

Analysis of Recurrent Stroke Volume and Prognosis between Warfarin and Four Non-Vitamin K Antagonist Oral Anticoagulants' Administration for Secondary Prevention of Stroke

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Objective: We investigated recurrent stroke volume with nonvalvular atrial fibrillation (NVAf) patients treated with non-vitamin K antagonist oral anticoagulants (NOACs) about clinical backgrounds and number of recurrent stroke. **Methods:** We administered 4 NOACs, dabigatran, rivaroxaban, apixaban, and edoxaban in 101 postcardioembolic strokes with NVAf. In a retrospective study, we measured recurrent stroke volume with magnetic resonance imaging volumetric software and compared them between 10 vitamin K anticoagulant (VKA: warfarin) cases and 13 NOAC cases under anticoagulant therapy. **Results:** Of 101 cases, 31 were started with a VKA and switched to NOACs after 10 recurrent strokes. Other 70 cases were directly started with NOACs and 13 cases with NOACs as first anticoagulants had recurrent stroke. The frequency of recurrent stroke during anticoagulant therapy is not different between the VKA group and the 3 NOACs group. Recurrent stroke volume is significantly larger in the VKA group (26.4 cm³) than in the NOACs group (1.2 cm³). **Conclusions:** Secondary prevention with NOACs after stroke might be more beneficial than a VKA by reducing recurrent infarct volume. **Key Words:** Stroke volume—recurrent—NOAC—DOAC—direct thrombin inhibitor—dabigatran—factor Xa inhibitor—rivaroxaban—apixaban—edoxaban—warfarin.

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Introduction

Non-vitamin K antagonist oral anticoagulants (NOACs) have gradually changed anticoagulant therapy with

noninferiority to vascular events and decreasing major bleeding in atrial fibrillation and venous thrombosis.¹⁻⁴ We have treated poststroke patients with 4 types of NOACs for 4 years. However, there is no clear consensus for the selection of NOACs. A meta-analysis showed that dabigatran (DA) 300 mg daily (odds ratio [OR], .66) and apixaban (AP) 5 mg daily (OR, .78) were more effective in preventing stroke and systemic embolism than other NOACs. It also showed that edoxaban (ED) 30 mg daily (OR, .46) and AP 5 mg daily (OR, .69) were more effective in preventing major bleedings than other NOACs.⁵ We selected 101 poststroke cases with NOACs for the prevention of recurrent ischemic strokes in a retrospective study. Although some studies revealed that patients taking NOACs appeared to present a lower risk of intracranial hemorrhage (ICH) and that NOACs inhibited the increase

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of hemorrhage volume, ischemic stroke has not been fully examined.⁶⁻¹⁰ We examined the recurrent stroke volumes and clinical outcomes under NOACs and compared them with recurrent cases under a vitamin K anticoagulant (VKA: warfarin).

Subjects and Method

There were 101 postembolic stroke patients with nonvalvular atrial fibrillation (NVAF) (median age, 80 years; interquartile range [IQR], 74-87) who were treated with 4 types of NOACs for 4 years from October 2011 to September 2016. NVAF was diagnosed by atrial fibrillation within 14 days after admission without rheumatic mitral valve disease, history of prosthetic mitral valve replacement, and infective endocarditis. During the study period, the direct thrombin inhibitor, DA (March 2011), the factor Xa inhibitors, rivaroxaban (RI) (April 2012), AP (February 2013), and ED (October 2015) were clinically available in Japan. The eligibility for anticoagulant drugs and the selection of NOACs have been freely determined by each stroke neurological physician without any definite intervention. NOAC administration in cardioembolic stroke cases due to NVAF were divided into 2 arms (Fig 1). Our enrolled 101 patients with NOACs contain 15 cases with DA, 43 cases with RI, 33 cases with AP, and 10 cases with ED as using NOACs finally. We divided 101 poststroke patients with 4 NOACs into 2 groups whose first anticoagulant therapy was with a VKA or NOACs as prevention therapy for cardioembolic stroke onset.

Basic clinical characteristics included age, gender, body weight (kilogram), and type of atrial fibrillation (chronic or paroxysmal). To stratify risk factors of a stroke event, we calculated the CHADS₂ score, CHA₂DS₂-VASc score, and HAS-BLED score after the onset of the first cardioembolic stroke and before the administration of a VKA and NOACs. Hypertension was defined as blood pressure levels of 140/90 mmHg or higher, or by use of antihypertensive drugs. Diabetes mellitus was defined as a hemoglobin A1c (HbA1c NGSP) level of 6.5% or higher, or by use of oral antidiabetic drugs or insulin. Dyslipidemia was defined as a serum cholesterol level of 220 mg/dL or higher, or by use of lipid-lowering

drugs including statin. Chronic kidney disease (CKD) was defined as either positive proteinuria or eGFR less than 60 mL/min per 1.73 m². The data of blood chemistry were noted with the prothrombin time–international normalized ratio (PT–INR), d-dimer, creatinine clearance (Ccr), and brain natriuretic peptide (BNP). The number of cases with recombinant tissue plasminogen activator on acute stroke therapy was also counted retrospectively.

The clinical outcomes were estimated with hospitalization period (days) of first stroke event without recurrence and the period of recurrent event. It also includes improvement in National Institute of Health Stroke Scale (NIHSS) between admission and discharge during VKA and NOACs, modified Rankin Scale (mRS) on discharge, and tube feeding on discharge. We calculated the total stroke volume, which was measured with the magnetic resonance imaging (MRI) volumetry software MRIcron (<https://www.nitrc.org/projects/mricron>). Total stroke volume (cubic centimeter) is Σ all slices of stroke lesions (square centimeter) \times slice thickness (centimeter) with diffusion-weighted image axial magnetic resonance images with the intensity threshold used by our previous reports.¹¹ mRS as a clinical outcome is the estimated correlation with total stroke volume. Cerebral microbleeds and hemorrhagic infarction were diagnosed with T2*-weighted MRI scans. The study protocol was approved by the ethics committees of Shimane University, Faculty of Medicine.

Statistical Analysis

We compared clinical factors in 2 groups of patients with a VKA or NOACs after the onset of cardioembolic stroke by a Mann–Whitney *U*-test (nonparametric data). We also compared recurrent stroke cases with a VKA or NOACs, no recurrent stroke cases with a VKA or NOACs, and recurrent versus no recurrent stroke in each VKA and NOAC by a Mann–Whitney *U*-test. We used a χ^2 test between the VKA group and the NOACs group for evaluating several clinical factors including type of atrial fibrillation, risk factors, concurrent antiplatelet drugs, treatment by t-PA, tube feeding, and recurrent stroke during a VKA or NOACs (nonparametric data). Multivariate analysis of covariance is used to assess the statistical significance of differences in recurrent stroke volumes and mRS after correcting heterogenous factors between the VKA and NOACs groups with recurrent stroke. And we used the multivariate linear regression analysis to evaluate which clinical factors (lower PT–INR on admission, inadequate low dose of NOACs, and so on) influence the recurrent stroke volume. Clinical backgrounds were presented with a median value with an IQR in Tables 1 and 2 because of relative small and nonparametric data. A *P* value of <.05 was considered statistically significant.

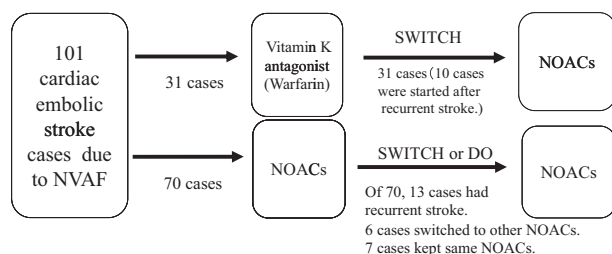


Figure 1. Two arms of NOACs administration. Abbreviations: NOACs, non-vitamin K antagonist oral anticoagulants; NVAF, nonvalvular atrial fibrillation.

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