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Thrombus Migration Paradox in Patients With Acute Ischemic Stroke

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Background and Purpose—The location of the thrombus as observed on first digital subtraction angiography during endovascular treatment may differ from the initial observation on initial noninvasive imaging. We studied the incidence of thrombus dynamics, its impact on patient outcomes, and its association with intravenous thrombolytics.

Methods—We included patients from the MR CLEAN registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke) with an initial target occlusion on computed tomography angiography located in the intracranial internal carotid artery, M1, or M2. The conventional angiography target occlusion was defined during endovascular treatment. Thrombus dynamics were classified as growth, stability, migration, and resolution. The primary outcome was functional outcome at 90 days (modified Rankin Scale). The secondary outcomes were successful and complete reperfusion (extended treatment in cerebral infarction scores of 2b-3 and 3, respectively).

Results—The analysis included 1349 patients. Thrombus migration occurred in 302 (22%) patients, thrombus growth in 87 (6%), and thrombus resolution in 39 (3%). Intravenous treatment with alteplase was associated with more thrombus migration (adjusted odds ratio, 2.01; CI, 1.29–3.11) and thrombus resolution (adjusted odds ratio, 1.85; CI, 1.22–2.80). Thrombus migration was associated with a lower chance of complete reperfusion (adjusted odds ratio, 0.57; CI, 0.42–0.78) and successful reperfusion (adjusted odds ratio, 0.74; CI, 0.55–0.99). In the subgroup of patients with M1 initial target occlusion, thrombus migration was associated with better functional outcome (adjusted common odds ratio, 1.49; CI, 1.02–2.17), and there was a trend towards better functional outcome in patients with thrombus resolution (adjusted common odds ratio, 2.23; CI, 0.93–5.37).

Conclusions—In patients with acute ischemic stroke, thrombus location regularly changes between computed tomography angiography and digital subtraction angiography. Administration of intravenous alteplase increases the chance of thrombus migration and resolution. Thrombus migration is associated with better functional outcome but reduces the rate of complete reperfusion. **(*Stroke*. 2019;50:3156-3163. DOI: 10.1161/STROKEAHA.119.026107.)**

Key Words: angiography ■ cerebral infarction ■ computed tomography angiography ■ internal carotid artery ■ workflow

Multiple randomized clinical trials demonstrated the benefit of endovascular treatment (EVT) for patients with an acute ischemic stroke caused by a large-vessel occlusion.[1,2] Thrombus location is a vital imaging selection criterion because the benefit of EVT for distal occlusions, especially M2, remains uncertain.[3–6] In the current workflow of acute ischemic

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stroke, thrombus location is determined at 2 moments: the initial target occlusion is determined on noninvasive imaging, usually by computed tomography angiography (CTA) at initial presentation. If a large-vessel occlusion is detected, the patient is considered for EVT. During this procedure, conventional angiography is performed, which allows the determination of the conventional angiography target occlusion.[7]

Despite recent progress, there is still a paucity of information about thrombus imaging on patients with stroke with large-vessel occlusion.[8,9] Thrombus dynamics (a difference between the initial and the conventional angiography target occlusions) have been described in few studies and reported anecdotally.[10–12] Distal thrombus migration has been defined as a more distal conventional angiography target occlusion than the initial target occlusion.[13] In patients with EVT, distal thrombus migration increased the risk of incomplete reperfusion, suggesting thrombus fragility.[13] Thrombus resolution has also been detailed, especially after intravenous administration of alteplase (IVT).[14–16] Moreover, thrombus growth has also been studied, and it has been associated with poor collaterals, blood stasis, and early neurological deterioration, suggesting that thrombus dynamics is related to thrombus composition.[17,18] Despite these previously reported studies, the impact of thrombus migration on patient outcomes and the association between IVT and thrombus dynamics is undetermined.[13,19,20]

The aim of this study is to determine the association of thrombus dynamics with IVT and its effect on patient outcome.

Methods

We included patients from the MR CLEAN registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke), an observational, prospective study, registering patients who underwent EVT (defined as receiving arterial puncture for angiography) for acute ischemic stroke in 16 intervention centers in the Netherlands from 2014 to 2016.[21] Patients with anterior and posterior circulation stroke were included. Neither Alberta Stroke Program Early CT Score nor collateral grade was an explicit exclusion criterion. The registry was approved by a central medical ethics committee and by the research board of all participating centers. Source data of this study are available from the corresponding author on reasonable request.

Initial target occlusion was defined as the most proximal thrombus location on CTA.[12] Conventional angiography target occlusion was defined as the most proximal thrombus location on first intracranial digital subtraction angiography. Target occlusion locations were determined by a core lab. Thrombus location was classified as cervical internal carotid artery (ICA), intracranial ICA, M1, M2, M3, M4, A1, A2, or no occlusions. In the current analysis, patients with an initial target occlusion of the intracranial ICA or the first and second segments of the middle cerebral artery (M1 and M2) were included.

Thrombus dynamics were classified as migration, growth, or resolution. Thrombus migration was defined as a shift to a more distal conventional angiography target occlusion than the initial target occlusion. Thrombus growth was defined as a shift to a more proximal conventional angiography target occlusion thrombus location than the initial target occlusion. Thrombus resolution was defined as the absence of conventional angiography target occlusion.

Statistical Analysis

Baseline, workflow, treatment, and outcome characteristics were compared between patients with stable thrombus and different types of thrombus dynamics. Group comparisons were performed using Student *t*, Kruskal-Wallis, and χ^2 tests. Binary regression models were used to assess whether IVT was associated with migration, growth, or resolution compared with stable thrombus. The primary outcome was functional outcome, expressed with the score on the modified Rankin Scale at 3 months. On this scale, a score of 0 corresponds to no symptoms and a score of 6 to death. The association between thrombus dynamics and functional outcome was expressed as a common odds ratio (cOR) for a shift towards a better functional outcome estimated with ordinal regression. The secondary outcome was reperfusion status (successful or complete reperfusion). Reperfusion was assessed on digital subtraction angiography using the expanded Thrombolysis in Cerebral Infarction (eTICI) score. Successful reperfusion was defined as an eTICI score of 2b, 2c, or 3.[22] Complete reperfusion was defined as an eTICI score of 3.[23] The association of different thrombus dynamics and reperfusion status was assessed using binary regression. The associations between different types of thrombus dynamics and primary and secondary outcomes as well as the associations between IVT and thrombus dynamics were assessed by univariable and multivariable models. The multivariable IVT models were adjusted for age, history of atrial fibrillation, history of peripheral artery disease, collateral score, serum glucose level, history of diabetes mellitus, arterial blood pressure, (international normalized ratio >1.7), time from onset to computed tomography, previous stroke and novel anticoagulants use. The multivariable outcome models (modified Rankin Scale and reperfusion status) were adjusted for age, baseline National Institutes of Health Stroke Scale, IVT treatment, prestroke modified Rankin Scale, time from onset to groin puncture, history of atrial fibrillation, symptomatic cervical carotid obstruction on CTA, and collateral grade. To reduce the influence of thrombus location on patient outcome, we also assessed the effect of the thrombus growth, migration, and resolution on primary and secondary outcomes including only patients with M1 initial target occlusion. On multivariable models, the associations were expressed as adjusted cOR for ordinal regression and adjusted odds ratio (aOR) for binary regressions. For the regression models, we performed multiple imputations for the missing data. All reported data were not imputed. The statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria; version 1.0.136).

Table 1. Conventional Angiography Target Occlusion Location Stratified by the Initial Target Occlusion Location

Target Occlusion	Conventional Angiography						
Initial	Intracranial ICA	M1	M2	M3	M4	None	Total
Intracranial ICA	215	121	24	1	2	6	369
M1	45	603	108	22	7	22	807
M2	2	40	103	11	6	11	173
Total	262	764	235	34	15	39	1349

ICA indicates internal carotid artery.

Table 2. Baseline Characteristics

	Thrombus Migration	Thrombus Resolution	Thrombus Growth	Stable Thrombus	*P* Value
n	302	39	87	921	
Age, median, IQR	70 (58–80)	70 (63–80)	69 (58–79)	71 (60–79)	0.77
Sex, male (%)	165 (55%)	32 (82%)	47 (54%)	476 (52%)	0.01
NIHSS, median (IQR)	16 (11–19)	15 (9–19)	16 (11–19)	16 (12–20)	0.46
SBP, mm Hg, mean (SD)	150 (131–166)	151 (132–163)	145 (130–160)	150 (131–167)	0.65
DBP, mm Hg, mean (SD)	80 (70–91)	80 (75–95)	80 (70–90)	80 (70–90)	0.75
Atrial fibrillation, n (%)	53/299(18%)	4/38 (11%)	21/86 (24%)	221/907 (24%)	0.02
Diabetes mellitus, n (%)	50/301 (17%)	10/39 (26%)	11/87 (13%)	151/915 (17%)	0.34
Hypertension, n (%)	149/300 (50%)	16/39 (41%)	44/87 (51%)	468/905 (51%)	0.67
Ischemic stroke, n (%)	44/300 (15%)	3/39 (8%)	14/87 (16%)	152/916 (17%)	0.51
Myocardial infarction, n (%)	44/298 (15%)	8/38 (21%)	13/87 (15%)	141/899 (16%)	0.76
Peripheral artery disease, n (%)	37/298 (12%)	3/39 (8%)	8/86 (9%)	75/902 (8%)	0.21
Prestroke mRS, n (%)					0.92
0	201/300 (67%)	28/39 (72%)	58/86 (67%)	618/904 (68%)	
1	36/300 (12%)	2/39 (5%)	12/86 (14%)	120/904 (13%)	
2	25/300 (8%)	3/39 (8%)	6/86 (7%)	68/904 (8%)	
≥3	38/300 (13%)	6/39 (15%)	10/86 (12%)	98/904 (11%)	
Medication					
DOAC, n (%)	5/299 (2%)	0/38 (0%)	2/84 (2%)	27/906 (3%)	0.61
Vitamin K antagonist, n (%)	30/301 (10%)	2/39 (5%)	10/86 (12%)	128/913 (14%)	0.15
Antiplatelet use, n (%)	106/299 (36%)	13/39 (33%)	29/87 (33%)	296/909 (33%)	0.83
Imaging					
Occlusion level on DSA, n (%)					<0.01
Intracranial ICA	0/302 (0%)	NA	47/87 (54%)	215/921 (23%)	
M1	121/302 (40%)	NA	40/87 (46%)	603/921 (66%)	
M2	132/302 (44%)	NA	0/87 (0%)	103/921 (11%)	
M3	34/302 (11%)	NA	0/87 (0%)	0/921 (0%)	
M4	15/302 (5%)	NA	0/87 (0%)	0/921 (0%)	
Other, non target lesion on DSA, n (%)	41/271 (15%)	1/35 (3%)	4/74(5%)	60/828 (7%)	<0.01
Occlusion level on CTA, n (%)					<0.01
Intracranial ICA	148/302 (49%)	6/39 (15%)	0/87 (0%)	215/921 (23%)	
M1	137/302 (45%)	22/39 (56%)	45/87 (52%)	603/921 (66%)	
M2	17/302 (6%)	11/39 (28%)	42/87 (48%)	103/921 (11%)	
Symptomatic cervical ICA obstruction on CTA, n (%)	101/250 (40%)	9/32 (28%)	18/75 (24%)	149/810 (18%)	<0.01
Carotid bifurcation atherosclerosis					
>50% stenosis, n (%)	32/250 (13%)	3/32 (9%)	8/75 (11%)	70/810 (9%)	0.26
<50% stenosis, n (%)	91/250 (36%)	13/32 (41%)	26/75 (35%)	393/ 810 (49%)	<0.01
Symptomatic cervical ICA occlusion on CTA, n (%)	49/250 (20%)	3/32 (9%)	7/75 (9%)	56/810 (7%)	<0.01
Intracranial atherosclerosis, n (%)	175/293 (60%)	21/38 (55%)	48/85 (57%)	541/905 (60%)	0.88
Collateral, n (%)					0.62
Absent	22/292 (8%)	3/39 (8%)	4/84 (5%)	65/902 (7%)	
<50% of occluded area	107/292 (37%)	11/39 (28%)	23/84 (27%)	287/902 (32%)	
50% to 100% occluded area	111/292 (38%)	15/39 (39%)	34/84 (41%)	350/902 (39%)	

(*Continued*)

Table 2. Continued

	Thrombus Migration	Thrombus Resolution	Thrombus Growth	Stable Thrombus	P Value
100% occluded area	52/292 (18%)	10/39 (26%)	23/84 (27%)	200/902 (22%)	
ASPECTS, median (IQR)	9 (7–10)	9 (8–10)	9 (7–10)	9 (7–10)	0.67
Clot burden score, median (IQR)	6 (3–7)	8 (5–9)	8 (5–9)	6 (4–8)	<0.01
Workflow					
Transferred from primary stroke center, n (%)	151/302 (50%)	18/39 (46%)	45/87 (52%)	504/921 (55%)	0.39
Intravenous thrombolysis, n (%)	256/301 (85%)	33/39 (85%)	64/87 (74%)	679/919 (74%)	<0.01
Performed procedure, n (%)					<0.01
Catheterization only	6/302 (2%)	0/39 (0%)	2/87 (2%)	18/921 (2%)	
DSA only	50/302 (17%)	30/39 (77%)	1/87 (1%)	19/921 (2%)	
Mechanical thrombectomy	242/302 (80%)	8/39 (21%)	84/87 (97%)	883/921 (96%)	
Other	4/302 (1%)	1/39 (3%)	0/87 (2%)	1/921 (0%)	
Cervical ICA stent placement, n%	39/294 (13%)	4/39 (10%)	8/83 (10%)	46/889 (5%)	<0.01
Balloon angioplasty, n (%)	29/281 (10%)	3/39 (8%)	3/81 (4%)	37/879 (4%)	<0.01
Onset to groin puncture time, median (IQR) in minutes	200 (155–264)	205 (158–236)	225 (174–290)	210 (160–270)	0.20
Onset to IVT time, median (IQR) in minutes	25 (18–33)	20 (16–27)	25 (20–30)	24 (18–33)	0.24

Group comparisons were evaluated using χ^2, Kruskal-Wallis, and Student *t* tests. ASPECTS indicates Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; DBP, diastolic blood pressure; DOAC, use of direct oral anticoagulants; DSA, digital subtraction angiography; ICA, internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

Results

A total of 1627 patients were included in the MR CLEAN Registry in our study period. Available data concerning outcome and baseline characteristics were reported for the 1349 patients with full data available concerning thrombus characteristics (Figure I in the online-only Data Supplement).

Thrombus migration was observed in 302/1349 (22%), thrombus growth in 87/1349 (6%) and thrombus resolution in 39/1349 (3%) patients. The most common change in occlusion location was ICA to M1 (121; 8%) followed by M1 to M2 (108; 7%). Thrombus migration occurred in 154/269 (42%) of ICA occlusions. Thrombus growth, resolution, or migration was also observed in 70/173 (40%) of patients with M2 occlusions (Table 1).

Most baseline characteristics were similar for the groups (Table 2). The Clot Burden Score[24] was significantly higher in patients with thrombus growth and resolution. The frequency of atrial fibrillation was lower in patients with thrombus migration and resolution. Patients with thrombus migration had a higher rate of multiple intracranial occlusions detected on digital subtraction angiography and of symptomatic cervical ICA occlusion on CTA. The rate of transfer from the referral center and other time metrics were not significantly different among the groups (Table 3).

Symptomatic cervical ICA obstruction (ie, atherosclerosis, dissection, carotid web, and previous stent), atherosclerotic cervical ICA occlusion and treatment (stent and balloon angioplasty) were significantly more frequent in patients with thrombus migration and resolution ($P<0.01$). We also found a trend towards higher frequency of significant atherosclerotic carotid stenosis (>50%) on patients with thrombus migration, but it did not reach statistical significance. Patients with stable thrombus had a significant higher incidence of nonsignificant atherosclerotic carotid stenosis ($P<0.01$).

IVT was significantly associated with thrombus migration and resolution. In patients with IVT, the rate of thrombus migration was 25% in contrast to a 14% rate in patients without IVT. Occurrence of thrombus growth was not significantly associated with IVT (Table 4).

Compared with patients who had a stable thrombus, patients with thrombus migration had better functional outcomes (Figure II in the online-only Data Supplement). In patients with M1 initial target occlusion, thrombus migration was associated with better functional outcome (adjusted cOR, 1.49; CI 95%, 1.02–2.17). Thrombus resolution patients also had better functional outcomes; however, statistical significance was not reached (adjusted cOR, 2.23; CI 95%, 0.93–5.37). Thrombus growth was not significantly associated with functional outcome. There was a trend towards a better functional outcome (adjusted cOR, 1.18; CI 95%, 0.77–1.81), but the association was in the opposite direction when including only M1 initial target occlusion (Table 5).

Thrombus migration was associated with worse reperfusion status. (Table 6) Patients with thrombus migration had a lower chance of complete reperfusion (aOR, 0.51; CI 95%, 0.36–0.73) and successful reperfusion (aOR, 0.74; CI 95%, 0.55–0.99). These findings were similar when including only M1 initial target occlusion. By definition, all patients in the thrombus resolution group had complete recanalization, but 5/39 (14%) did not achieve complete reperfusion. Thrombus resolution significantly increased the rates of successful reperfusion (aOR, 4.17; CI 95%, 1.44–12.1) and complete reperfusion (aOR, 14.5; CI 95%, 5.00–42.1). Thrombus growth was not significantly associated with reperfusion status.

Table 3. Patient Outcome

	Thrombus Migration	Thrombus Resolution	Thrombus Growth	Stable Thrombus	*P* Value
n	302	39	87	921	
Follow-up NIHSS (24 h), median (IQR)	10 (3–17)	6 (3–13)	8 (4–15)	11 (4–18)	0.03
Onset to recanalization time, median (IQR) in minutes	256 (209–328)	231 (185–297)	285 (218–342)	271 (222–325)	0.04
Procedure time, median (IQR) in minutes	65 (40–95)	30 (15–58)	62 (45–90)	65 (41–90)	<0.01
mRs, n (%)					0.07
0	21/281 (8%)	5/38 (13%)	6/77 (8%)	42/839 (5%)	
1	43/281 (15%)	8/38 (21%)	15/77 (20%)	97/839 (12%)	
2	59/281 (21%)	6/38 (16%)	9/77 (12%)	177/839 (21%)	
3	46/281 (16%)	2/38 (5%)	12/77 (16%)	120/839 (14%)	
4	36/281 (13%)	5/38 (13%)	10/77 (13%)	116/839 (14%)	
5	10/281 (4%)	4/38 (11%)	6/77 (8%)	44/839 (5%)	
6	66/281 (23%)	8/38 (21%)	19/77 (25%)	243/839 (29%)	
eTICI, n (%)					<0.01
0	47/295 (16%)	3/38 (8%)	14/87 (16%)	126/915 (14%)	
1	8/295 (3%)	0/38 (0%)	4/87 (5%)	35/915 (4%)	
2A	77/295 (26%)	1/38 (3%)	19/87 (22%)	201/915 (22%)	
2B	71/295 (24%)	1/38 (3%)	20/87 (23%)	167/915 (18%)	
2C	29/295 (10%)	0/38 (0%)	7/87 (8%)	94/915 (10%)	
3	63/295 (21%)	33/38 (87%)	23/87 (26%)	292/915 (32%)	
Symptomatic intracranial hemorrhage, n (%)	18/302 (6%)	3/39 (8%)	4/87 (5%)	56/921 (6%)	0.90
Stroke progression to clinical deterioration or death, n (%)	26/302 (9%)	2/39 (5%)	13/87 (15%)	83/921 (9%)	0.26

eTICI indicates expanded treatment in cerebral infarction score; IQR, interquartile range; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

Discussion

We demonstrated that preinterventional changes in thrombus location are common in acute ischemic stroke. In our study, thrombus migration was the most common change and was associated with improved functional outcome. Interestingly, it was also associated with worse reperfusion status. IVT increased the rates of thrombus migration and resolution.

The incidence of thrombus migration and growth in our study were similar to the incidence documented by other studies.[13,16,19,20] However, this study showed a lower incidence of thrombus resolution, which may be the result of a difference in definition; we defined thrombus resolution as complete recanalization before the intervention.[16,25] While the association of IVT and changes in thrombus location has been demonstrated,[20] especially in patients with preinterventional reperfusion,[25,26] the association was not present in other thrombus migration studies.[13,16] Our study found that in patients treated with IVT, both thrombus migration and resolution were more frequent. To the best of our knowledge, our study is the first to demonstrate a significantly higher frequency of cervical carotid stenosis in patients with thrombus migration. Further, the association between thrombus migration and better functional outcome was only significant in our study.[19] This might be due to the different methodology used to define migration. Kaesmacher et al[13] included patients with both direct (angiographic) and indirect evidence of thrombus migration by evaluating perfusion deficits within the lenticulostriate artery territory.[26] In our study, only direct evidence

Table 4. Associations Between the Administration of Intravenous Thrombolytics and Changes in Occlusion Location

	Thrombus Resolution		Thrombus Migration		Thrombus Growth	
	Univariate	Multivariable*	Univariate	Multivariable*	Univariate	Multivariable*
Intravenous thrombolytics—OR (95% CI)	1.97 (1.43–2.72)	1.85 (1.22–2.80)	1.89 (1.35–2.65)	2.01 (1.30–3.11)	0.72 (0.46–1.13)	0.91 (0.49–1.69)

OR indicates odds ratio.

*Models were adjusted for age, history of atrial fibrillation, history of peripheral artery disease, collateral score, serum glucose level, history of diabetes mellitus, arterial blood pressure, international normalized ratio (INR>1.7), time from onset to computed tomography, previous stroke, and novel anticoagulants use.

Table 5. Ordinal Logistic Regression Models Assessing the Associations of Thrombus Dynamics With Functional Outcome

Outcome	ICA, M1, and M2 CTA Occlusion		M1 CTA Occlusion	
	modified Rankin Scale			
Model	Univariate	Multivariable*	Univariate	Multivariable*
Stable thrombus	1.00 [Reference]			
Thrombus resolution, OR (CI)	1.74 (0.98–3.10)	1.41 (0.71–2.76)	2.23 (0.98–5.11)	2.23 (0.93–5.37)
Thrombus migration, OR (CI)	1.28 (1.02–1.61)	1.21 (0.93–1.58)	1.57 (1.12–2.19)	1.49 (1.02–2.17)
Thrombus growth, OR (CI)	1.21 (0.82–1.76)	1.18 (0.77–1.81)	0.91 (0.51–1.66)	0.92 (0.47–1.80)

CTA indicates computed tomography angiography; ICA, internal carotid artery; and OR, odds ratio.

*Models were adjusted for age, National Institutes of Health Stroke Scale, prestroke modified Rankin Scale, onset to groin time, previous atrial fibrillation, symptomatic cervical carotid obstruction on CTA, collateral score and administration of intravenous thrombolytics.

was used. The association between thrombus migration and a lower chance of successful reperfusion was also previously reported.[13,26]

The histological composition of a thrombus might influence the dynamics it exhibits. Red blood cell-rich thrombi have been reported to be more frequent in patients with thrombus migration.[27] This type of thrombus is more common in patients with large-vessel atherosclerosis, which may explain the increased rate of cervical carotid occlusion and the lower incidence of atrial fibrillation in our patients with thrombus migration and resolution.[28] These patients also had a higher rate of multiple intracranial occlusions on first digital subtraction angiography before EVT, potentially caused by thrombus fragmentation or multiple emboli, another finding that points to the influence of thrombus composition, and that tends to be more common in red blood cell-rich thrombi.[29] Thrombus fragmentation has also been associated with IVT administration before EVT.[16] The higher frequency of stent treatment and balloon angioplasty may also cause hemodynamic changes that leads to thrombus migration and resolution. The smaller thrombus burden in patients with thrombus resolution indicates that thrombus volume might influence thrombus dynamics. However, the smaller burden in patients with thrombus growth may be better explained by selection bias, since the thrombus growth group did not include patients with CTA ICA occlusions.

The better functional outcome after thrombus migration could have several causes. First, the most common changes in thrombus location were ICA to M1 and M1 to M2. This may allow flow through the lenticulostriate arteries and circle of Willis, filling the affected territory via collaterals, leading to better functional outcome.[30] Second, the higher incidence of distal occlusions is also associated with smaller ischemic core and better functional outcome.[31,32] Because of our definitions, the thrombus growth group did not include ICA occlusions on CTA, whereas almost one quarter of patients on the stable group had such ICA occlusions. This may explain why there was also a trend towards better functional outcome on patients with thrombus growth and why this association was lost when only M1 initial target occlusion was included on both groups. As expected, thrombus resolution was associated with the best functional outcomes, but statistical significance was only reached on the M1 initial target occlusion analyses, probably because its effect of early reperfusion compared with no reperfusion is relatively greater than in distal occlusions such as M2.

Our findings reveal a thrombus migration paradox—an improvement in functional outcome despite worse reperfusion

Table 6. Binary Logistic Regression Models Assessing the Associations of Thrombus Dynamics With Reperfusion Status

	ICA, M1, and M2 CTA Occlusion				M1 CTA Occlusion			
Reperfusion Status*	Successful Reperfusion		Complete Reperfusion		Successful Reperfusion		Complete Reperfusion	
Model	Univariate	Multivariable†	Univariate	Multivariable†	Univariate	Multivariable†	Univariate	Multivariable†
Stable thrombus	1.00 [Reference]							
Thrombus resolution, OR (CI)	6.25 (2.21–17.7)	4.17 (1.44–12.1)	15.8 (6.16–40.7)	14.5 (5.00–42.1)	5.84 (1.35–25.2)	4.41 (1.00–19.5)	19.1 (4.41–82.4)	17.26 (3.85–77.4)
Thrombus migration, OR (CI)	0.79 (0.61–1.03)	0.74 (0.55–0.99)	0.57 (0.41–0.77)	0.51 (0.36–0.73)	0.86 (0.58–1.27)	0.73 (0.48–1.13)	0.47 (0.30–0.75)	0.32 (0.17–0.57)
Thrombus growth, OR (CI)	0.99 (0.65–1.51)	0.93 (0.58–1.49)	0.96 (0.62–1.49)	0.87 (0.52–1.47)	1.43 (0.74–2.80)	1.77 (0.84–3.74)	1.15 (0.61–2.17)	1.45 (0.73–2.85)

CTA indicates computed tomography angiography; ICA, internal carotid artery; and OR, odds ratio.

*Reperfusion was assessed on digital subtraction angiography using the expanded treatment in cerebral infarction (eTICI) score. Successful reperfusion was defined as an eTICI score of 2b, 2c, or 3.[17] Complete reperfusion was defined as an eTICI score of 3.

†Models were adjusted for age, National Institutes of Health Stroke Scale, prestroke modified Rankin Scale, onset to groin time, previous atrial fibrillation, symptomatic cervical carotid obstruction on CTA, collateral score, and administration of intravenous thrombolytics.

status. The shift to a more distal thrombus location reflects partial recanalization and subsequent distal embolization of thrombus fragments, which is more common after IVT.[16,26] Given the smaller size and more tortuous course of the distal arterial branches, thrombectomy devices are not only more difficult to deliver to distal occlusions but also less likely to be effective.[4] The increased rate of thrombus inaccessibility explains why mechanical thrombectomy was less frequently performed in thrombus migration patients and also why these patients had a lower chance of successful reperfusion. Nevertheless, because thrombus migration improved functional outcome in this study, one could speculate that the benefit of early proximal revascularization in most cases outweighs the negative impact of reperfusion failure. However, the relationship between the timing and extent of revascularization must also depend on the extent of the final perfusion deficit. For example, an eTICI score of 2A in a patient with an M2 occlusion could correspond to more preserved tissue than an eTICI score of 2B in a patient with an M1 occlusion. Other factors that could influence the association of IVT and patient outcome: IVT may help recanalize remaining thrombi in the microvasculature or distal branches, but it is also more strongly associated with blood-brain barrier breakdown, increasing the risk of symptomatic intracranial hemorrhage.[33] A potential confounding factor that must be noted is that IVT treated patients have a more favorable treatment profile than their non-IVT treated counterparts. Patients treated with IVT have fewer comorbidities and present earlier at the hospital. While not significant, this trend can be seen in the thrombus dynamic subgroups as well, with more atrial fibrillation and marginally longer onset to groin times in the stable thrombus group. While we adjusted for these confounders, their effects might still contribute to the observed association. Current clinical trials investigating the value of additional IVT in the era of EVT treatment, such as MR CLEAN-NO IV (ISRCTN80619088), DIRECT MT (Direct Intra-arterial Thrombectomy In order to Revascularize AIS Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals; NCT03469206), and SWIFT DIRECT (Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke; NCT03192332), will aid to determine whether the chance of early lysis by IVT outweighs the potential negative effects of IVT.

The major limitation of our study is the lack of inclusion of patients in whom there was sufficient clinical recovery before groin puncture to forego EVT in the MR CLEAN Registry. This may have resulted in an underestimation of the occurrence of thrombus resolution and migration and their beneficial effect. Further, apparent differences in thrombus location between the initial and the conventional angiography target occlusions might also be caused by reduced flow leading to delayed contrast delivery proximal to the occlusion. The reduced flow may simulate a proximal occlusion on CTA, the so-called pseudo-occlusions.[34,35] Another limitation were disagreements between the interventionist and the core lab. This was observed on 8 patients from the thrombus resolution group on which the interventionist performed mechanical thrombectomy, and later, the core lab considered that there was no residual thrombus. We also did not consider occlusion location differences in subsegments of the intracranial ICA and between proximal and distal M1 to reduce the effect of the inter-observer disagreement. Stroke cause evaluation was limited, because TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria was not available.[36]

Conclusions

In patients with acute ischemic stroke due to proximal occlusion of the anterior circulation, preinterventional changes in thrombus location are common, especially after IVT. In our population, thrombus migration was associated with improved functional outcome, although there was an association with worse reperfusion status at the end of EVT.

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