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Original Article

Initiation of rivaroxaban in patients with nonvalvular atrial fibrillation at the primary care level: The **S**wiss **T**herapy in **A**trial Fibrillation for the **R**egulation of Coagulation (STAR) Study

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ABSTRACT

Background: Rivaroxaban has become an alternative to vitamin-K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF) patients due to its favourable risk–benefit profile in the restrictive setting of a large randomized trial. However in the primary care setting, physician's motivation to begin with rivaroxaban, treatment satisfaction and the clinical event rate after the initiation of rivaroxaban are not known.
Methods: Prospective data collection by 115 primary care physicians in Switzerland on consecutive nonvalvular AF patients with newly established rivaroxaban anticoagulation with 3-month follow-up.
Results: We enrolled 537 patients (73 ± 11 years, 57% men) with mean $CHADS_2$ and HAS-BLED-scores of 2.2 ± 1.3 and 2.4 ± 1.1, respectively: 301(56%) were switched from VKA to rivaroxaban (STR-group) and 236(44%) were VKA-naïve (VN-group). Absence of routine coagulation monitoring (68%) and fixed-dose once-daily treatment (58%) were the most frequent criteria for physicians to initiate rivaroxaban. In the STR-group, patient's satisfaction increased from 3.6 ± 1.4 under VKA to 5.5 ± 0.8 points ($P < 0.001$), and overall physician satisfaction from 3.9 ± 1.3 to 5.4 ± 0.9 points ($P < 0.001$) at 3 months of rivaroxaban therapy (score from 1 to 6 with higher scores indicating greater satisfaction). In the VN-group, both patient's (5.4 ± 0.9) and physician's satisfaction (5.5 ± 0.7) at follow-up were comparable to the STR-group. During follow-up, 1(0.19%; 95%CI, 0.01–1.03%) ischemic stroke, 2(0.37%; 95%CI, 0.05–1.34%) major non-fatal bleeding and 11(2.05%; 95%CI, 1.03–3.64%) minor bleeding complications occurred. Rivaroxaban was stopped in 30(5.6%) patients, with side effects being the most frequent reason.
Conclusion: Initiation of rivaroxaban for patients with nonvalvular AF by primary care physicians was associated with a low clinical event rate and with high overall patient's and physician's satisfaction.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a high risk of thromboembolic complications [1,2]. Vitamin-K antagonists (VKA) are highly effective in preventing these complications [3]. However, various practical limitations like drug–drug and drug–food interactions, the slow onset of action, the narrow therapeutic window, and the large variation in individual response requiring regular monitoring make the use of VKA challenging for the physician and burdensome for the patients [4–6]. These limitations together with the fear of bleeding complications contribute to the systematic underuse of VKA leaving patients exposed to the risk of stroke [7–10].

Abbreviations: AF, non-valvular atrial fibrillation; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, Stroke [doubled]; CHA_2DS_2-VASc, Congestive heart failure/left ventricular dysfunction, Hypertension, Age 75 [doubled], Diabetes, Stroke [doubled]—Vascular disease, Age 65–74, and Sex category [female]; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INRs, Elderly (>65 years), Drugs/alcohol concomitantly; INR, international normalized ratio; NOAC, non-VKA oral anticoagulant; STR-group, switch from VKA to rivaroxaban group; VKA, vitamin-K antagonists; VN-group, VKA-naïve-group.

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The non-VKA oral anticoagulant (NOAC) rivaroxaban is an oral direct factor Xa inhibitor and has been approved in many countries for stroke prevention in patients with non-valvular AF. Rivaroxaban has a predictable anticoagulant effect that enables the administration of a fixed dose without routine coagulation monitoring, rapid onset and offset of action, no interaction with dietary vitamin-K intake, and fewer drug–drug interactions than VKA [7,11]. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin-K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) of 14,264 patients with non-valvular AF at increased risk for stroke, rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism, and was associated with a lower risk of intracranial and fatal bleeding complications [11]. However, data from clinical trials may not necessarily apply to the primary care setting where many patients on anticoagulation therapy are being managed. Thus, there is a need to investigate efficacy and safety of rivaroxaban initiated at the primary care level in patients with AF.

Compliance is a major concern for all diseases requiring long-term drug intake. Patient's satisfaction and possibly also physician's satisfaction with oral anticoagulation therapy have a positive impact on compliance and therefore stroke prevention [12–14]. Wang and colleagues recently showed that better patient's knowledge and satisfaction regarding oral anticoagulation were associated with higher warfarin adherence [14]. Because of the short half-life of rivaroxaban, a high compliance is crucial and continuing patient education is recommended [15]. The impact of the NOACs on the overall and time investment for patient education by the primary care physician has not yet been evaluated.

According to the most recent international consensus guidelines, NOACs rather than VKA should be considered for stroke prevention in patients with non-valvular AF [2,15,16]. Aims of the present study were to investigate motivation and reasons for primary care physicians to start or to switch to rivaroxaban, to assess patient's and primary care physician's satisfaction with oral anticoagulation therapy, and to assess 3-month clinical outcomes following rivaroxaban initiation in patients with non-valvular AF in the primary care setting.

2. Methods

2.1. Study population and study design

This study was designed to prospectively collect the initial treatment experience with rivaroxaban by primary care physicians in charge of patients with AF. Randomly chosen primary care physicians in Switzerland were contacted by letter to participate in this study. Overall, 115 primary care physicians participated in the study. The study protocol was approved by the local Ethics Committees and conformed to the standards set by the Declaration of Helsinki [17]. All patients provided written informed consent prior to participation in the study.

We included consecutive patients with non-valvular AF, as documented on electrocardiography, not previously treated with a NOAC, with newly established rivaroxaban anticoagulation therapy by the primary care physician. Independently of the study protocol, the primary care physician was free to choose among the different oral anticoagulant drugs approved for this indication in Switzerland, and data on patients not initiated with rivaroxaban therapy were not collected. Patients with valvular AF, defined as AF in the presence of a mechanical heart valve or in the presence of rheumatic valvular disease were excluded. Patients were divided into two groups: the first consisted of patients who were switched from VKA to rivaroxaban (switch to rivaroxaban group, STR group); the second group consisted of patients in whom rivaroxaban was started without ongoing VKA therapy (VKA-naïve patients, VN group). The rivaroxaban dosing regimen was determined by the primary care physician.

The study consisted of two visits at the primary care physician's private practice. At the baseline visit, when rivaroxaban was initiated, the primary care physician recorded data on demographics, type of AF, thromboembolic and bleeding risk factors, concomitant medications, and his or her criteria to switch to or to start with rivaroxaban, using a standardized case report form. At the follow-up visit 3 months after the initiation of rivaroxaban therapy, the primary care physician recorded relevant side effects, complications and reasons for stopping rivaroxaban.

2.2. Endpoints

At both visits, patients and primary care physicians were asked to grade their overall satisfaction with the currently used oral anticoagulation using a score ranging from 1 to 6 points with higher scores indicating greater satisfaction. The same score was used by the primary care physician to grade the estimated overall investment for the management of the anticoagulation therapy, the estimated investment for the patient information, and to grade the estimated overall complexity of the anticoagulation management with higher scores indicating more investment or complexity.

The primary efficacy end point was the composite of stroke (ischemic or haemorrhagic) and systemic embolism at 3 months. The principal safety end point was a composite of major and minor bleeding events at 3 months, as defined by the International Society on Thrombosis and Haemostasis [18]. Primary efficacy and safety endpoints were centrally adjudicated (RPE, NK).

2.3. Statistics

Data are presented as means ± standard deviations or absolute numbers and percentages for continuous and categorical variables, respectively. Where appropriate, categorical outcomes are presented as percentage with 95% confidence intervals (95%CI). Event rates per 100 patient-years are presented as proportions of patients per year, and 95%CI was calculated assuming a Poisson distribution. Data were stratified with regard to the two groups, STR and VN group. P-values for differences between the groups were calculated from unpaired t-tests or Wilcoxon rank test where appropriate for continuous variables, and chi-square tests for categorical variables. Physician or patient satisfaction at baseline and follow-up visit was compared using paired t-tests. All statistical analyses were performed using STATA version 10.1 (StataCorp, College Station, Texas, USA).

3. Results

3.1. Patient characteristics

Between January 2012 and May 2013, a total of 537 patients were included: 301 (56%) in the STR group and 236 (44%) in the VN group (Table 1). Mean age of the total study group was 73.3 ± 10.7 years, with 6 (1.1%) patients younger than 45 years, 23 (4.3%) patients between 45 and 54 years, 81 (15.1%) patients between 55 and 64 years, 173 (32.2%) patients between 65 and 74 years, 180 (33.5%) patients between 75 and 84 years, and 74 (13.8%) patients 85 years or older. Patients in the STR group were older and with a higher mean body mass index than patients in the VN group. Paroxysmal AF was more frequent in the VN group while permanent AF was more frequent in the STR group (Table 1). Mean duration of AF was 3.5 ± 4.8 years (range 0 to 35 years) in the whole study group. Mean duration of AF was longer in the STR group than in the VN group (4.9 ± 5.1 years vs. 1.6 ± 3.5 years, $P < 0.001$), with similar differences for paroxysmal AF (3.2 ± 3.6 years vs. 1.7 ± 2.9 years, $P < 0.001$), persistent AF (4.7 ± 4.6 years vs. 0.9 ± 2.5 years, $P < 0.001$), and permanent AF (6.2 ± 6.0 years vs. 2.2 ± 4.4 years, $P < 0.001$). Congestive heart failure and labile international normalized ratio (INR) were more frequent in the STR group. Both $CHADS_2$ and CHA_2DS_2-VASc-scores were higher in the STR group (Table 1).