Online August 18, 2020
Journal of Neuroendovascular Therapy 2020; 14: 481–487 DOI: 10.5797/jnet.oa.2019-0118

Original Article

Results of Therapy Using Oral Anticoagulants in the Acute Phase after Mechanical Thrombectomy

Koichiro Shindo,[1,2] Tatsuya Ogino,[1,2] Kenji Kamiyama,[1] Mamoru Fukuda,[1] Naoyasu Okamura,[1] Tomoki Fuchizaki,[1] Tomoaki Ishizuka,[1] Kohei Ishikawa,[1] Yohei Yamaguchi,[1] Takeshi Muraki,[1,2] Yasuyuki Tatsuta,[1,2] Suguru Sakurai,[1,2] Hideki Endo,[1,2,3] Masahiro Ookuma,[1] Toshiaki Osato,[1] and Hirohiko Nakamura[1]

Objective: The usage of oral anticoagulants (OACs) in the acute phase of cerebral infarction has increased, but the optimal timing for starting OACs after mechanical thrombectomy (MT) is unclear. We report the usage of OACs after MT at our hospital and evaluated the outcomes.

Methods: OACs were selected as secondary preventive drugs for 64 patients who underwent MT for anterior circulatory embolism between July 2016 and January 2019. Of the 64 patients, 28 and 36 received direct oral anticoagulants (DOACs) and warfarin (Wf), respectively. We compared the frequency of intracranial hemorrhage in the acute phase and that of recurrent cerebral infarction within 30 days.

Results: The median diffusion-weighted imaging-Alberta Stroke Program Early Computed Tomography Scores + white matter (DWI-ASPECTS + W) score at admission was 7.5 (IQR 6–9)/8 (IQR, 6–9) in the DOACs group/Wf group. The rate of recanalization with modified thrombolysis in cerebral infarction (TICI) ≥2B by MT was 89.3/80.6%. In patients with subarachnoid hemorrhage (SAH) associated with MT and patients with hemorrhagic transformation (HT) on MRI the next day, administration was started after hemostasis. The median timing of the first anticoagulant administration was 3 (IQR, 2–4)/2 (IQR, 1–4) days. In the case of no HT the next day, the rate of new HT after 1 week was 7.1%/29.1%. In the case of HT the next day, the rate of HT deterioration the next day was 7.1%/16.6%. The percentage of symptomatic bleeding was 0%/2.8%. The percentage of recurrent cerebral infarction within 30 days was 0%/2.8%.

Conclusion: OACs in the acute phase after MT can be safely used and are expected to be effective at preventing recurrence.

Keywords ▶ direct oral anticoagulants, early phase, mechanical thrombectomy, stroke, non-valvular arterial fibrillation

Introduction

In March 2011, direct oral anticoagulants (DOACs) became available and case reports have been published. Previously, we selected warfarin (Wf) for secondary prevention in patients with cardiogenic embolism related to non-valvular atrial fibrillation (NVAF). However, since DOACs became available, they have been positively selected for patients with NVAF. According to a report from the RESCUE JAPAN project, mechanical thrombectomy (MT) has been increasingly performed, but the optimal timing of starting anticoagulant administration after MT remains to be clarified. We retrospectively evaluated the results of anticoagulant therapy after MT in our hospital.

Materials and Methods

Of 96 patients who had undergone MT at our hospital between July 2016 and January 2019, the subjects were 64 on whom magnetic resonance imaging (MRI) was performed due to anterior circulation embolism. DOACs were selected, if possible, in accordance with precautions for the indication/

[1]*Department of Neurosurgery, Nakamura Memorial Hospital, Sapporo, Hokkaido, Japan*
[2]*Center for Endovascular Neurosurgery, Nakamura Memorial Hospital, Sapporo, Hokkaido, Japan*
[3]*Department of Neurosurgery, Nakamura Memorial South Hospital, Sapporo, Hokkaido, Japan*

Received: December 31, 2019; Accepted: June 9, 2020
Corresponding author: Koichiro Shindo. Department of Neurosurgery, Nakamura Memorial Hospital, South 1, West 14, Chuo-ku, Sapporo, Hokkaido 060-8570, Japan
Email: k.shindo04hmrfc@gmail.com

dosage of each DOAC. For very elderly patients, low-body-weight patients, and renal failure patients with a low creatinine clearance (CCr), Wf, and low-dose heparin (continuous administration at 5000–10000 units/24 hours) were selected. As a result, DOACs were selected for secondary prevention for 28 patients (DOAC group) and Wf was combined with intravenous drip of low-dose heparin for 36 (Wf group). We evaluated the incidence of intracranial hemorrhage after the start of anticoagulant therapy, presence of exacerbation, and presence of recurrent cerebral infarction within 30 days. Furthermore, we assessed the presence of prognostic factors for the exacerbation/development of hemorrhagic changes after 1 week by our method of starting anticoagulant administration.

The age at the time of MT, sex, NVAF, body weight, CCr, underlying diseases (hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, malignant neoplasms, dialysis, and peripheral artery disease), use of antiplatelet drugs, CHA 2DS2-VASc and HAS-BLED scores before onset, and type/dose of DOAC were investigated based on medical records. Patients with a blood pressure of ≥140/90 mmHg or those taking hypotensive drugs were regarded as having hypertension. Those with a low-density lipoprotein (LDL) cholesterol level of ≥140 mg/dL, high-density lipoprotein (HDL) cholesterol level of <40 mg/dL, and triglyceride level of ≥150 mg/dL or those taking statins/fibrates/ezetimibe were regarded as having dyslipidemia. Those with an HbA1c value of ≥6.5 or those taking hypoglycemic drugs/insulin were regarded as having diabetes mellitus. Concerning antiplatelet drugs, we evaluated the presence of combination therapy with aspirin/clopidogrel/cilostazol/prasugrel.

For the start of anticoagulant therapy in our hospital, when computed tomography (CT) immediately after MT did not reveal hemorrhagic change, leakage of contrast medium, or extensive low-density area (LDA), intravenous drip of heparin was started immediately (24 hours after the completion of intravenous thrombolysis in combination with recombinant tissue plasminogen activator (rt-PA)), and when MRI the following day did not demonstrate hemorrhagic transformation (HT), the administration of an anticoagulant was started. When MRI the following day revealed HT or extensive LDA, the findings were compared with cephalic imaging findings after a few days, and anticoagulant therapy was started from the point when the stabilization of hemorrhagic change was confirmed. DOACs were selected according to the manual for usage (**Fig. 1**)[1] at our hospital. In the Wf group, Wf was combined with the continuous administration of heparin at 5000–10000 units/day. The initial dose of Wf was approximately 2 mg/day. It was adjusted in order for a target prothrombin time-international normalized ratio (PT-INR) (patients aged <70 years: 2.0–3.0, those aged ≥70 years: 1.6–2.6) to be reached. In some patients for whom DOAC administration was scheduled, heparin bridging therapy was not conducted.

On arrival, MRI was performed and the diffusion-weighted imaging-Alberta Stroke Program Early Computed Tomography Scores + white matter (DWI-ASPECTS+W) was measured. After confirming an occluded blood vessel, MT was conducted. For MT, the forced suction technique with a balloon-guiding catheter, or the use of a stent retriever or aspiration catheter alone or their combination was selected for each patient. Intravenous thrombolysis with rt-PA was adopted if possible. Patients with a modified thrombolysis in cerebral infarction (TICI) grade of ≥2b were regarded as achieving effective recanalization.

MRI was performed on admission, the day after admission, and after 1 week. The DWI-ASPECTS+W the day after MT was compared with that on admission, and the presence of the development/exacerbation of intracranial hemorrhage on admission and after 1 week was evaluated. Concerning intracranial hemorrhage, cephalic imaging findings the day after admission were compared with those after 1 week using the SITS-MOST criteria,[2] and patients with ≥1-grade deterioration were regarded as having exacerbation. For statistical analysis, SPPS software (version 23; IBM, Armonk, NY, USA) was used. Among background factors, category variables were compared between the two groups using Fisher's or chi-square tests. The mean values were compared between the two groups using the t-test. The medians were compared using the Mann–Whitney U test. Furthermore, multivariate analysis (logistic regression analysis) was additionally conducted to examine factors associated with exacerbation/development of hemorrhagic infarction.

Results

Patient background (**Table 1**): When selecting anticoagulants, DOACs were selected for patients in whom NVAF was detected on 12-lead, Holter's, or monitor electrocardiography, but as a rule, Wf was selected for very elderly, low-body-weight, or chronic renal failure patients with a CCr of ≤30 mL/min even in the presence of NVAF. There were no significant differences in the age, body weight, CCr, or complications between the two groups, but there

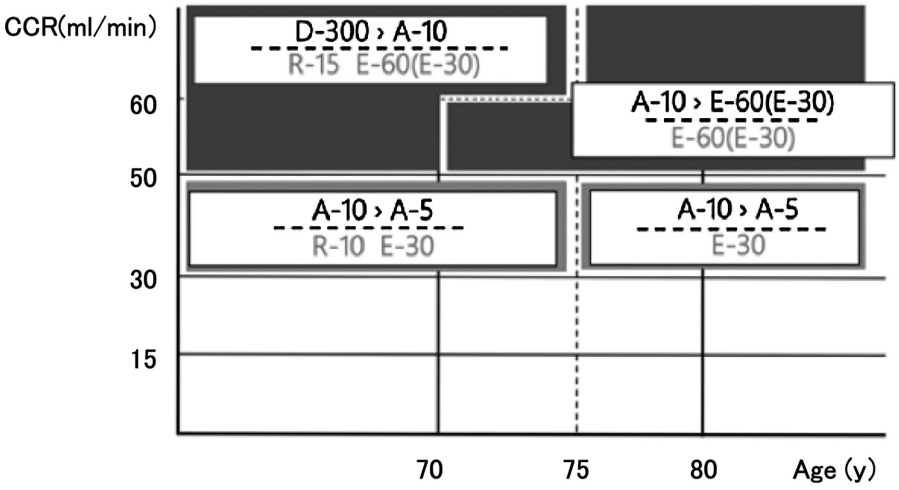

Fig. 1 Our clinical guidelines for selecting DOACs for patients with previous stroke or TIA. As the CCrs of 30 mL/min and 50 mL/min are important boundaries for each DOAC dose adjustment, two lines are drawn as boundaries. Patient groups with a CCr higher than 50 mL/min are considered to be groups in which renal function is relatively good, bleeding events are less, and efficacy is more important than safety. In addition, the group with a CCr of 30 mL/min or higher and 50 mL/min or less is considered a group in which safety is more important than efficacy because of concerns about bleeding events. DOACs for each group are selected taking into account the balance between efficacy and safety indicated above. For those aged 70–75 years, if their CCr is slightly above 50 mL/min, we choose DOACs that are considered to less frequently cause intracranial hemorrhage. In addition, DOACs considered to less frequently cause major hemorrhage are selected for those 75 years or older. The black text DOAC is the first choice, and the gray text DOAC is the second choice. Among the first choices, when the weight loss criteria are not met, as indicated by the inequality sign, the DOAC on the left side is selected. A-10: apixaban 10 mg/day; A-5: apixaban 5 mg/day; CCR: creatinine clearance; DOAC: direct oral anticoagulant; D-300: dabigatran 300 mg/day; E-60: edoxaban 60 mg/day; E-30: edoxaban 30 mg/day; R-15: rivaroxaban 15 mg/day; R-10: rivaroxaban 10 mg/day; TIA: transient ischemic attack

Table 1 Clinical characteristics of the DOAC and warfarin groups

	DOACs (n = 28)	Warfarin (n=36)	p
Age, years	76.6 ± 8.3	74.8 ± 15.0	NS
Age, over 80 years	13 (46.4%)	18 (50.0%)	NS
Male sex	12 (41.4%)	22 (61.1%)	NS
Body weight, kg	57.9 ± 10.3	58.7 ± 10.8	NS
Creatinine clearance, mL/min	66.5 ± 19.1	67.4 ± 36.3	NS
Creatinine clearance <30 mL/min	1 (3.6%)	5 (18.9%)	NS
CHA2DS2-Vasc score before the onset of stroke	3 (IQR, 3–5)	3 (IQR, 2–5)	NS
HAS-BLED score	2 (IQR, 1–2)	1.5 (IQR, 1–2)	NS
Combination with Antiplatelets	0	7 (19.4%)	0.035
Modified Rankin scale before the onset of stroke	0 (IQR, 0–1)	0 (IQR, 0–1)	NS
NIHSS score on admission	18 (IQR, 11–23)	18 (IQR, 8–24)	NS
NVAF	28 (100%)	12 (32.4%)	<0.01
Hypertension	18 (64.3%)	16 (44.4%)	NS
Hyperlipidemia	9 (32.1%)	16 (44.4%)	NS
Diabetes mellitus	8 (28.6%)	9 (25%)	NS
Coronary disease	2 (7.1%)	10 (27.7%)	NS
Malignancy	1 (3.6%)	4 (11.1%)	NS
Hemodialysis	0	1 (2.8%)	NS
Peripheral artery disease	0	1 (2.8%)	NS

Data are presented as the mean±standard deviation, median (interquartile range, IQR), or number (%). DOACs: direct oral anticoagulants; NIHSS: National Institutes of Health Stroke Scale; NVAF: non-valvular atrial fibrillation; NS: not significant

Table 2 Angiographic characteristics and the results of mechanical thrombectomy

	DOACs (n = 28)	Warfarin (n = 36)	p
Location of vessel occlusion, n (%)			
ICA	9 (34.6)	10 (26.3)	
M1P	4 (15.4)	5 (13.1)	
M1D	8 (30.8)	12 (31.6)	
M2	6 (23.1)	9 (23.7)	
M3	1 (3.8)	0	
IV rt-PA	12 (42.9)	15 (41.6)	NS
mTICI ≥2B	25 (89.3)	29 (80.6)	NS
SAH associated with MT	3 (10.7)	6 (16.6%)	NS
DWI ASPECTS + W score on admission	7.5 (IQR, 6–9)	8 (IQR, 6–9)	NS
ΔDWI ASPECTS + W score between on admission and next day	±0 (IQR, −1 to 1)	±0 (IQR, −1 to 1)	NS

Data are presented as the median (interquartile range, IQR) or number (%). DOACs: direct oral anticoagulants; DWI-ASPECTS + W, Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomography Scores + white matter; ICA: internal carotid artery; IV rt-PA: intravenous recombinant tissue plasminogen activator; M1P: proximal-M1 segment of the middle cerebral artery; distal-M1 segment of the middle cerebral artery; M2: M2 segment of the middle cerebral artery; M3: M3 segment of the middle cerebral artery; mTICI: modified thrombolysis in cerebral infarction flow grade; NS: not significant; SAH: subarachnoid hemorrhage

Table 3 Day of starting OACs, recurrence of ischemic stroke, and mortality during the observation period

	DOACs (n = 28)	Warfarin (n = 36)
Day of starting OACs after stroke onset	3 (IQR, 2–4)	2 (IQR, 1–4)
Recurrence of ischemic stroke, n (%)	0	1 (2.8%)
30-day mortality, n (%)	1 (3.6%) Infection	0

Data are presented as the median (interquartile range, IQR), or number (%). DOACs: direct oral anticoagulants; NS: not significant; OACs: oral anticoagulants

was a significant difference in the presence of NVAF due to compliance with indication criteria for DOACs (DOAC group: 28 patients [100%], Wf group: 12 [32.4%]; p <0.01). In the Wf group, risk factors for embolism other than NVAF included left asynergy related to old myocardial infarction in 8 patients (22.2%), valvular disease in 2 (5.6%), coagulation disorder in 2 (5.6%), cardiomyopathy in 1 (2.8%), and an organic abnormality related to a thoracic stab wound in 1 (2.8%). Furthermore, Wf was selected for one patient (2.8%) with recurrence during DOAC therapy and for nine (25%) in whom cardiogenic cerebral embolism was strongly suspected based on clinical findings, although paroxysmal atrial fibrillation was not detected. When selecting anticoagulants, the presence of combined antiplatelet drugs was not considered, but the number of patients receiving combination therapy with antiplatelet drugs was significantly larger in the Wf group (p = 0.035) (7 (19.4%) vs. 0 (DOAC group), respectively).

MT (**Table 2**): In our hospital, intravenous thrombolysis with rt-PA was combined with MT if possible. In the DOAC group, rt-PA was administered to 12 patients (42.9%). In the Wf group, it was administered to 15 (41.6%). The effective recanalization rates after MT were 89.3 and 80.6%, respectively. Procedure-related subarachnoid hemorrhage (SAH) developed in three (10.7%) and six (16.6%) patients, respectively. The median DWI-ASPECTS+W on admission was 7.5 (IQR: 6–9) and 8 (IQR: 6–9), respectively. The median rate of change in the score the day after admission was ±0 (IQR: −1 to 1) in the two groups.

Death associated with recurrent cerebral infarction or cerebral infarction (**Table 3**): The median intervals from onset until the start of administration were 3 days (IQR: 2–4) in the DOAC group and 2 days (IQR: 1–4) in the Wf group. When MRI the day after MT revealed HT, cephalic imaging was performed after 4 days (median, IQR: 2–6), and the oral administration of an anticoagulant was started after 4 days (median, IQR: 2–8). Recurrence within 30 days after treatment initiation by such a method was noted in one patient in the Wf group, but there was no significant difference. Before the use of DOACs, heparin bridging therapy was conducted for 20 patients (71.4%). Concerning mortality, one patient (3.6%) in the DOAC group died.

Table 4 Hemorrhagic events during the observation period

	DOACs (n = 28)	Warfarin (n = 36)	p
Intracranial hemorrhage (SAH and/or HT) observed the day after MT, n (%)	14 (50)	12 (33.3)	NS
Symptomatic intracranial hemorrhage, n (%)	0	1 (2.8)	NS
Other bleeding, n (%)	1 (3.6)	1 (2.8)	NS
HT the day after MT			
HI 1	1	1	
HI 2	3	2	
PH 1	3	4	
PH 2	5	2	
HT the week after MT			
HI 1	1	1	
HI 2	3	8	
PH 1	4	8	
PH 2	5	2	
Newly emerged HT, n (%)	1 (7.1)	7 (29.2)	NS
Worsened HT, n (%)	1 (7.1)	2 (16.7)	NS

Data are presented number (%). HI: hemorrhagic infarction; HT: hemorrhagic transformation; MT: mechanical thrombectomy; NS: not significant; PH: parenchymal hematoma; SAH: subarachnoid hemorrhage

However, death was related to an infectious disease, not to cerebral infraction or MT.

Hemorrhagic complications (**Table 4**): Hemorrhagic changes, including slight changes on T2-weighted MRI or MRI-FLAIR, the day after MT were observed in 14 patients (50.0%) in the DOAC group and in 12 (33.3%) in the Wf group. Symptomatic intracranial hemorrhage was confirmed on CT immediately after MT in 1 (2.8%) in the Wf group. The other types of hemorrhage included digestive-cancer-related melena in one (3.6%) in the DOAC group and a subcutaneous hematoma at the site of sheath puncture in one (2.8%) in the Wf group. MRI the day after MT revealed hemorrhagic infarction in 12 patients in the DOAC group and in 9 in the Wf group. MRI after 1 week revealed it in 13 patients in the former and in 19 in the latter. The incidence of fresh hemorrhagic infarction was slightly higher in the Wf group, although there was no significant difference ($p = 0.216$). Exacerbation was noted in one patient (7.1%) in the DOAC group and in two (16.6%) in the Wf group, but there was no significant difference ($p = 0.626$). Concerning combination therapy with antiplatelet drugs, no patient in the DOAC group received this combination therapy, whereas seven received it in the Wf group ($p = 0.035$). Multivariate analysis demonstrated an age of ≥80 years to be a significant prognostic factor for the presence of hemorrhage exacerbation or development on imaging after 1 week. Neither heparin bridging nor the HAS-BLED score/pre-MT DWI-ASPECTS+W was a significant factor (**Table 5**).

Discussion

Cardiogenic cerebral embolism recurs within 2 weeks in many cases.[3] The European Society of Cardiology recommended the "1-3-6-12 day" rule as the timing of OAC initiation in patients with atrial fibrillation.[4] This rule means that administration should be started the day after onset in patients with transient ischemic attack (TIA), 3 days after onset in those with a National Institutes of Health Stroke Scale (NIHSS) score of <8, after confirming the absence of hemorrhagic changes using cephalic imaging 6 days after onset in those with an NIHSS score of 8–15, and after confirming the absence of hemorrhage using cephalic imaging 12 days after onset in severe-status patients with an NIHSS score of ≥16. However, this is based on specialists' opinions, and there is no evidence.

According to the SAMURAI-NVAF study,[5] which was a survey in Japan, the median intervals from onset until the start of anticoagulant administration were 3 days in Wf-treated patients and 4 days in NOAC-treated patients. Regarding the NIHSS score, the median intervals were 2 days in TIA patients, 3 days in mild-status patients (NIHSS score: ≤4), 4 days in moderate-status patients (NIHSS score: 5–14), and 5 days in severe-status patients (NIHSS score: ≥15). In Japan, administration had been started relatively early.

Table 5 Multivariate analysis for exacerbating of development of hemorrhagic transformation

	p value	Odds ratio	95% confidence interval (minimum)	95% confidence interval (maximum)
OAC (Warfarin vs. DOACs)	0.0.53	19.576	.966	396.663
IV rt-PA	0.066	8.076	.872	74.833
Heparin bridge	0.999	90688502.51	0.000	
NVAF	0.062	20.489	0.862	487.053
Antiplatelet agent	0.451	.251	0.007	9.089
Sex (female vs. male)	0.066	.144	0.018	1.133
Creatinine clearance <30 mL/min	0.239	.106	0.003	4.448
NIHSS	0.314	.935	0.820	1.066
HAS-BLED	0.271	.454	0.111	1.851
DWI-ASPECTS + W	0.290	.775	0.484	1.242
Age (<80 vs. ≥80 y)	0.027	23.915	1.444	396.048

DOACs: direct oral anticoagulants; DWI-ASPECTS: Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomography Scores; IV rt-PA: intravenous recombinant tissue plasminogen activator; NIHSS: National Institutes of Health Stroke Scale; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant

An observational study regarding the acute-phase administration of rivaroxaban (RELAXED study)[6] revealed that the median interval until the start of administration in patients with small- to medium-size infarcted cerebral foci was 2.9 days, and that it was 5.8 days in those with large-size (>22.5 cm^3) infarcted foci. This administration method resulted in a recurrence rate within 90 days of 2.3% and an incidence of major hemorrhage of 0.8%, suggesting the effectiveness and safety of this drug. Even when administration was started within 3 days, the incidence of major hemorrhage was 0.7%; this drug may be used relatively safely.

In our study, the rates of patients with exacerbation or new development of hemorrhagic infarction in the Wf group were higher than in the DOAC group, although there were no significant differences. In the Wf group, to correct hypercoagulation of infarcted cerebral foci and reduce "warfarin dilemma" at the start of Wf administration, the continuous administration of low-dose heparin was started in the early phase. According to the RAF-NOACs Study,[7] heparin-bridging-free DOAC administration 3–14 days after onset the most markedly prevented recurrence and hemorrhage. In our study, the early start of low-dose heparin administration may have influenced the exacerbation/development of hemorrhagic infarction; the start of administration later than previously adopted, such as the start of low-dose heparin administration at the timing of Wf initiation, may lead to favorable results. In our study, there were no significant differences in the rates of patients with the exacerbation or development of hemorrhagic infarction related to the presence of heparin bridging in the DOAC group. However, it may be necessary to correct heparin bridging.

A previous study examined patients who had received DOAC administration after recanalization therapy.[8] Follow-up periods varied, but the median interval until the start of DOAC administration was 2–6 days. The incidence of recurrence or intracranial hemorrhage during the observation period was 1.9%, suggesting the efficacy and safety of acute-phase DOAC administration after recanalization therapy.

Specific complications immediately after MT include procedure-related SAH, subcutaneous hematoma/pseudoaneurysm formation at the site of sheath puncture, and early reperfusion disorder, such as hemorrhagic infarction, related to a high recanalization rate in comparison with intravenous thrombolysis with rt-PA. Regarding hemorrhagic complications related to acute-phase recanalization therapy, events to which attention must be paid may be more frequent than during/after intravenous thrombolysis with rt-PA alone. However, study demonstrated that DOAC administration after confirming hemostasis does not induce serious rebleeding.

Limitation: This study retrospectively examined the actual status of DOAC usage with respect to the start of anticoagulant therapy after MT at a single institution, but several attending physicians were responsible. Our criteria for DOAC selection included the presence of NVAF and a CCr of ≥30 mL/min. However, there was a selection bias: Wf was selected for patients with recurrence during DOAC therapy or for those with the risk of renal dysfunction in the near future despite a

CCr of >30 mL/min based on the attending physicians' evaluation.

Conclusion

The administration of anticoagulants in the acute phase after MT may prevent delayed symptomatic hemorrhage if the absence of hemorrhagic change exacerbation or development is confirmed, exhibiting prophylactic effects on recurrent cerebral infarction. There was no difference in the recurrence rate related to the presence of heparin bridging therapy before the start of DOCA administration; its necessity must be reviewed.

Disclosure Statement

The authors completed self-reporting of COI to the Japanese Society for Neuroendovascular Therapy. Concerning the publication of this article, the authors declare no conflicts of interest.

References

1) Kenji K, Toshiaki O, Toshiichi W, et al: Clinical evidence and in-hospital guideline for direct oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack. *J Hokkaido Brain Res Foundation* 2016; 27: 3–9. (in Japanese)

2) Wahlgren N, Ahmed N, Dávalos A, et al: Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (SITS-MOST): an observational study. *Lancet* 2007; 369: 275–282.

3) Hart RG, Coull BM, Hart D: Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study. *Stroke* 1983; 14: 688–693.

4) Heidbuchel H, Verhamme P, Alings M, et al: Updated European heart rhythm association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015; 17: 1467–1507.

5) Toyoda K, Arihiro S, Todo K, et al: Trends in oral anticoagulant choice for acute stroke patients with nonvalvular atrial fibrillation in Japan: the SAMURAI-NVAF study. *Int J Stroke* 2015; 10: 836–842.

6) Yasaka M, Minematsu K, Toyoda K, et al: Rivaroxaban administration after acute ischemic stroke: The RELAXED study. *PLoS One* 2019; 14: e0212354.

7) Paciaroni M, Agnelli G, Falocci N, et al: Early recurrence and major bleeding in patients with acute ischemic stroke and atrial fibrillation treated with non-vitamin-k oral anticoagulants (RAF-NOACs) Study. *J Am Heart Assoc* 2017; 6: e007034.

8) Luca M, Elisa G, Alessandro D, et al: Direct oral anticoagulants in patients undergoing urgent reperfusion for nonvalvular atrial fibrillation-related ischemic stroke: a brief report on literature evidence. *Neurol Res Int* 2019; 2019: 9657073.