Efficacy of Endovascular Treatment for Acute Cerebral Large-Vessel Occlusion: Analysis of Nationwide Prospective Registry

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Background: The aim of this nationwide, prospective registry of acute cerebral largevessel occlusion was to assess the efficacy of endovascular treatment (EVT) on outcome in the "real-world" settings. Methods: Medical information of the patients was anonymized and registered prospectively through a Web site from 84 medical centers in Japan. Reperfusion of the affected arteries was evaluated by the Thrombolysis in Cerebral Infarction grade on cerebral angiography or by the modified Mori grade on magnetic resonance angiography. Clinical outcome was evaluated by modified Rankin Scale (mRS) at 90 days after onset. Symptomatic intracranial hemorrhage and procedure-related complications were also analyzed. Results: Among intravenous tissue plasminogen activator (IV t-PA)-failed patients, no significant difference in favorable outcome was seen with or without EVT overall (41.7% versus 36.8%, P = .55). However, EVT significantly increased favorable outcomes (mRS score 0-2) in patients with internal carotid artery (ICA)/middle cerebral artery M1/basilar artery (BA) occlusion (41.3% versus 20.5%, P = .019). In contrast, among t-PA-ineligible patients, EVT significantly increased favorable outcomes overall (29.1% versus 19.5%; odds ratio, 1.70; P = .007). Furthermore, favorable outcomes were more common in patients with ICA/M1/BA occlusion (29.0% versus 10.3%; odds ratio, 3.56; P < .0001). Multivariate analysis also confirmed the efficacy of IV t-PA, EVT, and their combination for favorable outcome. Conclusions: EVT significantly improved clinical outcomes in IV t-PA-failed and t-PA-ineligible patients with ICA/M1/BA occlusion. These findings support the introduction of EVT for acute proximal artery occlusion. Key Words: Acute stroke-large-vessel occlusion-endovascular treatment-tissue plasminogen activator-national registry.

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Introduction

Although the introduction of intravenous (IV) administration of recombinant tissue plasminogen activator (t-PA) has had a significant impact on the treatment of acute stroke, problems with its use have become apparent. For example, IV t-PA is reportedly used in less than 5% of all ischemic stroke cases, and the rate of early recanalization of the affected artery, which reportedly correlates with better clinical outcomes, appears low.¹⁻³ The rate of recanalization is known to be higher with intra-arterial (IA) treatments, such as thrombolysis and mechanical procedures than with IV t-PA.² Endovascular treatment (EVT), such as mechanical thrombectomy, balloon angioplasty, or thrombolysis, has been associated with higher rate of reperfusion,⁴⁻¹⁰ but recent randomized, controlled trials have failed to confirm its clinical efficacy compared with IV t-PA or standard care.¹¹⁻¹³

As the first nationwide, prospective registry of acute cerebral large-vessel occlusion, this study was conducted to assess the impact of EVT on clinical outcome following approval of a mechanical clot retriever in Japan.

Methods

The registry covered all patients with acute stroke because of large-vessel occlusion who were admitted to 84 participating medical centers within 24 hours after onset between July 1, 2010, and June 30, 2011. Medical information of the patients was anonymized and registered prospectively through a Web site (http://www.rescue-japan. jp). Factors related to treatment selection and outcomes were investigated as follows: time to admission, type of stroke, occluded vessel, National Institutes of Health Stroke Scale (NIHSS) score on admission, modified Rankin scale (mRS) score 3 months after onset, and treatments including various devices for EVT, medications, and laboratory data. The methods, results, and complications of EVT were precisely recorded. The study was approved by the local institutional review committee in each hospital, and its protocol was registered (University Hospital Medical Information Network: UMIN000003412). The register of patients was monitored to rule out selection bias by monitoring committee.

Primary and Secondary Outcomes

The primary outcome was the rate of an mRS score of 0-2 at 90 days after onset. Secondary outcomes were (1) recanalization of the target vessel (immediately after treatment and 24 hours after onset), (2) rate of an mRS score of 0-1 at 90 days after onset, (3) NIHSS score on admission and 7 days after onset, (4) relationship between recanalization and prognosis, (5) symptomatic intracranial hemorrhage within 24 hours after onset, (6) death within 90 days after onset, and (7) other adverse events.

Neurologic Evaluation

NIHSS score was evaluated on admission, 1 hour after bolus injection of t-PA, immediately after EVT, 24 (± 8) hours after onset, and 7 (± 2) days after onset.

Computed Tomography and Magnetic Resonance Imaging

All patients underwent repeated computed tomography (CT) or magnetic resonance imaging (MRI) with MR angiography at 24 (± 8) hours after onset, except for patients admitted 16-24 hours after onset.

Intravenous Tissue Plasminogen Activator

IV t-PA was performed as the first-line treatment within 3 hours of symptom onset, in accordance with the standard protocol in Japan (.6 mg/kg dose, 10% bolus, 90% continuously infused over 60 minutes).¹⁴

Endovascular Treatment

EVT was performed basically IV t-PA-failed or t-PAineligible patients within 8 hours after onset. EVT was defined as IA catheter procedures such as clot removal/ aspiration, balloon angioplasty, stenting, and IA thrombolysis using a microcatheter.

Reperfusion Analysis

Neuroimaging studies at baseline with CT or MR angiography were performed for proving large arterial occlusion. When IV t-PA was performed, reperfusion of the affected artery was evaluated on cerebral angiography or MR angiography at 1-3 hours after t-PA bolus injection and at 24 (\pm 8) hours after onset. In cases of EVT, reperfusion of the affected artery was evaluated on final angiography and on MR angiography at 24 (\pm 8) hours after onset.

On cerebral angiography, reperfusion was classified according to the modified Thrombolysis in Cerebral Infarction (TICI) grade.¹⁵ Grade 0, no perfusion; grade 1, perfusion past the initial obstruction, but limited distal branch filling with little or slow distal perfusion; grade 2, penetration with minimal perfusion; grade 2A, perfusion of less than half of the vascular distribution of the occluded artery; grade 2B, perfusion of half or greater of the vascular distribution of the occluded artery; and grade 3, full perfusion with filling of all distal branches.

On MR angiography, reperfusion was evaluated according to the modified Mori grade.¹⁶ Grade 0, no reperfusion; grade 1, movement of thrombus not associated with any flow improvement; grade 2, partial (branch) recanalization in less than 50% of the branches in the occluded arterial territory; and grade 3, nearly complete recanalization with reperfusion in >50% of the branches in the occluded arterial territory.



Successful reperfusion in this study was defined as grades 2B and 3 using TICI grading or grade 3 using modified Mori's grading.

IV t-PA-failed patients were defined as those patients whose vessel was not significantly reperfused, that is, showing modified Mori's grade 0-1 on MR angiography or TICI grade 0-1 on cerebral angiography at 1-3 hours after the bolus injection of t-PA.

Evaluation of Clinical Outcome

Scale.

Patient outcomes were evaluated using the mRS on admission and 90 (±10) days after onset. A favorable outcome was defined as an mRS score of 0-2.

Evaluation of Symptomatic Hemorrhage

In this study, intracranial hemorrhage within 24 \pm 8 hours after onset was evaluated on follow-up imaging. Symptomatic hemorrhage was defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study definition,¹⁷ local or remote parenchymal hematoma type 2 on follow-up imaging, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or lowest value between baseline and 24 hours or hemorrhage leading to death.

Statistical Analysis

Statistical analysis was performed using commercially available software (JMP 7; SAS Institute, Cary, NC). The statistical significance of intergroup differences was assessed using the t test for quantitative scales, Pearson χ^2 test for categorical scales, and the Mann–Whitney U test or Wilcoxon signed-rank test for ordinal scales. Values of P less than .05 were considered significant. Statistical analysis was carried out by members of the writing committee.

Results

Backgrounds and Characteristics of Patients

Of the 1454 registered patients, 1442 patients (99.2%) met the inclusion criteria and were analyzed in this study (Fig 1, Table 1). Median baseline NIHSS score on admission was 16 (interquartile range, 9-21), and median time from onset to admission was 125 minutes (interquartile range, 60-300 minutes). In this study, 849 patients (58.9%) arrived within 3 hours and 312 patients (21.6%) arrived 3-8 hours after onset.

Cardioembolic infarction was diagnosed in 1023 patients (71.0%), and atherothrombotic infarction was diagnosed in 288 (20.0%). The occluded vessel was the internal carotid artery (ICA) in 407 patients (28.2%), the MCA in 760 (52.7%), the basilar artery (BA) in 99 (6.9%), and multiple in 57 patients (4.0%).

Reperfusion after IV t-PA and Clinical Outcome

In the 449 patients who received IV t-PA, 318 underwent a reperfusion study: 147 patients (46.2%) underwent cerebral angiography alone, 119 patients (37.4%) underwent repeated MR angiography alone, and 52 patients underwent both (16.3%).

On cerebral angiography, reperfusion was judged 1-3 hours after IV t-PA by the TICI grade.¹⁵ Successful reperfusion, defined as grade 2B or 3, was obtained in 11% of ICA cases, 29.2% of proximal M1 cases, 37.8% of distal M1 cases, 40.7% of M2 or distal cases, and 23.6% of BA cases (Fig 2).

Clinical outcomes of patients were also analyzed by location of vessel occlusion (Table 2). Overall, a significant difference in the rate of successful reperfusion was evident between patients treated by IV t-PA alone and IV t-PA + EVT (43.5% versus 62.8%, OR 2.19, P = .006), but clinical outcome showed no significant difference (42.2% versus 44.5%, OR 1.09, P = .65). In

Table 1. Baseline characteristics of patients

	Median (IQR) or n (%)
Total number of munched	1442
patients	
Mean age, y	75.5 (67-83)
Sex, female	634 (44.0)
Hypertension	818 (56.7)
Diabetes mellitus	282 (19.6)
Hyperlipidemia	283 (19.6)
Atrial fibrillation	853 (59.2)
Congestive heart failure	170 (11.8)
Smoking	203 (14.1)
Systolic BP, mm Hg	157 (139-174)
Diastolic BP, mm Hg	84 (72-97)
Serum glucose, mg/dL	127 (109-154.5)
Baseline NIHSS score	16 (9-21)
Onset to admission, min	125 (60-300)
Within 3 h	849 (58.9)
3-8 h	312 (21.6)
More than 8 h	192 (13.3)
Unknown	89 (6.2)
Stroke subtype	
Cardioembolic infarction	1023 (71.0)
Atherothrombotic infarction	288 (20.0)
Others/unclassified	131 (9.1)
Occluded vessel	
ICA	407 (28.2)
Extracranial ICA	195 (13.5)
Intracranial ICA	186 (12.9)
ICA (unknown)	26 (1.8)
МСА	760 (52.7)
Proximal M1	263 (18.2)
Distal M1	223 (15.5)
M1 (unknown)	5 (.3)
M2 or distal	269 (18.7)
BA	99 (6.9)
PCA	52 (3.6)
VA	32(3.0) 32(2.2)
ACA	17(12)
Multiple	57 (4.0)
Others	104(72)
Unknown	151(1.2) 15(1.0)
UIIKIIOWII	15 (1.0)

Abbreviations: ACA, anterior cerebral artery; BA, basilar artery; BP, blood pressure; ICA, internal carotid artery; IQR, interquartile range; M1, middle cerebral artery M1 portion; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery.

the ICA, successful reperfusion and favorable outcome (mRS score 0-2) were more common after IV t-PA + EVT than after IV t-PA alone (reperfusion: 56.0% versus 18.8%, OR 5.51, P = .0006; favorable outcome: 43.8% versus 21.4%, OR 2.85, P = .015). However, other vessels such as the M1 and BA showed no significant differences in rate of successful reperfusion or favorable outcome.



Figure 2. Reperfusion of the affected arteries on cerebral angiography after intravenous tissue plasminogen activator. Reperfusion of the affected arteries was evaluated by the TICI grade on cerebral angiography; grade 0, no perfusion; grade 1, perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion; grade 2, penetration with minimal perfusion; grade 2A, perfusion of less than half of the vascular distribution of the occluded artery; grade 2B, perfusion of half or greater of the vascular distribution of the occluded artery; and grade 3, full perfusion with filling of all distal branches. Successful reperfusion, defined as grade 2B or 3, was obtained in 11% of ICA cases, 29.2% of proximal M1 portion of middle cerebral artery cases, 37.8% of distal M1 cases, 40.7% of M2 or distal cases, and 23.6% of BA cases. Abbreviations: BA, basilar artery; ICA, internal carotid artery; TICI, Thrombolysis in Cerebral Infarction.

Effect of EVT for IV t-PA-Failed Patients

Next, the effect of EVT for IV t-PA–failed patients was analyzed. Of the 168 IV t-PA–failed patients, 110 were treated with EVT. The EVT group was younger (71.5 versus 76 years, P = .024) and contained fewer patients with hypertension (52.7% versus 69%, P = .041), but neurologic grade was significantly worse (median NIHSS score: 17 versus 14, P = .0019). Median duration to EVT was 210 minutes (range, 180-245 minutes) after onset.

A difference was seen in the rate of successful reperfusion (88.3% versus 42.0%, P < .0001, Table 3), but no significant difference in favorable outcome was seen between patients with or without EVT overall (41.7% versus 36.8%, P = .55). EVT significantly increased favorable outcomes (mRS score 0-2) in patients with ICA/M1/ BA occlusion (41.3% versus 20.5%, P = .019, Table 3, Fig 3, A). These results suggest that EVT was effective to obtain better clinical outcomes for IV t-PA–failed patients with ICA/M1/BA occlusion.

Effect of EVT for IV t-PA–Ineligible Patients

The effect of EVT for IV t-PA–ineligible patients was then evaluated. Among 993 patients who did not undergo IV t-PA, 636 patients with NIHSS score of 4 or more and arrived within 8 hours after onset were judged as candidates for EVT (Fig 1). Among these 636 patients, 220 were treated with EVT. The EVT group was significantly younger (73 versus 78 years, P < .0001) and included fewer women (37.7% versus 50.2%, P = .0025), although

	Reperfusion analysis ($n = 318$)		Outcome analysis (n = 442)			
	Successful reperfusion*, n (%)	OR (95% CI)	Р	Favorable outcome [†] , n (%)	OR (95% CI)	Р
Total	167 (52.5%)			190 (43.0%)		
IV t-PA alone	74 (43.5%)	2.19 (1.40-3.46)	.006	125 (42.2%)	1.09 (.74-1.64)	.65
IV t-PA + EVT	93 (62.8%)			65 (44.5%)		
ICA	34 (41.5%)			33 (31.7%)		
IV t-PA alone	6 (18.8%)	5.51 (2.03-17.0)	.0006	12 (21.4%)	2.85 (1.23-6.87)	.015
IV t-PA + EVT	28 (56.0%)			21 (43.8%)		
M1	73 (58.6%)			70 (39.3%)		
IV t-PA alone	36 (51.4%)	1.40 (.70-2.81)	.34	42 (36.2%)	1.45 (.77-2.72)	.25
IV t-PA + EVT	37 (59.7%)			28 (45.2%)		
BA	19 (79.2)			13 (43.3)		
IV t-PA alone	7 (70.0)	2.57 (.35-23.4)	.35	7 (43.8)	.96 (.22-4.15)	.96
IV t-PA + EVT	12 (85.7)			6 (42.9)		
Others	64 (50.8%)			106 (54.6%)		
IV t-PA alone	42 (47.7%)	1.51 (.70-3.28)	.29	88 (56.4%)	.70 (.34-1.42)	.32
IV t-PA + EVT	22 (57.9%)			18 (47.4%)		

 Table 2. Analysis of reperfusion and outcome by location of vessel occlusion

Abbreviations: EVT, endovascular treatment; IV t-PA, intravenous tissue plasminogen activator; M1, middle cerebral artery M1 portion; OR, odds ratio; CI, confidence interval.

*Successful reperfusion, Thrombolysis in Cerebral Infarction grades 2B and 3 or modified Mori's grade 3.

†Favorable outcome, modified Rankin Scale score 0-2 at 90 days after onset.

neurologic score was not different (NIHSS: 18 versus 17, P = .52). Median duration to EVT was 240 minutes (range, 179-346 minutes) after onset.

Against this background, EVT increased the rates of successful reperfusion (78.5% versus 44.5%, OR 4.54, P < .0001, Table 3) and favorable outcomes (29.1% versus 19.5%, OR 1.70, P = .007). Furthermore, favorable outcomes were more common in patients with ICA/M1/BA occlusion (29.0% versus 10.3%, OR 3.56, P < .0001, Fig 3, B).

These results suggest that EVT was effective for obtaining better clinical outcomes in IV t-PA–ineligible patients, particularly when the occlusion involved proximal arteries.

Symptomatic Intracranial Hemorrhage

Of the 1360 patients who underwent repeated CT or MRI at 24 ± 8 hours after onset, symptomatic hemorrhage was observed in 46 (3.4%) overall, comprising 13 of 644 patients (2.0%) in the conservative group treated without IV t-PA or EVT, 11 of 292 patients (3.8%) with IV t-PA, 8 of 148 patients (5.4%) with IV t-PA and EVT, and 13 of 264 patients (4.9%) with EVT only. The rate of symptomatic intracranial hemorrhage (sICH) in patients treated with IV t-PA alone was comparable with that seen in the Japanese postmarketing trial of alteplase.¹⁶ No significant increase in sICH was observed in either the IV t-PA

Table 3.	Analysis of reperfusion	and outcome in I	IV t-PA–failed or i	t-PA-ineligible patients

IV t-PA-failed patients	With EVT $(n = 110)$	Without EVT $(n = 58)$	Р	OR (95% CI)
Successful reperfusion Favorable outcome	68/77 (88.3)	21/50 (42.0)	<.0001	10.4 (4.42-26.7)
Overall	45/108 (41.7)	21/57 (36.8)	.55	1.22 (0.64-2.39)
ICA/M1/BA occlusion	38/92 (41.3)	8/39 (20.5)	.019	2.73 (1.17-6.96)
IV t-PA-ineligible patients	With EVT $(n = 220)$	Without EVT $(n = 416)$	Р	OR (95% CI)
Successful reperfusion* Favorable outcome†	135/172 (78.5)	110/247 (44.5)	<.0001	4.54 (2.94-7.14)
Overall	64/220 (29.1)	80/410 (19.5)	.007	1.70 (1.16-2.48)
ICA/M1/BA occlusion	51/176 (29.0)	29/282 (10.3)	<.0001	3.56 (2.17-5.95)

Abbreviations: BA, basilar artery; CI, confidence interval; EVT, endovascular treatment; ICA, internal carotid artery; M1, middle cerebral artery M1 portion; OR, odds ratio.

*Successful reperfusion, Thrombolysis in Cerebral Infarction grades 2B and 3 or modified Mori's grade 3.

†Favorable outcome, modified Rankin Scale score 0-2 at 90 days after onset.

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Figure 3. Functional outcome at 90 days in the patients with ICA/M1/BA occlusion. (A) Functional outcome at 90 days in the IV t-PA-failed patients with or without EVT. Shown are 90-day mRS scores in patients undergoing additional EVT or receiving standard medical care for the IV t-PA-failed patients with ICA/M1/BA occlusion. The percentages of patients are shown in, above, or below each cell. Additional EVT was superior to standard medical care in IV t-PA-failed patients with ICA/M1/BA occlusion (P = .019). (B) Functional outcome at 90 days in the IV t-PA-ineligible patients with or without EVT. EVT was superior to standard care in IV t-PA-failed patients with ICA/M1/BA occlusion (P = .019). (B) Functional outcome at 90 days in the IV t-PA-ineligible patients with or without EVT. EVT was superior to standard care in IV t-PA-ineligible patients with a superior to standard care in IV t-PA-ineligible patients with or without EVT. EVT was superior to standard care in IV t-PA-ineligible patients with ICA/M1/BA occlusion (P < .0001). Abbreviations: BA, basilar artery; EVT, endovascular treatment; ICA, internal carotid artery; IV t-PA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale.

and EVT group or EVT-alone group compared with the IV t-PA group (P = .42 and P = .50, respectively).

Procedure-Related Complications after EVT

Procedure-related complications were observed in 32 of 268 procedures (11.9%) in the EVT-alone group, of which 9 (3.4%) were clinically significant. On the other hand, procedure-related complications were seen with 16 of 148 procedures (10.8%) in the IV t-PA and EVT group, of which 4 (2.7%) were clinically significant. There was no significant difference between the EVT-alone group and IV t-PA and EVT group.

Characteristics for Favorable Outcome at 90 Days

Multivariate regression analysis indicated that higher baseline NIHSS and higher age were significantly related to unfavorable outcome, whereas IV t-PA + EVT, IV t-PA, and EVT were all associated with favorable outcome significantly (Table 4). Odds ratio was highest in combination with IV t-PA + EVT, IV t-PA alone, and EVT alone in order.

 Table 4. Characteristics associated with favorable outcome at 90 d

Characteristic	Р	OR (95% CI)
Baseline NIHSS, per 1-point increase	<.0001	.876 (.858894)
Age, per 1-y increase	<.0001	.963 (.951975)
Sex, male (0) vs female (1)	.534	.914 (.688-1.214)
IV t-PA + EVT	<.0001	3.244 (2.055-5.120)
IV t-PA alone	<.0001	2.971 (2.097-4.209)
EVT alone	.007	1.699 (1.156-2.498)

Abbreviations: NIHSS, National Institutes of Health Stroke Scale.

Discussion

In this nationwide registry study of acute large-vessel occlusion, EVT significantly increased the rate of favorable outcomes in patients with ICA occlusion but not with other vessel occlusion. Among IV t-PA-failed patients, EVT increased the rate of favorable outcomes in patients with ICA/M1/BA occlusion but not overall. In contrast, among IV t-PA-ineligible patients, EVT increased the rate of favorable outcomes regardless of the affected vessels, and favorable outcomes were more common in patients with ICA/M1/BA occlusion. The reason for better outcomes involving these proximal vessels might be that catheter interventions were feasible, and successful reperfusion by IV t-PA alone was rare. In fact, a significant increase in successful reperfusion was seen with addition of EVT in both IV t-PA-failed and t-PA-ineligible patients with ICA/M1/BA. Patient selection based on preprocedural vessel imaging is thus key to obtain a favorable effect with EVT.

On the other hand, recent randomized, controlled trials failed to show the efficacy of EVT for acute stroke.¹¹⁻¹³ For example, the Interventional Management of Stroke III trial was performed to determine whether a combined approach with IV t-PA and EVT is more effective than IV t-PA alone. However, that trial did not show any benefit in terms of functional outcome from the use of EVT.¹¹ The Synthesis Expansion and the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial likewise failed to show any efficacy of EVT.^{12,13} The failure of these trials might be attributable to delayed initiation of EVT and/or insufficient reperfusion using first-generation devices. In this registry, EVT was started much earlier (210 minutes after onset in RESCUE-Japan versus more than 360 minutes in MR RESCUE), and the reperfusion rate was much higher than that of MR RESCUE (TICI IIb-III: 52.5% in RESCUE-Japan versus 26% in MR RESCUE).¹³ The reason for the higher rate of reperfusion in the present study might be because of unlimited use of endovascular devices such as stents and balloons. These differences should be considered when designing future comparative studies.

The disadvantages of EVT also need to be kept in mind. For example, the device may injure the vessel, resulting in intracranial hemorrhage or infarction. The incidence of clinically significant procedure-related complications was 3.4% with EVT alone and 2.8% with IV t-PA and EVT in the present study, comparable with the 5.5% in the Multi MERCI trial.⁸ Furthermore, symptomatic hemorrhage was not significantly elevated by EVT after IV t-PA in this study. The incidence of complications with current EVT, thus, seems acceptable.

This study had some limitations. In this study, baseline characteristics were not balanced because the study was not a randomized trial. Also, treatment selection was made in each institute independently, which might have affected the clinical outcomes. To clarify the real clinical impact of EVT for acute stroke, randomized trials applying new-generation devices such as stent retrievers with appropriate patient selection using vessel imaging should be performed in the near future.

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