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Safety of Antithrombotic Therapy within 24 Hours after Recombinant Tissue-Plasminogen Activator Treatment for Large-Artery Atherosclerosis Stroke: Insights from Emergent PTA/CAS Cases

Yuki Sakamoto[1], Chikako Nito[1], Yasuhiro Nishiyama[1], Satoshi Suda[1], Noriko Matsumoto[1], Junya Aoki[1], Tomonari Saito[1], Kentaro Suzuki[1], Seiji Okubo[1], Masahiro Mishina[2] and Kazumi Kimura[1]

[1]Department of Neurology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan
[2]Department of Neurology, Tokyo Rosai Hospital, Tokyo, Japan

Background: Antithrombotic therapy (AT) should generally be avoided within 24 hours after recombinant tissue-plasminogen activator (rt-PA) treatment but should be considered in patients with large-artery atherosclerosis (LAA) who undergo concomitant emergent endovascular treatment (EVT). The aim of the present study was to assess the safety of AT within 24 hours after rt-PA treatment in patients with hyperacute ischemic stroke due to LAA who received concomitant EVT.

Methods: From January 2013 through July 2019, consecutive patients with acute ischemic cerebrovascular disease due to LAA who were admitted within 6 hours from symptom onset were recruited. The patients were classified into six groups based on the reperfusion treatment and early (within 24 hours) AT from rt-PA treatment. Safety outcomes were compared among the groups.

Results: A total of 155 patients (35 women [23%], median age 74 [IQR 66-79] years; NIHSS score 3 [1-10]) were included in the present study. Of these, 73 (47%) received no reperfusion therapy, 24 (15%) received rt-PA treatment and early AT, seven (6%) received rt-PA without early AT, 26 (17%) received EVT only, six (4%) received both rt-PA and EVT without early AT, and 19 (12%) received rt-PA and EVT with early AT. AT was administered a median of 3.9 (1.6-8.0) hours after rt-PA in patients with rt-PA+EVT with early AT. AT within 24 hours after rt-PA and EVT treatment did not increase hemorrhagic complications ($p > 0.05$ for all).

Conclusion: In this retrospective analyses, early AT administration for patients with hyperacute stroke due to LAA treated with rt-PA plus EVT did not increase hemorrhagic events.

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Key words: ischemic stroke, large-artery atherosclerosis, antithrombotic treatment, endovascular therapy, tissue plasminogen activator

Introduction

Antithrombotic therapy (AT) is a fundamental strategy for secondary stroke prevention and preventing symptom progression in patients with ischemic stroke[1]. Because the risk of recurrent stroke or symptom deterioration in ischemic stroke is highest in the hyperacute phase[2–4], prompt administration of AT is critical. However, for acute stroke patients treated with intravenous recombinant tissue-plasminogen activator (rt-PA), AT should generally be avoided within 24 hours after rt-PA treatment, because of the risk of increased hemorrhagic complications, especially symptomatic intracerebral hemorrhage (sICH)[1]. Indeed, in the Antiplatelet therapy in combination with Rt-PA Thrombolysis in Ischemic Stroke (ARTIS) trial, intravenous aspirin administered within 90 minutes after rt-PA treatment did not improve outcomes

Correspondence to Yuki Sakamoto, Department of Neurology, Graduate School of Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: ysakamoto02@gmail.com
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but increased hemorrhagic complications[5,6]. In contrast, an observational study found that AT within 24 hours after recanalization therapy (including rt-PA) did not affect the rate of hemorrhagic complications or functional outcomes in patients with acute stroke[7].

In some patients with hyperacute ischemic stroke due to large artery atherosclerosis (LAA), emergent percutaneous transcatheter angioplasty (PTA) and/or carotid artery stenting (CAS) is performed concomitant with rt-PA treatment. Sufficient AT, usually single or dual antiplatelet therapy (DAPT), is used to avoid intrastent thrombosis and re-stenosis of the treated vessel[8–10]. Therefore, hyperacute stroke patients treated with emergent PTA/CAS concomitant with rt-PA often receive early AT, even after rt-PA treatment[11,12]. Patients with hyperacute stroke due to LAA treated with PTA/CAS might be more appropriate candidates for early AT after rt-PA, because such patients are at risk for intrastent thrombosis and re-stenosis, in addition to stroke recurrence, and patients with LAA have a lower risk of hemorrhagic transformation than do those with stroke due to other causes, such as cardioembolism[13,14]. However, the safety and effectiveness of early AT in patients with stroke due to LAA treated with rt-PA plus emergent PTA/CAS are not well known. The aim of the present study was to assess the safety of AT within 24 hours after rt-PA treatment in patients with hyperacute ischemic stroke due to LAA who received concomitant emergent PTA and/or CAS.

Methods

Patients

From January 2013 through July 2019, consecutive patients with acute ischemic cerebrovascular disease (ischemic stroke and transient ischemic attack [TIA]) due to LAA who were admitted to our stroke unit within 6 hours after symptom onset were retrospectively recruited from a prospective registry[15,16]. The cause of stroke was determined by using the Trial of ORG 10172 Acute Stroke Treatment (TOAST) criteria[17] at hospital discharge. TIA due to LAA was also determined by the same criteria as LAA in the TOAST criteria. Patients with a concomitant cause for stroke other than LAA (applicable to "Stroke of undetermined etiology - two or more causes identified" in the TOAST criteria) were excluded. This study was approved by the relevant institutional ethics committee (B-2020-300). Written, informed consent for the prospective registry was obtained from all patients or their next-of-kin.

Clinical Characteristics

Clinical and background characteristics, including sex, age, cardiovascular risk factors, and medical histories, were recorded on admission. Cardiovascular risk factors were defined as: 1) hypertension-history of using antihypertensive agents, systolic blood pressure (BP) ≥140 mm Hg, or diastolic BP ≥90 mm Hg before or ≥2 weeks after stroke onset; 2) diabetes mellitus-use of hypoglycemic agents, random glucose level ≥200 mg/dL, or glycosylated hemoglobin ≥6.5% on admission; 3) hyperlipidemia-use of antihyperlipidemic agents, or a serum total cholesterol level ≥220 mg/dL or low-density lipoprotein cholesterol level ≥140 mg/dL; and 4) current smoking. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and functional status was assessed with the modified Rankin scale (mRS). Routine blood biochemistry examinations were performed on admission.

The decision to initiate AT and the details of AT administration were at the attending physicians' discretion and were generally based on the Japanese guideline[18]. Because our guidelines for appropriate use of rt-PA[19] recommends that early AT after rt-PA treatment should generally be avoided (but is not contraindicated), early AT would be given after obtaining informed consent from patients or their next-to-kin. Time metrics of treatment-onset to AT, onset to rt-PA treatment, and onset to reperfusion time (for patients treated with emergent endovascular treatment (EVT])-were collected from the registry and electronic medical records. EVT was generally conducted based on, but not limited to, Japanese guidelines[20,21]. When EVTs were performed, 4,000 or 5,000 units of unfractionated heparin were administered intravenously after sheath placement. In general, in cases of hemorrhagic complications during the EVT procedure, we immediately lower BP and reverse heparin anticoagulation with protamine sulfate, after which rescue procedures (such as embolization of the parent artery or open surgery for hematoma removal or decompression craniectomy) are considered.

Hemorrhagic and ischemic outcomes in the acute phase (within 48 hours from admission), defined below, were also collected.

Hemorrhagic outcomes included the following: all hemorrhagic events; hemorrhagic events associated with a hemoglobin decrease >2 g/dL; parenchymal hemorrhage (PH), defined as new hemorrhage in the ischemic lesion with a space-occupying effect; and sICH, defined as severe (blood clots >30% of infarcted area) PH and

corresponding to an increment in the NIHSS score of ≥2 points (slightly modified SITS-MOST criteria[22]).

Ischemic outcomes included the following: early neurological deterioration, defined as an increase in the NIHSS score of ≥2 points; and symptomatic acute thrombosis/re-stenosis of the treated vessel, defined as re-stenosis or occlusion of the treated vessel associated with END and/or additional endovascular intervention.

Statistical Analysis

The patients were classified into six groups based on the reperfusion treatment and early AT, as follows: 1) patients without reperfusion therapy (No Reperfusion Therapy group); 2) patients treated with rt-PA but not EVT, without early AT (rt-PA Only without early AT group); 3) patients treated with rt-PA but not EVT, with early AT (rt-PA Only with early AT group); 4) patients treated with EVT but not rt-PA (EVT Only group); 5) patients treated with rt-PA and EVT without early AT (Conventional AT group); and 6) patients treated with rt-PA and EVT and administered AT within 24 hours after rt-PA treatment (Early AT group). Early AT was defined as administration of antithrombotic agent(s) within 24 hours after commencement of rt-PA infusion.

First, clinical background characteristics were compared among the six groups. Univariate analyses were performed using the chi-square test, Fisher's exact test, and Mann-Whitney U test, as appropriate. The data are presented as medians (interquartile range [IQR]) or numbers (%). Next, hemorrhagic and ischemic outcomes in the acute phase were compared between the Early AT group and the other groups. All statistical analyses were performed using PASW for Windows version 26.0 software (SPSS Inc., Chicago, IL, USA). Results were considered significant at $p < 0.05$.

Results

Overall, 2,689 consecutive patients with acute ischemic cerebrovascular diseases were admitted to our stroke center during the study period. Of them, 432 were classified as having LAA at hospital discharge, and 155 (35 women [23%], median age 74 [IQR 66-79] years; NIHSS score 3 [1-10]; onset to arrival 1.8 [1.0-3.5] hours) had LAA and were admitted to hospital within 6 hours after symptom onset and therefore included in the present study. Of these 155 patients, 73 (47%) received no reperfusion therapy (No Reperfusion Therapy group), 24 (15%) received rt-PA treatment without early AT (rt-PA Only without early AT group), seven (6%) received rt-PA with early AT, 26 (17%) received EVT (EVT Only group), and 25 (16%) received both rt-PA and EVT. Although nine patients took anticoagulant drugs (direct oral anticoagulants in five and warfarin in four) before the event, no patient was withheld rt-PA treatment because of use of anticoagulants. In patients who received both rt-PA and EVT, six were administered AT after 24 hours or were treated with antithrombotic agents (Conventional AT group), whereas the remaining 19 were treated with antithrombotic agents within 24 hours after rt-PA therapy (Early AT group). Five patients were not treated with any antithrombotic agents within 48 hours after admission-one patient each because of symptomatic ICH and severe general condition in the rt-PA Only without early AT group, one patient because of severe general condition in the EVT only group, and one patient each because of subarachnoid hemorrhage and large ischemic volume in the Conventional AT group. **Table 1** shows the background characteristics of the included patients. The proportion of current smokers differed among the six groups (p=0.031). Not surprisingly, time from onset to hospital arrival tended to be longer in the EVT Only group (p=0.067), and patients treated with EVT (EVT Only group, Conventional AT group, and Early AT group) had more severe symptoms (p<0.001) and worse outcomes (p=0.002) than the other groups.

AT was initiated at a median of 7.2 (IQR 4.2-10.9) hours after stroke onset in the No Reperfusion Therapy group, 30.7 (27.9-37.0) hours in the rt-PA Only without early AT group, 21.5 (17.3-25.4) in the rt-PA Only with early AT group, 7.0 (3.6-8.0) hours in the EVT Only group, 30.0 (27.0-43.4) hours in the Conventional AT group, and 7.1 (4.5-11.0) hours in the Early AT group (**Table 2**). AT was administered as early as a median of 3.9 (1.6-8.0) hours after rt-PA in the Early AT group. Emergent PTA/CAS or intracranial stenting was performed for 37 cases, including 17 patients in the EVT only group, three in the Conventional AT group, and 17 in the Early AT group. Therefore, 85% (17 of 20) of the patients treated with emergent PTA/CAS concomitant with rt-PA received AT within 24 hours from rt-PA treatment. All patients in the Early AT group underwent PTA, CAS, or stenting on an intracranial artery. Most patients in the Early AT group were administered DAPT during EVT orally or via a nasoenteral tube when neurointerventionalists decided to perform PTA/CAS and obtained consent from the patients. The antithrombotic agents used varied, probably because multiple agents are approved for LAA in Japan and the effectiveness of DAPT was proven for minor strokes/TIAs during the study pe-

Table 1 Baseline clinical characteristics of patients

Variables	No reperfusion therapy n=73	rt-PA Only		EVT Only n=26	rt-PA + EVT		p
		Without early AT n=24	With early AT n=7		Conventional AT n=6	Early AT n=19	
Female sex, n (%)	21 (29)	6 (25)	3 (43)	4 (15)	0 (0)	1 (5)	0.105
Age, years, median (IQR)	73 (66-81)	75 (71-83)	77 (64-78)	71 (67-77)	76 (72-81)	68 (60-79)	0.315
Prior history of stroke, n (%)	28 (38)	7 (29)	1 (14)	6 (23)	3 (50)	2 (11)	0.137
Prior history of vascular disease*, n (%)	13 (18)	4 (17)	0 (0)	7 (27)	1 (17)	1 (5)	0.393
Risk factors							
Hypertension, n (%)	54 (74)	18 (75)	5 (71)	16 (62)	3 (50)	10 (53)	0.386
Dyslipidemia, n (%)	57 (78)	19 (79)	5 (71)	17 (65)	5 (83)	12 (63)	0.633
Diabetes Mellitus, n (%)	30 (40)	11 (46)	2 (29)	11 (42)	3 (50)	3 (16)	0.340
Current smoker, n (%)	23 (32)	2 (8)	1 (14)	11 (42)	2 (33)	10 (53)	0.031
Preadmission mRS, median (IQR)	0 (0-1)	0 (0-2)	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)	0.466
Prior antiplatelet therapy, n (%)	26 (36)	8 (33)	2 (29)	6 (23)	2 (33)	1 (5)	0.188
Onset to arrival, h, median (IQR)	1.7 (1.0-3.9)	1.70 (1.1-2.6)	1.7 (0.9-1.8)	3.3 (1.7-4.3)	1.0 (0.76-2.0)	1.7 (0.8-2.6)	0.067
NIHSS score on admission, median (IQR)	1 (0-3)	4 (2-9)	4 (3-7)	10 (6-17)	17 (12-18)	8 (5-14)	<0.001
Biochemistry sign at admission, median (IQR)							
Hemoglobin, g/dL	13.6 (12.2-14.8)	13.7 (12.3-14.6)	14.2 (12.9-16.0)	13.4 (11.2-14.6)	14.1 (11.6-15.3)	14.0 (13.3-15.0)	0.563
Low density lipoprotein cholesterol, mg/dL	108 (87-129)	108 (83-142)	111 (100-152)	106 (68-128)	122 (92-127)	120 (94-176)	0.485
eGFR, mL/min	65 (49-79)	64 (49-75)	81 (69-83)	64 (49-85)	52 (32-69)	65 (58-84)	0.304
Blood glucose, mg/dL	126 (104-165)	113 (97-171)	114 (100-155)	133 (104-211)	160 (111-228)	129 (100-144)	0.669
D-dimer, μg/mL	1.0 (0.6-1.5)	1.3 (0.83-2.1)	0.8 (0.6-1.1)	1.2 (1.0-2.8)	1.7 (0.9-16.3)	0.9 (0.6-3.3)	0.061
C-reactive protein, mg/dL	0.14 (0.06-0.52)	0.16 (0.06-0.99)	0.12 (0.05-0.36)	0.21 (0.07-0.81)	1.12 (0.31-2.74)	0.14 (0.04-0.44)	0.304
Responsible artery, n (%)							0.469
Internal carotid artery	33 (45)	13 (54)	4 (57)	12 (46)	4 (67)	13 (68)	
Middle cerebral artery	25 (34)	7 (29)	2 (29)	10 (39)	2 (33)	4 (21)	
Anterior cerebral artery	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	
Vertebral artery	11 (15)	3 (13)	0 (0)	2 (8)	0 (0)	1 (5)	
Basilar artery	3 (4)	0 (0)	0 (0)	2 (8)	0 (0)	1 (5)	
Posterior cerebral artery	1 (1)	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	
mRS at discharge, n (%)	1 (0-2)	2 (0-4)	2 (1-4)	3 (2-5)	3 (2-5)	2 (1-4)	0.002

*including ischemic heart disease and peripheral vascular diseases.

rt-PA, recombinant tissue plasminogen activator; AT, antithrombotic treatment; EVT, endovascular therapy; mRS, modified Rankin scale; BP, blood pressure; NIHSS, National Institutes of Health Stroke scale; eGFR, estimated glomerular filtration rate.

Table 2 Clinical characteristics in relation to acute therapy selected

Variables	No reperfusion therapy n=73	rt-PA Only		EVT Only n=26	rt-PA + EVT		p
		Without early AT n=24	With early AT n=7		Conventional AT n=6	Early AT n=19	
Time metrics, hours (IQR)							
Onset to antithrombotic treatment	7.2 (4.2-10.9)	30.7 (27.9-37.0) *	21.5 (17.3-25.4)	7.0 (3.6-8.0) †	30.0 (27.0-43.4) ‡	7.1 (4.5-11.0)	<0.001
Onset to rt-PA	N/A	3.2 (2.1-3.8)	2.7 (2.2-4.3)	N/A	2.3 (1.7-4.4)	2.9 (2.3-3.3)	0.859
Onset to reperfusion	N/A	N/A	N/A	5.1 (3.5-7.5)	3.1 (2.3-4.7)	4.1 (2.7-4.9)	0.079
rt-PA to antithrombotic treatment	N/A	27.8 (24.3-33.3) *	19.8 (15.1-21.1)	N/A	27.0 (24.5-40.9) ‡	3.9 (1.6-8.0)	<0.001
Antithrombotic treatment							
SAPT	30 (41)	11 (46)	1 (14)	6 (23)	2 (33)	3 (16)	0.130
DAPT	16 (22)	5 (21)	4 (57)	8 (31)	2 (33)	13 (68)	0.002
AC	19 (26)	5 (21)	2 (29)	6 (23)	0 (0)	1 (5)	0.328
AC+SAPT	6 (8)	1 (4)	0 (0)	1 (4)	0 (0)	1 (5)	0.864
AC+DAPT	2 (3)	0 (0)	0 (0)	4 (15)	0 (0)	1 (5)	0.093
No antithrombotic therapy	0 (0)	2 (8)	0 (0)	1 (4)	2 (33)	0 (0)	<0.001
EVT procedures							
Stentrievers	N/A	N/A	N/A	9 (35)	1 (17)	2 (11)	0.156
Aspiration catheter	N/A	N/A	N/A	15 (58)	5 (83)	11 (58)	0.484
PTA	N/A	N/A	N/A	7 (27)	2 (33)	6 (32)	0.921
CAS	N/A	N/A	N/A	10 (39)	1 (17)	9 (47)	0.403
Intracranial stenting	N/A	N/A	N/A	0 (0)	0 (0)	2 (11)	0.173

* 2 cases without AT

† 1 case without AT

‡ 2 cases without AT

rt-PA, recombinant tissue plasminogen activator; EVT, endovascular therapy; AT, antithrombotic treatment; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; AC, anticoagulant therapy; PTA, percutaneous transluminal angioplasty; CAS, carotid artery stenting.

Table 3 Hemorrhagic and ischemic events within 48 h after hospital admission

Variables	No reperfusion therapy n=73	p (vs. Early AT)	rt-PA Only without early AT n=24	p (vs. Early AT)	rt-PA Only with early AT n=7	p (vs. Early AT)	EVT Only n=26	p (vs. Early AT)	rt-PA + EVT		
									Conventional AT n=6	p (vs. Early AT)	Early AT n=19
Acute hemorrhagic events, n (%)											
All hemorrhagic events	2 (3)	0.058	4 (17)	1.000	0 (0)	0.540	3 (12)	0.686	3 (50)	0.125	3 (16)
Hemorrhage with >2 g/dL Hb decline	0 (0)	0.207	0 (0)	0.442	0 (0)	1.000	0 (0)	0.422	1 (17)	0.430	1 (5)
Parenchymal hemorrhage	2 (3)	0.505	3 (13)	0.618	0 (0)	1.000	1 (4)	1.000	1 (17)	0.430	1 (5)
sICH	1 (1)	1.000	2 (8)	0.495	0 (0)	-*	1 (4)	1.000	1 (17)	0.240	0 (0)
Acute ischemic events, n (%)											
END	8 (11)	0.037	5 (21)	0.495	3 (43)	0.661	6 (23)	0.734	2 (33)	1.000	6 (32)
END without sICH	7 (10)	0.024	3 (13)	0.153	3 (43)	0.661	5 (19)	0.485	1 (17)	0.637	6 (32)
Thrombosis/Re-stenosis in PTA/CAS/Stenting	N/A		N/A				2 out of 17 (12%)	1.000	2 out of 3 (67%)	0.046	1 out of 17 (6%)

rt-PA, recombinant tissue plasminogen activator; EVT, endovascular therapy; AT, antithrombotic treatment; sICH, symptomatic intracerebral hemorrhage; END, early neurological deterioration; PTA, percutaneous transluminal angioplasty; CAS, carotid artery stenting.
* p values cannot be calculated because of the absence of events in both groups.

riod[4,23]. Antiplatelet agents included aspirin (enterally), clopidogrel (enterally), cilostazol (enterally), and ozagrel (intravenously), and most patients received argatroban (intravenously), a direct thrombin inhibitor, as the anticoagulant agent.

Acute hemorrhagic events occurred in 15 (9.7%) patients, and sICH was observed in five (3.2%) of the present patients. Although patients in the Conventional AT group avoided early AT, they more frequently developed hemorrhagic events within 48 hours after hospital admission (**Table 3, 4**, and **Fig. 1**). AT within 24 hours from rt-PA and EVT treatment (i.e., Early AT group in **Table 3** and **Fig. 1**) seemed not to increase hemorrhagic or ischemic complications, at least compared to the rt-PA Only group (with or without early AT) or the EVT only group.

Discussion

The present study showed that a considerable number of patients treated with emergent PTA/CAS concomitant with rt-PA were administered AT within 24 hours after rt-PA treatment. DAPT was performed for most such patients, and early AT administration for patients treated with rt-PA and EVT seemed to be safe, because hemorrhagic risks in the early phase were as low as for those treated with only rt-PA with or without early AT or only EVT with early AT.

Most hyperacute LAA patients (76%) treated with rt-PA and EVT, and as many as 85% of LAA patients treated with emergent PTA/CAS concomitant with rt-PA, received AT early after rt-PA treatment. These percentages are partly consistent with a retrospective study that showed 64.1% of patients treated with reperfusion therapy received AT within 24 hours after reperfusion therapy[7]. The present study included patients with all stroke subtypes, and LAA was more common in the early AT initiation group than in the standard therapy (AT >24 hours after reperfusion therapy) group. However, in contrast with the past study, in which early AT initiation was widely seen across various stroke subtypes and reperfusion therapy modalities, early AT initiation was observed mostly in patients treated with emergent PTA/CAS in the present study. The present study seems to reflect the clinical settings under current guidelines[1,18]; early AT is generally avoided within 24 hours from rt-PA treatment but is considered for patients treated with emergent PTA/CAS concomitant with rt-PA treatment. The median time from reperfusion therapy to AT was 13.9 hours in the previous study[7] but was as short as 3.9 hours in the

Table 4 Hemorrhagic and ischemic events within 48 h after hospital admission in patients who received emergent PTA/CAS (n=37).

Variables	EVT Only n=17	rt-PA + EVT		p
		Conventional AT n=3	Early AT n=17	
Acute hemorrhagic events, n (%)				
All hemorrhagic events	3 (18)	1 (33)	2 (12)	0.631
Hemorrhage with >2 g/dL Hb decline	0 (0)	1 (33)	1 (6)	0.062
Parenchymal hemorrhage	1 (6)	0 (0)	1 (6)	0.911
sICH	1 (4)	0 (0)	0 (0)	0.546
Acute ischemic events, n (%)				
END	6 (35)	1 (33)	5 (29)	0.935
END without sICH	5 (29)	1 (33)	5 (29)	0.990
Thrombosis/Restenosis in PTA/CAS/Stenting	2 (12)	2 (67)	1 (6)	0.017

PTA, percutaneous transluminal angioplasty; CAS, carotid artery stenting; rt-PA, recombinant tissue plasminogen activator; EVT, endovascular therapy; AT, antithrombotic treatment; sICH, symptomatic intracerebral hemorrhage; END, early neurological deterioration

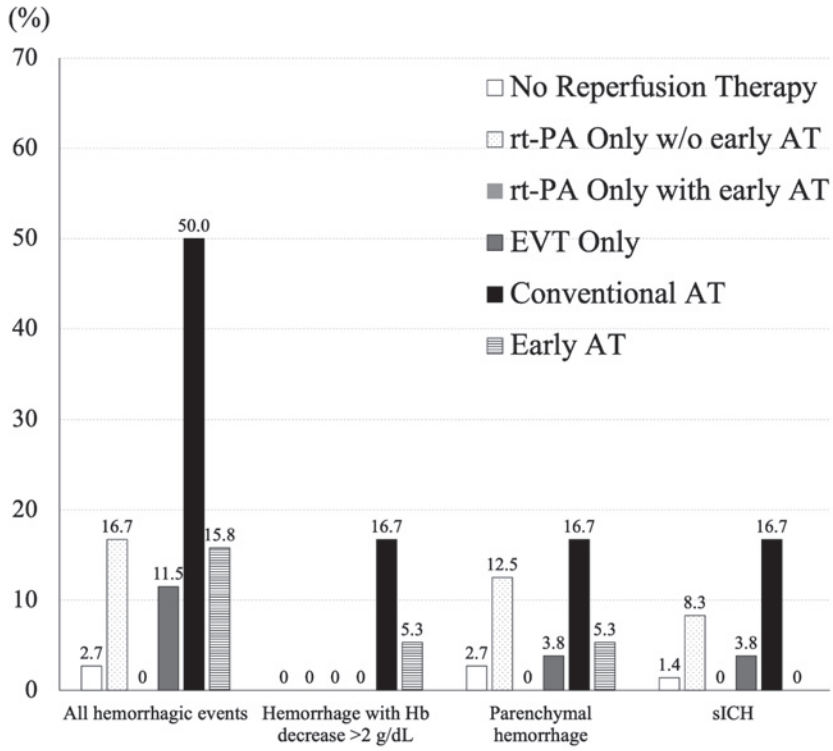

Fig. 1 Proportion of acute (within 48 hours after admission) hemorrhagic events, by reperfusion modality, in patients with acute stroke due to large-artery atherosclerosis.
sICH, symptomatic intracerebral hemorrhage; rt-PA, recombinant tissue-plasminogen activator; EVT, endovascular therapy; AT, antithrombotic treatment.

present study. Aggressive AT was performed when neurointerventionalists decided to perform PTA/CAS, even shortly after rt-PA treatment. Because some patients with acute stroke due to LAA can be treated with emergent PTA/CAS, an optimal management strategy including AT for patients with acute stroke due to LAA and treated with rt-PA plus emergent PTA/CAS should be urgently established.

Early AT for LAA patients treated with rt-PA and EVT seemed to be safe, because the risks of hemorrhagic

events were as low as for those treated with rt-PA only (with or without early AT) or EVT only (and started AT median 7 hours after onset). The present results are partly consistent with a previous small study that showed that early argatroban treatment for patients treated with rt-PA and EVT was safe[24]. However, the randomized ARTIS trial showed that early aspirin administration after rt-PA treatment increased hemorrhagic events and had no effect on clinical outcomes[5]. There are some possible explanations for the discrepant results between the present and the previous study. First, only patients with acute stroke due to LAA were included in the present study, whereas all acute stroke patients who had indications for rt-PA were included in the previous study. In addition, the timing and route of AT differed between the present and previous study: AT was administered through the gastrointestinal tract 3.9 hours after starting rt-PA infusion in the present study but was administered intravenously 90 min after starting rt-PA in the previous study. Patients with stroke due to LAA have a lower risk of hemorrhagic transformation than patients with stroke due to other causes, such as cardioembolism[13,14], and the relatively delayed effect of AT after rt-PA treatment through the gastrointestinal tract may contribute to the low rate of hemorrhagic events in the present study. Early enteral AT administration, approximately 4 hours after rt-PA treatment, can be safe for LAA patients treated with rt-PA and EVT.

The strengths of the present study are that it included consecutive LAA patients, that it compared hemorrhagic events, as well as the ischemic events, among the hyperacute treatment modalities, and that it involved a relatively large number of patients treated with emergent PTA/CAS. There are a few case series reporting AT early after rt-PA treatment in patients treated with emergent CAS, but these reports included relatively small numbers of patients and had no control group[11,12].

However, there are several limitations that need to be addressed. First, because of the retrospective nature of the study, the decision to administer AT early after rt-PA treatment was made by the attending physician. In patients with procedural complications, such as perforation of the intracranial arteries (and applicable to hemorrhagic events and those who exhibited early neurological deterioration thereafter), early AT is naturally avoided. Indeed, one patient each in the rt-PA Only without early AT group and Conventional AT group had an acute intracranial hemorrhagic event. Furthermore, because patients in the Conventional AT group clearly had severe symptoms (**Table 1**), attending physicians may have avoided early AT because of the risk of hemorrhagic transformation. The large number of hemorrhagic events in the Conventional group can be partly explained by such bias. Second, because this study assessed the safety of early AT for thrombolysed patients with LAA, the present results cannot be generalized to all LAA patients. Third, although the present study included a relatively large number of patients with hyperacute stroke due to LAA treated with EVT, some groups had only a small number of patients. These small numbers precluded further analyses such as multivariate analyses. Lastly, only short-term (within 48 hours after admission) outcomes and mRS scores at discharge were assessed. The present results should therefore be confirmed in prospective, randomized, controlled trials.

In conclusion, early AT after rt-PA treatment was performed for most patients treated with emergent PTA/CAS and seemed to be safe, as the incidence of acute hemorrhagic events was as low as that for those treated with only rt-PA or only EVT.

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