ORIGINAL ARTICLE

# Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

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## ABSTRACT

### BACKGROUND

The effect of endovascular thrombectomy that is performed more than 6 hours after the onset of ischemic stroke is uncertain. Patients with a clinical deficit that is disproportionately severe relative to the infarct volume may benefit from late thrombectomy.

### METHODS

We enrolled patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume, with mismatch criteria defined according to age (<80 years or ≥80 years). Patients were randomly assigned to thrombectomy plus standard care (the thrombectomy group) or to standard care alone (the control group). The coprimary end points were the mean score for disability on the utility-weighted modified Rankin scale (which ranges from 0 [death] to 10 [no symptoms or disability]) and the rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability) at 90 days.

### RESULTS

A total of 206 patients were enrolled; 107 were assigned to the thrombectomy group and 99 to the control group. At 31 months, enrollment in the trial was stopped because of the results of a prespecified interim analysis. The mean score on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group (adjusted difference [Bayesian analysis], 2.0 points; 95% credible interval, 1.1 to 3.0; posterior probability of superiority, >0.999), and the rate of functional independence at 90 days was 49% in the thrombectomy group as compared with 13% in the control group (adjusted difference, 33 percentage points; 95% credible interval, 24 to 44; posterior probability of superiority, >0.999). The rate of symptomatic intracranial hemorrhage did not differ significantly between the two groups (6% in the thrombectomy group and 3% in the control group, P=0.50), nor did 90-day mortality (19% and 18%, respectively; P=1.00).

### CONCLUSIONS

Among patients with acute stroke who had last been known to be well 6 to 24 hours earlier and who had a mismatch between clinical deficit and infarct, outcomes for disability at 90 days were better with thrombectomy plus standard care than with standard care alone. (Funded by Stryker Neurovascular; DAWN ClinicalTrials.gov number, NCT02142283.)

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*A complete list of sites and investigators in the DAWN trial is provided in the Supplementary Appendix, available at NEJM.org.

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Previous randomized trials that involved patients with acute stroke[1-6] showed that endovascular thrombectomy had a clinical benefit when it was performed within 6 hours after the onset of stroke symptoms[7] and that the benefit diminished as the interval between the time that the patient was last known to be well and thrombectomy increased.[8] For the purposes of determining eligibility for thrombolysis or thrombectomy, the time that the patient was last known to be well has typically been considered to be the time of stroke onset, including among patients who wake up with stroke symptoms or have an uncertain time of stroke onset. There is limited information on the effect of thrombectomy that is performed more than 6 hours after the time that the patient was last known to be well, particularly among patients with ischemic brain tissue that has not yet undergone infarction and may be salvaged with reperfusion. Patients with brain tissue that may be salvaged with reperfusion can be identified by the presence of a clinical deficit that is disproportionately severe relative to the volume of infarcted tissue on imaging studies (see Section S3 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[9]

Results of previous nonrandomized studies have suggested that patients who have a mismatch between the volume of brain tissue that may be salvaged and the volume of infarcted tissue could benefit from reperfusion of occluded proximal anterior cerebral vessels, even when the reperfusion is performed more than 6 hours after the patient was last known to be well.[10,11] In the DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) trial, we compared endovascular thrombectomy plus standard medical care with standard medical care alone for the treatment of patients with acute stroke who had last been known to be well 6 to 24 hours earlier and who had a mismatch between clinical deficit and infarct.

## Methods

### Trial Design

The DAWN trial was a multicenter, prospective, randomized, open-label trial with a Bayesian adaptive–enrichment design and with blinded assessment of end points.[12] The trial protocol was approved by the institutional review board at each participating site. Enrolled patients or their surrogates provided written informed consent. The trial was designed and conducted by a steering committee, which was composed of independent academic investigators and statisticians, in collaboration with the sponsor, Stryker Neurovascular, which provided funding and the thrombectomy devices for the trial and performed regulatory monitoring at each site and central database maintenance. The first drafts of the manuscript were written by the first and last authors, with input from all the authors and with no writing assistance from the sponsor. The authors had unrestricted access to the data. The data analysis was performed by a data-management staff from Stryker Neurovascular, with oversight from independent statisticians. All the authors vouch for the completeness and accuracy of the reported data and the fidelity of the trial to the protocol. Decisions related to safety, adaptive–enrichment techniques, and trial discontinuation were made at the recommendation of an independent data and safety monitoring board.

Information on the inclusion and exclusion criteria, interventions, and assessments has been published previously.[12] The trial protocol and statistical analysis plan are available at NEJM.org.

### Patients

Patients were eligible for inclusion in the trial if they had evidence of occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both on computed tomographic (CT) angiography or magnetic resonance angiography. In addition, patients had to have a mismatch between the severity of the clinical deficit and the infarct volume, which was defined according to the following criteria: those in Group A were 80 years of age or older, had a score of 10 or higher on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating a more severe deficit), and had an infarct volume of less than 21 ml; those in Group B were younger than 80 years of age, had a score of 10 or higher on the NIHSS, and had an infarct volume of less than 31 ml; and those in Group C were younger than 80 years of age, had a score of 20 or higher on the NIHSS, and had an infarct volume of 31 to less than 51 ml. Infarct volume was assessed with the use of diffu-

sion-weighted magnetic resonance imaging (MRI) or perfusion CT and was measured with the use of automated software (RAPID, iSchemaView).

Other inclusion criteria were an age of 18 years or older, an interval between the time that the patient was last known to be well and randomization of 6 to 24 hours, a prestroke score of 0 or 1 on the modified Rankin scale (which ranges from 0 to 6, with a score of 0 indicating no disability and higher scores indicating more severe disability), no evidence of intracranial hemorrhage on CT or MRI, and no evidence of an infarct involving more than one third of the territory of the middle cerebral artery on CT or MRI at baseline. Patients either did not meet the usual criteria for treatment with intravenous alteplase because of a late presentation or received treatment with intravenous alteplase and had persistent occlusion of the vessel at the time that they were eligible for enrollment in the trial.

### TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to thrombectomy plus standard medical care (the thrombectomy group) or to standard medical care alone (the control group). Randomization was performed with the use of a central, Web-based procedure, with block minimization processes to balance the two treatment groups, and was stratified according to mismatch criteria (Group A, Group B, or Group C), the interval between the time that the patient was last known to be well and randomization (6 to 12 hours or >12 to 24 hours), and the occlusion site (intracranial internal carotid artery or the first segment of the middle cerebral artery).

The trial was conducted at 26 centers in the United States, Canada, Europe, and Australia; at least 40 mechanical thrombectomy procedures had been performed at each center annually. Enrolled patients were admitted to stroke units or intensive care units. Patients who had not received intravenous alteplase could receive therapy with antiplatelet agents, which could be started within 24 hours after randomization. Standard medical care was provided in accordance with local guidelines (see Section S6 in the Supplementary Appendix).[12] Thrombectomy was performed with the use of the Trevo device (Stryker Neurovascular), a retrievable self-expanding stent that is used to remove occlusive thrombi and restore blood flow. Rescue reperfusion therapy with other devices or pharmacologic agents was not permitted. Concomitant stenting of the cervical internal carotid artery at the time of thrombectomy was not permitted, but carotid angioplasty was permitted if necessary to allow for intracranial access for the catheter to deploy the retriever device.

### END POINTS

For the coprimary end points, scores on the modified Rankin scale were obtained through in-person, formal, structured interviews with patients and caregivers that were performed by local certified assessors[13,14] who were unaware of the treatment assignments.[15] For the 43 patients for whom in-person assessment was not possible, telephone interviews with patients, caregivers, or both were performed.

The first primary end point was the mean score for disability on the utility-weighted modified Rankin scale at 90 days. To determine the utility-weighted score, the score on the modified Rankin scale is weighted according to average values calculated from patient-centered and clinician-centered studies.[16-18] The following weights are assigned to scores 0 through 6 on the modified Rankin scale: 10.0, 9.1, 7.6, 6.5, 3.3, 0, and 0, respectively. The utility-weighted modified Rankin scale ranges from 0 (death) to 10 (no symptoms or disability).

The second primary end point was the rate of functional independence (defined as a score of 0, 1, or 2 on the modified Rankin scale) at 90 days. This end point was changed from a secondary end point to a coprimary end point at the request of the Food and Drug Administration at 30 months after the start of the trial, when the trial was still blinded.

Prespecified secondary end points were an early therapeutic response (defined as a decrease in the NIHSS score of ≥10 from baseline or an NIHSS score of 0 or 1 on day 5, 6, or 7 of hospitalization or at discharge if it occurred before day 5), death from any cause at 90 days, centrally adjudicated infarct volume and change from baseline in the infarct volume at 24 hours, and evidence of recanalization of the occluded vessel on CT angiography or magnetic resonance angiography at 24 hours (see Section S3 in the Supplementary Appendix). In the thrombectomy group, a secondary end point was centrally adjudicated successful re-

canalization (on the basis of findings on postprocedural conventional angiography), which was defined as a grade of 2b or 3 on the modified Thrombolysis in Cerebral Infarction scale (which ranges from 0 to 3, with a grade of 2b or 3 indicating reperfusion of >50% of the affected territory). A prespecified subgroup analysis for heterogeneity of treatment effect was performed, with subgroups defined according to mismatch criteria (Group A, Group B, or Group C), the interval between the time that the patient was last known to be well and randomization (6 to 12 hours or >12 to 24 hours), occlusion site (intracranial internal carotid artery or the first segment of the middle cerebral artery), sex, age (<80 years or ≥80 years), baseline NIHSS score (10 to 17 or >17), type of stroke onset (on awakening, unwitnessed stroke, or witnessed stroke), and time from the first observation of symptoms to randomization (0 to 6 hours or >6 hours).

The main safety end point was stroke-related death at 90 days. Other safety end points included neurologic deterioration (defined as an increase in the NIHSS score of ≥4 points within 5 days after stroke that was not attributed to intracranial hemorrhage or malignant cerebral edema) and symptomatic intracranial hemorrhage (defined according to European Cooperative Acute Stroke Study III criteria as the presence of extravascular blood in the cranium that was associated with an increase in the NIHSS score of ≥4 points or death and was judged to be the predominant cause of neurologic deterioration) within 24 hours after randomization.[19] Safety end points, procedure-related complications, and serious adverse events were adjudicated by an independent clinical-events committee.

### STATISTICAL ANALYSIS

The adaptive trial design allowed for a sample size ranging from 150 to 500 patients. During interim analyses, the decision to stop or continue enrollment was based on a prespecified calculation of the probability that thrombectomy plus standard care would be superior to standard care alone with respect to the first primary end point. The enrichment trial design gave us the flexibility to identify whether the benefit of the trial intervention was restricted to a subgroup of patients with relatively small infarct volumes at baseline. The interim analyses, which included patients with available follow-up data at the time of the analysis, were prespecified to test for the futility, enrichment, and success of the trial.

The first primary analysis, which evaluated the posterior probability that thrombectomy plus standard care would be superior to standard care alone with respect to the mean score for disability on the utility-weighted modified Rankin scale at 90 days, was conducted with the use of a Bayesian statistical model with adjustment for infarct volume at baseline. The threshold for significance was a one-sided posterior probability of superiority of at least 0.986, which was increased from 0.975 to account for the potential for enrichment and different final sample sizes. The second primary analysis, which evaluated the posterior probability that thrombectomy plus standard care would be superior to standard care alone with respect to the rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale) at 90 days, was conducted with the use of the same statistical model (with an assumption of normal distribution) and was carried out in a nested hierarchical fashion. The trial had 86% power to detect an adjusted difference between the two treatment groups in the mean score on the utility-weighted modified Rankin scale of 1.0. No additional adjustments for multiplicity were made for analyses of the secondary end points. Bayesian multiple imputations were used for patients who had missing values for the primary analyses. Descriptive statistics were calculated with the use of the last-observation-carried-forward method for patients who had missing values for the subgroup analyses.

Enrollment in the trial was stopped at 31 months, because the results of an interim analysis met the prespecified criterion for trial discontinuation, which was a predictive probability of superiority of thrombectomy of at least 95% for the first primary end point. This was the first prespecified interim analysis that permitted stopping for this reason, and it was based on the enrollment of 200 patients. Because enrichment thresholds had not been crossed, the analysis included the full population of patients enrolled in the trial, regardless of infarct volume. (For details about the statistical analysis, see Section S4 in the Supplementary Appendix.)

## RESULTS

### PATIENT CHARACTERISTICS

From September 2014 through February 2017, a total of 206 patients were enrolled in the trial; 107 were randomly assigned to the thrombectomy group and 99 to the control group (Fig. S1 in the Supplementary Appendix). Baseline characteristics are shown in Table 1, and in Table S1 in the Supplementary Appendix. At baseline, the median NIHSS score, which indicates the severity of the stroke deficit, was 17 in both treatment groups; the median infarct volume was 7.6 ml in the thrombectomy group and 8.9 ml in the control group. The median interval between the time that a patient was last known to be well and randomization was 12.2 hours in the thrombectomy group and 13.3 hours in the control group. Baseline characteristics were generally balanced between the two groups, except for the percentage of patients with a history of atrial fibrillation and the percentage who had the onset of stroke symptoms on awakening, which were higher in the thrombectomy group than in the control group, and the percentage of patients who received intravenous alteplase, which was higher in the control group than in the thrombectomy group.

Thrombectomy was performed in 105 of the 107 patients in the thrombectomy group. Ipsilateral carotid angioplasty was performed in 3 of the 107 patients. In 11 patients in the thrombectomy group (10%), thrombectomy was performed while the patient was under general anesthesia. In 102 of the 105 patients who underwent thrombectomy, the procedure was performed with the use of the Trevo device only; the other 3 patients underwent treatment with alternative endovascular reperfusion devices after the initial treatment with the Trevo device failed, although this approach was not permitted in the protocol.

### EFFICACY OUTCOMES

The first primary end point of the mean score for disability on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group (adjusted difference [Bayesian analysis], 2.0 points; 95% credible interval, 1.1 to 3.0; posterior probability of superiority, >0.999). The second primary end point of the rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale) at 90 days was 49% in the thrombectomy group as compared with 13% in the control group (adjusted difference, 33 percentage points; 95% credible interval, 21 to 44; posterior probability of superiority, >0.999) (Table 2 and Fig. 1). In post hoc sensitivity analyses that adjusted for between-group differences in baseline characteristics that had a P value of less than 0.10, the posterior probability of superiority of thrombectomy remained significant for both coprimary end points (see Section S7 in the Supplementary Appendix).

Among the patients who underwent thrombectomy, immediate reperfusion was achieved in 84% according to results of central laboratory assessments and in 82% according to results of evaluations by local interventionists; the median interval between the time the patient was last known to be well and reperfusion was 13.6 hours (interquartile range, 11.3 to 18.0). Recanalization was achieved at 24 hours in 77% of the patients in the thrombectomy group and in 36% of the patients in the control group. For all the secondary end points, the comparisons between the two treatment groups favored thrombectomy (Table 2). In prespecified subgroup analyses, no evidence of heterogeneity of treatment effect was detected (Fig. 2); the relatively small sample size limited the power of some of these analyses. (For details about secondary and subgroup analyses, see Figs. S2 through S8 in the Supplementary Appendix.)

### SAFETY OUTCOMES

The rates of safety end points and serious adverse events — including stroke-related death at 90 days, death from any cause at 90 days, and symptomatic intracerebral hemorrhage — did not differ significantly between the two treatment groups (Table 3, and Table S2 in the Supplementary Appendix). The rate of neurologic deterioration was lower in the thrombectomy group than in the control group (14% vs. 26%; absolute difference, −12 percentage points; 95% confidence interval, −23 to −1; P=0.04).

## DISCUSSION

The DAWN trial showed that, among patients with stroke due to occlusion of the intracranial internal carotid artery or proximal middle cerebral artery

**Table 1. Characteristics of the Patients at Baseline.***

| Variable | Thrombectomy Group (N=107) | Control Group (N=99) |
|---|---|---|
| Age — yr | 69.4±14.1 | 70.7±13.2 |
| Age ≥80 yr — no. (%) | 25 (23) | 29 (29) |
| Male sex — no. (%) | 42 (39) | 51 (52) |
| Atrial fibrillation — no. (%) | 43 (40) | 24 (24) |
| Diabetes mellitus — no. (%) | 26 (24) | 31 (31) |
| Hypertension — no. (%) | 83 (78) | 75 (76) |
| Previous ischemic stroke or transient ischemic attack — no. (%) | 12 (11) | 11 (11) |
| NIHSS score† | | |
| Median | 17 | 17 |
| Interquartile range | 13–21 | 14–21 |
| 10 to 20 — no. (%) | 78 (73) | 72 (73) |
| Treatment with intravenous alteplase — no. (%) | 5 (5) | 13 (13) |
| Infarct volume — ml | | |
| Median | 7.6 | 8.9 |
| Interquartile range | 2.0–18.0 | 3.0–18.1 |
| Type of stroke onset — no. (%)‡ | | |
| On awakening | 67 (63) | 47 (47) |
| Unwitnessed stroke | 29 (27) | 38 (38) |
| Witnessed stroke | 11 (10) | 14 (14) |
| Occlusion site — no. (%)§ | | |
| Intracranial internal carotid artery | 22 (21) | 19 (19) |
| First segment of middle cerebral artery | 83 (78) | 77 (78) |
| Second segment of middle cerebral artery | 2 (2) | 3 (3) |
| Interval between time that patient was last known to be well and randomization — hr | | |
| Median | 12.2 | 13.3 |
| Interquartile range | 10.2–16.3 | 9.4–15.8 |
| Range | 6.1–23.5 | 6.5–23.9 |
| Time from first observation of symptoms to randomization — hr | | |
| Median | 4.8 | 5.6 |
| Interquartile range | 3.6–6.2 | 3.6–7.8 |

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. There were no significant differences between the two treatment groups with respect to the baseline characteristics, except for a history of atrial fibrillation (P=0.01), treatment with intravenous alteplase (P=0.04), and the onset of stroke on awakening (P=0.03).

† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a more severe deficit.

‡ A patient with the onset of stroke on awakening had last been known to be well before going to bed and had the first observation of symptoms on awakening. In a patient with an unwitnessed stroke, the time that the patient had last been known to be well and the first observation of symptoms were different and the first observation of symptoms did not occur on awakening. In a patient with a witnessed stroke, the time that the patient had last been known to be well and the first observation of symptoms were the same; all patients with a witnessed stroke had a time from first observation of symptoms to randomization of more than 6 hours.

§ Patients who had occlusion of the intracranial internal carotid artery may also have had occlusion of the first segment of the middle cerebral artery.

**Table 2. Efficacy Outcomes.***

| Outcome | Thrombectomy Group (N=107) | Control Group (N=99) | Absolute Difference (95% CI)† | Adjusted Difference (95% Credible Interval)‡ | Posterior Probability of Superiority |
|---|---|---|---|---|---|
| **Primary end points** | | | | | |
| Score on utility-weighted modified Rankin scale at 90 days§ | 5.5±3.8 | 3.4±3.1 | 2.1 (1.2–3.1) | 2.0 (1.1–3.0) | >0.999 |
| Functional independence at 90 days — no. (%)¶ | 52 (49) | 13 (13) | 36 (24–47) | 33 (21–44) | >0.999 |
| | | | | **Risk Ratio (95% CI)** | **P Value** |
| **Secondary end points** | | | | | |
| Early response — no. (%)‖ | 51 (48) | 19 (19) | 29 (16–41) | 3 (2–4) | <0.001** |
| Recanalization at 24 hr — no. (%)†† | 82 (77) | 39 (39) | 40 (27–52) | 2 (2–4) | <0.001** |
| Change from baseline in infarct volume at 24 hr — ml†† | | | | | 0.003‡‡ |
| Median | 1 | 13 | | | |
| Interquartile range | 0–28 | 0–42 | | | |
| Infarct volume at 24 hour — ml†† | | | | | <0.001‡‡ |
| Median | 8 | 22 | | | |
| Interquartile range | 0–48 | 8–68 | | | |
| Grade of 2b or 3 on mTICI scale — no. (%)§§ | 90 (84) | NA | | | |

* Plus–minus values are means ±SD. CI denotes confidence interval, and NA not applicable.
† Absolute differences are reported in percentage points, except for the absolute difference in the score on the utility-weighted modified Rankin scale, which is reported in points.
‡ Adjusted differences were estimated with the use of a Bayesian general linear model with adjustment for infarct volume at baseline.
§ The utility-weighted modified Rankin scale ranges from 0 (death) to 10 (no symptoms or disability).
¶ Functional independence was defined as a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability.
‖ Early response was defined as a decrease in the NIHSS score of 10 points or more from baseline or an NIHSS score of 0 or 1 on day 5, 6, or 7 of hospitalization or at discharge if it occurred before day 5.
** The P value was calculated with the use of Fisher's exact test.
†† For details on the assessment of this end point, see Section S2 in the Supplementary Appendix.
‡‡ The P value was calculated with the use of the nonparametric Wilcoxon test.
§§ The modified Thrombolysis in Cerebral Infarction (mTICI) scale ranges from 0 to 3, with a grade of 2b or 3 indicating reperfusion of more than 50% of the affected territory.

who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume, outcomes for disability and functional independence at 90 days were better with thrombectomy plus standard medical care than with standard medical care alone. For every 2 patients who underwent thrombectomy, 1 additional patient had a better score for disability at 90 days (as compared with the results in the control group); for every 2.8 patients who underwent thrombectomy, 1 additional patient had functional independence at 90 days (see Section S1 in the Supplementary Appendix). The benefit of thrombectomy was consistent across prespecified subgroups that were defined according to age, stroke severity, occlusion site, time to treatment, and type of stroke onset, but the power of the trial to assess differences between subgroups was limited.

Endovascular thrombectomy in patients with stroke is usually performed within 6 hours after the onset of stroke. However, the rate of functional independence in the thrombectomy group in our trial, in which patients received treatment 6 to 24 hours after stroke onset, was similar to the rate reported in a pooled analysis of five trials of thrombectomy, in which patients predominantly received treatment within 6 hours after stroke on-

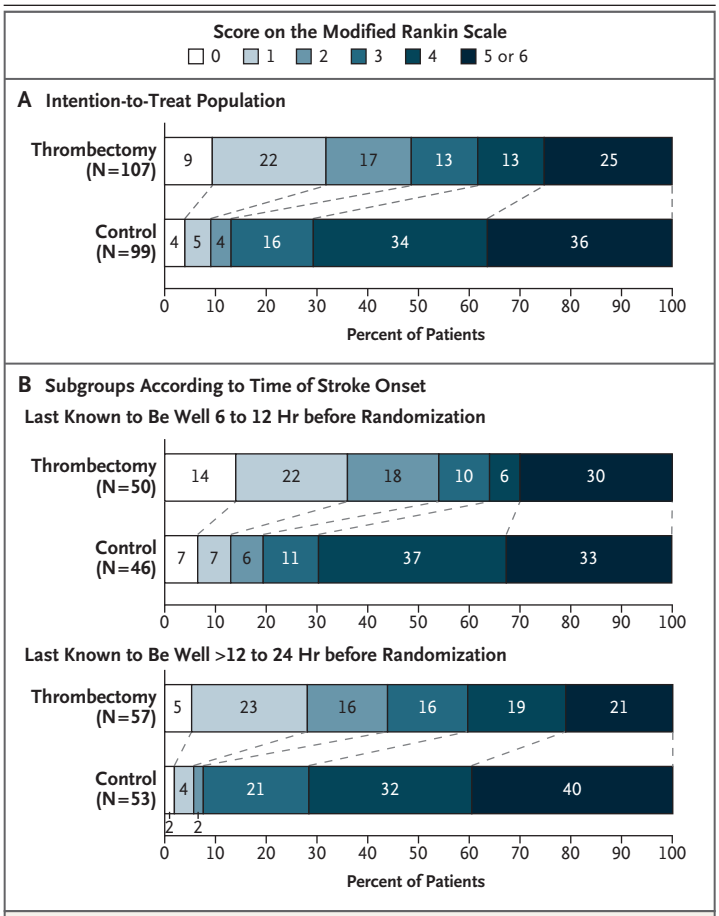


**Figure 1. Distribution of Scores on the Modified Rankin Scale at 90 Days.**

Shown is the distribution of scores for disability on the modified Rankin scale (which ranges from 0 to 6, with higher scores indicating more severe disability) among patients in the thrombectomy group and the control group, both in the overall intention-to-treat population (Panel A) and in subgroups defined according to time of stroke onset (Panel B). The numbers in the bars are percentages of patients who had each score; the percentages may not sum to 100 because of rounding. For the first primary end point, scores on the modified Rankin scale were weighted according to average values calculated from patient-centered and clinician-centered studies. For the second primary end point, functional independence was defined as a score of 0, 1, or 2 on the modified Rankin scale.

set (49% and 46%, respectively).[7] In contrast, the rate of functional independence in the control group in our trial was lower than the rate in the control group in the pooled analysis (13% vs. 26%). It is possible that the worse outcomes in our control group were related to the lower rate of treatment with intravenous alteplase (14% in our trial vs. 88% in the pooled analysis); patients were enrolled in our trial after the accepted window of time in which intravenous thrombolytic therapy is typically administered. An additional possible determinant of the worse outcomes in our control group was a higher percentage of patients with adverse prognostic features, particularly an age of 80 years or older and an NIHSS score after stroke of 10 or higher. The rates of functional independence that were observed in our control group are similar to those reported in prospective observational studies that included older patients with occlusion of a proximal large vessel who had a severe deficit and did not receive treatment with intravenous alteplase or thrombectomy.[20-22] Other recent randomized trials of thrombectomy have used enrollment criteria that are similar to those used in our trial.[23]

This trial has limitations. Randomization was stratified according to prognostic variables that the investigators determined to be most pertinent in the patient population; these variables were balanced between the two treatment groups. However, there were significant differences between the two groups in other baseline variables. In post hoc sensitivity analyses that adjusted for these differences, the benefit of thrombectomy remained.

We found that, among patients with acute stroke who have a mismatch between the severity of the clinical deficit and the infarct volume, the safety profile for thrombectomy performed 6 to 24 hours after the onset of stroke was similar to a previously observed safety profile for thrombectomy performed within 6 hours after the onset of stroke[7]; the rates of death and symptomatic intracerebral hemorrhage did not differ significantly from the rates seen with standard medical care. Because our trial restricted enrollment to patients with infarcts of a small or medium volume, our findings may be concordant with previous reports that the extent of tissue injury is a determinant of the risk of symptomatic intracerebral hemorrhage after reperfusion therapy.[24]

On the basis of retrospective studies, approximately one third of the patients with occlusion of a proximal anterior cerebral vessel who present within 6 to 24 hours after the onset of stroke may meet the imaging-based eligibility criteria that were used in this trial.[25,26] Further studies are needed to establish the prevalence of patients who would be eligible for thrombectomy among the entire population of patients with ischemic stroke. Further studies are also needed to determine whether late thrombectomy has a benefit when more widely available imaging techniques are used to estimate the infarct volume at presenta-

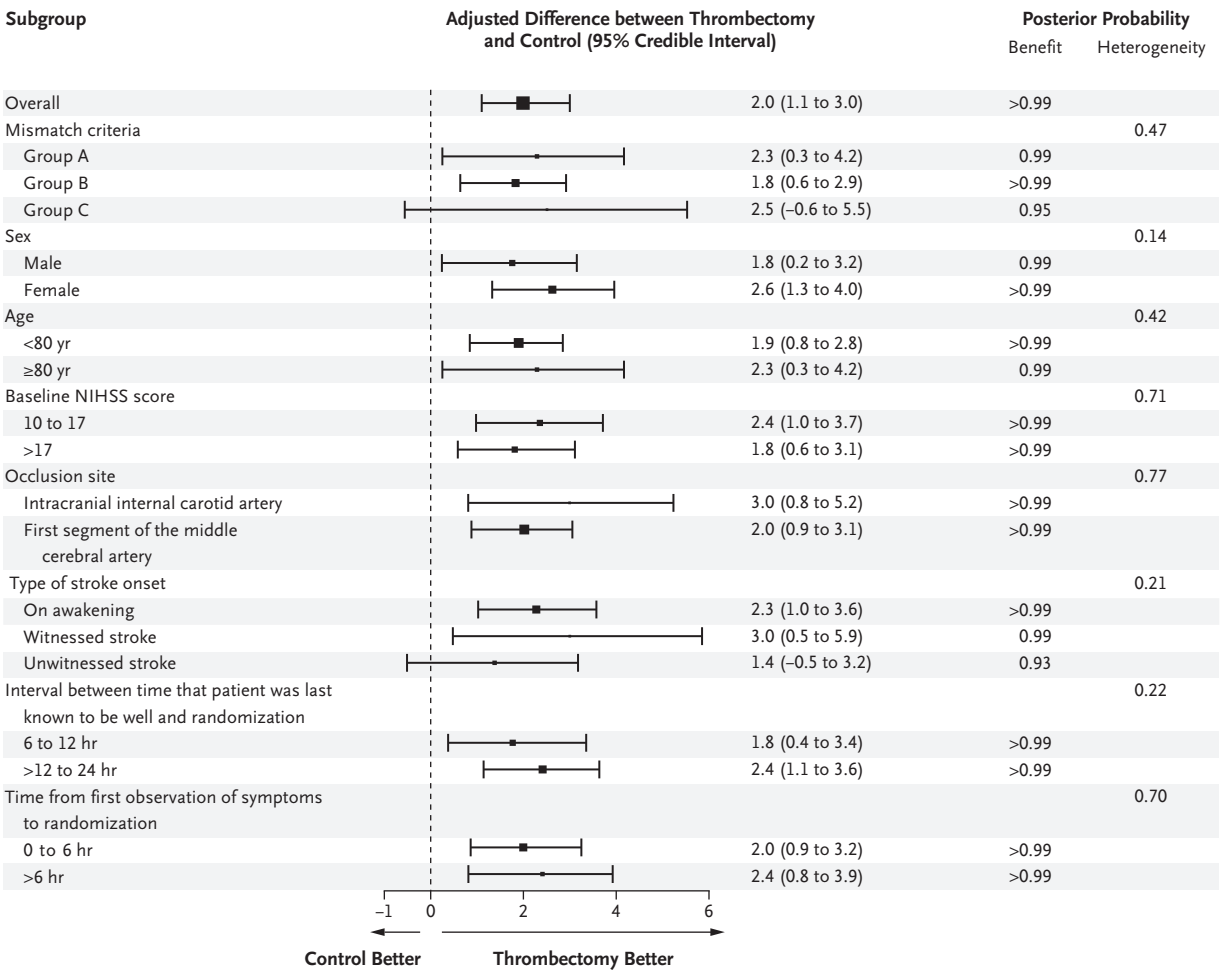


**Figure 2. Subgroup Analyses of the First Primary End Point.**

The first primary end point was the mean score for disability on the utility-weighted modified Rankin scale at 90 days. To determine the utility-weighted score, the score on the modified Rankin scale is weighted according to average values calculated from patient-centered and clinician-centered studies. The following weights are assigned to scores 0 through 6 on the modified Rankin scale: 10.0, 9.1, 7.6, 6.5, 3.3, 0, and 0, respectively. The utility-weighted modified Rankin scale ranges from 0 (death) to 10 (no symptoms or disability). Adjusted differences were estimated with the use of a Bayesian general linear model with adjustment for infarct volume. In the forest plots, the size of the box is proportional to the sample size. The Bayesian posterior probability of heterogeneity is the probability of an interaction between the subgroup and the treatment benefit; a probability of greater than 0.975 or less than 0.025 was considered to be a significant interaction. Subgroups for mismatch between the severity of the clinical deficit and the infarct volume were defined according to the following criteria: patients in Group A were 80 years of age or older, had a score of 10 or higher on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating a more severe deficit), and had an infarct volume of less than 21 ml; those in Group B were younger than 80 years of age, had a score of 10 or higher on the NIHSS, and had an infarct volume of less than 31 ml; and those in Group C were younger than 80 years of age, had a score of 20 or higher on the NIHSS, and had an infarct volume of 31 to less than 51 ml. The analysis for occlusion site did not include a subgroup with occlusion of the second segment of the middle cerebral artery because of the small number of patients in that subgroup.

tion, such as assessment of the extent of hypodensity on non–contrast-enhanced CT.

In conclusion, we found that outcomes for disability were better with thrombectomy plus standard medical care than with standard medical care alone among patients with acute stroke who received treatment 6 to 24 hours after they had last been known to be well and who had a mismatch between the severity of the clinical deficit and the infarct volume, which was assessed

**Table 3. Safety Outcomes.***

| Outcome | Thrombectomy Group (N=107) | Control Group (N=99) | Absolute Difference (95% CI) | Risk Ratio (95% CI) |
|---|---|---|---|---|
| | *no. (%)* | | *percentage points* | |
| Stroke-related death at 90 days | 17 (16) | 18 (18) | −2 (−13 to 8) | 1 (1 to 2) |
| Death from any cause at 90 days | 20 (19) | 18 (18) | 1 (−10 to 11) | 1 (1 to 2) |
| Symptomatic intracranial hemorrhage at 24 hr† | 6 (6) | 3 (3) | 3 (−3 to 8) | 2 (1 to 7) |
| Neurologic deterioration at 24 hr‡ | 15 (14) | 26 (26) | −12 (−23 to −1) | 1 (0 to 1) |
| Procedure-related complications | 7 (7) | NA | | |
| Distal embolization in a different territory | 4 (4) | NA | | |
| Intramural arterial dissection | 2 (2) | NA | | |
| Arterial perforation | 0 | NA | | |
| Access-site complications leading to intervention | 1 (1) | NA | | |

* There were no significant differences between the two treatment groups with respect to safety outcomes, except for neurologic deterioration (P=0.04). All safety outcomes were adjudicated by an independent clinical-events committee.
† Symptomatic intracranial hemorrhage was defined according to European Cooperative Acute Stroke Study III criteria as the presence of extravascular blood in the cranium that was associated with an increase in the NIHSS score of 4 points or more or death and was judged to be the predominant cause of neurologic deterioration.
‡ Neurologic deterioration was defined as an increase in the NIHSS score of 4 or more points within 5 days after stroke that was not attributed to intracranial hemorrhage or malignant cerebral edema.

with the use of diffusion-weighted MRI or perfusion CT and measured with the use of automated software.

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## APPENDIX

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## REFERENCES

1. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11-20.
2. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009-18.
3. 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.
4. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372:2296-306.
5. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285-95.
6. 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.
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. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA 2016;316:1279-88.
9. Dávalos A, Blanco M, Pedraza S, et al. The clinical-DWI mismatch: a new diagnostic approach to the brain tissue at risk of infarction. Neurology 2004;62:2187-92.
10. Jovin TG, Liebeskind DS, Gupta R, et al. Imaging-based endovascular therapy for acute ischemic stroke due to proximal intracranial anterior circulation occlusion treated beyond 8 hours from time last seen well: retrospective multicenter analysis of 237 consecutive patients. Stroke 2011;42:2206-11.
11. Lansberg MG, Cereda CW, Mlynash M, et al. Response to endovascular reperfusion is not time-dependent in patients with salvageable tissue. Neurology 2015;85:708-14.
12. Jovin TG, Saver JL, Ribo M, et al. Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods. Int J Stroke 2017;12:641-52.
13. Stryker. Welcome to the DAWN trial campus (http://dawntrial.trainingcampus.net).
14. NETT mRS test. Ann Arbor: University of Michigan (https://lessons.ummu.umich.edu/2k/nett_mrs/test).
15. Patel RD, Starkman S, Hamilton S, et al. The Rankin Focused Assessment-Ambulation: a method to score the Modified Rankin Scale with emphasis on walking ability. J Stroke Cerebrovasc Dis 2016;25:2172-6.
16. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Med Decis Making 2010;30:341-54.
17. Hong KS, Saver JL. Quantifying the value of stroke disability outcomes: WHO Global Burden of Disease Project disability weights for each level of the modified Rankin Scale. Stroke 2009;40:3828-33.
18. Chaisinanunkul N, Adeoye O, Lewis RJ, et al. Adopting a patient-centered approach to primary outcome analysis of acute stroke trials using a utility-weighted modified Rankin scale. Stroke 2015;46:2238-43.
19. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-29.
20. Hernández-Pérez M, Pérez de la Ossa N, Aleu A, et al. Natural history of acute stroke due to occlusion of the middle cerebral artery and intracranial internal carotid artery. J Neuroimaging 2014;24:354-8.
21. Lima FO, Furie KL, Silva GS, et al. Prognosis of untreated strokes due to anterior circulation proximal intracranial arterial occlusions detected by use of computed tomography angiography. JAMA Neurol 2014;71:151-7.
22. Janardhan V, Venizelos A, Gianatasio RM, et al. Natural history of acute stroke from large vessel proximal occlusion: a comparison with the IMS III patients. Stroke 2014;45:Suppl 1:AWMP8.
23. Albers GW, Lansberg MG, Kemp S, et al. A multicenter randomized controlled trial of endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3). Int J Stroke 2017;12:896-905.
24. Mishra NK, Christensen S, Wouters A, et al. Reperfusion of very low cerebral blood volume lesion predicts parenchymal hematoma after endovascular therapy. Stroke 2015;46:1245-9.
25. Copen WA, Rezai Gharai L, Barak ER, et al. Existence of the diffusion-perfusion mismatch within 24 hours after onset of acute stroke: dependence on proximal arterial occlusion. Radiology 2009;250:878-86.
26. Rai AT, Seldon AE, Boo S, et al. A population-based incidence of acute large vessel occlusions and thrombectomy eligible patients indicates significant potential for growth of endovascular stroke therapy in the USA. J Neurointerv Surg 2017;9:722-6.