Original Article

Infarct Volumes of Patients with Acute Ischemic Stroke Receiving Direct Oral Anticoagulants due to Non-Valvular Atrial Fibrillation

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Abstract

Direct oral anticoagulants (DOACs) have been shown to decrease the risk of ischemic stroke in non-valvular atrial fibrillation (NVAF). This study aims to investigate whether DOACs result in a significant change in lesion volume and the severity of the subsequent disability in patients who have experienced a stroke. **Methods:** The study included a total of 137 patients with NVAF and acute stroke. The cohort included 76 patients using DOACs, 21 patients using acetylsalicylic acid (ASA), and 40 patients with newly diagnosed atrial fibrillation (NDAF) who did not use antiaggregants or anticoagulants. Diffusion-weighted MRI was performed 6–12 hours after the first stroke symptoms and infarct volumes were measured by two independent observers. Baseline National Institutes of Health Stroke Scale (NIHSS) score, modified Rankin Scale (mRS) score at discharge and period of hospitalization were calculated. **Results:** When patients using DOACs due to NVAF and patients with NDAF were compared, the volumes of patients using DOACs (median 7.8 vs 23.1 cm^3; $P \leq 0.01$) were statistically significantly smaller. However, there was no difference in volume between ASA users (median 16.9 cm^3; $P = 0.16$) and patients with NDAF. The DOACs group was significantly different compared to the NDAF group in terms of NIHSS scores (median 4.4 vs 8.3; $P \leq 0.01$) and mRS scores at discharge (median 1.7 vs 2.7; $P \leq 0.01$), and period of hospitalization (median 6.4 vs 10.4 days; $P \leq 0.01$). **Conclusion:** We observe, while using DOACs, the infarct volumes of patients who experience stroke are smaller than those with NDAF and using ASA, as well as mRS scores at discharge are low and length of hospital stay is short.

Keywords: ASA, atrial fibrillation, direct oral anticoagulants, DWI, infarct volumes, stroke

Introduction

Atrial fibrillation (AF) is one of the major causes of stroke. Non-valvular AF (NVAF) is responsible for 15–25% of all ischemic strokes. The annual incidence of ischemic stroke in patients with NVAF ranges from 5 to 23%, where the risk is highest for patients aged 80 and older.[1] Anticoagulant therapy conducted with vitamin K antagonists (VKAs) reduces the incidence of ischemic stroke in patients with NVAF. However, the use of VKAs is limited by their inter-individual variability with respect to pharmacokinetics, requirements of monitoring, interactions with drugs and foods, and risk of bleeding.[2]

Direct oral anticoagulant (DOAC) therapy has been shown to reduce the risk of ischemic stroke in patients with NVAF. Dabigatran is a direct inhibitor of thrombin, while rivaroxaban and apixaban reduce thrombus formation through the inhibition of factor Xa. DOACs have been shown to be as effective as VKAs in patients with NVAF.[3] There are several experiments that have investigated the association between DOACs and the severity and outcomes of ischemic stroke.[4] In this study, we aimed to investigate the effect of DOACs on stroke volumes and disability levels in patients with NVAF.

Methods

The study included a total of 137 patients with NVAF who were treated in the emergency department between January 2018 and December 2019 and were clinically and radiologically diagnosed with acute stroke. The cohort included 76 patients who were using DOACs, 21 patients who were using acetylsalicylic acid (ASA), and 40 patients with newly diagnosed AF (NDAF) who did not use antiaggregants or anticoagulants. Of the patients receiving DOACs, 26 were on dabigatran (110 mg twice daily), 23 were on rivaroxaban (20 mg once daily), and 27 were on apixaban (5 mg twice daily). Previous history of stroke, warfarin use, and the presence of renal failure were considered exclusion criteria. In addition, patients with NVAF due to reversible causes, such as thyrotoxicosis and acute pulmonary embolism post-cardiac surgery, were also excluded. The demographic and laboratory data of patients (international normalization ratio [INR],

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prothrombin time [PT], partial thromboplastin time [aPTT], HbA1c, etc.), as well as the history of treatment, were recorded. Risk factors such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, transient ischemic attack or previous stroke, vascular disease, age 65–74 years, and gender (female) were evaluated, and CHA2DS2-VASc scores were calculated.[5] Baseline National Institutes of Health Stroke Scale (NIHSS) score, modified Rankin Scale (mRS) score at discharge and period of hospitalization were recorded. Heparin and warfarin were given to all patients after the stroke.

Brain imaging protocol

Diffusion-weighted MRI imaging (DWI) was performed 6-12 hours after the first stroke symptoms. Images for ischemic volumes were taken using a 1.5T Siemens Aera device using a repetition time of 5400 ms, a minimum echo time of 89 ms, a field of view (FOV) of 220 mm, a matrix of 128 x 128, a slice thickness of 4 mm and gap of 1 mm, and b values of 0 s/mm^2 (b zero) and 1000 s/mm^2. Volume measurements were performed by one radiologist and one radiology assistant in ExtremePACS Viewer Software (Version 3.4 A 32-bit) by manually outlining the lesion. Volume values were obtained by multiplying the sum of the surface areas obtained from outlining the ischemic area by the sum of the slice thickness and gap.

Statistical analysis

Patients were categorized as DOACs users, ASA users, or NDAF. In each of these groups, patient characteristics were reported as the median (min-max range) for continuous variables or as a number and percentage for categorical variables. The DWI lesion volumes were not normally distributed (Shapiro-Wilk test $P \leq 0.01$). We used the Kruskal-Wallis test with post-hoc tests (Tamhane). Correlations among DWI lesion volume and NIHSS score, mRS score at discharge, period of hospitalization, aPTT, PT, INR, CHA2DS2-VASc score, and age were calculated using the Pearson correlation coefficient. We also estimated an additional univariate model to investigate the possible effects of volume on the NIHSS score, mRS score at discharge, and period of hospitalization. All analyses were performed using the SPSS for Windows software (Version 17.0.0, SPSS Inc., Chicago).

All patients were informed of the study details; the study was approved by the Local Ethics Committee of the Dışkapı Education and Research Hospital. All investigators confirmed the ethical standards as described in the Declaration of Helsinki.

Results

The mean age of the patients with NVAF was 75.8 ± 7.8 years. In all, 69 patients were female and 68 were male. The patients were divided into three groups according to the protocol: those with NDAF ($n = 40$), patients using ASA ($n = 21$), and patients treated with DOACs for NVAF ($n = 76$; dabigatran, $n = 26$; rivaroxaban, $n = 23$; and apixaban, $n = 27$). The CHA2DS2-VASc scores of patients using DOACs were significantly higher than those of patients with NDAF ($P = 0.04$). The CHA2DS2-VASc scores of the NDAF and ASA groups were similar ($P = 0.99$). The infarct volume was significantly smaller in the DOAC group compared to the NDAF group (median 7.8 vs 23.1 cm^3; $P \leq 0.01$). There was no statistically significant difference in the lesion volumes between the NDAF and ASA groups (median 16.9 vs 23.1 cm^3; $P = 0.16$). The rivaroxaban (median 2.5 cm^3) and apixaban (median 3.4 cm^3) subgroups had significantly smaller lesions compared to the NDAF group ($P \leq 0.01$ and $P = 0.02$, respectively). The infarct sizes of the dabigatran subgroup (median 9.5 cm^3) and NDAF group were not statistically different ($P = 0.87$).

The volumes of the patients were not correlated with age, CHA2DS2-VASc score, aPTT, PT, or INR ($P = 0.91$, $P = 0.22$, $P = 0.052$, $P = 0.056$, and $P = 0.055$, respectively). However, a significant positive correlation was observed in the univariate regression analysis of the NIHSS score and infarct volume ($\beta = 0.82$, $t = 16.40$, and $P \leq 0.01$). In addition, we found a positive and significant relationship between the infarct volume, period of hospitalization and mRS score at discharge ($\beta = 0.82$, $t = 18.57$, and $P \leq 0.01$; $\beta = 0.14$, $t = 3.20$, and $P \leq 0.01$, respectively).

Furthermore, the DOAC group was significantly different than the NDAF group in terms of the NIHSS score (4.4 vs 8.3; $P \leq 0.01$), mRS score at discharge (1.7 vs 2.7; $P \leq 0.01$), and period of hospitalization (6.4 vs 10.4 days; $P \leq 0.01$). The NIHSS scores, mRS scores at discharge and periods of hospitalization of the NDAF and ASA groups were not significantly different ($P = 0.80$, $P = 0.67$, and $P = 0.58$, respectively). The demographic and clinical data of the patients are presented in Table 1.

Discussion

Ischemic stroke is one of the most common complications of NVAF. NVAF accounts for 15–25% of all ischemic strokes. Warfarin, a vitamin K antagonist, is mainly used in the treatment of AF and greatly reduces the risk of stroke.[6] However, its application has disadvantages due to its limited therapeutic range, interaction with drugs and food, difficulties in monitoring and risk of bleeding. The RE-LY trial showed that dabigatran, a direct thrombin inhibitor, is useful in the prevention of cardioembolic stroke in patients with NVAF.[7] Rivaroxaban and apixaban, both factor Xa inhibitors, are also reported to be effective in stroke prevention.[8,9] DOACs are at least as effective as warfarin in preventing strokes.[10] Studies investigating infarct volumes in warfarin users have shown that infarct volumes vary according to PT-INR levels. Although the PT-INR values of the patients were in the therapeutic range, differences in infarct volume were observed between ischemia that developed close to the lower limit and close to the upper limit.[11] Therefore, in order not to cause confusion, those using warfarin were excluded from the study. We found the infarct volume to be significantly lower in the DOAC group compared to the ASA and NDAF groups among

Table 1: Comparison of demographics and medical history of patients with NDAF versus all users of DOACs and ASA

	NDAF (n = 40)	All DOACs (n = 76)	ASA (n = 21)	p	p*
Sex (female/male)	21/19	36/40	12/9		
Age	77 (51-92)	75 (60-80)	75 (58-88)	0.14	0.25
Age (65-74 years)	11 (27.5%)	22 (28.9%)	8 (38%)	0.86	0.80
Age ≥ 75 years	27 (67.5%)	46 (60.5%)	13 (65%)	0.96	0.84
Hypertension (*n*, %)	29 (72.5%)	56 (73.6%)	14 (66%)	0.70	0.96
Vascular disease* (*n*, %)	17 (42.5%)	40 (52.6%)	9 (42%)	0.50	0,82
Congestive heart failure (*n*, %)	9 (22.5%)	30 (39.4%)	6 (28%)	0.10	0.86
Diabetes mellitus (*n*, %)	21 (52.5%)	42 (55.2%)	10 (47%)	0.81	0.76
Hba1c (%)	6.4 (5-10.9)	6.6 (5-9.7)	6.7 (5.2-12.1)	0.62	0.48
aPTT	27.2 (18.3-34.1)	31.6 (21.1-48.5)	28.1 (21.8-43.7)	≤0.01	0.9
PT	12.8 (11.1-16.6)	15.1 (10-28)	12.4 (10.6-14.5)	≤0.01	0.24
INR	1.1(0.9-1.4)	1.2(0.8-2.3)	1.07(0.9-1.2)	≤0.01	0.24
CHA2DS2-VASc	3.8 (2-6)	4.3 (1-6)	3.6 (2-6)	0.04	0.99
NIHSS score on admission	8.3 (1-19)	4.4 (1-16)	7.9 (3-19)	≤0.01	0.80
mRS score at discharge	2.7 (1-5)	1.7 (1-4)	2.1 (1-4)	≤0.01	0.67
Period of hospitalization (d)	10.4 (5-27)	6.4 (5-17)	7.8 (4-25)	≤0.01	0.58
Infarct volume (cm^3)	23.1 (1.5-91.9)	7.8 (1.2-72.1)	16.9 (1.1-83.2)	≤0.01	0.16

$p < 0.05$ NDAF versus all DOAC users; *$p < 0.05$ NDAF versus ASA users; vascular disease* including prior MI or peripheral artery disease; INR: international normalization ratio; PT: prothrombin time; aPTT: partial thromboplastin time; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale

patients with NVAF. Infarction volume was significantly smaller in the rivaroxaban and apixaban subgroups, but only a partial effect was observed in the dabigatran subgroup. In our study, we investigated the volume measurements of DWIs taken 6-12 hours after the stroke, because some research findings showed that measurements within the first 6 hours may be inaccurate.[12] There are controversial opinions on the measurement time of infarct volumes with DWIs. Infarct volume reaches its maximum value 3-4 days after the stroke. However, both cytotoxic and vasogenic edema contribute to the maximum size of the lesion measured with DWIs, resulting in an overestimation of the infarct volume.[13] In contrast, later T2-weighted MRI images were thought to underestimate the actual volume due to atrophy. However, recent studies have found that early DWI measurements were correlated with later T2-weighted MRI measurements and histologic infarct volume findings in animal stroke models. Another study confirmed this finding in a human model, where early DWI measurements were correlated with later T2-weighted MRI measurements and the final infarct volume.[14,15] Kanai *et al*. measured the volume of recurrent stroke in patients with NVAF and found that the infarct volume was smaller with DOACs compared to warfarin.[16] They suggest that DOACs act as a neuroprotector by inhibiting the activation of MMP-9, and early inhibition reduces final infarct volume.[17] If therapeutic anticoagulation is achieved in NVAF, this can prevent the expansion of the thrombus in the left atrium, if not the formation. Furthermore, it facilitates recanalization if the thrombus leads to cerebral artery embolism. This effect not only prevents infarct formation but also reduces the volume of any possible infarct.[18] It can be speculated that DOACs also lead to a smaller infarct volume due to their anticoagulative affect within the therapeutic range.

One study proved that, like thrombin, prothrombin is also locally found in the central nervous system. High thrombin activity and concentration in the acute stage of ischemic stroke causes direct cellular toxicity, impaired blood-brain barrier transport, oxidative stress, and an inflammatory response. These factors all contribute to stroke pathology.[19] DOACs can prevent these acute stage effects of thrombin. Experimental studies have shown that pretreatment with dabigatran, a direct thrombin inhibitor, can alleviate pro-inflammatory thrombin-induced tissue changes and reduce blood-brain barrier leakage.[20] The application of dabigatran before ischemic stroke is generally meant to decrease infarct volume, prevent intracranial hypertension and facilitate the improvement of neurological deficits.[21] In our study, we did not find the infarct volume to be statistically different in the dabigatran subgroup compared to the NDAF group; however, a minimal effect was reported. The minimal effect of dabigatran might be due to the comparatively low average dose (110 mg) taken by the patients in this study. Studies have shown that rivaroxaban and apixaban pharmacologically block FXa, reducing thrombin and antithrombin activity and reducing thrombin-induced inflammation and secondary thrombin damage.[22,23] We have similarly found reduced infarct volume in the rivaroxaban and apixaban subgroups. We believe that DOACs not only affect peripheral thrombin activity but also affect cerebral thrombin.

The two most commonly used risk classification scores to evaluate the risk of stroke in patients with non-valvular AF are the CHADS2 scheme and the CHA2DS2-VASc scheme.[5] In our study, we preferred to use the CHA2DS2-VASc scheme, which is considered to be superior because it evaluates additional risk factors that were ignored in the CHADS2

scheme. We evaluated risk factors such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, transient ischemic attack or previous stroke, vascular disease, age 65-74 years, and sex (female) using the CHA2DS2-VASc score. The comparison of CHA2DS2-VASc scores for different groups revealed that the DOAC groups were associated with higher risk factors. There was no direct relationship between CHA2DS2-VASc scores and infarct volume.

A slight increase in the aPTT, PT, and INR levels of patients using DOACs has been reported.[24] In our study, there was a statistically significant difference between patients using DOACs and patients with NDAF in terms of aPTT, PT, and INR levels. However, it was lower than the values accepted as the safety range in those using warfarin. The infarct volumes of the patients were not correlated with aPTT, PT, or INR levels.

NDAF was associated with a longer hospital stay, more severe disability, higher incidence of middle cerebral artery infarction, and higher mortality, as well as a smaller chance of discharge within the first 30 days.[25] In our study, 10% of patients with NDAF developed total anterior circulation infarct (TACI), with this rate being 1.3% in the DOAC group and 4.7% in the ASA group [Table 2].

We found that the NIHSS scores of patients using DOACs were significantly lower than those of the NDAF and ASA groups. Recent studies have reported that DOACs were associated with lower NIHSS scores in stroke patients.[26] On the other hand, in evaluation and functionality studies, a positive correlation between NIHSS score and DWI lesion volume was shown, and it was concluded that functional independence was an independent predictor.[27]

We have similarly found that the DOAC group had significantly shorter hospital stays and lower mRS scores at discharge. The use of DOACs results in a small infarct volume, providing better disability outcomes. When we compared the NDAF and ASA groups, we found that there was no statistically significant difference between the NIHSS scores, mRS scores at discharge and length of hospital stay. The effects of ASA on lesion volume are controversial. However, antiplatelet therapy can inhibit platelet activation and platelet-derived vasoconstrictors and improve microcirculation in the ischemic penumbra. This can limit the clot size and create protection against thrombus dilation and any subsequent embolism. Antiplatelet therapy seems to have beneficial effects in acute ischemic stroke due to its neuroprotective and anti-inflammatory properties.[28]

Table 2: Stroke locations according to Bamford classification

	NDAF (n = 40)	All DOACs (n = 76)	ASA (n = 21)
TACI	4 (10%)	1 (1.3%)	1 (4.7%)
PACI	26 (65%)	62 (81.5%)	13 (61.9%)
POCI	7 (17.5%)	6 (7.8%)	5 (23.8%)
LACI	3 (7.5%)	8 (10.5%)	2 (9.5%)

TACI: Total anterior circulation infarct , PACI: Partial anterior circulation infarct,POCI: Posterior circulation infarct, LACI: Lacunar infarct

ASA causes a decrease in brain tissue death after cerebral ischemia due to its anti-inflammatory effects, such as reducing the risk of stroke due to its antiplatelet effect through cyclooxygenase (COX) inhibition. ASA has an anti-inflammatory effect, mainly by inhibiting COX-1 and COX-2, which are dose-dependent.[29] COX-2 inhibition can be induced with an ASA dose above 30 mg/kg.[30] Our patients were using only 300 mg/day for prophylactic purposes. Therefore, we did not observe a significant positive effect in terms of DWI lesion volume, NIHSS scores, post-discharge mRS scores, period of hospitalization in our patients using ASA.

The limitation of this study was that we did not evaluate long-term disability scores, because we investigated both the NIHSS and mRS scores in the acute-subacute phase.

In our study, we demonstrated that patients using rivaroxaban and apixaban had smaller lesions than those not using DOACs, and the effect of dabigatran on ischemic volume was not statistically significant, but had a partial effect. This suggests that, when patients using DOACs have a stroke, it causes less functional loss due to the smaller lesion size. The limitation of our study is that our patients were using 110 mg dabigatran. The reason for this was that we did not include patients with a history of previous stroke or TIA or the majority of patients were aged over 80 years. However, in the RE-LY study, it was shown that 150 mg dabigatran reduced the relative risk of systemic embolism for stroke more than warfarin when directly compared. In our study, we observed that the affected area was smaller when ischemic stroke developed. This suggests that ischemic stroke may lead to less disability in patients using DOACs. Although the sample size is small, we are of the opinion that this study is of importance because there have not been enough studies performed on lesion volume to date. Large-scale studies need to be conducted in this regard.

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Conflicts of interest

There are no conflicts of interest.

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