

Early Administration of Edoxaban After Acute Ischemic Stroke in Patients With Non-valvular Atrial Fibrillation: A Pilot Randomized Trial

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Dear Sir:

Without anticoagulation, the risk of early recurrence in the first 14 days after atrial fibrillation (AF)-related ischemic stroke is approximately 0.5%–1.3% per day.¹ Anticoagulation is an essential strategy for preventing recurrent stroke in patients with AF-related stroke. However, it increases the incidence of intracranial hemorrhage (ICH) in the early stages of stroke. For the timing of anticoagulation, the “1–3–6–12 days rule” has been used: administration of anticoagulant at day 1 for transient ischemic attack (TIA), day 3 for mild stroke (National Institutes of Health Stroke Scale [NIHSS] <8), day 6 for moderate stroke (NIHSS 8–16), and day 12 for severe stroke (NIHSS >16).² However, this rule was established when vitamin K-dependent anticoagulation was used. Non-vitamin K-dependent oral anticoagulants (NOACs) have a similar efficacy and are associated with a lower bleeding risk;³ they may be administered earlier than warfarin in patients with acute ischemic stroke (AIS).⁴ However, no randomized controlled trials have focused on the timing of NOAC administration in patients with AF-related AIS. The purpose of this study was to examine the feasibility and possible efficacy of NOAC administration at timepoints earlier than the conventional rules. Considering that early recurrent infarcts identified using diffusion-weighted imaging (DWI) and ICH identified using gradient-echo imaging (GRE) are common in patients with AF-related AIS,⁵ we used these imaging endpoints in this pilot study.

This was a multicenter, randomized, open-label, blinded endpoint trial. Patients with AIS identified by DWI were included if

they (1) were ≥ 20 years old, (2) had cardioembolic infarction (due to AF) identified before randomization, (3) had mild to moderately severe stroke (TIA and severe strokes were excluded), and (4) could be administered edoxaban within 48 hours of symptom onset. The exclusion criteria are summarized in Supplementary Table 1. Patients were randomized to either the conventional edoxaban treatment group (C-group) or the early edoxaban treatment group (E-group). In the C-group, a standard dose of edoxaban was administered to patients on day 3 for mild stroke and on day 6 for moderate stroke after symptom onset. Before administration of edoxaban, the use of anticoagulants was prohibited. In the E-group, a half-dose of edoxaban was administered from onset until day 3 (for mild stroke) or day 6 (for moderate stroke), and a standard dose of edoxaban was then administered as in the C-group. Baseline magnetic resonance imaging (MRI) was performed 24–48 hours after symptom onset, and follow-up MRI was performed between days 10 and 14. MRI images, including DWI, GRE, fluid-attenuated inversion recovery, and magnetic resonance angiography, were collected at the Asan Medical Center Central Image Laboratory and read by neuroradiologists blinded to treatment allocation. Thrombolysis or endovascular therapy was permitted if appropriate. Edoxaban was administered 24 hours later to patients who received thrombolysis therapy. This trial was performed in accordance with the Good Clinical Practice guidelines and approved by the Institutional Review Boards of all participating centers. Written informed consent was obtained from all patients (clinicaltrials.gov–NCT03433235).

The primary outcome was the occurrence of new symptomatic

or asymptomatic infarcts detected on DWI on days 10–14, in comparison with the baseline DWI findings at 24–48 hours. Secondary endpoints included (1) recurrent infarcts that were associated with clinical deterioration (increased NIHSS ≥ 4) within 10–14 days, (2) neurological deterioration (increased NIHSS ≥ 2), (3) any ICH detected by GRE at days 10–14, (4) recanalization of the occluded vessels in patients who did not undergo thrombolysis or endovascular therapy, and (5) functional status (modified Rankin Scale [mRS]) at 3 months. Although the sample size could not be calculated for this exploratory trial, a total of 66 patients were enrolled.

The primary and secondary endpoints were assessed in the modified intention to treat (ITT) population, which included patients who were randomized and completed follow-up MRI. Per-protocol analysis was performed in patients who had no major protocol violation and took $\geq 80\%$ of the assigned study medications. Adverse events were assessed in the safety population, i.e., those who received at least 1 dose of study drugs. For statistical analysis, chi-square test, Fisher’s exact test, or Cochran-Mantel-Haenszel shift test was performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

In total, 66 patients (E-group, $n=33$; C-group, $n=33$) were enrolled from four hospitals (Asan Medical Center, Kyung Hee University Hospital, Soonchunhyang University Hospital, and Dong-A University Hospital). Thirty patients from the E-group and 31 from the C-group were included in the ITT group. There were no differences between the E-group and C-group in terms of demographic characteristics, baseline NIHSS, CHA₂DS₂-VASc score, HAS-BLED score, and the incidence of thrombolysis/endovascular therapy (Table 1). With respect to the primary endpoint (Table 2), DWI-identified ischemic lesions occurred at 10–14 days in 10 (33.3%) and 6 (19.4%) patients in the E-group and C-group, respectively (relative risk 1.72, 95% confidence interval: 0.72–4.15, $P=0.2147$). All lesions were asymptomatic and none were associated with clinical deterioration. The results obtained using the per-protocol analysis were similar. ICH detected by GRE occurred in 14 (46.7%) and 17 (54.8%) patients in E-group and C-group, respectively, and all were asymptomatic microbleeds (<1 cm in diameter). The neurological deterioration rate, recanalization rate, and mRS score did not differ between the groups (Table 2).

We found that the administration of a half-dose of edoxaban earlier than the conventional strategy was safe and feasible, at least in patients with mild to moderately severe AIS. Contrary to our expectations, DWI-identified ischemic lesions occurred in 10 (33.3%) and 6 (19.4%) patients in the E-Group and C-Group, respectively. The prevalence of new MRI-identified lesions was generally in line with the findings of a previous study;⁵ 29.5% and

35.6% of the patients in the rivaroxaban and warfarin groups, respectively, had such lesions at 4 weeks. Because we focused on feasibility and safety in this pilot study, we administered a half-dose, rather than full dose, of edoxaban to the E-group patients during the early period, which was associated with lower bleeding risk than the full dose.⁶ The half-dose of edoxaban we used might have been insufficient in preventing recurrent MRI-identified ischemic lesions in these high-risk patients. Although the small sample size in this study did not allow us to interpret the results, the trend of an increased incidence of DWI-identified lesions in the E-group needs to be investigated in future research. During the process of this manuscript, a randomized trial was published that showed that early (≤ 4 days) NOAC initiation was non-inferior to delayed (5–10 days) initiation in patients with AIS.

Table 1. Demographics and characteristics of patients in the modified ITT population

	Early initiation group (n=30)	Conventional initiation group (n=31)	P
Age (yr), mean \pm SD	73.9 \pm 8.9	72.7 \pm 11.6	0.6645
Female sex (%)	43.3	45.2	0.8857
Body mass index (kg/m ²), mean \pm SD	23.8 \pm 3.4	25.2 \pm 3.7	0.1170
NIHSS			0.4664
Mean \pm SD	6.5 \pm 5.0	5.5 \pm 4.1	
Median (IQR)	5.0 (2.0–11.0)	6.0 (2.0–9.0)	
CHA ₂ DS ₂ -VASc score, n (%)			0.8646
2	1 (3.3)	2 (6.5)	
3	1 (3.3)	3 (9.7)	
4	10 (33.3)	8 (25.8)	
5	7 (23.3)	7 (22.6)	
6	9 (30.0)	6 (19.4)	
7	1 (3.3)	5 (16.1)	
8	1 (3.3)	0 (0.0)	
Median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	0.8710
HAS-BLED score, n (%)			0.1938
1	0 (0.0)	1 (3.2)	
2	4 (13.3)	2 (6.5)	
3	7 (23.3)	15 (48.4)	
4	14 (46.7)	10 (32.3)	
5	4 (13.3)	2 (6.5)	
6	1 (3.3)	1 (3.2)	
Median (IQR)	4.0 (3.0–4.0)	3.0 (3.0–4.0)	0.2014
t-PA infusion (yes)	8 (26.7)	6 (19.4)	0.4972
Endovascular therapy	6 (20.0)	3 (9.7)	0.3006

ITT, intention to treat; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; t-PA, tissue plasminogen activator.

Table 2. Primary and secondary endpoints (modified ITT set)

	Early initiation group (n=30)	Conventional initiation group (n=31)	Relative risk or common OR (95% CI)	P
DWI lesion at day 10–14	10 (33.3)	6 (19.4)	1.72 (0.72–4.15)	0.2147
Recurrent ischemic lesions with significant clinical worsening* (yes)	0 (0.0)	0 (0.0)	-	-
Clinical neurological deterioration [†] (yes)	0 (0.0)	0 (0.0)	-	-
Intracranial hemorrhages on follow-up gradient echo MRI between days 10–14 (yes)	14 (46.7)	17 (54.8)	0.85 (0.52–1.40)	0.5233
Recanalization of occluded vessels on follow-up MRA between days 10–14 (yes) [‡]	18 (90.0)	24 (96.0)	0.94 (0.79–1.11)	0.5772
mRS score at 3 months [§]			1.86 (0.73–4.78)	0.2011
0	6 (21.4)	13 (44.8)		
1	9 (32.1)	6 (20.7)		
2	8 (28.6)	3 (10.3)		
3	1 (3.6)	5 (17.2)		
4	2 (7.1)	1 (3.4)		
5	2 (7.1)	1 (3.4)		

Data are presented as n (%) unless otherwise indicated.

ITT, intention to treat; OR, odds ratio; CI, confidence interval; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; mRS, modified Rankin Scale.

*Increased NIHSS ≥ 4 until days 10–14; [†]Increased NIHSS ≥ 2 until days 10–14; [‡]Those who received recanalization therapy were excluded (10 in early initiation group, 6 in conventional initiation group); [§]Data could not be obtained in missing patients (2 in early initiation group, 2 in conventional initiation group).

However, there were no differences in the mortality and recurrent stroke rates between the two groups.⁷ Currently, three other randomized clinical trials, ELAN (Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillation),⁸ OPTIMAS (OPTimal TIMing of Anticoagulation After Acute Ischaemic Stroke),⁹ and START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation)¹⁰ are undergoing to determine the optimum start time of anticoagulation in AF-associated AIS, which will hopefully provide more definitive answer.

Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2023.00325>.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: JSK. Study design: JSK. Methodology: JSK.

Data collection: JSK, KBL, DIC, JKC. Investigation: JSK, KBL, DIC, JKC. Statistical analysis: JSL. Writing—original draft: JSK. Writing—review & editing: JSK, KBL, DIC, JKC. Funding acquisition: JSK. Approval of final manuscript: all authors.

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This study was performed and reported according to Good Clinical Practice guidelines and the Declaration of Helsinki, and the protocol was reviewed and approved by the review boards of Asan Medical Center, Soochunhyang University Hospital, Kyung Hee University Hospital, and Dong-A University Hospital, with approval numbers 2018-0033, 2017-12-003, 2018-01-008, and DAUHIRB-19-140, respectively. Written informed consent was obtained from all eligible patients or their legally authorized representatives.

References

- Hart RG, Coull BM, Hart D. Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study. *Stroke* 1983;14:688–693.
- Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013;34:2094–2106.
- Bruins Slot KM, Berge E. Factor Xa inhibitors versus vitamin K antagonists for prevention of cerebral or systemic embo-

- lism in patients with atrial fibrillation. *Stroke* 2018;49:e235–e236.
4. Munn D, Abdul-Rahim AH, Fischer U, Werring DJ, Robinson TG, Dawson J. A survey of opinion: when to start oral anticoagulants in patients with acute ischaemic stroke and atrial fibrillation? *Eur Stroke J* 2018;3:355–360.
 5. Hong KS, Kwon SU, Lee SH, Lee JS, Kim YJ, Song TJ, et al. Rivaroxaban vs warfarin sodium in the ultra-early period after atrial fibrillation-related mild ischemic stroke: a randomized clinical trial. *JAMA Neurol* 2017;74:1206–1215.
 6. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–2104.
 7. Oldgren J, Åsberg S, Hijazi Z, Wester P, Bertilsson M, Norrving B. Early versus delayed non-vitamin K antagonist oral anticoagulant therapy after acute ischemic stroke in atrial fibrillation (TIMING): a registry-based randomized controlled non-inferiority study. *Circulation* 2022;146:1056–1066.
 8. Fischer U, Trelle S, Branca M, Salanti G, Paciaroni M, Ferrari C, et al. Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillation (ELAN): protocol for an international, multicentre, randomised-controlled, two-arm, open, assessor-blinded trial. *Eur Stroke J* 2022;7:487–495.
 9. Best JG, Arram L, Ahmed N, Balogun M, Bennett K, Bordea E, et al. Optimal timing of anticoagulation after acute ischemic stroke with atrial fibrillation (OPTIMAS): protocol for a randomized controlled trial. *Int J Stroke* 2022;17:583–589.
 10. King BT, Lawrence PD, Milling TJ, Warach SJ. Optimal delay time to initiate anticoagulation after ischemic stroke in atrial fibrillation (START): Methodology of a pragmatic, response-adaptive, prospective randomized clinical trial. *Int J Stroke* 2019;14:977–982.
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Supplementary Table 1. Exclusion criteria

Transient ischemic attack or severe (National Institutes of Health Stroke Scale >16) infarction
Infarcts that are not considered to be caused by atrial fibrillation (AF), or associated with two or more causes; e.g., lacunar infarction and AF, or ipsilateral significant (>50%) steno-occlusion and AF
Significant hemorrhagic transformation (grade I or II in European Cooperative Acute Stroke Study criteria) on screening magnetic resonance imaging (MRI)
Mechanical valve replacement or rheumatic heart disease
Intracranial hemorrhage within 3 months of study initiation
Active internal bleeding or clinically significant bleeding
Severe anemia (hemoglobin <10 g/dL) or hemorrhagic tendency (platelets <100,000/ μ L or prothrombin time/international normalized ratio >1.7); however, hemoglobin <9 g/dL or platelet count <70,000/ μ L were allowed when there was no sign of active bleeding
Bleeding-prone conditions such as recent gastric ulcer, hemorrhagic malignant tumor, recent head trauma, recent surgery on the brain, spinal cord, or the eye
Esophageal varices, arteriovenous malformation in the brain or spinal cord, or cerebral vascular aneurysm of >3.5 mm
Persistent systolic blood pressure (BP) >180 mm Hg or diastolic BP >110 mm Hg
Terminal medical diseases or cancer with a life expectancy of <6 months
Severe renal dysfunction (creatinine clearance <30 mL/min)
Those who needed to intake drugs that are known to influence the efficacy of edoxaban, e.g., carbamazepine, dexamethasone, doxorubicin, nefazodone, pentobarbital, phenobarbital, prazosin, rifampin, trazodone, vinblastine
Those who could not undergo brain MRI for any reason
Pregnant or planning pregnancy or lactation
Participating in another clinical trial
Those who needed to receive anticoagulants such as heparin, warfarin, or other non-vitamin K-dependent oral anticoagulants for any reason