Effect of Recanalization on Cerebral Edema in Ischemic Stroke Treated With Thrombolysis and/or Endovascular Therapy

Magnus Thorén, MD; Anand Dixit, MD; Irene Escudero-Martínez, MD; Zuzana Gdovinová, MD, PhD; Lukas Klecka, MD; Viiu-Marika Rand, MD; Danilo Toni, MD, PhD; Aleksandras Vilionskis, MD, PhD; Nils Wahlgren, MD, PhD; Niaz Ahmed, MD, PhD

***Background and Purpose*—**A large infarct and expanding cerebral edema (CED) due to a middle cerebral artery occlusion confers a 70% mortality unless treated surgically. Reperfusion may cause blood-brain barrier disruption and a risk for cerebral edema and secondary parenchymal hemorrhage (PH). We aimed to investigate the effect of recanalization on development of early CED and PH after recanalization therapy.

***Methods*—**From the SITS-International Stroke Treatment Registry, we selected patients with signs of artery occlusion at baseline (either Hyperdense Artery Sign or computed tomography/magnetic resonance imaging angiographic occlusion). We defined recanalization as the disappearance of radiological signs of occlusion at 22 to 36 hours. Primary outcome was moderate to severe CED and secondary outcome was PH on 22- to 36-hour imaging scans. We used logistic regression with adjustment for baseline variables and PH.

Results—Twenty two thousand one hundred eighty-four patients fulfilled the inclusion criteria (n=18 318 received intravenous thrombolysis, n=3071 received intravenous thrombolysis+thrombectomy, n=795 received thrombectomy). Recanalization occurred in 64.1%. Median age was 71 versus 71 years and National Institutes of Health Stroke Scale score 15 versus 16 in the recanalized versus nonrecanalized patients respectively. Recanalized patients had a lower risk for CED (13.0% versus 23.6%), adjusted odds ratio (aOR), 0.52 (95% CI, 0.46–0.59), and a higher risk for PH (8.9% versus 6.5%), adjusted odds ratio, 1.37 (95% CI, 1.22–1.55), than nonrecanalized patients.

***Conclusions*—**In patients with acute ischemic stroke, recanalization was associated with a lower risk for early CED even after adjustment for higher rate for PH in recanalized patients. **(*Stroke*. 2020;51:216-223. DOI: 10.1161/STROKEAHA.119.026692.)**

Key Words: blood-brain barrier ■ cerebral edema ■ cerebral infarction ■ intracranial hemorrhages ■ odds ratio ■ reperfusion ■ thrombectomy

Cerebral edema (CED) in acute ischemic stroke worsens the prognosis and can, if severe, cause life-threatening intracranial tissue shifts.[1] Transvascular flow of plasma over the damaged blood-brain-barrier (BBB) causes tissue swelling which, if the BBB is severely compromised, is aggravated by hemorrhage.[2] The size of the infarct is a major determinant of the extent and clinical severity of the ensuing edema and potential hemorrhage. In supratentorial large artery occlusion, the risk of life-threatening edema is the highest in occlusion of the middle cerebral artery (MCA), called malignant MCA infarct in patients with large infarcts and signs of expanding edema. Up to 10% of patients with supratentorial ischemia develop subtotal or complete MCA infarction.[3] The clinical deterioration caused by edema after a large MCA infarction is usually observed within 48 hours after symptom onset with one-third of the patients undergoing early deterioration within 24 hours.[4] The mortality is close to 80% within a few days, unless treated with early surgery.[5]

While earlier data indicated an increased risk of severe edema in reperfused brain tissues,[6] recent studies indicate that recanalization decreases the risk of edema.[7–9] On one hand,

Received June 20, 2019; final revision received September 3, 2019; accepted October 2, 2019.

From the Department of Neurology, Karolinska University Hospital and Department of Clinical Neuroscience, Karolinska Institutet, Sweden (M.T., N.A.); Newcastle upon Tyne NHS Foundation Trust, University of Newcastle upon Tyne, United Kingdom (A.D.); Department of Neurology, University Hospital Virgen del Rocío, Sevilla and Biomedicine Institute of Sevilla, Spain (I.E.-M.); Department of Neurology, Faculty of Medicine, P.J. Safarik University Košice, Slovak republic (Z.G.); Departement of Neurology, Municipal hospital of Ostrava, Czech Republic (L.K.); Department of Neurology, North Estonia Medical Centre, Tallinn (V.-M.R.); Unità di Trattamento Neurovascolare, University La Sapienza Rome, Italy (D.T.); Department of Neurology, Institute of Clinical Medicine, Vilnius University, Republican Vilnius University hospital, Lithuania (A.V.); and Department of Clinical Neuroscience, Karolinska Institutet, Sweden (N.W.)

Presented in part at the European Stroke Organisation Conference, Milan, Italy, May 22–24, 2019.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.119.026692.

Correspondence to Magnus Thorén, MD, Karolinska Stroke Research Unit, Department of Neurology (Tema neuro), Section for Neurovascular Diseases, Carolina Tower 3rd floor, Karolinska University Hospital—Solna, S-17176 Stockholm, Sweden. Email magnus.thoren@sll.se

preclinical data have indicated that tPA (tissue-type plasminogen activator) may facilitate the development of BBB damage in acute ischemic stroke, on the contrary, intravenous thrombolysis (IVT) with recombinant tPA facilitates early recanalization which decreases infarct size. In addition to edema, recanalization is associated with intracranial hemorrhage in particular when treated with IVT. We hypothesized that recanalization therapies would decrease the risk for development of CED within 22 to 36 hours, that is, early after recanalization, despite an increased risk of hemorrhagic transformation. Using real life clinical data from a large registry, we aimed to investigate the association of recanalization with development of early CED and parenchymal hemorrhage (PH) after recanalization therapy.

Methods

Study Sample

We included a subset of patients from the SITS-International Stroke Treatment Registry (ISTR), an internet-based academic interactive, prospective register for the monitoring of treatment in acute ischemic stroke. Access to the anonymized SITS-ISTR data will be available from the corresponding author on reasonable request and approval by the SITS Scientific Committee. Methods of data collection in SITS-ISTR have been described in detail elsewhere[10] and are also provided in the online-only Data Supplement. From SITS-ISTR, we collected all patients with data entered according to IVT Standard Protocol or Thrombectomy Protocol. All patients had presumed ischemic stroke treated with IVT and endovascular thrombectomy (EVT) and were recorded during 2002 to 2017. At baseline, we included only patients who had a recorded National Institutes of Health Stroke Scale (NIHSS) score and recorded indirect or direct radiological evidence for a cerebral arterial occlusion at baseline. Indirect evidence was a hyperdense artery sign on computed tomography or visible arterial thrombus on MRI. Direct evidence was a finding of any arterial occlusion on angiographic sequences (computed tomography or MRI). With the aim of assessing the disappearance of arterial occlusions at 22 to 36 hours after recanalization therapy, we excluded the following: patients with uncertain or missing data regarding signs of arterial occlusion and patients who did not have data of the same type (direct or indirect) at both baseline and at 22 to 36 hours.

As the Total Anterior Circulation Syndrome (TACS) has a high compatibility with infarctions of the MCA territory, we determined to use this as a proxy of large vessel occlusion.[11–13] The TACS subgroup consisted of patients with clinical characteristics of TACS according to the Oxfordshire Community Stroke Scale, inferred when all the following 3 criteria were met: first, aphasia (NIHSS item 9) or inattention (NIHSS item 11), second, a right or a left sensorimotor deficit (NIHSS items 4, 5, and 6) and, third, any visual defect (NIHSS item 3).

Exposure

We inferred recanalization from disappearance of radiological signs of occlusion on computed tomography, MRI, or angiographic examination at 22 to 36 hours. If records of >1 modality was available, we gave precedence to angiographic data.

Outcomes and Covariates

The primary outcome measure was CED which was rated by local investigators on imaging at 22 to 36 hours. We used the SITS-MOST edema scale which has been used previously.[14,15] We defined mild CED as focal brain swelling up to one-third of the hemisphere (grade 1), moderate CED as focal brain swelling greater than one-third of the hemisphere (grade 2), and severe CED as focal brain swelling with midline shift (grade 3). Although not explicitly mentioned in the SITS-MOST study protocol, signs of focal brain edema usually are defined as narrowing of the cerebrospinal fluid space, for example, effacement of cortical sulci or ventricular compression.[14,16] We specified in advance that the 2 higher grades of the scale would be put together into a compound outcome so that moderate to severe edema would be compared with no or mild edema. Early secondary outcomes were the proportion of patients with parenchymal hemorrhage (PH) type 1 or 2 of the infarct area on follow-up imaging at 22 to 36 hours, total NIHSS score at 24 hours, and Early Neurological deterioration (END). PH type 1 is defined as hemorrhage <30% of the infarct area with mild, local, space-occupying effect; type 2 is hemorrhage >30% of the infarct area, with substantial space-occupying effect. Remote hemorrhages were not included. END was defined as an increase of 4 points or more between baseline and 24 hours. Late secondary outcomes, measured at 3 months, were mortality and functional outcome assessed by modified Rankin Scale (mRS) score. Covariates collected for this study were baseline and demographic characteristics and any acute intervention.

Ethics

Ethics approval was obtained from the Stockholm Regional Ethics Committee for this project as part of the SITS-MOST II study framework. Ethics approval and patient consent for participation in the SITS-ISTR were obtained in countries that required this; other countries approved the register for anonymized audit

Statistical Analysis

In an initial univariate analysis, we compared baseline characteristics and outcomes between recanalized and nonrecanalized patients. We also compared baseline characteristics between patients with no or mild versus moderate to severe edema. We used linear regression methods and Pearson's χ^2 test. Estimation of proportions was based on reported cases, excluding unknown or uncertain values from the denominator. A significance level of $P<0.05$ was used through the whole study. mRS was analyzed either dichotomized into mRS score ≤2 and >2 or in 7 steps with ordered logistic regression using the proportional odds model. Next, we used logistic regression methods to compare crude and adjusted odds for outcomes in recanalized versus nonrecanalized patients in the full study sample and the TACS subgroup, adjusted for baseline factors or PH, or both.

Next, we used multivariable regression analysis to quantify the effect of recanalization on moderate to severe CED in the study sample and in the TACS subgroup. We chose covariates from demographic and baseline characteristics using 2 different approaches. In an approach based on statistical significance testing, we used stepwise backwards elimination ($P\geq0.05$ to eliminate) of the baseline variables that were associated with either recanalization or moderate to severe CED. In an approach based on an a priori hypothesis, depicted as a directed acyclic graph in Figure I in the online-only Data Supplement, we selected the following covariates that could potentially confound the association between recanalization and edema: age, NIHSS at baseline, onset-to-treatment time and stroke unit care. As intracerebral hemorrhage causes edema, we hypothesized that PH can mediate part of the effect of recanalization on CED. To account for mediation, we calculated the effect of recanalization on CED with and without adjustment for PH. We evaluated the predictive ability of these models by calculating the area under the curve. We evaluated the robustness of the results with a sensitivity analysis using calculated E-values for the effect of recanalization on CED. E-values can be interpreted as the minimum strength of association on the risk ratio scale that an unmeasured confounder needs to have with both recanalization and CED, given covariates, to fully explain away the estimated effects; larger E-values indicate more robust results.[17,18] Finally, we investigated the effect of CED on the secondary outcomes, both crude associations and controlled for the baseline factors associated with moderate to severe CED. We used the statistical software Stata version 15 with the addition of user-written modules for ordinal logistic regression (OMODEL)[19] and calculation of E-values (EVALUE).[20]

Results

Figure 1 shows a flowchart of the study. Of the 152 924 recorded patients in the SITS-ISTR database, 118 764 patients

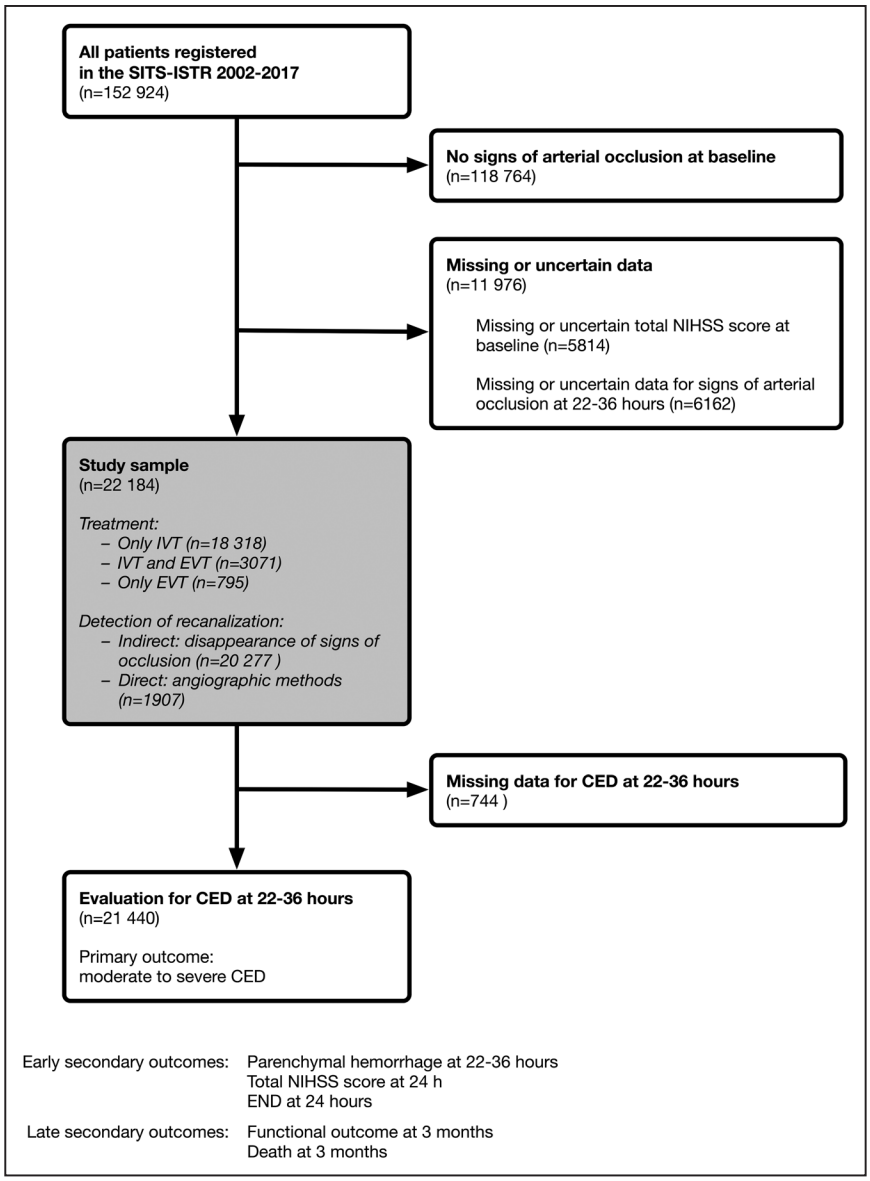

Figure 1. Flowchart of the study. CED indicates cerebral edema; EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; and NIHSS, National Institutes of Health Stroke Scale.

had no signs of arterial occlusion at baseline. Of the remaining patients, 11 976 had to be excluded because of missing or uncertain data regarding NIHSS at baseline (N=5814) and regarding radiological findings at 22 to 36 hours (N=6162). Among the 22 184 patients who met the study criteria and were included in the study sample, median age was 71 years and NIHSS score was 16 at baseline. In the study sample, 18 318 patients (82.6%) had received IVT treatment but no EVT, 3071 patients (13.8%) had received both IVT and EVT, and 795 patients (3.6%) had received EVT but no IVT. Recanalization status was indirectly derived from data on hyperdense artery sign or visible arterial thrombus on noncontrast imaging scans for 20 277 patients (91.4%) and directly derived, using angiographic methods, for 1907 patients (8.6%). Overall, 14 224 patients (64.1%) had been recanalized at 22 to 36 hours. Table 1 shows a comparison of baseline variables between nonrecanalized and recanalized patients. A comparison between patients with no or mild versus moderate to severe CED is seen in Table I in the online-only Data Supplement.

The Effect of Recanalization on CED

As seen in Table 2, 21 440 patients (96.6%) of the study sample had reliable (ie, not uncertain or missing) data on CED at 22 to 36 hours. Recanalization was associated with a significantly lower incidence of moderate to severe CED (13.0% versus 23.6%; $P<0.001$), a 10.6% absolute risk reduction, with relative risk (RR) 0.55 (95% CI, 0.52–0.58), corresponding to a 45% relative risk reduction. Figure II in the online-only Data Supplement shows distribution of CED by recanalization status. Ordered logistic regression showed a significant shift toward lower grade of CED in recanalized versus nonrecanalized patients; however, the test for proportionality of odds indicated that the proportionality assumption did not hold. As seen in Table 3, in multivariable logistic regression analysis, recanalization was associated with a lower risk for moderate to severe CED versus no or mild CED, crude odds ratio (OR) 0.48 (95% CI, 0.45–0.52), adjusted OR (aOR), 0.47 (95% CI, 0.43–0.51). Controlling for PH resulted in a small change in risk for moderate to

Table 1. Baseline Variables by Recanalization Status at 22 to 36 Hours

Variable	N	Nonrecanalization, n=7960	Recanalization, n=14224	*P* Value
Age, y, median (IQR)	22160	71	71	0.47*
Male sex, %	22183	54.2	52.3	0.006†
NIHSS score, median (IQR)	22184	17	16	<0.001*
TACS	22184	60.0	65.6	<0.001†
OTT for IVT, min, median (IQR)	20974	145	140	0.02*
Signs of acute infarction on imaging, %	21100	28.9	23.3	<0.001†
Blood glucose, mmol/L, median (IQR)	20369	6.7	6.6	0.25*
Mean arterial pressure, mm Hg	21577	104.0	104.1	0.60*
Diabetes mellitus, %	22012	15.6	16.2	0.27†
Hypertension, %	21972	65.5	66.3	0.20†
Congestive heart failure, %	21931	9.05	9.17	0.77†
Aspirin treatment, %	21968	31.7	31.1	0.38†
Clopidogrel treatment, %	22046	4.7	5.2	0.10†
Other antiplatelet treatment, %	22056	1.2	1.6	0.69†
Oral anticoagulant treatment, %	20501	4.1	6.4	<0.001†
Oral antihypertensive treatment, %	21983	56.2	59.5	<0.001†
Smoking status				
Current smoker, %	20866	17.4	17.1	0.60†
Previous smoker, %	18195	17.6	14.0	<0.001†
Previous stroke				
Stroke >3 mo before, %	21904	8.3	8.5	0.57†
Stroke within 3 mo before, %	21418	1.3	1.4	0.37†
Previous TIA	15547	5.8	5.0	0.04†
Atrial fibrillation	21912	27.1	27.7	0.32†
Decreased consciousness (NIHSS 1a≥1), %	21427	34.2	26.1	<0.001†
EVT with or without prior IVT, %	22184	5.25	24.2	<0.001†
Decompressive hemicraniectomy, % treated	22184	1.2	0.8	0.003†
Stroke unit care	22184	43.1	56.5	<0.001†

EVT indicates endovascular thrombectomy; IQR, interquartile range; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; and TACS, Total Anterior Circulation Syndrome.

*ANOVA.

†Pearson χ^2 test.

severe CED, aOR, 0.42 (95% CI, 0.38–0.45). Similar values were seen in the TACS subgroup.

Table 4 shows estimates from the 8 regression models for the effect of recanalization on moderate to severe CED in the study sample and in the TACS subgroup. Predictive ability (area under the curve) was better for models that were adjusted for PH, the best 2 values were 0.76 and 0.79. E-values were very similar (2.1–2.4) across all models, indicating that any unmeasured confounder would need to have a twofold association with both exposure and outcome to shift the odds ratio point estimate to 1.0. Results are consistent. Restriction to the TACS subgroup (versus full study sample) resulted in slightly lower point estimates. Two models with high predictive ability and high E-values showed the following estimates: OR 0.52 (95% CI, 0.46–0.59), which was not adjusted for PH, and OR 0.46 (95% CI, 0.41–0.52), which was adjusted for PH. Thus, adjustment for PH resulted in slightly lower point estimates; however, the relative difference was small, at most 12%.

The Effect of Recanalization on Secondary Outcomes

As seen in Table 2, 21718 patients (97.9% of the study sample) had reliable data on any PH, versus no hemorrhage or hemorrhagic infarcts. Comparing recanalized versus nonrecanalized patients, a significantly higher (8.9% versus 6.5%; *P*<0.001) incidence of PH was seen in recanalized patients, RR, 1.37 (95% CI, 1.24–1.51). Recanalized patients had a significantly lower incidence of END (8.3% versus 14.5%; *P*<0.001), RR 0.57 (95% CI, 0.53–0.62) and a significantly lower NIHSS

Table 2. Outcomes by Recanalization Status at 22 to 36 Hours

Outcome	N	Nonrecanalization, n=7960	Recanalization, n=14 224	*P* Value
CED at 22–36 h	21 440			<0.001*
No CED, %		55.4	70.6	
Mild CED, %		20.8	16.4	
Moderate CED, %		11.7	6.8	
Severe CED, %		11.9	6.2	
Moderate to severe CED at 22–36 h, %	21 440	23.6	13.0	<0.001*
PH at 22–36 h, %	21 718	6.5	8.9	<0.001*
END at 24 h, %	20 115	14.5	8.3	<0.001*
NIHSS at 24 h, median (IQR)	20 115	16 (10–20)	8 (3–16)	<0.001†
Dead at 3 mo, %	17 897	31.9	18.3	<0.001*
mRS score ≤2 at 3 mo, %	17 591	22.6	48.7	<0.001*

CED indicates cerebral edema; END, Early Neurological deterioration; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and PH, parenchymal hemorrhage.

*Pearson χ^2 test.

†ANOVA.

at 24 hours, median 8 versus 16 (P<0.001). About 81% of the study sample (N=17 897) had reliable mortality data at 3 months. Recanalized patients had a lower incidence of mortality (18.3% versus 31.9%, P<0.001), RR, 0.58 (95% CI, 0.55–0.61). About 79.2% (N=17 591) of the study sample had reliable data on mRS at 3 months. Recanalized patients had a better functional outcome: the proportion of patients that scored mRS 0 to 2 at 3 months was 48.7% versus 22.6% (P<0.001), RR 2.16 (95% CI, 2.06–2.26). Figure 2 shows functional outcome at 3 months by recanalization status.

Table 3 shows risks for secondary outcomes in recanalized versus nonrecanalized patients with adjustment for baseline variables, in the study sample and the TACS subgroup. Recanalization was associated with a higher risk for PH, crude OR 1.40 (95% CI, 1.26–1.56); aOR, 1.37 (95% CI, 1.22–1.55). Similar values were seen in the TACS subgroup, although the risk for PH was somewhat higher, aOR, 1.53 (95% CI, 1.28–1.83). Regarding details for END, mortality and mRS at 3 months, see Table 3. Unadjusted and adjusted odds ratios were consistent and showed that recanalization was associated with lower END and mortality, and a better functional outcome, similar in study sample and TACS subgroup. Ordered logistic regression showed a significant shift in mRS toward better functional outcome in recanalized

Table 3. Odds Ratios for Outcomes in Recanalized Versus Not Recanalized Patients in the Study Sample and Subgroups

Patients	Outcome	Unadjusted		Adjusted for Baseline Variables*		Adjusted for Baseline Variables* and PH	
		OR	95% CI	OR	95% CI	OR	95% CI
Study sample	Moderate to severe CED	0.48	0.45–0.52	0.47	0.43–0.51	0.42	0.38–0.45
	PH	1.40	1.26–1.56	1.37	1.22–1.55		
	END	0.54	0.49–0.59	0.50	0.45–0.55	0.48	0.43–0.54
	Dead at 3 mo	0.48	0.45–0.51	0.48	0.45–0.53	0.46	0.42–0.50
	mRS score ≤2 at 3 mo	3.25	3.04–3.49	3.20	2.96–3.46	3.31	3.05–3.58
TACS subgroup	Moderate to severe CED	0.50	0.45–0.55	0.47	0.42–0.54	0.43	0.37–0.48
	PH	1.62	1.38–1.90	1.53	1.28–1.83		
	END	0.55	0.47–0.65	0.52	0.43–0.63	0.50	0.41–0.60
	Dead at 3 mo	0.47	0.42–0.53	0.48	0.42–0.54	0.45	0.40–0.52
	mRS score ≤2 at 3 mo	3.95	3.48–4.48	3.82	3.31–4.41	3.95	3.42–4.56

CED indicates cerebral edema; END, Early Neurological deterioration; mRS, modified Rankin Scale; OR, odds ratio; OTT, onset-to-treatment time; PH, parenchymal hemorrhage; and TACS, Total Anterior Circulation Syndrome.

*Baseline variables associated with moderate to severe CED: OTT, signs of acute infarction on imaging, blood glucose, mean arterial pressure, diabetes mellitus, hypertension, congestive heart failure, aspirin treatment, oral antihypertensive treatment, current smoker, atrial fibrillation, decreased consciousness, EVT, and decompressive hemicraniectomy.

Table 4. Regression Models for the Effect of Recanalization on Moderate to Severe CED, Versus No or Mild CED

Procedure for Selection of Covariates	Patients	Adjusted for Covariates				Adjusted for Covariates and PH			
		OR	95% CI	AUC	E-Value*	OR	95% CI	AUC	E-Value*
Approach based on statistical significance: stepwise backward elimination†	Study sample	0.52	0.46–0.59	0.74	2.1	0.46	0.41–0.52	0.79	2.3
	TACS subgroup	0.47	0.40–0.56	0.69	2.3	0.43	0.36–0.51	0.74	2.4
Apriori hypothesis‡	Study sample	0.52	0.48–0.56	0.71	2.1	0.46	0.42–0.50	0.76	2.3
	TACS subgroup	0.49	0.44–0.55	0.64	2.2	0.43	0.38–0.49	0.70	2.4

AUC indicates area under curve for the model; CED, cerebral edema; OR, odds ratio; and TACS, Total Anterior Circulation Syndrome.
*E-value calculated for the point estimate of the OR.
†Number of covariates: 10–13, varying between models.
‡Selected covariates: age, OTT, NIHSS score, stroke unit care.

versus nonrecanalized patients; however, the test for proportionality of odds indicated that the proportionality assumption did not hold.

Discussion

In this large study based on multinational data of patients with acute ischemic stroke treated with recanalization therapy, and radiological evaluation of CED at 22 to 36 hours after start of treatment, we found a significantly lower rate of moderate to severe CED in recanalized patients than nonrecanalized patients at 22 to 36 hours after start of treatment. We found consistent risk reductions of the same magnitude for moderate to severe CED when we adjusted for relevant baseline variables that were selected using 2 alternate procedures and the results were consistent after restriction to the TACS subgroup in which we presume large vessel occlusion is common. Adjustment for PH resulted in only a small change in the effect of recanalization on CED, indicating that most of the effect is not mediated by PH. Recanalization, although associated with higher risk of PH, resulted in lower rates of END, mortality within the first 3 months, and a better functional outcome at 3 months.

Our study strengthens the evidence for the hypothesis that recanalization decreases the risk of CED after cerebral infarct. In particular, our study adds evidence that early (within 22–36 hours) CED is decreased in recanalized patients. Previous studies on the association between recanalization and CED were not consistent.[21] Furthermore, in animal models, reperfusion has been shown to accentuate CED.[6,22–24] In contrast, recent clinical studies with different lengths of radiological follow-up indicate that recanalization decreases CED.[7–9] Using computed tomography angiography scans acquired 24 hours after the reperfusion procedure, similar to our study, researchers doing a post hoc analysis of the MR CLEAN cohort found that patients with successful recanalization on computed tomography angiography at 24 hours had a lower frequency of midline shift compared with those without recanalization (32.7% versus 56%; aOR, 0.34).[8] Together with our results, with differences about patient populations and definitions of edema taken into account, this strengthens the evidence for a decreased risk of early CED after recanalization. There is also evidence that the risk of later CED is decreased.[7,9,25] In a cohort of 130 consecutive patients undergoing mechanical thrombectomy, successful recanalization reduced the occurrence of midline shift ≥5 mm on imaging within 72 hours.[9] Using diffusion-weighted MRI, a post hoc analysis of 2 interventional cohorts found that increasing reperfusion was associated with, and independently predicted, less midline shift and lower swelling volume at 3 to 8 days after the baseline examination.[7] In patients with a low (≤5) ASPECTS (Alberta Stroke Program Early CT Score) at baseline, successful recanalization resulted in a significant reduction of ischemic lesion water uptake 24 to 48 hours after admission as well as a lower frequency of malignant MCA infarctions (26.1% versus 44.3%).[25] A clinical scoring system for malignant brain edema found that nonrevascularization at 24 hours was an independent predictor.[26]

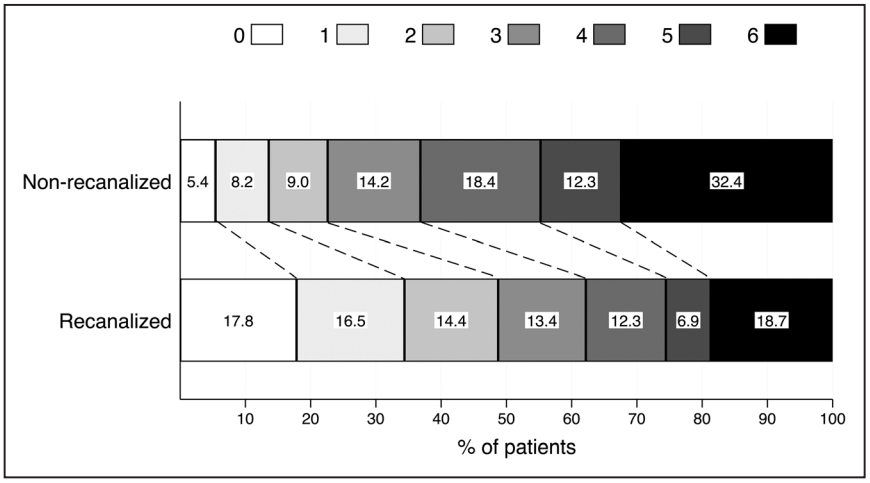

Figure 2. Distribution of modified Rankin Scale score at 3 mo in nonrecanalized vs recanalized patients. Percentages inside bars may not add to 100% because of rounding errors.

Our study showed that recanalization confers a lower risk of CED after ischemic stroke and that this effect remains despite an increased rate of PH. As the development of edema in ischemic stroke is multifactorial, persistent occlusion should be regarded as one important predictor together with other predictors that include the size of the ischemic lesion which reflects on the NIHSS score, collateral status, and size of the occluded artery and the effect of thrombolytic drugs.[14,27–31] On the tissue level, however, both edema and bleeding result from the same process of gradually increasing BBB permeability and damage.[2] Signs of increased permeability, detected as early BBB disruption on computed tomography scan, is seen in 26.7% of patients after EVT.[32] Increased BBB permeability is associated with hemorrhagic transformation and cerebral edema.[33]

This study has several limitations, in addition to the retrospective design with its inherent limitations. First, the exact time of recanalization is not known although it probably tended to occur early as all patients received recanalizing treatment. Second, for most patients, we indirectly detected recanalization through hyperdense artery sign as a surrogate marker for vessel occlusion. Third, we have no data on site of arterial occlusion; we inferred the site through a clinical classification system with the aim of collecting patients with supratentorial large-vessel occlusion. However, data indicate that this is reasonable.[13] Fourth, as there was no central reading of imaging scans, the interpretation of the SITS edema scale may vary between investigators. In favor of the reliability of the SITS edema scale, however, several researchers have used similar imaging findings to classify swelling in cerebral infarcts.[13,21,34,35] A classification scheme that was based on similar imaging findings but consisted of 7 levels was used in IST-3[36] and could classify brain swelling with excellent interrater reliability among experienced neuroradiologists.[37,38] Interrater reliability between experienced and less experienced radiologists was poorer but improved to good or excellent when the classification was simplified to 2 levels,[37] similar to our dichotomized primary outcome of no or mild edema versus moderate to severe edema. Fifth, we cannot exclude that IVT, which 96.4% of patients received, has an effect on the development of edema.[30] Sixth, there may be residual confounding. However, we selected covariates on both statistical and nonstatistical grounds and furthermore used a test of robustness, the E-value, that indicated that to negate the observed results, any unmeasured confounder would need to have an association by a risk ratio of >2.0 with both exposure and outcome above and beyond the included covariates, a situation that is improbable in view of earlier data on risk factors for CED.[14,27,28] Seventh, there is a possibility that, for various reasons, important outcomes were not registered and that some data for outcomes might be missing due to fatal CED or PH, which could have influenced our results. Furthermore, as the protocol specified that only the imaging scan at 22 to 36 hours was obligatory, edema may have developed at a later time point in some patients. The strengths of our study are the large sample size and consistent results regardless of multivariable model and also in the subpopulation including adjusted for PH.

In conclusion, we observed that in patients with acute ischemic stroke, recanalization was associated with a lower risk for CED even after adjustment for higher rate for PH in recanalized patients compared to nonrecanalized patients at 22 to 36 hours. Our results strengthen recent study results and should be taken into account in future trials for EVT with signs of large ischemia.

Acknowledgments

We thank all SITS–ISTR (Safe Implementations of Treatments in Stroke – International Stroke Treatment Registry) investigators and their centers for their participation. We also pass on our thanks to all patients who participated in SITS-ISTR. The current SITS registry is developed, maintained and upgraded by Zitelab, Copenhagen, Denmark, in close collaboration with SITS.

Sources of Funding

Dr Thorén has received grants from Stiftelsen Tornspiran, Stiftelsen Sigurd och Elsa Goljes Minne, STROKE-Riksförbundet, and Capio forskningsstiftelse. Dr Escudero-Martínez has received a grant from Fundación Progreso y Salud, Junta de Andalucía (grant EF-0437-2018). SITS is financed directly and indirectly by grants from Karolinska Institutet, Stockholm County Council, the Swedish Heart-Lung Foundation, the Swedish Order of St. John, Friends of Karolinska Institutet, and private donors, as well as from an unrestricted sponsorship from Boehringer-Ingelheim. SITS has previously received grants from the European Union Framework 7, the European Union Public Health Authority and Ferrer Internacional. SITS is currently conducting studies supported by Boehringer-Ingelheim and EVER Pharma, as well as in collaboration with Karolinska Institutet, supported by Stryker, Covidien, and Phenox. No funding sources had part in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Disclosures

Dr Gdovinova reports grants, personal fees, and nonfinancial support from Boehringer Ingelheim, personal fees and nonfinancial support from Pfizer, personal fees from Bayer, and personal fees from MSD outside the submitted work. Dr Toni reports grants and personal fees from Boehringer Ingelheim, personal fees from Bayer, personal fees from Abbot, personal fees from Daiichi Sankyo, personal fees from Medtronic and personal fees from Pfizer, outside the submitted work. Dr Ahmed reports that he is chair of SITS International which receives grants from the following companies: grants from Boehringer-Ingelheim, grants from Ferrer Internacional, grants from EVER Pharma, grants from Stryker, grants from Covidien, and grants from Phenox, all outside the submitted work. The other authors report no conflicts.

References

1. Battey TW, Karki M, Singhal AB, Wu O, Sadaghiani S, Campbell BC, et al. Brain edema predicts outcome after nonlacunar ischemic stroke. *Stroke*. 2014;45:3643–3648. doi: 10.1161/STROKEAHA.114.006884
2. Stokum JA, Gerzanich V, Simard JM. Molecular pathophysiology of cerebral edema. *J Cereb Blood Flow Metab*. 2016;36:513–538. doi: 10.1177/0271678X15617172
3. Huttner HB, Schwab S. Malignant middle cerebral artery infarction: clinical characteristics, treatment strategies, and future perspectives. *Lancet Neurol*. 2009;8:949–958. doi: 10.1016/S1474-4422(09)70224-8
4. Qureshi AI, Suarez JI, Yahia AM, Mohammad Y, Uzun G, Suri MF, et al. Timing of neurologic deterioration in massive middle cerebral artery infarction: a multicenter review. *Crit Care Med*. 2003;31:272–277. doi: 10.1097/00003246-200301000-00043
5. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, et al; DECIMAL, DESTINY, and HAMLET Investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol*. 2007;6:215–222. doi: 10.1016/S1474-4422(07)70036-4
6. Bai J, Lyden PD. Revisiting cerebral postischemic reperfusion injury: new insights in understanding reperfusion failure, hemorrhage, and edema. *Int J Stroke*. 2015;10:143–152. doi: 10.1111/ijs.12434

7. Irvine HJ, Ostwaldt AC, Bevers MB, Dixon S, Battey TW, Campbell BC, et al. Reperfusion after ischemic stroke is associated with reduced brain edema. *J Cereb Blood Flow Metab*. 2018;38:1807–1817. doi: 10.1177/0271678X17720559
8. Kimberly WT, Dutra BG, Boers AMM, Alves HCBR, Berkhemer OA, van den Berg L, et al; MR CLEAN Investigators. Association of reperfusion with brain edema in patients with acute ischemic stroke: a aecondary analysis of the MR CLEAN Trial. *JAMA Neurol*. 2018;75:453–461. doi: 10.1001/jamaneurol.2017.5162
9. Huang X, Yang Q, Shi X, Xu X, Ge L, Ding X, et al. Predictors of malignant brain edema after mechanical thrombectomy for acute ischemic stroke. *J Neurointerv Surg*. 2019;11:994–998. doi: 10.1136/neurintsurg-2018-014650
10. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al; SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke - Montoring Study (SITS-MOST): an observational study. *Lancet*. 2007;369:275–282. doi: 10.1016/S0140-6736(07)60149-4
11. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;337:1521–1526. doi: 10.1016/0140-6736(91)93206-o
12. Mead GE, Lewis SC, Wardlaw JM, Dennis MS, Warlow CP. How well does the Oxfordshire community stroke project classification predict the site and size of the infarct on brain imaging? *J Neurol Neurosurg Psychiatry*. 2000;68:558–562. doi: 10.1136/jnnp.68.5.558
13. Kobayashi A, Wardlaw JM, Lindley RI, Lewis SC, Sandercock PA, Czlonkowska A; IST-3 Collaborative Group. Oxfordshire community stroke project clinical stroke syndrome and appearances of tissue and vascular lesions on pretreatment ct in hyperacute ischemic stroke among the first 510 patients in the Third International Stroke Trial (IST-3). *Stroke*. 2009;40:743–748. doi: 10.1161/STROKEAHA.108.526772
14. Thorén M, Azevedo E, Dawson J, Egido JA, Falcou A, Ford GA, et al. Predictors for cerebral edema in acute ischemic stroke treated with intravenous thrombolysis. *Stroke*. 2017;48:2464–2471. doi: 10.1161/STROKEAHA.117.018223
15. Strbian D, Meretoja A, Putaala J, Kaste M, Tatlisumak T; Helsinki Stroke Thrombolysis Registry Group. Cerebral edema in acute ischemic stroke patients treated with intravenous thrombolysis. *Int J Stroke*. 2013;8:529–534. doi: 10.1111/j.1747-4949.2012.00781.x
16. von Kummer R, Allen KL, Holle R, Bozzao L, Bastianello S, Manelfe C, et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. *Radiology*. 1997;205:327–333. doi: 10.1148/radiology.205.2.9356611
17. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167:268–274. doi: 10.7326/M16-2607
18. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. *JAMA*. 2019;321:602–603. doi: 10.1001/jama.2018.21554
19. Wolfe R. *OMODEL: Stata Modules to Perform Tests on Ordered Probit and Ordered Logit Models*. Boston College Department of Economics: Statistical Software Components S320901; 1997.
20. Linden A, Mathur MB, VanderWeele TJ. *EVALUE: Stata Module for Conducting Sensitivity Analyses for Unmeasured Confounding in Observational Studies*. Boston College Department of Economics: Statistical Software Components S458592; 2019.
21. Cheripelli BK, Huang X, MacIsaac R, Muir KW. Interaction of recanalization, intracerebral hemorrhage, and cerebral edema after intravenous thrombolysis. *Stroke*. 2016;47:1761–1767. doi: 10.1161/STROKEAHA.116.013142
22. Bell BA, Symon L, Branston NM. CBF and time thresholds for the formation of ischemic cerebral edema, and effect of reperfusion in baboons. *J Neurosurg*. 1985;62:31–41. doi: 10.3171/jns.1985.62.1.0031
23. Gartshore G, Patterson J, Macrae IM. Influence of ischemia and reperfusion on the course of brain tissue swelling and blood-brain barrier permeability in a rodent model of transient focal cerebral ischemia. *Exp Neurol*. 1997;147:353–360. doi: 10.1006/exnr.1997.6635
24. Nour M, Scalzo F, Liebeskind DS. Ischemia-reperfusion injury in stroke. *Interv Neurol*. 2013;1:185–199. doi: 10.1159/000353125
25. Broocks G, Hanning U, Flottmann F, Schönfeld M, Faizy TD, Sporns P, et al. Clinical benefit of thrombectomy in stroke patients with low ASPECTS is mediated by oedema reduction. *Brain*. 2019;142:1399–1407. doi: 10.1093/brain/awz057
26. Jo K, Bajgur SS, Kim H, Choi HA, Huh PW, Lee K. A simple prediction score system for malignant brain edema progression in large hemispheric infarction. *PLoS One*. 2017;12:e0171425. doi: 10.1371/journal.pone.0171425
27. Hofmeijer J, Algra A, Kappelle LJ, van der Worp HB. Predictors of life-threatening brain edema in middle cerebral artery infarction. *Cerebrovasc Dis*. 2008;25:176–184. doi: 10.1159/000113736
28. Wartenberg KE. Malignant middle cerebral artery infarction. *Curr Opin Crit Care*. 2012;18:152–163. doi: 10.1097/MCC.0b013e32835075c5
29. Horsch AD, Dankbaar JW, Stemerdink TA, Bennink E, van Seeters T, Kappelle LJ, et al; DUST Investigators. Imaging findings associated with space-occupying edema in patients with large middle cerebral artery infarcts. *AJNR Am J Neuroradiol*. 2016;37:831–837. doi: 10.3174/ajnr.A4637
30. Paciaroni M, Balucani C, Agnelli G, Caso V, Silvestrelli G, Grotta JC, et al. Systemic thrombolysis in patients with acute ischemic stroke and Internal Carotid ARtery Occlusion: the ICARO study. *Stroke*. 2012;43:125–130. doi: 10.1161/STROKEAHA.111.630624
31. Fredriksson L, Lawrence DA, Medcalf RL. tPA Modulation of the blood-brain barrier: a unifying explanation for the pleiotropic effects of tPA in the CNS. *Semin Thromb Hemost*. 2017;43:154–168. doi: 10.1055/s-0036-1586229
32. Shi ZS, Duckwiler GR, Jahan R, Tateshima S, Szeder V, Saver JL, et al. Early blood-brain barrier disruption after mechanical thrombectomy in acute ischemic stroke. *J Neuroimaging*. 2018;28:283–288. doi: 10.1111/jon.12504
33. Hom J, Dankbaar JW, Soares BP, Schneider T, Cheng SC, Bredno J, et al. Blood-brain barrier permeability assessed by perfusion CT predicts symptomatic hemorrhagic transformation and malignant edema in acute ischemic stroke. *AJNR Am J Neuroradiol*. 2011;32:41–48. doi: 10.3174/ajnr.A2244
34. Kasner SE, Demchuk AM, Berrouschot J, Schmutzhard E, Harms L, Verro P, et al. Predictors of fatal brain edema in massive hemispheric ischemic stroke. *Stroke*. 2001;32:2117–2123. doi: 10.1161/hs0901.095719
35. Dora B, Mihçi E, Eser A, Ozdemir C, Cakir M, Balci MK, et al. Prolonged hyperglycemia in the early subacute period after cerebral infarction: effects on short term prognosis. *Acta Neurol Belg*. 2004;104:64–67.
36. The IST-3 collaborative group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [ist-3]): a randomised controlled trial. *Lancet*. 2012;379:2352–2363. doi: 10.1016/S0140-6736(12)60768-5
37. Wardlaw JM, Sellar R. A simple practical classification of cerebral infarcts on CT and its interobserver reliability. *AJNR Am J Neuroradiol*. 1994;15:1933–1939.
38. Wardlaw JM, von Kummer R, Farrall AJ, Chappell FM, Hill M, Perry D. A large web-based observer reliability study of early ischaemic signs on computed tomography. The Acute Cerebral CT Evaluation of Stroke Study (ACCESS). *PLoS One*. 2010;5:e15757. doi: 10.1371/journal.pone.0015757