Thrombosis Research 136 (2015) 744–748

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Warfarin persistence among stroke patients with atrial fibrillation

Fredrik Björck [a,*], Henrik Renlund [b], Peter J. Svensson [c], Anders Själander [a]

[a] Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[b] Uppsala Clinical Research Centre, Uppsala University, Uppsala, Sweden
[c] Department for Coagulation disorders, University of Lund, Malmö, Sweden

ARTICLE INFO

Article history:
Received 4 March 2015
Received in revised form 25 July 2015
Accepted 27 July 2015
Available online 30 July 2015

Keywords:
Atrial fibrillation
Discontinuation
Persistence
Stroke
Treatment
Warfarin

ABSTRACT

Introduction: Warfarin treatment discontinuation is significant among patients with atrial fibrillation (AF). For AF patients with stroke a warfarin persistence rate of 0.45 after 2 years has previously been reported. No consistent predictors for discontinuation have been established.
Aims: Evaluation of warfarin persistence and variables associated with discontinuation, in a large Swedish cohort with unselected stroke/TIA patients with AF treated with warfarin.
Materials and methods: 4 583 patients with stroke/TIA and AF in the Swedish National Patient Register (NPR), from 1. Jan 2006 to 31. Dec 2011, were matched with the Swedish national quality register AuriculA. They were followed until treatment cessation, death or end of study. Baseline characteristics and CHA_2DS_2VASc score were retrieved from NPR. Treatment-time was retrieved from AuriculA.
Results: Overall proportion of warfarin persistence was 0.78 (95% confidence interval (CI) 0.76 to 0.80) after one year, 0.69 (95% CI 0.67 to 0.71) after 2 years and 0.47 (95% CI 0.43 to 0.51) after 5 years. Variables clearly associated with higher discontinuation were dementia (hazard ratio (HR) 2.22, CI 1.51-3.27) and alcohol abuse (HR 1.66, CI 1.19-2.33). Chronic obstructive pulmonary disease (COPD), cancer and chronic heart failure (CHF) were each associated with over 20% increased risk of treatment discontinuation. Higher CHA_2DS_2VASc score and start-age lead to lower persistence ($p < 0.001$).
Conclusions: Persistence to warfarin in unselected stroke/TIA patients with AF is in Sweden greater than previously reported. Lower persistence is found among patients with high treatment start-age, incidence of dementia, alcohol abuse, cancer, CHF, COPD and/or high CHA_2DS_2VASc score.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia with a prevalence of 3% in Sweden [1]. It is an independent risk factor for ischemic stroke [2,3]. Age and other comorbidities can, using scoring systems like $CHADS_2$ and CHA_2DS_2-VASc, predict a yearly stroke risk up to 18% [4,5]. Treatment with oral anticoagulants can reduce this risk by 2/3, but also confers a significant risk of serious bleeding [6]. Warfarin is in the era of new oral anticoagulants (NOACs) still the most common anticoagulant in Sweden [7,8]. This is partly due to a longstanding tradition with computerised dosing systems and specialised nurses caring for these patients, resulting in a high treatment quality with warfarin as measured by time in therapeutic range (TTR) [9–11].

For patients with AF and previous stroke, there is a strong indication for oral anticoagulation. In clinical reality there is however an under-treatment with oral anticoagulants in this patient group, especially in the elderly population [12–14]. A recent report shows that only 42% of patients with known AF in Sweden are receiving adequate stroke prophylaxis with oral anticoagulants [1]. Under-treatment with oral anticoagulation in AF patients confers an unnecessary risk of stroke. Apart from not prescribing oral anticoagulation at all to these patients at risk, premature cessation of properly instituted oral anticoagulation treatment will also result in preventable strokes. Factors influencing the discontinuation rate are therefore of clinical importance.

Previous studies on warfarin treatment persistence among AF patients, points to a significant discontinuation rate [15–19]. A Swedish study on secondary stroke-prophylaxis shows that only 45% of AF patients are still on warfarin two years after start of treatment [20]. Warfarin discontinuation is associated with male sex, homelessness, the susceptibility to adverse side effect of drugs and cognitive impairment as seen in dementia and depression. However, until now, no consistent predictors have been established [21,22].

The aim of this study was to evaluate warfarin persistence and variables associated with discontinuation in a large Swedish cohort with

Abbreviations: AF, Atrial Fibrillation; CDR, Cause of Death Register; CHF, Chronic Heart Failure; COPD, Chronic Obstructive Pulmonary Disease; NPR, The Swedish National Patient Register; TIA, Transient Ischemic Attack.

* Corresponding author at: Department of Public Health and Clinical Medicine, Umeå University, 901 87 Umeå, Sweden.
E-mail address: fredrik.bjorck@lvn.se (F. Björck).

http://dx.doi.org/10.1016/j.thromres.2015.07.028
0049-3848/

unselected patients with previous stroke and diagnosed AF under well-defined warfarin treatment.

2. Materials and Methods

A retrospective multicentre cohort study based on the national quality register AuriculA.

2.1. AuriculA

AuriculA is a Swedish national quality register for AF and oral anticoagulation, which since 2008 is funded by the Swedish Association of Local Authorities and Regions. The register was started in 2006, and now includes over 110.000 patients from 224 participating centers nationwide, both specialized anticoagulation clinics as well as primary health care centers. Approximately 50% of all patients on warfarin in Sweden are included in AuriculA. Participation in AuriculA is mostly within whole regions with no apparent selection bias. Over 5.000.000 INR samples are registered [8]. Everything done with the patients in the anticoagulation centers in everyday clinical practice is recorded and transferred to the quality register automatically once every 24 hours, provided that the patient has not declined to participate. AuriculA also provides a clinical decision tool, aiding in the dosage of warfarin using a dosing algorithm [23]. If certain criteria are met, the algorithm can give a dose suggestion that can be accepted or manually changed.

2.2. Swedish National Patient Register

The Swedish National Patient Register (NPR) contains information about hospital admissions as well as visits in outpatient clinics in Sweden for all patients with a Swedish personal identity number [24]. The register includes information about patient's age and sex, dates for admission and discharge, ICD10 codes for primary and secondary diagnoses as well as codes for surgical procedures.

2.3. Cause of Death Register

The Cause of Death Register (CDR) includes deceased persons with a Swedish personal identity number and contains information about their age and sex, date and cause of death and whether or not autopsy was performed.

2.4. Methods

All patients diagnosed with the combination of AF and stroke/TIA in NPR from 1. Jan 2006 to 31. Dec 2011, were matched with AuriculA. No exclusions were made. Overall 4 583 patients, all on warfarin treatment started during the study period, were included and followed until treatment cessation, death or end of the study period at 31. Dec 2011.

Baseline characteristics and CHA_2DS_2VASc score were retrieved from NPR, using its ICD-10 codes and surgical procedure codes (se Appendix A). Date of death was retrieved from CDR. Treatment-time was retrieved from AuriculA, where exact date for treatment cessation is registered. Persistence to warfarin treatment was defined as ongoing treatment registered in AuriculA, till death of patient or end of study. Persistent treatment could include a maximum of 7 days continuous temporal suspension when need for tests, invasive procedures or surgeries. If treatment cessation was within one day from date of death, treatment stop was considered due to death. All other treatment discontinuations were defined as non-persistence.

3. Statistical Methods

Data were analysed using SPSS Statistics (Version 21; SPSS Inc., IBM Corporation, NY, USA), and R version 3.0.0, R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/. For analysis of predictors of warfarin treatment discontinuation Cox regression was used, while Kaplan-Meier-method with Log rank test was used when analysing treatment non-persistence for different CHA_2DS_2VASc score. Confidence intervals (CI) are 95%.

4. Results

In total 4 583 patients, 45.8% females, with a mean age at study start of 75.6 years (SD ± 9.0) were included. Median CHA_2DS_2-VASc score at start was 5, indicating existing comorbidities, as presented in Table 1.

Of the 4 583 patients, 3 063 (66.8%) were persistent to the warfarin treatment. Overall 465 (10.1%) patients died during the study period. 207 (4.5%) patients died with on-going warfarin treatment. The overall proportion of warfarin treatment persistence was 0.78 (95% CI 0.76 to 0.80) after one year, 0.69 (95% CI 0.67 to 0.71) after 2 years and 0.47 (95% CI 0.43 to 0.51) after 5 years (Table 2 and Fig. 1).

Patients with diagnosed dementia were more than two-times likely of discontinuation of warfarin than others (hazard ratio (HR) 2.22, CI 1.51-3.27). Patients with excessive alcohol use had 66% higher risk of discontinuing treatment than others (HR 1.66, CI 1.19-2.33). Chronic obstructive pulmonary disease (COPD), cancer and chronic heart failure (CHF) were baseline diagnoses each associated with over 20% increased risk of treatment discontinuation (HR 1.28, CI 1.08-1.51, HR 1.27, CI 1.09-1.49 and HR 1.23, CI 1.09-1.39). The risk of warfarin discontinuation increased significantly with treatment start-age. For every year the risk increased with 1.5% (HR 1.01, CI 1.01-1.02). Furthermore, patients with diagnosed hypertension, previous myocardial infarction, anemia or with a history of fall, were slightly more likely to be non-persistent to warfarin treatment compared with others (HR ranging from 1.12-1.20) (Table 3).

Patients with a TTR < 60% had a higher risk of treatment discontinuation as compared to patients with TTR ≥ 60%, odds ratio 1.93 (95% CI 1.69 – 2.20).

The patients were represented in every CHA_2DS_2-VASc score from 2–9, but a fairly small proportion fell in the score of 2 (2.4%) and 9

Table 1
Baseline characteristics of 4 583 stroke/TIA patients with atrial fibrillation on warfarin treatment. Presented in n (%), if other not indicated.

Baseline variables	n (%)
Start age, mean year (SD)	75.6 (± 9.0)
Male	2486 (54.2)
Female	2097 (45.8)
Stroke	3548 (77.4)
TIA	1442 (31.5)
Hypertension	3022 (65.9)
Chronic heart failure	1001 (21.8)
Diabetes mellitus	872 (19.0)
Prior myocardial infarction	755 (16.5)
CHA_2DS_2-VASc, median score	5
0-1 point	0
2 points	108 (2.4)
3 points	417 (9.1)
4 points	837 (18.3)
5 points	1209 (26.4)
6 points	1152 (25.1)
7 points	628 (13.7)
8 points	203 (4.4)
9 points	29 (0.6)
Cancer	481 (10.5)
Chronic obstructive pulmonary disease	411 (9.0)
Renal failure	195 (4.3)
Excessive alcohol use	80 (1.7)
Dementia	45 (1.0)
Liver disease	30 (0.7)
History of fall	620 (13.5)
Anemia	356 (7.8)
Any previous major bleeding	345 (7.5)
Gastrointestinal bleeding	146 (3.2)
Intracranial bleeding	113 (2.5)