ORIGINAL RESEARCH

Endovascular Therapy in Ischemic Stroke With Acute Large-Vessel Occlusion: Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism Japan Registry 2

Shinichi Yoshimura, MD, PhD; Nobuyuki Sakai, MD, PhD; Kazutaka Uchida, MD; Hiroshi Yamagami, MD, PhD; Masayuki Ezura, MD, PhD; Yasushi Okada, MD, PhD; Kazuo Kitagawa, MD, PhD; Kazumi Kimura, MD, PhD; Makoto Sasaki, MD, PhD; Norio Tanahashi, MD, PhD; Kazunori Toyoda, MD, PhD; Eisuke Furui, MD, PhD; Yuji Matsumaru, MD, PhD; Kazuo Minematsu, MD, PhD; Takeshi Morimoto, MD, PhD, MPH

***Background*—**Endovascular therapy has been shown to be effective in patients with acute cerebral large-vessel occlusion, but real-world efficacies are unknown.

***Methods and Results*—**We conducted a prospective registry at 46 centers between October 2014 and January 2017. Eligible patients were those who were aged 20 years or older, with acute cerebral large-vessel occlusion, and who were hospitalized within 24 hours of the onset. We enrolled both consecutive patients who were treated with or without endovascular therapy. Endovascular therapy included thrombectomy, balloon angioplasty, stenting, local fibrinolysis, and piercing. The primary outcome was a favorable outcome as defined by a modified Rankin Scale of 0 to 2 at 90 days after onset. Secondary outcomes were modified Rankin Scale of 0 to 1 and mortality. Safety outcomes were intracerebral hemorrhage or a recurrence of ischemic stroke. We constructed the 2242 (1121 each) propensity score–matched patients cohort based on a propensity score for endovascular therapy and estimated the adjusted odds ratio, followed by sensitivity analyses on original 2399 (1278 in endovascular therapy versus 1121 in no endovascular therapy) patients. In the propensity score–matched cohort, favorable outcomes were observed in 35.3% and 30.7% of patients in the endovascular therapy and no endovascular therapy groups, respectively (P=0.02). The adjusted odds ratio for the favorable outcome was 1.44 (95% confidence interval, 1.10–1.86, P=0.007). The efficacy of endovascular therapy in achieving favorable outcomes did not differ between our subgroups and in the sensitivity analyses.

***Conclusions*—**Endovascular therapy decreased disabilities at 90 days in real-world patients with acute cerebral large-vessel occlusion.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT02419794. **(*J Am Heart Assoc*. 2018;7: e008796. DOI: 10.1161/JAHA.118.008796.)**

Key Words: endovascular therapy • large-vessel occlusion • propensity score • registry • stroke

Endovascular therapy (EVT) for acute stroke caused by large-vessel occlusion (LVO) has been shown in several randomized controlled trials (RCTs) to effectively reduce disabilities.[1–5] These randomized trials attested to the efficacy of EVT in patients with occlusions of solely the anterior circulation. Moreover, 12.3% of acute strokes were caused by

From the Department of Neurosurgery, Hyogo College of Medicine, Nishinomiya, Japan (S.Y., K.U.); Department of Neurosurgery, Kobe City Medical Center General Hospital, Kobe, Japan (N.S.); Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Suita, Japan (H.Y.); Department of Neurosurgery, National Hospital Organization Sendai Medical Center, Sendai, Japan (M.E.); Cerebrovascular Center, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan (Y.O.); Department of Neurology, Tokyo Women's Medical University, Tokyo, Japan (K. Kitagawa); Department of Neurological Science, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan (K. Kimura); Institute for Biomedical Sciences, Iwate Medical University, Iwate, Japan (M.S.); Department of Neurology, Saitama Medical University International Medical Center, Saitama, Japan (N.T.); Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan (K.T., K.M.); Stroke Center, Saiseikai Toyama Hospital, Toyama, Japan (E.F.); Department of Neurosurgery, Tsukuba University, Tsukuba, Japan (Y.M.); Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan (K.U., T.M.).

Correspondence to: Takeshi Morimoto, MD, PhD, MPH, Department of Clinical Epidemiology, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan. E-mail: t-morimoto@umin.net

Received February 19, 2018; accepted March 28, 2018.

Clinical Perspective

What Is New?

- This is the largest registry of 2399 consecutive patients with acute cerebral large-vessel occlusions.
- Endovascular therapy decreased disabilities at 90 days without apparent safety concerns in patients with acute cerebral large-vessel occlusion at real-world settings.

What Are the Clinical Implications?

- Endovascular therapy should be considered in patients with acute cerebral large-vessel occlusions in any setting if there were no definitive contraindications.
- The effectiveness of endovascular therapy for some patients off the current guidelines should be attested in future research, such as those with larger stroke volume, mild disability, posterior circulations, or later arrival time.

occlusions in the posterior circulation,[6] and mortality rates during hospitalization were 30% in patients with posterior circulation occlusions, which was higher than their counterparts.[7] In addition, most of the enrolled patients received recombinant intravenous tissue plasminogen activator (rt-PA) before EVT, but the efficacy of EVT without intravenous rt-PA was uncertain in the previous RCTs that evaluated EVT.

The effectiveness of EVT for acute cerebral LVO, other than intracranial internal carotid artery or M1 portion of the middle cerebral artery, is still unclear. Also, the dosages used in intravenous rt-PA in Japan are different from those in other countries such as Europe and the United States based on previous observational studies.[8] Therefore, we conducted a prospective registry of consecutive patients with acute LVO, irrespective of the site of occlusions or treatment modalities used, in order to clarify the generalizability of the effectiveness of EVT in real-world patients.

Methods

The RESCUE-Japan Registry 2 (Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Registry 2) was a prospective, multicenter registry enrolling consecutive patients with acute cerebral LVO in 46 centers in Japan between October 2014 and September 2016. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. We enrolled consecutive patients who were aged 20 years or older and hospitalized within 24 hours of the onset of acute cerebral LVO. If the exact onset time was unknown, it was regarded to be the time when the patients were witnessed as safe. If the stroke was too severe to evaluate the occlusion site and the information was not available, such patients were not registered. The institutional review boards of all 46 participating centers approved the protocol. Written informed consent from each patient was waived in this study because we used clinical information obtained in routine clinical practice. Institutional review boards approved the exemption in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The Independent Data Safety Monitoring Board periodically reviewed the progress of this study. All study centers were regularly alerted by the study secretariat not to miss the consecutive patients with acute LVO.

Endovascular Therapy

The diagnostic and treatment modalities were determined by the physician in charge. EVT consisted of thrombectomy using any devise approved in Japan, such as stent retrievers and/or aspiration catheter, balloon angioplasty, stenting, local fibrinolysis, piercing using guidewires and/or microcatheters, or a combination of these treatments. The stent retrievers used in this study were the Solitaire™ 2 Revascularization Device (Covidien Irvine, CA), the Trevo® ProVue Retriever/Trevo® XP ProVue Retriever (Stryker, Fremont, CA), and the Revive® (Codman, MA). The aspiration catheter used was the Penumbra System® (Penumbra, CA). Other devices for EVT procedures such as stenting or angioplasty were selected by the physicians in charge.

Other systemic treatments including antithrombotic therapies were also determined by the physician in charge, according to the most current and best available evidence.

Outcomes

We measured the patients' disabilities using the modified Rankin Scale (mRS).[9] If the mRS could not be assessed, the patients or their legally authorized representatives were contacted via telephone to estimate the mRS. The assessments of mRS were required to be conducted by an independent physician who had not treated the patient.

We set the primary outcome to be a favorable outcome, as defined by mRS ranging 0 to 2, and evaluated at 90 days after the stroke onset. Secondary outcomes were considered to be either an excellent outcome, as defined by mRS ranging 0 to 1 at 90 days, or mortality at 90 days. Safety outcomes included any intracranial hemorrhage, symptomatic intracranial hemorrhage within 72 hours after the onset of the stroke,[10] or recurrence of stroke or transient ischemic attack within 90 days. Symptomatic intracranial hemorrhage indicated neurological worsening more than 4 points in National Institutes of Health Stroke Scale (NIHSS).[11]

Data Collection and Definitions

The collection of clinical information was conducted through a review of the hospital charts. Follow-up information up to 90 days was mainly collected by a review of the hospital charts, and any additional information was collected by making contact with patients, relatives, and referring physicians. In addition to patients' characteristics, we collected the data on mRS before the onset of the stroke, NIHSS score, the time from onset of symptoms or stroke to receipt of medical care, the use of intravenous rt-PA, and the classification of the stroke. Acute ischemic stroke was classified as cardioembolic, atherothrombotic, cryptogenic, or others.[12] Because the diagnostic modalities were different between the centers, we measured the extent of the stroke using the Alberta Stroke Program Early CT Score (ASPECTS), as seen on diffusion-weighted image (DWI) in magnetic resonance imaging (MRI) or noncontrast computed tomography (NCCT). We evaluated these findings on the day of admission and 3 days after the onset of the stroke.[13,14] In patients who had stroke in the area of the posterior circulation, we measured the pc-ASPECTS (posterior circulation ASPECTS) on DWI with magnetic resonance imaging.[15] All ASPECTS results of ASPECTS on NCCT, ASPECTS on DWI, or DWI pc—ASPECTS measurements from either of the diagnostic modalities provided scores ranging from 0 to 10, with the higher scores representing smaller early ischemic change. ASPECTS or pc-ASPECTS were defined as ASPECTS on NCCT, ASPECTS on DWI, or DWI pc-ASPECTS. We also classified the location of the occlusion by using either magnetic resonance angiography, computed tomography angiography, or digital subtraction angiography.[16–18]

Data were recorded on a standardized electronic data capture and sent to a centralized center over a secured internet. All fields were examined for missing data or outliers, and investigators were asked to complete or correct the data wherever possible and necessary. Outlying data were checked and excluded if they were erroneous, but such exclusions accounted for <1% of the data.

Statistical Analysis

Categorical variables were presented as numbers and percentages and were compared using the χ^2 test. Continuous variables were expressed as either mean and SD or median and interquartile range. Based on their distributions, continuous variables were compared using the Student *t* test or the Wilcoxon rank sum test. Because clinical judgment was based on the qualitative not quantitative values of continuous variables, we dichotomized the continuous variables according to the clinically relevant thresholds in the analyses thereafter.

Because the selection of EVT was determined by physicians, and the patients' characteristics were supposed to be highly different between the groups, we chose to develop a propensity score–matched cohort. We used a logistic regression model to develop the propensity score for the choice of EVT, with 11 independent variables relevant to the choice of EVT. The variables for the propensity score included the following: study period (before February 2015 or after March 2015), use of intravenous rt-PA, age (≥75 or <75 years), NIHSS (≥16 or <16), ASPECTS (≥6 or <6), creatinine value (≥2.0 or <2.0 μmol/L), the site of main occlusions (anterior circulation or posterior circulation), the vessels of main occlusions (internal carotid artery and M1 segment middle cerebral artery or other arteries), the presence of multiple occlusions, the cause of the stroke (cardioembolic or others), and the presence of a history of stroke. The 2 study periods were determined by the publication of 4 randomized controlled trials,[1–4] which had changed the practice of acute cerebral LVO. Because the number of patients who did not receive EVT was fewer than those with EVT, the patients in the EVT group were matched to those in the no-EVT group using a 1:1 matching technique.[19,20]

The primary and secondary outcomes were compared between the EVT and the no-EVT groups in the propensity score–matched cohort. We developed conditional logistic models that considered the matched pairs of EVT and no EVT. Because the prognostic factors were still imbalanced after the propensity score matching, we constructed the multivariable conditional logistic regression models by adjusting the following variables: age (≥75 or <75 years), ASPECTS (≥6 or <6), NIHSS (≥16 or <16), mRS before onset of stroke (>2 or <2), time from onset of stroke to hospital door (≥180 or <180 minutes), use of intravenous rt-PA, and the site of the main occlusions (anterior circulation or posterior circulation), the vessels of main occlusions (internal carotid artery and M1 segment middle cerebral artery or other arteries). We dichotomized ages above and below 75 years based on the criteria for advanced age used by the Japanese health insurance system. Because the threshold of 6 of both anterior circulation ASPECTS and pc-ASPECT were reported to show good discrimination ability,[21] we dichotomized both scores at 6 and combined both scores into a single risk factor. The threshold of 16 for NIHSS was determined by the median value of 15 of previous registry data.[6] The thresholds of 2 for mRS before onset were determined by the same threshold of primary outcome. The threshold of 180 minutes for time from stroke onset to hospital door was determined by the report.[22] The effects of EVT relative to no EVT were expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

The subgroups for primary outcomes were the following: study period (before February 2015 or after March 2015), ASPECTS or pc-ASPECTS (≥6 or <6), NIHSS (≥6 or <6), mRS

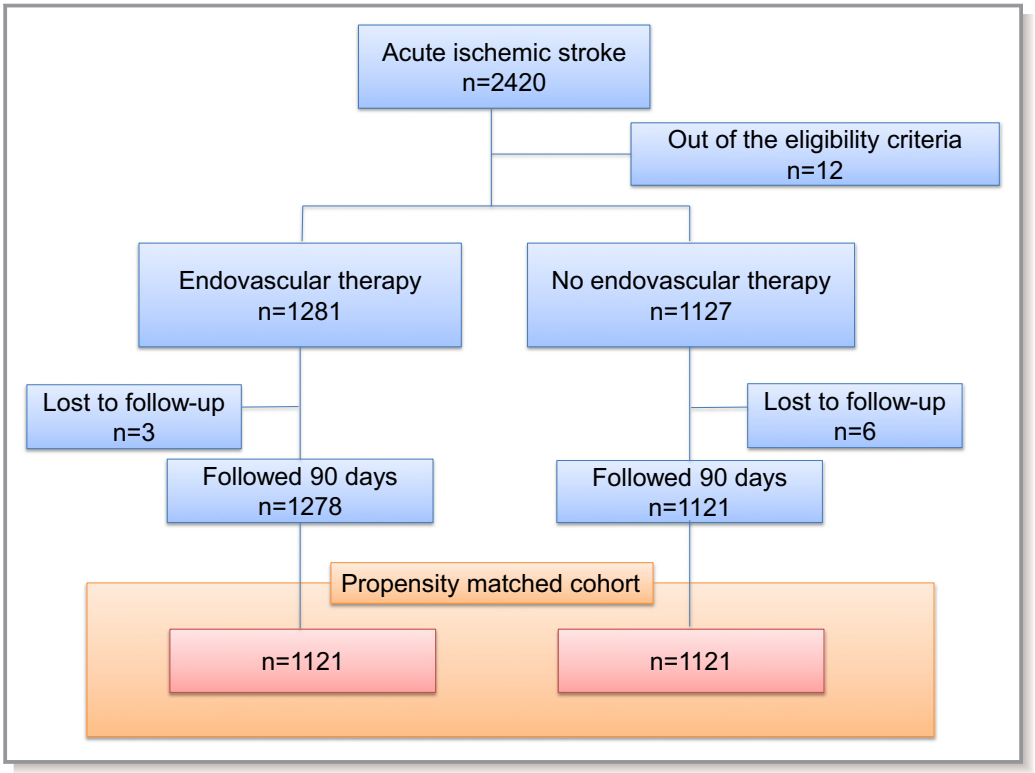

Figure 1. Study flow chart.

before the onset of stroke (>2 or <2), time from stroke onset to hospital door (≥285 or <285 minutes),[23] use of intravenous rt-PA, and the site of the main occlusions (anterior circulation or posterior circulation), the vessels of main occlusions (internal carotid artery and M1 segment middle cerebral artery; M2 segment middle cerebral artery; other arteries). The threshold of 6 for NIHSS was determined by the threshold of indication of EVT.[24] The threshold of 285 minutes for time from stroke onset to hospital door was determined by the recommended time windows of 6 hours from onset to puncture and 75 minutes from door to puncture (360−75=285).[23,24]

We also constructed multivariable logistic regression models for all enrolled patients as sensitivity analyses. We included all variables used in the development of propensity score and adjustment in the conditional logistic regression models as adjusting variables. The dichotomized variables were treated as both dichotomized and not-dichotomized to assess the robustness of the models.

All statistical analyses were conducted by a physician (Uchida K.) and study statistician (Morimoto T.) by using JMP 13.0 (SAS Institute Inc, Cary, NC) or SAS 9.4 (SAS Institute Inc, Cary, NC). The study statistician was blinded to the treatment modalities during the analyses. All reported *P* values were 2-tailed, and $P<0.05$ were considered to be statistically significant.

Results

Patients Characteristics

Among the 2420 patients who were initially enrolled in the registry, 12 patients did not meet the eligibility criteria. A total 2408 patients were subsequently enrolled, of which 1281 patients received EVT, and 1127 patients did not (Figure 1). Because of a lack of follow-up at 90 days for 9 of the patients, 1278 and 1121 patients were ultimately analyzed in the EVT and the no-EVT groups, respectively. Patients who received EVT were significantly younger (74.7 years versus 77.4 years, $P<0.0001$), and there were more men (59.2% versus 49.5%, $P<0.0001$) in that group (Table 1). The EVT group had significantly higher baseline NIHSS and had less extended areas of infarction as measured by ASPECTS. Patients with occlusions in the posterior circulation, and longer times from the onset of stroke to hospital door, were less likely to have received EVT. The median time from the onset of stroke to hospital door and ultimately to reperfusion, in patients who received EVT, were 120 minutes (interquartile range 50–260) and 270 minutes (interquartile range 190–435), respectively. Intravenous rt-PA was administered more often in patients with EVT (46.7%), than in patients without EVT (31.8%) ($P<0.0001$).

After the propensity score matching, 1121 patients in each group were matched with their counterparts. Even after the

Table 1. Characteristics of Entire Patient Cohort

	EVT (n=1278)	No EVT (n=1121)	*P* Value
Study period after March 2015, n (%)	1100 (86.1)	896 (79.9)	<0.0001
Age (y), mean (SD)	74.7 (11.4)	77.4 (12.5)	<0.0001
Men, n (%)	757 (59.2)	555 (49.5)	<0.0001
Current smoker, n (%)	183 (14.3)	152 (13.6)	0.59
Hypertension, n (%)	739 (57.8)	687 (61.3)	0.09
Diabetes mellitus, n (%)	236 (18.5)	220 (19.6)	0.47
Atrial fibrillation, n (%)	658 (51.4)	528 (47.1)	0.032
History of stroke, n (%)	95 (7.4)	101 (9.0)	0.16
pre-mRS, median [IQR]	0 [0–1] (n=1271)	0 [0–2] (n=1115)	<0.0001
Baseline NIHSS score, median [IQR]	18 [13–23] (n=1266)	15 [7–22] (n=1108)	<0.0001
Baseline blood glucose (mg/L), median [IQR]	128 [110–157] (n=1240)	125 [109–152] (n=1069)	0.074
Imaging modality			
MRA, n (%)	676 (52.9)	948 (84.6)	<0.0001
DSA, n (%)	498 (40.0)	103 (9.2)	
CTA, n (%)	104 (8.1)	70 (6.2)	
ASPECTS on baseline NCCT, median [IQR]	10 [8–10] (n=762)	9 [5–10] (n=607)	<0.0001
ASPECTS on baseline DWI, median [IQR]	7 [6–9] (n=936)	7 [4–8] (n=866)	<0.0001
DWI pc-ASPECTS, median [IQR]	7 [6–8] (n=106)	8 [7–9] (n=138)	0.0002
ASPECT ≥6 or pc-ASPECT ≥6, n (%)	1095 (85.7)	782 (70.0)	<0.0001
Site of occlusion			
Anterior circulation, n (%)	1126 (88.1)	954 (85.1)	0.031
Extracranial internal carotid artery, n (%)	144 (11.3)	117 (10.4)	0.51
Intracranial internal carotid artery, n (%)	264 (20.1)	153 (13.7)	<0.0001
Internal carotid artery, n (%)	18 (1.4)	24 (2.1)	0.025
M1 segment middle cerebral artery, n (%)	511 (40.0)	356 (31.8)	<0.0001
M2 segment middle cerebral artery, n (%)	224 (17.5)	250 (22.3)	0.0034
M3 segment middle cerebral artery, n (%)	11 (0.9)	68 (6.1)	<0.0001
A1 segment anterior cerebral artery, n (%)	6 (0.5)	8 (0.7)	0.43
A2 segment anterior cerebral artery, n (%)	16 (1.3)	36 (3.2)	0.001
Posterior circulation, n (%)	152 (11.9)	167 (14.9)	0.031
Basilar artery, n (%)	136 (10.6)	46 (4.1)	<0.0001
Vertebral artery, n (%)	16 (1.3)	42 (3.8)	<0.0001
P1 segment posterior cerebral artery, n (%)	17 (1.3)	44 (3.9)	<0.0001
P2 segment posterior cerebral artery, n (%)	3 (0.2)	54 (4.8)	<0.0001
Others, n (%)	1 (0.1)	3 (0.3)	0.26
Multiple lesions in anterior and posterior circulation, n (%)	7 (0.5)	9 (0.8)	0.44
Use of intravenous rt-PA, n (%)	597 (46.7)	356 (31.8)	<0.0001
Onset to door time (min), median [IQR]	120 [50–260] (n=1202)	180 [75–510] (n=1054)	<0.0001
Onset to puncture time (min), median [IQR]	200 [135–355] (n=1272)	…	
Onset to reperfusion time (min), median [IQR]	270 [190–435] (n=1253)	…	

Continued

Table 1. Continued

	EVT (n=1278)	No EVT (n=1121)	*P* Value
Stroke classification	n=1277	n=1120	
Cardioembolic, n (%)	937 (73.4)	795 (71.0)	0.39
Atherothrombotic, n (%)	197 (15.4)	196 (17.5)	
Cryptogenic, n (%)	77 (6.0)	62 (6.5)	
Others, n (%)	66 (5.2)	67 (6.0)	

A1 indicates A1 segment anterior cerebral artery; A2, A2 segment anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; DSA, digital subtraction angiography; DWI, diffusion-weighted image; EVT, endovascular therapy; IQR, interquartile range; M1, M1 segment middle cerebral artery occlusion; M2, M2 segment middle cerebral artery occlusion; M1, M1 segment middle cerebral artery occlusion; M3, M3 segment middle cerebral artery occlusion; MRA, magnetic resonance angiography; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; pc-ASPECTS, diffusion-weighted image posterior circulation Alberta Stroke Program Early CT Score; Pre-mRS, Modified Rankin Scale before onset; rt-PA, recombinant tissue plasminogen activator.

propensity score matching, there were differences in several characteristics between the 2 groups (Table 2).

Outcomes

In the propensity score–matched cohort, the favorable outcome, defined by mRS of 0 to 2 at 90 days, was observed in 35.3% and 30.7% of the EVT and no-EVT group patients, respectively (P=0.02). The unadjusted and adjusted ORs of the favorable outcomes of EVT relative to no-EVT groups were 1.23 (95% CI, 1.03–1.47) and 1.44 (95% CI, 1.10–1.86), respectively (Table 3).

EVT was also associated with excellent outcomes, defined by mRS of 0 to 1 at 90 days, with an adjusted OR of 1.34 (95% CI, 1.02–1.74), but not in the crude model (P=0.17). Mortality at 90 days was significantly lower in the EVT than in the no-EVT group (9.8% versus 13.6%, P=0.006), but the adjusted OR of EVT was 0.75 (95% CI, 0.54–1.04).

In terms of safety outcomes, intracranial hemorrhage within 72 hours was significantly more frequent in the EVT group than in the no-EVT group (27.5% versus 18.8%, P<0.0001), and the adjusted OR of EVT was 1.97 (95% CI, 1.56–2.49). However, symptomatic intracranial hemorrhage was similar between the 2 groups (Table 4). The recurrence of stroke or transient ischemic attack was also similar between the 2 groups.

Subgroup Analyses

The subgroup analyses of the favorable outcome of mRS of 0 to 2 at 90 days suggested that the EVT was generally effective in all subgroups (Figure 2). EVT was apparently effective in patients who met the indications of current guidelines, such as those with ASPECTS ≥6; with mRS before the onset <2; presented to the hospital door <285 minutes after the onset of stroke; with occlusion in the anterior circulation; and with the vessels of main occlusions of internal carotid artery or M1 segment middle cerebral artery. On the other hand, EVT seemed effective for those with NIHSS score <6 with adjusted OR 1.75 (95% CI, 1.27–2.43). EVT was effective in patients without rt-PA with adjusted OR 1.52 (95% CI, 1.07–2.15). Although these estimates were statistically significant, EVT seemed effective in patients with stroke in the posterior circulation (adjusted OR 1.65 [95% CI, 0.71–3.84]), and in the occlusion vessels of M2 segment of the middle cerebral artery (adjusted OR 1.37 [95% CI, 0.77–2.43]). All interaction P values were not statistically significant.

Sensitivity Analyses

In the original cohort, the favorable outcome was observed in 41.7% and 30.7% of the EVT and no-EVT group patients, respectively (P<0.0001). The adjusted ORs of the favorable outcomes of EVT relative to no-EVT groups were 1.59 (95% CI, 1.27–1.98) in the dichotomized model and 2.24 (95% CI, 1.67–2.99) in the not-dichotomized model (Table 5). The adjusted ORs for excellent outcome and mortality were consistent in the same models. The intracranial hemorrhage within 72 hours was also more frequent in the EVT group than in the no-EVT group (26.0% versus 18.8%, P<0.0001) in the original cohort, and the adjusted ORs of EVT were similar to the main results (Table 5). The findings of symptomatic intracranial hemorrhage and recurrence of stroke or transient ischemic attack were also similar to the main results.

Discussion

Our registry of real-world patients demonstrated that EVT reduced the disability measured at 90 days in patients with acute LVO. We confirmed the findings from previous RCTs with large number of patients exceeding the enrolled patients in the previous RCTs.[1–5] The effectiveness of EVT was prominent in patients with either ASPECTS or NIHSS scores ≥6 at the onset. Also, EVT was effective for those who

Table 2. Patients Characteristics of Propensity Score–Matched Cohort

Variables	EVT (n=1121)	No EVT (n=1121)	*P* Value
Study period after March 2015, n (%)	901 (80.5)	896 (79.9)	0.79
Age (y), mean (SD)	76.0 (12.5)	77.4 (12.5)	0.004
Men, n (%)	688 (61.4)	555 (49.5)	<0.0001
Current smoker, n (%)	129 (11.5)	152 (13.6)	0.14
Hypertension, n (%)	665 (59.3)	687 (61.3)	0.34
Diabetes mellitus, n (%)	175 (15.6)	220 (19.6)	0.013
Atrial fibrillation, n (%)	544 (48.5)	528 (47.1)	0.5
History of stroke, n (%)	78 (7.0)	101 (9.0)	0.073
pre-mRS, median [IQR]	0 [0–1]	0 [0–2]	<0.0001
Baseline NIHSS score, median [IQR]	15 [10–22]	15 [7–22]	0.005
Baseline blood glucose (mg/L), median [IQR]	128 [111–149]	125 [109–152]	0.48
Imaging modality			
MRA, n (%)	641 (57.2)	948 (84.6)	<0.0001
DSA, n (%)	406 (36.2)	103 (9.2)	
CTA, n (%)	74 (6.6)	70 (6.2)	
ASPECTS on baseline NCCT, median [IQR]	10 [7–10] (n=627)	9 [5–10] (n=607)	<0.0001
ASPECTS on baseline DWI, median [IQR]	7 [5–8] (n=828)	7 [4–8] (n=866)	0.48
DWI pc-ASPECTS, median [IQR]	8 [6–8] (n=116)	8 [7–9] (n=138)	0.0002
ASPECTS ≥6 or pc-ASPECTS ≥6	770 (68.7)	782 (69.8)	0.58
Site of occlusion			
Anterior circulation, n (%)	930 (85.1)	954 (85.1)	0.17
Extracranial internal carotid artery, n (%)	86 (7.7)	117 (10.4)	0.047
Intracranial internal carotid artery, n (%)	184 (16.4)	153 (13.7)	0.037
Internal carotid artery, n (%)	24 (2.1)	24 (2.1)	0.5
M1 segment middle cerebral artery, n (%)	353 (31.5)	356 (31.8)	0.89
M2 segment middle cerebral artery, n (%)	301 (26.9)	250 (22.3)	0.012
M3 segment middle cerebral artery, n (%)	5 (0.5)	68 (6.1)	<0.0001
A1 segment anterior cerebral artery, n (%)	2 (0.5)	8 (0.7)	0.11
A2 segment anterior cerebral artery, n (%)	11 (1.0)	36 (3.2)	0.0003
Posterior circulation, n (%)	191 (17.0)	167 (14.9)	0.17
Basilar artery, n (%)	144 (12.9)	46 (4.1)	<0.0001
Vertebral artery, n (%)	27 (2.4)	42 (3.8)	0.07
P1 segment posterior cerebral artery, n (%)	28 (2.5)	44 (3.9)	0.06
P2 segment posterior cerebral artery, n (%)	1 (0.09)	54 (4.8)	<0.0001
Others, n (%)	1 (0.1)	3 (0.3)	0.31
Multiple lesions in anterior and posterior circulation, n (%)	3 (0.3)	9 (0.8)	0.62
Use of intravenous tPA, n (%)	364 (32.5)	356 (31.8)	0.72
Onset to door time (min), median [IQR]	140 [60–321]	180 [75–510]	<0.0001
Onset to puncture time (min), median [IQR]	240 [145–465]	…	
Onset to reperfusion time (min), median [IQR]	308 [210–540]	…	

Continued

Table 2. Continued

Variables	EVT (n=1121)	No EVT (n=1121)	*P* Value
Stroke subtype			
Cardioembolic, n (%)	761 (68.0)	795 (71.0)	<0.0001
Atherothrombotic, n (%)	172 (15.4)	196 (17.5)	
Cryptogenic, n (%)	144 (12.9)	62 (6.5)	
Others, n (%)	43 (3.8)	67 (6.0)	

ASPECTS indicates Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; DSA, digital subtraction angiography; DWI, diffusion-weighted image; EVT, endovascular therapy; IQR, interquartile range; MRA, magnetic resonance angiography; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; pc-ASPECTS, diffusion-weighted image posterior circulation Alberta Stroke Program Early CT Score; Pre-mRS, modified Rankin Scale before onset; t-PA, tissue plasminogen activator.

presented to the hospital door <285 minutes after the onset of stroke or those with stroke in the anterior circulation. Thus, our findings were consistent with previous RCTs[1–5] and the guideline.[24] Our study also suggested the potentials of EVT for those without explicit indications in the guideline. Although the number of subgroups were too small to show statistical significance, EVT seemed similarly effective in patients, when comparing the patients with posterior circulation to anterior circulation, without rt-PA before EVT, to with rt-PA before EVT, and who appeared later than 285 minutes after the onset, to <285 minutes after onset.

Less than half of the patients received rt-PA before EVT in our study, compared with 68% to 100% of patients who received rt-PA in previous RCTs, which attested to the effectiveness of EVT. Our study suggested that the efficacy of EVT was promising, with an OR of favorable outcomes of 1.52, even without rt-PA. EVT was generally recommended to those who received rt-PA, and the RCT of EVT for acute phase of patients without rt-PA was not available to date.[24] We were reassured that EVT could be considered in patients with acute LVO, even if they did not receive rt-PA.

LVO in the posterior circulation accounted for 15% of patients in our study. These patients were not primarily considered as candidates for EVT for several reasons, including difficulties with diagnosis on NCCT, difficulties in the assessment of ASPECT, or varying severities.[7] A lack of evidence about the effectiveness of EVT in those patients was the reason for the discrete use of EVT in those patients. One observational study reported that EVT was not effective in patients with acute basilar artery occlusion.[25] Our study suggested that there is a chance of effectiveness of EVT in patients with such occlusions of the posterior circulation. In light of this dichotomy of findings, well-conducted RCTs in those patients are mandatory.

Because we routinely assessed posttreatment bleeding or recurrence of stroke by magnetic resonance imaging or NCCT, we could systematically assess the natural course of EVT, by looking at postprocedural complications such as asymptomatic intracranial hemorrhage or recurrence of stroke. We found that the incidence of intracranial hemorrhage within 72 hours after EVT was high (one fourth of patients), and there was a 97% increase in risk compared with those who did not have EVT. Even with this high rate of intracranial hemorrhage, the rate of symptomatic hemorrhage was minor (5.3%) and similar to those who had not had EVT. These rates were similar to those of previous RCTs.[26]

Based on the findings from previous RCTs and meta-analyses,[26] EVT became the standard therapy for patients with acute LVO in the anterior circulation. Our study validated their findings to general patients. The ASPECTS of 85.7% of patients with EVT were 6 or more in our study. The American Heart Association has recommended that

Table 3. Outcomes

Outcomes	EVT (n=1121)	No EVT (n=1121)	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Primary outcome						
mRS score 0–2 at 90 d, n (%)	396 (35.3)	344 (30.7)	1.23 (1.03–1.47)	0.02	1.44 (1.10–1.86)	0.007
Secondary outcomes						
mRS score 0–1 at 90 d, n (%)	290 (24.0)	242 (21.6)	1.15 (0.94–1.40)	0.17	1.34 (1.02–1.74)	0.03
Mortality at 90 d, n (%)	110 (9.8)	152 (13.6)	0.69 (0.53–0.90)	0.006	0.75 (0.54–1.04)	0.09

CI indicates confidence interval; EVT, endovascular therapy; mRS, modified Rankin Scale; OR, odds ratio.

Table 4. Safety Outcomes

Safety Outcomes	EVT (n=1121)	No EVT (n=1121)	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Intracranial hemorrhage within 72 h, n (%)	308 (27.5)	211 (18.8)	1.63 (1.34–1.99)	<0.0001	1.97 (1.56–2.49)	<0.0001
Symptomatic intracranial hemorrhage within 72 h, n (%)	59 (5.3)	32 (2.9)	1.33 (0.83–2.12)	0.24	4.79 (0.55–41.67)	0.16
Recurrence of stroke or TIA within 90 d, n (%)	31 (2.8)	52 (4.6)	0.58 (0.37–0.92)	0.019	0.54 (0.31–0.94)	0.03

CI indicates confidence interval; EVT, endovascular therapy; OR, odds ratio; TIA, transient ischemic attack.

EVT should be considered for those with an ASPECTS of 6 or more,[24] but our study suggested that EVT might be associated with better clinical outcomes in the subgroup of ASPECTS <6 because the point estimate of adjusted OR was 1.83, which was larger than that in the subgroup of ASPECTS ≥6.

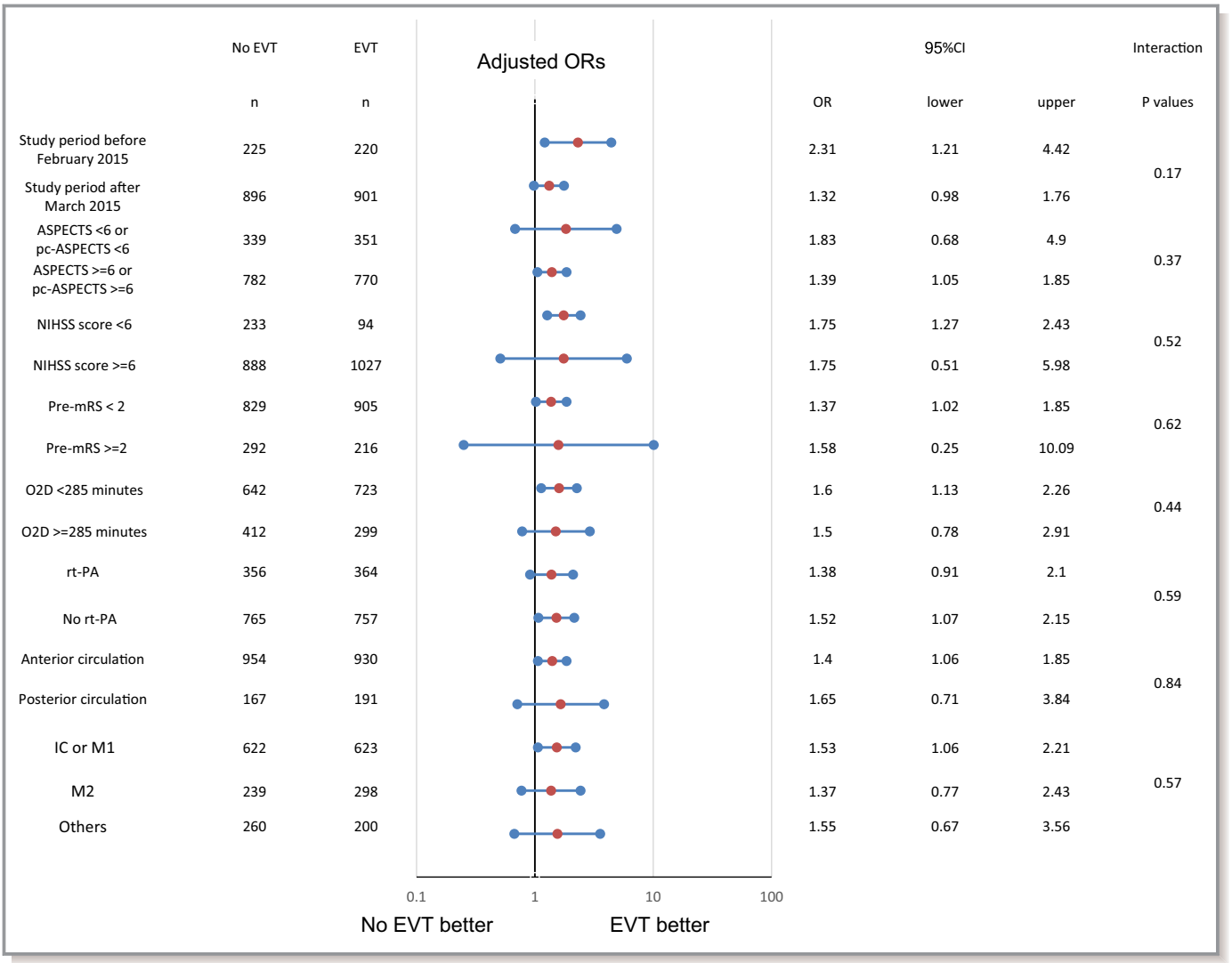

Figure 2. Subgroup analyses. ASPECTS indicates Alberta Stroke Program Early CT Score on baseline noncontrast computed tomography or diffusion-weighted image; CI, confidence interval; EVT, endovascular therapy; IC, internal carotid artery occlusion; M1, M1 segment middle cerebral artery occlusion; M2, M2 segment middle cerebral artery occlusion; NIHSS, National Institutes of Health Stroke Scale; O2D, onset to door time; OR, odds ratio; Others, other artery occlusions; pc-ASPECTS, diffusion-weighted image posterior circulation Alberta Stroke Program Early CT Score; pre-mRS, modified Rankin Scale before onset; rt-PA, recombinant tissue plasminogen activator.

Table 5. Sensitivity Analyses

Outcomes	EVT (n=1278)	No EVT (n=1121)	Crude OR (95% CI)	*P* Value	Adjusted OR * (95% CI)	*P* Value	Adjusted Odds Ratio † (95% CI)	*P* Value
Primary outcome								
mRS score 0–2 at 90 d, n (%)	533 (41.7)	344 (30.7)	1.62 (1.37–1.91)	<0.0001	1.59 (1.27–1.98)	<0.0001	2.24 (1.67–2.99)	<0.0001
Secondary outcomes								
mRS score 0–1 at 90 d, n (%)	340 (26.6)	242 (21.6)	1.32 (1.09–1.59)	0.004	1.25 (0.99–1.60)	0.07	1.69 (1.24–2.32)	0.001
Mortality at 90 d, n (%)	112 (8.8)	152 (13.6)	0.61 (0.47–0.79)	0.0002	0.78 (0.57–1.06)	0.11	0.66 (0.44–0.97)	0.04
Safety outcomes								
Intracranial hemorrhage within 72 h, n (%)	332 (26.0)	211 (18.8)	1.51 (1.25–1.84)	<0.0001	1.85 (1.48–2.33)	<0.0001	2.06 (1.57–2.70)	<0.0001
Symptomatic intracranial hemorrhage within 72 h, n (%)	35 (2.7)	23 (2.1)	1.34 (0.79–2.29)	0.27	1.57 (0.86–2.88)	0.14	1.51 (0.76–3.00)	0.24
Recurrence of stroke or TIA within 90 d, n (%)	59 (4.6)	52 (4.6)	0.99 (0.68–1.46)	0.98	1.16 (0.77–1.78)	0.47	1.09 (0.65–1.84)	0.74

CI indicates confidence interval; EVT, endovascular therapy; mRS, modified Rankin Scale; OR, odds ratio; TIA, transient ischemic attack.
*Model with dichotomized variables.
†Model with not-dichotomized variables.

Limitations

This study has several limitations. First and most critically, this study was a prospective registry and the selection of EVT depended on the practicing physicians. Therefore, it was inevitable that there would be residual confounding and selection biases in the comparisons between EVT and no EVT, even though we constructed propensity score–matched cohorts and constructed extensive multivariate models to account for the factors associated with the selection of EVT and prognosis. Second, we systematically registered patients with acute stroke caused by LVO for 2 years at 46 centers, and, to the best of our knowledge, this study is the largest study to date. However, the sample size was still not large enough to fully evaluate the effects of EVT in some important subgroups, such as those with stroke in the posterior circulation or with lower ASPECTS. However, our registry study shed light on the effectiveness of EVT in such groups, despite a paucity of evidence that has been presented in the past. Third, the imaging methods in this study were not standardized and not the cutting-edge in this era, such as CT perfusion.[27] Therefore, a well-conducted randomized trial with modern standardized imaging methods to attest to the effects of EVT, especially focusing on such understudied subgroups, is warranted. Finally, assessments of our mRS could be biased because the treatment modality was not masked, even though mRS assessment was regulated to be conducted by an independent physician other than the treating physician. In addition, the mortality rate was less likely to be biased, and the findings were consistent between mild symptoms (mRS 0–2) and mortality (mRS 6).

Conclusion

Our large prospective registry of consecutive patients with acute stroke caused by LVO revealed that EVT was effective in reducing the level of disability at 90 days. Our promising findings indicating the efficacy of EVT in those with severe disabilities or posterior circulation should be confirmed through future RCTs that target these understudied populations.

Acknowledgments

We are indebted to the RESCUE-Japan Registry 2 Investigators Study Organization:

Principal Investigators: Shinichi Yoshimura, MD, PhD—Department of Neurosurgery, Hyogo College of Medicine; Nobuyuki Sakai, MD, PhD—Department of Neurosurgery, Kobe City Medical Center General Hospital.

Steering Committee: Masayuki Ezura, MD, PhD—Department of Neurosurgery, National Hospital Organization Sendai Medical Center; Yasushi Okada, MD, PhD—Cerebrovascular Center, National Hospital Organization Kyushu Medical Center; Kazuo Kitagawa, MD, PhD—Department of Neurology, Tokyo Women's Medical University; Kazumi Kimura, MD, PhD—Department of Neurological Science, Graduate School of Medicine, Nippon Medical School; Makoto Sasaki, MD, PhD—Institute for Biomedical Sciences, Iwate Medical University; Norio Tanahashi, MD, PhD—Department of Neurology, Saitama Medical University International Medical Center; Kazunori Toyoda, MD, PhD—Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center; Eisuke Furui, MD, PhD—Department of Stroke Neurology, Saiseikai Toyama Hospital; Yuji Matsumaru, MD, PhD—Division for Stroke Prevention and Treatment, Department of Neurosurgery, University of Tsukuba; Kazuo Minematsu, MD, PhD—Department of Cerebrovascular

Medicine, National Cerebral and Cardiovascular Center; Hiroshi Yamagami, MD, PhD—Division of Stroke Care Unit, National Cerebral and Cardiovascular Center.

Study Statistician: Takeshi Morimoto, MD, PhD, MPH—Department of Clinical Epidemiology, Hyogo College of Medicine.

Study Secretariat: Kazutaka Uchida, MD—Department of Neurosurgery, Hyogo College of Medicine.

Independent Data Safety Monitoring Board: Naoya Kuwayama, MD, PhD (Chair)—Department of Neurosurgery, University of Toyama Faculty of Medicine; Kuniaki Ogasawara, MD, PhD—Department of Neurosurgery, Iwate Medical University; Koji Iihara, MD, PhD—Department of Neurosurgery, Graduate School of Medical Sciences, Kyushu University.

List of Participating Centers and Investigators: Kazunori Toyoda—Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center; Masataka Takeuchi—Department of Neurosurgery, Seisho Hospital; Masafumi Morimoto—Department of Neurosurgery, Yokohama Shintoshi Neurosurgical Hospital; Toshiyuki Onda—Department of Neurosurgery, Sapporo Shiroishi Memorial Hospital; Masunari Shibata—Department of Neuroendovascular Treatment, Japanese Red Cross Ise Hospital; Shinichi Yoshimura–Department of Neurosurgery, Hyogo College of Medicine; Nobuyuki Sakai—Department of Neurosurgery, Kobe City Medical Center General Hospital; Takahiro Ohta—Department of Neurosurgery, Tokyo Metropolitan Tama Medical Center; Keisuke Imai—Department of Neuroendovascular Treatment, Japanese Red Cross Kyoto Daiichi Hospital; Ryo Itabashi—Department of Stroke Neurology, Kohnan Hospital; Masayuki Ezura—Department of Neurosurgery, National Hospital Organization Sendai Medical Center; Taro Yamashita—Department of Neurosurgery, Shimizu Hospital; Norihito Fukawa—Department of Neurosurgery, Kinki University; Naoto Kimura—Department of Neurosurgery, Iwate Prefectural Central Hospital; Ryosuke Doijiri—Department of Neurology, Iwate Prefectural Central Hospital; Hajime Ohta—Department of Neurosurgery, Miyakonojo Medical Association Hospital; Yukiko Enomoto—Department of Neurosurgery, Gifu University Hospital; Chisaku Kanbayashi—Department of Neurosurgery, Kawasaki Saiwai Hospital; Ikuya Yamaura—Department of Neurosurgery, Yoshida Hospital and Cerebrovascular Research Institute; Hideyuki Ishihara—Department of Neurosurgery, Yamaguchi University Hospital; Yuki Kamiya—Department of Neurology, Showa University Koto-Toyosu Hospital; Makoto Hayase—Department of Neurosurgery, Fukui Red Cross Hospital; Kouhei Nii—Department of Neurosurgery, Fukuoka University Chikushi Hospital; Junya Kobayashi—Department of Vascular Neurology, Osaka-Minami Medical Center; Hiroaki Yasuda—Department of Neurosurgery, Yamaguchi Prefectural Grand Medical Center; Ryushi Kondo, Daisuke Yamamoto—Department of Neurosurgery, Kitasato University Hospital; Manabu Sakaguchi—Department of Neurology, Osaka University Hospital; Junichiro Satomi—Department of Neurosurgery, Tokushima University Hospital; Yoshiki Yagita—Department of Stroke Medicine, Kawasaki Medical School Hospital; Akira Handa—Department of Neurosurgery, Kurashiki Central Hospital; Atsushi Shindo—Department of Neurological Surgery, Kagawa University Faculty of Medicine; Nagayasu Hiyama—Department of Neurosurgery, Goshi Hospital; Naoki Toma—Department of Neurosurgery, Mie University Hospital; Tomoyuki Tsumoto—Cerebrovascular Center, National Hospital Organization Kyushu Medical Center; Kazumi Kimura—Department of Neurological Science, Graduate School of Medicine, Nippon Medical School; Wataro Tsuruta—Department of Neurology, Toranomon Hospital; Keigo Matsumoto—Department of Neurosurgery, Kobe Central Hospital; Yoshihiro Kiura—Department of Neurology, Hiroshima Prefectural Hospital; Takaaki Yamazaki—Department of Neurosurgery, Hakodate Neurosurgical Hospital; Taketo Hatano—Department of Neurosurgery, Kokura Kinen Hospital; Yoshihisa Matsumoto—Department of Neurosurgery, Tanushimaru Central Hospital; Takao Kojima—Department of Neurosurgery, Japanese Red Cross Nagoya Daini Hospital; Norio Ikeda—Department of Neurosurgery, Ube-kohsan Central Hospital; Shigeyuki Sakamoto—Department of Neurosurgery, Hiroshima University Hospital; Hiroyuki Ohnishi—Department of Neurosurgery, Osaka Medical College Hospital; Koichi Haraguchi—Department of Neurosurgery, Hakodate Shintoshi Hospital; Naoyuki Uchiyama—Department of Neurosurgery, Kanazawa University.

Sources of Funding

This study was supported in part by the Japan Agency for Medical Research and Development (AMED), the Japanese Society for Neuroendovascular Therapy (JSNET), the Ministry of Health, Labour and Welfare of Japan, Medtronic, Stryker, and Medicos Hirata. The funding sources did not participate in any part of the study, from study conception to article preparation.

Disclosures

Dr Yoshimura discloses research grants from Medtronic, Medicos Hirata, Termo, Bristol-Myers Squibb, and Otsuka; lecturer's fees from Boehringer-Ingelheim, Otsuka, Bayer, Sanofi, Pfizer, Bristol-Myers Squibb, Stryker, Medtronic, and Mitsubishi Tanabe. Dr Sakai reports a research grant from Termo; lecturer's fees from Jimro, Otsuka, Johnson & Johnson, Medtronic, Stryker, and Medico's Hirata; membership on the advisory boards for Medtronic and Jimro. Dr Uchida reports lecturer's fees from Nihon Medi-Physics. Dr Yamagami discloses research grants from Bristol-Myers Squibb; lecturer's fees from Bayer, Daiichi-Sankyo, Bristol-Myers Squibb, Boehringer Ingelheim, and Striker; reports lecturer's fees from Bayer; membership of the advisory boards for Daiichi-Sankyo, Bayer, and Boehringer Ingelheim. Dr Ezura reports lecturer's fees from Boehringer Ingelheim, Termo, Medtronic, Nichi-Iko, Pfizer, and Otsuka; manuscript fee from Medtronic. Dr Okada reports lecturer's fees from Medtronic. Dr Kitagawa discloses research grants from Boehringer Ingelheim, Daiichi Sankyo, MSD, Astellas, AstraZeneca, Kyowa Hakko Kirin, Otsuka, Sanofi, Shionogi, Pfizer, Bristol-Myers Squibb, and Bayer; lecturer's fees from Boehringer Ingelheim, Daiichi Sankyo, MSD, Astellas, AstraZeneca, Kyowa Hakko Kirin, Otsuka, Sanofi, Shionogi, Pfizer, Bristol-Myers Squibb, and Bayer. Dr Kimura discloses research grants from Boehringer-Ingelheim, Otsuka, Eisai, Nihon Medi-Physics, Astellas, MSD, Daiichi Sankyo, and Mitsubishi Tanabe; lecturer's fees from Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Daiichi Sankyo, Mitsubishi Tanabe, and Otsuka. Dr Sasaki reports research

grants from Hitachi and Actelion Pharmaceuticals Japan.; lecturer's fees from Mitsubishi Tanabe, Nihon Medi-Physics, Eisai, Fujifilm RI, Daiichi Sankyo, Boehringer Ingelheim, Bayer, Otsuka, Chugai, Sanofi, Shionogi, Novartis, Bristol-Myers Squibb, and AstraZeneca. Dr Tanahashi reports lecturer's fees from Daiichi-Sankyo, Bayer, Bristol-Myers Squibb, Sanofi, and Pfizer. Dr Toyoda reports lecturer's fees from Daiichi Sankyo, Boehringer Ingelheim, Bayer, and Bristol-Myers Squibb. Dr Matsumaru reports lecturer's fees from Medtronic, Stryker, Termo, Medicos Hirata, and Johnson & Johnson. Dr Minematsu reports lecturer's fees from Bayer Healthcare, Boehringer Ingelheim, AstraZeneca, Pfizer, Mitsubishi Tanabe Pharma, Stryker, and Medico's Hirata. Dr Morimoto reports a research grant from Nexis; lecturer's fees from AbbVie, AstraZeneca, Daiichi Sankyo, Kyorin, Mitsubishi Tanabe, and Pfizer; a manuscript fee from Pfizer; membership in the advisory boards for Asahi Kasei, Boston Scientific, and Bristol-Myers Squibb. Dr Furui has no disclosures to report.

References

1. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama a Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20.
2. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018.
3. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030.
4. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295.
5. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Roman L, Serena J, Abilleira S, Ribo M, Millan M, Urra X, Cardona P, Lopez-Cancio E, Tomasello A, Castano C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Perez M, Goyal M, Demchuk AM, von Kummer R, Gallofre M, Davalos A. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306.
6. Yoshimura S, Sakai N, Okada Y, Kitagawa K, Kimura K, Tanahashi N, Hyogo T, Yamagami H, Egashira Y. Efficacy of endovascular treatment for acute cerebral large-vessel occlusion: analysis of nationwide prospective registry. *J Stroke Cerebrovasc Dis*. 2014;23:1183–1190.
7. Mokin M, Sonig A, Sivakanthan S, Ren Z, Elijovich L, Arthur A, Goyal N, Kan P, Duckworth E, Veznedaroglu E, Binning MJ, Liebman KM, Rao V, Turner RD IV, Turk AS, Baxter BW, Dabus G, Linfante I, Snyder KV, Levy EI, Siddiqui AH. Clinical and procedural predictors of outcomes from the endovascular treatment of posterior circulation strokes. *Stroke*. 2016;47:782–788.
8. Mori E, Minematsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). *Stroke*. 2010;41:461–465.
9. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607.
10. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007;369:275–282.
11. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, Haley EC, Grotta J, Marler J. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke*. 1994;25:2220–2226.
12. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41.
13. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, Hu WY, Buchan AM. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol*. 2001;22:1534–1542.
14. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JH, Hudon ME, Tomanek A, Frayne R, Buchan AM. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *J Neurol Neurosurg Psychiatry*. 2005;76:1528–1533.
15. Tei H, Uchiyama S, Usui T, Ohara K. Posterior circulation ASPECTS on diffusion-weighted MRI can be a powerful marker for predicting functional outcome. *J Neurol*. 2010;257:767–773.
16. Gibo H, Carver CC, Rhoton AL Jr, Lenkey C, Mitchell RJ. Microsurgical anatomy of the middle cerebral artery. *J Neurosurg*. 1981;54:151–169.
17. Perlmutter D, Rhoton AL Jr. Microsurgical anatomy of the distal anterior cerebral artery. *J Neurosurg*. 1978;49:204–228.
18. Zeal AA, Rhoton AL Jr. Microsurgical anatomy of the posterior cerebral artery. *J Neurosurg*. 1978;48:534–559.
19. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107.
20. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Miyake M, Mitsuoka H, Kato M, Hirano Y, Matsuda S, Nagao K, Inada T, Murakami T, Takeuchi Y, Yamane K, Toyofuku M, Ishii M, Minamino-Muta E, Kato T, Inoko M, Ikeda T, Komasa A, Ishii K, Hotta K, Higashitani N, Kato Y, Inuzuka Y, Maeda C, Jinnai T, Morikami Y, Sakata R, Kimura T. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2015;66:2827–2838.
21. Luo G, Mo D, Tong X, Liebeskind DS, Song L, Ma N, Gao F, Sun X, Zhang X, Wang B, Jia B, Fernandez-Escobar A, Miao Z. Factors associated with 90-day outcomes of patients with acute posterior circulation stroke treated by mechanical thrombectomy. *World Neurosurg*. 2018;109:e318–e328.
22. Liebeskind DS, Jahan R, Nogueira RG, Jovin TG, Lutsep HL, Saver JL. Early arrival at the emergency department is associated with better collaterals, smaller established infarcts and better clinical outcomes with endovascular stroke therapy: SWIFT study. *J Neurointerv Surg*. 2016;8:553–558.
23. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, Cardona P, Devlin TG, Frei DF, du Mesnil de Rochemont R, Berkhemer OA, Jovin TG, Siddiqui AH, van Zwam WH, Davis SM, Castano C, Sapkota BL, Fransen PS, Molina C, van Oostenbrugge RJ, Chamorro A, Lingsma H, Silver FL, Donnan GA, Shuaib A, Brown S, Stouch B, Mitchell PJ, Davalos A, Roos YB, Hill MD. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288.
24. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. 2018 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*. 2018;49:e46–e110.
25. Schonewille WJ, Wijman CA, Michel P, Rueckert CM, Weimar C, Mattle HP, Engelter ST, Tanne D, Muir KW, Molina CA, Thijs V, Audebert H, Pfefferkorn T, Szabo K, Lindsberg PJ, de Freitas G, Kappelle LJ, Algra A. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International

Cooperation Study (BASICS): a prospective registry study. *Lancet Neurol*. 2009;8:724–730.

26. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millan M, Davis SM, Roy D, Thornton J, Roman LS, Ribo M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731.

27. Albers GW, Goyal M, Jahan R, Bonafe A, Diener HC, Levy EI, Pereira VM, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, de Rochemont Rdu M, Singer OC, Bammer R, Saver JL. Ischemic core and hypoperfusion volumes predict infarct size in SWIFT PRIME. *Ann Neurol*. 2016;79:76–89.