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FULL PAPER

Utility of a rescue endovascular therapy for the treatment of major strokes refractory to full-dose intravenous thrombolysis

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Objective: Large artery occlusion (LAO) in patients with major stroke predicts poor revascularization by intravenous thrombolysis (IVT) and more likely results in a poor outcome. We focused on the effects of intra-arterial thrombolysis (IAT) and endovascular mechanical recanalization (EMR) as rescue therapies in major strokes refractory to IVT.

Methods: A retrospective analysis of 87 patients (National Institutes of Health Stroke Scale >20), who did not respond to full-dose IVT due to LAO, was performed based on their endovascular therapy status. IAT was performed as an intraclot infusion of alteplase, and EMR was provided by the Solitaire device™ (Covidien, Dublin, Ireland). The recanalization and 3-month outcome rates after IAT/EMR were correlated with a group of patients who were scheduled to receive endovascular treatment but who underwent only IVT.

Results: We achieved successful recanalization by IAT and EMR in 68.7% and 76.1% of patients, respectively. Despite no significant differences in mortality between IAT and EMR, a trend towards better outcomes after IAT and a statistically significant increase for outcome-modified Rankin scale (mRS) 0–3 (45.7%) and mRS 0–2 (34.9%) after EMR was noted when compared with IVT. The degree of recanalization did not correlate with the functional results except for the good-moderate outcome after successful recanalization by EMR.

Conclusion: EMR by the Solitaire device is a safe and beneficial method for the rescue treatment of patients with major stroke whose neurological status does not improve and who fail to recanalize the LAO after a 1-h full dose of IVT.

Advances in knowledge: The article verifies efficiency of the Solitaire device in major strokes.

Stroke is the third most common cause of death in developed countries, exceeded only by coronary heart disease and cancer. Generally, acute ischaemic strokes (AIS) account for >80% of the total number of strokes, and up to 20% of these strokes are severe due to a large artery occlusion (LAO). The World Health Organization estimates that approximately 15 million people suffer stroke worldwide each year. One-third of whom die and another third are permanently disabled. Although the incidence of stroke is declining in many developed countries as a result of better high blood pressure control and smoking reduction, the absolute number of strokes is increasing because of the ageing population.

Moreover, owing to health comorbidities and behavioural risks, the severity of AIS after the onset is an independent prognostic factor associated with outcome. The most

commonly used scale for the measurement of stroke severity that has demonstrated prognostic value is the National Institutes of Health Stroke Scale (NIHSS). Generally, patients with mild strokes (NIHSS <4) have no visible or only minimal arterial occlusion, and they are likely to have a good outcome even without therapy. By contrast, patients with the most severe strokes (NIHSS >20) have a high probability of large and more proximal vessel occlusions, which predicts poor revascularization by intravenous thrombolysis (IVT) alone and leads to poorer outcomes regardless of treatment methods.¹

Prompt reperfusion of the ischaemic brain is the cornerstone of effective therapy for AIS and results in better clinical outcomes. IVT is currently the only validated approach for the effective treatment of stroke patients. Its administration to patients is recommended during a period

from 3 h to a maximum of 4.5 h from stroke onset.² An intravenous route also remains the fastest way to initiate treatment, particularly at primary stroke centres. The traditional time window for AIS treatment is prolonged for intra-arterial thrombolysis (IAT) to 6 h and for endovascular mechanical recanalization (EMR) up to 8 h from stroke onset or from the last time the patient was known to be without symptoms.^{1,2}

Although IAT is the standard treatment in many centres, it remains an off-label therapy for any available fibrinolytic agent that requires further confirmation of its safety and efficacy for on-label applications. The hypothesis of our study is that intra-arterial delivery of a fibrinolytic agent directly into the thrombus forms a relatively high local concentration of the agent that cannot be achieved by systemic administration. We subsequently propose that combined IVT and IAT might be a more efficient way to achieve rapid recanalization in cases of LAO. A higher potential for more complete recanalization by IAT has been studied, mainly in two randomized, multicentre, controlled trials [Prolyse in Acute Cerebral Thromboembolism (PROACT)-I and PROACT-II] and numerous other case series.¹ Despite a demonstrated high recanalization rate for IAT, the number of patients who demonstrate a positive and long-term functional outcome cannot be predicted as a result of the outcome of IVT alone.³

From a mechanical viewpoint, artery occlusion results in a need for the development of devices for endovascular removal of blood clots. There are currently four devices cleared by the Food and Drug Administration (FDA) for EMR of arterial occlusion in patients with AIS, including the Merci retrieval system®, the Penumbra system®, the Solitaire device™ and the Trevo® retriever. Although these devices have been successfully approved for restoring blood flow within occluded arteries, none of them currently has FDA clinical approval because of the need for a demonstrated superior effect compared with IVT in comparative randomized trials. According to recent studies, there are strong advantages to using the Solitaire device, including a higher recanalization level, better safety and improved clinical outcomes than for the Merci retrieval system.⁴

Many recent studies do not demonstrate the benefits of endovascular techniques as primary therapy procedures in AIS treatment compared with IVT. On the other hand, these studies have mostly tried to prove the efficiency of endovascular *vs* intravenous treatment in patients across all spectrums of stroke severity, with a predominance of patients with NIHSS ≤ 20 . However, patients with a major AIS (M-AIS; NIHSS > 20) who have a high probability of LAO and/or large thrombus length respond less well to IVT, thus these specific patients could profit from endovascular techniques.¹ The aim of our study was to compare recanalization rates and outcomes of rescue IAT and EMR in patients with M-AIS who do not improve after full-dose IVT.

METHODS AND MATERIALS

A prospectively collected database of patients with AIS, who received treatment at the Stoke Unit of the St Anne's University Hospital in Brno, Czech Republic, were analysed retrospectively. A total of 87 patients refractory to full-dose IVT were indicated for an additional endovascular procedure (IAT or EMR) from

February 2008 to September 2012. In accordance with the development of endovascular procedures, our centre changed its treatment strategy during the time interval of this study from IAT to EMR. IAT was the primary additional therapy with IVT until the introduction of EMR techniques in April 2010.

All patients were evaluated by a stroke neurologist after admission to the hospital, and the initial NIHSS was recorded. Then, they underwent emergency brain CT and head–neck CT angiography according to the local protocol. CT scans were evaluated for evidence of early signs of infarction, vessel thrombosis or bleeding. All patients received full-dose IVT by recombinant tissue plasminogen activator (rtPA) (0.9 mg kg^{-1} , maximum dose 90 mg) within 3 h of AIS onset. The patients with LAO who presented as refractory to IVT were selected for rescue endovascular treatment. The failure of IVT corresponded to no improvement or worsening of neurological status, as assessed by NIHSS score, and/or no signs of recanalization or early arterial reocclusion during the 1-h rtPA infusion as detected by transcranial Doppler ultrasonography obtained every 30 min.⁵ The degree of LAO in patients indicated for endovascular treatment was thereafter confirmed by intraprocedural digital subtraction angiography. All patients were admitted to the stroke unit with standard monitoring. Anticoagulant therapy was started 24 h after the procedure if a control brain CT ruled out the presence of a haemorrhage. Any intracranial bleeding leading to neurological deterioration was marked as symptomatic. Repeat brain CT scans were routinely obtained after another 24 h or whenever a patient's neurological condition worsened.

Procedure and techniques

All endovascular procedures were performed under general anaesthesia in a biplane neuroangiography suite equipped with digital subtraction angiography and road mapping capabilities. IAT was performed by direct microcatheter as an intraclot infusion of rtPA (up to 22 mg) following full-dose IVT. From 2010, interventional neuroradiologists attempted EMR using the Solitaire device, continuing until successful recanalization was achieved or until three passes of the device through any vessel had been completed.

Data analysis

Only patients with a M-AIS corresponding to NIHSS > 20 and an LAO [*i.e.* the internal carotid artery (ICA), the proximal M1 segment of the middle cerebral artery (MCA) or the basilar artery (BA)] according to CT angiography were enrolled in the study. They were divided according to prescribed endovascular technique into either an IAT or EMR group. In addition to the patients observed after endovascular treatment, we also observed a small control group of patients with NIHSS > 20 undergoing unsuccessful IVT (IVT group), who were indicated for endovascular treatment that could not ultimately be completed owing to anatomical or technical hindrances.

Anonymized angiograms before and after the endovascular treatment were analysed by the same independent neuroradiologist, and the degree of revascularization was expressed according to the thrombolysis in cerebral infarction (TICI) classification.⁶ In-line with published studies, we marked TICI ≥ 2 involving the partial

Table 1. Overview of the intravenous thrombolysis (IVT), intra-arterial thrombolysis (IAT), and endovascular mechanical recanalization (EMR) groups

Characteristics	IVT		IAT		EMR	
Number of patients	10.3% (9/87)		36.8% (32/87)		52.9% (46/87)	
Age, years (median, years)	69 (range, 53–83)		65 (range, 25–86)		63 (range, 13–83)	
Gender						
Male	66.7% (6/9)		53.1% (17/32)		54.3% (25/46)	
Female	33.3% (3/9)		46.9% (15/32)		45.7% (21/46)	
Artery						
ICA	11.1% (1/9)		43.8% (14/32)		17.4% (8/46)	
MCA	66.7% (6/9)		12.4% (4/32)		58.7% (27/46)	
BA	22.2% (2/9)		43.8% (14/32)		23.9% (11/46)	
Admission						
Time to IAT/EMR, hours			3.9 (range, 2.7–4.7)		4.4 (range, 3.1–5.5)	
NIHSS	27 (range, 22–30)		24 (range, 21–29)		23 (range, 21–28)	
Before treatment						
TICI 0	88.9% (8/9)		75% (24/32)		69.6% (32/46)	
TICI 1	11.1% (1/9)		25% (8/32)		30.4% (14/46)	
Treatment						
Treatment time, hours			1.8 (range, 1.5–2.2)		1.6 (range, 0.7–3.0)	
After treatment						
TICI 0	88.9% (8/9)		6.3% (2/32)		8.7% (4/46)	
TICI 1	11.1% (1/9)		25.0% (8/32)		15.2% (7/46)	
TICI 2a	0% (0/9)	0% (0/9)	15.6% (5/32)	68.7% (22/32)	21.7% (10/46)	76.1% (35/46)
TICI 2b	0% (0/9)		25.0% (8/32)		19.6% (9/46)	
TICI 3	0% (0/9)		28.1% (9/32)		34.8% (16/46)	
ICH	0% (0/9)		6.25% (2/32)		4.3% (2/46)	
Outcome (3 months)						
mRS 0–2 per minor	0% (0/9)	0% (0/9)	28.1% (9/32)	34.4% (11/32)	^a 34.9% (16/46) ^a	45.7% (21/46)*
mRS 3 per moderate	0% (0/9)		6.3% (2/32)		10.8% (5/46)	
mRS 4–5 per major	22.2% (2/9)		28.1% (9/32)		10.7% (5/46)	
mRS 6 per death	77.8% (7/9)		37.5% (12/32)		43.5% (20/46)	

BA, basilar artery; ICA, internal carotid artery; ICH, intracerebral haemorrhage; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Score; TICI, thrombolysis in cerebral infarction score.

Bracket denotes the significant difference to IVT group when comparing outcome categories in general.

^aDifferences to IVT with statistical significance $p < 0.05$.

(TICI 2a) and complete recanalization (TICI 2b and 3) as successful vessel recanalization.

Clinical functional outcome was measured using the modified Rankin scale (mRS) after 3 months. The patients were divided according to their outcomes into groups with minor disability (mRS 0–2), moderate disability (mRS 3), major disability (mRS 4–5) and death (mRS 6). Generally, only results in the range from mRS 0–2 are considered to be good outcomes. Because we focused on patients with M-AIS, we defined a group of favourable “good–moderate” outcomes as “minor–moderate

disability” (mRS 0–3), where minor disability corresponded with functional independence of the patient and patients with acceptable moderate disability who required some help but were able to walk unassisted.

The data were analysed using the SPSS® Statistics software (IBM Corporation, Armonk, NY). Non-parametric Mann–Whitney tests were used to analyse significant differences between median values. A Student’s *t*-test of independent samples was performed to compare means, and either a Pearson’s χ^2 test or Fisher’s exact test was used to compare proportions.

RESULTS

A total of 87 patients with M-AIS (NIHSS >20) due to LAO (ICA, MCA and BA) at admission to a hospital were eligible for an endovascular treatment between February 2008 and September 2012. The patients ($n = 32$) undergoing IAT between February 2008 and March 2010 comprised 17 males and 15 females, with a median age at treatment of 65 years. Subsequently, the rest of the patients ($n = 46$) treated by EMR between April 2010 and September 2012 comprised 25 males and 21 females, with a median age at treatment of 63 years. Overall, nine patients indicated for endovascular treatment underwent initial digital subtraction angiography without any following endovascular treatment owing to anatomical and/or technical hindrance. This control group treated by IVT alone included six males and three females with a median age of 69 years. Owing to an absence of any significant differences in the non-Gaussian distribution of age among the IVT, IAT and EMR groups ($p = 0.093$), subsequent comparisons were processed regardless of patient age.

The main baseline characteristics for all patient sets are presented in Table 1. Differences in distribution of vascular territories between IAT and EMR groups are caused by an extension of treatment possibilities owing to the introduction of EMR in our centre. Thus, the transport of patients with MCA occlusion (and expected better prognosis) from local stroke units to our complex cerebrovascular centre could probably account for the increase in the total number of patients in the EMR group, especially those with MCA occlusion.

Degree of revascularization

The degree of vessel recanalization of both endovascular procedures was assessed by the TIC1 score in the final angiography finding (Table 1). Overall, arteries displayed successful recanalization of expected vascular territory (TIC1 ≥ 2) in 73.1% of cases after the endovascular treatment (IAT and EMR). Taking the prescribed endovascular method into consideration, EMR results showed a non-significantly higher degree of successful revascularization (76.1%) compared than those of IAT (68.7%; $p = 0.605$). The success of the endovascular treatment was significantly gender dependent in the EMR group ($p = 0.008$). Complete recanalization (TIC1 2b and 3) by EMR was mainly achieved in males, whereas partial filling of the vascular territory (TIC1 2a) was achieved more frequently in females. Neither the sex of the patients nor the age of the patient influenced the degree of vessel recanalization in the IAT group ($p = 0.596$), regardless of the endovascular technique used, i.e. IAT or EMR ($p = 0.633$ or 0.133 , respectively). We found no significant difference in the degree of recanalization among the occluded ICA, MCA and BA after IAT ($p > 0.999$) or after EMR ($p = 0.795$; Figure 1). The degrees of vessel recanalization in ICA, MCA and BA were also not dependent on the prescribed endovascular technique ($p = 0.343$, >0.999 and >0.999 , respectively).

Functional outcome

The functional results of the patients undergoing the appropriate endovascular treatment were assessed by mRS after 3 months (Table 1). In addition to a good outcome, usually defined as mRS 0–2, the range 0–3 of mRS was considered to

represent a favourable good–moderate outcome, and a mRS of 6 determined mortality.

Outcome of intravenous thrombolysis vs both the endovascular techniques

All patients with M-AIS who did not respond to initial IVT and underwent digital subtraction angiography but received no endovascular treatment eventually had a major disability (22.2% mRS 5) or died (77.8% mRS 6) within 3 months. 32 (41.0%) patients treated with IAT/EMR had good–moderate outcomes with minor–moderate disability and 25 (32.1%) of them even had good–excellent outcomes after 3 months. Moreover, 14 (18.0%) patients had major disability (mRS 4–5) after the same period of time. Neurologic deterioration and/or major comorbidities resulting in death were present in 32 (41.0%) patients, regardless of the endovascular treatment. The outcomes of the patients treated by both the endovascular methods differed significantly from the outcomes of the patients undergoing only IVT ($p = 0.024$). Despite non-significant results between mortality rates ($p = 0.072$), good–moderate outcomes were significantly more frequent after the endovascular treatment ($p = 0.023$) than the group of patients undergoing only IVT.

Outcome of intravenous thrombolysis vs each endovascular technique separately

When the outcome in patients with M-AIS and persisting LAO after IVT was compared with the outcome in patients undergoing endovascular treatment by IAT, there were no significant differences in good as well as good–moderate outcomes or in mortality after 3 months ($p = 0.167$, 0.083 and 0.057 , respectively). On the other hand, the proportions of good–moderate outcomes ($p = 0.009$) and even good outcomes (mRS ≤ 2 ; $p = 0.043$) were significantly higher after EMR than the outcome in patients who underwent only unsuccessful IVT. However, there were no significant differences in mortality between IVT and EMR groups after 3 months ($p = 0.078$).

Figure 1. Dependence of successful recanalization [thrombolysis in cerebral infarction (TIC1) ≥ 2] on the endovascular technique used in separate occluded arteries. BA, basilar artery; EMR, endovascular mechanical recanalization group; IAT, intra-arterial thrombolysis group; ICA, internal carotid artery; MCA, middle cerebral artery.

Outcome of intra-arterial thrombolysis vs endovascular mechanical recanalization

The differences in functional outcomes did not reach statistical significance between the IAT and EMR sets ($p = 0.163$), as well as when comparing individual outcome groups after the same period of time (minor disability vs minor-moderate disability vs major disability vs death; $p = 0.6255, 0.354, 0.072$ and 0.646 , respectively; Table 1). The degree of disability after 3 months did not differ significantly when comparing the occluded arteries (ICA, MCA and BA) separately for IAT ($p = 0.315$) and EMR ($p = 0.935$), nor did the outcome between IAT and EMR for a particular artery occlusion ($p = 0.998, 0.345$ and 0.692 ; Figure 2).

Relationship between degree of recanalization and functional outcome

The comparison of outcomes 3 months after IAT and the degree of recanalization described by TICI showed a trend towards more good-moderate outcomes after a successful recanalization (TICI ≥ 2), and severe disability (mRS 4–5) or death were more frequent after failed recanalization (TICI < 2). Nevertheless, these correlations were not statistically significant with regard to the occluded artery (Table 2). Although, there was no significant correlation between the 3-month outcome and the degree of recanalization for particular arteries after EMR, we found a positive correlation when the comparison was made, regardless of the occluded artery ($p = 0.014$). The good-moderate outcome after EMR was significantly more frequent in patients with successful artery recanalization, but failed revascularization did not significantly determine a bad functional result.

Relationship between time to recanalization and functional outcome

There was no significant correlation between time to recanalization and outcome in both the endovascular groups (IAT and EMR; $p = 0.443$ and 0.329 , respectively).

Figure 2. Dependence of the good-moderate outcome [modified Rankin scale (mRS) ≤ 3] and mortality (mRS 6) on the used endovascular technique in the separate occluded arteries. BA, basilar artery; EMR, endovascular mechanical recanalization group; IAT, intra-arterial thrombolysis group; ICA, internal carotid artery; MCA, middle cerebral artery.

Risk of intracerebral bleeding

Our endovascular procedures were complicated by symptomatic intracerebral bleeding in two (6.25%) patients after IAT and two (4.3%) patients after EMR. Both patients after IAT died within 3 months, as did one patient after EMR. The final patient observed after EMR had a severe disability (mRS 5) after 3 months. The rate of bleeding complications was not significantly different between the two endovascular methods of treatment ($p > 0.999$).

DISCUSSION

The most important variable predicting good outcomes after AIS treatment is the early and successful recanalization of the occluded artery, corresponding to Grades 2a, 2b and 3 using the TICI classification. Based on a meta-analysis of >2000 patients with AIS, Rha and Saver⁷ determined the overall spontaneous recanalization rate to be 24.1%. The recanalization rate after IVT was approximately twice the spontaneous rate and reached 46.2%.

Nevertheless, IVT has only a modest effect in stroke due to LAO and nearly no potential to recanalize occluded vessels if the thrombus length exceeds 8 mm.⁸ In addition, stroke caused by cholesterol and calcified emboli or based on atherosclerotic stenosis responds poorly to IVT. Because AIS due to LAO have a higher morbidity and mortality than other AIS types, new treatment strategies as alternative options to IVT have been studied in an attempt to improve the degree of revascularization, as have outcomes in major strokes due to proximal occlusions of the large cerebral vessels, such as the ICA, MCA and BA.⁹ Although there is a growing interest in recanalization of artery occlusions by endovascular techniques, their efficacy in treatment of AIS remains unclear.

Unfortunately, IVT is available only within a period of 3–4.5 h and has contraindications, such as recent surgery. Another disadvantage of IVT is that the recanalization rate is $<50\%$.¹⁰ Intra-arterial delivery of fibrinolytic agents directly into the thrombus results in a relatively high local concentration of the agent that cannot be reached by systemic administration. The higher potential for more complete recanalization by IAT has mainly been explored in two randomized, multicentre, controlled trials (PROACT-I and PROACT-II) and numerous other case series.¹ Despite the demonstrated higher recanalization rate of IAT, only 40–50% of patients with favourable angiographic findings demonstrate a positive, long-term, functional outcome.³ Because many of these studies, including the most recent Interventional Management of Stroke III study, have demonstrated only a minor or non-significant increase in good outcomes, IAT with recombinant pro-urokinase or rtPA still represents an “off-label” therapy that may be considered as a supplementary therapy for carefully selected patients with an M-AIS of <6 h duration and who do not recanalize or clinically improve after IVT.²

In our retrospective study, we assessed the effect of IAT in patients with M-AIS (NIHSS >20) who do not show an improvement in their neurological status and who failed to

Table 2. Relationship between the degree of recanalization [thrombolysis in cerebral infarction (TICI)] and the functional outcome [modified Rankin Scale (mRS)] in the intra-arterial thrombolysis (IAT) and endovascular mechanical recanalization (EMR) groups

Assessment	IAT		EMR	
	TICI <2	TICI ≥2	TICI <2	TICI ≥2
ICA				
mRS 0–2 (%)	0.0 (0/5)	44.4 (4/9)	0.0 (0/2)	33.3 (2/6)
mRS 0–3 (%)	20.0 (1/5)	44.4 (4/9)	0.0 (0/2)	50.0 (3/6)
mRS 4–5 (%)	20.0 (1/5)	22.2 (2/9)	50.0 (1/2)	16.7 (1/6)
mRS 6 (%)	60.0 (3/5)	33.4 (3/9)	50.0 (1/2)	33.3 (2/6)
MCA				
mRS 0–2 (%)	0.0 (0/1)	66.7 (2/3)	16.7 (1/6)	52.4 (11/21)
mRS 0–3 (%)	100.0 (1/1)	66.7 (2/3)	16.7 (1/6)	57.1 (12/21)
mRS 4–5 (%)	0.0 (0/1)	33.3 (1/3)	33.3 (2/6)	9.5 (2/21)
mRS 6 (%)	0.0 (0/1)	0.0 (0/3)	50.0 (3/6)	33.4 (7/21)
BA				
mRS 0–2 (%)	0.0 (0/4)	30.0 (3/10)	0.0 (0/3)	25.0 (2/8)
mRS 0–3 (%)	0.0 (0/4)	30.0 (3/10)	0.0 (0/3)	50.0 (4/8)
mRS 4–5 (%)	25.0 (1/4)	40.0 (4/10)	33.3 (1/3)	12.5 (1/8)
mRS 6 (%)	75.0 (3/4)	30.0 (3/10)	66.7 (2/3)	37.5 (3/8)
Overall				
mRS 0–2 (%)	0.0 (0/10)	40.9 (9/22)	9.1 (1/11)	^a 42.9 (15/35)
mRS 0–3 (%)	20.0 (2/10)	40.9 (9/22)	9.1 (1/11)	54.3 (19/35) ^a
mRS 4–5 (%)	20.0 (2/10)	31.8 (7/22)	36.4 (4/11)	11.4 (4/35)
mRS 6 (%)	60.0 (6/10)	27.3 (6/22)	54.5 (6/11)	34.3 (12/35)

BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery.

Bracket denotes positive correlation between the degree of recanalization and outcome in general.

^aPositive correlation between the outcome category and the degree of recanalization with statistical significance $p < 0.05$.

recanalize the LAO within 1 h after IVT as measured by transcranial Doppler ultrasound.⁵ This IAT was the primary supplement therapy in addition to IVT in our institution until the introduction of EMR techniques in April 2010. We achieved an overall successful recanalization rate (TICI ≥2) of approximately two-thirds (68.7%) of patients, which is comparable to other studies.¹ Despite the generally poor prognosis of patients with M-AIS and failed IVT, we found only a general trend towards better functional results after 3 months in the group undergoing additional IAT and no statistically significant differences compared with the IVT treatment alone. A good-moderate functional result (mRS ≤3) was observed in approximately one-third of patients (34.4%), which corresponds to the approximately 50% of patients with long-term functional outcomes after successful recanalization as noted by Hallevi *et al.*³

Some researchers believe that IAT may be beneficial for patients with diminished collateral circulation; typically, in proximal MCA occlusions, approximately a quarter of patients have a poor collateral flow measured by the Sylvian fissure and the

leptomeningeal convexity vessels on CT angiography.¹⁰ Because the lenticulostriate arteries are not collateralized from the cortex in patients with a proximal MCA occlusion, the use of treatment strategies such as IAT, which result in a higher recanalization rate, may decrease the risk of a poor outcome due to infarction of the internal capsule. Despite the lack of statistical significance for IAT efficiency in M-AIS due to LAO, we must note that some of our patients benefitted from additional IAT, mainly those with the proximal MCA occlusion. Thus, the collateral circulation providing retrograde filling of ischaemic territory is an additional important element of revascularization that still must be considered.

Because recanalization of a long-segment artery occlusion by IAT alone was often unsuccessful in spite of the larger volume of fibrinolytic agent and results of the pilot studies showing the superior recanalization rate of EMR, the endovascular approach for AIS is now shifting from IAT to EMR. Initial studies researching efficiency of EMR in AIS treatment used the Merci® retriever (Concentric Medical, Fremont, CA; Merci and

multi-Merci trials) and reported an overall successful revascularization rate in approximately 65% of the patients. Afterwards, in the multi-Merci trial that analysed data from the largest prospective registry of mechanical embolectomy in patients who failed IVT, successful recanalization was reported in 80% of patients, but a good clinical outcome was noted in only approximately one-third (31.6%) of patients enrolled, the same as the portion (33.4%) who died.¹¹

According to the most recent guidelines from the American Heart Association/American Stroke Association² the Merci, Penumbra system, Solitaire and Trevo thrombectomy devices can be used for mechanical recanalization in carefully selected patients (Class IIa; Level of Evidence B), but their ability to improve patient outcomes has not yet been established. The Solitaire, a self-expanding retrievable stent originally designed for the treatment of cerebral aneurysms, is the most widely used device at present because its recanalization rate was confirmed by the SWIFT study to be near 90%, which is superior to findings in the Penumbra Pivotal Stroke trial (81.6%) and the multi-Merci trial (69.5%).¹²

At our institution, we are using the Solitaire device for EMR in patients with M-AIS due to LAO refractory to IVT as of April 2010. Based on our data, we have achieved a good recanalization rate (marked as TICI >2) in 76.1% of patients, which corresponds with the generally reported recanalization success rate of the Solitaire device. Despite the high recanalization rate, the outcomes of our patients were inferior to the results of the SWIFT study and even lower than the generally presented good results (mRS ≤2) with IVT. 34.9% of all the patients with NIHSS >20 at admission to a hospital were fully independent (mRS ≤2), and 45.7% of patients had good-moderate outcomes (mRS ≤3) after 3 months. Although a good outcome after stroke is usually considered to include only full functional independence (mRS ≤2), we think that a good-moderate functional result corresponding to mRS ≤3 in patients with M-AIS should be considered an acceptable outcome because mRS 3 denotes, at worst, moderately disabled people who require some help, but who are able to walk unassisted.

The results of the studies that focused on EMR treatment of IAS are equivocal because some trials in patients with stroke found that EMR therapy is not superior to the standard systemic treatment with intravenous rtPA. For example, one of the most recent studies focused on the benefit of a combined endovascular approach towards intravenous rtPA alone but was stopped early because it did not find a significant difference in functional outcomes after IVT followed by an endovascular therapy, as compared with IVT alone.¹³ However, our results cannot be directly compared with those of studies comprising patients with the full spectrum of stroke severity because the severity of a stroke as expressed by NIHSS at admission is only one important predictor of the outcome.¹

Broderick et al¹³ also speculated that the efficacy of endovascular therapy would be greater mainly in participants with severe stroke (NIHSS score ≥20). Nevertheless, they have found no significant difference in the proportion of patients with a good

outcome (mRS ≤2) after 90 days when comparing their endovascular-therapy group and their group undergoing IVT alone; they achieved only 23.8% good outcomes after endovascular treatment. We, however, have achieved a higher proportion of patients with a good outcome (34.9% with mRS ≤2). This discrepancy could be explained by our choice of device. While the authors of the aforementioned study used not only the Solitaire but also other devices that have generally lower recanalization rates, we used only the Solitaire device for EMR treatment.

In addition to patients observed after endovascular treatment, we also observed a small group of patients with M-AIS undergoing unsuccessful IVT who were indicated for endovascular treatment but could not be operated on owing to anatomical or technical hindrances. When we compared our results from EMR with the outcomes of this control group, we found significantly better results not only for good-moderate outcomes (mRS ≤3) but also for fully independent patients (mRS ≤2) at 3 months from EMR. Thus, the difference between Broderick et al's¹³ and our study may not only be due to a different type of revascularization device but also be due to the different profiles of the patients for the validation of EMR efficiency. Broderick et al used patients with no angiographic evidence of a treatable occlusion, who may have had generally better prognoses than patients with persistent artery occlusion in our study. Generally, patients with mild strokes (NIHSS <4) often have no visible or only minimal arterial occlusion, and they are likely to have a good outcome without any therapy. By contrast, patients with the most severe strokes (NIHSS >20) are more likely to have a poor outcome regardless of treatment methods.¹ Thus, it is questionable to directly compare the effectiveness of endovascular techniques and the results of IVT in the whole spectrum of stroke patients because endovascular treatment is preferentially designated for treatment of LAO that causes more severe AIS with generally worse outcomes.

Similar to the IAT group, we found no significant differences in the degree of recanalization or in clinical outcomes when we compared results after EMR according to the individual arteries.

Because our study focused on patients with a severe type of AIS, we predicted a high mortality rate regardless of the endovascular treatment. Overall mortality did not significantly differ between the IAT and EMR groups (37.5% and 43.5%, respectively). Although other studies have found overall lower mortality rates, our findings correspond to the results of the Merci registry study in which mortality was 40–50% in patients with NIHSS >25 despite successful recanalization.¹ Moreover, similar mortality rates of 33.8% have been described in patients with NIHSS >20 after the endovascular treatment of stroke in the most recent study by Broderick et al.¹³ Because our rate of significant intracerebral haematoma reached 6.25% after IAT and 4.3% after EMR, this high mortality corresponds to the natural course of M-AIS rather than to direct complications of the endovascular procedures. Because an approximately 40% mortality rate has been found in published studies comprising patients with AIS and NIHSS >20 at admission who were treated only by IVT, we conclude that our endovascular procedures do not improve

mortality rates in patients with M-AIS treated primarily by full-dose IVT.

As we have noted, the rate of successful recanalization in M-AIS due to LAO is comparable to the general values in patients with all degrees of a stroke severity. Thus, the recanalization rate is a feature of the endovascular procedure rather than the nature of the stroke. On the other hand, the outcomes of patients with M-AIS do not correspond to the high degrees of recanalization. When we compared the recanalization rate and the outcome of our patients, we found no correlation between these results in either group of endovascular treatment, except for a significant correlation between successful recanalization (TICI ≥ 2) and a good-moderate outcome (mRS ≤ 3) after EMR treatment. In addition, we did not confirm any significant correlation between time to recanalization and 3-month outcome after IAT as well as after EMR. However, recanalization is a more minor predictor of clinical outcome than reperfusion and the initial NIHSS score.¹⁴ Because recanalization, *i.e.* restoration of proximal vessel patency, does not guarantee tissue reperfusion owing to distal branch occlusions, a higher probability of persistent reperfusion failure after endovascular treatment of LAO and a high initial NIHSS score of patients with M-AIS could affect the 3-month outcome more strongly than time to recanalization up to 6 h for AIT and 8 h for EMR. Thus, multimodal imaging techniques including perfusion imaging seem to be very helpful for the selection of patients with M-AIS who have a good likelihood of profiting from endovascular revascularization techniques.¹⁵

Although we have found no statistical correlation between time to recanalization and outcome in the both endovascular groups (IAT and EMR), short time from symptom onset to recanalization is one of main prognostic factors for predicting a good clinical

outcome after thrombectomy at 3 months.¹⁶ Thus, it is presumable that longer time to recanalization in a rescue endovascular therapy is another factor that negatively affects the 3-month outcome and results in generally worse outcomes in our study compared than those reported in the recent literature.²

A major limitation of our single-centre study is its retrospective nature and a relatively small number of cases mainly in the control IVT group. It is caused by a limited number of patients with M-AIS and persistent LAO who failed IVT and did not undergo additional endovascular treatment in the time window. Thus, large multicentric prospective clinical trials are needed to prove the benefit of a rescue endovascular therapy for patients with M-AIS who fail to IVT.

In conclusion, we demonstrated that EMR by the Solitaire device is safe and beneficial for the rescue treatment of patients with M-AIS of up to 8 h of duration who do not improve their neurological status and who fail to recanalize the LAO by full-dose IVT within 1 h. The findings support a recommendation in the most recent guidelines of the American Heart Association/American Stroke Association for the early management of stroke patients with LAO non-responding to IVT. Because of a disconnect between artery recanalization rates and functional outcomes, the success of endovascular methods in the treatment of an ischemic stroke is a question of correct and early indication rather than a question of method effectiveness in general. Thus, the determination of selection criteria for the patients who could primarily benefit from endovascular treatment after M-AIS needs to be further investigated with additional studies.

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REFERENCES

1. Abou-Chebl A. Intra-arterial therapy for acute ischemic stroke. *Neurotherapeutics* 2011; **8**: 400–13. doi: 10.1007/s13311-011-0059-8
2. Jauch EC, Saver JL, Adams HP, Bruno A, Connors JJB, Demers BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**: 870–947. doi: 10.1161/STR.0b013e318284056a
3. Hallevi H, Barreto AD, Liebeskind DS, Morales MM, Martin-Schild SB, Abraham AT, et al. Identifying patients at high risk for poor outcome after intra-arterial therapy for acute ischemic stroke. *Stroke* 2009; **40**: 1780–5. doi: 10.1161/STROKEAHA.108.535146
4. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* 2012; **380**: 1241–9. doi: 10.1016/S0140-6736(12)61384-1
5. Rubiera M, Ribo M, Pagola J, Coscojuela P, Rodriguez-Luna D, Maisterra O, et al. Bridging intravenous-intra-arterial rescue strategy increases recanalization and the likelihood of a good outcome in non-responder intravenous tissue plasminogen activator-treated patients: a case-control study. *Stroke* 2011; **42**: 993–7.
6. Kallmes DF. TICI: if you are not confused, then you are not paying attention. *AJNR Am J Neuroradiol* 2012; **33**: 975–6. doi: 10.3174/ajnr.A2905
7. Rha J-H, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke* 2007; **38**: 967–73. doi: 10.1161/01.STR.0000258112.14918.24
8. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingle R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke* 2011; **42**: 1775–7. doi: 10.1161/STROKEAHA.110.609693
9. Kondziella D, Cortsen M, Eskesen V, Hansen K, Holtmannspötter M, Højgaard J, et al. Update on acute endovascular and surgical stroke treatment. *Acta Neurol Scand* 2013; **127**: 1–9. doi: 10.1111/j.1600-0404.2012.01702.x
10. Ishkanian A, McCullough-Hicks ME, Appelboom G, Piazza MA, Hwang BY, Bruce SS, et al. Improving patient selection for endovascular treatment of acute cerebral ischemia:

- a review of the literature and an external validation of the Houston IAT and THRIVE predictive scoring systems. *Neurosurg Focus* 2011; **30**: E7.
11. Alshekhlee A, Pandya DJ, English J, Zaidat OO, Mueller N, Gupta R, et al. Merci mechanical thrombectomy retriever for acute ischemic stroke therapy: literature review. *Neurology* 2012; **79**(Suppl. 1): S126–34. doi: [10.1212/WNL.0b013e3182697e89](https://doi.org/10.1212/WNL.0b013e3182697e89)
  12. Koh JS, Lee SJ, Ryu C-W, Kim HS. Safety and efficacy of mechanical thrombectomy with solitaire stent retrieval for acute ischemic stroke: a systematic review. *Neurointervention* 2012; **7**: 1–9. doi: [10.5469/neuroint.2012.7.1.1](https://doi.org/10.5469/neuroint.2012.7.1.1)
  13. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013; **368**: 893–903. doi: [10.1056/NEJMoa1214300](https://doi.org/10.1056/NEJMoa1214300)
  14. Eilaghi A, Brooks J, d'Estre C, Zhang L, Swartz RH, Lee TY, et al. Reperfusion is a stronger predictor of good clinical outcome than recanalization in ischemic stroke. *Radiology* 2013; **269**: 240–8. doi: [10.1148/radiol.13122327](https://doi.org/10.1148/radiol.13122327)
  15. Bivard A, Spratt N, Levi C, Parsons M. Perfusion computer tomography: imaging and clinical validation in acute ischaemic stroke. *Brain* 2011; **134**(Pt 11): 3408–16. doi: [10.1093/brain/awr257](https://doi.org/10.1093/brain/awr257)
  16. Raoult H, Eugène F, Ferré JC, Gentric JC, Ronzière T, Stamm A, et al. Prognostic factors for outcomes after mechanical thrombectomy with solitaire stent. *J Neuro-radiol* 2013; **40**: 252–9. doi: [10.1016/j.neurad.2013.04.001](https://doi.org/10.1016/j.neurad.2013.04.001)