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ORIGINAL RESEARCH

Endovascular Therapy for Acute Ischemic Stroke in Patients With Prestroke Disability

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BACKGROUND: Outcomes after stroke as a result of large-vessel occlusion in patients with prestroke disability were compared between endovascular therapy (EVT) and medical management.

METHODS AND RESULTS: Of 2420 patients with acute stroke with large-vessel occlusion in a prospective, multicenter, nationwide registry in Japan, patients with prestroke modified Rankin Scale scores 2 to 4 with occlusion of the internal carotid artery, or M1 of the middle cerebral artery were analyzed. The primary effectiveness outcome was the favorable outcome, defined as return to at least the prestroke modified Rankin Scale score at 3 months. Safety outcomes included symptomatic intracranial hemorrhage. A total of 339 patients (237 women; median 85 [interquartile range (IQR), 79–89] years of age; median prestroke modified Rankin Scale score of 3 [IQR, 2–4]) were analyzed. EVT was performed in 175 patients (51.6%; mechanical thrombectomy, n=139). The EVT group was younger ($p<0.01$) and had lower prestroke modified Rankin Scale scores ($p<0.01$) than the medical management group. The favorable outcome was seen in 28.0% of the EVT group and in 10.9% of the medical management group ($p<0.01$). EVT was associated with the favorable outcome (adjusted odds ratio, 3.01; 95% CI, 1.55–5.85; mixed effects multivariable model with inverse probability of treatment weighting). Symptomatic intracranial hemorrhage rates were similar between the EVT (4.0%) and medical management (4.3%) groups ($p=1.00$).

CONCLUSIONS: Patients who underwent EVT showed better functional outcomes than those with medical management. Given proper patient selection, withholding EVT solely on the basis of prestroke disability might not offer the best chance of favorable outcome.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02419794.

Key Words: disability ■ endovascular therapy ■ outcome ■ stroke ■ thrombectomy

Endovascular therapy (EVT) is recommended for large-vessel occlusion (LVO) stroke on the basis of evidence from randomized clinical trials and a meta-analysis.[1–8] However, patients with prestroke modified Rankin Scale (pRS) scores ≥2 were basically not included in these trials.[9,10] The current guidelines for stroke treatment do not have statements on EVT for patients with prestroke disabilities.[11] Nevertheless, in clinical practice, a treatment decision for EVT is frequently required in patients with stroke with prestroke disabilities because of orthostatic issues, impaired cognition, concomitant acute illnesses, or other neurological problems.[9,10] An analysis of the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke) registry revealed that the chance of a favorable outcome, defined as modified Rankin Scale (mRS) scores of 0 to 2 or return to the pRS score, was not lower in patients with prestroke dependency than in patients who were prestroke independent.[12] Although this analysis also showed that patients who were prestroke dependent did not have an increased risk of

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CLINICAL PERSPECTIVE

What Is New?

- Observational studies of endovascular therapy (EVT) for patients with acute large-vessel occlusion stroke suggested that the chance of a favorable outcome, defined as a return to at least the prestroke modified Rankin Scale score, was not necessarily lower in patients with prestroke dependency than in patients who were prestroke independent.
- Although these analyses also showed that patients with prestroke dependency did not have an increased risk of symptomatic intracranial hemorrhage, data for patients not treated with EVT were lacking.
- Here we compared outcomes of patients with large-vessel occlusion stroke who had prestroke disability undergoing EVT with outcomes of those receiving medical management alone.

What Are the Clinical Implications?

- In clinical practice, the treatment decision for EVT is frequently required in patients with stroke with prestroke disabilities.
- The present analysis involving 339 patients with large-vessel occlusion stroke with a prestroke modified Rankin Scale score of 2 to 4 showed that the favorable outcome was seen in 28% of the EVT group and in 10.9% of the medical management group; there was a significant association between EVT and the favorable outcome without an increase in symptomatic intracranial hemorrhage compared with medical management alone.
- Given proper patient selection, withholding EVT solely on the basis of prestroke disability might not offer the best chance of favorable outcome.

Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early Computed Tomographic Score
EVT	endovascular therapy
ICA	internal carotid artery
ICH	intracranial hemorrhage
IPTW	inverse probability of treatment weighting
IVT	intravenous thrombolysis
LKW	last known well
LVO	large-vessel occlusion
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
pRS	prestroke modified Rankin Scale
PS	propensity score
RESCUE	Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism

symptomatic intracranial hemorrhage (ICH), data for patients not treated with EVT were lacking.[12] Here we compared the outcomes of patients with LVO stroke who had prestroke disability (defined as a pRS score ≥2) undergoing EVT with the outcomes of those receiving medical management alone using data from the RESCUE (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism)–Japan Registry 2 in which patients with LVO stroke were registered irrespective of the treatment modalities used.[13–16] We hypothesized the presence of a positive treatment effect of EVT in patients with LVO stroke with prestroke disabilities without an increase in symptomatic ICH.[17]

METHODS

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author on reasonable request and with approval from the RESCUE-Japan Registry 2 investigators.

Study Population

The RESCUE-Japan Registry 2 was a prospective, multicenter, observational study of acute ischemic stroke attributed to LVO. The participants were registered from 46 stroke centers in Japan between October 2014 and September 2016 and were followed up for 3 months. The study design and data have been published elsewhere.[13–16] Briefly, patients with acute LVO who were ≥20 years of age and were hospitalized within 24 hours from the last known well (LKW) were enrolled. All study centers were regularly alerted by the study secretariat not to miss the consecutive patients with acute LVO. All study procedures were reviewed and approved by the ethics committees of the participating institutions. 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 study was registered with the ClinicalTrials.gov (NCT02419794) and the Japanese UMIN (University Hospital Medical Information Network) Clinical Trials Registry (UMIN000015273).

In the present substudy of the RESCUE-Japan Registry 2, patients who met the following criteria were included: (1) pRS score ≥2 and (2) occlusion of the internal carotid artery (ICA) or M1 segment of the middle cerebral artery. ICA occlusion included that of both the intracranial ICA and extracranial ICA. Tandem occlusions, such as concomitant occlusions of the extracranial ICA and M2 segment of the middle cerebral artery, were also included. Patients with a pRS score of 5 were excluded.[17] Patient selection flows are shown in Figure 1.

Treatment of LVO

The treatment modalities were determined by the physician in charge. Medical management included intravenous thrombolysis (IVT) with alteplase at 0.6 mg/kg (the dose approved in Japan) in patients presenting within the first 4.5 hours from the LKW when appropriate.[18,19] EVT mainly included mechanical thrombectomy with stent retrievers or aspiration techniques; balloon angioplasty, stenting, clot disruption using guidewires and/or microcatheters, intra-arterial thrombolysis, or some combination thereof were performed in some cases. The device for the EVT procedure was selected from among any device approved for use in Japan at the discretion of the treating physician. For reperfusion grading, the modified Thrombolysis in Cerebral Infarction scale was used, with successful reperfusion defined as a modified Thrombolysis in Cerebral Infarction scale score of 2b or 3.[20]

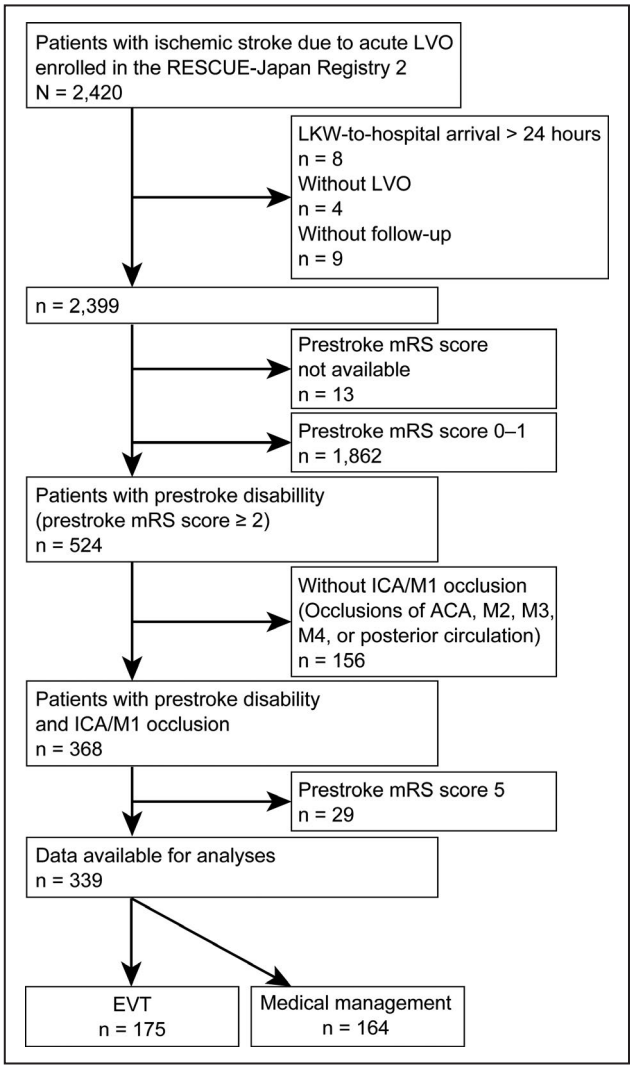

Figure 1. Study flow chart.
ACA indicates anterior cerebral artery; EVT, endovascular therapy; ICA, internal carotid artery; LKW, last known well; LVO, large-vessel occlusion; mRS, modified Rankin Scale; and RESCUE, Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism.

Clinical Data Collection

The baseline data for the following 22 variables were collected: sex, age, pRS score, atrial fibrillation, vascular risk factors (hypertension, diabetes mellitus, and dyslipidemia), past medical history (stroke before the index events and congestive heart failure), prestroke anticoagulation, smoking habit, time from LKW to hospital arrival, baseline National Institutes of Health Stroke Scale (NIHSS) score, the Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) on non-contrast computed tomography or diffusion-weighted magnetic resonance imaging at baseline, occlusion of the ICA, occlusion of the M1 middle cerebral artery, tandem occlusion, baseline systolic blood pressure, laboratory data (white blood cell count, glucose, and creatinine), and IVT.[21–23] The pRS score was estimated at admission by a stroke-trained physician with experience with measuring mRS on the basis of information from the reliable informant such as family members. Occlusion sites were determined using magnetic resonance angiography, computed tomography angiography, or digital subtraction angiography on admission. Computed tomography, magnetic resonance imaging, and digital subtraction angiograms were adjudicated locally at the treating facilities.

Outcomes

The primary effectiveness outcome of this study was favorable outcome, defined as a return to at least the pRS score as measured using the mRS at 3 months after the onset.[12,17] Measurements of the mRS score were performed personally in the clinic or by telephone interview of the patients or their legally authorized representatives. The assessments of mRS were conducted by a stroke-trained physician with experience measuring mRS who had not treated the patient. Other outcomes for measuring treatment effectiveness were severe disability (mRS score 5) or death at 3 months, death within 3 months, neurological improvement in the first 72 hours (a ≥4-point decrease in the NIHSS

score from baseline), and a shift in the overall distribution of mRS scores at 3 months.

The safety outcomes were any ICH and symptomatic ICH within 72 hours after the onset (Table S1). Hemorrhagic transformation was classified into the following 4 categories as described by the ECASS (European Cooperative Acute Stroke Study): hemorrhagic infarction 1, hemorrhagic infarction 2, parenchymal hematoma 1, and parenchymal hematoma 2.[24] The definition of symptomatic ICH was based on the ECASS II criteria (any ICH with a ≥4-point increase in the NIHSS score from baseline), the ECASS III criteria (any ICH that was identified as the predominant cause of a ≥4-point increase in the NIHSS score from baseline), and Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria (parenchymal hematoma 2 combined with a ≥4-point increase in the NIHSS score from baseline).[25–27]

Statistical Analysis

The data between the patients who underwent EVT (EVT group) and those who received medical management (medical management group) were summarized as median (interquartile range [IQR]) for continuous variables and as frequencies and percentages for categorical variables. Statistical differences between the 2 groups were assessed using the Mann–Whitney *U* test or Fisher exact test as appropriate (Table 1). We constructed logistic regression models for the dichotomous effectiveness outcomes. For shifts in the mRS score at 3 months, an ordinal logistic regression model was used.

To account for the selection bias between the EVT and medical managements groups, we applied inverse probability of treatment weighting (IPTW) and multivariable adjustment to all the models used for effectiveness assessment. The propensity score (PS) for each group was estimated using a logistic regression model, which included a quadratic term of ASPECTS, an interaction term of ASPECTS-by-ICA occlusion, and an interaction term of ASPECTS-by-M1 occlusion as well as all of the 22 variables included as baseline data (Table 1). This model yielded a C-statistic of 0.79. After calculating weight values by the IPTW estimators (1/PS

Table 1. Baseline Clinical Data in the EVT and Medical Management Groups

	EVT (n=175)	Medical Management (n=164)	*P* Value	Missing Data
Women	114 (65.1)	123 (75.0)	0.05	0 (0.0)
Age, y	82 (76–87)	87 (82–91)	<0.01	0 (0.0)
Prestroke mRS score			<0.05	0 (0.0)
2	70 (40.0)	42 (25.6)		
3	54 (30.9)	54 (32.9)		
4	51 (29.1)	68 (41.5)		
Atrial fibrillation	93 (53.1)	93 (56.7)	0.51	0 (0.0)
Hypertension	97 (55.4)	106 (64.6)	0.09	0 (0.0)
Diabetes mellitus	38 (21.7)	30 (18.3)	0.49	0 (0.0)
Dyslipidemia	35 (20.0)	26 (15.9)	0.32	0 (0.0)
Stroke history before index event	24 (13.7)	27 (16.5)	0.54	0 (0.0)
Congestive heart failure	40 (22.9)	48 (29.3)	0.21	0 (0.0)
Premorbid oral anticoagulants	45 (25.7)	31 (18.9)	0.15	0 (0.0)
Current smoker	9 (5.1)	4 (2.4)	0.26	0 (0.0)
From LKW to hospital arrival, min	125 (55–270)	180 (95–540)	<0.01	12 (3.5)
Baseline NIHSS score	19 (15–23)	22 (17–27)	<0.01	2 (0.6)
ASPECTS*	7 (6–9)	7 (5–9)	<0.01	3 (0.9)
ICA occlusion	73 (41.7)	74 (45.1)	0.58	0 (0.0)
M1 occlusion	108 (61.7)	92 (56.1)	0.32	0 (0.0)
Tandem occlusion	9 (5.1)	10 (6.1)	0.81	0 (0.0)
Baseline systolic BP, mm Hg	154 (135–173)	156 (140–173)	0.46	11 (3.2)
White blood cell count, μL	7640 (6000–9430)	6730 (5600–8700)	0.01	3 (0.9)
Blood glucose, mg/dL	125 (108–158)	122 (107–144)	0.22	10 (2.9)
Creatinine, mg/dL	0.78 (0.64–1.03)	0.77 (0.60–1.04)	0.48	3 (0.9)
IVT	69 (39.4)	33 (20.1)	<0.01	0 (0.0)

Data are provided as median (interquartile range) or number (percentage). ASPECTS indicates Alberta Stroke Program Early Computed Tomographic Score; BP, blood pressure; EVT, endovascular therapy; ICA, internal carotid artery; IVT, intravenous thrombolysis; LKW, last known well; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*ASPECTS on noncontrast computed tomography (n=231) and ASPECTS on diffusion-weighted magnetic resonance imaging (n=105).

for patients with EVT; 1/(1−PS) for those with medical management alone), weight was trimmed at the first and 99th percentiles to avoid extreme weight.[28] Thereafter, data balancing was assessed using absolute standardized differences, almost all of which were within the margin of 0.10 after IPTW.[29,30] The absolute standardized difference in glucose consistently remained at 0.10 (Figure 2). Accordingly, glucose, as well as sex, age, pRS score, time from LKW to hospital arrival, baseline NIHSS score, ASPECTS, ICA occlusion, M1 occlusion, and IVT were selected as the prespecified fixed effect covariates for the multivariable models. In addition, to account for the heterogeneity caused by unmeasured covariates between registering centers, we constructed mixed effects models considering center identifiers as a random effect. For each model, the odds ratio (OR) with 95% CI was calculated using the medical management group as a reference.

We performed sensitivity analyses for the effectiveness outcomes using a PS-matched cohort. The PS for EVT was developed using the same logistic model as in the IPTW analysis and a greedy, nearest neighbor 1-to-1 matching without replacement using a caliper (=

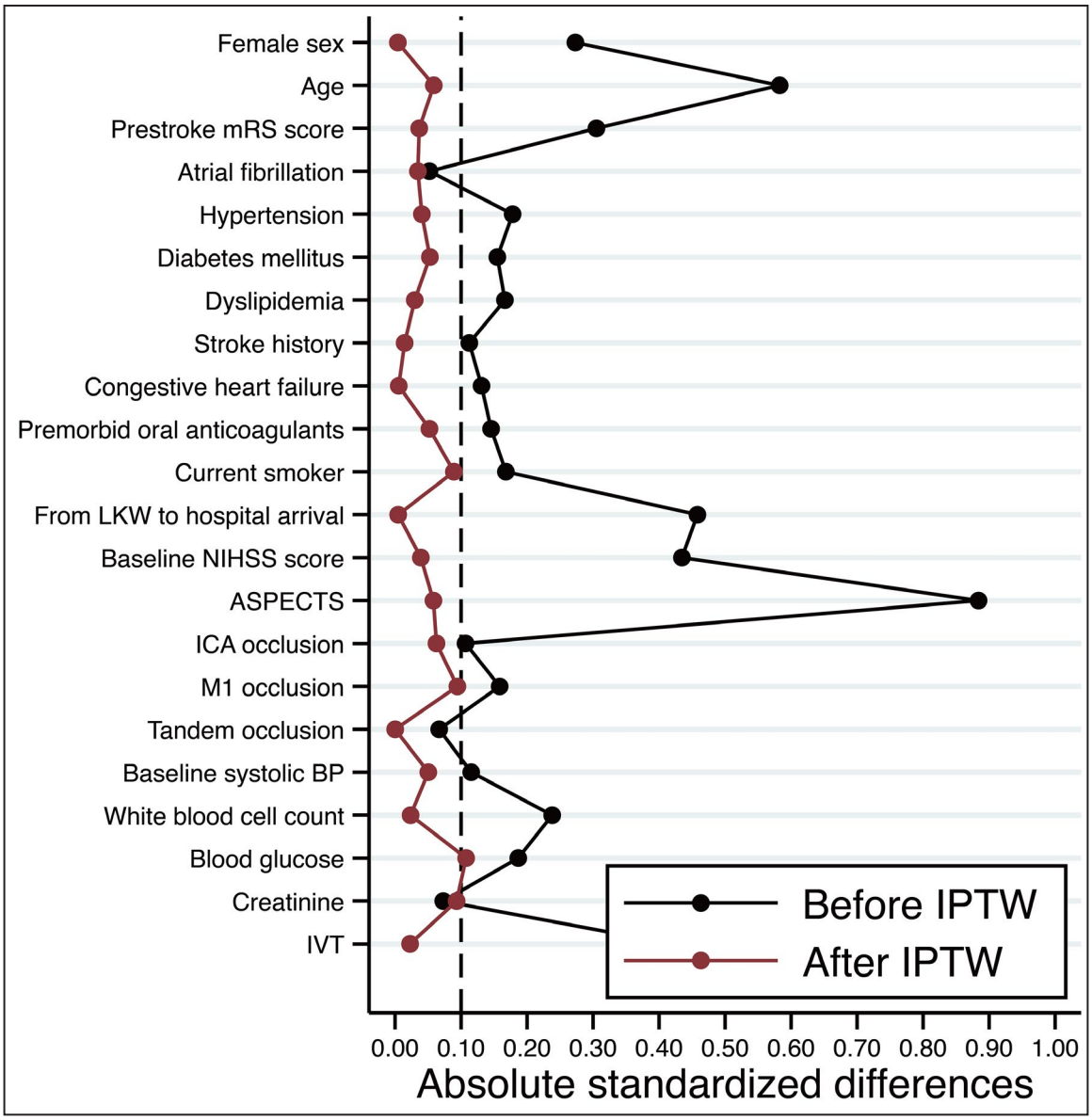

Figure 2. Intergroup absolute standardized differences before and after IPTW.
ASPECTS indicates Alberta Stroke Program Early Computed Tomographic Score; BP, blood pressure; ICA, internal carotid artery; IPTW, inverse probability of treatment weighting; IVT, intravenous thrombolysis; LKW, last known well; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

standard deviation of the PS×0.20) was implemented. Data balancing was assessed using standardized mean differences.[30]

All reported *p* values were 2-tailed, and $p<0.05$ was considered statistically significant. Pairwise deletion was used for missing data handling. All analyses were performed with using the Stata/IC statistical package, version 15.1 (Stata Corp LP, College Station, TX).

RESULTS

Patient Characteristics

Data for a total of 339 patients (237 women [69.9%]; median age 85 [IQR, 79–89] years of age) were available for analyses (Figure 1). The median pRS score was 3 (IQR, 2–4), and the median baseline NIHSS score was 21 (IQR, 16–25). A total of 147 (43.4%) patients had ICA occlusion, and 200 (59.0%) patients had M1 occlusion. Tandem occlusion was encountered in 19 (5.6%) patients. The median ASPECTS was 8 (IQR, 5–10), and IVT was implemented in 102 (30.1%) patients. The stroke etiology was determined as cardioembolism in 261 (76.9%) patients.

EVT was performed in 175 (51.6%) patients. Clinical characteristics according to the treatment status are listed in Table 1. The EVT group was younger ($p<0.01$) and had a lower pRS scores (3 [2–4] versus 3 [2–4]; $p<0.01$), shorter times from LKW to hospital arrival ($p<0.01$), lower baseline NIHSS scores ($p<0.01$), higher ASPECTS ($p<0.01$), higher white blood cell counts ($p=0.01$), and higher rates of IVT ($p<0.01$) than the medical management group.

EVT Procedures

Among the 175 patients treated with EVT, mechanical thrombectomy was performed in 139 patients (with a Solitaire stent retriever [Medtronic, Irvine, CA] in 58 patients, Trevo stent retriever [Stryker Neurovascular, Fremont, CA] in 40 patients, and Penumbra aspiration catheter [Penumbra Inc., Alameda, CA] in 84 patients). Other EVT procedures included balloon angioplasty (n=16), intracranial stenting (n=1), clot disruption (n=5), intra-arterial thrombolysis (n=10), and carotid artery stenting (n=15). The median time from hospital arrival to arterial puncture was 80 (IQR, 52.5–115 [n=168]) minutes. EVT led to successful reperfusion in 79.4% (139/175) of patients. The median time from puncture to successful recanalization was 50 (IQR, 35–80) minutes.

Effectiveness Outcomes

The distribution of pRS scores and mRS scores at 3 months in the EVT and medical management groups are shown in Figure 3. The EVT group demonstrated a tendency to have lower mRS scores at 3 months compared with the medical management group. The favorable outcome (return to at least the baseline pRS score) was seen more frequently in the EVT group (28.0%) than in the medical management group (10.9%; $p<0.01$). The fixed effects multivariable model with IPTW showed a significant association between EVT and the favorable outcome (adjusted OR, 3.07; 95% CI, 1.41–6.65). This statistical significance was maintained in the mixed effects IPTW model (adjusted OR, 3.01; 95% CI, 1.55–5.85). There was no significant difference in the risk of severe disability or death between patients with EVT and those receiving medical management. The effectiveness outcomes are summarized in Table 2.

In the PS-matched cohort (70 patients with EVT and 70 patients with medical management), there were no statistically significant differences in the baseline variables between the 2 groups. Regarding the standardized mean differences, the values were sufficiently small (<0.1) for the majority of the variables, including age, atrial fibrillation, hypertension, dyslipidemia, smoking habit, time from LKW to hospital arrival, baseline NIHSS score, ASPECTS, ICA occlusion, systolic blood pressure, white blood cell count, blood glucose, and creatinine (Table S2). For the other variables, the corresponding values were in the 0.1 to 0.2 range, except for premorbid oral anticoagulants (standard mean difference=0.24). The PS-matched cohort showed almost the same results achieved by the main analyses (Table S3). The fixed effects multivariable model showed a significant association between EVT and the favorable outcome (adjusted OR, 3.90; 95% CI, 1.36–11.22). The risk difference of severe disability or death was not significant between the groups.

Safety Outcomes

No statistically significant intergroup differences in the rates of any ICH was seen (EVT group, 27.4%; medical management group, 20.1%; $p=0.12$). The rate of parenchymal hematoma was numerically higher in the EVT group (9.1%) than the rate in the medical management group (5.5%; $p=0.21$). Symptomatic ICH (ECASS II) rates were similar between the EVT (4.0%) and medical management (4.3%) groups ($p=1.00$). The safety outcomes are shown in Table 3.

DISCUSSION

The present substudy of the RESCUE-Japan Registry 2 involving 339 patients with stroke with pRS scores of 2 to 4 and having occlusion of the ICA or the M1 middle cerebral artery had a major finding that the favorable outcome (return to at least the pRS score) was seen

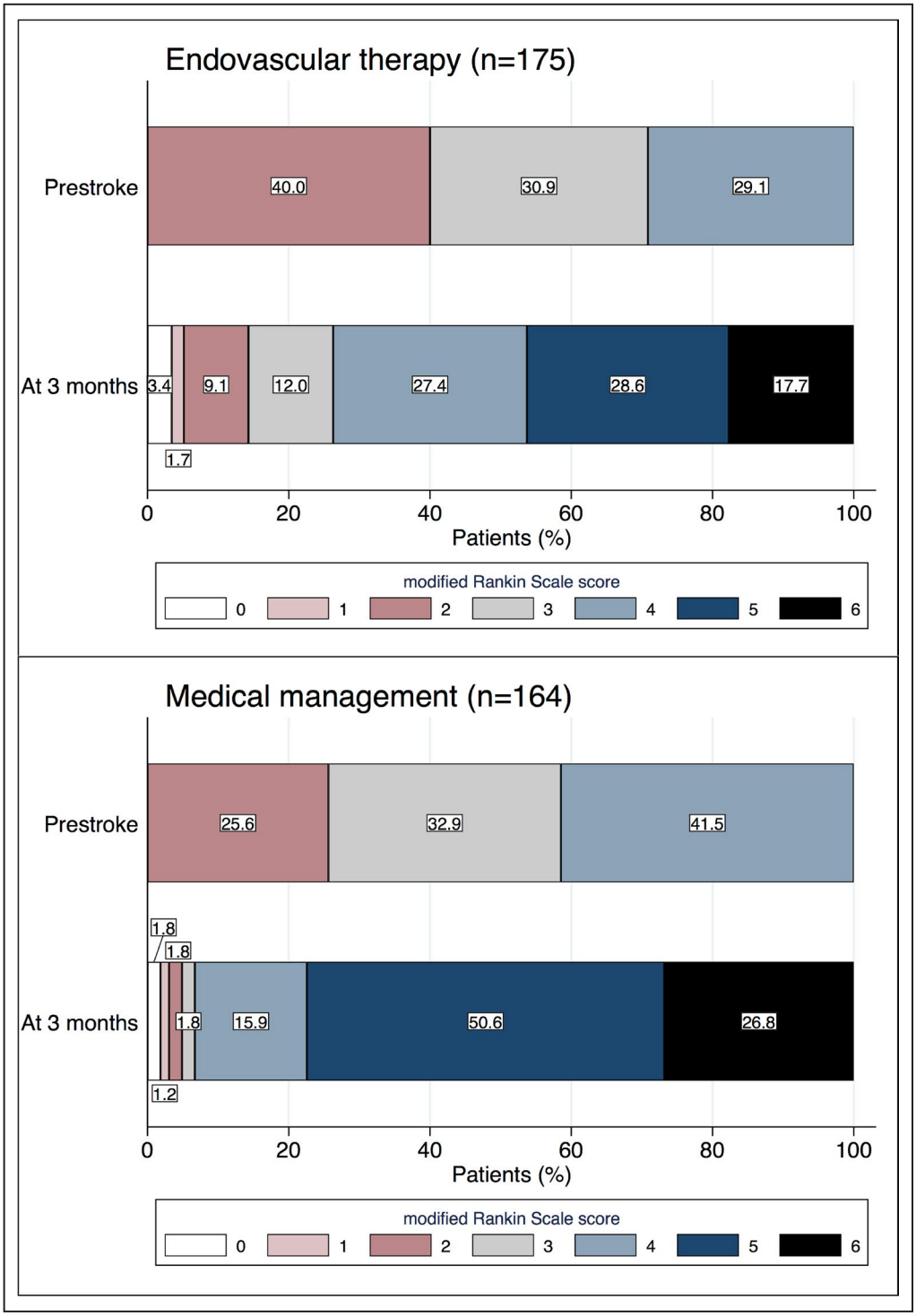

Figure 3. Distribution of prestroke modified Rankin Scale scores and modified Rankin Scale scores at 3 months.

in 28.0% of the EVT group and in 10.9% of the medical management group. This rate of the favorable outcome in the EVT group was comparable with that of a recent report in which 26.7% of patients with stroke with pRS scores 2 to 3 (n=259) showed 90-day mRS scores 0 to 1 or no worsening of pRS after mechanical thrombectomy.[31] There was a significant association between EVT and the favorable outcome without an

Table 2. Effectiveness Outcomes

	EVT (n=175), No. (%)	Medical Management (n=164), No. (%)	Crude OR (95% CI)	Adjusted OR (95% CI), Fixed Effects Model*	Adjusted OR (95% CI), Mixed Effects Model*†
Favorable outcome: return to at least the pRS score at 3 mo	49 (28.0)	18 (10.9)	3.15 (1.75–5.69); *P*<0.01	3.07 (1.41–6.65); *P*<0.01	3.01 (1.55–5.85); *P*<0.01
Death or severe disability at 3 mo	81 (46.3)	127 (77.4)	0.25 (0.16–0.40); *P*<0.01	0.59 (0.31–1.15); *P*=0.12	0.48 (0.22–1.04); *P*=0.06
Death within 3 mo	31 (17.7)	44 (26.8)	0.59 (0.35–0.99); *P*=0.04	1.17 (0.55–2.51); *P*=0.68	1.28 (0.48–3.38); *P*=0.62
Neurological improvement at 72 h	90 (62.1), n=145	36 (26.9), n=134	4.45 (2.68–7.41); *P*<0.01	5.21 (2.48–10.94); *P*<0.01	6.52 (2.23–19.08); *P*<0.01
Favorable shift in mRS score at 3 mo	…	…	2.96 (1.98–4.43); *P*<0.01	1.61 (0.93–2.81); *P*=0.09	1.67 (0.91–3.08); *P*=0.10

EVT indicates endovascular therapy; mRS, modified Rankin Scale; OR, odds ratio; and pRS, prestroke modified Rankin Scale.
*Adjusted for sex, age, pRS score, time from last known well to hospital arrival, baseline National Institutes of Health Stroke Scale score, Alberta Stroke Program Early Computed Tomographic Score, internal carotid artery occlusion, M1 occlusion, glucose, and intravenous thrombolysis with inverse probability of treatment weighting. OR was calculated using the medical management group as a reference.
†Center identifiers were used as a random effect.

increase in symptomatic ICH compared with medical management alone.

This was a nonrandomized study, and the indication for EVT was determined by each investigator in charge. Thus, differences in background features between the EVT and medical management groups should be understood well to interpret the present results. Patients who underwent EVT were younger and had lower pRS scores than patients without EVT. Aging is an important predictor for poor functional outcomes and for ICH after EVT.[32] Withholding EVT from older patients with stroke and those with higher pRS scores might be a common practice and could represent a major reason for the fact that the EVT group more frequently achieved the favorable outcome than the medical management group in this study. The EVT group had a shorter time from LKW to hospital arrival and a higher rate of IVT. These findings suggest that the EVT group had a higher potential to achieve better functioning. Importantly, ASPECTS was higher in the EVT group. Although the IPTW approach effectively suppressed the absolute standardized difference in ASPECTS between the 2 groups to <0.10, this strong predictor for the functional outcomes might not have been adequately adjusted by the analysis in this study.

Symptomatic ICH rates were similar between the 2 groups. However, any ICH was nonsignificantly more frequent in the EVT group than in the medical management group, and PH mainly contributed to the higher rate of any ICH in the EVT group. Although the numerically greater frequency of any ICH in the EVT group than in the medical management group lacked

Table 3. Safety Outcomes

	EVT (n=175)	Medical Management (n=164)	*P* Value*
Any ICH within 72 h	48 (27.4)	33 (20.1)	0.12
HI1 (ECASS)	4 (2.3)	7 (4.3)	0.36
HI2	19 (10.9)	15 (9.2)	0.71
PH1	15 (8.6)	7 (4.3)	0.12
PH2	1 (0.6)	2 (1.2)	0.61
Any PH	16 (9.1)	9 (5.5)	0.21
Symptomatic ICH within 72 h			
ECASS II criteria	7 (4.0)	7 (4.3)	1.00
ECASS III criteria	6 (3.4)	2 (1.2)	0.28
SITS-MOST criteria	1 (0.6)	1 (0.6)	1.00

Data are provided as number (percentage). ECASS indicates European Cooperative Acute Stroke Study; EVT, endovascular therapy; HI, hemorrhagic infarction; ICH, intracranial hemorrhage; PH, parenchymal hematoma; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.
*Fisher exact test.

statistical significance, it should be noted because of its clinical importance.

This study has several limitations. First, there was a strong selection bias between the 2 groups. The indication for EVT was determined by each investigator based on the patient characteristics, including age, prestroke disability, stroke severity, or ischemic core volume. Patients' and their relatives' preferences or opinions in each stroke center might also have influenced the process of decision making for EVT. Such biases might have affected the present analyses. Second, the presence of unmeasured confounders, including prestroke cognitive impairment or frailty, should be considered.[33,34] Third, the outcome measurements were not performed by evaluators blinded from clinical information; the presence of information bias in the outcomes should be assumed in this study. The mRS score at 3 months might have been influenced by the treatment status. A small number of patients achieved scores of 0 to 1 on the mRS at 3 months at a slightly higher rate in the EVT group than in the medical management group. However, this observation could have been attributed to the presence of reversible medical conditions as comorbidities at stroke onset.[12] In this study, the information on such medical conditions is not available. Fourth, the mRS score might not be a proper way to measure functional outcomes in patients with pRS scores ≥2. In particular, comparison of outcomes in patients with pRS scores of 4 might be underpowered. Fifth, the sample size in this study was relatively small. Last, the applicability of our findings to other settings is unknown because stroke characteristics differ among global regions.

Although the aforementioned limitations must be recognized, they do not invalidate the overall findings in the present study. Given proper patient selection, withholding EVT solely on the basis of prestroke disability might not offer the best chance of favorable outcome.

ARTICLE INFORMATION

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Disclosures

Dr Tanaka reports lecturer's fees from Johnson and Johnson, Medico's Hirata, and Stryker. Dr Yamagami reports research grants from Bristol-Myers Squibb; lecturer's fees from Stryker, Terumo, Medtronic, Medico's Hirata, Johnson and Johnson, Bayer, Daiichi-Sankyo, Bristol-Myers Squibb, Boehringer Ingelheim, Takeda, and Otsuka Pharmaceutical; and membership of the advisory boards for Daiichi-Sankyo. Dr Morimoto reports lecturer's fees from Bristol-Myers Squibb, Daiichi Sankyo, Japan Lifeline, Kowa, Kyocera, Novartis, and Toray; manuscript fees from Bristol-Myers Squibb and Kowa; and membership of the advisory board for Sanofi. Dr Toyoda reports lecturer's fees from Daiichi Sankyo, Boehringer Ingelheim, Bayer, Takeda, and Bristol-Myers Squibb outside of the submitted study. Dr Sakai reports a research grant from Terumo; lecturer's fees from Jimro, Johnson and Johnson, Medico's Hirata, Medtronic, and Stryker; and membership of the advisory boards for Jimro and Medtronic. Dr Yoshimura reports research grants from Medtronic, Medico's Hirata, and Terumo and lecturer's fees from Stryker and Medtronic. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S3

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Supplemental Material

Table S1. Definitions of safety outcomes.

Hemorrhagic transformation	
HI 1	Small petechiae along the margins of the infarct
HI 2	Confluent petechiae within the infarcted area without space-occupying effect
PH 1	Blood clots in 30% or less of the infarcted area with some slight space-occupying effect
PH 2	Blood clots in more than 30% of the infarcted area with substantial space-occupying effect
Symptomatic ICH	
ECASS II criteria	Any ICH with a ≥4-point increase in the NIHSS score from baseline
ECASS III criteria	Any ICH as the predominant cause of a ≥4-point increase in the NIHSS score from baseline
SITS-MOST criteria	PH2 combined with a ≥4-point increase in the NIHSS score from baseline

ECASS = European Cooperative Acute Stroke Study; HI = hemorrhagic infarction; ICH = intracranial hemorrhage; NIHSS = NIH Stroke Scale; PH = parenchymal hematoma; SITS-MOST = Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

Table S2. Baseline data in the propensity score-matched cohort.

	EVT (n = 70)	**Medical management (n = 70)**	***p***	***SMD***
Women, n (%)	44 (62.9)	49 (70.0)	0.47	0.15
Age, median (IQR), y	83.5 (79–89)	85 (80–90)	0.34	0.03
Prestroke mRS score, n (%)			0.56	0.15
2	24 (34.3)	18 (25.7)		
3	22 (31.4)	25 (35.7)		
4	24 (34.3)	27 (38.6)		
Atrial fibrillation, n (%)	38 (54.3)	39 (55.7)	1.00	0.02
Hypertension, n (%)	40 (57.1)	42 (60.0)	0.86	0.05
Diabetes mellitus, n (%)	11 (15.7)	14 (20.0)	0.66	0.11
Dyslipidemia, n (%)	10 (14.3)	11 (15.7)	1.00	0.03
Stroke history prior to index event, n (%)	9 (12.9)	13 (18.6)	0.48	0.15
Congestive heart failure, n (%)	16 (22.9)	20 (28.6)	0.56	0.13
Premorbid oral anticoagulants, n (%)	7 (10.0)	13 (18.6)	0.22	0.24
Current smoker, n (%)	3 (4.3)	3 (4.3)	1.00	0.00
From LKW to hospital arrival, median (IQR), min	147.5 (55–370)	142.5 (70–350)	0.57	0.05
Baseline NIHSS score, median (IQR)	20.5 (16–24)	20.5 (14–26)	0.90	0.02
ASPECTS, median (IQR) *	8.5 (7–10)	9 (7–10)	0.63	0.07
ICA occlusion, n (%)	26 (37.1)	29 (41.4)	0.72	0.08
M1 occlusion, n (%)	46 (65.7)	41 (58.6)	0.48	0.14
Tandem occlusion, n (%)	3 (4.3)	1 (1.4)	0.62	0.17
Baseline systolic BP, median (IQR), mmHg	154.5 (138–171)	156 (140–173)	0.82	0.00
White blood cell count, median (IQR), /μL	7200 (5840–8550)	6800 (5920–8700)	0.97	0.06
Blood glucose, median (IQR), mg/dL	120 (108–136)	124.5 (107–140)	0.46	0.00
Creatinine, median (IQR), mg/dL	0.765 (0.68–1.04)	0.76 (0.63–1.00)	0.45	0.08
IVT, n (%)	25 (35.7)	21 (30.0)	0.59	0.12

ASPECTS = Alberta Stroke Program Early Computed Tomographic Score; BP = blood pressure; EVT = endovascular therapy; ICA = internal carotid artery; IQR = interquartile range; IVT = intravenous thrombolysis; LKW = last known well; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; SMD = standardized mean difference.

* ASPECTS on non-contrast CT (n = 100) and ASPECTS on diffusion-weighted MRI (n = 40).

Table S3. Effectiveness outcomes in the propensity score-matched cohort.

	EVT (n = 70)	Medical management (n = 70)	Crude OR (95% CI)	Adjusted OR (95% CI) †
Return to at least the pRS score at 3 months, n (%)	20 (28.6)	9 (12.9)	2.71 (1.13–6.48); $p = 0.02$	3.90 (1.36–11.22); $p = 0.01$
Death or severe disability at 3 months, n (%)	35 (50.0)	45 (64.3)	0.56 (0.28–1.09); $p = 0.08$	0.48 (0.21–1.09); $p = 0.08$
Death within 3 months, n (%)	11 (15.7)	14 (20.0)	0.75 (0.31–1.78); $p = 0.50$	0.86 (0.33–2.25); $p = 0.76$
Neurological improvement at 72 hours *, n (%)	38 (65.5)	15 (27.8)	4.94 (2.21–11.05); $p < 0.01$	5.99 (2.51–14.26); $p < 0.01$
Favorable shift in mRS score at 3 months, n (%)	--	--	1.81 (0.99–3.33); $p = 0.05$	1.93 (1.01–3.67); $p = 0.04$
mRS score 0	1 (1.4)	2 (2.9)	--	--
1	1 (1.4)	1 (1.4)	--	--
2	5 (7.2)	2 (2.9)	--	--
3	11 (15.7)	1 (1.4)	--	--
4	17 (24.3)	19 (27.1)	--	--
5	24 (34.3)	31 (44.3)	--	--
6	11 (15.7)	14 (20.0)	--	--

ASPECTS = Alberta Stroke Program Early Computed Tomographic Score; BP = blood pressure; CI = confidence interval; EVT = endovascular therapy; ICA = internal carotid artery; IVT = intravenous thrombolysis; LKW = last known well; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio; pRS = prestroke mRS.

* Defined as a ≥ 4-point decrease in the NIHSS score from baseline.

† Adjusted for sex, age, pRS score, time from LKW to hospital arrival, baseline NIHSS score, ASPECTS, ICA occlusion, M1 occlusion, glucose, and IVT. OR was calculated using the medical management group as a reference.