



Original Article

Non-vitamin K antagonist oral anticoagulants versus warfarin for cardioversion of atrial fibrillation in clinical practice: A single-center experience

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ABSTRACT

Background: Anticoagulation therapy with the vitamin K antagonist (VKA) warfarin has been demonstrated to reduce thromboembolic risk after electrical cardioversion (ECV). However, data concerning ECV with non-VKA oral anticoagulants (NOACs) is limited. The objective of this study was to determine the efficacy and safety of NOACs in patients undergoing ECV in a real-world clinical practice at a single center in Japan.

Methods: We retrospectively analyzed the data of 406 consecutive patients who underwent ECV for atrial fibrillation (AF) or flutter under anticoagulation with one of the three NOACs ($n=149$) or with a VKA ($n=257$).

Results: The CHADS2 and HAS-BLED scores were significantly higher in the VKA group, whereas the NOACs group had a tendency toward greater spontaneous echo contrast grades. After ECV, ischemic stroke occurred in three patients of the VKA group and one patient in the NOAC group, all of whom had persistent AF, indicating no significant difference in the thromboembolic event rate within 30 days following ECV. No other thromboembolic events, major bleeding, or death occurred in either group. Among the NOAC and VKA patients in whom we newly introduced an oral anticoagulant to perform ECV, the number of days leading to ECV was significantly lesser for the NOAC patients.

Conclusion: NOACs may be used as an alternative to VKAs for ECV and may allow prompt ECV in clinical practices.

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1. Introduction

Cardiac arrhythmia is a major source of chest discomfort, light-headedness, dyspnea, and presyncope, occasionally leading to syncope, heart failure, and death. In particular, atrial fibrillation (AF) is the most frequently encountered sustained cardiac arrhythmia [1]. Even if individuals with AF or atrial flutter (AFL) do not have symptoms initially, they may develop tachycardia-induced ventricular dysfunction, followed by heart failure due to non control of the ventricular rate. AF also confers an increased risk of ischemic stroke and systemic

thromboembolism due to the formation of atrial thrombi in the left atrial appendages (LAA) [1,2]. In patients with a recent occurrence of AF or AFL, the termination of the arrhythmias can reasonably be expected to have an impact on the clinical outcome.

Electrical cardioversion (ECV) is used to restore the sinus rhythm in patients with arrhythmia such as AF and AFL. The efficacy of conversion to sinus rhythm in patients with symptomatic AF is known; it improves the patients' hemodynamics, functional status, and quality of life. However, ECV is associated with a thromboembolic risk after conversion to sinus rhythm. In non-anticoagulated patients, there is a 5–7% risk of thromboembolic complications such as ischemic stroke and systemic embolism [3,4]. If anticoagulation therapy such as those using vitamin K antagonists (VKAs) is adequate, the risk of thromboembolic events by cardioversion, including both electric and pharmacological methods is reduced to 0.5–1.6% [5,6].

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As an alternative to oral anticoagulation therapy using the VKA oral anticoagulant warfarin—which has been administered for decades—non-VKA oral anticoagulants (NOACs) were recently developed and are available for ordinary clinicians. NOACs were reported to have several advantages over warfarin: a lower risk of intracranial hemorrhage, the lack of a need to frequently check the international normalized ratios (INRs), and their quicker action [7]. Posthoc analyses of phase III trials have found new NOACs: dabigatran, rivaroxaban, and apixaban to be as safe and effective as VKA treatment in the setting of cardioversion [8–10]. However, this finding has not been confirmed in a real-world clinical practice. In the present study, we estimated the efficacy and safety of NOACs in patients with AF and AFL who underwent ECV in a real-world setting, in comparison with warfarin therapy.

2. Material and methods

2.1. Patient population

A total of 426 consecutive AF or AFL patients under oral anticoagulation therapy for whom ECV was performed at Ogaki Municipal Hospital from January 2008 to July 2015 were enrolled. In order to compare the efficacy and safety of the use of NOACs as alternative therapies for anticoagulation with that of VKA, we excluded four patients with mitral stenosis and 16 patients with prosthetic valves. The study population consisted of the remaining 406 patients including the patients taking warfarin as the VKA group ($n=257$, 63.3%), and those taking dabigatran, rivaroxaban or apixaban as the NOACs group ($n=149$, 36.7%) (Fig. 1).

For the VKA group's patients, warfarin was given once daily to adjust the dose with a target INR in the range of 2.0–3.0 for the patients < 70 years old and in the range 1.6–2.6 for the patients ≥ 70 years old, as recommended by the guideline of the Japanese Circulation Society for patients with non-valvular AF [11].

The three NOACs were administered as per the instructions provided by the manufacturer/supplier. Briefly, dabigatran was administered twice daily at 150 mg per dose. A dose reduction of dabigatran to 110 mg was considered for patients whose serum creatinine clearance was under 50 mL/min, or when the patient was over 70 years old, or the patient had a history of gastrointestinal bleeding. Rivaroxaban was administered once daily at 15 mg. A 10-mg dose of rivaroxaban was used for the patients with serum creatinine clearance of 30–49 mL/min. Apixaban was administered twice daily at 5 mg, but a 2.5-mg dose was used for patients who met two or more of the following

criteria: over 80 years old, body weight under 60 kg, and serum creatinine level > 1.5 mg/dL.

We evaluated the risk scores for predicting ischemic stroke in clinical practice by using the CHADS2 [12] and CHA2DS2-VASc [13] scores. We used the HAS-BLED score [14] as the risk score for major bleeding among the patients on anticoagulation to assess quality of the AF care.

2.2. ECV strategies

All patients were treated with one of the above-described oral anticoagulation therapies for ≥ 3 weeks before ECV, and for ≥ 4 weeks after ECV. On the same day before ECV, transthoracic echocardiography was done for all patients to determine the presence/absence of left atrial thrombus and to assess the left atrial dimension (LAD) and left ventricle ejection fraction (LVEF).

We also performed trans-esophageal echocardiography (TEE) whenever possible to exclude left atrial appendage (LAA) thrombus. The severity of spontaneous echo contrast was graded using TEE according to the criteria proposed by Fatkin et al.: 0=none; 1=mild; 2=mild to moderate; 3=moderate; 4=severe [15,16]. A strong spontaneous echo contrast is associated with a high risk for LA thrombus.

2.3. Study outcomes

The primary end point of the study was defined as the presence/absence of one or more systemic thromboembolic events within 30 days after each patient's ECV. We divided the systemic thromboembolic event into ischemic stroke and other embolic events such as renal infarction and acute limb ischemia. The secondary end point of the study was the composite of the occurrence of any major bleeding event and all-cause mortality within 30 days after the ECV.

We also examined the patients for whom oral anticoagulants were newly introduced (OAC-naïve patients) in order to perform ECV. We compared the number of days from the drug induction to ECV between the OAC-naïve patients in the NOAC group and those in the VKA group.

The medical ethics committee of Ogaki Municipal Hospital approved the study (IRB#20150723-1, July 23, 2015), which was also carried out in accord with the Declaration of Helsinki.

2.4. Statistical analysis

Continuous baseline and outcome variables are expressed as mean \pm SD, while discrete variables are given as absolute values, percentages, or both. Continuous variables were compared using Student's *t*-test. To compare the rates of categorical variables, the χ^2 test (with Yates' correction when necessary) was used. The Mann-Whitney *U*-test was used for ordinal variables. Statistics were performed on SPSS software, ver. 19 (IBM, Somers, NY). *P*-values < 0.05 were considered significant.

3. Results

Overall, the mean age of the patients was 65.7 ± 10.3 years (range, 32–86 years); 63% ($n=257$) were male, and 37% ($n=149$) were female. AF was observed in 87.5% ($n=355$) of the patients, and AFL was observed in 12.5% ($n=51$). The basal clinical characteristics of the VKA and NOACs groups are shown in Table 1. AF patients accounted for 86.4% and 89.3% of the VKA and NOACs groups, respectively. There were no significant between-group differences in age, gender, features of atrial arrhythmia, or the CHA2DS2-VASc score. However, the CHADS2 and HAS-BLED scores were significantly higher in the VKA group than in the NOACs group ($P=0.029$ and $P=0.001$, respectively).

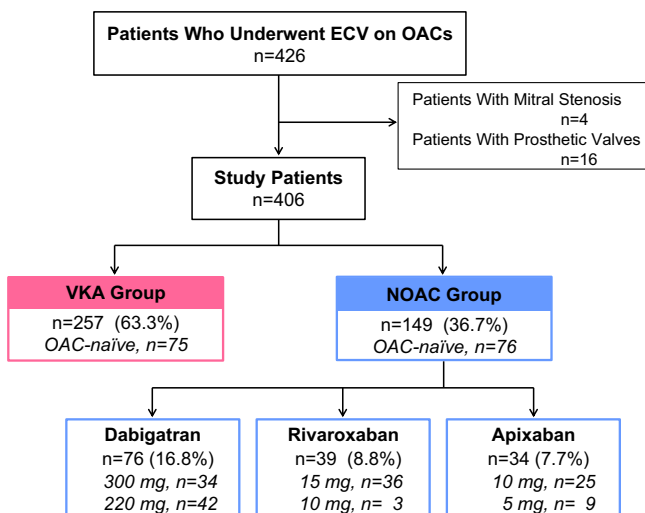


Fig. 1. Study flow chart of patient eligibility.

Anti-platelets were prescribed significantly more often in the VKA group than in the NOAC group ($P=0.004$).

Complete TEE findings were available in 66.1% and 73.2% of the VKA and NOACs patients, respectively. As shown in Table 2, there were also no significant differences between the two groups for LAD, LVEF, LAA flow velocity, or the spontaneous echo contrast grade measurements through echocardiographic and Doppler findings.

Table 3 shows the results of achieving ECV for atrial arrhythmia in this study. There was no significant between-group difference in the number of ECV attempts or the prevalence of successful ECV. The number of days to ECV in OAC-naïve patients was significantly less in the NOACs group ($n=72$) compared to the VKA group ($n=59$) ($P < 0.001$).

During the 30 day follow-up after ECV achievement, ischemic stroke occurred in three patients (1.1%) in the VKA group and one patient (0.7%) in the NOACs group, and there were no instances of any other systemic thromboembolism or any major bleeding (Table 4). The difference in adverse events between the two groups did not reach significance ($P=0.63$). The complication after ECV was only stroke, probably resulting from a detached atrial thrombus, and the prevalence was approx. 1%. In contrast, no clinical relevant bleeding such as intracranial bleeding was observed. In addition, no thromboembolic events occurred in the

Table 1
Baseline characteristics of the study population ($n=406$) assigned to the VKA or NOACs group.

	VKA ($n=257$)	NOACs ($n=149$)	P-value
Age (years)	66.0 ± 9.8	65.2 ± 11.0	0.45
Males	182 (70.8%)	75 (67.8%)	0.52
Rhythm status			0.40
AF	222 (86.4%)	133 (89.3%)	0.063
Paroxysmal	71 (27.6%)	40 (26.8%)	
Persistent	91 (35.5%)	78 (52.4%)	
Long-standing persistent	60 (23.3%)	15 (10.1%)	
AFL	35 (16.6%)	16 (10.7%)	
CHADS2 score	1.7 ± 1.2	1.5 ± 1.3	0.029
CHA2DS2-VASc score	2.8 ± 1.6	2.6 ± 1.8	0.25
HAS-BLED score	1.8 ± 1.0	1.3 ± 1.0	< 0.001
HAS-BLED score without labile PT-INRs	1.7 ± 0.9	1.3 ± 0.9	0.001
D-dimer (µg/ml)	0.6 ± 0.4	0.7 ± 0.4	0.008
Ccre (ml/min)	72.9 ± 34.1	77.5 ± 30.0	0.17
Antiplatelet therapy	33 (12.8%)	6 (4.0%)	0.004

Values are means ± SDs or numbers (percentages). Comparisons were done by employing Student's *t*-test, the χ^2 test (with Yates' correction when necessary) for categorical variables, or the Mann–Whitney *U*-test for ordinal variables. AF was sub classified as paroxysmal, persistent, and long-standing persistent AF with a duration of ≤ 1 week, > 1 week, and > 1 year, respectively. AF, atrial fibrillation; AFL, atrial flutter; Ccre, creatinine clearance; PT-INR, prothrombin time-international normalized ratio; NOACs, novel oral anticoagulants; VKA, vitamin-K antagonist.

Table 2
Echocardiographic and Doppler findings of the VKA and NOACs Groups.

	VKA ($n=257$)	NOACs ($n=149$)	P-value
TTE	100%	100%	NS
TEE	66.1%	73.2%	0.18
Spontaneous echo contrast grade	1.3 ± 1.1	1.5 ± 1.0	0.05
LAD (mm)	42.7 ± 6.0	43.0 ± 6.4	0.68
LVEF (%)	59.2 ± 11.8	59.4 ± 12.0	0.83
Left atrium appendage flow velocity (cm/s)	46.9 ± 11.8	47.5 ± 20.1	0.78

Values are means ± SDs or numbers (percentages). LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NOACs, novel oral anticoagulants; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; VKA, vitamin-K antagonist.

20 patients who were initially excluded from the analysis based on their prosthetic valves or mitral stenosis.

Table 5 provides the detailed profiles of the four patients with stroke after ECV. Their ages were all over 70 years, and three of the four were female ($P=0.16$). For all four patients, the rhythm status was persistent AF. The CHADS2 and CHA2DS2-Vasc scores were relatively high in the three patients in the VKA group compared to the patient without stroke. The PT-INR was within the therapeutic range or higher on both ECV and ischemic stroke in all three VKA patients. The spontaneous echo contrast score was grade 3 in two of the four patients with no left atrial thrombus.

We had only one patient complicated by stroke in the NOACs group resulting from a thromboembolism. The patient was treated initially with dabigatran at 300 mg/day, followed by a dose reduction to 220 mg/day after successful ECV because of the

Table 3
The results of electrical cardioversion (ECV) for atrial arrhythmia.

	VKA ($n=257$)	NOACs ($n=149$)	P-value
Number of attempts	1.6 ± 0.9	1.5 ± 0.9	0.57
Sinus rhythm restoration	249 (90.6%)	138 (92.6%)	0.36
Days to ECV for OAC-naïve patients (n)	99 ± 57 (59)	53 ± 31 (72)	< 0.001

Values are means ± SDs or numbers (percentages). Comparisons were done by employing Student's *t*-test or the χ^2 test. OAC, oral anticoagulants.

Table 4
Adverse events within 30 days after ECV.

	VKA ($n=257$)	NOACs ($n=149$)	P-value
Stroke	3 (1.1%)	1 (0.7%)	0.63
Other systemic thromboembolisms	0	0	NS
Major bleeding events	0	0	NS
All-cause mortality	0	0	NS

Comparisons were done by employing χ^2 test with Yates' correction. Values represent numbers (percentages).

Table 5
Patients with stroke.

OACs	Case 1 VKA 5 mg	Case 2 VKA 2 mg	Case 3 VKA 5 mg	Case 4 Dabigatran 300 mg
Age, sex	78, F	71, M	77, F	70, F
Rhythm status	PEF	PEF	PEF	PEF
CHADS2 score	3	5	3	0
CHA2DS2-VASc score	5	7	5	2
HAS-BLED score	2	3	3	1
D-dimer (µg/ml)	0.6	0.9	0.6	0.6
TEE performed	Done	Done	Done	Done
Spontaneous echo contrast	1	3	3	0
LVEF (%)	53	59	58	70
LAD (mm)	39	43	43	33
Left atrial appendage flow velocity (cm/s)	38.	26	23	52
PT-INR/APTT (sec) on ECV	2.93/–	1.69/–	1.69/–	–/40.2
PT-INR/APTT (sec) on stroke	3.61/–	1.87/–	1.84/–	–/29.3 ^a
Days after ECV	3	4	3	3
Modified Rankin Scale	3	4	2	1

APTT, activated partial thromboplastin time; ECV, electrical cardioversion; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; OACs, oral anticoagulant; PEF, persistent atrial fibrillation; PT-INR, prothrombin time-international normalized ratio.

^a Dabigatran was decreased to 220 mg, a day after successful electrical cardioversion.

CAHDS2 score of 0. The activated partial thromboplastin time (APTT) of this patient was 40.2 s on ECV, and it decreased to 29.3 s when the ischemic stroke occurred with the change in dabigatran dose. Fortunately, in this case the modified Rankin Scale score at hospital discharge was only 1, indicating small changes in activity and lifestyle after stroke.

4. Discussion

The results of the present study indicated that NOAC usage with ECV was apparently as safe and effective as VKA in a real-world clinical practice in Japan. NOACs may allow prompt ECV compared to VKA.

For AF/AFL patients, it is often necessary to terminate the arrhythmias either with drugs or by direct current cardioversion to improve the symptoms and clinical status of the patients. In the present study, 36.7% of the patients were prescribed an NOAC as anticoagulation therapy, and we retrospectively examined the complications (in particular, thromboembolism such as stroke) associated with the restoration of sinus rhythm by ECV, with the patients divided into VKA and NOAC therapy groups.

The need to decrease the risk of thromboembolism following cardioversion is well recognized. According to a recent guideline [1,11], anticoagulation should be considered mandatory in cases of elective cardioversion for AF of longer than 48 h or of unknown duration. For this purpose, VKA treatment is usually administered for at least 3 weeks before ECV because AF favors a prothrombotic and hypercoagulable state, and the VKA treatment is continued for a minimum of 4 weeks to decrease the risk of thromboembolic events due to post-cardioversion of left atrial dysfunction [1,11]. In addition, the assessment of ECV by TEE is associated with a greatly reduced thromboembolic risk [17].

Several NOACs have recently appeared on the market, and their use as an alternative to warfarin is increasing. In patients undergoing ECV, however, the safety of anticoagulation with NOACs has not been thoroughly established yet. The data from well-controlled clinical studies including the post hoc analyses of phase III trials [8–10] and one prospective study comparing rivaroxaban and VKA [18] have demonstrated that NOACs appear to be safe and effective compared to VKA.

Other than those studies, few reports are available concerning the effects of NOAC usage on cardioversion in clinical practice. An investigation of 53 patients including 43 AF patients treated with dabigatran or rivaroxaban reported no patients with episodes of thromboembolic events within 60 days after ECV [19], but that study did not compare these patients' results with those of patients treated with warfarin. In 2015, Coleman et al. reported that NOAC utilization in clinical practice in North America has now increased to one-third of ECV procedures with safety and effectiveness equal to those of warfarin [20]. The present study confirmed the findings of this report in a Japanese population.

In addition, our present findings demonstrated that NOACs may offer advantages over warfarin therapy besides efficiency and safety. The time to ECV in the present OAC-naïve patients was significantly shorter in the NOAC group compared to the VKA group. This may be explained by the delayed achievement of adequate anticoagulation prior to ECV in the VKA group. In a prospective study, Cappato et al. showed that rivaroxaban is safe and effective for ECV and may shorten the period of premedication to ECV compared to warfarin [18], similar to what we observed in the present study.

The current guideline from the Japanese Circulation Society recommends a reduced INR target level of 1.6–2.6 in AF patients aged ≥ 70 years [11]. The reasons for this include the relatively high incidence of intracranial hemorrhage among Asians on OAC treatment compared with Caucasians, especially among the

elderly [21]. Therefore, theoretically, the results from the studies comparing NOACs and VKAs with a target INR of 2.0–3.0 [8–10,18–20] may not be reproducible in Japanese patients. In this regard, the present study provides information of clinical significance.

Of our 406 patients, there were only four cases of systemic thromboembolism (all stroke) (0.99%); three in the VKA group and one patient who was treated with the NOAC dabigatran. The patients with stroke were relatively old, at > 70 years. The prevalence of thromboembolic events was so low that we could not determine the significance between the VKA and NOACs groups. All three patients in the VKA group appeared to have high CHAD2 and CHA2DS-VASc scores. By contrast, in the NOACs group, there was only one patient complicated by stroke. The patient was treated initially with 300 mg/day dabigatran, but after successful ECV and a day after dose replacement with 220 mg/day, a stroke occurred despite the patient's CAHDS2 score of 0. Apparently, the clinical benefit of NOACs over warfarin is to allow fixed-dose regimens without laboratory monitoring. However, in this particular patient, the APTT decreased from 40.2 s to 29.3 s by reducing the dose from 300 mg daily to 220 mg daily, suggesting that the reversal of the anticoagulation status may have been involved in the occurrence of the patient's ischemic stroke. This case, which shows a pitfall of NOAC usage, should be kept in mind. Since atrial stunning that promotes thromboembolic stroke is observed in patients after ECV [22], anticoagulation therapy should be strictly maintained until the recovery of atrial function.

4.1. Limitations

The number of thromboembolic events was not great enough to allow the application of logistic regression, and this study thus does not provide a clear answer regarding which strategy is better (VKA vs. NOACs). We also could not make any conclusion about the non-inferiority of NOACs due to the retrospective nature of the study. The first NOAC dabigatran has been commercially available since 2011 in Japan, and all eligible patients were prescribed warfarin in the earlier time period. Therefore, the difference in the time period between the warfarin treated group and the NOACs treated group may have some effect on the outcome of the study, although the same protocol in periprocedural anticoagulation was followed throughout the study.

5. Conclusions

NOAC usage may be safe and effective for Japanese patients undergoing ECV, comparable to VKAs. NOACs may also enable ECV with a shorter premedication period compared to VKAs.

Conflict of interest

All authors declare no conflict of interest related to this study.

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