

Predictors of Unexpected Early Reocclusion After Successful Mechanical Thrombectomy in Acute Ischemic Stroke Patients

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Background and Purpose—Sustained successful reperfusion is an important prognostic factor for good clinical outcome in acute ischemic stroke. We aimed to identify the prevalence, clinical impact, and predictors of early reocclusion after initially successful thrombectomies within a prospective cohort.

Methods—A total of 711 stroke patients with successful reperfusion (modified Thrombolysis in Cerebral Infarction, 2b/3) followed with magnetic resonance or computed tomographic angiography at 24 to 48 hours were included. Multivariable logistic regression analysis was used to evaluate associated factors and clinical impact. Results are displayed as adjusted odds ratio (aOR) and 95% CI. Improvement in accuracy of additional imaging findings on angiography control runs after the intervention was evaluated by area under the curve.

Results—Early reocclusion was observed in 16 of 711 successfully reperfused patients (2.3%; 95% CI: 1.1–3.3; median delay: 20 hours). Suggestive predictors were higher platelets on admission (aOR, 1.01; 95% CI: 1.01–1.02), prestroke functional dependence (aOR, 7.12; 95% CI: 1.49–34.03), and stroke of undetermined or other specified pathogenesis in the TOAST classification (aOR, 7.19; 95% CI: 1.10–47.05 and aOR, 36.50; 95% CI: 4.47–298.11, respectively). When implementing residual embolic fragments or stenosis at the thrombectomy site into the logistic regression model, discrimination between patients with and without reocclusion improved significantly (area under the curve, 0.955 versus 0.854; $P=0.023$). Early reocclusion was an independent predictor of unfavorable outcome at 90 days (aOR for modified Rankin Scale ≤ 2 , 0.13; 95% CI: 0.03–0.57).

Conclusions—Early reocclusion within 48 hours after successful mechanical thrombectomy is rare but associated with poor outcome. Patients with high platelets on admission and residual embolic fragments or stenosis at the thrombectomy site are at high risk for reocclusion, which may be prevented or corrected after carefully re-evaluating the past angiographic run. (*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021685.)

Key Words: angiography ■ ischemia ■ reperfusion ■ stroke ■ thrombectomy

Landmark randomized trials established mechanical endovascular thrombectomy as the most effective reperfusion therapy for patients with acute ischemic stroke presenting with large vessel occlusions.^{1–7} However, despite successful recanalization, reocclusion of the target vessel occurs in 3% to 9% of patients.^{8–10} Because rapid, sustained, and complete reperfusion is the most important modifiable prognostic factor for a favorable clinical outcome,¹¹ we aimed to identify the prevalence and predictors of early reocclusion within 48 hours after an initially successful endovascular thrombectomy

within a prospective cohort of consecutive patients with acute ischemic stroke from a single center.

Methods

Study Cohort

This article adheres to the American Heart Association Journals' implementation of the Transparency and Openness Promotion Guidelines (available online at <http://www.ahajournals.org/content/TOP-guidelines>). The data that support the findings of this study are available from the corresponding author on reasonable request. All

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patients with acute ischemic stroke (n=972) treated by mechanical thrombectomy between January 2010 and July 2017 with a Solitaire stent retriever (Medtronic, Dublin, Ireland)±distal aspiration catheters (SOFIA, Microvention, Tustin, CA; Catalyst, Stryker, Cork, Ireland; ACE, Penumbra, Alameda, CA) were reviewed. The final study population consisted of patients successfully treated with thrombectomy (n=809), defined as modified Thrombolysis in Cerebral Infarction (mTICI) score 2b or 3,¹² with magnetic resonance angiography or computed tomographic angiography imaging available at follow-up within 48 hours (n=711; Figure 1 for study flow chart). The reviewed patient cohort was extracted from the prospective institutional Bernese Stroke Registry. Ethical committee approval for this retrospective analysis was obtained (Kantonale Ethikkommission für die Forschung Bern, Bern, Switzerland, amendment access number: 231/2014). The prospective registry database contains patient baseline characteristics, risk factors profile, time metrics, and clinical follow-up data, including a standardized 3-month clinical visit, which was available for 666 of 711 patients (93.7%).

Secondary Prevention and Postinterventional Medication

Deep vein prophylaxis and start of secondary prevention were performed according to institutional Standard Operating Procedures (see excerpt from the Standard Operating Procedure depicted in Data I in the [online-only Data Supplement](#)). In short, in case of bridging or additional administration of intra-arterial urokinase during the interventional procedure, prophylaxis of deep vein thrombosis using low molecular weight heparin was started after exclusion of cerebral hemorrhage on 24-hour follow-up imaging. After mechanical thrombectomy without intravenous thrombolysis or intra-arterial urokinase, low molecular weight heparin was started immediately after the intervention. Type and initiation of secondary prevention (oral anticoagulants or antithrombotic treatment) depended on the presumed pathogenesis, treatment modality, and infarct size. In case of undetermined pathogenesis and mechanical thrombectomy only (without intravenous thrombolysis or intra-arterial urokinase), a loading dose of 250 mg aspirin was administered directly after the procedure followed by 100 mg aspirin or 75 mg clopidogrel daily. After bridging or additional administration of intra-arterial urokinase, antithrombotic treatment was started only if 24-hour follow-up ruled out intracerebral hemorrhage. In case of imminent space-occupying brain edema and if a potential hemispherectomy was considered, administration of platelets was withheld. In cases of nonvalvular atrial fibrillation, direct oral anticoagulant treatment was started after 3 to 12 days depending on the size of the infarct (see Data I in the [online-only Data Supplement](#) for details). No intermediate antiplatelet therapy until the start of the direct oral anticoagulant treatment was administered. In cases of highly embolic source of embolism (eg, mechanical heart valve), immediate initiation of a therapeutic heparinization was

considered. When large artery-to-artery embolism was considered, the presumed cause and the degree of cervical stenosis were >50%, and acute stenting or CEA was routinely performed. In case of acute stenting, a loading dose of 250 to 500 mg aspirin (during the procedure) was administered followed by daily 100 mg aspirin and 75 mg clopidogrel. In cases of CEA, 100 mg aspirin was administered daily. Transient therapeutic heparinization with low molecular weight heparin was used for transient bridging until CEA in some cases. In cases of <50% cervical stenosis, an individual decision was made. In addition, all cases with presumed large artery-to-artery embolism were treated with a high-dose statin (eg, 80 mg atorvastatin) from the index day on. For other pathogeneses and special cases, please see Data I in the [online-only Data Supplement](#) for further details on the type and start of secondary prevention.

Image Analysis

The following variables were evaluated: occlusion site (intracranial ICA/carotid-T/L versus M1 versus M2/M3/ACA versus posterior circulation), tandem occlusion (defined as cervical occlusion/90% stenosis and intracranial occlusion), number of clot retrieval maneuvers, use of balloon-guide catheter and distal access aspiration catheter, intra- or extracranial stenting, and final mTICI score. Iatrogenic emboli in previously unaffected territories were not considered as reocclusions. The final mTICI score and complete set of angiographic images were operator reported and reviewed by a second independent neuroradiologist (P.J.M.) not directly involved in the intervention. In an occlusion, site-matched analysis (5:1 random matching of the control group, see Statistical Analysis section), the presence of residual nonoccluding thrombus fragments or vessel wall irregularities/stenosis on final angiographic control runs (excluding obvious material-induced vasospasm) was further analyzed by 2 independent observers (P.J.M. and J.K.; Figures I and II in the [online-only Data Supplement](#) for exemplary cases).

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Statistical Analysis

Univariate comparison was performed by Fischer exact test for categorical variables. Mann-Whitney *U* test was used for non-normally distributed continuous and ordinal scaled variables and Welsch *t* test for normally distributed variables. Variables with $P < 0.2$ in univariate comparison entered a backward likelihood ratio multivariable binary logistic regression model. Output of the logistic regression model is displayed as adjusted odds ratios (aOR) and corresponding 95% CI. In a second step, analyses were rerun in an occlusion site-matched cohort (5:1 univariate random matching) implementing the variable nonoccluding thrombus fragments or vessel wall irregularities into the model. Incremental value of this imaging variable on accuracy of the model was evaluated using receiver operator characteristics analysis with area under the curve (AUC) calculation and

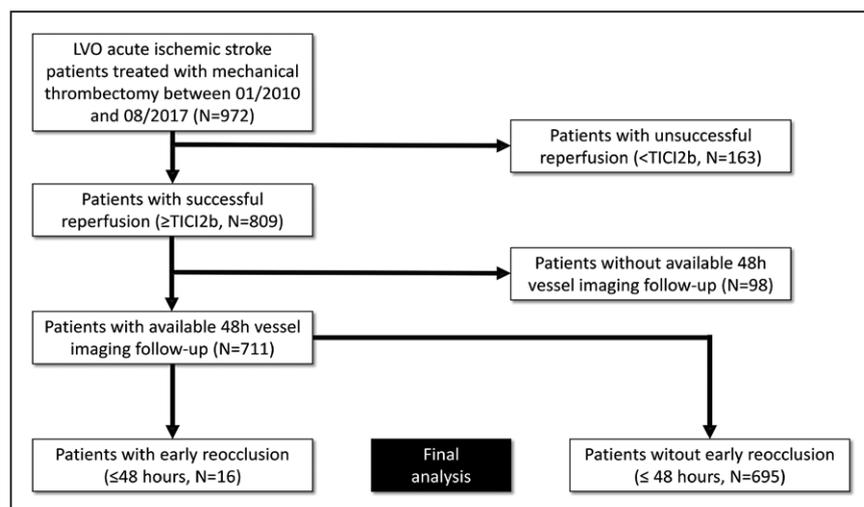


Figure 1. Study flow chart. Study flow chart of included patients and respective exclusion criteria. LVO indicates large vessel occlusions; and TICI, Thrombolysis in Cerebral Infarction.

AUC comparison according to Delong.² Furthermore, integrated discrimination improvement and net reclassification improvement³ after versus before implementation of the variable nonoccluding thrombus fragments or vessel wall irregularities were evaluated. To determine the clinical impact of early reocclusion, early reocclusion was entered as a variable in a multivariable binary logistic regression term together with potential clinical confounders, including age, sex, National Institutes of Health Stroke Scale on admission, independence prior the stroke, TIC13 versus TIC12b, bridging IVT, time to admission, initial ASPECTS, and site of occlusion. Receiver operating characteristic analysis and AUC comparison were performed in R (R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria) using the R package pROC.⁴ Calculation of integrated discrimination improvement and net reclassification improvement was performed with the R package Hmisc. All other statistical analyses were performed with SPSS version 25 (IBM, Armonk, NY).

Results

Prevalence of Early Reocclusion

Early reocclusion was observed in 16 of 711 patients in whom an mTICI 2b/3 result had been obtained on the past angiographic run (2.3%; 95% CI: 1.1%–3.3%). A detailed description of the 16 patients with early reocclusion can be found in Table I in the [online-only Data Supplement](#). Median time interval to the diagnosis of early reocclusion was 20 hours after imaging on admission (interquartile range, 15–24 hours). Most reocclusions were associated with a lack of clinical improvement (n=3) after intervention or secondary worsening as evidenced by a drop in National Institutes of Health Stroke Scale (n=11; Table I in the [online-only Data Supplement](#)). Silent or asymptomatic occlusions were observed in 2 patients with excellent collaterals. Repeated thrombectomy for early reocclusion was performed in 3 of 16 patients (18.8%) only. Reasons for withholding repeated endovascular thrombectomy were extensive infarction in the reoccluded territory without any relevant residual perfusion mismatch (n=8), severe blood-brain barrier breakdown with early hemorrhagic transformation (n=1), a presumed benign course because of excellent collaterals (n=2), or further distal clot location within the same M2 segment (n=2).

Baseline Factors and Imaging Characteristics Associated With Early Reocclusion

A comparison of patients with and without reocclusion (n=16 and 695, respectively) is provided in Table 1. Patients with early reocclusion had significantly higher platelet counts on admission (265 versus 216 g/L; $P=0.001$), higher frequencies of stroke of undetermined (50.0% versus 39.0%), and other specified (31.3% versus 5.9%) pathogenesis in the TOAST classification ($P=0.002$) and M2/M3/A1 as the initial occlusion site (37.5% versus 10.1%; $P=0.020$). There were no differences in the rate of cervical artery dissection (6.6% versus 3.3%; $P=0.427$), tandem occlusion (6.3% versus 13.7%; $P=0.710$), or interventional characteristics, including use of a balloon-guiding catheter (68.6% versus 70.0%; $P>0.999$), distal aspiration catheter (50.0% versus 43.9%; $P=0.622$), number of passes or retrievals (median 1 versus 1; $P=0.462$), and frequency of extracranial stenting (6.3% versus 12.4%; $P=0.708$). In multivariable logistic regression analysis,

functional dependency before the stroke, site of occlusion, stroke pathogenesis, and admission platelet count were factors significantly associated with early reocclusion within 48 hours (Table 2). Univariate receiver operating characteristic analyses revealed an AUC of 0.734, 95% CI: 0.614 to 0.855 for platelet count with early reocclusion set as dependent variable (Figure III in the [online-only Data Supplement](#)). The best cutoff between early and no reocclusion was a platelet count of ≥ 220 g/L (Youden index), yielding a sensitivity of 87.5% and specificity of 46.9%.

Thirteen of 16 (81.3%) patients with reocclusion had angiographic irregularities on the past angiographic run, which were not reported or misinterpreted by the neurointerventionalist as material-induced vasospasm. In an occlusion site-matched cohort (n=96; 16 reocclusion patients, 80 occlusion site-matched nonreocclusion patients), univariate comparison revealed comparable differences (see Table 3). Admission platelet count (aOR for every g/L increase, 1.01; 95% CI: 1.00–1.03; $P=0.042$), residual thrombus/vessel wall irregularities after thrombectomy (aOR, 58.94; 95% CI: 4.94–703.16; $P=0.001$), and other determined pathogenesis according to the TOAST classification (aOR, 43.10; 95% CI: 1.99–935.00; $P=0.017$) were the only significant predictors of early reocclusion in a multivariable logistic regression analysis in this subgroup (Table 4). The receiver operating characteristic curve of the predicted probability output of the logistic regression model, including factors in Table 4, is shown in Figure 2A (AUC, 0.955; 95% CI: 0.916–0.994). This AUC was significantly higher than the prediction derived from the same logistic regression model without the term residual thrombus/vessel wall irregularities after thrombectomy (Figure 2B; new AUC: 0.854; 95% CI: 0.757–0.952, DeLong test for testing the difference of AUC not equal to 0: $P=0.028$), suggesting an important added value of this imaging variable. Correspondingly, the integrated discrimination improvement was 0.27 (95% CI: 0.14–0.40; $P<0.001$) with a net reclassification improvement of 1.27 (95% CI: 0.85–1.59; $P<0.001$), suggesting improvement in a corrected classification.

Because 98 of 809 patients (12%) were excluded from the study because of absent computed tomographic angiography or magnetic resonance angiography on early follow-up imaging, despite our institutional policy, we conducted a sensitivity analysis to compare their baseline characteristics and outcome variables with the included patients (see Table II in the [online-only Data Supplement](#) for details). On average, patients without arterial imaging were 4 years older, had 4× more sICH, twice the mortality rate, and twice as less good functional outcomes at 90 days.

Clinical Outcome

Patients with early reocclusion compared with those with sustained recanalization had a worse clinical outcome at day 90 (modified Rankin Scale ≤ 2 , 20.0% versus 51.3%; $P=0.019$) although mortality did not differ (20.0% versus 19.0%; $P>0.999$). The 3 patients with early reocclusion in whom thrombectomy was repeated showed no clinical improvement. Early reocclusion was an independent predictive factor related to lower rates of functional independence

Table 1. Baseline Characteristics

	All Patients With Available 48-Hour Follow-Up Intracranial Vessel Imaging (n=711)	Early (<48 Hours) Reocclusion (n=16)	No Early Reocclusion (n=695)	P Value
Age	70.2±14.9	73.3±13.0	70.2±15.0	0.354
Sex, female	49.1% (349/711)	68.8% (11/16)	48.6% (338/695)	0.133
Preadmission independence (mRS >2)	92.0% (652/709)	81.3% (13/16)	92.2% (639/693)	0.131
Secondary transferal	30.7% (218/710)	31.3% (5/16)	30.7% (213/694)	>0.999
Admission NIHSS	15 (9–20; n=709)	10 (5–19; n=16)	15 (10–20; n=693)	0.070
Risk factors				
Hypertension	70.4% (499/709)	81.3% (13/16)	70.1% (486/693)	0.417
Hyperlipidemia	59.6% (412/706)	56.3% (9/16)	59.7% (412/690)	0.801
Smoking	29.3% (206/704)	31.3% (5/16)	29.2% (201/688)	0.789
Previous CVE	12.3% (87/709)	6.3% (1/16)	12.4% (86/693)	0.708
CAD	20.3% (143/705)	0% (0/15)	20.7% (143/690)	0.050
Medication				
Antiplatelet (dual, aspirin, none)				0.845
Dual	2.0% (14/708)	0% (0/16)	2.0% (14/692)	
Aspirin	30.6% (217/708)	25.0% (4/16)	30.8% (213/692)	
None	67.4% (477/708)	75.0% (12/16)	67.2% (465/692)	
Anticoagulation				0.489
OAC	9.0% (64/708)	0% (0/16)	9.2% (64/692)	
NOAC	4.7% (33/708)	0% (0/16)	4.8% (33/692)	
None	86.3% (611/708)	100% (16/16)	86.0% (595/692)	
Statin	26.9% (190/706)	25.0% (4/16)	27.0% (186/690)	>0.999
Systolic blood pressure, mm Hg	153 (133–171; n=672)	162 (130–182; n=16)	152 (133–171; n=656)	0.369
Diastolic blood pressure, mm Hg	81 (71–94; n=673)	79 (71–105; n=16)	81 (71–94; n=657)	0.952
Admission glucose, mmol/L	6.7 (5.8–7.9; n=685)	6.8 (5.7–8.4; n=15)	6.7 (5.8–7.9; n=670)	0.850
Admission INR	1.0 (1.0–1.1; n=702)	1.0 (1.0–1.1; n=16)	1.0 (1.0–1.1; n=686)	0.216
Admission platelet count	218 (176–260; n=705)	265 (227–392; n=16)	216 (175–259; n=689)	0.001*
TOAST				0.002*
Large-artery atherosclerosis	10.7% (76/711)	0% (0)	10.9% (76/695)	
Cardioembolic	43.6% (310/711)	18.8% (3/16)	44.2% (307/695)	
Other pathogenesis	6.5% (46/711)	31.3% (5/16)	5.9% (41/695)	
Unknown pathogenesis	39.2% (279/711)	50.0% (8/16)	39.0% (271/695)	
Symptom-onset to admission (witnessed symptom onset only, min)	102 (65–180; n=464)	106 (77–163; n=9)	101 (65–180; n=455)	0.881
Symptom-onset to admission (including last-seen-well, min)	142 (75–249; n=684)	162 (101–307; n=15)	141 (75–248; n=669)	0.370
Initial modality for imaging diagnosis				0.804
CT	47.8% (339/709)	43.8% (7/16)	47.9% (332/693)	
MRI	52.2% (370/709)	56.3% (9/16)	52.1% (361/693)	
Intravenous tPA bridging	42.3% (301/711)	31.3% (5/16)	42.6% (296/695)	0.448
Intracranial occlusion site				0.020†
Intracranial ICA or carotid T	23.1% (164/711)	12.5% (2/16)	23.3% (162/695)	

(Continued)

Table 1. Continued

	All Patients With Available 48-Hour Follow-Up Intracranial Vessel Imaging (n=711)	Early (<48 Hours) Reocclusion (n=16)	No Early Reocclusion (n=695)	P Value
M1	57.5% (409/711)	43.8% (7/16)	57.8% (402/695)	
M2/M3/A1	10.7% (76/711)	37.5% (6/16)	10.1% (70/695)	
Posterior circulation	8.7% (62/711)	6.3% (1/16)	8.8% (61/695)	
Tandem occlusion (cervical occlusion or >90% stenosis)	13.5% (96/710)	6.3% (1/16)	13.7% (95/694)	0.710
Underlying cervical dissection (on admission)	3.4% (24/709)	6.3% (1/16)	3.3% (23/693)	0.427
Intervention				
General anesthesia	68.5% (486/710)	56.3% (9/16)	68.7% (477/694)	0.288
No. of maneuvers	1 (1–2)	1 (1–4)	1 (1–2)	0.462
Time from groin to TICI2b (min)	38 (27–59)	43 (29–59)	38 (27–59)	0.423
BGC	70.0% (497/710)	68.8% (11/16)	70.0% (486/694)	>0.999
Distal aspiration catheter	44.0% (313/711)	50.0% (8/16)	43.9% (305/695)	0.622
Intracranial stenting	2.8% (20/709)	0% (0/16)	2.9% (20/693)	>0.999
Extracranial stenting	12.3% (87/710)	6.3% (1/16)	12.4% (86/694)	0.708
TICI3	56.5% (402/711)	56.3% (9/16)	56.5% (393/695)	>0.999

Dual antiplatelet medication refers to aspirin+another antiplatelet drug (clopidogrel, prasugrel, etc). BGC indicates balloon-guiding catheter; CAD, coronary artery disease; CT, computed tomography; CVE, cerebrovascular event; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, novel oral anticoagulant (rivaroxaban, apixaban, etc); OAC, oral anticoagulant (coumarins); TICI, Thrombolysis in Cerebral Infarction; and tPA, tissue-type plasminogen activator.

*P<0.01, †P<0.05.

at day 90 after adjusting for age, sex, admission National Institutes of Health Stroke Scale, prestroke independence, TICI3 versus TICI2b, bridging IVT, time to admission, admission ASPECTS, and site of occlusion (aOR, 0.13; 95% CI: 0.03–0.57; P=0.007).

Discussion

In our cohort of 711 patients with available computed tomographic angiography or magnetic resonance angiography follow-up imaging, we identified 4 factors associated with early reocclusion despite an initial mTICI2b/3 result: elevated platelet counts at admission >220 g/L, missed residual thrombus or stenosis on the past angiographic run after thrombectomy, M2 occlusion as the initial occlusion site, and stroke of undetermined cause. Reports on early reocclusion in the era of modern endovascular treatment are scarce. According to our results, unexpected early reocclusion within 48 hours after successful mechanical thrombectomy occurs in 2.3% of cases, which compares favorably to the 3% to 4% reocclusion rate within 24 hours after successful intravenous or intra-arterial thrombolysis.^{13–15} In a post hoc analysis of the REVASCAT study assessing 24-hour revascularization rates after stent retriever therapy,⁸ the authors observed 2 early reocclusions of 63 mTICI2b/3 patients (3.1%) for all occlusion sites, except M2. In our cohort, however, M2 location was a statistically significant predictor of early reocclusion in univariate analysis. Given a 10-fold larger sample size in our study, which appears to be the largest so far, we think that limited statistical power in the REVASCAT subgroup analysis may explain this difference.

Residual atherosclerotic, stenosis of a pre-existing lesion at the target site can lead to immediate or delayed occlusion in 25% of cases.¹⁶ Only one of our patients presented with early reocclusion because of an underlying atherosclerotic stenosis that had been missed, underlying the importance of repeating an angiographic run after corrective measures to



Table 2. Logistic Regression With P<0.2 in Univariate Comparison

Variable	Adjusted OR	95% CI	P Value
TOAST (indicator: cardioembolic)			0.007*
Large-artery atherosclerosis	Did not converge		
Unknown pathogenesis	7.19	1.10–47.05	0.039†
Other pathogenesis	36.50	4.47–298.1	0.001*
Admission platelets	1.01	1.01–1.02	<0.001*
Sex	Variable excluded from model		
Prestroke independence	0.14	0.03–0.67	0.014†
Risk factor CAD	Did not converge		
Admission NIHSS	Variable excluded from model		
Site of occlusion (indicator: posterior circulation)			0.007*
Intracranial ICA or carotid T	0.67	0.05–8.93	0.764
M1	1.20	0.13–11.63	0.873
M2/M3/A1	9.35	0.91–96.10	0.060

n=698; Nagelkerkes R²: 0.386. CAD indicates coronary artery disease; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*P<0.01, †P<0.05.

Table 3. Baseline Characteristics (Matched Cohort)

	Early (<48 Hours) Reocclusion (n=16)	No Early Reocclusion (1:5 Matching, n=80)	P Value
Age	73.3±13.0	72.1±14.8	0.743
Sex, female	68.8% (11/16)	42.5% (34/80)	0.098
Preadmission independence (mRS >2)	81.3% (13/16)	92.5% (74/80)	0.169
Secondary transferal	31.3% (5/16)	36.3% (29/80)	0.782
Admission NIHSS	10 (5–19; n=16)	14 (8–18; n=80)	0.251
Risk factors			
Hypertension	81.3% (13/16)	62.0% (49/80)	0.163
Hyperlipidemia	56.3% (9/16)	64.6% (51/79)	0.577
Smoking	31.3% (5/16)	26.6% (21/79)	0.761
Previous CVE	6.3% (1/16)	8.8% (7/80)	>0.999
CAD	0% (0/15)	18.8% (15/80)	0.117
Medication			
Antiplatelet (dual, aspirin, none)			0.769
Dual	0% (0/16)	0% (0/80)	
Aspirin	25.0% (4/16)	32.5% (26/80)	
None	75.0% (12/16)	67.5% (54/80)	
Anticoagulation			0.283
OAC	0% (0/16)	15.0% (12/80)	
NOAC	0% (0/16)	2.5% (2/80)	
None	100% (16/16)	82.5% (66/80)	
Statin	25.0% (4/16)	20.3% (16/79)	0.738
Systolic blood pressure, mm Hg	162 (130–182; n=16)	157 (135–171; n=77)	0.558
Diastolic blood pressure, mm Hg	79 (71–105; n=16)	79 (69–90; n=77)	0.562
Admission glucose, mmol/L	6.8 (5.7–8.4; n=15)	6.5 (5.9–7.6; n=77)	0.711
Admission INR	1.0 (1.0–1.1; n=16)	1.0 (1.0–1.1; n=77)	0.177
Admission Platelet count	265 (227–392; n=16)	201 (168–257; n=79)	0.001*
TOAST			0.029†
Large-artery atherosclerosis	0% (0)	8.8% (7/80)	
Cardioembolic	18.8% (3/16)	43.8% (35/80)	
Other pathogenesis	31.3% (5/16)	8.8% (7/80)	
Unknown pathogenesis	50.0% (8/16)	38.8% (31/80)	
Symptom-onset to admission (witnessed symptom onset only, min)	106 (77–163; n=9)	108 (67–200; n=48)	0.896
Symptom-onset to admission (including last-seen-well, min)	162 (101–307; n=15)	152 (74–249)	0.392
Initial modality for imaging diagnosis			0.788
CT	43.8% (7/16)	48.8% (39/80)	
MRI	56.3% (9/16)	51.2% (41/80)	
Intravenous tPA bridging	31.3% (5/16)	40.0% (32/80)	0.584
Intracranial occlusion site			Matched
Intracranial ICA or carotid T	12.5% (2/16)	12.5% (10/80)	
M1	43.8% (7/16)	43.8% (35/80)	
M2/M3/A1	37.5% (6/16)	37.5% (30/80)	
Posterior circulation	6.3% (1/16)	6.3% (5/80)	

(Continued)

Table 3. Continued

	Early (<48 Hours) Reocclusion (n=16)	No Early Reocclusion (1:5 Matching, n=80)	P Value
Tandem occlusion (cervical occlusion or >90% stenosis)	6.3% (1/16)	15.0% (12/80)	0.688
Underlying cervical dissection (on admission)	6.3% (1/16)	2.5% (2/80)	0.425
Intervention			
General anesthesia	56.3% (9/16)	66.3% (53/85)	0.568
No. of maneuvers	1 (1–4)	1 (1–2)	0.265
Time from groin to TICl2b, min	43 (29–59)	36 (26–55)	0.284
BGC	68.8% (11/16)	63.3% (50/80)	0.780
Distal aspiration catheter	50.0% (8/16)	48.8% (39/80)	>0.999
Intracranial stenting	0% (0/16)	0% (0/80)	...
Extracranial stenting	6.3% (1/16)	13.8% (11/80)	0.684
TICl3	56.3% (9/16)	56.3% (45/80)	>0.999
Residual thrombus not impeding distal flow	81.3% (13/16)	15.0% (12/80)	<0.001*

Dual antiplatelet medication refers to aspirin+another antiplatelet drug (clopidogrel, prasugrel, etc). BGC indicates balloon-guiding catheter; CAD, coronary artery disease; CT, computed tomography; CVE, cerebrovascular event; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, novel oral anticoagulant (rivaroxaban, apixaban, etc); OAC, oral anticoagulant (coumarins); TICl, Thrombolysis in Cerebral Infarction; and tPA, tissue-type plasminogen activator.

*P<0.01, †P<0.05.

differentiating atherosclerotic changes from material-induced spasm. The majority of reocclusions occurred in patients with residual embolic fragments at the thrombectomy site that had not been recognized on the final control run, either because the distal flow was not hindered or because the image settings were not optimal (overlapping branches, contrast too dark, large field of view). These residual fragments may have acted as kernels to which the higher concentration of circulating platelets may have adhered to, explaining why a new occlusive thrombus may have formed in the same location.

High preprocedural mean platelet volume has been shown to promote restenosis after carotid stenting, which may possibly be hindered by intensifying antiplatelet therapy.¹⁷ Similarly, patients with elevated platelet counts on admission undergoing thrombectomy might benefit from more aggressive antiaggregation therapy because it does not necessarily increase the risk of intracranial hemorrhage or impact clinical outcome negatively in those who benefit from carotid stenting despite having received intravenous recombinant tissue-type plasminogen activator.¹⁸ Aspirin may not be sufficient, however, since 4 of 16 (25%) with early reocclusion were under such therapy at the time of admission in our cohort. However, although sustained reperfusion is of utmost importance, an overly aggressive antiplatelet might be counterproductive by theoretically increasing the risk of intracranial hemorrhage. Future studies are needed to answer this question.

To avoid missing residual debris or an underlying plaque that could lead to early reocclusion, careful reinspection of the original occlusion site on the past angiographic run is advised. Adjustment of contrast/windowing levels, pixel shift, and zoom in the region of interest, followed by another run in different projections or 10 minutes later may be necessary, especially after tentative corrective measures have been applied, such as spasmolytic therapy, intensified antiplatelet medication, or PTA/stenting. Prompt identification of early

reocclusion may lead to timely repeated thrombectomy and thus improve outcome.¹⁹

The rates of early (24–48 hours) and late (90 days) good functional outcome and the rate of repeated thrombectomy were low in our series, stressing the importance of identifying reocclusion as early as possible to be able to offer a timely rescue therapy and improve clinical outcome.¹¹ Indeed, effective repeated thrombectomy for recurrent large vessel occlusions has been reported in 2% of cases in a registry of 697 patients.¹⁹ In this study of comparable size, the overall reocclusion rate was similar to ours but lower in the 24- to 48-hour range, which may relate to the low number of M2 occlusions in their collective (n=4). Moreover, the dominant

Table 4. Logistic Regression With P<0.2 in Univariate Comparison (1:5 Occlusion Site Matching)

Variable	Adjusted OR	95% CI	P Value
TOAST (indicator: cardioembolic)			0.121
Large-artery atherosclerosis	Did not converge		
Unknown pathogenesis	4.16	0.41–42.28	0.228
Other pathogenesis	43.10	1.99–935.00	0.017*
Admission platelets	1.01	1.00–1.03	0.042*
Sex	Variable excluded from model		
Prestroke independence	0.05	0.00–1.01	0.055
Risk factor CAD	Variable excluded from model		
Admission INR	Variable excluded from model		
Risk factor arterial hypertension	Variable excluded from model		
Residual thrombus, vessel wall irregularities on control runs	58.94	4.94–703.16	0.001†

n=91; Nagelkerkes R²: 0.676. CAD indicates coronary artery disease; and OR, odds ratio.

*P<0.05, †P<0.01.

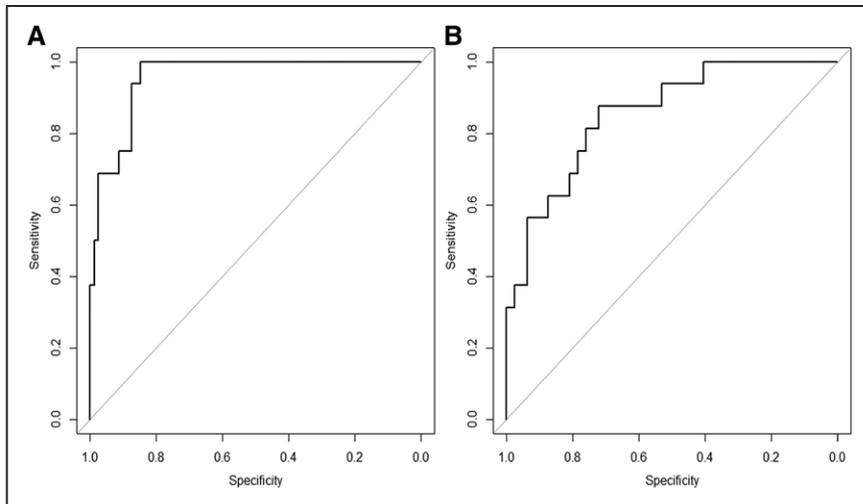


Figure 2. Comparison of area under the curve (AUC) for early reocclusion with and without implementation of imaging findings on final control runs. **A**, AUC for predicted probabilities derived from a logistic regression model including all variables denoted in Table 4; **(B)**, AUC for predicted probabilities derived from a logistic regression model with all variables from Table 4 except residual thrombus, vessel wall irregularities on control runs

underlying pathogenesis for reocclusion was cardioembolic stroke, which is probably more predictive of late than early reocclusion (median time between first and last procedures in their study: 18 days).

Despite the risk of vessel wall damage caused by material-induced endothelial injury in animal models,^{20–22} the number of clot retrieval attempts with stent retrievers or the use of distal aspiration catheters was not associated with an increased risk of early reocclusion. This is in line with an immunohistochemical analysis of retrieved thrombi in humans.²³

This study had limitations. Despite our best efforts, inherent bias because of the retrospective and monocentric study design study was inevitable. Some successfully thrombectomized patients had no arterial imaging on follow-up despite our institutional policy and were not included in the present analysis. A sensitivity analysis comparing the excluded and included patients revealed that those without arterial imaging on early follow-up were 4 years older on average, had 4× more sICH, twice the mortality rate, and twice as less good functional outcomes at 90 days (Table II in the [online-only Data Supplement](#)). Therefore, although the prevalence of reocclusion might be higher than what we report, we presume that this exclusion bias probably had little, if any, influence on our results. Another limitation worth mentioning is that there was no blinded core lab evaluation of the final angiographic results. Last, despite a 5:1 random matched occlusion site cohort, not all interventional DSA images of the complete collective of mTICI 2b/3 patients were reviewed, which may have disclosed different or unexpected observations compared with the sampled population.

Conclusions

Early reocclusion within 48 hours after successful mechanical thrombectomy is rare but associated with a poor clinical outcome. In our cohort, predictors were higher platelets on admission, prestroke functional dependency, missed residual thrombotic fragments or stenosis at the primary occlusion site, and stroke of undetermined or other specified pathogenesis. Swift identification of these risk factors may allow prompt corrective measures towards sustained recanalization, including immediate repeated thrombectomy, which may

improve outcome. The number of stent retriever passes, use of distal aspiration catheters, or other interventional parameters had no influence.

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References

- Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
- Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al; THRACE Investigators. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol*. 2016;15:1138–1147. doi: 10.1016/S1474-4422(16)30177-6
- Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780
- Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587

5. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792
6. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061
7. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905
8. Millán M, Remollo S, Quesada H, Renú A, Tomasello A, Minhas P, et al; REVASCAT Trial Investigators. Vessel patency at 24 hours and its relationship with clinical outcomes and infarct volume in REVASCAT Trial (Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset). *Stroke*. 2017;48:983–989. doi: 10.1161/STROKEAHA.116.015455
9. Qureshi AI, Hussein HM, Abdelmoula M, Georgiadis AL, Janjua N. Subacute recanalization and reocclusion in patients with acute ischemic stroke following endovascular treatment. *Neurocrit Care*. 2009;10:195–203. doi: 10.1007/s12028-008-9161-0
10. Enomoto Y, Yoshimura S, Egashira Y, Takagi T, Tsujimoto M, iwama T. Long-term magnetic resonance angiography follow-up for recanalized vessels after mechanical thrombectomy. *J Stroke Cerebrovasc Dis*. 2014;23:2834–2839. doi: 10.1016/j.jstrokecerebrovasdis.2014.07.011
11. Kaesmacher J, Dobrocky T, Heldner MR, Bellwald S, Mosimann PJ, Mordasini P, et al. Systematic review and meta-analysis on outcome differences among patients with tici2b versus tici3 reperfusion: success revisited [published online March 8, 2018]. *J Neurol Neurosurg Psychiatry*. 2018. doi: 10.1136/jnnp-2017-317602. <https://jnnp.bmj.com/content/early/2018/03/08/jnnp-2017-317602>.
12. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, et al; Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. 2013;44:2650–2663. doi: 10.1161/STROKEAHA.113.001972
13. von Kummer R, Holle R, Rosin L, Forsting M, Hacke W. Does arterial recanalization improve outcome in carotid territory stroke? *Stroke*. 1995;26:581–587.
14. Ribo M, Alvarez-Sabín J, Montaner J, Romero F, Delgado P, Rubiera M, et al. Temporal profile of recanalization after intravenous tissue plasminogen activator: selecting patients for rescue reperfusion techniques. *Stroke*. 2006;37:1000–1004. doi: 10.1161/01.STR.0000206443.96112.d9
15. Wunderlich MT, Goertler M, Postert T, Schmitt E, Seidel G, Gahn G, et al; Duplex Sonography in Acute Stroke (DIAS) Study Group; Competence Network Stroke. Recanalization after intravenous thrombolysis: does a recanalization time window exist? *Neurology*. 2007;68:1364–1368. doi: 10.1212/01.wnl.0000260604.26469.8e
16. Hwang YH, Kim YW, Kang DH, Kim YS, Liebeskind DS. Impact of target arterial residual stenosis on outcome after endovascular revascularization. *Stroke*. 2016;47:1850–1857. doi: 10.1161/STROKEAHA.116.013046
17. Dai Z, Gao J, Li S, Li R, Chen Z, Liang M, et al. Mean platelet volume as a predictor for restenosis after carotid angioplasty and stenting. *Stroke*. 2018;49:872–876. doi: 10.1161/STROKEAHA.117.019748
18. Broeg-Morvaj A, Mordasini P, Slezak A, Liesirova K, Meisterernst J, Schroth G, et al. Does antiplatelet therapy during bridging thrombolysis increase rates of intracerebral hemorrhage in stroke patients? *PLoS One*. 2017;12:e0170045. doi: 10.1371/journal.pone.0170045
19. Bouslama M, Haussen DC, Rebello LC, Grossberg JA, Frankel MR, Nogueira RG. Repeated mechanical thrombectomy in recurrent large vessel occlusion acute ischemic stroke. *Interv Neurol*. 2017;6:1–7. doi: 10.1159/000447754
20. Abraham P, Scott Pannell J, Santiago-Dieppa DR, Cheung V, Steinberg J, Wali A, et al. Vessel wall signal enhancement on 3-T MRI in acute stroke patients after stent retriever thrombectomy. *Neurosurg Focus*. 2017;42:E20. doi: 10.3171/2017.1.FOCUS16492
21. Peschillo S, Diana F, Berge J, Missori P. A comparison of acute vascular damage caused by ADAPT versus a stent retriever device after thrombectomy in acute ischemic stroke: a histological and ultrastructural study in an animal model. *J Neurointerv Surg*. 2017;9:743–749. doi: 10.1136/neurintsurg-2016-012533
22. Gory B, Bresson D, Kessler I, Perrin ML, Guillaudeau A, Durand K, et al. Histopathologic evaluation of arterial wall response to 5 neurovascular mechanical thrombectomy devices in a swine model. *AJNR Am J Neuroradiol*. 2013;34:2192–2198. doi: 10.3174/ajnr.A3531
23. Singh P, Doostkam S, Reinhard M, Ivanovas V, Taschner CA. Immunohistochemical analysis of thrombi retrieved during treatment of acute ischemic stroke: does stent-retriever cause intimal damage? *Stroke*. 2013;44:1720–1722. doi: 10.1161/STROKEAHA.113.000964