Stroke

CLINICAL AND POPULATION SCIENCES

Thrombus Migration and Fragmentation After Intravenous Alteplase Treatment

The INTERRSeCT Study

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BACKGROUND AND PURPOSE: There is interest in what happens over time to the thrombus after intravenous alteplase. We study the effect of alteplase on thrombus structure and its impact on clinical outcome in patients with acute stroke.

METHODS: Intravenous alteplase treated stroke patients with intracranial internal carotid artery or middle cerebral artery occlusion identified on baseline computed tomography angiography and with follow-up vascular imaging (computed tomography angiography or first run of angiography before endovascular therapy) were enrolled from INTERRSeCT study (Identifying New Approaches to Optimize Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV Alteplase and Other Treatments Using Serial CT Angiography). Thrombus movement after intravenous alteplase was classified into complete recanalization, thrombus migration, thrombus fragmentation, and no change. Thrombus migration was diagnosed when occlusion site moved distally and graded according to degrees of thrombus movement (grade 0–3). Thrombus fragmentation was diagnosed when a new distal occlusion in addition to the primary occlusion was identified on follow-up imaging. The association between thrombus movement and clinical outcome was also evaluated.

RESULTS: Among 427 patients in this study, thrombus movement was seen in 54% with a median time of 123 minutes from alteplase administration to follow-up imaging, and sub-classified as marked (thrombus migration grade 2–3 + complete recanalization; 27%) and mild to moderate thrombus movement (thrombus fragmentation + thrombus migration grade 0–1; 27%). In patients with proximal M1/internal carotid artery occlusion, marked thrombus movement was associated with a higher rate of good outcome (90-day modified Rankin Scale, 0–2) compared with mild to moderate movement (52% versus 27%; adjusted odds ratio, 5.64 [95% CI, 1.72–20.10]). No difference was seen in outcomes between mild to moderate thrombus movement and no change. In M1 distal/M2 occlusion, marked thrombus movement was associated with improved 90-day good outcome compared with no change (70% versus 56%; adjusted odds ratio, 2.54 [95% CI, 1.21–5.51]).

CONCLUSIONS: Early thrombus movement is common after intravenous alteplase. Marked thrombus migration leads to good clinical outcomes. Thrombus dynamics over time should be further evaluated in clinical trials of acute reperfusion therapy.

Key Words: angiography ■ computed tomography angiography ■ internal carotid artery ■ middle cerebral artery ■ reperfusion

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Nonstandard Abbreviations and Acronyms

CTA	computed tomography angiography
EVT	endovascular thrombectomy
ICA	internal carotid artery
INTERRSeCT	Identifying New Approaches to Optimize Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV Alteplase and Other Treatments Using Serial CT Angiography
MCA	middle cerebral artery
NIHSS	National Institutes of Health Stroke Scale

Alteplase treatment of patients with acute ischemic stroke promotes recanalization of occluded intracranial arteries leading to better clinical outcomes. However, recanalization rates are low among thrombolysed acute stroke patients with proximal intracranial occlusions.[1–6] Thrombolysis and partial recanalization may result in thrombus migration. By causing pieces of the native thrombus to migrate distally and occlude collateral vessels or perforators, thrombolysis may be harmful. A recent study suggested thrombus migration causes occlusions of middle cerebral artery (MCA) perforators from internal carotid artery (ICA) and proximal M1 segment thrombus movement.[7] Kaesmacher et al[8] showed preinterventional intravenous alteplase may cause perfusion worsening by inducing fragmentation of the thrombus into the same or new territories (ie, anterior cerebral artery A2 segment) in about 10% of ICA occlusions. Thrombus migration may also make endovascular thrombectomy more difficult due to thrombus fragmentation into more distal arteries.[7,9,10] Alternately, thrombus migration may be a marker of improved outcome as an indicator of successful or partially successful medical thrombolysis.

In previous studies, recanalization and reperfusion status as Arterial Occlusive Lesion Scale and Thrombolysis in Cerebral Infarction scale have been evaluated as the primary vascular outcome after intravenous thrombolysis.[3,11] However, to better understand and quantitate the benefit and harm of thrombus migration after intravenous thrombolysis with alteplase, a detailed evaluation of thrombus over time in acute stroke with large artery occlusions is needed.[4,7,8,12]

Recently, we showed that successful recanalization of intracranial artery occlusion by intravenous alteplase was associated with more distal thrombus location, greater thrombus permeability, and longer time to recanalization assessment in patients with acute ischemic stroke using Arterial Occlusive Lesion scoring system in the INTERRSeCT study (Identifying New Approaches to Optimize Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV Alteplase and Other Treatments Using Serial CT Angiography).[1] We extend the analysis of the INTERRSeCT study and now aim to examine intravenous alteplase related thrombus migration in patients with ICA or MCA occlusion in a more detailed manner and the association of the thrombus movement status with clinical outcome.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request, after clearance by the local ethics committee.

Study Subjects

The INTERRSeCT study was a multicenter prospective observational cohort study that enrolled patients with acute ischemic stroke with intracranial occlusion documented on computed tomography angiography (CTA) to examine recanalization over time with and without intravenous alteplase between 2010 and 2016. All patients underwent a head and neck CTA at baseline and repeated a head CTA at 4 (±2) hours after initial CTA, unless a conventional cerebral digital subtraction angiography was performed within that time frame for diagnostic or neurointerventional purposes.[1] Local medical ethics committees approved the study. Once a physician identified an eligible patient, written informed consent was provided by the patient or a surrogate.

The current analysis is a post hoc analysis of the INTERRSeCT study. We included subjects fulfilling the following criteria: (1) receiving intravenous alteplase (0.9 mg/kg), (2) visible intracranial ICA or MCA occlusion, and (3) having repeated intracranial vascular imaging (CTA or the first run of cerebral angiography) within 360 minutes from baseline CTA.

Clinical Data

Information collected at baseline included age; sex; baseline National Institutes of Health Stroke Scale score (NIHSS; score ranges from 0–42 with higher scores indicating greater stroke severity); history of hypertension, dyslipidemia, diabetes, smoking, atrial fibrillation, previous stroke/transient ischemic attack, or coronary artery disease; prior anticoagulation or antiplatelet use; baseline vital signs; serum glucose level; serum creatinine level; and presence of endovascular thrombectomy (EVT). Interval times from symptom onset (last known well) to intravenous alteplase initiation and the time from intravenous alteplase initiation to follow-up vascular imaging (time from alteplase to reassessment) were also collected. NIHSS score change at 24 hours and 90-day modified Rankin Scale were used as outcome measures. Dramatic recovery was defined as NIHSS score reduction at 24 hours of 10 or more points or a decrease to a NIHSS score at 24 hours of 3 or less; neurological deterioration was defined as NIHSS score worsening at 24 hours of 4 or more points.[13] Good functional outcome was defined as 90-day modified Rankin Scale score ≤2.

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Imaging Evaluation

Thrombus Migration and Fragmentation

A stroke physician with 18-year clinical experience (Dr Ohara) evaluated the occlusion site and reperfusion status on baseline CTA and follow-up vascular imaging (CTA or first angiographic acquisition of digital subtraction angiography) using OsiriX version 3.5, confirmed these findings by comparing the data in the original INTERRSeCT database and judged thrombus movement grading using the following methodology. Thrombus movement was classified into no change; thrombus fragmentation, thrombus migration grade 0, 1, 2, 3, and complete recanalization (Figure 1).

Step 1: Determine if There Is a Change of Occlusion Site

Evaluate the proximal end of thrombus comparing the baseline and follow-up vascular imaging. When no thrombus is seen at all at follow-up, this is complete recanalization. When the proximal end moved distally, this is thrombus migration (proceed to step 2). When there is no change in proximal end of thrombus, proceed to step 3.

Step 2: Determine Grading of Thrombus Migration

Grade the movement distally of the proximal end of thrombus based on the following 6 vascular segments (ICA/proximal M1 MCA segment, distal MCA M1 segment, M2 proximal segment, M2 distal segment, M3 segment, M4 segment) thrombus migration grade is then defined as follows:

Grade 0: Movement of the occlusion site within the same vascular segment,

Grade 1: Movement of the occlusion site by 1 vascular segment distally,

Grade 2: Movement of the occlusion site by 2 vascular segments distally, and

Grade 3: Movement of the occlusion site by 3 or more vascular segments distally.

Examples for thrombus migration are shown in Figure I in the Data Supplement.

Step 3: Determine if Thrombus Fragmentation

Evaluate the patency of distal artery beyond the primary occlusion site at follow-up vascular imaging in cases without change at proximal end of thrombus. If there is a new thrombus in the distal artery, classify as thrombus fragmentation (Figure II in the Data Supplement). Otherwise, classify as no change.

Other Imaging Variables

Clot burden score and residual flow grade were also assessed to evaluate thrombus characteristics based on previously published methods.[1] A clot burden score of 0 implies complete occlusion of the ipsilateral anterior circulation vessels; a score of 10 implies no occlusion.[14] Clot burden score ≥7 was used as an indicator of short thrombus.[15] Residual flow grade was assessed on the CTA source images as follows: grade 0, no contrast permeation of thrombus; grade 1, contrast permeating diffusely through thrombus; and grade 2, tiny hairline lumen or streak of well-defined contrast within the

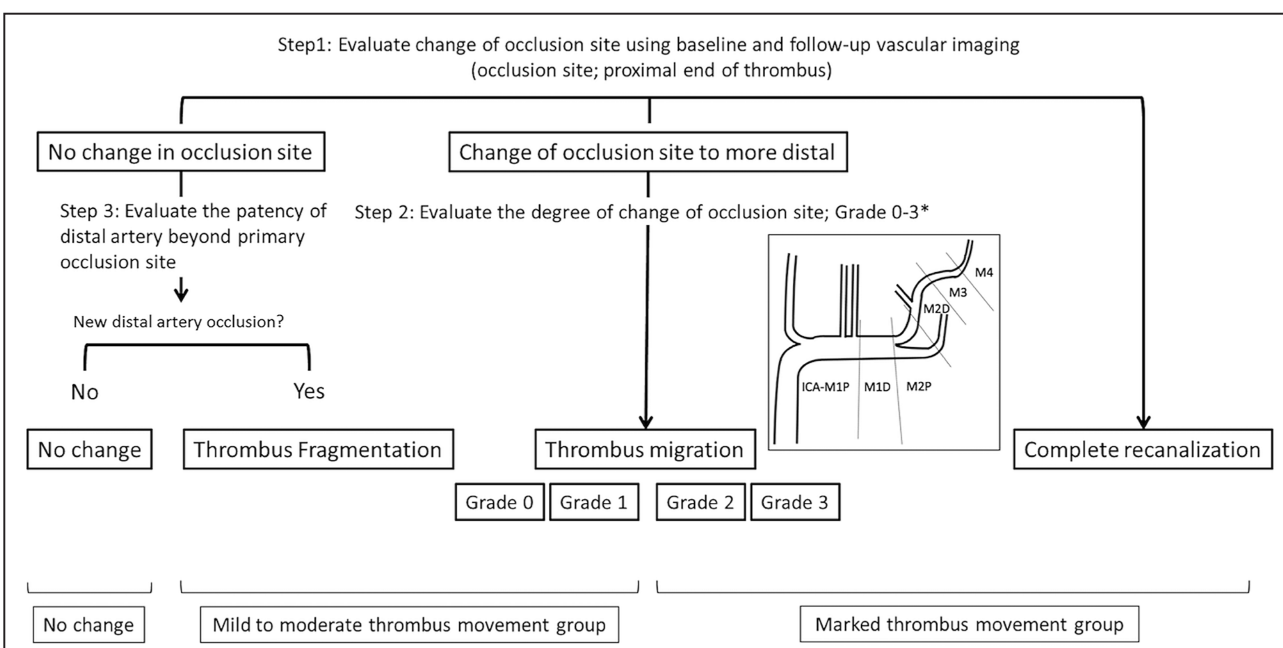

Figure 1. A flowchart for evaluation of thrombus movement status.

Thrombus status is classified into no change, thrombus fragmentation, thrombus migration grade 0–3, and complete recanalization. *Grading of thrombus migration according to the vascular segments: Anterior circulation was divided to 6 vascular segments (internal carotid artery [ICA]-middle cerebral artery [MCA] M1 proximal segment [M1P]/MCA M1 distal segment [M1D]/M2 proximal segment [M2P]/M2 distal segment [M2d]/M3 segment/M4 segment). Grade was defined as follows: grade 0, movement of the occlusion site within the same vascular segment; grade 1, the movement of the occlusion site distal to 1 vascular segment; grade 2, distal to 2 vascular segments; and grade 3, distal to ≥3 vascular segments.

thrombus extending either through its entire length or part of the thrombus.[1]

Statistical Analysis

The distribution of thrombus movement by occlusion site and time from alteplase to reassessment was analyzed. The occlusion site was classified as ICA, proximal M1 MCA, distal M1 MCA, and M2 to M3 segment. Proximal artery occlusion was defined as ICA or proximal M1 occlusion, whereas distal artery occlusion as distal M1 and M2 to M3 segment occlusion. Thrombus movement was classified into 3 groups as follows: (1) no change group, (2) mild to moderate thrombus movement group (thrombus fragmentation and thrombus migration grade 0–1), and (3) marked thrombus movement group (thrombus migration grade2–3 and complete recanalization). Comparisons of proportions were performed using the Fisher

Table 1. Baseline Characteristics According to Thrombus Movement Status

	All patients, N=427	No change, N=197	Mild to moderate movement, N=116	Marked movement, N=114	*P* value
Age, median (IQR), y	73 (63–80)	72 (61–80)	73 (63–81)	74 (63–81)	0.43
Male sex, n (%)	210 (49)	106 (54)	47 (41)	57 (50)	0.07
Baseline NIHSS score, median (IQR)	15 (10–20)	16 (10–20)	15 (10–19)	14.5 (9–19)	0.22
Hypertension, n (%)	264 (62)	111 (56)	82 (71)	71 (62)	0.04
Dyslipidemia, n (%)	145 (34)	68 (35)	35 (30)	42 (37)	0.57
Diabetes, n (%)	66 (15)	32 (16)	20 (17)	14 (12)	0.53
Smoking, n (%)	74 (18)	39 (20)	13 (11)	22 (20)	0.11
Previous stroke/transient ischemic attack, n(%)	65 (15)	26 (13)	19 (17)	20 (18)	0.50
Atrial fibrillation, n (%)	122 (29)	55 (28)	35 (30)	32 (28)	0.91
Prior antiplatelet use, n (%)	150 (35)	66 (34)	45 (39)	39 (34)	0.62
Prior anticoagulation, n (%)	47 (11)	23 (12)	10 (9)	14 (12)	0.62
Systolic blood pressure, median (IQR), mm Hg	148 (132–168)	146 (130–166)	150 (137–169)	150 (133–171)	0.16
Blood glucose, median (IQR), mg/dL	116 (104–138)	117 (103–137)	116 (104–144)	114 (104–135)	0.84
Etiology of ischemic stroke, n (%)					
Extracranial large artery disease	66 (15)	29 (15)	19 (16)	18 (16)	0.89
Intracranial artery disease	9 (2)	4 (2)	2 (2)	3 (3)	
Cardioembolic	223 (52)	97 (49)	63 (54)	63 (55)	
Other causes	8 (2)	5 (3)	1 (1)	2 (2)	
Undetermined	121 (28)	62 (31)	31 (27)	28 (25)	
Baseline ASPECTS, median (IQR)	9 (7–10)	9 (7–9)	9 (7–9)	9 (8–10)	0.31
Site of intracranial occlusion at baseline, n (%)					
Internal carotid artery	92 (21)	53 (27)	27 (23)	12 (11)	<0.01
MCA: proximal M1 segment	101 (24)	61 (31)	21 (18)	19 (17)	
MCA: distal M1 segment	84 (20)	20 (10)	28 (24)	36 (32)	
MCA: M2–M3 segment	150 (35)	63 (32)	40 (34)	47 (41)	
Proximal artery occlusion	193 (45)	114 (58)	48 (41)	31 (27)	<0.01
Thrombus characteristics					
Clot burden score, median (IQR)	6 (4–9)	6 (4–9)	6 (4–9)	8 (6–9)	<0.01
Residual flow, n (%)					
Grade 0	340 (80)	172 (89)	93 (81)	68 (61)	<0.01
Grade 1	43 (10)	13 (7)	11 (10)	18 (16)	
Grade 2	44 (10)	7 (4)	10 (9)	25 (23)	
Endovascular thrombectomy	180 (42)	124 (63)	45 (39)	11 (10)	<0.01
Stroke workflow process					
Time from intravenous alteplase to reassessment, median (IQR), min	123 (61–236)	83 (45–169)	127 (62–245)	225 (152–276)	<0.01
Time from onset (last known well) to intravenous alteplase, median (IQR), min	130 (91–179)	129 (89–176)	127 (91–176)	132 (92–185)	0.76

Marked movement indicates complete recanalization and thrombus migration grade 2–3. Mild to moderate movement indicates thrombus migration grade 0–1 and thrombus fragmentation. ASPECTS indicates Alberta Stroke Program Early CT Score; IQR, interquartile range; MCA, middle cerebral artery; and NIHSS, National Institutes of Health Stroke Scale score.

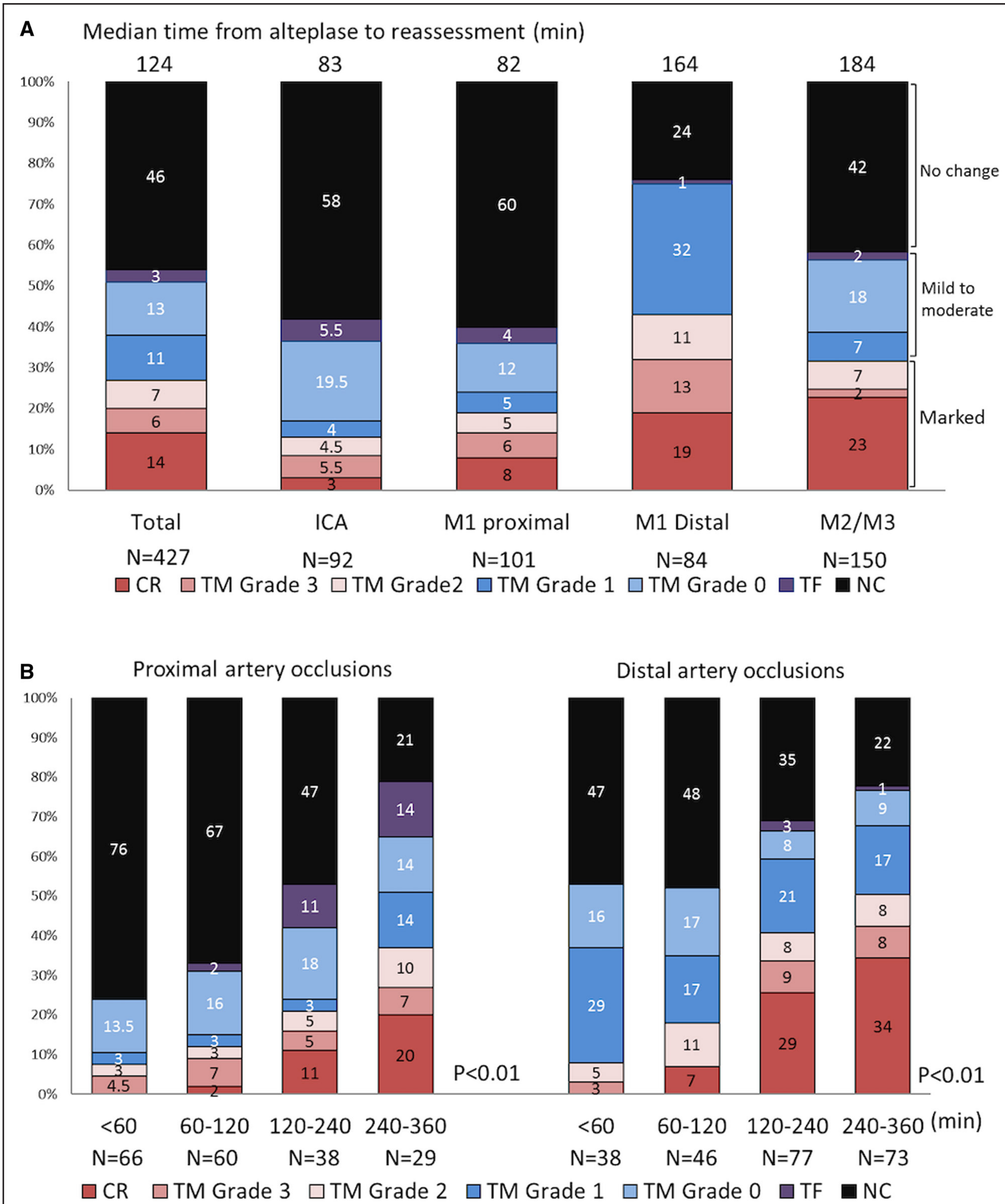

Figure 2. Early thrombus movement after intravenous alteplase.
A, Thrombus movement status according to the occlusion site. **B**, Thrombus movement status according to time from alteplase to reassessment in proximal artery occlusion (intracranial internal carotid artery [ICA] and M1 proximal) and distal artery occlusion (M1 distal/M2–M3). Marked indicates complete recanalization and thrombus migration grade 2–3. Mild to moderate indicates thrombus migration grade 0–1 and thrombus fragmentation. M1 proximal, middle cerebral artery proximal M1 segment; M1 distal, middle cerebral artery distal M1 segment; M2, middle cerebral artery M2 segment; M3, middle cerebral artery M3 segment. CR indicates complete recanalization; NC, no change; TF, thrombus fragmentation; and TM, thrombus migration.

exact test or χ^2 test based on cell size for categorical variables. Kruskal-Wallis test or ANOVA was used to compare continuous valuables. Logistic regression models were used to analyze variables associated with the binary outcome marked thrombus movement and good clinical outcome versus neither. Multivariable models for thrombus movement included age, sex, a history of hypertension, diabetes and atrial fibrillation, baseline NIHSS score, residual flow, clot burden score, primary occlusion site, time from stroke onset to alteplase time, and time from alteplase to reassessment. Multivariable models for clinical outcome included age, sex, a history of hypertension, diabetes and atrial fibrillation, baseline NIHSS score, baseline Alberta Stroke Program Early CT Score, time from onset to alteplase and thrombus migration status. Patients with baseline modified Rankin Scale of more or 3 were excluded in clinical outcome models. In each model, backward elimination method was used to arrive at final parsimonious models. Goodness of fit test for multivariable regression analysis models were evaluated using Hosmer-Lemeshow test. Results were reported as odds ratio (OR) with 95% CI. Statistical analysis was performed in R version 3.5.1 (R Development Core Team. (2018) R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of 636 patients enrolled in the INTERRSeCT study, the following patients were excluded; vertebrobasilar occlusion (17 patients), a time from baseline to follow-up vascular imaging CTA >360 minutes (39 patients), received intravenous alteplase at a different hospital before being transferred to the enrolling site (5 patients), not treated with intravenous alteplase (99 patients), posterior cerebral artery occlusion (26 patients), anterior cerebral artery occlusion (12 patients), and incomplete data (11 patients) (Figure III in the Data Supplement). Finally, 427 subjects with intracranial ICA or MCA occlusion receiving intravenous alteplase were analyzed.

Baseline data are shown in Table 1. Primary occlusion site was ICA in 92 patients (21%), proximal M1 segment in 101 (24%), distal M1 segment in 84 (20%), M2 to M3 segment in 150 (35%). Tandem occlusion (extracranial ICA+intracranial artery occlusion) was observed in 23 patients (5.4%). Time from onset to alteplase initiation was 0 to 3 hours in 323 patients (76%) and 3 to 4.5 hours in 104 (24%). Baseline imaging modality for assessment were single phase CTA in 278 (65%) and multi-phase CTA in 149 (35%); follow-up imaging was single phase CTA (55%) and first angiographic acquisition of digital subtraction angiography (45%). Median time from alteplase to reassessment was 123 minutes (interquartile range, 61–236 minutes). Thrombus movement status in the whole patients and by occlusion site is shown in Figure 2A. In the whole patients, no change in thrombus status was seen in 46%, mild to moderate thrombus movement in 27% (thrombus fragmentation in 3%, thrombus migration grade 0 in 13%, thrombus migration grade 1 in 11%), and marked thrombus movement in 27% (thrombus migration grade 2 in 7%, thrombus migration grade 3 in 6%, complete recanalization 14%). There was no difference in thrombus movement status between patients evaluated by single phase CTA and multi-phase CTA at baseline (Table I in the Data Supplement). Thrombus movement differed by occlusion site. Marked thrombus movement was highest with thrombus in distal M1 MCA occlusion (43%) and lowest with thrombus in ICA segment (13%). Mild to moderate thrombus movement was relatively common even in proximal occlusions (29% in ICA and 21% in proximal M1). Thrombus fragmentation was seen in 9 patients in proximal artery occlusions. In addition, new additional distal occlusion beyond primary occlusion site were identified in 8 patients among 39 proximal occlusion patients with thrombus migration grade 0 to 1. Thrombus movement by time from alteplase to reassessment and occlusion site is shown in Figure 2B and Figure IV in the Data Supplement. As the time from alteplase administration to reassessment becomes longer, greater thrombus movement is seen in both proximal and distal artery occlusions (*P*<0.01, respectively).

Comparison of clinical and imaging characteristics among the 3 prespecified thrombus movement categories are shown in Table 1. In multivariable logistic regression analysis, distal artery occlusion, a longer time from alteplase to reassessment and residual flow grade 1 to 2 were independently associated with marked thrombus

Table 2. Clinical and Radiological Predictors for Marked Thrombus Movement

	Adjusted OR	95% CI
All patients		
Distal artery occlusion (vs proximal artery occlusion)	2.35	1.33–4.22
Time from alteplase to reassessment (per 30min increase)	1.21	1.10–1.42
Residual flow 1–2 (vs grade 0)	4.13	2.38–7.26
Baseline NIHSS (every 1 point increase)	1.04	0.99–1.08
Proximal artery occlusion patients		
Time from alteplase to reassessment (per 30 min increase)	1.31	1.15–1.50
Residual flow 1–2 (vs grade 0)	2.74	1.02–7.15
Clot burden score ≥7 (vs clot burden score <7)	4.53	1.36–14.88
Distal artery occlusion patients		
Time from alteplase to reassessment (per 30 min increase)	1.32	0.85–1.02
Residual flow 1–2 (vs grade 0)	5.16	2.56–10.77
Baseline NIHSS (every 1 point increase)	1.04	0.99–1.09
Time from onset to alteplase administration (per 30 min increase)	0.94	0.85–1.02

Proximal artery occlusion; internal carotid artery/M1 proximal segment, distal artery occlusion; M1 distal segment/M2–M3 segment. NIHSS indicates National Institutes of Health Stroke Scale; and OR, odds ratio.

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movement (Table 2). In proximal artery occlusions, a longer time from alteplase to reassessment (adjusted OR, 1.31 per 30 minutes increase [95% CI, 1.15–1.50]), clot burden score ≥7, which means shorter thrombus length (adjusted OR, 4.53 [95% CI, 1.36–14.88]), and residual flow grade 1 to 2 (adjusted OR, 2.74 [95% CI, 1.02–7.15]) were independently associated with marked thrombus movement.

NIHSS score change at 24 hours and 90-day good outcome rate (modified Rankin Scale score, 0–2) according to thrombus movement status are shown in Figure 3. In proximal artery occlusions (Figure 3A), dramatic recovery within 24 hours was observed in 45% in no change group, in 24% in mild to moderate movement, and 55% in marked movement, whereas neurological deterioration was observed in 7% in no change group, and in 20% in mild to moderate movement. Consequently, mild to moderate thrombus movement group showed a lower rate of 90-day good outcome (27%) compared with those with no change group (55%) in univariate analysis, but the difference did not reach statistical significance when adjusting age, baseline NIHSS, baseline Alberta Stroke Program Early CT Score, and EVT rate. Marked thrombus movement showed significant improved outcome compared with mild to moderate movement (52% versus 27%; adjusted OR, 5.64 [95% CI, 1.72–20.01]; Table 3). On the contrary, a similar trend of 24-hour NIHSS score changes in mild to moderate movement in proximal artery occlusions was not seen in patients with distal artery occlusion (Figure 3B). Marked thrombus movement was significantly associated with improved 90-day clinical outcome compared with no change (70% versus 56%; adjusted OR, 2.54 [95% CI, 1.21–5.51]) in distal occlusion patients (Table 3).

DISCUSSION

Various degrees of early thrombus movement occurred in more than half of intravenous alteplase treated patients with ICA or MCA occlusions. In assessing what actually happens to the thrombus in the first 2 hours after alteplase treatment, we are redefining what recanalization of the arterial occlusive lesion with intravenous

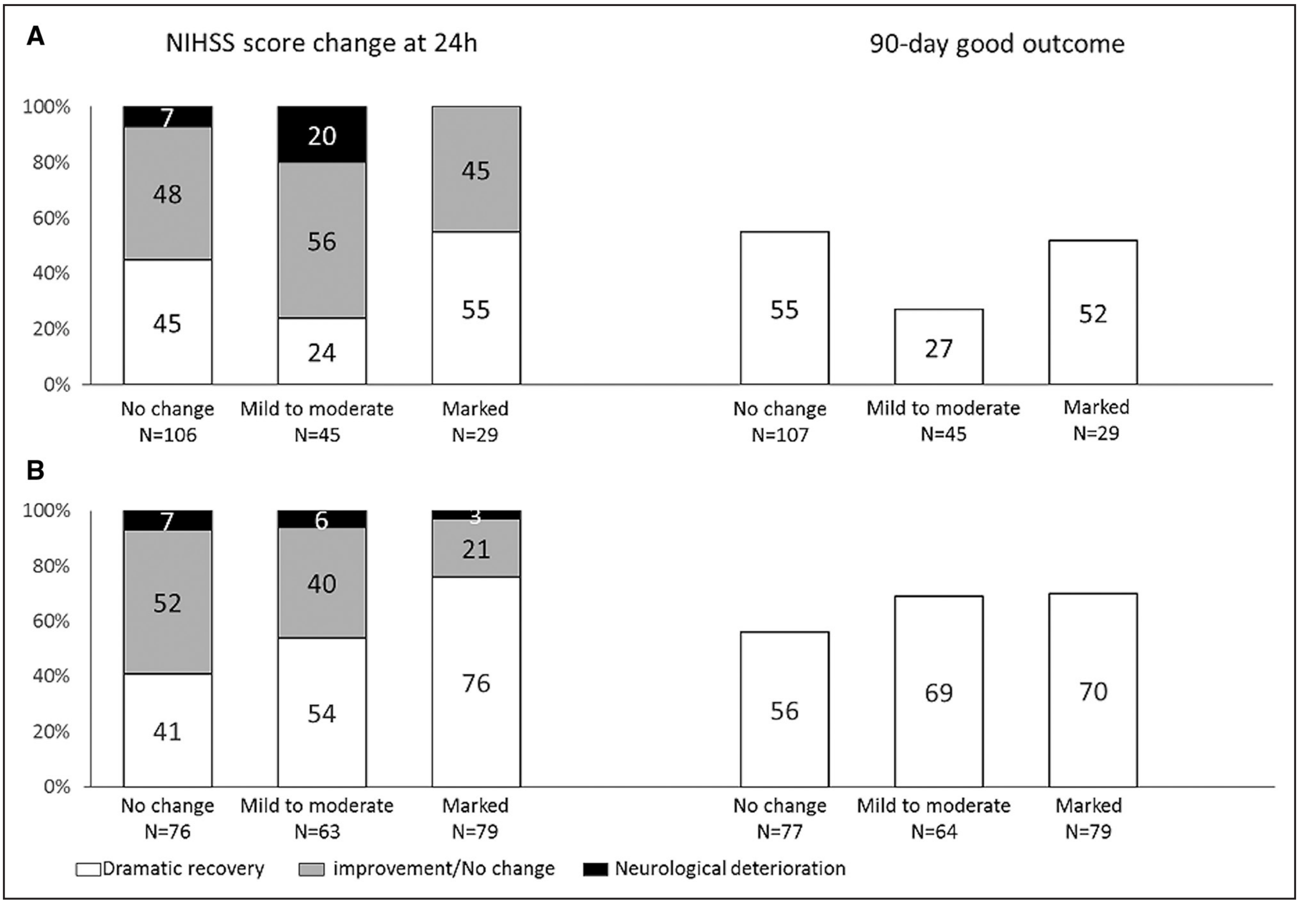

Figure 3. National Institutes of Health Stroke Scale (NIHSS) score change at 24 h and 90-d good outcome (modified Rankin Scale [mRS], 0–2) rate stratified by thrombus movement status.

A, Proximal artery occlusion patients (intracranial internal carotid artery [ICA] and proximal M1). **B**, Distal artery occlusion patients (distal M1 and M2–M3). Marked indicates complete recanalization or thrombus migration grade 2–3. Mild to moderate indicates thrombus migration grade 0–1 or thrombus fragmentation. Dramatic recovery: NIHSS score reduction at 24 h of 10 or more points or a decrease to a NIHSS score at 24 h of 3 or less. Neurological deterioration was defined as NIHSS score worsening at 24 h of 4 or more points.

Table 3. Univariable and Multivariable Analysis of Factors Associated With Clinical Good Outcome According to the Occlusion Site

	Good outcome 90-d mRS 0-2	Poor outcome 90-d mRS 3-6	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Proximal artery occlusion				
N	86	95		
Age	66 (57, 74)	75 (67, 82)	0.94 (0.92–0.97)	0.94 (0.91–0.97)
Male sex	52 (60)	42 (44)	0.93 (1.07–3.51)	...
Baseline NIHSS score	17 (13, 20)	20 (17, 23)	0.91 (0.85–0.96)	0.90 (0.84–0.96)
Hypertension	39 (45)	63 (66)	0.42 (0.23–0.76)	...
Dyslipidemia	24 (28)	24 (26)	1.10 (0.56–2.13)	...
Diabetes	9 (10)	18 (19)	0.50 (0.20–1.16)	...
Atrial fibrillation	25 (29)	32 (34)	0.81 (0.43–1.51)	...
Baseline ASPECTS	9 (7, 9.25)	7 (6, 9)	1.41 (1.18–1.71)	1.33 (1.08–1.66)
Endovascular thrombectomy	66 (78)	44 (46)	3.82 (2.04–7.39)	3.42 (1.40–8.86)
Time from onset to alteplase initiation, (per 30 min increase)	107 (80, 152)	134 (91, 179)	0.95 (0.84–1.06)	...
Thrombus movement				
No change	59 (69)	48 (51)	3.38 (1.61–7.48)	2.30 (0.93–5.88)
Mild to moderate movement	12 (14)	33 (35)	Reference	Reference
Marked movement	15 (17)	14 (15)	2.95 (1.11–8.06)	5.64 (1.72–20.01)
Distal artery occlusion				
N	142	78		
Age	70 (58, 79)	78 (73, 84)	0.92 (0.89–0.95)	0.93 (0.89–0.95)
Male sex	70 (49)	39 (50)	0.97 (0.56–1.69)	...
Baseline NIHSS score	10.5 (7, 15)	14.5 (11, 19)	0.90 (0.86–0.95)	0.91 (0.86–0.96)
Hypertension	91 (64)	53 (68)	0.84 (0.46–1.50)	...
Dyslipidemia	53 (37)	29 (37)	1.01 (0.57–1.79)	...
Diabetes	19 (13)	17 (22)	0.55 (0.27–1.15)	...
Atrial fibrillation	36 (25)	20 (26)	0.98 (0.53–1.88)	...
Baseline ASPECTS	9 (8, 10)	9 (8, 10)	1.22 (1.00–1.51)	...
Endovascular thrombectomy	41 (29)	22 (28)	1.03 (0.56–1.93)	...
Time from onset to alteplase initiation (per 30 min increase)	140 (96, 196)	131 (100, 181)	1.03 (0.96–1.12)	...
Thrombus movement				
No change	43 (30)	34 (44)	Reference	Reference
Mild to moderate movement	44 (31)	20 (26)	1.73 (0.87–3.52)	2.14 (0.98–4.79)
Marked movement	55 (39)	24 (31)	1.81 (0.94–3.52)	2.54 (1.21–5.51)

Marked movement indicates complete recanalization and thrombus migration Grade 2–3. Mild to moderate movement indicates thrombus migration Grade 0–1 or thrombus fragmentation. Proximal artery occlusion indicates internal carotid artery/M1 proximal segment. Distal artery occlusion indicates M1 distal segment/M2–M3 segment. ASPECTS indicates Alberta Stroke Program Early CT Score; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

thrombolysis means. Distal occlusions, longer intravenous alteplase to reassessment time, and thrombus characteristics such as clot burden and residual flow were associated with marked thrombus movement leading to favorable outcomes. Mild to moderate thrombus movement in proximal artery occlusion was not associated with better clinical outcomes compared with no change in thrombus movement.

We graded the degree of thrombus migration and fragmentation in a more granular manner compared with our previous study and recent other studies.[1,8–10] We focused on a small degree of movement and perfusion worsening in cases without movement in primary occlusion site. As a result, this study showed that more than half of patients with acute stroke with intracranial occlusions had some degrees of thrombus movement within a median of 120 minutes after intravenous alteplase bolus. Even in proximal occlusions, 16% had marked thrombus migration, while 24% had mild to moderate thrombus movement. These results, therefore, suggest that when including thrombus fragmentation and small degrees of thrombus migration in analysis, early thrombus movement

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after intravenous alteplase is common. These findings attest to the fact that intravenous alteplase is lysing not just small thrombi but even large thrombi within proximal intracranial arteries.

A recent study reported perfusion worsening by thrombus migration was observed in about 10% of ICA occlusion patients treated with intravenous alteplase before EVT.[8] We also showed that some patients with proximal artery occlusion with no change or mild movement distally of the occlusion site had an additional new distal occlusion equivalent to perfusion worsening, although we failed to demonstrate mild to moderate thrombus movement group including the patients with perfusion worsening was associated with worse clinical outcome compared with no change group. On the contrary, marked thrombus migration resulted in better clinical outcomes across all sites of arterial occlusion. This is similar to past concepts of complete reperfusion of the arterial occlusive lesion. Occlusion locations as distal artery occlusions and radiological thrombus characteristics that are associated with marked thrombus movement are best treated with intravenous alteplase. Given a lower rate of early marked thrombus movement in proximal occlusion, augmented thrombolytic strategies increasing the rate of marked thrombus movement as tenecteplase and combined therapy of thrombolytics plus antithrombotic agents could enhance the ability of intravenous thrombolysis in offering better clinical outcomes overall in acute stroke patients due to proximal occlusions.[16–18]

Current American Heart Association and European Stroke Organisation guidelines recommend patients eligible for intravenous alteplase should receive intravenous alteplase even if EVT are being considered.[19,20] The role of intravenous alteplase bridging for patients with large vessel occlusion that arrive directly to comprehensive stroke centers is now being questioned.[21–26] Recently, 2 randomized trials have reported results comparing EVT alone with intravenous alteplase bridging before EVT.[27] Other ongoing clinical trials will provide further prospective data to evaluate the combined medical and endovascular treatment of this kind of acute ischemic stroke. Detailed analysis of the results in these randomized trials may require a similar in-depth analysis of thrombus migration from baseline to when EVT is administered.

Our study has several limitations. First, single phase CTA was at baseline for evaluation of thrombus in half of the study patients. This modality may underestimate the extent of the thrombus due to variability in timing of contrast filling within arteries and around the occlusion overestimating the full extent of occlusion site. Evaluation of thrombus dynamics by multi-phase CTA and thin-slice non contrast CT can estimate the occlusion site more precisely.[28,29] However, when we compared single phase CTA with multi-phase CTA, there was no difference in thrombus movement in our study. Second, follow-up vascular imaging in half of the patients was digital subtraction angiography with only a one vessel study of the symptomatic territory. Therefore, thrombus fragmentation may have been underestimated because distal arteries beyond primary occlusion site were not visualized in the cases. Third, we analyzed only patients with intracranial ICA and MCA occlusion. Therefore, our findings cannot be extrapolated in patients with vertebrobasilar occlusion. Fourth, we did not conduct interrater reliability testing for thrombus movement grading. Lastly, all analyses in this study were post hoc and should be considered as exploratory. Therefore, our results should be validated in future prospective studies.

In conclusion, this study proposes a refined and detailed methodology for evaluating thrombus movement including migration and fragmentation after intravenous alteplase administration. The study found that early thrombus movement after intravenous alteplase is common even in patients with proximal artery occlusion when evaluating in a more detailed manner. Thrombus dynamics over time should be further evaluated in clinical trials of acute reperfusion therapy.

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