Prognostic Value of Thrombus Volume and Interaction With First-Line Endovascular Treatment Device Choice

Stroke

CLINICAL AND POPULATION SCIENCES

Prognostic Value of Thrombus Volume and Interaction With First-Line Endovascular Treatment Device Choice

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BACKGROUND: A larger thrombus in patients with acute ischemic stroke might result in more complex endovascular treatment procedures, resulting in poorer patient outcomes. Current evidence on thrombus volume and length related to procedural and functional outcomes remains contradicting. This study aimed to assess the prognostic value of thrombus volume and thrombus length and whether this relationship differs between first-line stent retrievers and aspiration devices for endovascular treatment.

METHODS: In this multicenter retrospective cohort study, 670 of 3279 patients from the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) for endovascularly treated large vessel occlusions were included. Thrombus volume (0.1 mL) and length (0.1 mm) based on manual segmentations and measurements were related to reperfusion grade (expanded Treatment in Cerebral Infarction score) after endovascular treatment, the number of retrieval attempts, symptomatic intracranial hemorrhage, and a shift for functional outcome at 90 days measured with the reverted ordinal modified Rankin Scale (odds ratio >1 implies a favorable outcome). Univariable and multivariable linear and logistic regression were used to report common odds ratios (cORs)/adjusted cOR and regression coefficients (B/aB) with 95% CIs. Furthermore, a multiplicative interaction term was used to analyze the relationship between first-line device choice, stent retrievers versus aspiration device, thrombus volume, and outcomes.

RESULTS: Thrombus volume was associated with functional outcome (adjusted cOR, 0.83 [95% CI, 0.71–0.97]) and number of retrieval attempts (aB, 0.16 [95% CI, 0.16–0.28]) but not with the other outcome measures. Thrombus length was only associated with functional independence (adjusted cOR, 0.45 [95% CI, 0.24–0.85]). Patients with more voluminous thrombi had worse functional outcomes if endovascular treatment was based on first-line stent retrievers (interaction cOR, 0.67 [95% CI, 0.50–0.89]; *P*=0.005; adjusted cOR, 0.74 [95% CI, 0.55–1.0]; *P*=0.04).

CONCLUSIONS: In this study, patients with a more voluminous thrombus required more endovascular thrombus retrieval attempts and had a worse functional outcome. Patients with a lengthier thrombus were less likely to achieve functional independence at 90 days. For more voluminous thrombi, first-line stent retrieval compared with first-line aspiration might be associated with worse functional outcome.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: functional status ■ ischemic stroke ■ prognosis ■ stents ■ thrombosis

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Nonstandard Abbreviations and Acronyms

AD	aspiration device
cOR	common odds ratio
CT	computed tomography
CTA	computed tomography angiography
eTICI	expanded Treatment in Cerebral Infarction
EVT	endovascular treatment
FAR	first-attempt reperfusion
IQR	interquartile range
LL	log-likelihood
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
mRS	modified Rankin Scale
sICH	symptomatic intracranial hemorrhage
SR	stent retriever

The size of a thrombus occluding an artery in acute ischemic stroke has been suggested as a prognostic marker for patients with a large vessel occlusion receiving endovascular treatment (EVT) as it could result in a more complex and prolonged procedure.[1–9] Moreover, an EVT procedure requiring more retrieval attempts or achieving suboptimal reperfusion is associated with more ischemic damage,[10] infarct growth,[11] remote embolization,[11] and complications such as intracranial hemorrhages,[12] negatively affecting patient functional outcomes. If thrombus volume or length is associated with any of these procedural outcomes, it might be possible to improve patient care by altering EVT strategies or optimizing device choices.

Thrombus length was associated with worse functional outcomes in some studies,[1,3] whereas in other studies, no association was found.[4,5] Similarly, 3 studies found that thrombus volume was associated with less successful reperfusion, more retrieval attempts, and a lower first-attempt reperfusion (FAR) effect,[2,6,9] whereas 2 other studies did not find any association with procedural or patient outcomes.[7,8] Thus, the prognostic value of thrombus volume remains a matter of debate. Additionally, it remains unclear whether thrombus volume has a stronger prognostic value than thrombus length. Furthermore, current evidence suggests that similar patient outcomes can be achieved using either a stent retriever (SR) or aspiration device (AD).[13–15] It is unclear whether the effect of thrombus volume on procedural and functional outcome differs between first-line EVT with an SR or AD.

We aimed to study the prognostic value of thrombus volume as an alternative to thrombus length regarding procedural and functional outcomes. Furthermore, we aimed to determine whether the associations between thrombus volume and procedural and functional outcomes differ between SR- and AD-based first-line EVT.

METHODS

Study Design and Patient Inclusion

We used data from patients included in the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; March 18, 2014, to November 1, 2017). The MR CLEAN Registry was a national, multicenter, observational prospective registry including patients treated with EVT from 17 stroke centers in the Netherlands after the completion of the MR CLEAN trial.[16] For this study, patients from the MR CLEAN Registry parts 1 and 2 were considered; inclusion dates ranged between March 2014 and January 2017.[16] The Central Medical Ethics Committee of Erasmus MC, Rotterdam, the Netherlands, evaluated the study protocol of the MR CLEAN Registry and granted permission to carry out the study as a registry (MEC-2014-235). We conducted this study in line with the Strengthening the Reporting of Observational Studies in Epidemiology guideline.[17] Data will be made available upon reasonable request while adhering to privacy regulations.

Patients aged ≥18 years with an intracranial vessel occlusion in the anterior circulation—internal carotid artery, internal carotid artery terminus, middle cerebral artery (M1/M2/M3), or anterior cerebral artery (A1/A2)—who received EVT within 6.5 hours after stroke onset were included. Furthermore, for the current study, patients were required to have a baseline noncontrast computed tomography (CT) and CT angiography (CTA) available with a slice thickness ≤1.0 mm. Patients were excluded if spontaneous reperfusion was visible on digital subtraction angiography before EVT, the occlusion site could not be reached for EVT, data regarding primary device choice were missing, or if a different first-line approach than SR or AD was used. The EVT device choice was at the discretion of the treating neurointerventionist. Patients received intravenous alteplase (0.9 mg/kg) before EVT if they presented <4.5 hours after stroke onset and had no contraindications according to the European Stroke Organization guidelines.[18] Since our database did not include accurate data for secondary device choice or combined device use, all treatment approach analyses consider the first-line device choice. Patients treated with a combined approach, aspiration on one of the catheters during SR EVT, were included in the SR group.

Imaging Assessment

All baseline imaging was assessed by an independent central core laboratory of neuroradiologists who were blinded for all clinical data except the occlusion side. The following imaging parameters were reported: occluded arterial segment, Alberta Stroke Program Early CT Score, CTA collateral score, reperfusion grade on the final digital subtraction angiography (expanded Treatment in Cerebral Infarction [eTICI] score), and the presence of symptomatic intracranial hemorrhage (sICH).

Thrombus Measurements

Thrombi were segmented manually by an expert dedicated core laboratory (H.v.V., A.A.E.B., W.Y., J.A., P.R.K., N.A.T., J.W.H., M.K., and J.B.) using 3-dimensional imaging software ITK-SNAP[19] with coregistered baseline noncontrast CT and CTA using Elastix.[20] The data processing and segmentation methods have been described previously.[9] In short, thrombi were segmented considering both CTA and noncontrast CT in axial, coronal, and sagittal views (Figure 1). Patients were excluded if the visibility of the thrombus was poor due to very poor or uncorrectable alignment of CTA and noncontrast CT, severe movement, or beam hardening artifacts, an incomplete field of view on CT imaging resulting in incomplete thrombus visibility, excessive noise leading to very-poor-quality imaging, no thrombus present on imaging according to the core laboratory, and no visible hyperdense artery sign in combination with an absent collateral filling or insufficient CTA contrast opacification. In cases that were difficult to segment, a consensus reading under the supervision of C.B.L.M.M. or B.J.E. was held. Following previous work by Dutra et al,[3] we excluded patients with a thrombus restricted to the petrous, cavernous, and clinoid segments of the internal carotid artery because volume measurement in these segments is less reliable due to blooming artifacts of the surrounding bone. Thrombus length, density, and perviousness were measured and reported previously.[3,21]

Outcome Measures and Statistical Analyses

Our primary outcome was functional outcome as measured with the ordinal modified Rankin Scale (mRS) 90 days after acute ischemic stroke. Ordinal mRS values were inverted and studied with a shift analysis in line with previous studies of the MR CLEAN Registry.[16,22] Using an inverted mRS results in odds ratios below 1 for worse functional outcome. Our secondary outcome measures were functional independence (mRS score, ≤2), ordinal eTICI post-EVT, successful reperfusion post-EVT (eTICI score, ≥2B), FAR, sICH, and the number of thrombus retrieval attempts. Odds ratios and slopes with 95% CIs from logistic and linear regression models were reported for both univariable unadjusted (common odds ratio [cOR]/B) and multivariable adjusted analysis (adjusted cOR/aB). Multivariable analyses were used to statistically adjust for potential confounders. The following variables were used for adjustments: age, sex, prestroke mRS, collateral score, baseline National Institutes of Health Stroke Scale, Alberta Stroke Program Early CT Score, first-line EVT device (SR versus AD), administration of intravenous thrombolysis, time from symptom onset to arterial puncture, occlusion location, thrombus perviousness,[23] and the number of months since start of the MR CLEAN Registry to correct for the improving outcomes of EVT through time.

First, since thrombus length is easier and faster to measure manually than volume, we compared the prognostic relationship of thrombus length and volume with the outcome measures. Second, we evaluated the interaction of thrombus volume with first-line EVT device on the outcome measures by introducing a multiplicative interaction term in the regression models. To assess whether device choice modified the relationship of thrombus volume with outcome, thrombus volume and device choice were also added as independent variables to the models with the multiplicative interaction terms.[24] Log-likelihood (LL) values were reported to describe and compare the goodness of fit of the (logistic) regression models to the data. Based on the LL, we compare models using thrombus volume and thrombus length and models with (thrombus volume–device choice) multiplicative interaction term to those without.

Baseline characteristics were described with median and interquartile range (IQR) or mean and SD for non-normally and normally distributed variables, respectively. Mann-Whitney *U* test, independent *t* test, χ^2 test, Kruskal-Wallis test, and ANOVA test were used to compare the baseline characteristics between our study cohort and the remainder of the MR CLEAN Registry population. Multiple imputation considering all the variables used for statistical adjustment, all the studied variables, and outcome measures were used for handling missing values in the regression analyses. Multiple imputation was performed using the R package mice. We imputed 5 data sets and used 4 knots for modeling nonlinear relationships. All statistical analyses were performed in R (R Statistical Software, V3.6.3, R: a language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Inclusion and Baseline Characteristics

Of all 3279 patients in the MR CLEAN Registry, 670 were included in this study (Figure 2). Table 1 compares the baseline characteristics of the included patients to those of the remainder of the MR CLEAN Registry and the first-line AD and SR groups. Table S1 describes the thrombus volume per occlusion location. Patients included in the current study had a lower collateral score, were less often treated with thrombolysis before EVT (71.9% versus 75.8%), were included earlier in the MR CLEAN Registry (months since the start of registry: median, 28

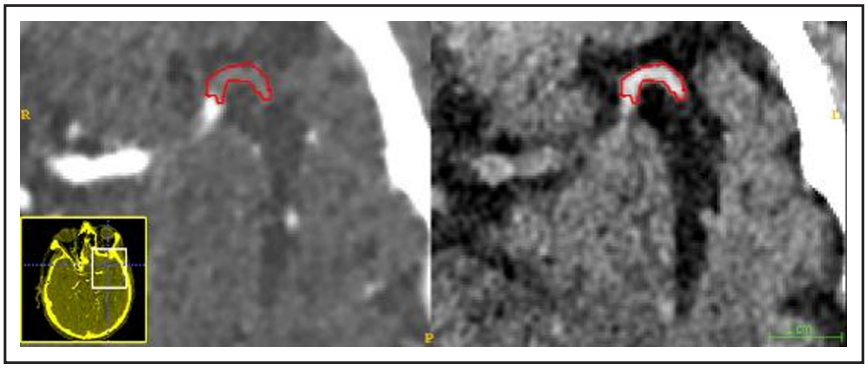

Figure 1. Example of a patient with a left middle cerebral artery occlusion. A combination of the hyperdense artery sign on noncontrast computed tomography (**right**) and contrast filling defect on computed tomography angiography (**left**) to define the proximal thrombus border was used.

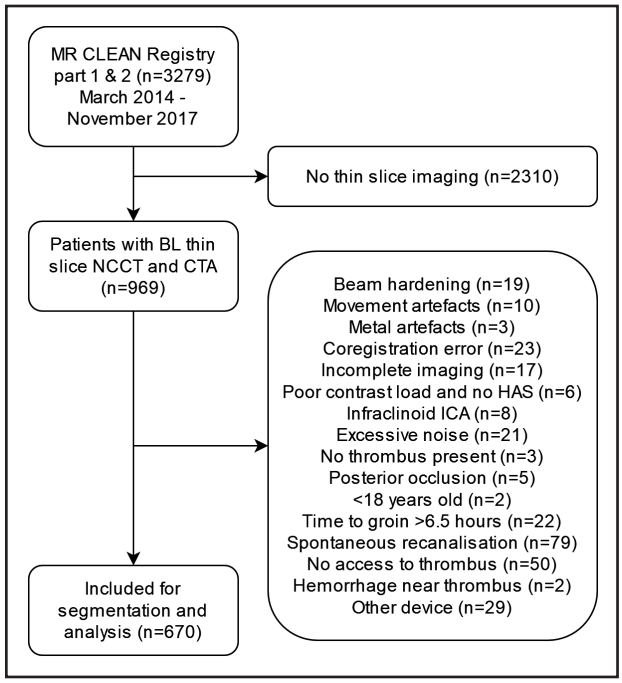

Figure 2. Inclusion flowchart.
Thin-slice imaging was defined as ≤1.0 mm slice thickness. BL indicates baseline; CTA, computed tomography angiography; HAS, hyper dense artery sign; ICA, internal carotid artery; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; and NCCT, noncontrast computed tomography.

[IQR, 20–36] versus 30 [IQR, 21–38]), were treated faster (minutes from onset to groin puncture: mean, 194 [SD, 78] versus 219 [SD, 105]), and had less thrombus retrieval attempts (median, 2 [IQR, 1–3] versus 1 [IQR, 1–3]). Compared with the first-line AD group, patients in the SR group were included earlier (months since start: median, 27 [IQR, 19–35] versus 34 [IQR, 23–38]) and had a lower thrombus perviousness (median, 3 [IQR, 1–10] versus 7 [IQR, 0–14]) with denser thrombi (Hounsfield units: mean, 50 [SD, 10] versus 47 [SD, 11]).

Prognostic Value of Thrombus Volume and Length

Table 2 describes the associations of thrombus volume and length with the outcome measures. Thrombus volume was associated with worse functional outcome (cOR, 0.80 [95% CI, 0.71–0.91]; acOR, 0.83 [95% CI, 0.71–0.97]), whereas thrombus length was not (cOR, 0.87 [95% CI, 0.75–1.01]). Thrombus length was only associated with a lower probability of functional independence (mRS score ≤2 acOR, 0.45 [95% CI, 0.24–0.85]) and not with any of the other outcome measures. Thrombus volume was associated with a lower probability of functional independence (mRS score ≤2 acOR, 0.78 [95% CI, 0.64–0.96]) and number of retrieval attempts (aB, 0.16 [95% CI, 0.04–0.28]). The statistically significant relationship between thrombus volume and a lower probability of FAR was only present in the unadjusted model but was absent after adjustment for confounders (cOR, 0.79 [95% CI, 0.67–0.94]; acOR, 0.86 [95% CI, 0.71–1.05]). Specifically, the adjustment variable months since start of the registry had a strong relationship with an improved probability of FAR (acOR, 1.02 [95% CI, 1.01–1.04]; *P*=0.008), possibly explaining part of the initially observed relation with thrombus volume. The LL was higher for all (logistic) regression models with significant associations that used thrombus volume compared with thrombus length as an independent variable except for the models using functional independence (mRS score ≤2): thrombus volume versus length, unadjusted model LL: mRS, 11.66 versus 7.13; mRS score ≤2, 10.87 versus 11.22; FAR, 8.41 versus 0.25; number of retrieval attempts, 16.43 versus 2.96; adjusted model LL: mRS, 257.98 versus 256.99; mRS score ≤2, 201.79 versus 204.70; FAR, 41.77 versus 39.46; number of retrieval attempts, 50.44 versus 43.60. Tables S2 through S4 contain more extensive goodness-of-fit measures.

Thrombus Volume and Device Choice

Table 3 describes the results from unadjusted and adjusted (logistic) regression models with the multiplicative interaction term (device choice [SR, 1 versus AD, 0]×thrombus volume). The multiplicative interaction term of first-line device choice and thrombus volume was significantly associated with worse functional outcome (mRS: cOR, 0.67 [95% CI, 0.5–0.89]; *P*=0.005; acOR, 0.74 [95% CI, 0.55–1.0]; *P*=0.04) but not with any other outcome measure. The ordinal logistic regression models for functional outcome had a higher LL when the interaction term was added (with interaction term versus without mRS models: unadjusted LL, 19.84 versus 11.60; adjusted LL, 262.11 versus 257.98). This indicates that patients with more voluminous thrombi had worse functional outcomes when an SR was used as first-line EVT device compared with an AD.

Results for the (logistic) regression models including a multiplicative interaction term of device choice and volume with each outcome measure are presented for the unadjusted (cOR/B) and the adjusted (acOR/aB) analyses. The reference device choice was an AD; results represent the effect of SR multiplied by thrombus volume per 0.1 mL (cOR, common odds ratio in unadjusted analysis; B, slope of the regression for continuous outcome in unadjusted analysis; acOR, adjusted common odds ratio after adjustment for confounders; aB, slope of the regression line after adjustment for confounders). Odds ratios are reported for the first 6 rows; the slope of the regression line is reported for number of attempts since it is a continuous outcome.

Table 1. Baseline Characteristics

	Remainder MR CLEAN registry	Included cohort (AD+SR)	*P* value	AD	SR	*P* value
No. of patients	2609	670		198	472	
Baseline characteristics						
Age, y; mean (SD)	69 (14)	68 (15)	0.33	68 (165)	69 (15)	0.82
Sex, n (%)			0.86			0.30
Women	1257 (48.2%)	326 (48.7%)		103 (52.0%)	223 (47.2%)	
Men	1352 (51.8%)	344 (51.3%)		95 (48.0%)	249 (52.8%)	
History of diabetes, n (%)			0.59			0.11
No	2165 (83.5%)	558 (84.4%)		172 (88.2%)	386 (82.8%)	
Yes	429 (16.5%)	103 (15.6%)		23 (11.8%)	80 (17.2%)	
Prestroke mRS score, n (%)			0.87			0.37
0	1730 (67.7%)	440 (67.7%)		124 (66.0%)	316 (68.4%)	
1	343 (13.4%)	81 (12.5%)		19 (10.1%)	62 (13.4%)	
2	192 (7.5%)	49 (7.5%)		18 (9.6%)	31 (6.7%)	
3	163 (6.4%)	48 (7.4%)		14 (7.4%)	34 (7.4%)	
4	105 (4.1%)	28 (4.3%)		12 (6.4%)	16 (3.5%)	
5	24 (0.9%)	4 (0.6%)		1 (0.5%)	3 (0.6%)	
Systolic blood pressure, mm Hg; mean (SD)	150 (25)	149 (24)	0.45	150 (24)	148 (24)	0.54
Baseline NIHSS, median (IQR)	16 (11 to 19)	16 (11 to 20)	0.30	17 (11 to 20)	15 (11 to 19)	0.18
Baseline ASPECTS, median (IQR)	9 (7 to 10)	9 (7 to 10)	0.16	9 (7 to 10)	9 (7 to 10)	0.76
Collateral score, n (%)			0.03			0.65
0	146 (6.0%)	41 (6.3%)		14 (7.3%)	27 (5.9%)	
1	857 (35.4%)	243 (37.4%)		75 (39.1%)	168 (36.7%)	
2	923 (38.1%)	267 (41.1%)		72 (37.5%)	195 (42.6%)	
3	496 (20.5%)	99 (15.2%)		31 (16.1%)	68 (14.8%)	
Occlusion location, n (%)			0.63			0.09
ICA	135 (5.5%)	26 (4.0%)		3 (1.6%)	23 (5.0%)	
ICA-T	527 (21.4%)	136 (20.9%)		42 (21.9%)	94 (20.4%)	
M1	1428 (57.9%)	387 (59.4%)		120 (62.5%)	267 (58.0%)	
M2	357 (14.5%)	98 (15.0%)		24 (12.5%)	74 (16.1%)	
Other: A1, A2, or M3	20 (0.8%)	5 (0.8%)		3 (1.6%)	2 (0.4%)	
Thrombolysis given, n (%)			0.04			0.26
No	629 (24.2%)	188 (28.1%)		49 (24.9%)	139 (29.5%)	
Yes	1970 (75.8%)	480 (71.9%)		148 (75.1%)	332 (70.5%)	
Months since start registry, median (IQR)	30 (21 to 38)	28 (20 to 36)	<0.01	34 (23 to 38)	27 (19 to 35)	<0.001
Time from onset to groin puncture, min; mean (SD)	219 (105)	194 (78)	$<1\times10^{-9}$	192 (76)	195 (79)	0.60
Manual thrombus measurements						
Thrombus length, mm; median (IQR)	18 (11 to 28)	18 (11 to 29)	0.65	19 (10 to 32)	17 (11 to 27)	0.55
Thrombus perviousness, HU; median (IQR)	4 (−2 to 13)	4 (−1 to 12)	0.58	7 (0 to 14)	3 (−1 to 10)	<0.01
Thrombus density, HU;, mean (SD)	50 (9.6)	49 (10.0)	0.10	47 (11)	50 (10)	<0.01
Thrombus volume, mL; median (IQR)				0.08 (0.04 to 0.14)	0.09 (0.05 to 0.15)	0.07
Primary device choice, n (%)			0.21			
AD	514 (27.0%)	198 (29.6%)		198 (100.0%)		
SR	1392 (73.0%)	472 (70.4%)			472 (100.0%)	

Data are stratified by the included cohort and the remainder of the registry and by endovascular device choice: AD or SR. AD indicates aspiration device; ASPECTS, Alberta Stroke Program Early CT Score; HU, Hounsfield unit; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; IQR, interquartile range; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SR, stent retriever.

Table 2. Prognostic Value of Thrombus Volume and Thrombus Length

Outcome	Thrombus volume (per 0.1 mL)		Thrombus length (per 0.1 mm)	
	cOR/B (95% CI)	acOR/aB (95% CI)	cOR/B (95% CI)	acOR/B (95% CI)
Functional outcome (ordinal mRS, lower is worse)	0.80 (0.71 to 0.91)‡	0.83 (0.71 to 0.97)*	0.87 (0.75 to 1.01)	0.65 (0.41 to 1.03)
Functional independence (mRS score ≤2)	0.78 (0.67 to 0.91)†	0.78 (0.64 to 0.96)*	0.77 (0.63 to 0.95)†	0.45 (0.24 to 0.85)*
Reperfusion rate (ordinal eTICI score)	0.92 (0.82 to 1.04)	0.90 (0.78 to 1.03)	0.96 (0.83 to 1.11)	0.89 (0.57 to 1.38)
Successful reperfusion (eTICI score ≥2B)	0.94 (0.81 to 1.08)	0.90 (0.75 to 1.07)	1.02 (0.85 to 1.24)	1.08 (0.6 to 1.94)
First-attempt reperfusion	0.79 (0.67 to 0.94)†	0.86 (0.71 to 1.05)	1.01 (0.85 to 1.19)	1.02 (0.6 to 1.73)
Symptomatic intracranial hemorrhage	1.06 (0.8 to 1.4)	1.07 (0.76 to 1.5)	1.28 (0.88 to 1.85)	2.15 (0.68 to 6.8)
Number of thrombus retrieval attempts	0.2 (0.1 to 0.31)‡	0.16 (0.04 to 0.28)†	0.04 (−0.05 to 0.13)	0.02 (−0.10 to 15)

Functional outcome: reversed mRS so that an OR below 1 and B below 0 corresponds to worse functional outcome. Odds ratios are reported for the first 6 rows, the slope of the regression line is reported for the number of attempts. acOR indicates adjusted common odds ratio; cOR, common odds ratio; eTICI, expanded Treatment in Cerebral Infarction; mRS, modified Rankin Scale; and OR, odds ratio.

*P<0.05, †P<0.01, ‡P<0.0001.

DISCUSSION

Thrombus volume had a stronger association with poor procedural and worse functional outcomes than thrombus length. Moreover, more voluminous thrombi were associated with more retrieval attempts, a lower probability of achieving functional independence, and a worse ordinal functional outcome. Thrombus volume and length were not associated with eTICI, sICH, and FAR. Our findings might indicate that more voluminous thrombi cause a more difficult EVT procedure, resulting in more permanent and severe neurological deficits. When SR was used, functional outcome was more affected by volume compared with when an AD was used as first-line EVT device. We did not identify a potential statistically significant causal factor in eTICI, sICH, FAR, or number of thrombus retrieval attempts that might explain the interaction of device choice and volume on functional outcome.

Our findings regarding thrombus length and outcomes are in line with some previous studies[1,3] but not with other previous studies.[4,5] Regarding associations of thrombus volume with outcome measures, our nonsignificant results are partially conflicting for the effect on successful reperfusion and FAR[2,6] and for our association with functional outcome.[7,8] Part of these deviations are likely due to the much larger sample size we adopted compared with other studies.[4,5,7,8] The nonsignificant association between thrombus volume and successful reperfusion found in our study might be due to the improvement of EVT care; compared with the study by Yoo et al,[2] successful reperfusion was much higher in our cohort. Although we found an effect between thrombus volume and FAR, this effect became nonsignificant after adjusting for potential confounders, partially conflicting with findings by Baek et al[6] who used less extensive statistical adjustments than we did. Findings from this study might indicate that patients with larger thrombi achieve a worse functional outcome due to more retrieval attempts irrespective of reperfusion status. The association between more retrieval attempts and a worse functional outcome irrespective of the reperfusion status has been described previously.[10] This association might be due to an increased rate of (unobserved) hemorrhagic complications,[12] a more time-consuming intervention, or due to an

Table 3. Interaction of Device Choice on the Relationship of Thrombus Volume With Outcome

Outcome measure	Multiplicative interaction term first-line device choice (SR=1 vs AD=0) and thrombus volume (0.1 mL)			
	cOR/B	*P* value	acOR/aB	*P* value
Functional outcome (ordinal mRS score <1 indicates worse functional outcome)	0.67 (0.5 to 0.89)*	0.005*	0.74 (0.55 to 1)*	0.047*
Functional independence (mRS score ≤2)	0.76 (0.54 to 1.06)	0.108	0.86 (0.59 to 1.27)	0.454
Reperfusion rate (ordinal eTICI score)	1.13 (0.86 to 1.48)	0.381	1.19 (0.91 to 1.57)	0.210
Successful reperfusion (eTICI score ≥2B)	1.04 (0.74 to 1.46)	0.807	1.1 (0.78 to 1.55)	0.569
First-attempt reperfusion	0.95 (0.66 to 1.37)	0.789	1.04 (0.71 to 1.52)	0.845
Symptomatic intracranial hemorrhage	1.59 (0.71 to 3.54)	0.385	1.69 (0.76 to 3.78)	0.202
Number of thrombus retrieval attempts	0.15 (−0.07 to 0.38)	0.398	0.10 (−0.13 to 0.33)	0.184

acOR indicates adjusted common odds ratio; AD, aspiration device; cOR, common odds ratio; eTICI, expanded Treatment in Cerebral Infarction; mRS, modified Rankin Scale; and SR, stent retriever.

*Statistical significance (P<0.05).

impaired microvascular reperfusion and thus persistent brain tissue ischemia.[25] Moreover, more physical strain and damage to the vessel wall during the intervention could induce inflammatory cascades that results in an impaired microvascular reperfusion.[25,26] To the best of our knowledge, this is the first study performing an interaction analysis on first-line device choice and thrombus volume. Our findings on the relationship between thrombus volume and outcomes considering the device choice were in line with Dutra et al where a higher clot burden score, associated with a less voluminous thrombi, was associated with better outcomes when an SR was used.[3] Part of these findings related to the interaction of thrombus volume and first-line EVT device could be explained based on pathophysiological and physical mechanisms. Namely, an important difference between SR- and AD-based EVT is the way the thrombus is removed. In AD EVT, only the proximal part of the thrombus is touched with a device causing suction while in SR EVT, a stent is deployed in and past the thrombus to provide traction. This implies a larger contact surface of SR devices with the thrombus. The contact surface could relate to functional outcome in 3 different ways: first, due to the larger contact surface, the use of SR could lead to an easier and more successful intervention for patients with more voluminous thrombi. Second, the larger contact surface could cause more friction and adhesion during EVT, resulting in a higher chance of intracerebral hemorrhages and activation of inflammatory cascades associated with the no-reflow phenomenon after the procedure and in turn affect functional outcome.[25,27] Third, a previous study advocated that the thrombus length/SR length ratio should be as small as possible to have a greater chance to achieve FAR,[28] potentially improving outcome. Our findings are in line with the second theory as the interaction between first-line EVT device choice and thrombus volume indicated increasingly worse functional outcome for SR- compared with AD-treated patients for more voluminous thrombi. However, since we did not include asymptomatic intracranial hemorrhage or the occurrence of no reflow as an outcome measure, we could not verify this proposed causal pathway to functional outcome. In addition, we could not verify the value of the length/SR length ratio presented in the third theory due to lacking data. An alternative explanation for the interaction effect between first-line device and thrombus volume could lie in a selection effect. If the interventionalist would prefer AD for smaller or easier-to-treat thrombi, indirectly the more profound effect of thrombus volume in first-line SR compared with first-line AD EVT could have been affected. Additionally, SR was the EVT standard before the introduction of AD. Due to the improvement of EVT workflows, interventionalists' experience, and patient outcomes over time, this might also have affected the interaction of first-line SR with thrombus volume. However, we did not observe a difference in thrombus volume and thrombus characteristics between the first-line AD EVT and SR EVT patients. Furthermore, we adjusted our (logistic) regression models for EVT experience by using months since the start of the MR CLEAN Registry. Therefore, the effects of patient selection are likely to be limited in this study.

Our study has limitations. First, this study considers a selected cohort as a post hoc analysis of the MR CLEAN Registry. Thus, the found effects might be caused by inclusion bias. Furthermore, deviations in the baseline characteristics between our population and the remainder of the MR CLEAN Registry might complicate the ability to generalize our findings to the broader population. Second, only data on the first-line device choice were available. Switching from AD to SR when the initial attempts failed or combined used of AD and SR could have occurred but were not registered and considered in this study. Third, there were no interventionalist-specific data available. If such data were available, it would become possible to correct or stratify for interventionalist-based effects. Procedural outcome might depend on the interventionalist experience with either device and their relationship to thrombus volume. Ideally, the interaction of device choice and thrombus volume would be tested in a randomized trial with interventionalists having proper training or experience with AD and SR devices. Fourth, the use of AD or SR as first-line device was not a random choice but at the discretion of the treating interventionalist. This might be a source of bias in the reported interaction effects. Fifth, thrombus measurements were performed with single-phase CTA for patients with deviating collateral statuses. Therefore, if a hyperdense artery sign was absent, in some cases, it was difficult to determine the distal thrombus border due to a lack of contrast filling causing potential volume measurement errors. Ideally, multiphase CTA or CT perfusion should be used to determine the distal part of the thrombus. Finally, the difficulty to remove a thrombus could also be related to factors other than thrombus size, such as thrombus composition and occlusion patterns such as bifurcation and trifurcation thrombi. These factors require further studies. Future research should focus on more fine-grained device choice modeling and should consider interventionalist-specific differences or at least differences in EVT experience. Furthermore, the optimal moment to switch from SR to AD—or vice versa—and its relationship to thrombus volume remains a subject for future research.

CONCLUSIONS

In this multicenter retrospective cohort study, thrombus volume in patients with endovascularly treated acute ischemic stroke was associated with worse functional outcome and more EVT attempts but not with first-attempt recanalization, sICHs, or reperfusion rate. Thrombus length was only associated with functional

independence. Patients with more voluminous thrombi had worse functional outcome when treated with a first-line stent retrieval compared with a first-line AD. This might indicate that thrombus volume could be used to optimize first-line EVT device choice. A randomized clinical trial is required to asses whether voluminous thrombi are best treated with first-line SRs or ADs.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Results
Tables S1–S4

APPENDIX

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