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Intravenous Alteplase at 0.6 mg/kg for Unknown Onset Stroke with Prior Antithrombotic Medication: THAWS Randomized Clinical Trial

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Aim: This study aimed to assess the potential effect of prior antithrombotic medication for thrombolysis in an unknown onset stroke.

Methods: This was a predefined sub-analysis of the THAWS trial. Stroke patients with a time last known well >4.5 h who had a DWI-fluid-attenuated inversion recovery mismatch were randomly assigned (1:1) to receive alteplase at 0.6 mg/kg (alteplase group) or standard medical treatment (control group). Patients were dichotomized by prior antithrombotic medication.

Results: Of 126 patients (intention-to-treat population), 40 took antithrombotic medication (24 with antiplatelets alone, 13 with anticoagulants alone, and 3 with both), and the remaining 86 did not before stroke onset. Of these, 17 and 52 patients, respectively, received alteplase, and 23 and 34, respectively, had standard medical treatment. Antithrombotic therapy was initiated within 24 h after randomization less frequently in the alteplase group (12% vs. 86%, $p<0.01$). Both any intracranial hemorrhage within 22–36 h (26% vs. 14%) and a modified Rankin Scale score of 0–1 at 90 days (good outcome) (47% vs. 48%) were comparable between the two groups. A good outcome was more common in the alteplase group than in the control group in patients with prior antithrombotic medication [relative risk (RR) 2.25, 95% confidence interval (CI) 1.02–4.99], but it tended to be less common in the alteplase group in those without (RR 0.69, 95% CI 0.46–1.03) ($p<0.01$ for interaction). The frequency of any intracranial hemorrhage did not significantly differ between the two groups in any patients dichotomized by prior antithrombotic medication.

Conclusion: Alteplase appears more beneficial in patients with prior antithrombotic medication.

Key words: Prior antithrombotic medication, Wake-up stroke, Diffusion-weighted imaging, Fluid-attenuated inversion recovery, Thrombolysis

Introduction

Magnetic resonance imaging (MRI)-based thrombolysis in acute ischemic stroke with unknown onset time was proven effective in an individual data meta-analysis. Although the efficacy and safety of MRI-based Thrombolysis in Wake-up Stroke Thrombolysis in Wake-up Stroke (WAKE-UP) trials showed the efficacy of alteplase[1], the Thrombolysis for Acute Wake-up and unclear-onset Strokes with alteplase at 0.6 mg/kg (THAWS) trial, having a similar trial design except for the use of alteplase at 0.6 mg/kg in the alteplase group and standard medical treatment instead of placebo use, failed to show the efficacy of intravenous thrombolysis[2].

Pretreatment antiplatelet use is known to be one of the potential contributors to symptomatic intracerebral hemorrhage following intravenous thrombolysis[3, 4]. In general, prior anticoagulation, mainly with warfarin, was proven to be associated with better clinical outcomes[5, 6], and early initiation of antiplatelet medications could improve clinical outcomes following acute ischemic stroke[7, 8]. However, the efficacy of prior antithrombotic medication in intravenous thrombolysis for acute ischemic stroke is not generally expected.

Aim

This study aimed to assess the potential effect and risk of prior antithrombotic medication for thrombolysis using alteplase at 0.6 mg/kg in unknown onset stroke.

Methods

The data that support the findings of this study are not publicly available due to ethical grounds but are available from the corresponding author upon reasonable request.

This study was a predefined sub-analysis of the THAWS trial, an investigator-initiated, Phase III, multicenter, randomized, open-label, blinded-endpoint trial (Clinical Trials.gov Identifier: NCT02002325; UMIN clinical trial ID: UMIN000011630). The details were described elsewhere[2, 9, 10]. Briefly, acute ischemic stroke patients with unknown onset time and diffusion-weighted imaging (DWI)-fluid-attenuated inversion recovery (FLAIR) mismatch on initial brain MRI evaluation were enrolled. Standard indications for intravenous thrombolysis[11], other than time last known well >4.5 h (e.g., wake-up stroke), were followed. DWI-FLAIR mismatch was defined as an acute ischemic lesion on DWI with no remarkable corresponding hyperintensity on FLAIR. In this sub-analysis, patients were dichotomized by prior antithrombotic medication.

This research complied with the guidelines for human studies and should include evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The trial was approved by the local ethics committee (M25-015-11 and R19046-3) or institutional review board at each participating center. Patients or their relatives provided written, informed consent according to ethical regulations.

Randomization and Treatment

Patients were randomly assigned (1:1) to receive alteplase at 0.6 mg/kg (alteplase group) or standard medical treatment (control group), based on a minimization scheme with stratification by severity of symptoms as assessed using the National Institutes of Health Stroke Scale (NIHSS) score (≤ 11 or >11). Both patients and investigators were aware of treatment allocation. Immediately after randomization, patients in the alteplase group were treated with intravenous alteplase at 0.6 mg/kg within 4.5 h after symptom recognition, and those randomized to the control group were treated with the standard medical treatment using one to three antithrombotic drugs, including oral aspirin, oral clopidogrel, intravenous argatroban, or intravenous unfractionated heparin, but excluding the combination of argatroban and heparin. According to the guidelines[11], all antithrombotics were basically prohibited for use in the alteplase group but were allowed as the standard medical treatment in the control group within the initial 25 h.

Clinical and Imaging Assessments

Certified neurologists or neurosurgeons performed clinical assessments including the NIHSS at baseline. Outcomes at 90 days were blindly assessed without information regarding treatment allocation by independent and accredited examiners. Brain MRI was performed at baseline, at 22–36 h to identify

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intracranial hemorrhage, and at 7–14 days to delineate final infarct volume.

Efficacy outcomes were a good outcome defined as a modified Rankin Scale score of 0–1 at 90 days, recanalization of the culprit artery on magnetic resonance angiography (MRA) at 22–36 h, and infarct volume at 7 days. Recanalization was defined as modified Mori grade 3 [12]. Safety outcomes were any intracranial hemorrhage (ICH) on MRI at 22–36 h after initiation of treatment, hemorrhagic infarction (HI) types 1 and 2 ICH, parenchymal hematoma (PH) types 1 and 2 ICH on MRI at 22–36 h, and symptomatic ICH within 22–36 h on MRI at 22–36 h and death at 90 days[13]. The definition of symptomatic ICH was assessed with an increase in the NIHSS score by 4 or more from baseline[14].

Statistical Analysis

Data are presented as medians [interquartile range (IQR)] or numbers (%). Efficacy analyses were performed on the intention-to-treat population, and safety analyses were conducted using the treated data set. Intergroup comparisons were made using the *t*-test or Wilcoxon rank-sum test, as appropriate, for continuous variables and the chi-squared test or Fisher's exact test, as appropriate, for categorical variables. The effects of alteplase on each outcome were compared between the assigned treatment groups (alteplase and control groups) in the patients who had prior antithrombotic medication (anticoagulant or antiplatelet) and those who did not, separately. In each group, crude analysis was performed to determine the difference in frequencies of outcomes between the alteplase and control groups. Direct comparison of the continuous variable of infarct volume was also performed between the alteplase and control groups. For outcomes, an interaction was assessed between assigned treatment group and prior antithrombotic medication. A value of $p<0.05$ based on a two-tailed test was considered significant. Statistical analysis was performed using Stata/MP version 17.0 software (Stata Corp LP, College Station, TX).

Results

Of 131 patients undergoing randomization in the THAWS trial, 126 patients (median age 77 years, 53 women) with 90-day follow-up assessment within the allowed schedule (intention-to-treat population) were studied, and they were identical with the cohort for the primary outcome analysis in the main report[2]. Of these, 40 patients had one or more prior antithrombotic medications: 24 with prior antiplatelets alone, 13 with prior anticoagulants alone, and 3 with both. Patients with prior antithrombotic medication were significantly older and had more dyslipidemia, a history of ischemic stroke/transient ischemic attack, vessel occlusion on baseline MRA, and higher premorbid modified Rankin Scale scores **(Table 1)**. The prothrombin time/international normalized ratio was 1.36 [1.07–1.44] in seven patients who had prior warfarin. Just after randomization, 17 patients with and 52 without prior antithrombotic medication received intravenous alteplase (alteplase group). On the other hand, 20 and 30, respectively, had early antithrombotic therapy initiation within 24 h after randomization as standard medical treatment (control group) **(Table 2)**.

Clinical and imaging efficacy outcomes are presented in **Table 3**. A good outcome was more frequently observed in the alteplase group than in the control group in patients with prior antithrombotic medication [59% vs. 26%; relative risk (RR) 2.25, 95% confidence interval (CI) 1.02–4.99, $p=0.037$], although it tended to occur less frequently in the alteplase group in patients without prior antithrombotic medication (43% vs. 63%, $p=0.072$; RR 0.69, 95% CI 0.46–1.03) **(Fig. 1)**. There was a significant treatment-by-cohort interaction for a good outcome between patients with and without prior antithrombotic medication ($p=0.006$). There was a trend for a higher recanalization rate of the culprit artery in the alteplase group than in the control group in patients with prior antithrombotic medication (91% vs. 55%, $p=0.056$), but no difference in patients without (65% vs. 58%, $p=0.728$). Infarct volume and infarct growth at 7 days were similar between the treatment assignment groups, both in patients with and without prior antithrombotic medication.

Safety outcomes are shown in **Table 4**. Overall, any ICH was present in 26 patients (21%) at 22–36 h and classified into HI type 1 ICH in 10, HI type 2 ICH in 11, PH type 1 ICH in 1, and PH type 2 ICH in 4. Of these, only one patient with prior aspirin who showed PH type 2 ICH had symptomatic ICH. Any ICH, PH type 2 ICH, and symptomatic ICH were comparable between patients with alteplase (one patient in the control group had alteplase) and those without, both in patients with and without prior antithrombotic medication. Death at 90 days was not common and similarly observed between the two groups, both in patients with and without prior antithrombotic medication.

Discussion

The potential effect of prior antithrombotic

Table 1. Baseline characteristics

Variable	With prior antithrombotic medication ($n=40$)	Without prior antithrombotic medication ($n=86$)	p
Age, y	78.1 ± 9.0	72.6 ± 13.2	0.020
Female sex	20 (50)	33 (38)	0.218
Medical history			
Hypertension	31 (78)	55 (64)	0.128
Diabetes mellitus	10 (25)	15 (17)	0.322
Dyslipidemia	22 (55)	23 (27)	0.002
Atrial fibrillation	15 (38)	15 (17)	0.014
Prior antithrombotic medication			
Prior antiplatelet alone	24 (60)	None	-
Prior warfarin alone	4 (10)	None	-
Prior direct oral anticoagulant alone	9 (23)	None	-
Prior antiplatelet and warfarin	3 (8)	None	-
Prothrombin time / international normalized ratio on admission (prior warfarin)	1.36 [1.07-1.44] ($n=7$)	-	-
History of ischemic stroke/TIA	18 (45)	2 (2)	<0.0001
Premorbid modified Rankin Scale score	0 [0-1]	0 [0-0]	0.0032
Recognition at awaking (wake-up stroke)	26 (65)	63 (73)	0.344
Initial NIHSS score	8 [5-12.5]	7 [4-13]	0.842
Baseline DWI-ASPECTS	9 [7.25-10]	9 [8-10]	0.425
negative DWI at baseline	4 (10)	17 (20)	0.171
Vessel occlusion on baseline MRA	18 (45)	21 (24)	0.020
LKW to symptom recognition - min	463.5 [367.5-540]	420 [300-540]	0.111
Symptom recognition to randomization - h	181.5 [144.25-228]	174.5 [132-224]	0.313
LKW to randomization - h	646.5 [552-765]	599.5 [448.5-708.75]	0.147

Data are reported as numbers (%), means ± standard deviation, or medians [interquartile range].
TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale; DWI: diffusion-weighted imaging; ASPECTS: Alberta stroke programme early CT score; MRA: magnetic resonance angiography; LKW: last known well

Table 2. Acute treatment just after randomization

	With prior antithrombotic medication ($n=40$)		Without prior antithrombotic medication ($n=86$)	
Intravenous alteplase at 0.6 mg/kg	Given $n=17$	Not given $n=23$	Given $n=52$	Not given $n=34$
Antithrombotic therapy within 24 h after randomization	0	20 (87)	8 (15)	30 (88)
Antiplatelet therapy	0	10 (43)	5 (10)	20 (59)
Single antiplatelet therapy	0	6 (26)	4 (8)	10 (29)
Dual antiplatelet therapy	0	4 (17)	1 (2)	10 (29)
Anticoagulant therapy	0	18 (78)	4 (8)	20 (59)
Intravenous argatroban	0	7 (30)	2 (4)	8 (24)
Intravenous unfractionated heparin	0	11 (48)	2 (4)	12 (35)

Data are reported as numbers (%).

medication was assessed in acute ischemic stroke patients randomized into the alteplase and control groups. Since this was an open-label trial with blinded outcome assessment, it was possible to start early antithrombotic treatment in about 90% of the control group, but not in the alteplase group. There was a significant treatment-by-cohort interaction for a good outcome between patients with and without prior antithrombotic medication. Alteplase at 0.6 mg/kg was significantly more effective in patients with prior

Table 3. Efficacy outcomes

	Alteplase group (n=68)	Control group (n=58)	Value (95% CI)	P Value	P for interaction
Good outcome at 90 days, n/total n (%): relative risk					
With prior antithrombotic medication	10/17 (59%)	6/23 (26%)	2.14 (1.03-4.45)	0.037	0.007
Without prior antithrombotic medication	22/51 (43%)	22/35 (63%)	0.72 (0.51-1.04)	0.072	
Recanalization of the culprit artery on MRA at 22-36 h (n=22), n/total n (%): relative risk					
With prior antithrombotic medication	5/7 (71%)	3/11 (27%)	3.13 (0.81, 12.06)	0.145 (Fisher)	0.504
Without prior antithrombotic medication	8/11 (73%)	5/10 (50%)	1.64 (0.61, 4.43)	0.387 (Fisher)	
Infarct volume on FLAIR at 7 days, ml, mean ± SD: estimated difference					
With prior antithrombotic medication	29.1 ± 40.7	39.8 ± 58.4	-10.7 (-45.0, 23.5)	0.530	0.431
Without prior antithrombotic medication	22.9 ± 36.0	20.4 ± 37.8	2.4 (-13.9, 18.8)	0.768	
Infarct growth on FLAIR at 7 days, ml, mean ± SD: estimated difference					
With prior antithrombotic medication	18.1 ± 39.8	25.5 ± 45.8	-7.5 (-36.2, 21.2)	0.601	0.497
Without prior antithrombotic medication	14.1 ± 24.8	13.0 ± 25.5	1.16 (-10.0, 12.4)	0.837	

MRA: magnetic resonance imaging; SD: standard deviation

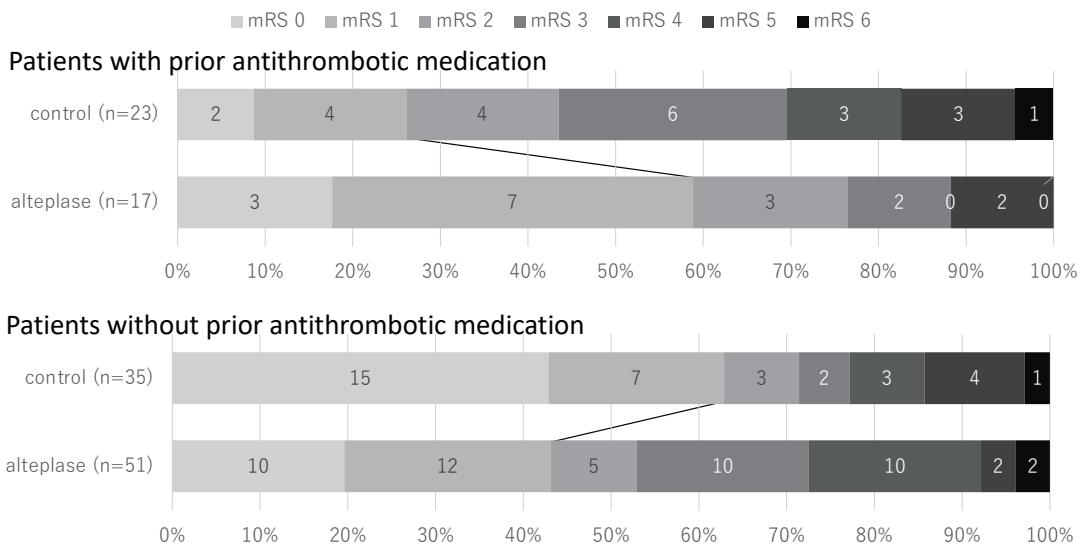

Fig. 1. Bar graphs show the distributions of modified Rankin Scale (mRS) scores 3 months after stroke onset in the alteplase and control groups by prior antithrombotic medication

antithrombotic medication than in those without. Safety outcomes were comparable between the alteplase and control groups in both patients.

Although early initiation of antiplatelet therapy (monotherapy or dual therapy) could improve clinical outcomes in acute stroke, patients with prior antithrombotic medication might not have an additional benefit in the control group due to the long half-life of prior antiplatelet therapy, which has an effect for several days. In other words, both groups might receive a comparable benefit from antiplatelet therapy in patients with prior antithrombotic medication. Prior warfarin within the therapeutic range (PT-INR ≥ 2) was reported as an independent contributor to mild stroke symptoms and a good outcome after ischemic stroke[5], and alteplase could be used in patients with a suboptimal therapeutic range (PT-INR <1.7)[15]. We recently reported that warfarin treatment with PT-INR <2.0, including treatment with alteplase at 0.6 mg/kg, was also associated with non-severe stroke symptoms and a good outcome at 3 months after onset[6]. Patients on warfarin may have

Table 4. Safety outcomes

	With alteplase (n=69)	Without alteplase (n=57)	Value (95% CI)	P Value	P for interaction
Any ICH† at 36 h: n/total n (%): relative risk					
With prior antithrombotic medication	5/17 (29%)	4/23 (17%)	1.44 (0.69-2.99)	0.368	0.939
Without prior antithrombotic medication	13/52 (25%)	4/34 (12%)	1.35 (0.97-1.89)	0.132	
PH type 2 ICH at 36 h: n/total n (%): relative risk					
With prior antithrombotic medication	1/17 (6%)	1/23 (4%)	1.19 (0.28-4.99)	1.0 (Fisher)	0.712
Without prior antithrombotic medication	1/52 (2%)	1/34 (3%)	0.82 (0.20-3.33)	1.0 (Fisher)	
Symptomatic ICH† at 36 h: n/total n (%): relative risk					
With prior antithrombotic medication	1/17 (6%)	0		0.425 (Fisher)	NA
Without prior antithrombotic medication	0	0		NA	
Death at 90 days: n/total n (%): relative risk					
With prior antithrombotic medication	0	1/23 (4%)		1.0 (Fisher)	NA
Without prior antithrombotic medication	2/52 (4%)	1/34 (3%)	1.11 (0.49, 2.51)	1.0 (Fisher)	

ICH: intracranial hemorrhage; PH: parenchymal hematoma; NA: not applicable

fragile blood clots that are likely to be effectively treated using alteplase. As patients with underdose warfarin might be hypercoagulable state, this could be a reason why thrombolytic assist was more beneficial in patients with prior warfarin. Furthermore, most patients with prior antithrombotic medication were less likely stroke mimics because they more frequently had a history of stroke/TIA and baseline vessel occlusion than those without prior antithrombotic medication. Since patients with prior antithrombotics could have more frequent atrial fibrillation or atherothrombotic diseases such as stroke, ischemic heart disease, or peripheral artery disease, those having thrombus burden with severe endothelial disorder or treatment resistance might be associated with the beneficial effect of thrombolysis. However, these hypotheses require confirmation in future studies.

Due to the open-treatment trial design, antithrombotic treatment within 24 h after randomization was commonly performed in the control group. Therefore, alteplase therapy and early initiation of antithrombotics in acute ischemic stroke were eventually compared. Unlike the patients with prior antithrombotic medication, those without could benefit from early antiplatelet initiation in the control group. Early antiplatelet initiation might be beneficial in antiplatelet agent-naïve patients. In addition, patients without prior antithrombotic medication had numerically more negative DWI than those with, although not significantly. Patients without prior antithrombotic medication less frequently had dyslipidemia and atrial fibrillation. Some patients with negative DWI might be stroke mimics, and therefore, alteplase might not be effective in those without prior antithrombotic medication.

Probably due to the low dose of alteplase, comparable low rates of safety outcomes (symptomatic ICH and death) between thrombolysis and standard medical treatment were observed in patients with DWI-FLAIR imaging selection. Prior antithrombotic medication was reportedly associated with hemorrhagic complications such as symptomatic ICH following intravenous alteplase. Alteplase-treated patients with prior antiplatelet treatment had higher symptomatic ICH in the ENCHANTED trial than those without, although low dose of alteplase at 0.6 mg/kg was associated with a lower rate of symptomatic ICH than standard-dose alteplase at 0.9 mg/kg[16]. One study reported that patients taking warfarin faced an approximately fourfold higher risk for symptomatic ICH after intravenous alteplase at 0.9 mg/kg than those not taking warfarin[17]. However, another study found that patients treated with warfarin did not have an increased risk of symptomatic ICH than those not treated with warfarin[18]. A recent systematic review and meta-analysis showed that prior intake of a direct oral anticoagulant was not associated with symptomatic ICH after intravenous alteplase[19]. This study showed that alteplase at 0.6 mg/kg was generally safe in patients with prior antithrombotic medication.

This study had several limitations. First, each class of antithrombotics could not be separately assessed due to the small number of patients. A critical limitation of this subanalysis was the small number of

patients in each dichotomized group, which might weaken statistical power and especially make multivariable adjustment difficult. Second, we were not able to assess the effect of adherence of antithrombotic medication because we did not collect these data. Third, the general limitations of the THAWS trial[2], such as the ethnicity limited to Japanese, the premature termination with a small sample size, open-treatment design, enrolment exclusion for endovascular therapy, and different alteplase dose from 0.9 mg/kg, also applied to this sub-analysis.

Conclusions

Alteplase at 0.6 mg/kg appears more beneficial in patients with prior antithrombotic medication. Standard medical treatment with early antithrombotic initiation might be beneficial in antithrombotic medication-naïve patients.

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Conflicts of Interest Statement

All of the following conflicts are outside the submitted work.

Koga reports honoraria from Bayer and Daiichi Sankyo; consultant fee from Ono pharmaceutical co., LTD; and research funds from Takeda, Daiichi Sankyo, Nippon Boeringer Ingelheim, Astellas and Shionogi.

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None of the other authors has any conflicts of interest to declare.

Author Contributions

MK, MI, KM, SY, MFD, JA, TK, KK, KM, HY, and KT were involved in study design and data interpretation. MK, MI, SY, MFD, JA, TK, MO, KK, YY, SI, RD, YI, YT KK and KT were involved in the data collection. MK and KA were involved in the data analysis. MI and MS were involved in the imaging data collection and analysis. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

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