Rates and Quality of Preinterventional Reperfusion in Patients With Direct Access to Endovascular Treatment

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Background and Purpose—Preinterventional reperfusion before endovascular treatment (ET) is a benefit of bridging with intravenous tPA (tissue-type plasminogen activator). However, detailed data on reperfusion quality and rates of obviating ET in a cohort of patients with immediate access to ET is lacking. Purpose of this analysis was to evaluate prevalence and quality of preinterventional reperfusion in mothership patients.

Methods—All mothership patients (n=627) from a prospective registry subjected to angiography with an intention to perform ET were reviewed. Preinterventional change of occlusion site (COS) was categorized into COS with Thrombolysis in Cerebral Infarction (TICI) 0/1, COS with TICI ≥2a, COS with TICI ≥2b, and COS with perfusion worsening. Predictors and clinical relevance were evaluated using multivariable logistic regression and results are displayed as adjusted odds ratios (aOR) and corresponding 95% confidence intervals (95% CI).

Results—Prevalence of COS in all patients was 10.7% (95% CI, 8.3%–13.1%), subdividing into 2.7% COS with TICI 0/1, 6.2% COS with ≥TICI 2a (including 2.9% with TICI ≥2b), and 1.8% COS with perfusion worsening. Factors related to COS with ≥TICI 2a were intravenous tPA (aOR, 11.98; 95% CI, 4.5–31.6), cardiogenic thrombus origin (aOR, 2.3; 95% CI, 1.1–4.6), and thrombus length (aOR per 1 mm increase 0.926; 95% CI, 0.87–0.99). Additional ET was performed despite COS with ≥TICI 2a in 51.3%. COS with ≥TICI 2a showed a tendency for favorable outcomes (modified Rankin Scale, ≤2; aOR, 2.65; 95% CI, 0.98–7.17). Rates of COS with ≥TICI 2a were particularly low in internal carotid artery and proximal M1 occlusions (2.2%; 95% CI, 0.9%–5%), where intravenous tPA was associated with perfusion worsening (aOR, 4.33; 95% CI, 1.12–16.80).

Conclusions—Prevalence of preinterventional reperfusion is non-negligible in patients with direct access to ET and is clearly favored by intravenous tPA treatment. However, it is often incomplete and often requires additional ET. Preinterventional reperfusion of internal carotid artery and proximal M1 occlusions is rare and usually of low quality, where intravenous tPA may also promote perfusion worsening. **(*Stroke*. 2018;49:1924-1932. DOI: 10.1161/STROKEAHA.118.021579.)**

Key Words: angiography ■ cerebral infarction ■ prevalence ■ reperfusion ■ thrombectomy ■ tissue-type plasminogen activator

Whether preinterventional intravenous tPA (tissue-type plasminogen activator) in large vessel occlusion strokes is of additional benefit has become a matter of debate.[1–9] Because tPA favors recanalization in large vessel occlusions,[10] preinterventional reperfusion obviating the need for thrombectomy is one important conceivable benefit of the bridging approach.[11]

According to a recently published meta-analysis, preinterventional reperfusion occurs in about every tenth patient with an intention to bridge.[11] However, heterogeneity was substantial, given the lack of a precise definition of recanalization, uneven intravenous tPA to thrombectomy metrics (including drip-and-ship and directly admitted patients), and different occlusion patterns.[11] Because of its study-level design, more detailed and stratified analyses and comprehensive comparisons with patients not treated with intravenous tPA were not possible.[11] The latter is of interest because some studies found no difference in the rates of preinterventional reperfusion in patients treated with intravenous tPA compared with those without.[12,13]

Because reperfusion of large vessel occlusion after intravenous tPA was shown to be time-dependent,[10] reperfusion may not occur early enough, that is, before the start of thrombectomy, and therefore in patients with direct access

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to endovascular treatment (ET), the prevalence, and extent of preinterventional reperfusion associated with intravenous tPA deserves further evaluation. The aim of this analysis was to assess the prevalence and quality of ultraearly preinterventional reperfusion in a predefined cohort of patients directly admitted to a comprehensive stroke center with immediate access to ET. Furthermore, a comprehensive analysis of factors associated with its occurrence was performed.

Methods

Study Population

For this project, the prospective Bernese Stroke registry was assessed from January, 2012 to June, 2017. All patients who were directly admitted to our tertiary care comprehensive stroke center and subjected to angiography with an intention to perform endovascular stroke treatment (either stent retriever–based thrombectomy or intraarterial [IA] thrombolysis with urokinase or both) were assessed (n=737). Importantly, we also included patients in whom no endovascular intervention was performed after diagnostic angiography. Exclusion criteria were (1) missing images/low image quality, (2) false-positive diagnosis of a vascular occlusion (stenosis), (3) iatrogenic occlusions which occurred during endovascular procedures, and (4) multifocal thrombi. Multilocular thrombi were excluded because the second occlusion usually is located in the distal vascular architecture and is usually not considered as a target for endovascular interventions. The final study population consisted of 627 patients. The study flow chart is depicted in Figure I in the online-only Data Supplement. The registry was approved by the local ethics committee (Kantonale Ethikkommission für die Forschung Bern, Bern, Switzerland, amendment access number: 231/2014). The raw patient-level data that support the findings of this study are available from the corresponding author on reasonable request and after clearance by the local ethics committee.

Preinterventional Diagnostic Work Up

In accordance with in-house standard operation procedure protocols, the initial acute diagnostic work-up consisted of either noncontrast computed tomography (CT) with CT angiography (CTA, including early arterial and late venous phase) and CT perfusion (N=201) or magnetic resonance imaging (MRI) with angiographic and perfusion sequences (N=373). In 34 cases, CT was followed by MRI. These were usually cases within the early observational period of this study and were based on the rational to evaluate the infarct core on diffusion-weighted imaging, potentially altering eligibility for mechanical thrombectomy. In 19 cases, incomplete MRI was followed by CT in case of severe moving artifacts. CT work-up consisted of 1 mm slice thickness noncontrast CT, 0.6 mm slice thickness bolus triggered CTA, 1 mm slice thickness late venous CTA with a 75-second delay after bolus administration, and CT perfusion with automatically processed perfusion maps using the software syngo.via (Siemens, Erlangen, Germany). The standard MRI protocol included axial fluid-attenuated inversion recovery, diffusion-weighted imaging, susceptibility-weighted imaging, intracranial time-of-flight magnetic resonance angiography (MRA), contrast-enhanced cervical and intracranial angiography MRA, gradient-echo dynamic susceptibility contrast perfusion±T1w postcontrast. MR studies were performed on a 3T or 1.5T scanner (Magnetom Avanto, Magnetom Verio and Magnetom Aera; Siemens, Erlangen, Germany). Perfusion maps were calculated using the Olea Sphere Software environment (Olea Sphere v2.3; Olea Medical, La ciotat, France). On MRIs, the exact proximal thrombus end was evaluated using the synopsis of information provided by a proximal susceptibility vessel sign, contrast fade on time-of-flight MRA or contrast-enhanced MRA, which have shown to reliably represent the proximal thrombus end when compared with digital subtraction angiography (DSA) in stable thrombi.[14] Perfusion delays on time-to-maximum of the tissue residue function or time-to-peak maps helped to aid the decision of occlusion site changes within, for example, the M1 main stem by evaluating perfusion deficits within the lenticulostriate artery territory and comparing this to preinterventional perfusion of the distinct lenticulostriate artery groups arising from the M1 on initial DSA runs.[15]

The occlusion sites on preinterventional imaging were compared with 3-vessel diagnostic DSA before the intervention in every case. Preinterventional diagnostic DSA was performed using a 5F catheter, with injection of a minimum of 3-vessel, including bilateral common carotid artery and one of the vertebral arteries. Along with the occlusion site grading, we assessed whether parenchymal perfusion status differed between initial diagnostic work-up and first diagnostic angiography runs. For this purpose, time-to-maximum and time-to-peak perfusion maps were reviewed and compared with the initial 3-vessel diagnostic angiography parenchymal phase. Perfusion worsening was usually observed in carotid-T occlusions, which allowed for collateral flow in the ipsilateral anterior cerebral artery territory via the anterior communicating artery on first diagnostic work-up. Then, however, on 3-vessel DSA, a new embolus within the ipsilateral A2 or distal anterior cerebral artery territory was observed, now impeding flow to the anterior cerebral artery territory and revealing a new parenchymal phase deficit clearly visible on 3-vessel DSA (compare section diagnostic angiography and ET). Distal thrombus ends were evaluated either directly on susceptibility-weighted imaging, postcontrast T1, or thin-slice noncontrast CT or indirectly as indicated by the flow-stagnation of collateralized vessels on late phase contrast-enhanced MRA or late phase CTA.[16] Thrombus length was calculated using a freehand curve function as measurements between the proximal and distal thrombus ends.

All preinterventional images together with pre- and postprocedural angiography runs were reevaluated by an experienced neuroradiologist with a focus on the following parameters: site of occlusion, thrombus length in millimeter, unifocal versus multifocal thrombi, and CT or MR perfusion maps (cerebral blood volume, cerebral blood flow, mean transit time, time-to-peak, and time-to-maximum) showing deficits/delays.

Site of occlusion was categorized into the following:

- Posterior circulation (basilar artery, vertebral artery, posterior cerebral artery)
- Intracranial internal carotid artery (ICA) and carotid-T
- Proximal M1, defined as involving the lenticulostriate arteries
- Distal M1, defined as middle cerebral artery mainstem not involving the lenticulostriate arteries until bifurcation or trifurcation knowing that the temporopolar artery may branch beforehand
- M2
- Other (including M3/M4, A1 and A2, or more distal)

Diagnostic Angiography and ET

The institutional eligibility criteria for ET and the acute management of thrombectomy candidates have been described before,[17] and the current standard operating procedures can be found online (http://www.neurologie.insel.ch/fileadmin/neurologie/neurologie_users/Unser_Angebot/Dokumente/english_Pocket_Guide_Stroke_Richtlinien.pdf). Once indication for endovascular management was confirmed, all patients underwent at least a diagnostic angiography, even in cases of substantial clinical improvement. Diagnostic angiography and ET were performed only by experienced interventional neuroradiologists. Before starting any intervention, angiographic runs of all vascular territories (typically contralateral common carotid artery, unilateral vertebral artery, and ipsilateral ICA) were evaluated. Any change of the proximal thrombus end between initial imaging and the first angiographic runs was rated as change of occlusion site (COS). Pre- and postinterventional TICI grading was performed by an independent neuroradiologist not involved in the treatment and blinded to clinical data. A grade of TICI 2b was defined as reperfusion of more than half of the initially occluded target territory according to the modified TICI scale.[18] The following subcategories were predefined: (1) COS with TICI 0/1, (2) COS with ≥TICI 2a, (3) COS with ≥TICI 2b, and (4) COS with perfusion worsening (ie, more perfusion deficit than on initial diagnostic work up). Any new proximal

Table 1. Factors Associated With TICI ≥2a on First Intracranial Angiography Series

	All (n=627)	No COS or COS With TICI <2a (n=588)	COS With TICI ≥2a (n=39)	*P* Value	aOR and 95% CI From Logistic Regression Model 1 (Backward-Likelihood Ratio)	aOR and 95% CI From Logistic Regression Model 2 (Backward-Likelihood Ratio)
Age, y	72±14	72±14	74±12	0.335		
Preadmission dependence (mRS >2)	10.6% (58/546)	10.5% (54/512)	11.8% (4/34)	1.000		
Sex, female	49.9% (313)	49.5% (291)	56.4% (22)	0.414		
Risk factors						
Atrial fibrillation	41.3% (259)	41.0% (241)	46.2% (18)	0.615		
Arterial hypertension	73.2% (459)	73.5% (432)	69.2% (27)	0.577		
Smoking	30.1% (184/611)	30.0% (172/573)	31.6% (12/38)	0.856		
Diabetes mellitus	21.1% (132)	21.9% (129)	7.7% (3)	0.040	0.31 (0.09–1.1)	0.31 (0.09–1.1)
Previous stroke	13.6% (85)	13.6% (80)	12.8% (5)	1.000		
Previous TIA	6.5% (41)	6.3% (37)	10.3% (4)	0.312		
Medication						
Aspirin	31.7% (199)	31.3% (184)	38.5% (15)	0.376		
OAC	9.1% (57)	9.2% (54)	7.7% (3)	1.000		
Statin	29.5% (185)	29.6% (174)	28.2% (11)	1.0000		
Systolic blood pressure, mm Hg	153 (133–172; n=609)	154 (133–172; n=571)	145 (126–162; n=38)	0.278		
Diastolic blood pressure, mm Hg	81 (70–95; n=607)	82 (70–96; n=569)	76 (66–92; n=38)	0.197		
Admission glucose, mmol/L	6.6 (5.8–8.1; n=582)	6.6 (5.8–8.1; n=547)	6.7 (5.8–7.9; n=35)	0.636		
Admission NIHSS	14 (9–19; n=624)	14 (9–19; n=585)	13 (8–17; n=39)	0.260		
TOAST				0.134		
Large-artery atherosclerosis	10.7% (67)	10.5% (62)	12.8% (5)			
Cardioembolic	43.7% (274)	42.7% (251)	59.0% (23)			
Other cause	6.5% (41)	6.6% (39)	5.1% (2)			
Unknown cause	39.1% (245)	40.1% (236)	23.1% (9)			
Cardioembolic vs all	43.7% (274)	42.7% (251)	59.0% (23)	0.065	2.3 (1.1–4.6)	2.3 (1.2–4.7)
Last seen well or symptom-onset to first imaging (min)	129 (91–224; n=558)	134 (92–231; n=519)	106 (83–133; n=39)	0.006	VE	VE
Initial modality for admission imaging				0.344		
CT	32.1% (201)	31.5% (185)	41.0% (16)			
MRI	59.5% (373)	59.7% (351)	56.4% (22)			
CT→MRI	5.4% (34)	5.8% (34)	0% (0)			
MRI→CT	3.0% (19)	3.1% (18)	2.6% (1)			
Intracranial occlusion				0.001		
Posterior circulation	9.3% (58)	9.0% (53)	12.8% (5)			
Intracranial ICA or carotid-T	21.7% (136)	23.0% (135)	2.6% (1)			
Proximal M1	21.4% (134)	21.9% (129)	12.8% (5)			
Distal M1	28.2% (177)	27.7% (163)	35.9% (14)			
M2	17.2% (108)	16.0% (94)	35.9% (14)			

(*Continued*)

Table 1. Continued

	All (n=627)	No COS or COS With TICI <2a (n=588)	COS With TICI ≥2a (n=39)	*P* Value	aOR and 95% CI From Logistic Regression Model 1 (Backward-Likelihood Ratio)	aOR and 95% CI From Logistic Regression Model 2 (Backward-Likelihood Ratio)
Other	2.2% (14)	2.4% (14)	0% (0)			
Intracranial ICA or carotid-T vs other	21.7% (136)	23.0% (135)	2.6% (1)	0.001	NI	0.12 (0.02–0.88)
Thrombus length, mm	10.4 (6.8–16.7; n=573)	10.5 (7–17.2; n=535)	8.6 (6.4–10.8; n=38)	0.023	0.926 (0.87–0.99)	NI
Tandem lesion	16.4% (103)	16.8% (99)	10.3% (4)	0.374		
Intavenous tPA	39.9% (250)	36.7% (216)	87.2% (34)	<0.001	11.98 (4.5–31.6)	11.47 (4.37–30.14)
Diagnosis to first intracranial DSA (min)	73 (58–90)	73 (58–89)	73 (55–93)	0.668		
Intravenous tPA to first intracranial series (min)	47 (33–66; n=250)	46 (33–66)	50 (37–69)	0.464		

aOR indicates adjusted odds ratio; 95% CI, 95% confidence interval; COS, change of occlusion site; CT, computed tomography; DSA, digital subtraction angiography; ICA, internal carotid artery; M1/M2, Segment 1/2 of the middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NI, not included into analysis despite univariate *P*<0.15 (see methods); NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; TIA; transient ischemic attack; TICI, Thrombolysis in Cerebral Infarction; TOAST, Trial of ORG 10 172 in Acute Stroke Treatment; tPA, tissue-type plasminogen activator; and VE, variable excluded based on backward likelihood ratio model.

thrombus end location was recorded (ie, change from proximal M1 to inferior division M2). Imaging examples of the respective scenarios can be found in the online-only Data Supplement (Figures II through IV in the online-only Data Supplement).

Statistical Analysis Plans

Group comparisons were performed using standard statistical measures (Whitney-Mann *U* for non-normally distributed continuous and ordinally scaled variables, Welsch *t* test for normally distributed

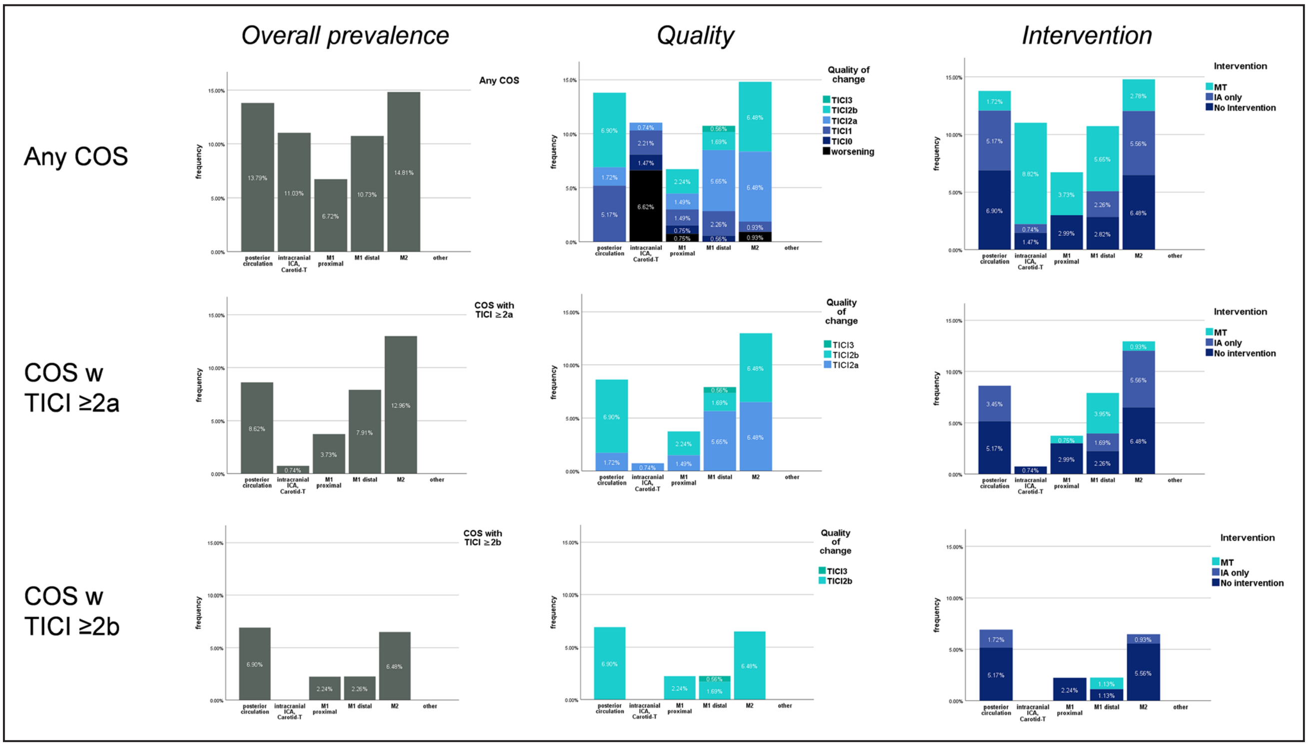

Figure. Change of occlusion site (COS) stratified according to occlusion sites. **Upper row**: COS, any type of change of occlusion site; **left**, overall prevalence of COS; **middle**, quality of COS with regards to Thrombolysis in Cerebral Infarction (TICI) score or perfusion worsening; **right**, pursued treatment (no intervention versus thrombectomy versus intra-arterial (IA) thrombolysis only). **Middle** row: COS with TICI ≥2a, change of occlusion with at least TICI 2a reperfusion; **left**, overall prevalence of COS with TICI ≥2a; middle, quality of COS with TICI ≥2a (TICI 2a vs TICI 2b vs TICI 3); **right**, pursued treatment (no intervention versus thrombectomy versus IA thrombolysis only). **Lower** row: COS with TICI ≥2b, change of occlusion with at least TICI 2b reperfusion; **left**, overall prevalence of COS with TICI ≥2b; **middle**, quality of COS with TICI ≥2b (TICI 2b vs TICI 3); **right**, pursued treatment (no intervention versus thrombectomy versus IA thrombolysis only). N were 58 for posterior circulation occlusions, 136 for intracranial internal carotid artery (ICA) or carotid-T (CT) occlusions, 134 for proximal M1 occlusions, 177 for distal M1 occlusions, 108 for M2 occlusions and 14 for other occlusions. Fisher exact test indicated significant differences of prevalences of COS, COS with TICI ≥2a and COS with TICI ≥2b across the different occlusion sites (*P*<0.001).

Table 2. Differences in Preinterventional Reperfusion in IV-tPA Versus no IV-tPA Patients Stratified According to Occlusion Sites

COS with TICI ≥2a	No IV-tPA	IV-tPA	*P* Value
All	1.3% (5/377)	13.6% (34/250)	<0.001
Posterior circulation	0% (0/38)	25% (5/20)	0.003
iICA/carotid-T	0% (0/96)	2.5% (1/40)	0.294
M1 proximal	2.9% (2/68)	4.5% (3/66)	0.678
M1 distal	1% (1/100)	16.9% (13/77)	<0.001
M2	3.1% (2/65)	27.9% (12/43)	<0.001
Other	0% (0/10)	0% (0/4)	…
COS with TICI ≥2b			
All	0.8% (3/377)	6.0% (15/250)	<0.001
Posterior circulation	0% (0/38)	20.0% (4/20)	0.011
iICA/carotid-T	0% (0/96)	0% (0/40)	…
M1 proximal	1.5% (1/68)	3.0% (2/66)	0.617
M1 distal	0% (0/100)	5.2% (4/77)	0.034
M2	3.1% (2/65)	11.6% (5/43)	0.112
Other	0% (0/10)	0% (0/4)	…

COS indicates change of occlusion site; iICA, intracranial internal carotid artery; IV-tPA, intravenous tissue-type plasminogen activator; M1/M2, segment 1/2 of the middle cerebral artery; and TICI, Thrombolysis in Cerebral Infarction.

continuous variables, Fisher exact test for frequency tables). Variables with *P*<0.15 in univariate comparison were included into logistic regression models. Multivariable logistic regressions were performed using a backward-likelihood ratio model. Because of high interdependency, the thrombus length and the occlusion site were included separately in the model in case both were found to be significant in univariate analysis (model 1 and model 2 in Table 1, respectively). Results derived from logistic regression analyses are displayed as adjusted odds ratios (aOR) and corresponding 95% confidence intervals (95% CI). Proportions (95% CI; eg, prevalences) were calculated using the asymptomatic method (Wald) based on a normal approximation.[19] Numbers needed to treat and respective 95% CIs were calculated with the use of the Software GraphPad QuickCalcs (https://www.graphpad.com/quickcalcs/NNT1/). All other statistics were computed using the software SPSS version 22.0 (IBM, Armonk, NY).

Results

Prevalence and Quality of COS

For baseline characteristics, see Table 1. Prevalence of any COS was 10.7% (95% CI, 8.3%–13.1%), subdivided into COS with TICI 0-1 (2.7%, 95% CI, 1.7%–4.3%), COS with TICI ≥2a (6.2%, 95% CI, 4.6%–8.4%), and COS with perfusion worsening (1.8%, 95% CI, 0.9%–3.1%), respectively. COS with TICI ≥2b occurred in 2.9% (95% CI, 1.8%–4.5%) of cases, hence in about half of all patients with TICI ≥2a preinterventional reperfusions. COS with TICI ≥2a differed according to the site of occlusion, with the highest prevalence in M2 occlusions (13.0%) and the lowest prevalence in intracranial ICA occlusions (0.7%, *P* for overall difference across occlusion sites <0.001; Figure). A similar distribution was observed for COS with TICI ≥2b (Figure). COS with TICI ≥2a was nearly never complete (only 1 case with TICI 3), with relative rates of TICI 2a and TICI 2b of 53.8% and 43.6%, respectively (Figure). Despite COS with TICI ≥2a, ET was performed in 51.3% of these patients (23.1% mechanical thrombectomy and 28.2% IA lysis, Figure). Occlusion site worsening was rarely observed and almost exclusively occurred in patients with ICA occlusions (9/136 ICA occlusions versus 2/491 non-ICA occlusions; *P*<0.001; Table I in the online-only Data Supplement). Rates of COS with TICI ≥2a and TICI ≥2b were significantly higher in patients pretreated with intravenous tPA, and this effect was evident across all occlusion sites except ICA and proximal M1 occlusions (Table 2; Figure V in the online-only Data Supplement).

Predictors of COS

Multivariable logistic regression revealed pretreatment with intravenous tPA (aOR, 11.98; 95% CI, 4.5–31.6) and cardiogenic thrombus origin (aOR, 2.3; 95% CI, 1.1–4.6) as the only positive predictors of COS with TICI ≥2a (Table 1). Factors negatively associated with COS with TICI ≥2a were thrombus length (aOR for every 1 mm increase 0.926; 95% CI, 0.87–0.99) and a history of diabetes mellitus (aOR, 0.31; 95% CI, 0.09–1.1; Table 1). Nearly the same factors were found significant in an analysis confined to COS with TICI ≥2b (Table 3). Independent factors associated with COS with perfusion worsening were ICA occlusion (aOR, 18.62; 95% CI, 3.77–92; Table I in the online-only Data Supplement), higher admission National Institutes of Health Stroke Scale (aOR for every point increase 1.10; 95% CI, 1.01–1.21), and pretreatment with intravenous tPA (aOR, 4.33; 95% CI, 1.12–16.80).

Number Needed to Treat

According to the frequencies in the cohort under study, the numbers needed to treat with intravenous tPA before thrombectomy to achieve 1 additional case of COS with TICI ≥2a or 1 additional case of COS with TICI ≥2b reperfusion were 9 (95% CI, 6–13) and 20 (95% CI, 12–47), respectively. These numbers increased to 13 (95% CI, 8–27) and 35 (95% CI, 18–464) when analysis was confined to M1 (proximal and distal) and ICA occlusions (SWIFT DIRECT trial cohort [Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke], URL: http://www.clinicaltrials.gov. Unique identifier: NCT03192332). The number needed to harm with intravenous tPA before thrombectomy about the occurrence of perfusion worsening was calculated to be 58 when considering all occlusion sites (95% CI, not calculable because nonsignificant risk increase). This number decreased to 9 (95% CI, 4–364) when analysis was confined to ICA occlusions.

Impact on Final TICI and Clinical Relevance

Final reperfusion success was less often complete in patients with preinterventional COS than in those without (rates of TICI 3, 17.9% versus 41.8%; *P*<0.001; Figure VI in the online-only Data Supplement). Nevertheless, COS with preinterventional reperfusion (≥TICI 2a) tended to be associated with a favorable clinical outcome after adjusting for potential confounders (aOR, 2.65; 95% CI, 0.98–7.17; Table II in the online-only Data Supplement).

Table 3. Factors Associated With TICI ≥2b on First Intracranial Angiography Series

	All (n=627)	No COS or COS With TICI <2b (n=609)	COS With TICI ≥2b (n=18)	*P* Value	aOR and 95% CI From Logistic Regression (Backward Likelihood Ratio)
Age, y	72±14	72±14	73±11	0.728	
Preadmission dependence (mRS >2)	10.6% (58/546)	10.5% (56/532)	14.3% (2/14)	0.652	
Sex, female	49.9% (313)	49.8% (303)	55.6% (10)	0.642	
Risk factors					
Atrial fibrillation	41.3% (259)	40.7% (248)	61.1% (11)	0.093	VE
Arterial hypertension	73.2% (459)	73.6% (448)	61.1% (11)	0.279	
Smoking	30.1% (184/611)	30.3% (180/594)	23.5% (4/17)	0.789	
Diabetes mellitus	21.1% (132)	21.7% (132)	0% (0)	0.019	Did not converge
Previous Stroke	13.6% (85)	13.5% (82)	16.7% (3)	0.724	
Previous TIA	6.5% (41)	6.4% (39)	11.1% (2)	0.332	
Medication					
Aspirin	31.7% (199)	31.4% (191)	44.4% (8)	0.303	
OAC	9.1% (57)	9.0% (55)	11.1% (2)	0.675	
Statin	29.5% (185)	29.6% (180)	27.8% (5)	1.000	
Systolic blood pressure, mm Hg	153 (133–172) (n=609)	153 (133–171) (n=592)	153 (128–190) (n=17)	0.637	
Diastolic blood pressure, mm Hg	81 (70–95; n=607)	81 (70–95; n=590)	89 (68–97; n=17)	0.890	
Admission glucose, mmol/L	6.6 (5.8–8.1; n=582)	6.6 (5.8–8.0; n=567)	7.0 (5.8–8.4; n=15)	0.706	
Admission NIHSS	14 (9–19; n=624)	14 (9–19; n=606)	13 (6–16; n=18)	0.202	
TOAST				0.045	
Large-artery atherosclerosis	10.7% (67)	10.8% (66)	5.6% (1)		
Cardioembolic	43.7% (274)	42.7% (260)	77.8% (14)		
Other etiology	6.5% (41)	6.7% (41)	0% (0)		
Unknown etiology	39.1% (245)	39.7% (242)	16.7% (3)		
Cardioembolic vs all	43.7% (274)	42.7% (260)	77.8% (14)	0.004	7.13 (1.99–25.64)
Last seen well or symptom-onset to first imaging (min)	129 (91–224; n=558)	130 (91–227; n=540)	126 (94–203; n=18)	0.719	
Initial modality for admission imaging				0.523	
CT	32.1% (201)	31.9% (194)	38.9% (7)		
MRI	59.5% (373)	59.6% (363)	55.6% (10)		
CT→MRI	5.4% (34)	5.6% (34)	0% (0)		
MRI→CT	3.0% (19)	3.0% (18)	5.6% (1)		
Intracranial occlusion				0.014	
Posterior circulation	9.3% (58)	8.9% (54)	22.2% (4)		
Intracranial ICA or carotid-T	21.7% (136)	22.3% (136)	0% (0)		
Proximal M1	21.4% (134)	21.5% (131)	16.7% (3)		
Distal M1	28.2% (177)	28.4% (173)	22.2% (4)		
M2	17.2% (108)	16.6% (101)	38.9% (7)		
other	2.2% (14)	2.3% (14)	0% (0)		
Intracranial ICA or carotid-T vs other	21.7% (136)	22.3% (136)	0% (0)	0.018	Did not converge
Thrombus length, mm	10.4 (6.8–16.7; n=573)	10.4 (6.8–17.0; n=556)	8.3 (6.7–10.8; n=17)	0.126	VE
Tandem lesion	16.4% (103)	16.9% (103)	0% (0)	0.055	Did not converge

(*Continued*)

Table 3. Continued

	All (n=627)	No COS or COS With TICI <2b (n=609)	COS With TICI ≥2b (n=18)	*P* Value	aOR and 95% CI From Logistic Regression (Backward Likelihood Ratio)
Intravenous tPA	39.9% (250)	38.6% (235)	83.3% (15)	<0.001	6.97 (1.94–25.09)
Diagnosis to first intracranial DSA (min)	73 (58–90)	73 (58–89)	81 (64–103)	0.253	
Intravenous tPA to first intracranial series (min)	47 (33–66; n=250)	46 (33–66)	55 (42–80)	0.213	

aOR indicates adjusted odds ratio; 95% CI, 95% confidence interval; COS, change of occlusion site; DSA, digital subtraction angiography; ICA, internal carotid artery; M1/M2, segment 1/2 of the middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; TIA; transient ischemic attack; TICI, Thrombolysis in Cerebral Infarction; TOAST, Trial of ORG 10 172 in Acute Stroke Treatment; tPA, tissue-type plasminogen activator; and VE, variable excluded based on backward likelihood ratio model.

Discussion

Preinterventional reperfusion before the start of thrombectomy is a potentially important benefit of the bridging approach.[8,9] Important data about the prevalence of preinterventional reperfusion was extracted from the latest large randomized trials, as shown in a recently published meta-analysis,[11] suggesting the prevalence of preinterventional reperfusion to be ≈11%. Because of the heterogeneity of reported prevalences and insufficiently detailed reperfusion quality grading,[13,20] subgroup analyses and a systematic comparison with patients not having received tPA were not performed. Moreover, patients with intention to IA lysis were not included. Obviously, intravenous tPA in a drip-and-ship scenario should not be withheld or delayed, because reperfusion, if achieved, may occur decisively earlier than with subsequent ET. In contrast, in patients admitted directly to a comprehensive stroke center with access to ET, the value of preinterventional intravenous tPA to facilitate reperfusion is less clear considering the substantially shorter time intervals. In the present analysis, we evaluated a precisely defined cohort of consecutive endovascular candidates with direct access to ET in whom thrombectomy or IA lysis was intended, although not always performed. Despite short diagnosis/lysis-to-intervention metrics, preinterventional reperfusion with TICI ≥2a occurred in approximately every 20th patient (≈1/10 treated with intravenous tPA and ≈1/100 not treated with intravenous tPA). Reperfusion was almost never complete, and more than half of these patients required additional ET. Preinterventional reperfusion was clearly facilitated by intravenous tPA administration, corroborating earlier findings on the effectiveness of intravenous tPA in large vessel occlusion,[10] despite a relatively small yield. Other factors influencing preinterventional reperfusion were occlusion site and respective thrombus length, cardioembolic origin, and a history of diabetes mellitus, in line with previous reports.[20–25]

As expected, the numbers needed to treat with intravenous tPA to achieve 1 additional preinterventional reperfusion was high, especially when considering ICA and M1 occlusions. Furthermore, intravenous tPA may also induce occlusion site worsening by inducing fragmentation of the thrombus in the same or new territories. This topic is of particular importance, as preprocedural worsening because of partial fragmentation or thrombus growth was previously reported.[13,20,26]

Although rarely complete, preinterventional reperfusion was independently associated with a more favorable clinical outcome, whether additional ET was performed or not (data not shown). Although other benefits and harms of preinterventional tPA deserve to be addressed, we advocate that a randomized trial evaluating the value of pretreatment intravenous tPA in patients directly admitted to comprehensive stroke centers offering prompt ET should remain confined to occlusion sites with low chances of reperfusion, namely the ICA and proximal M1 occlusions, in order not to unnecessarily lower the chances of preinterventional reperfusion. Larger datasets may allow a more accurate prediction of preinterventional reperfusion in a case-by-case manner and may in the future support individualized decision making on pretreatment with intravenous tPA.

Recently, the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke) results were published, suggesting that preinterventional reperfusion rates are higher in patients receiving intravenous tenecteplase as compared with patients receiving intravenous tPA. Figure VII in the online-only Data Supplement provides a comparison of our results with the EXTEND-IA TNK treatment arms. The prevalence of preinterventional reperfusion in our cohort closely matched the prevalence of the EXTEND IA-TNK tPA-arm, however, significantly lower rates were observed compared with the intravenous tenecteplase arm.[27] These differences are mainly caused by higher rates of preinterventional reperfusion after tenceteplase among patients presenting with M1 or M2 occlusions. Although confirmation of these results is urgently needed, currently recruiting randomized-controlled trials evaluating direct mechanical thrombectomy versus bridging have to adopt to these results in the near future and analyses regarding the value of preinterventional reperfusion in patients undergoing ET need to be updated constantly.

The most prominent limitation of this study probably lies in the absence of randomization on the decision to administer or withhold intravenous tPA before starting the angiography because mostly ineligible patients did not receive intravenous tPA, thereby prompting a selection bias. Given the a priori likelihood of increased preinterventional reperfusion in patients eligible for intravenous tPA, this may have impacted their clinical outcome too favorably. Patients with contraindication to intravenous tPA on the other hand had worse risk factor profiles, more comorbidities and were on average treated later, which may also have influenced their outcome more negatively. Furthermore, their thrombi may have been histologically different, which may impact reperfusion success.[28,29] Although we have tried to account for some of these variables using multivariable logistic regression, we cannot exclude that this bias affected the results of our analyses. Second, we have analyzed data over a period of 6 years during which the pivotal thrombectomy studies were published. As such, indications for treatment and time metrics between intravenous tPA administration to groin puncture/first intracranial series may have changed over time. In fact, we have observed declining intravenous tPA administration to first intracranial DSA series intervals during the first year (2012–2014), which have reached a plateau afterward (data not shown). Although we agree that these changes may have influenced our analysis, it is important to stress that the present analysis did not provide consistent evidence that time from intravenous tPA administration to recanalization assessment was a significant determinant of preinterventional reperfusion within this cohort of mothership patients. This of course does not contradict other observations, but rather may reflect the confinement of our analysis to mothership patients and thus relatively short intervals between intravenous tPA administration to recanalization assessment. Third, definition of occlusion sites was based on imaging extrapolation of a synopsis of either MRA time-of-flight, contrast-enhanced MRA, perfusion MR, and susceptibility-weighted imaging or native CT, CTA, and CT perfusion. Although we have tried to define the preinterventional occlusion site as accurate as possible, also considering the extent of the perfusion deficit, we cannot exclude that contrast stagnation before the proximal thrombus end or contrast penetration into the thrombus may have led to false-positive or false-negative localization of the exact proximal thrombus end. Furthermore, thrombus length measurements were performed on both, CT and MR images, which may prompt intermodality bias with regards to the delineation of the distal thrombus end. Last, decisions to pursue ET despite preinterventional reperfusion had occurred were not standardized and may differ from current practices in other centers. Decisions were reached case-by-case in a consensus by the treating neurologist and neurointerventionalist. Multiple factors were considered, including residual neurological deficits, presumed functional relevance of the nonreperfused tissue, time elapsed from symptom-onset, and technical feasibility.

Conclusions

In a highly preselected cohort of patients with direct access to ET, the prevalence of preinterventional reperfusion (TICI ≥2a) is non-negligible (≈6%). Its occurrence is clearly facilitated by pretreatment with intravenous tPA but is angiographically successful (≥TICI 2b) only in about half of the cases, is almost never complete (only 1 case with TICI 3), and requires additional ET in >50%. Nonetheless, preinterventional reperfusion is associated with a more favorable clinical course. Patients with a substantial likelihood of preinterventional reperfusion are nondiabetics and those presenting with a cardiogenic embolus and small cerebral clots. Given their low rate of preinterventional reperfusion regardless of pretreatment with intravenous tPA, the most appropriate cohorts for skipping preinterventional intravenous tPA in the framework of a randomized-controlled trial seem to be intracranial ICA and proximal M1 occlusions, where intravenous tPA might also have a negative impact by promoting clot fragmentation and perfusion worsening. The recently reported superiority of intravenous tenecteplase versus intravenous tPA on preinterventional reperfusion also needs further evaluation and might change the design and inclusion criteria of aforementioned randomized-controlled trials.

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