Původní sdělení | Original research article

Efficacy and safety of non-vitamin K antagonist oral anticoagulants one year after electrical cardioversion

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SOUHRN

Úvod: Fibrilace síní (FS) je celosvětově nejčastější formou arytmie, která postihuje přibližně 33 milionů jedinců. Antikoagulanciem volby v prevenci cévní mozkové příhody u jedinců s FS je již dlouho warfarin. Několik velkých studií prokázalo, že nová (přímá) perorální antikoagulancia (non-vitamin K antagonist oral anticoagulant, NOAC) mají z hlediska bezpečnosti a účinnosti řadu předností, jako například fixní dávku a předvídatelnější farmakokinetiku.
Metody: Naše studie, provedená v lotyšském kardiocentru Fakultní nemocnice Pauls Stradins (Pauls Stradins Clinical University Hospital, Latvian Centre of Cardiology), probíhala od října 2015 do června 2017. Do studie bylo zařazeno celkem 356 pacientů, u nichž byla provedena elektrická kardioverze (EKV).
Výsledky: Jeden rok po EKV užívalo 27,5 % pacientů warfarin, 33,7 % pacientů NOAC, zatímco 38,8 % jich neužívalo žádná perorální antikoagulancia. Devět (2,5 %) pacientů, kteří se studie zúčastnili, v následujícím roce zemřelo. Celkem u osmi pacientů (2,2 %) došlo k významnému krvácení a tři pacienti (0,8 %) prodělali nefatální ischemickou cévní mozkovou příhodu. Incidence nefatální ischemické cévní mozkové příhody u pacientů užívajících warfarin byla 2 %, přičemž u pacientů užívajících NOAC nebyla žádná taková příhoda zaznamenána (p = 0,20). Incidence významného krvácení byla 5,1 % versus 2,5 % ve skupinách s warfarinem, resp. NOAC (p = 0,12).
Závěry: Ve srovnání s podobnými studiemi prokázala naše studie nízkou incidenci ischemických cévních mozkových příhod a významného krvácení i nízkou celkovou mortalitu. Jeden rok po EKV se užívání warfarinu snížilo o 2,8 % (p = 0,63) a v případě rivaroxabanu a dabigatranu o 17,5 % (p = 0,001), resp. 17,4 % (p = 0,001). Naše studie tak prokázala, že NOAC představují bezpečnou a účinnou alternativu k warfarinu.

ABSTRACT

Introduction: Atrial fibrillation (AF) is the most common arrhythmia in the world, affecting around 33 million people. Warfarin has been the anticoagulant of choice for the prevention of ischemic stroke in AF patients for a long time. Several large studies have shown that non-vitamin K antagonist oral anticoagulants (NOACs) offer numerous advantages regarding safety and effectiveness, such as fixed dose and more predictable pharmacokinetics.
Methods: The study was conducted at Pauls Stradins Clinical University Hospital, Latvian Centre of Cardiology. The study took place from October 2015 to June 2017. A total of 356 patients who had undergone electrical cardioversion (ECV) was included in this study.
Results: One year after ECV, 27.5% of patients used warfarin, 33.7% of patients used NOACs, whereas 38.8% did not use any oral anticoagulants. Nine (2.5%) of the patients who participated in the study died during the following year. Overall, eight patients (2.2%) suffered from significant bleeding and three patients (0.8%) had a non-fatal ischemic stroke. The rate of non-fatal ischemic stroke in patients who used warfarin was 2% and no cases were observed in patients who used NOACs (p = 0.20). The rate of significant bleeding was 5.1% versus 2.5% in warfarin and NOAC groups, respectively (p = 0.12).
Conclusions: Compared with similar studies, our study showed a low rate of ischemic stroke and significant bleeding, and a low total death rate. One year after ECV, the use of warfarin decreased by 2.8% (p = 0.63), the use of rivaroxaban and dabigatran decreased by 17.5% (p = 0.001) and 17.4% (p = 0.001). The study shows that NOACs are a safe and effective alternative to warfarin.

Keywords:
Atrial fibrillation
Electrical cardioversion
Oral anticoagulants

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the world affecting around 33 million people. It is estimated that by 2030 there will be 20 million patients with AF in Europe.[1,2]

Patients with AF have a five times greater risk of suffering from stroke and an increased risk of myocardial infarction, heart failure and death. Moreover, AF creates large economic burden due to its rapidly increasing prevalence and incidence.[3,4]

Rhythm and rate control are the two basic principles of AF treatment. Regarding mortality and cardiovascular disease, rate control is similar to rhythm control. Accordingly, rate control is often recommended as the first choice for symptomatic AF patients. However, many patients are symptomatic even with lower heart rate, therefore electrical cardioversion (ECV) or pharmacological cardioversion are offered to these patients as the next step. In general, ECV is a safe method for restoring sinus rhythm. However, without adequate anticoagulation, the post--procedure risk of cardioembolic events is 57%. If an episode of AF persists for more than 48 hours or the duration of episode is unknown, anticoagulants are considered mandatory before cardioversion. Due to increased peri- and post-procedural thromboembolic risk, the European Society of Cardiology guidelines recommend that anticoagulant therapy should be started at least three weeks before and continued four weeks after cardioversion.[5–7]

Historically, warfarin has been the anticoagulant of choice for the prevention of ischemic stroke in AF patients. However, several large-scale studies have shown that non-vitamin K antagonist oral anticoagulants (NOACs) rivaroxaban, dabigatran and apixaban offer numerous advantages regarding safety and effectiveness. In contrast to warfarin, they have a fixed dose, more predictable pharmacokinetics, fewer interactions with food and other medications, and no need for controlling coagulation parameters. Based on these factors, NOACs are a safe and suitable alternative to warfarin for thromboembolic prophylaxis in patients with non-valvular AF.[8–12]

The goal of the study was to determine the most frequently prescribed anticoagulants and their usage in the patient population of the study. In addition, safety of the respective medications and thromboembolic event rate one year after ECV was evaluated.

Methods

Study design and patients

The study was conducted at Pauls Stradins Clinical University Hospital, Latvian Centre of Cardiology from October 2015 to June 2017. A total of 356 patients who had undergone ECV were included in this study. Patients were admitted with AF, which was confirmed with an ECG carried out by a general practitioner, cardiologist, or emergency medical services personnel. Another ECG was performed in the ward where the patient was hospitalized.

Study inclusion criteria were age ≥18 years, confirmed AF in a 12-lead ECG, and ECV during hospitalization. Patients were excluded if their life expectancy after ECV was less than 12 months or if atrial fibrillation spontaneously reverted to sinus rhythm.

An anonymous patient questionnaire was used to collect the patient demographic data, information about hospitalization, duration of arrhythmia, medication used for rhythm control and anticoagulation, and history of electrical or pharmacological cardioversion. Information about comorbidities and ECV results was obtained from the patient case record. Based on the information obtained, the CHA_2DS_2-VASc score was calculated for each patient.

Patients also participated in a phone survey one year after hospitalization. The following information was collected: number of hospitalizations during the previous year and reasons for hospitalization, medication used for heart rhythm and rate control, medication used for thromboembolic prophylaxis, medication side effects (significant bleeding etc.). Significant bleeding was defined as bleeding events, including gastrointestinal bleeding, haemorrhagic strokes, other intracranial bleeding events and bleeding at other sites that requires hospitalization.

In the case of the patient death, the relatives were asked to provide detailed information about the cause of death and the medications used.

The study was approved by the Ethics Committee of Riga Stradins University. All patients received informative materials with the description of the study and all patients gave written consent after familiarizing themselves with the description.

Statistical methods

All data obtained during this study were processed with Microsoft Excel 365 and IBM SPSS Statistics 22.0. Descriptive statistical methods were used to characterize patient parameters: summary tables with columns, bar graphs or histograms, mean arithmetic and standard deviation. Unpaired t-test or Mann-Whitney test were used to compare continuous variables, and Pearson ^{2} or Fisher's exact test (if the number of expected cases was $n < 5$ in one of the columns in the table) were used to compare categorical variables in the study subgroups, as appropriate.

The McNemar test was conducted to compare the use of anticoagulants upon leaving the hospital and one year later. All *p*-values were considered statistically significant at a 5% confidence level.

Results

The mean age of patients was 65.3 (±10.6) years; 55.1% of patients were male. The mean characteristics of patients can be seen in Table 1. ECV was successful and sinus rhythm was restored in 325 (91.3%) patients. In patients with an AF episode lasting 48 hours or more or an unknown duration, the frequency of sinus rhythm restoration was lower, compared with patients with AF episode of less than 48 hours: 90.8% and 96.8%, respectively, $p = 0.023$. A total of 185 (51.9%) patients had at least one episode of AF over a period of one year.

Following ECV, warfarin was prescribed to 108 (30.3%) patients, NOACs were prescribed to 244 (68.6%) patients, 106 (29.8%) were prescribed dabigatran, and 138 (38.8%)

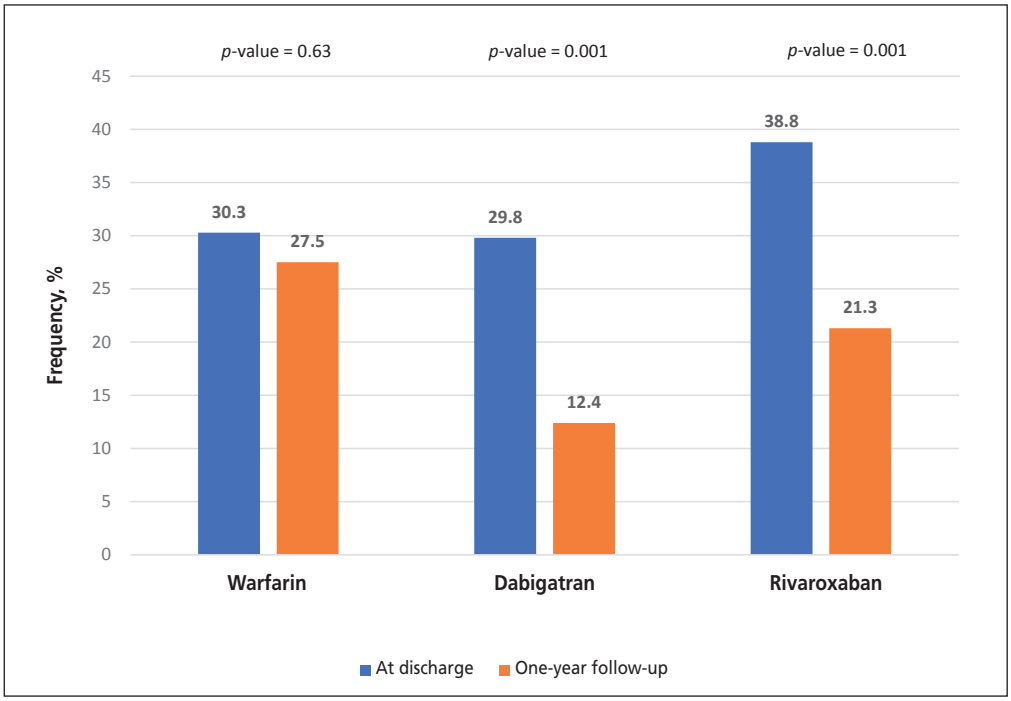

Fig. 1 – Change in the use of antithrombotic therapy one year after discharge.

Table 1 – Patient baseline characteristics

	Total, n (%)
Age (mean±SD)	65.3±10.6
Age >65 years	208 (58.4%)
Sex, male	196 (55.1%)
Body mass index (kg/m^2) (mean±SD)	31.5±5.7
History of arterial hypertension	241 (67.7%)
History of heart failure	182 (51.1%)
History of diabetes mellitus	62 (17.4%)
Prior myocardial infarction	42 (11.8%)
Prior stroke	37 (10.4%)
Implanted pacemaker	26 (7.3%)
History of radiofrequency catheter ablation	19 (5.3%)
History of AF	188 (52.8%)
Duration of paroxysm	
<48 h	31 (8.7%)
>48 h	253 (71.1%)
Unknown time	72 (20.2%)
Previous ECV	143 (40.2%)
CHA_2DS_2-VASc score	
0	19 (5.3%)
1	54 (15.2%)
≥2	283 (79.5%)

AF – atrial fibrillation; ECV – electrocardioversion; SD – standard deviation.

patients were prescribed rivaroxaban. One year after ECV, 98 (27.5%) patients used warfarin, 120 (33.7%) patients used NOACs, 44 (12.4%) used dabigatran and 76 (21.3%) used rivaroxaban, while 138 (38.8%) did not use any oral anticoagulants. Within one year after ECV, the use of warfarin decreased by 2.8% (p = 0.63), the use of rivaroxaban and dabigatran decreased by 17.5% (p = 0.001) and 17.4% (p = 0.001), respectively (Fig. 1). At follow-up, 15 (13.9%) patients who were prescribed warfarin had switched to NOACs and 47 (19.2%) patients who initially received NOACs had switched to warfarin.

Patients who used warfarin were significantly older than patients who used NOACs (68.1±1.3 vs. 63.2±1.1, p = 0.003) and had more risk factors for thromboembolic events: female sex (49.0% vs. 41.3% p = 0.028), chronic heart failure (60.4% vs. 45.4%, p = 0.019), diabetes mellitus (26.6% vs. 13.2%, p = 0.003) (Table 2).

No peri-procedural cardioembolic events were observed in this study.

Nine (2.5%) patients who participated in the study died during the following year. Three patients died from stroke, one from complications arising from myocardial

Table 2 – The distribution of CHA_2DS_2-VASc scores for warfarin and NOACs groups

	Warfarin	NOAC	*p*-value
Mean age	68.1	63.2	0.003
Sex, female	49.0%	41.3%	0.028
Heart failure	60.4%	45.4%	0.019
Hypertension	82.6%	77.8%	0.47
Age >75 years	17.7%	14.2%	0.57
Diabetes mellitus	26.6%	13.2%	0.003
Vascular disease	11.3%	9.2%	0.65
Stroke	8.2%	13.3%	0.27

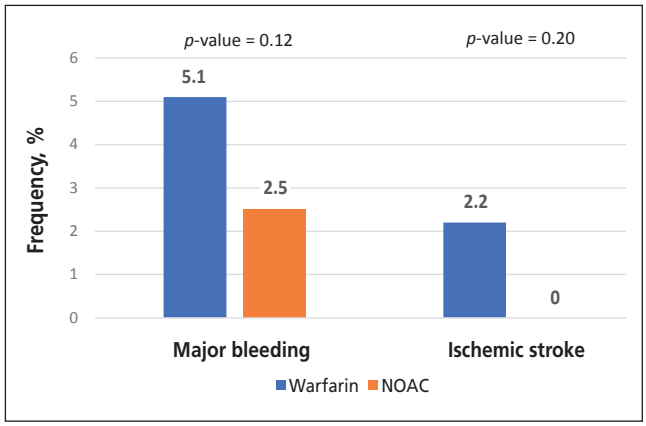

Fig. 2. – The incidence of non-fatal ischemic stroke and major bleeding events in patients treated with warfarin and non-vitamin K antagonist oral anticoagulants (NOACs).

infarction, and five patients died from non-cardiac diseases. Two of the patients who died from ischemic stroke used anticoagulants (warfarin and rivaroxaban) and one patient did not use any medication for antithrombotic prophylaxis.

The rate of significant bleeding and non-fatal ischemic stroke was low among the patients who participated in this study, without significant differences between the warfarin and NOAC groups. The rate of non-fatal ischemic stroke in patients who used warfarin was 2% (two cases), and no cases of non-fatal ischemic stroke were observed in patients who used NOACs, $p = 0.20$. The rate of significant bleeding was 5.1% (five cases) vs. 2.5% (three cases) in warfarin and NOAC groups, respectively; $p = 0.12$ (Fig. 2).

For 70.3% (n = 97) of patients who did not use any oral anticoagulant one year after discharge from hospital, the CHA_2DS_2-VASc score was 2 or higher. Out of all patients who did not use any oral anticoagulants, one had had ischemic stroke (0.8%) and none of the patients mentioned any episodes of significant bleeding.

Discussion

Compared with similar studies, the present study showed a low rate of ischemic stroke, significant bleeding, as well as a low total death rate in the patient population of the study.[13–15]

During the year following discharge from hospital, three patients died from ischemic stroke; two of them were taking anticoagulants. One of the patients used warfarin and the other one used rivaroxaban. Both patients had a high risk of thromboembolic events, as their CHA_2DS_2-VASc score was ≥2. The European Society of Cardiology guidelines state that optimal international normalised ratio (INR) in patients with nonvalvular AF is 2.0–3.0. In some patients, the target INR could be difficult to reach due to several factors, such as interactions with other medications and diet-related errors.[13] A meta-analysis by Shin et al. showed that patients taking warfarin were in the therapeutic range about 60% of the time.[16] Unfortunately, there are no accurate data available whether a patient had achieved the target INR. We assume that patient's INR was below therapeutic range and this may be the reason for fatal outcome.

Warfarin might not be the only culprit here, as the second patient who died of ischemic stroke was taking rivaroxaban. Studies show that oral bioavailability of a 10 mg tablet dose of rivaroxaban is up to 80–100% irrespective of fasting or fed conditions, unlike the 20 mg rivaroxaban tablet, whose maximum bioavailability under fasting conditions is only 66%.[17] 25% of patients participating in the present study took rivaroxaban on a fasting condition. This in turn increases the risk of thromboembolic events.

One year after electrical cardioversion, three (0.8%) patients suffered non-fatal ischemic stroke. This rate is lower than reported in the study by Apostolakis et al., where clinical outcomes six months after electrical cardioversion were analysed, showing a 0.9% rate of stroke and transient ischemic attack.[13] A different study, conducted by Shin et al, reported that the rate of stroke one month after electrical cardioversion was 0.5% in their patient group.[15] Our study shows a low stroke rate, even in patients who were not taking anticoagulants. This could be attributed to a low number of patients participating in study and a relatively short follow-up period. A limitation of the follow-up was that patients were not inquired for how long they stopped taking oral anticoagulants after electrical cardioversion. Some patients may have stopped their oral anticoagulant therapy shortly before the follow-up.

The rate of significant bleeding in this study was 2.2%. Compared with Shin et al, who reported a 0.5% rate of significant bleeding during the one month follow-up after electrical cardioversion,[15] and Apostolakis et al, who reported a 0.8% rate of significant bleeding six months after electrical cardioversion,[13] our study shows a low rate of significant bleeding one year after electrical cardioversion. Further examining the study results, we can see that NOACs are a safe and effective alternative to warfarin. Significant bleeding and ischemic stroke rates were lower in the NOAC group than in the warfarin group. Our results are similar to data reported in a study by Femia et al., although, compared to NOACs, warfarin showed a non-significantly higher rate of stroke (1.8% vs. 0.6%) as well as a higher rate of significant bleeding (3.6% vs. 1.7%).[14]

The study results show that the number of warfarin users didn't change significantly, whereas NOAC usage decreased one year after electrical cardioversion. Most of the patients (38.9%) who discontinued the use of NOACs did not switch to any other anticoagulants, whereas 19.2% of patients switched to warfarin. Studies have shown that NOACs offer numerous advantages regarding safety and effectiveness, such as fixed dose, more predictable pharmacokinetics, fewer interactions with food and other medications, and no need to control coagulation parameters. The present study found that adherence to oral anticoagulant therapy was lower in patients taking NOACs. In a study conducted by Barret et al., approximately 2% of participants switched from NOACs to warfarin; the most common reasons for switching where bleeding episodes, recurrent venous thromboembolism, and re-

nal deterioration.[18] The fact that many patients stopped taking NOACs and some switched to warfarin could be explained by various factors associated with the patient, general practitioner and medication price differences. At the time of this study, NOACs were not included in the government reimbursement system, therefore many patients, especially those with low income, could not afford NOACs. The large price difference between warfarin and NOACs was the main reason why so many patients discontinued the use of NOACs.

The main limitation of the study is the fact that we don't know the ratio of patients with and without atrial fibrillation at follow-up and that the patients were not inquired at what point they stopped taking oral anticoagulants following electrical cardioversion. Therefore ischemic and bleeding event rate in patients who didn't receive OAK should be interpreted with caution.

Conclusions

The study shows a low rate of ischemic stroke and significant bleeding, and a low death rate. The usage of warfarin did not change one year after ECV, whereas NOAC usage decreased significantly. NOACs are a safe and effective alternative to warfarin.

Conflict of interest
None declared.

Funding body
None.

Ethical statement
Authors state that the research was conducted according to ethical standards.

Informed consent
I declare, on behalf of all authors, that informed consent was obtained from all patients participating in the study.

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