combined therapy with OAC and ASA were classified as treated with OAC, since ASA was likely prescribed for other indications than atrial fibrillation.

2.4. Statistical analysis

Proportions of patients receiving DOAC, ASA, warfarin or no treatment were assessed per age and gender category in patients with CHA_2DS_2-VASc score ≥ 2. Prescription patterns in patients with CHA_2DS_2-VASc score ≥ 2 and 0 respectively were analysed in regard to the medical specialties where AF was initially diagnosed. Categorical variables were reported as percentages. Among-group comparisons were made using Chi-2 test. Continuous variables were reported as median and interquartile range. Among group-comparisons were made using Kruskal-Wallis test and Mann-Whitney test when appropriate. Prescription trends and guideline adherence through 2011–2014 were assessed.

For patients with CHA_2DS_2-VASc score ≥ 2 odds ratios (OR) were calculated to estimate the association between the independent stroke risk factors and the use of OAC. Multiple logistic regression model included variables of CHA_2DS_2-VASc score (congestive heart failure, hypertension, age, diabetes mellitus, ischemic stroke, unspecified stroke, TIA, peripheral arterial embolism, myocardial infarction, peripheral arterial disease and gender). Variables with P-value > 0.10 were removed stepwise. Variables with P-value < 0.05 were considered to be significant contributors and retained in the final model. The adjusted odds ratios and associated 95% intervals for OAC prescription were determined. Goodness-of-fit was tested with Hosmer-Lemeshow test.

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

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

3. Results

3.1. Study population

Overall, 17,790 patients were newly diagnosed with AF between the 1st of January 2011 and the 31st of December 2014. Patients with