The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 7, 2022 VOL. 386 NO. 14

Endovascular Therapy for Acute Stroke with a Large Ischemic Region

S. Yoshimura, N. Sakai, H. Yamagami, K. Uchida, M. Beppu, K. Toyoda, Y. Matsumaru, Y. Matsumoto, K. Kimura, M. Takeuchi, Y. Yazawa, N. Kimura, K. Shigeta, H. Imamura, I. Suzuki, Y. Enomoto, S. Tokunaga, K. Morita, F. Sakakibara, N. Kinjo, T. Saito, R. Ishikura, M. Inoue, and T. Morimoto

ABSTRACT

BACKGROUND

Endovascular therapy for acute ischemic stroke is generally avoided when the infarction is large, but the effect of endovascular therapy with medical care as compared with medical care alone for large strokes has not been well studied.

METHODS

We conducted a multicenter, open-label, randomized clinical trial in Japan involving patients with occlusion of large cerebral vessels and sizable strokes on imaging, as indicated by an Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) value of 3 to 5 (on a scale from 0 to 10, with lower values indicating larger infarction). Patients were randomly assigned in a 1:1 ratio to receive endovascular therapy with medical care or medical care alone within 6 hours after they were last known to be well or within 24 hours if there was no early change on fluid-attenuated inversion recovery images. Alteplase (0.6 mg per kilogram of body weight) was used when appropriate in both groups. The primary outcome was a modified Rankin scale score of 0 to 3 (on a scale from 0 to 6, with higher scores indicating greater disability) at 90 days. Secondary outcomes included a shift across the range of modified Rankin scale scores toward a better outcome at 90 days and an improvement of at least 8 points in the National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating greater deficit) at 48 hours.

RESULTS

A total of 203 patients underwent randomization; 101 patients were assigned to the endovascular-therapy group and 102 to the medical-care group. Approximately 27% of patients in each group received alteplase. The percentage of patients with a modified Rankin scale score of 0 to 3 at 90 days was 31.0% in the endovascular-therapy group and 12.7% in the medical-care group (relative risk, 2.43; 95% confidence interval [CI], 1.35 to 4.37; P=0.002). The ordinal shift across the range of modified Rankin scale scores generally favored endovascular therapy. An improvement of at least 8 points on the NIHSS score at 48 hours was observed in 31.0% of the patients in the endovascular-therapy group and 8.8% of those in the medical-care group (relative risk, 3.51; 95% CI, 1.76 to 7.00), and any intracranial hemorrhage occurred in 58.0% and 31.4%, respectively (P<0.001).

CONCLUSIONS

In a trial conducted in Japan, patients with large cerebral infarctions had better functional outcomes with endovascular therapy than with medical care alone but had more intracranial hemorrhages. (Funded by Mihara Cerebrovascular Disorder Research Promotion Fund and the Japanese Society for Neuroendovascular Therapy; RESCUE-Japan LIMIT ClinicalTrials.gov number, NCT03702413.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Morimoto can be contacted at t-morimoto@umin.net or at the Department of Clinical Epidemiology, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan.

This article was published on February 9, 2022, and updated on February 17, 2022, at NEJM.org.

N Engl J Med 2022;386:1303-13.
DOI: 10.1056/NEJMoa2118191

A Quick Take is available at NEJM.org

Endovascular therapy has become one of the standard treatments for acute stroke caused by large-vessel occlusion. Guidelines recommend consideration of endovascular therapy when there is occlusion of the M1 segment (main trunk) of the middle cerebral artery or internal carotid artery[1,2] and when imaging findings indicate that the size of the infarct area (also called the ischemic core) is not large, as defined by an Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) value of at least 6 (range from 0 to 10, with lower values indicating greater infarct burden), or when there is a mismatch between the ischemic core volume and the volume of perfusion delay area.[3-5]

Patients with large infarctions (e.g., those with an ASPECTS value of ≤5) have been generally excluded from clinical trials of endovascular therapy or represented in small numbers, partly owing to concerns that bleeding will occur in the area of infarction after reperfusion.[6-8] A meta-analysis that included observational studies has suggested that endovascular therapy may be associated with better functional outcomes and lower mortality at 90 days than medical care alone in patients with an ASPECTS value of 5 or less.[9]

We aimed to evaluate the effect of endovascular therapy with medical care, as compared with medical care alone, in patients with acute ischemic stroke caused by large-vessel occlusion and a large ischemic region, defined as an ASPECTS value of 3 to 5. We did not evaluate patients with an ASPECTS value of 2 or lower because they have extensive infarction and are unlikely to regain functional independence.[10]

Methods

Trial Design and Oversight

The Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core Trial (RESCUE-Japan LIMIT) was an open-label, parallel-group, randomized clinical trial conducted in 45 hospitals in Japan (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[11] The steering committee designed and supervised the trial with the support from other committees, including an independent monitoring committee, in accordance with the ethical guidelines for medical and health research involving humans in Japan (committee members are listed in Table S2). The protocol and consent forms were approved by the institutional review boards at Hyogo College of Medicine and all participating hospitals. Patients or their legally authorized representatives provided written informed consent before enrollment. There was no industry involvement in the trial. The funding sources were nonprofit organizations that did not participate in any part of the trial, from conception through manuscript preparation. The trial protocol and statistical analysis plan are available at NEJM.org.

Patients

Patients were eligible for enrollment if they had acute ischemic stroke, were 18 years of age or older, had a score of at least 6 on the National Institutes of Health Stroke Scale (NIHSS) at admission (scores range from 0 to 42, with higher scores indicating greater neurologic deficit),[12] had a score of 0 or 1 on the modified Rankin scale before the onset of stroke (scores range from 0 to 6, with 0 indicating no disability, 1 no clinically significant disability, 2 slight disability, 3 moderate disability but able to walk unassisted, 4 moderately severe disability, 5 severe disability, and 6 death),[15] had an occlusion of the internal carotid artery or M1 segment of the middle cerebral artery on computed tomographic angiography (CTA) or magnetic resonance angiography (MRA), and had an ASPECTS value of 3 to 5, as determined with the use of computed tomography (CT) or diffusion-weighted magnetic resonance imaging (MRI); if they underwent randomization within 6 hours after the time the patient was last known to be well or within 6 to 24 hours after the time the patient was last known to be well and there was no signal change in the initial image on fluid-attenuated inversion recovery (FLAIR) indicating that the infarction was recent[13]; and if endovascular therapy could be initiated within 60 minutes after randomization. Patients were excluded if they had a clinically significant cerebral mass effect with midline shift or an acute intracranial hemorrhage on CT or MRI or if site investigators considered that there was a high risk of hemorrhage. A full list of exclusion criteria is provided in the protocol.[11]

RANDOMIZATION AND INTERVENTION

Enrollment, randomization, and data collection were performed with the use of an electronic data-capture system. Randomization was performed centrally with the use of a stochastic minimization algorithm to balance trial-group assignments within hospitals on the basis of age (<75 or ≥75 years), interval between the time that a patient was last known to be well and the time of hospital arrival (<120 or ≥120 minutes), NIHSS score at admission (<21 or ≥21), and use of recombinant tissue plasminogen activator (rt-PA). Patients were randomly assigned in a 1:1 ratio to receive endovascular therapy with medical care (endovascular-therapy group) or medical care alone (medical-care group). Trial-group assignments were not concealed from patients or treating physicians. Patients with indications for rt-PA (alteplase at a dose of 0.6 mg per kilogram of body weight [a lower dose than that recommended in some other guidelines]) were treated according to Japanese guidelines at the discretion of the treating physician.[14]

The method of endovascular therapy was selected by the treating physicians and could include stent retriever, aspiration catheter, balloon angioplasty, intracranial stent, and carotid-artery stent. Other aspects of medical care in both groups were in line with the guidelines from the American Heart Association and the American Stroke Association.[1]

OUTCOMES

The primary outcome was a score of 0 to 3 on the modified Rankin scale at 90 days after the onset of stroke.[1] Secondary outcomes were a modified Rankin scale score of 0 to 2, a modified Rankin scale score of 0 or 1, and an ordinal shift across the range of modified Rankin scale scores toward a better outcome at 90 days and an improvement of at least 8 points on the NIHSS at 48 hours after randomization. Safety outcomes were symptomatic intracranial hemorrhage (parenchymal hematoma type 2, defined as clots in at least 30% of the infarcted area with space-occupying effect) in combination with worsening of NIHSS score by at least 4 points within 48 hours after randomization, any intracranial hemorrhage within 48 hours after randomization,[16] death within 90 days after the onset of stroke, recurrence of ischemic stroke within 90 days after randomization, and need for decompressive craniectomy within 7 days after randomization. The scores on the modified Rankin scale at 90 days were determined by physicians or physical therapists who were trained to obtain this score and were unaware of the trial-group assignments.

We added the utility-weighted modified Rankin scale as a post hoc outcome because this score has been used in other stroke trials.[4,17] On the utility-weighted modified Rankin scale, weights are assigned to the scores of 0 through 6 according to the patients' assessment of the value of quality of life at that level of function; scores range from 0.00 to 1.00, with higher scores indicating better quality of life.[18]

CLINICAL AND IMAGING ASSESSMENTS

Clinical assessments were performed at baseline, 12 hours after randomization, 24 to 72 hours after randomization, 5 to 9 days after randomization or at discharge, and 60 to 120 days after randomization. Clinical assessments included patient characteristics, medical history, vital signs and laboratory data, medication use, modified Rankin scale score, and NIHSS score.

Before randomization, the treating neurologist evaluated the ASPECTS value using diffusion-weighted MRI or noncontrast CT and determined the site of occlusion using MRA or CTA[19,20] Perfusion imaging was not available in most hospitals in Japan during the conduct of the trial. All site investigators were certified assessors of the ASPECTS. In the patients assigned to the endovascular-therapy group, the degree of vessel recanalization after the procedure was measured with the use of the Thrombolysis in the Cerebral Infarction (TICI) grading system; TICI grade 2b (antegrade reperfusion of more than half the previously occluded target artery ischemic territory) was used as a threshold for successful recanalization.[21] Follow-up imaging was performed 24 to 72 hours and 5 to 9 days after randomization or at discharge. Imaging data were submitted to the central core laboratory and independently evaluated by an imaging-evaluation committee.

STATISTICAL ANALYSIS

Our previous registry study showed that 55 of 146 patients (37.7%) with acute large-vessel oc-

clusion and an ASPECTS value of 3 to 5 had a modified Rankin scale score of 0 to 3 at 90 days among those who received endovascular therapy, as compared with 24 of 192 patients (12.5%) who did not receive endovascular therapy.[22] In our registry study, an adjusted odds ratio for a modified Rankin scale score of 0 to 3 was 3.42 in favor of the group that received endovascular therapy over the group that did not. Because the registry study was observational and the treatment effect could be larger than that in a clinical trial, we deducted 20% of the effect and assumed an odds ratio in the trial of 2.7 ($3.42 \times 0.8 = 2.7$) for the effect of endovascular therapy as compared with medical care. On the basis of these assumptions, we estimated that 81 patients would need to be assigned to each trial group, and assuming a possible dropout rate of 15%, we calculated that the required sample size was 191 patients in total. Considering potential withdrawal of consent, we set the final sample size at 200 patients to provide the trial with 90% power to show superiority of endovascular therapy over medical care at a two-sided alpha level of 0.05.[11]

The primary analysis was performed in the full analysis population, which included all the patients who underwent randomization and had assessable outcome data. Patients who underwent randomization and had available baseline data were included in the safety analysis. After evaluations by the event-adjudication committee and imaging-evaluation committee, patients who did not meet the inclusion criteria were excluded from the per-protocol population. The analyses in the per-protocol population were performed as secondary analyses.

We compared the results for the primary, secondary, and safety outcomes between the trial groups without adjustment for stratification variables. The effects of endovascular therapy, as compared with medical care alone, are presented as relative risks with 95% confidence intervals. The shift of modified Rankin scale toward a better functional outcome was estimated with the use of an ordinal logistic model, and a common odds ratio with 95% confidence intervals was derived after verification of the proportional odds assumption. Because there was no plan for adjustment of the widths of 95% confidence intervals for multiple comparisons, no definite conclusions can be drawn from these data. There was no plan for imputation of the missing data.

We performed subgroup analyses of the primary outcome on the basis of age (<75 or ≥75 years), interval between the time that a patient was last known to be well to the time of hospital arrival (<120 or ≥120 minutes), NIHSS score at admission (<21 or ≥21), and rt-PA use. A subgroup analysis of the interval between the time that a patient was last known to be well and the time of randomization (<6 or ≥6 hours) was added as a post hoc analysis. The results of the subgroup and post hoc analyses are reported descriptively. Statistical analyses were performed with the use of JMP software, version 15.1, and SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENT CHARACTERISTICS

From November 2018 through September 2021, a total of 203 patients were enrolled (Fig. S1); 101 were assigned to endovascular-therapy group and 102 to the medical-care group. Of the 203 patients, 202 completed follow-up in December 2021 and were included in the primary analyses (Fig. 1). One patient in the endovascular-therapy group withdrew consent; otherwise, no patient had missing data regarding the primary outcome in the full analysis population. The event-adjudication committee and imaging-evaluation committees excluded 14 patients from the per-protocol analysis (6 in the endovascular-therapy group and 8 in the medical-care group) because they had a modified Rankin scale score other than 0 or 1 before the onset of stroke, had undergone randomization more than 6 hours after the time the patient was last known to be well without MRI information being obtained, had an occlusion site other than the internal carotid artery or M1 segment of the middle cerebral artery, or had an ASPECTS value other than 3 to 5.

The demographic and clinical characteristics of the patients at baseline were similar in the trial groups (Table 1 and Table S3). The representativeness of enrolled patients is summarized in Table S4, and the details of the endovascular-therapy devices are provided in Table S5. The mean age of the patients was 76 years, and 44.3% of the patients were women. The median NIHSS score at trial entry was 22, and the median ASPECTS value was 3 at admission. Occlu-

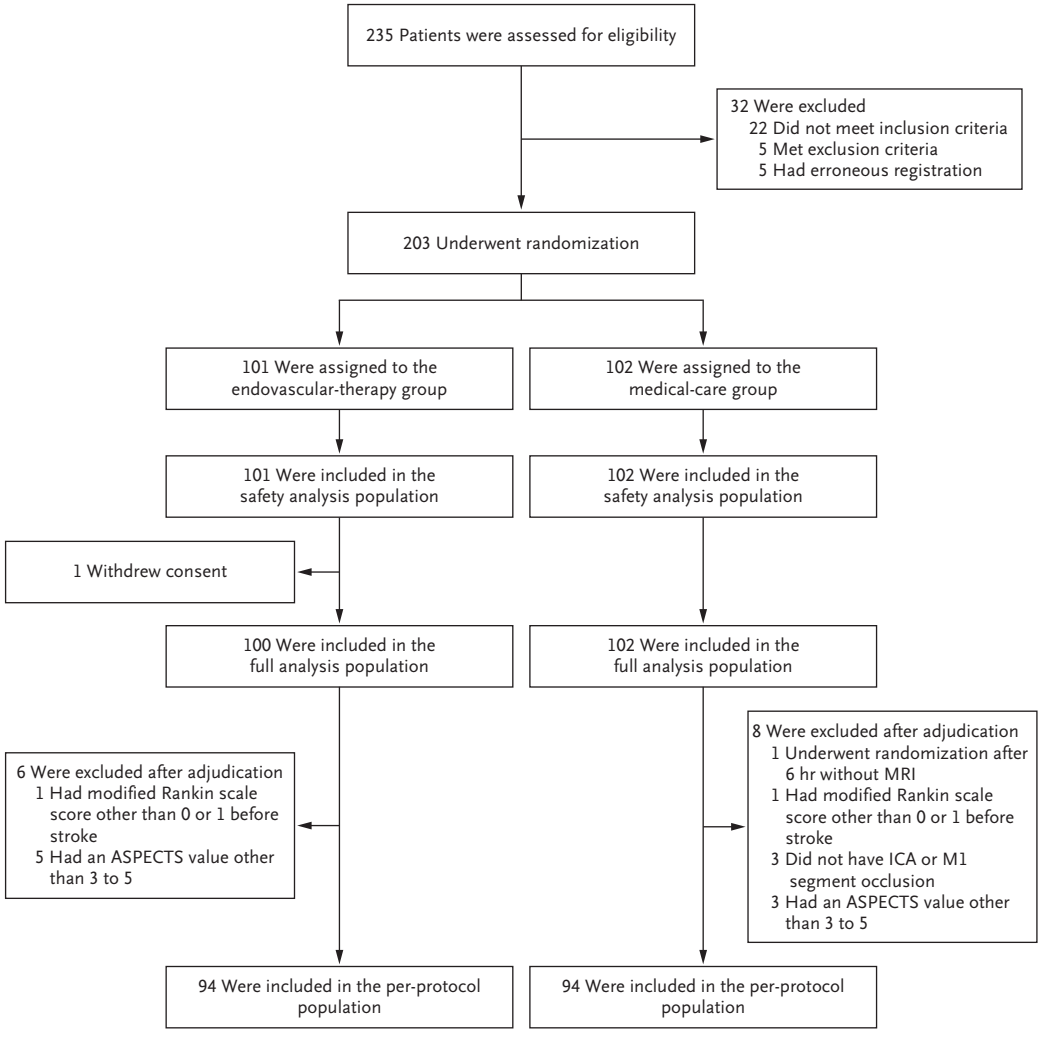


Figure 1. Screening, Randomization, and Analyses.

The endovascular-therapy group received endovascular therapy with medical care, and the medical-care group received medical care alone. The safety analysis population included all the patients who underwent randomization and had available baseline data. The full analysis population included all the patients who underwent randomization and had assessable outcome data. Patients were included in the per-protocol population after evaluation by the event-adjudication committee and the imaging-evaluation committee. Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability. Alberta Stroke Program Early Computed Tomographic Score (ASPECTS) values range from 0 to 10, with lower scores indicating larger infarction. The M1 segment is the main trunk of the middle cerebral artery. ICA denotes internal carotid artery.

sions of the internal carotid artery occurred in 47.3% of the patients, and occlusions of the M1 segment of the middle cerebral artery occurred in 70.9%; tandem lesions occurred in approximately 20% of the patients in each trial group. Atrial fibrillation was present in 59% of the patients, and rt-PA was administered in approximately 27% of the patients in each group. A total of 86.0% of the patients in the endovascular-therapy group had a TICI reperfusion grade of 2b or higher.

PRIMARY AND SECONDARY OUTCOMES

The percentage of patients with a score of 0 to 3 on the modified Rankin scale at 90 days was 31.0% in the endovascular-therapy group and

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Variable	Endovascular-Therapy Group (N=101)	Medical-Care Group (N=102)
Age — yr	76.6±10.0	75.7±10.2
Male sex — no. (%)	55 (54.5)	58 (56.9)
Median modified Rankin scale score before stroke (IQR)†	0 (0–1)	0 (0–1)
Median NIHSS score at baseline (IQR)‡	22 (18–26)	22 (17–26)
Occlusion site — no. (%)§		
Internal carotid artery	47 (46.5)	49 (48.0)
M1 segment	74 (73.3)	70 (68.6)
M2 segment	0	3 (2.9)
Tandem lesion of internal carotid artery and M1 segment of the middle cerebral artery	20 (19.8)	20 (19.6)
Patients with an ASPECTS value based on MRI — no.	88	87
Patients with an ASPECTS value based on CT — no.	13	15
ASPECTS¶		
Median value (IQR)	3 (3–4)	4 (3–4)
0–2 — no. (%)	5 (5.0)	3 (2.9)
3 — no. (%)	51 (50.5)	47 (46.1)
4 — no. (%)	25 (24.8)	32 (31.4)
5 — no. (%)	20 (19.8)	20 (19.6)
Median infarction volume (IQR) — ml	94 (66–152)	110 (74–140)
Intravenous rt-PA use — no. (%)	27 (26.7)	29 (28.4)
Median interval between time of stroke onset and hospital arrival (IQR) — min	190 (85–390)	170 (83–335)
Patients with an interval of <120 min between time of stroke onset and hospital arrival — no. (%)	36 (35.6)	35 (34.3)
Median interval between time of stroke onset and time of imaging (IQR) — min	181 (101–413)	170 (103–350)
Interval between time of stroke onset and time of randomization		
Median (IQR) — min	229 (144–459)	214 (142–378)
<4.5 hr — no. (%)	56 (55.4)	67 (65.7)
4.5 to <6.0 hr — no. (%)	15 (14.9)	7 (6.9)
6.0 to <12.0 hr — no. (%)	18 (17.8)	13 (12.7)
12.0 to 24.0 hr — no. (%)	12 (11.9)	15 (14.7)
Median interval between time of stroke onset and puncture time (IQR) — min	254 (165–479)	NA
Median interval between time of stroke onset and time of reperfusion (IQR) — min	308 (213–503)	NA
TICI reperfusion grade ≥2b — no./total no. (%)‖	86/100 (86.0)	NA

* Plus–minus values are means ±SD. The endovascular-therapy group received endovascular therapy with medical care, and the medical-care group received medical care alone. Data were missing for the following outcomes: infarction volume (missing in 20 patients [8 in the endovascular-therapy group and 12 in the medical-care group]), interval between time of stroke onset and puncture time (missing in 1 patient), interval between time of stroke onset and time of reperfusion (missing in 1 patient), and Thrombolysis in the Cerebral Infarction (TICI) reperfusion grade of 2b or higher (missing in 1 patient). CT denotes computed tomography, IQR interquartile range, M1 segment main trunk, M2 segment first-order branch of the main trunk, MRI magnetic resonance imaging, NA not applicable, and rt-PA recombinant tissue plasminogen activator.

Table 1. (Continued.)

† Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating greater deficit.
§ The M1 segment is the main trunk of the middle cerebral artery, and the M2 segment is the first-order branch of the main trunk of the middle cerebral artery.
¶ Alberta Stroke Program Early CT Scores (ASPECTS) values range from 0 to 10, with lower scores indicating larger infarction.
‖ A TICI reperfusion grade of 2b or higher indicates antegrade reperfusion of more than half the previously occluded target artery ischemic territory.

Table 2. Trial Outcomes.

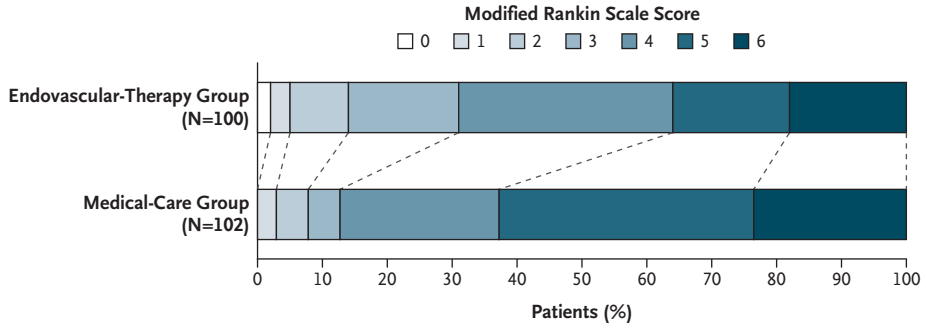
Outcome	Endovascular-Therapy Group (N=100)	Medical-Care Group (N=102)	Treatment Effect (95% CI)*	P Value
	number (percent)			
Primary outcome				
Modified Rankin scale score of 0 to 3 at 90 days	31 (31.0)	13 (12.7)	2.43 (1.35–4.37)	0.002
Secondary outcomes				
Modified Rankin scale score of 0 to 2 at 90 days	14 (14.0)	8 (7.8)	1.79 (0.78–4.07)	
Modified Rankin scale score of 0 or 1 at 90 days	5 (5.0)	3 (2.9)	1.70 (0.42–6.93)	
Ordinal shift across the range of modified Rankin scale scores toward a better outcome	NA	NA	2.42 (1.46–4.01)	
Improvement of ≥8 points on the NIHSS at 48 hr	31 (31.0)	9 (8.8)	3.51 (1.76–7.00)	
Safety outcomes				
Symptomatic intracranial hemorrhage within 48 hr	9 (9.0)	5 (4.9)	1.84 (0.64–5.29)	0.25
Any intracranial hemorrhage within 48 hr	58 (58.0)	32 (31.4)	1.85 (1.33–2.58)	<0.001
Death within 90 days	18 (18.0)	24 (23.5)	0.77 (0.44–1.32)	0.33
Recurrence of cerebral infarction within 90 days	5 (5.0)	7 (6.9)	0.73 (0.24–2.22)	0.58
Decompressive craniectomy within 7 days	10 (10.0)	14 (13.7)	0.73 (0.34–1.56)	0.41

* Treatment effects are reported as relative risks with 95% confidence intervals for all outcomes, except for the ordinal shift across the range of modified Rankin scale scores toward a better outcome, for which the treatment effect is reported as a common odds ratio with the 95% confidence interval. The widths of confidence intervals for secondary outcomes were not adjusted for multiple comparisons, and no definite conclusions can be drawn from these data.

12.7% in the medical-care group (relative risk, 2.43; 95% confidence interval [CI], 1.35 to 4.37; P=0.002) (Table 2). For the secondary outcomes of modified Rankin scale scores of 0 to 2 and 0 or 1 at 90 days, the 95% confidence intervals for the relative risks included 1. The shift of modified Rankin scale ordinal categories generally favored the endovascular-therapy group (common odds ratio, 2.42; 95% CI, 1.46 to 4.01) (Fig. 2). The percentage of patients with an improvement of at least 8 points on the NIHSS at 48 hours after admission was 31.0% in the endovascular-therapy group and 8.8% in the medical-care group (relative risk, 3.51; 95% CI, 1.76 to 7.00). However, the widths of the confidence intervals for secondary outcomes were not adjusted for multiple comparisons.

SAFETY

The occurrence of any intracranial hemorrhage within 48 hours was higher in the endovascular-therapy group than in the medical-care group (58.0% vs. 31.4%; relative risk, 1.85; 95% CI, 1.33 to 2.58; P<0.001), but there was no significant between-group difference in symptomatic intracranial hemorrhage within 48 hours or in deaths at 90 days (Table 2). The percentage of patients who had recurrence of an ischemic



Modified Rankin Scale Score at 90 Days	0	1	2	3	4	5	6
Endovascular-therapy group — no. (%)	2 (2.0)	3 (3.0)	9 (9.0)	17 (17.0)	33 (33.0)	18 (18.0)	18 (18.0)
Medical-care group — no. (%)	0	3 (2.9)	5 (4.9)	5 (4.9)	25 (24.5)	40 (39.2)	24 (23.5)

Figure 2. Distribution of Modified Rankin Scale Scores at 90 Days.

A modified Rankin scale score of 0 indicates no disability, 1 no clinically significant disability, 2 slight disability, 3 moderate disability but able to walk unassisted, 4 moderately severe disability, 5 severe disability, and 6 death.

stroke within 90 days was similar in the trial groups, as was the percentage of those who had decompressive craniectomy within 7 days. Other adverse events occurred in 33.7% of the patients in the endovascular-therapy group and in 18.6% of those in the medical-care group, including cardiovascular events in 9.9% and 2.9% of the patients, respectively (Table S6).

SUBGROUP AND PER-PROTOCOL ANALYSES

Subgroup analyses are shown in Figure 3. The scores on the post hoc median utility-weighted modified Rankin scale were numerically higher (better) in the endovascular-therapy group than in the medical-care group (Table S7). After review by the event-adjudication committee and imaging-evaluation committee, 14 patients were excluded from the per-protocol population (Table S8), but the patient characteristics remained similar in the two groups (Table S9). The results of the analyses in the per-protocol population were generally in the same direction as those of the main analyses for the primary, secondary, and safety outcomes. The results of the post hoc analyses are shown in Figures S2 and S3 and Table S10, but no definite conclusions can be drawn from these data.

DISCUSSION

In this trial, the percentage of patients with large ischemic regions of acute stroke, as gauged by an ASPECTS value of 3 to 5, who had good functional status at 90 days with respect to the primary outcome (a modified Rankin scale score of 0 to 3) was significantly higher with endovascular therapy plus medical care than with standard medical care alone. The percentages of patients who had good functional status at 90 days with respect to the two secondary outcomes of other categories of good functional status (modified Rankin scale scores of 0 to 2 and 0 or 1) were small relative to the number of patients assigned to each trial group, but our expectations for patients with large infarctions to meet these secondary outcome criteria were limited. The favorable effect of endovascular therapy was generally apparent in the subgroups, including the post hoc subgroup with intervals longer than 6 hours between the time of stroke onset and randomization, but the trial was not powered for an analysis of these groups and there was no adjustment for multiple comparisons. Overall, there were significantly more intracranial hemorrhages in the endovascular-therapy group than in the medical-care group, but the difference in the percentage of patients with symptomatic intracranial hemorrhage was not significant. These results are consistent with those of previous subgroup analyses of intracranial hemorrhages in randomized trials and observational studies.

The scoring of infarct size with the use of ASPECTS involves the anatomical mapping of lesions within the middle cerebral artery territory

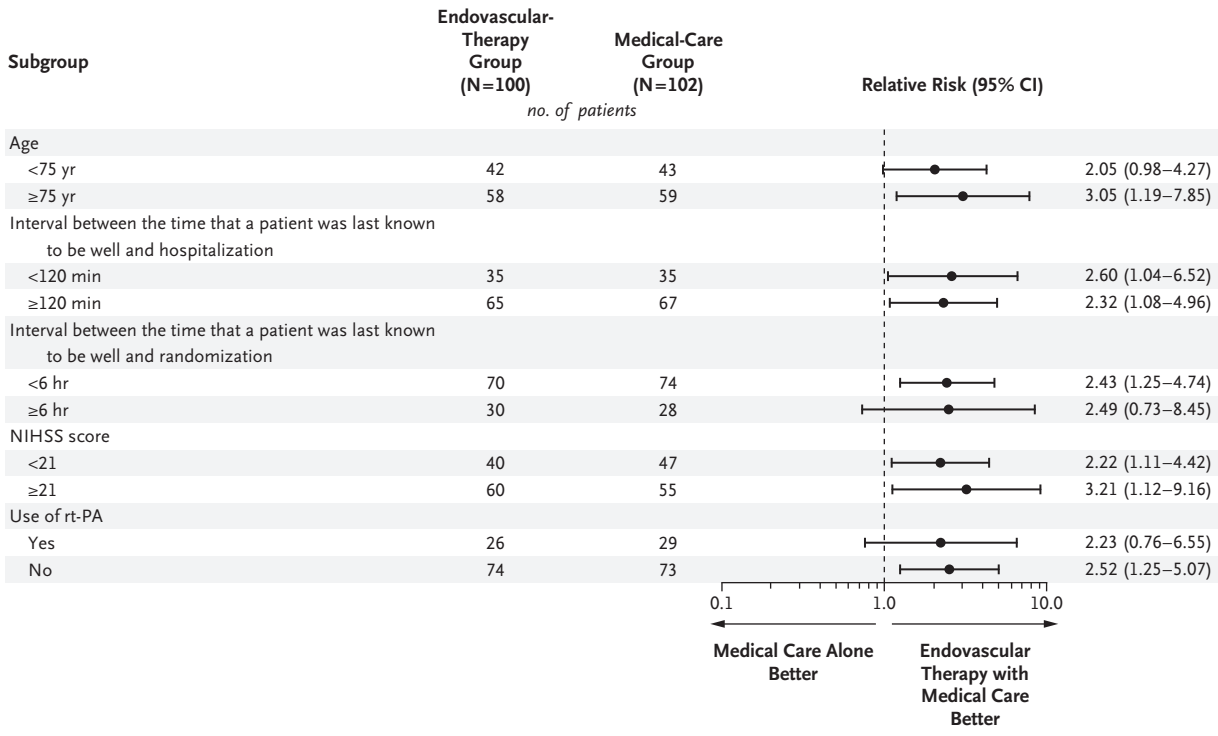


Figure 3. Subgroup Analyses of a Modified Rankin Scale Score of 0 to 3 at 90 Days (Primary Outcome).

The analysis of the interval between the time that a patient was last known well and randomization was performed on a post hoc basis. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating greater deficit. The trial was not powered and had no prespecified correction for multiple comparisons for a definitive analysis of subgroups. The term rt-PA denotes recombinant tissue plasminogen activator.

and provides a semiquantitative measure of size without requiring more elaborate volumetric imaging analysis. The range of ASPECTS values used as an inclusion criterion in this trial conducted in an emergency medical setting allowed the identification of patients who are likely to have poor outcomes because of large infarctions.[3,23] Although ASPECTS does not allow for the precise quantitation of infarct volume, it is frequently used as a surrogate to stratify patients with acute stroke in clinical trials and has been used in meta-analyses of outcomes of endovascular therapy for acute stroke caused by large-vessel occlusion.[10] Among 202 patients who were determined by treating physicians to have large infarct sizes corresponding to an ASPECTS value of 3 to 5, a total of 8 were adjudicated as having been misclassified. The analyses in the per-protocol population excluded 14 patients who did not meet inclusion criteria but showed results that were generally similar to those of the main analysis. The use of automated software to determine the ASPECTS value may have allowed more precise measurement of infarct size from the MRI or CT scan with lower interrater variability.[24] In addition, the ASPECTS value in most of our patients was determined with the use of diffusion-weighted MRI, because MRI is widely used in Japan for the diagnosis of acute ischemic stroke. Many institutions use CT for the assessment of acute ischemic stroke, and the differences between ASPECTS values based on CT results and those based on diffusion-weighted MRI results should be considered in the interpretation of our trial results. Previous studies have suggested that an ASPECTS value determined with the use of diffusion-weighted MRI may be one level lower (i.e., a larger infarction) than that determined with the use of CT[20]; therefore, patients in our trial with an ASPECTS value of 3 or 4 as determined with the use of MRI might have had an ASPECTS value of up to

5 if CT had been used. The inclusion of patients in whom there was a mismatch between imaging findings in the same region (i.e., no changes detected on FLAIR images and infarction detected on diffusion-weighted MRI) is consistent with the determination that a stroke is of recent onset, and such patients have been included in other trials involving patients with stroke. Perfusion imaging, which was not available in many of our participating hospitals, might have provided more accurate information regarding recoverable tissue and infarct size.

This trial has several other limitations. First, generalizability is limited beyond the Japanese population, in which the trial was conducted. Second, because this trial was pragmatic and the treating neurologists enrolled patients on the basis of their judgment regarding the indication for endovascular therapy, we performed the primary analysis in the full analysis population and confirmed the findings with an analysis in the per-protocol population, in which patients were included after the adjudication of images and events. Third, the relatively low use of rt-PA among the enrolled patients might have altered the outcomes in both groups and disadvantaged the medical-care group. However, most guidelines recommend against the use of alteplase when there is extensive ischemic change on imaging. Furthermore, the standard dose of rt-PA used in Japan is lower than that in many other countries.[25] If rt-PA had been used more often or at higher doses in our trial, the outcomes might have been improved in both groups, but there might have been an increased percentage of patients with intracranial hemorrhage in both groups. Finally, we did not collect information regarding the causes of death and could not determine whether they were due to adverse events associated with endovascular therapy or thrombolysis.

This trial conducted in Japan showed that among patients with acute stroke and a large ischemic region, functional outcomes at 90 days were better with endovascular therapy and medical care than with medical care alone, but endovascular therapy was associated with an increased incidence of intracranial hemorrhage.

Supported in part by the Mihara Cerebrovascular Disorder Research Promotion Fund and the Japanese Society for Neuroendovascular Therapy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the investigators for their efforts in conducting the trial; Drs. Naoya Kuwayama, Kuniaki Ogasawara, and Teruyuki Hirano for their role as members of the independent monitoring committee; and Drs. Kumiko Ando, Kanta Tanaka, Atsushi Yoshida, Takeshi Yoshimoto, and Junpei Kouge for their management of the imaging-evaluation committee.

APPENDIX

The authors' full names and academic degrees are as follows: Shinichi Yoshimura, M.D., Ph.D., Nobuyuki Sakai, M.D., Ph.D., Hiroshi Yamagami, M.D., Ph.D., Kazutaka Uchida, M.D., Ph.D., Mikiya Beppu, M.D., Ph.D., Kazunori Toyoda, M.D., Ph.D., Yuji Matsumaru, M.D., Ph.D., Yasushi Matsumoto, M.D., Kazumi Kimura, M.D., Ph.D., Masataka Takeuchi, M.D., Ph.D., Yukako Yazawa, M.D., Ph.D., Naoto Kimura, M.D., Ph.D., Keigo Shigeta, M.D., Ph.D., Hirotoshi Imamura, M.D., Ph.D., Ichiro Suzuki, M.D., Ph.D., Yukiko Enomoto, M.D., Ph.D., So Tokunaga, M.D., Kenichi Morita, M.D., Ph.D., Fumihiro Sakakibara, M.D., Norito Kinjo, M.D., Takuya Saito, M.D., Reiichi Ishikura, M.D., Ph.D., Manabu Inoue, M.D., Ph.D., and Takeshi Morimoto, M.D., Ph.D., M.P.H.

The authors' affiliations are as follows: the Departments of Neurosurgery (S.Y., K.U., M.B., F.S., N. Kinjo) and Clinical Epidemiology (K.U., F.S., N. Kinjo, T.S., T.M.), Hyogo College of Medicine, Nishinomiya, the Departments of Neurosurgery (N.S., H.I.) and Diagnostic Radiology (R.I.), Kobe City Medical Center General Hospital, Kobe, the Department of Stroke Neurology, National Hospital Organization Osaka National Hospital, Osaka (H.Y.), the Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita (K.T., M.I.), the Division of Stroke Prevention and Treatment, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Ibaraki (Y. Matsumaru), the Department of Neuroendovascular Therapy (Y. Matsumoto) and the Department of Stroke Neurology (Y.Y., T.S.), Kohnan Hospital, Sendai, the Department of Neurology, Graduate School of Medicine, Nippon Medical School, Tokyo (K.K.), the Department of Neurosurgery, Seisho Hospital, Odawara (M.T.), the Department of Neurosurgery, Iwate Prefectural Central Hospital, Morioka (N. Kimura), the Department of Neurosurgery, National Hospital Organization Disaster Medical Center, Tachikawa (K.S.), the Department of Neuroendovascular Therapy, Hachinohe City Hospital, Hachinohe (I.S.), the Department of Neurosurgery, Gifu University Hospital, Gifu (Y.E.), the Department of Neuroendovascular Therapy, National Hospital Organization Kyusyu Medical Center, Fukuoka (S.T.), and the Department of Cerebrovascular Medicine, Niigata City General Hospital, Niigata (K.M.) — all in Japan.

REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50(12):e344-e418.

2. Yamagami H, Hayakawa M, Inoue M, et al. Guidelines for mechanical thrombectomy in Japan, the fourth edition, March 2020: a guideline from the Japan Stroke Society, the Japan Neurosurgical Society, and the Japanese Society for Neu-

roendovascular Therapy. Neurol Med Chir (Tokyo) 2021;61:163-92.
3. Pexman JH, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol 2001;22:1534-42.
4. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018;378:11-21.
5. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018;378:708-18.
6. Cucchiara B, Kasner SE, Tanne D, et al. Factors associated with intracerebral hemorrhage after thrombolytic therapy for ischemic stroke: pooled analysis of placebo data from the Stroke-Acute Ischemic NXY Treatment (SAINT) I and SAINT II trials. Stroke 2009;40:3067-72.
7. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723-31.
8. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 2016;15:1138-47.
9. Sarraj A, Grotta JC, Pujara DK, Shaker F, Tsivgoulis G. Triage imaging and outcome measures for large core stroke thrombectomy — a systematic review and meta-analysis. J Neurointerv Surg 2020;12:1172-9.
10. Román LS, Menon BK, Blasco J, et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. Lancet Neurol 2018;17:895-904.
11. Yoshimura S, Uchida K, Sakai N, et al. Randomized clinical trial of endovascular therapy for acute large vessel occlusion with large ischemic core (RESCUE-Japan LIMIT): rationale and study protocol. Neurol Med Chir (Tokyo) 2021 December 24 (Epub ahead of print).
12. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH Stroke Scale using video training. Stroke 1994;25:2220-6.
13. Sakakibara F, Yoshimura S, Numa S, Uchida K, Kinjo N, Morimoto T. Diffusion-weighted imaging-fluid-attenuated inversion recovery mismatch is associated with 90-day functional outcomes in patients undergoing mechanical thrombectomy. Cerebrovasc Dis 2020;49:292-300.
14. Toyoda K, Koga M, Iguchi Y, et al. Guidelines for intravenous thrombolysis (recombinant tissue-type plasminogen activator), the third edition, March 2019: a guideline from the Japan Stroke Society. Neurol Med Chir (Tokyo) 2019;59:449-91.
15. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.
16. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-82.
17. Grotta JC, Yamal JM, Parker SA, et al. Prospective, multicenter, controlled trial of mobile stroke units. N Engl J Med 2021;385:971-81.
18. Rebchuk AD, O'Neill ZR, Szefer EK, Hill MD, Field TS. Health utility weighting of the Modified Rankin Scale: a systematic review and meta-analysis. JAMA Netw Open 2020;3(4):e203767.
19. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Lancet 2000;355:1670-4.
20. Nezu T, Koga M, Nakagawara J, et al. Early ischemic change on CT versus diffusion-weighted imaging for patients with stroke receiving intravenous recombinant tissue-type plasminogen activator therapy: stroke acute management with urgent risk-factor assessment and improvement (SAMURAI) rt-PA registry. Stroke 2011;42:2196-200.
21. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke 2013;44:2650-63.
22. Kakita H, Yoshimura S, Uchida K, Sakai N, Yamagami H, Morimoto T. Impact of endovascular therapy in patients with large ischemic core: subanalysis of recovery by endovascular salvage for cerebral ultra-acute embolism Japan Registry 2. Stroke 2019;50:901-8.
23. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019-30.
24. Albers GW, Wald MJ, Mlynash M, et al. Automated calculation of Alberta Stroke Programe Early CT score: validation in patients with large hemispheric infarct. Stroke 2019;50:3277-9.
25. 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;41:461-5.