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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Rivaroxaban in secondary cardiogenic stroke prevention: two-year single-centre experience based on follow-up of 209 patients

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Abstract

Background: The main goal of treatment in patients with atrial fibrillation is to counteract the effects of embolisation, considering the relatively high risk of cerebral embolic events.

Aim: An assessment of the efficacy and safety of rivaroxaban in secondary stroke prevention in patients with non-valvular atrial fibrillation (NVAF).

Methods: The study concerned 209 NVAF patients (male/female: 117/92; mean age 65.3 years [41–85]), who used rivaroxaban as secondary prevention of cardiogenic stroke. The patients were followed up for 24 months: the control visits were performed 12 and 24 months after the onset of the inclusion. The following aspects were analysed: the occurrence of recurrent stroke and/or transient ischaemic attack (TIA) during rivaroxaban treatment, bleeding episodes with their placement and severity assessment, drug tolerance, and evaluation of the patient's medical records including laboratory tests (e.g. creatinine clearance) and concomitant therapy. All patients underwent physical examination as well as neurological assessment.

Results: The mean CHA_2DS_2-VASc in the study group was 4.16, and the mean HAS-BLED value was 3.31. During the follow-up 13 deaths were noted (6.22%), ischaemic stroke was diagnosed in five (2.39%) subjects, and TIA in three (1.43%) patients. Bleeding complications were reported in 25 (11.96%) patients, two of which were classified as major bleedings (0.95%): an intracranial bleeding (1) and a bleeding from the genital tract (1).

Conclusions: For patients with NVAF and cerebrovascular events, the use of rivaroxaban in a real-world clinical setting results in a highly efficacious treatment profile and acceptable safety.

Key words: rivaroxaban, stroke, atrial fibrillation

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INTRODUCTION

Atrial fibrillation (AF) is the cause of 18–23% of all cerebral strokes [1]. In comparison to other non-cardiogenic brain ischaemic events, AF-related strokes often result in a severe clinical course, higher mortality, and significantly greater post-stroke disability [2, 3]. Besides the clinically-confirmed brain ischaemic event in the population of AF patients, at least 15% of subjects exhibit clinically-silent foci (silent strokes) in neuroimaging [4]. Depending on their amount and location, these foci may form the cause of bradykinesia and/or cognitive impairment.

The main aim of treatment provided to AF patients is to counteract the effects of embolisation while considering the relatively high risk of cerebral embolic events. It is worth noting that a serious risk of stroke is associated with silent AF, which relate to approximately 1.4% of the population ≥ 65 years old

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and concern patients who do not use anticoagulant protection [5]. Inclusion of new oral anticoagulant pharmacotherapy in AF patient management may render better patient compliance and high clinical efficacy of treatment in this patient group. In terms of efficacy, new oral anticoagulants (NOAC) are at least non-inferior to warfarin. Additionally, the results of the studies performed reveal a promising trend in terms of reduction in major and intracranial bleedings in comparison with standard warfarin therapy. One of the new oral anticoagulant molecules first investigated in a clinical setting is the selective factor Xa inhibitor — rivaroxaban, which is currently approved to prevent and treat venous thromboembolic events and reduce the risk of stroke and systemic embolisation in patients with non-valvular atrial fibrillation (NVAF). As in the case of other anticoagulant drugs, approval of rivaroxaban was based on previous clinical studies performed in carefully selected patient populations. In light of the results presented in randomised controlled studies, it is also important to evaluate the efficacy and safety of new therapies during long-term follow-up and in a real-world clinical setting. The aim of our study was to assess the efficacy and safety of rivaroxaban in secondary stroke prevention in NVAF patients. This article presents a single-centre experience with the application of rivaroxaban in the treatment of 209 AF patients followed-up at least 24 months following the start of NOAC therapy.

METHODS

The prospective observational study (2011–2014) covered 209 NVAF patients (male/female: 117/92; mean age 65.3 years [41–85]) who used rivaroxaban as a secondary prevention of cardiogenic stroke. In the period between 2011 and 2014, 277 patients with ischaemic stroke or transient ischaemic attack (TIA) and NVAF were treated in the Department of Neurology. As part of secondary prevention of stroke, 26 patients used vitamin K antagonists (acenocoumarol was administered to nine, warfarin to 17 subjects), dabigatran was used by 42, and rivaroxaban by 209 subjects. The present study enrolled NVAF patients with a history of acute cerebral ischaemia. Non-valvular AF was used to imply that AF was not related to rheumatic valvular disease (predominantly mitral stenosis), other forms of mitral stenosis, or prosthetic heart valves. The contraindications for rivaroxaban therapy specified in product characteristics were applied to formulate the criteria for study inclusion and exclusion. An estimate of renal function (the estimated creatinine clearance (eCrCl) was based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, and patients with eCrCl values < 30 mL/min were excluded. The whole study group consisted of 31 TIA subjects and 178 subjects with confirmed ischaemic stroke. All of the patients qualified to the anticoagulant therapy started rivaroxaban administration within the acute phase of stroke or after a TIA. NOAC therapy was initiated on the second to tenth day of the onset of neurological symptoms. The decision to start treatment depended on the patient's clinical status. Rivaroxaban was introduced a day after a neurological episode occurred in TIA patients. In the group of patients with stroke, rivaroxaban therapy was started on the third day after an ischaemic episode, if the score on the National Institute Stroke Scale (NIHSS) was ≤ 4 points; on the fifth day, if NIHSS score was 5–10 points; and on the ninth day, if NIHSS score was > 10 points.

In 185 patients, AF was already recognised before the neurological episode; in 24 patients AF was diagnosed during hospitalisation in the Department of Neurology (based on electrocardiogram [ECG] results or 24-h ECG monitoring). To exclude the presence of valvular heart disease, in all patients a cardiological consultation was performed including transthoracic echocardiography. The estimated risk of cerebral stroke was calculated on the basis of the CHA_2DS_2-VASc score; the risk of bleeding was assessed by the HAS-BLED scale. Patients previously receiving oral NOAC were excluded from the study. In all cases the data relating to the comorbidities as well as previous anticoagulant therapies were collected.

The patients were followed up 24 months from the inclusion into the study and the beginning of rivaroxaban therapy; control visits were performed 12 and 24 months after the onset of the NOAC administration. The following aspects were analysed during the follow-up visits performed by an experienced neurologist at the outpatient clinic: the occurrence of recurrent stroke and/or TIA during rivaroxaban treatment, bleeding episodes with their placement and severity assessment, and drug tolerance, as well as evaluation of the patient's medical records including laboratory tests (e.g. creatinine clearance) and concomitant therapy. All patients underwent physical examination as well as neurological assessment. Deaths in that group were reported either by the family of the deceased patient (if he/she died at home) or by the physicians from other sites (if he/she was treated there). The following definition of 'major bleeding' was adopted to assess the results of our observation: a clinically manifested bleeding associated with a decrease in haemoglobin values by at least 2 g/dL; a bleeding requiring transfusion of at least two units of blood; an intracranial bleeding; a bleeding into the retroperitoneal space or from another prominent location; or a bleeding resulting in death. The patients completed follow-up visits in accordance with the algorithm of management adopted by the site and related to those patients who experienced an acute cerebrovascular episode.

One hundred and seventy-one patients initiated therapy with rivaroxaban at a dose of 20 mg per day and 38 patients at a dose of 15 mg per day (according to product characteristics and instructions for use, a reduced dose was administered to patients aged over 80 years, with creatinine clearance 30–49 mL/min, or with high risk of bleeding). Additionally, in the follow-up period, concomitant aspirin therapy due to peripheral arterial atheromatosis was used by 28 (13.39%) subjects.

Study subjects were also asked to complete a survey presenting their opinions on new oral anticoagulant therapy. The survey questions concerned the advantages and disadvantages of that therapy.

RESULTS

Characteristics of patients during the eligibility visit are presented in Table 1.

The mean CHA_2DS_2-VASc score in the study group was 4.16 (4–9 points) and the mean HAS-BLED value was 3.31 (2–8 points). None of the 209 NVAF patients was lost to follow-up within the 24-month period following the start of rivaroxaban therapy. Thirteen (6.22%) deaths were reported during follow-up. There were no autopsies performed, and the reports concerning death causes were based on clinical diagnosis. Myocardial infarction was diagnosed in six cases, acute respiratory failure was identified in three cases, three patients died of cancer, and one death was related to stroke. There were no reports of death caused by haemorrhagic complications associated with NOAC therapy and, as mentioned before, only one ischaemic stroke-related death occurred as a result of rivaroxaban therapy. The mean age at death was 76.92 (69–85) years.

Among patients receiving rivaroxaban therapy, ischaemic stroke during follow-up was diagnosed in five (2.39%) subjects and TIA was reported in three (1.43%) subjects. The mean age of subjects with secondary neurological events was 67.11 (58–79) years. At the start of rivaroxaban therapy, the CHA_2DS_2-VASc score was as follows: 4 points in two patients, 5 points in one patient, 6 points in one patient, 7 points in two patients, and 8 points in two patients. One patient's functional status (4 points on mRankin scale) deteriorated as a result of stroke (despite using NOAC), and one patient died.

Bleeding complications were reported in 25 (11.96%) patients, two of which were classified as major bleedings (0.95%): an intracranial bleeding (1) and a bleeding from the genital tract (1). In 11 cases, haemorrhagic complications concerned those patients who were receiving concomitant aspirin therapy at a dose of 75 mg. No haemorrhagic events occurred during a 30-day period following the start of rivaroxaban therapy. Bleeding characteristics (bleeding location) are presented in Table 2. During follow-up, NOAC therapy was discontinued by 45 (21.53%) subjects. The reasons for discontinuation are presented in Table 3.

A survey concerning the use of oral rivaroxaban in anticoagulant therapy for NVAF was taken by 173 subjects (82.77% of patients). The most commonly reported advantages of the new therapy included (in order of importance) a fixed dose (170; 98.26%) and no need for laboratory monitoring (162; 93.64%). The most common disadvantages emphasised by the respondents were: high cost of treatment (137; 79.19%), pain/vertigo during the initial period of treatment, and/or gastrointestinal symptoms (25; 14.45%); 47.39% of respondents would strongly recommend new treatment; 39 (22.54%) respondents would recommend it; 39 (22.54%) respondents could not express their opinion; and 13 (7.51%) respondents would not recommend NOAC treatment.

Table 1. Characteristics of patients

Patients	209
Age, mean (range)	65.3 (41–83)
Male/female	117/92
Arterial hypertension	173 (82.7%)
Dyslipidaemia	49 (23.4%)
Coronary heart disease	44 (21%)
Diabetes mellitus	59 (28.2%)
Carotid or/and cerebral AS > 50%	32 (15.31%)
Previous anticoagulant treatment: VKA	81 (38.7%)
NVAF de novo	24 (11.48%)
Stroke/TIA	178/31
Rivaroxaban 20 mg/15 mg	171/38
CHA_2DS_2VASc, mean (range)	4.16 (4–9)
HAS-BLED, mean (range)	3.31 (2–8)

AS — artery stenosis; VKA — vitamin K antagonist; NVAF — non-valvular atrial fibrillation; TIA — transient ischaemic attack

Table 2. Location of bleeding episodes in 25 patients receiving rivaroxaban therapy

Nose	13 (6.22%)
Intraocular	6 (2.87%)
Urinary tract	4 (1.91%)
Gastrointestinal tract	1 (0.47%)
Genital tract	1* (0.47%)
Intracranial	1* (0.47%)

*Major bleeding

Table 3. Reasons for discontinuation of therapy in 45 patients

Dyspepsia	14 (6.69%)
Bleeding	12 (5.74%)
Worsening of the renal insufficiency	10 (4.78%)
Undefined reasons	6 (2.87%)
Financial reasons	3 (1.43%)

DISCUSSION

For many years, anticoagulant therapy has been successfully applied to AF patients to avoid the formation of atrial thrombus or its consequences, e.g. embolisation. The introduction of vitamin K antagonists (VKA) in that patient group resulted in a significant, 64% reduction of annual stroke rate, thus exceeding the efficacy of antiplatelet treatment with aspirin

[6]. However, the following problems arising from anticoagulant treatment with VKA are significant and must be considered. These problems include: treatment-related bleedings, a relatively narrow therapeutic window, a need for continuous anticoagulation monitoring, proper patient education, and cooperation with patients. The dose-response relationship associated with VKA may be influenced by genetic factors, drug interactions, and the consumption of foods containing vitamin K [7]. The above problems result in limited clinical efficacy and insufficient clinical use of VKA among patients with AF.

Rivaroxaban is a reversible factor Xa inhibitor, the efficacy and safety of which in NVAF patients was assessed in the ROCKET study in comparison to warfarin. The per-protocol analysis demonstrated that the incidence of stroke or systemic embolism (SE) was lower for rivaroxaban than for warfarin (1.7% per year vs. 2.2%; $p < 0.001$ for non-inferiority, respectively). Intention-to-treat analysis reported annual stroke or SE rates of 2.1% for rivaroxaban and 2.4% for warfarin ($p < 0.001$ for non-inferiority) [8]. In terms of the incidence of bleeding (major and clinically non-major bleeding) the study exhibited no differences between rivaroxaban and warfarin; the group of patients treated with rivaroxaban had significantly lower rates of haemorrhagic stroke and other forms of intracranial bleeding. There is no evidence that the relative efficacy and safety profiles for rivaroxaban and warfarin were different between the patients with a history of stroke or TIA and those without it [9].

Our study presents the results of a two-year follow-up conducted in a group of patients of a fairly homogeneous neurological profile treated with rivaroxaban. In contrast to numerous study reports, all of our study patients underwent early introduction of rivaroxaban following the onset of stroke or TIA. The vast majority of subjects participating in previous studies on rivaroxaban and other NOAC had the drug introduced with delay [10].

In the present study, ischaemic events (stroke and TIA) were observed in eight (3.8%) patients during a two-year follow-up after the application of rivaroxaban. It should be stressed that in our study group the one-year risk of stroke was clinically significant (with the CHA_2DS_2-VASc score ranging from 4% to 9.8%). During study enrolment, a significantly higher CHA_2DS_2-VASc score was noted in six out of eight subjects with stroke or TIA (5–8 points). One stroke-related death was reported in the stroke group. It is likely that among the patients with additional stroke during the study period persistent AF played an important role. As earlier reports suggest a comparable risk of stroke in subjects with persistent and paroxysmal AF, we did not assume that an analysis of the incidence of stroke related to AF type should be included in our study protocol [11, 12]. Among the AF subjects at a moderate-to-high risk of stroke, who receive anticoagulant treatment, patients with persistent AF run a higher risk of thromboembolic events and they show a lower survival rate than those with paroxysmal AF [13]. A considerable minority (18%) of subjects in the ROCKET-AF trial had paroxysmal AF at baseline. Patients with persistent AF showed some higher-risk characteristics, whereas those with paroxysmal AF obtained equivalent $CHADS_2$ and CHA_2DS_2-VASc scores. After adjustment, thromboembolic and mortality outcomes were consistently higher for the subjects with persistent AF; such an association was also true for the high-risk subgroups (including patients with a prior stroke) [13]. That leads to the suggestion that the worse outcomes related to AF are unlikely to be attributable to stroke risk only, and may therefore be related to electromechanical or haemodynamic sequelae of the rhythm.

The mean risk of iatrogenic bleeding in the present study was rated as moderate on the basis of the HAS-BLED scale. During follow-up, 25 (11.96%) bleeding episodes were observed among patients treated with rivaroxaban. The initial HAS-BLED score reported for patients with subsequent bleeding episodes ranged from 2 to 7 points. Two major bleedings were observed, including one patient with intracranial bleeding in the area of ischaemic lesion, but there was no significant deterioration in the patient's neurological condition.

Anticoagulant therapy increases the risk of intracranial bleeding; uncontrolled arterial hypertension, diabetes, and angiopathy may additionally influence intracranial bleeding complications during anticoagulant therapy [14–18]. Interestingly, the majority of intracranial bleeding episodes were observed during warfarin treatment with international normalised ratio within the therapeutic range [14, 19]. The possible causes of bleeding during NOAC therapy listed in literature include: erroneous patient selection, renal failure, concomitant antiplatelet therapy, and the advanced age of patients [20]. Aspirin was added to rivaroxaban at a dose of 75 mg in the treatment of 13% of our study subjects. Steinberg et al. [21] revealed that there was a significant risk (17%) of iatrogenic haemorrhage among AF patients undergoing concomitant anticoagulant and antiplatelet therapies (with ATRIA bleeding risk score ≥ 5).

Thirteen (6.22%) patients died during follow-up. Death most often followed myocardial infarction, respiratory insufficiency, or malignancy; however, no autopsy was performed in that group. There were no reports of death caused by a clinically-confirmed bleeding.

Despite the fact that the group of AF patients treated with NOAC is presently larger (approximately 78% according to the European registry), the mortality rate within a one-year follow-up in that group of patients remains high (5–6%). That is most often due to cardiovascular reasons (70%) [22]. According to a report by the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) registry team, independent death factors in AF patients include: age, chronic renal disease, past TIA, chronic obstructive pulmonary disease, neoplasm, minor bleeding, and the use of diuretics [22].

In the present study, 45 (21.53%) patients discontinued rivaroxaban treatment. In most cases the reason for discontinuing the NOAC therapy was a bleeding episode (24 individuals). In other cases, discontinuation was due to worsened renal function (six subjects), and dyspeptic symptoms and financial reasons (ten subjects). It should be mentioned that the majority of patients with abnormal renal parameters also suffered from diabetes mellitus, which is associated with a higher risk of kidney failure. We were unable to clearly establish the reasons for discontinuation in six individuals whose records were incomplete and whose motivations were unknown. According to the EORP-AF general registry, 86% of patients who are NOAC users at baseline maintain such therapies for a year; 11.8% of those patients shift to VKA or antiplatelet drugs (1.1%) [22]. According to the study by Yap et al. [23], the following factors (in order of importance) most often influenced the decision to discontinue NOAC treatment: the patient was willing to use warfarin; the patient followed the treatment plan (status after ablation), or iatrogenic bleeding events occurred.

According to patient satisfaction survey, the main advantages of the new treatment method were 'a fixed drug dose' and 'no need to monitor the therapy.' The main disadvantage of rivaroxaban treatment was its cost. Most of our patients, like the subjects from the EINSTEIN-PE trial, appreciated the advantages of rivaroxaban therapy [24].

The results of a post-approval observation study confirm the benefits of NOAC application demonstrated in earlier registration studies; in many cases, those results also point to greater efficacy and safety [23]. In order to establish the selection criteria for the formulation and dose optimisation while determining the risks/benefits, particularly for elderly patients with impaired renal function and other markers of increased bleeding risk, further studies are required. Gorczyca-Michta et al. [25] revealed that the following factors increase the likelihood of NOAC administration: bleeding (odds ratio [OR] 3.43), hospitalisation due to an AF episode (OR: 2.82), age ≥ 80 years (OR: 2.8), paroxysmal AF (OR: 1.77), the patient's rural area of residence (OR: 1.77).

Limitations of the study

The analysis does not cover AF types (persistent vs. paroxysmal AF), and there are no autopsy results to confirm the causes of deaths during follow-up, which forms the main limitation to our study.

CONCLUSIONS

1. In a real-world clinical setting, the use of rivaroxaban in patients with NVAF and cerebrovascular events results in a highly efficacious treatment profile and acceptable safety in the long-term treatment period.
2. Initiation of rivaroxaban therapy among NVAF patients during the acute phase of stroke does not cause a significant increase in their clinically-relevant bleeding rates.
3. Improved patient compliance and a relatively low treatment discontinuation rate encourage us to offer the therapy to a wider population of NVAF patients experiencing neurological ischaemic events.
4. In order to achieve proper safety and efficacy profiles, each patient will require an individual bleeding risk assessment and evaluation of indications for treatment.

Conflict of interest: *none declared*

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Riwaroksaban we wtórnej profilaktyce kardiogennego udaru mózgu: dwuletnie doświadczenie jednego ośrodka obejmujące 209 chorych

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Streszczenie

Wstęp: Migotanie przedsionków (AF) stanowi przyczynę 18–23% udarów mózgu. Biorąc pod uwagę wysokie ryzyko niedokrwienia mózgu, głównym celem terapii pacjentów z AF jest przeciwdziałanie zatorowości mózgowej.

Cel: Celem niniejszego badania była ocena skuteczności, bezpieczeństwa i tolerancji riwaroksabanu we wtórnej profilaktyce udaru mózgu u pacjentów z niezastawkowym AF (NVAF).

Metody: Do prospektywnego badania obserwacyjnego w latach 2011–2014 zakwalifikowano 209 pacjentów z NVAF [117 mężczyzn i 92 kobiety w śr. wieku 65,3 roku (41–85 lat)], u których we wtórnej profilaktyce udaru mózgu zastosowano riwaroksaban. Pacjentów objęto 2-letnim okresem obserwacji z planowymi wizytami w 12. i 24. miesiącu od włączenia terapii, podczas których przeprowadzono wywiad z uwzględnieniem incydentów neurologicznych, zdarzeń krwotocznych, tolerancji leczenia i oceny wyników badań, w tym klirensu kreatyniny.

Wyniki: W całej grupie pacjentów średni wynik wg skali CHA_2DS_2-VASc wynosił 4,16 (4–9) punktów, a średni wynik w skali HAS-BLED — 3,31 (2–8) punktów. Udar mózgu wystąpił u 5 (2,39%) chorych, a przejściowy atak niedokrwienny — u 3 (1,43%). Incydenty krwotoczne zaobserwowano u 25 (11,96%) pacjentów, w tym u 2 (0,95%) sklasyfikowane jako duże: wewnątrzczaszkowe (1) oraz z dróg rodnych (1). Podczas badania 45 (21,53%) chorych przerwało terapię riwaroksabanem, a 13 (6,22%) pacjentów zmarło.

Wnioski: 1. Zastosowanie riwaroksabanu w warunkach praktyki klinicznej (tzw. *real-world*) u pacjentów z ostrym niedokrwieniem mózgu w przebiegu NVAF wiąże się z wysoką skutecznością i akceptowalnym profilem bezpieczeństwa w obserwacji długoterminowej. 2. Włączenie riwaroksabanu w pierwszym miesiącu od wystąpienia udaru mózgu u pacjentów z NVAF nie powoduje wzrostu częstości krwawień istotnych klinicznie w ostrym okresie choroby. 3. Współpraca z chorym i względnie rzadki wskaźnik rezygnacji z terapii riwaroksabanem są czynnikami zachęcającymi do poszerzenia grupy pacjentów stosujących lek w profilaktyce wtórnej udaru mózgu. 4. W celu uzyskania optymalnej skuteczności i profilu bezpieczeństwa terapii riwaroksabanem każdy chory przed jej włączeniem wymaga ewaluacji ryzyka krwawienia oraz określenia ścisłych wskazań do terapii.

Słowa kluczowe: riwaroksaban, udar mózgu, migotanie przedsionków

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