ORIGINAL ARTICLE

Two-Year Outcome after Endovascular Treatment for Acute Ischemic Stroke

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ABSTRACT

BACKGROUND

Several trials involving patients with acute ischemic stroke have shown better functional outcomes with endovascular treatment than with conventional treatment at 90 days after initiation of treatment. However, results on long-term clinical outcomes are lacking.

METHODS

We assessed clinical outcomes 2 years after patients were randomly assigned to receive either endovascular treatment (intervention group) or conventional treatment (control group) for acute ischemic stroke. The primary outcome was the score on the modified Rankin scale at 2 years; this scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). Secondary outcomes included all-cause mortality and the quality of life at 2 years, as measured by means of a health utility index that is based on the European Quality of Life–5 Dimensions questionnaire (scores range from −0.329 to 1, with higher scores indicating better health).

RESULTS

Of the 500 patients who underwent randomization in the original trial, 2-year data for this extended follow-up trial were available for 391 patients (78.2%) and information on death was available for 459 patients (91.8%). The distribution of outcomes on the modified Rankin scale favored endovascular treatment over conventional treatment (adjusted common odds ratio, 1.68; 95% confidence interval [CI], 1.15 to 2.45; P=0.007). There was no significant difference between the treatment groups in the percentage of patients who had an excellent outcome (i.e., a modified Rankin scale score of 0 or 1). The mean quality-of-life score was 0.48 among patients randomly assigned to endovascular treatment as compared with 0.38 among patients randomly assigned to conventional treatment (mean difference, 0.10; 95% CI, 0.03 to 0.16; P=0.006). The cumulative 2-year mortality rate was 26.0% in the intervention group and 31.0% in the control group (adjusted hazard ratio, 0.9; 95% CI, 0.6 to 1.2; P=0.46).

CONCLUSIONS

In this extended follow-up trial, the beneficial effect of endovascular treatment on functional outcome at 2 years in patients with acute ischemic stroke was similar to that reported at 90 days in the original trial. (Funded by the Netherlands Organization for Health Research and Development and others; MR CLEAN Current Controlled Trials number, ISRCTN10888758, and Netherlands Trial Register number, NTR1804, and MR CLEAN extended follow-up trial Netherlands Trial Register number, NTR5073.)

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We reported previously the 90-day outcomes of a trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN]) in which standard treatment was compared with endovascular treatment, administered within 6 hours after the onset of acute ischemic stroke caused by an intracranial arterial occlusion of the anterior circulation.[1] Most patients in the intervention group were treated by mechanical thrombectomy with the use of retrievable stents. The trial showed that functional recovery at 90 days was better with the intervention than with standard treatment. Subsequently, the beneficial effect of mechanical thrombectomy on 90-day outcomes was shown in several other trials, as well as in a meta-analysis of individual patient data from these trials.[2-6] Information regarding long-term outcomes may be useful for clinical practice and for health care policy decisions. We report the results of clinical follow-up at 2 years after randomization among patients in the MR CLEAN trial.

Methods

Trial Design and Oversight

MR CLEAN was a randomized, multicenter trial in which endovascular treatment plus conventional care (intervention group) was compared with conventional care alone (control group) in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation.[1,7] Conventional care consisted of care that represented the most appropriate medical management according to national and international guidelines and could include intravenous administration of alteplase. Trial treatment was open-label, and the evaluation of outcomes was blinded. The protocol, which is available with the full text of this article at NEJM.org, was amended during the trial to include follow-up assessments up to 2 years after randomization. An economic evaluation was prespecified as part of the amended protocol (results are not included here). Trial investigators at the coordinating center collected the data for this extended follow-up trial. Members of the MR CLEAN executive committee designed the extended follow-up trial, analyzed the data, prepared the manuscript, and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the available data from the extended follow-up trial and for the fidelity of the trial to the amended protocol.

Patients and Trial Activities

Eligible patients had a score of 2 or higher on the National Institutes of Health Stroke Scale (NIHSS) (scores range from 0 to 42, with higher scores indicating more severe neurologic deficits) and could be treated within 6 hours after the onset of stroke.[8] The intracranial artery occlusion had to be confirmed by means of computed tomographic angiography, magnetic resonance angiography, or digital-subtraction angiography.

Funding for the extended follow-up trial became available in May 2013, when enrollment in the MR CLEAN trial was approximately halfway to the projected number of patients to be included. Consequently, many patients had already completed their 90-day follow-up assessment, and the 2-year follow-up time point had passed for some patients. After trial personnel consulted the Dutch Municipal Personal Records Database to determine the vital status of patients who had completed the MR CLEAN trial, eligible patients who were alive were invited to take part in the extended follow-up trial. Patients received an invitation letter and were subsequently contacted by telephone so that we could confirm their participation and explain additional trial goals and activities. Patients who wished to participate in the extended follow-up trial provided informed consent by telephone. For patients who declined to provide informed consent for the long-term follow-up, permission was obtained from the institutional review board to use information regarding the patients' vital status from the Dutch Municipal Personal Records Database.

For the remaining patients who were continuing in the MR CLEAN trial after May 2013, the longer duration of follow-up and additional trial activities were part of the new informed consent process described above. All patients (or their primary caregiver if they were unable to respond) who provided informed consent to participate in the extended follow-up were contacted by telephone at 6 months, 1 year, 18 months, and 2 years. One trial investigator, who was unaware of the treatment-group assignments, assessed functional outcome by means of a structured questionnaire, which was validated for assessment by telephone, to determine the patient's modified Rankin scale

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score.[9] Medical events that occurred between follow-up contacts were recorded during this interview. Furthermore, the patient or the primary caregiver was invited to complete the three-level version of the European Quality of Life 5–Dimensions (EQ-5D-3L) questionnaire, for assessment of quality of life.[10] Consensus with respect to final functional outcome on the modified Rankin scale was reached among three trial investigators (all of whom were unaware of the treatment-group assignments) on the basis of the structured questionnaire for the modified Rankin scale and of additional information available in the detailed reports of the telephone interviews.

OUTCOME MEASURES

The primary outcome was the score on the modified Rankin scale at 2 years. The modified Rankin scale is an ordinal scale that ranges from 0 (no symptoms) to 6 (death).[11,12] Secondary outcomes included categories scores of the modified Rankin scale at 2 years (0 or 1 [excellent outcome], 0 to 2 [good outcome, indicating functional independence], and 0 to 3 [favorable outcome]); death from any cause during the 2-year period after randomization; the first major vascular event after the index stroke that occurred between 90 days and 2 years after randomization; and quality of life at 2 years as assessed by the EQ-5D-3L.[10] The EQ-5D-3L consists of a descriptive system that assesses five dimensions of quality of life: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three levels of severity: 1 (no problems), 2 (some problems), or 3 (extreme problems). Scores range from −0.329 (indicating the worst health status [serious problems in all domains]) to 1 (indicating the best health status [no problems at all]), with death assigned a value of zero.[13] Major vascular events included fatal or nonfatal cardiac events, fatal or nonfatal recurrent stroke, and fatal or nonfatal major peripheral arterial or thromboembolic events (details regarding the classification of major vascular events are provided in the Supplementary Appendix, available at NEJM.org). All major vascular events were confirmed by clinical reports or by the treating physician or the general practitioner. Two trial investigators who were unaware of the treatment-group assignments reviewed all events. In the event of disagreement, classification was based on consensus.

STATISTICAL ANALYSIS

Analyses were based on the modified intention-to-treat principle. The treatment effect on the primary outcome at 2 years was calculated as an adjusted common odds ratio for a better distribution of outcomes on the modified Rankin scale; this ratio was estimated with ordinal logistic regression. Dichotomized scores of the modified Rankin scale at 2 years (0 or 1 versus 2 to 6, 0 to 2 versus 3 to 6, and 0 to 3 versus 4 to 6) were analyzed with the use of logistic regression, with the odds ratio as the effect variable. All-cause mortality was assessed by means of the Kaplan–Meier method and a Cox proportional-hazards model, with the hazard ratio as the effect variable. Data from all 500 patients who underwent randomization in the original trial were included in the analysis of death from any cause. Additional information from the Dutch Municipal Personal Records Database on vital status at 2 years was used for the outcome analysis, and data for patients whose vital status was missing were censored at the time of their withdrawal from the trial. For the analysis of quality of life, a utility value for each observed EQ-5D-3L health status profile was calculated with the use of an existing algorithm on the basis of valuations elicited by time trade-off techniques applied to the general Dutch population. An unstandardized regression parameter beta was estimated with the use of a multivariable linear regression model and represented the difference between the two treatment groups in the health utility score. As in the original trial, all effect variables were adjusted for potential imbalances between the intervention group and the control group in the following prognostic variables at baseline: age; stroke severity (as assessed by the NIHSS); time from stroke onset to randomization; status with respect to previous stroke, atrial fibrillation, and diabetes mellitus; and occlusion of the internal-carotid-artery terminus (yes vs. no). To assess the difference between the two treatment groups in the occurrence of long-term major vascular events, a rate ratio was calculated on the basis of person-years at risk. Treatment-effect modification was evaluated in the same prespecified subgroups of patients as in the original trial (see the Supplementary Appendix).

To evaluate potential selection bias, we used conventional statistics to compare patients whose 2-year outcome data were missing with patients

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whose 2-year outcome data were available with respect to the main prognostic variables, treatment assignment, and 90-day functional outcome. In addition, a sensitivity analysis was performed with the use of a regression-based multiple imputation to account for missing data on the functional outcome at 2 years. A detailed description of the multiple imputation method is provided in the Supplementary Appendix.

Two-sided P values of 0.05 or less were considered to indicate statistical significance for all statistical tests. Because our trial had a single primary outcome, no adjustments for multiple tests were made. All analyses were performed with the use of SPSS software, version 24.0 (IBM).

RESULTS

TRIAL POPULATION

In the original trial, 502 patients underwent randomization at 16 Dutch hospitals from December 2010 through March 2014 (Table S1 in the Supplementary Appendix). Two patients, whose representatives withdrew consent immediately after randomization and assignment to the control group, could not be included in the intention-to-treat analysis of the original trial. A total of 233 patients (46.6%) were randomly assigned to the intervention group and 267 (53.4%) to the control group. Endovascular treatment was never initiated in 17 of the 233 patients (7.3%) who had been assigned to the intervention group, and 1 patient received endovascular treatment after being assigned to the control group.[1]

At the time of the inception of the extended follow-up trial, 332 patients were already included in the original trial and an additional 168 patients would be enrolled and prospectively followed for up to 2 years after randomization. Of the 332 patients already enrolled in the original trial, 14 (4.2%) had passed the 2-year follow-up time point, and 87 (40 in the intervention group and 47 in the control group) died before the extended follow-up period began. Of the remaining 231 patients who were included in the original trial, those who did not provide informed consent to participate in the extended follow-up trial initially were reinvited to participate: 61 patients declined and 8 patients withdrew consent during the follow-up period (of these 69 patients, 18 were in the intervention group and 51 were in the control group). A total of 26 patients were lost to follow-up. In total, 391 of the 500 patients (78.2%) had 2-year follow-up data and were included in the primary analysis for functional outcome (194 in the intervention group and 197 in the control group) (Fig. S1 in the Supplementary Appendix).

Demographic characteristics, risk factors for a poor outcome, clinical risk factors for stroke, and the use of intravenous alteplase treatment for the 391 patients included in the analysis of the primary outcome were evenly distributed between the two treatment groups at baseline (Table 1). The median age of the patients was 66 years and 58.6% were men. The median NIHSS score was 18 (interquartile range, 14 to 22).

PRIMARY OUTCOME

Among the 391 patients with available data on the modified Rankin scale at 2 years after randomization, the adjusted common odds ratio was 1.68 (95% confidence interval [CI], 1.15 to 2.45; P=0.007) for a better distribution of outcomes on the modified Rankin scale with endovascular treatment than with conventional treatment (Fig. 1). The median and interquartile range of the scores on the modified Rankin scale for the two treatment groups and the effect size favoring endovascular treatment are shown in Table 2.

SECONDARY OUTCOMES

Dichotomized Scores on the Modified Rankin Scale

Patients in the intervention group were more likely than patients in the control group to have a good outcome (i.e., a modified Rankin scale score of 0 to 2) (37.1% vs. 23.9%; adjusted odds ratio, 2.21; 95% CI, 1.30 to 3.73; P=0.003) and to have a favorable outcome (i.e., a modified Rankin scale score of 0 to 3) (55.2% vs. 40.6%; adjusted odds ratio, 2.13; 95% CI, 1.30 to 3.43; P=0.003). Among patients with an excellent outcome (i.e., a modified Rankin scale score of 0 or 1), no significant difference between the treatment groups was observed (7.2% in the intervention group and 6.1% in the control group; adjusted odds ratio, 1.22; 95% CI, 0.53 to 2.84; P=0.64) (Table 2).

All-Cause Mortality

Information regarding vital status at 2 years was available for 459 of the original 500 patients who

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Table 1. Baseline Characteristics of the 391 Patients Included in the Analysis of the Primary Outcome, According to Treatment Assignment.*

Characteristic	Intervention (N=194)	Control (N=197)
Age — yr		
Median	65.9	65.5
Interquartile range	55.8–76.2	56.6–76.6
Male sex — no. (%)	111 (57.2)	118 (59.9)
NIHSS score†		
Median	17	18
Interquartile range	14–21	14–22
Location of stroke in left hemisphere — no. (%)	96 (49.5)	116 (58.9)
History of ischemic stroke — no. (%)	24 (12.4)	23 (11.7)
Atrial fibrillation — no. (%)	53 (27.3)	44 (22.3)
Diabetes mellitus — no. (%)	29 (14.9)	25 (12.7)
Prestroke modified Rankin scale score — no. (%)‡		
0	155 (79.9)	156 (79.2)
1	19 (9.8)	24 (12.2)
2	10 (5.2)	8 (4.1)
>2	10 (5.2)	9 (4.6)
Systolic blood pressure — mm Hg	147.5±27.0	144.8±23.7
Treatment with IV alteplase — no. (%)	168 (86.6)	182 (92.4)
Time from stroke onset to start of IV alteplase — min		
Median	85	85
Interquartile range	68–110	65–112
ASPECTS§		
Median	9	9
Interquartile range	8–10	8–10
Intracranial arterial occlusion — no. (%)		
Intracranial ICA	1 (0.5)	1 (0.5)
ICA with involvement of the M1 middle cerebral artery segment	49 (25.3)	54 (27.4)
M1 middle cerebral artery segment	130 (67.0)	124 (62.9)
M2 middle cerebral artery segment	13 (6.7)	16 (8.1)
A1 or A2 anterior cerebral artery segment	1 (0.5)	2 (1.0)
Extracranial ICA occlusion — no. (%)¶	60 (30.9)	51 (25.9)
Time from stroke onset to randomization — min		
Median	205	190
Interquartile range	152–249	148–248
Time from stroke onset to groin puncture — min		
Median	263	NA
Interquartile range	210–307	

* Plus–minus values are means ±SD. There were no significant between-group differences with respect to any of the variables listed in this table. ICA denotes internal carotid artery (intracranial segment), IV intravenous, and NA not applicable.
† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits.
‡ Scores on the modified Rankin scale of functional disability range from 0 (no symptoms) to 6 (death). A score of 0 or 1 indicates an excellent outcome; 0 to 2 a good outcome, indicating functional independence; and 0 to 3 a favorable outcome.
§ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a measure of the extent of stroke. Scores range from 0 to 10, with higher scores indicating fewer early ischemic changes. Scores were not available for four patients assigned to the control group: noncontrast computed tomography was not performed in one patient, and three patients had strokes in the territory of the anterior cerebral artery.
¶ Extracranial ICA occlusions were reported by local investigators.

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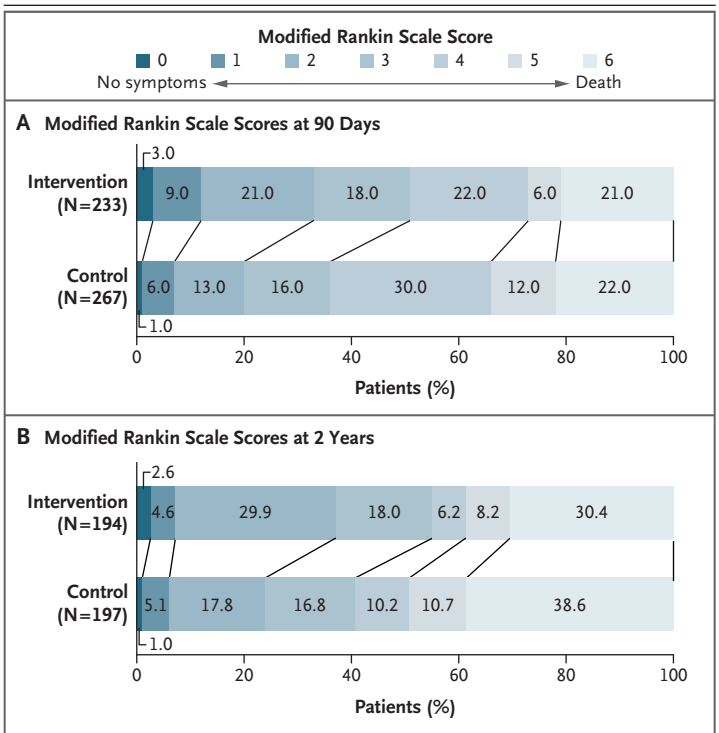

Figure 1. Modified Rankin Scale Scores at 90 Days and 2 Years According to Treatment Assignment.

Shown are the distribution of scores on the modified Rankin scale at 90 days (Panel A) and at 2 years (Panel B). Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability (patient is able to look after own affairs without assistance but is unable to carry out all previous activities), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to bodily needs without assistance and is unable to walk unassisted), 5 severe disability (patient requires constant nursing care and attention), and 6 death. The adjusted common odds ratio was 1.68 (95% CI, 1.15 to 2.45; P=0.007), which indicated a distribution of the scores on the modified Rankin scale in favor of endovascular treatment as compared with conventional treatment.

underwent randomization (91.8%). The cumulative 2-year rate of death was 26.0% in the intervention group and 31.0% in the control group (adjusted hazard ratio for death, 0.9; 95% CI, 0.6 to 1.2; P=0.46) (Fig. 2).

Major Vascular Events

Eight major vascular events were reported between 90 days and 2 years after randomization (the maximum duration of follow-up per patient was 1.75 years [i.e., 21 months, which represents the duration of time between the 90-day and 2-year time points for all patients included in the extended follow-up trial]). Five of the events occurred during 239 person-years of follow-up in the intervention group (incidence rate, 0.02 per year), and the remaining three events occurred during 235 person-years of follow-up in the control group (incidence rate, 0.01 per year) (rate ratio for major cerebrovascular events, 1.64; 95% CI, 0.40 to 6.78; P=0.50) (Table S3 in the Supplementary Appendix).

Quality of Life

At 2 years, patients in the intervention group had a higher quality of life, as assessed with the EQ-5D-3L instrument, than did patients in the control group (mean health utility score, 0.48 vs. 0.38). The treatment effect size, which was estimated with the use of multiple linear regression, was 0.10 (95% CI, 0.03 to 0.16; P=0.006) in favor of endovascular treatment (Table 2). The difference in the treatment effect between the two groups was attributable mainly to the EQ-5D-3L dimensions of "mobility," "self-care," and "usual activities" (Fig. S2 in the Supplementary Appendix).

SENSITIVITY ANALYSIS

Of the 109 patients whose outcome data were missing at 2 years, 6 patients died between 90 days and 2 years after randomization and were assigned a score of 6 on the modified Rankin scale at 2 years for an initial sensitivity analysis. The missing outcome data for the remaining 103 patients were imputed with the use of multiple imputation. The pooled effect on the primary outcome after multiple imputation (adjusted common odds ratio, 1.59; 95% CI, 1.08 to 2.35; P=0.02) was similar to the result of the main analysis of the primary outcome (adjusted common odds ratio, 1.68; 95% CI, 1.15 to 2.45; P=0.007). The subgroup of patients whose outcome data were missing had a higher incidence of atrial fibrillation at baseline than the subgroup of patients who had outcome data at 2 years (35.9% vs. 26.4%, P=0.02), were more likely to have been randomly assigned to the control group (62.1% vs. 48.9%, P=0.05), had a longer median time from onset of stroke to randomization (218 minutes vs. 195 minutes, P=0.003), and were more likely to have poor functional outcomes (i.e., a modified Rankin scale score of 4 or 5, indicating moderately severe or severe disability) at 90 days (57.3% vs. 30%, P=0.005) (Table S2 in the Supplementary Appendix).

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Table 2. Primary and Secondary Outcomes and Treatment Effects.*

Outcome	Intervention (N=194)	Control (N=197)	Effect Variable	Unadjusted Value (95% CI)	Adjusted Value (95% CI)†	P Value‡
Primary outcome						
Modified Rankin scale score at 2 years — median (IQR)	3 (2–6)	4 (3–6)	Common odds ratio	1.63 (1.14–2.32)	1.68 (1.15–2.45)	0.007
Secondary outcomes						
Modified Rankin scale score of 0 or 1 at 2 years — no. (%)	14 (7.2)	12 (6.1)	Odds ratio	1.20 (0.54–2.66)	1.22 (0.53–2.84)	0.64
Modified Rankin scale score of 0–2 at 2 years — no. (%)	72 (37.1)	47 (23.9)	Odds ratio	1.88 (1.22–2.92)	2.21 (1.30–3.73)	0.003
Modified Rankin scale score of 0–3 at 2 years — no. (%)	107 (55.2)	80 (40.6)	Odds ratio	1.80 (1.20–2.69)	2.13 (1.30–3.43)	0.003
EQ-5D-3L score at 2 years§	0.48±0.40	0.38±0.39	Beta	0.10 (0.02–0.18)	0.10 (0.03–0.16)	0.006

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Values were adjusted for age, NIHSS at baseline, time to randomization, previous stroke, atrial fibrillation, diabetes mellitus, and presence of ICA terminus occlusion.
‡ P values are for the comparisons of the adjusted values of each effect variable, as determined byordinal logistic regression analysis for the primary outcome, by logistic regression analysis for the dichotomizations of the modified Rankin scale, and by multivariable linear regression analysis for the European Quality of Life 5–Dimensions (EQ-5D-3L) score.
§ The three-level version of the EQ-5D-3L questionnaire is a standardized instrument for the measurement of health status. The health status profiles on five domains (mobility, self-care, daily activities, pain or discomfort, and anxiety or depression), each differentiating three levels of severity (no problems, some problems, or extreme problems), were converted to a score between –0.329 and 1, with higher scores indicating better health and with death assigned a value of zero. The EQ-5D-3L score was missing for two patients.

SUBGROUP ANALYSES

No significant interactions (effect modifications) were observed between the prespecified subgroups, which were defined according to baseline characteristics, and treatment at 2 years. The treatment effect remained consistent in all prespecified subgroups (Fig. S3 in the Supplementary Appendix). However, some subgroups were small, which resulted in wide confidence intervals.

DISCUSSION

The results of the extended follow-up evaluation of the MR CLEAN trial showed that endovascular treatment in patients with acute ischemic stroke resulted in functional recovery, as measured on the modified Rankin scale, that was similar to the originally reported results at 90 days. The odds ratio for better scores on the modified Rankin scale in the endovascular group than in the conventional treatment group was 1.67 at 90 days, as compared with an odds ratio of 1.68 at 2 years. The percentage of patients in the intervention group who were functionally independent (i.e., a modified Rankin scale score of 0 to 2) at 2 years (37.1%) was also similar to the results at 90 days (32.6%). Although the above results are similar, notable differences were observed between the two time points. First, during the extended follow-up period, the mortality rate was lower with endovascular intervention than with conventional treatment, although this difference was not statistically significant, whereas at 90 days, the risk of death was similar in the two groups. Second, the percentages of patients with modified Rankin scale scores of 0 or 1 at 2 years were lower than the percentages at 90 days in both groups. A possible explanation for the lower rate of modified Rankin scale scores of 0 or 1 at 2 years is that patients with stroke undergo a period of rehabilitation in the first months after the event, during which the effect of the stroke on their daily activities may not be fully apparent. Thereafter, when patients are living at home with less assistance, small changes in functional ability may become apparent that could move patients from a modified Rankin scale score of 0 (no symptoms) to a score of 1 (no significant disability), or to a score of 2 (slight disability).

Other studies of reperfusion therapy for ischemic stroke have suggested that the effects of intravenous alteplase and of endovascular treat-

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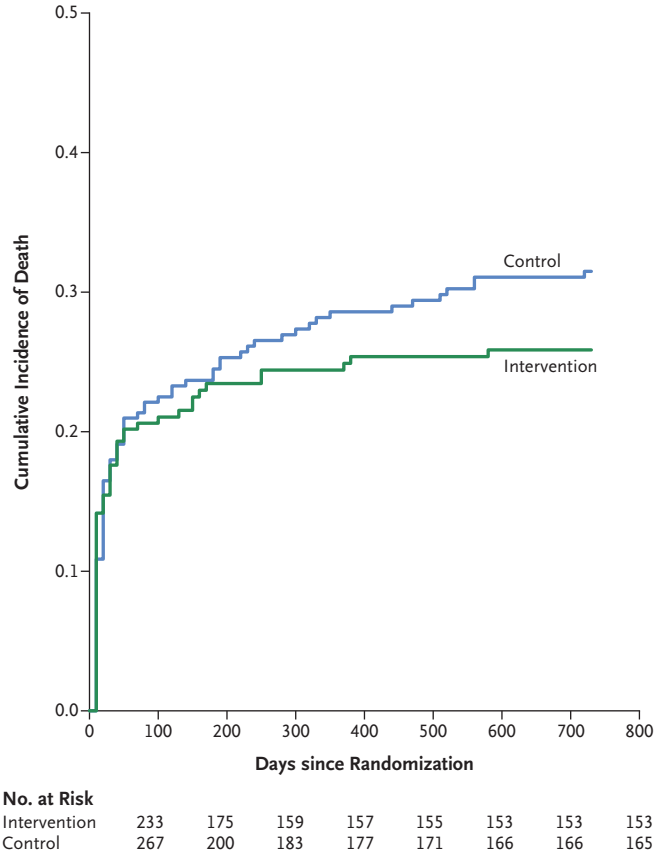

Figure 2. Kaplan–Meier Estimates of All-Cause Mortality during the 2-Year Follow-up Period after Randomization.

The adjusted hazard ratio for death in the intervention group, as compared with the control group, was 0.9 (95% CI, 0.6 to 1.2; P=0.46).

ment do not diminish over time.[14-18] The National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study showed that patients treated with intravenous alteplase were 30% more likely than patients in the placebo group to have an excellent outcome (i.e., a modified Rankin scale score of 0 or 1) at 1 year, which was similar to the 90-day results of the MR CLEAN trial.[15] Furthermore, in the Interventional Management of Stroke Phase III Trial, the percentage of patients with a good outcome (i.e., a modified Rankin scale score of 0 to 2) at 1 year was higher among patients who received endovascular treatment than among patients who received intravenous alteplase alone in a subgroup of patients with severe stroke (NIHSS score ≥20) (32.5% vs. 18.6%, P=0.04).[16,17] In the REVASCAT trial (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours), the common odds ratio for the distribution of scores on the modified Rankin scale at 1 year was 1.80 (95% CI, 1.10 to 2.99) in favor of endovascular revascularization, which was similar to the finding at 90 days (common odds ratio, 1.71; 95% CI, 1.05 to 2.81).[18] Although all these trials were smaller and had a shorter follow-up period than our trial, their results regarding longer-term functional outcomes are consistent with ours.

We observed few major vascular events between 90 days and 2 years after randomization (1.6% in 474 person-years at risk). A possible explanation for this low rate is that patients with large-vessel extracranial or intracranial occlusion could have had either embolic strokes (artery-to-artery or cardiogenic) or extracranial or intracranial atherosclerotic occlusion of vessels, and these conditions are treated or prevented more effectively than are other causes of ischemic stroke.[19-21]

Our trial has several limitations. The trial was powered to detect an effect at 90 days and did not take into account loss to follow-up during the 2-year follow-up period. Furthermore, patients whose outcome data were missing at 2 years had worse clinical characteristics and worse functional outcomes at 90 days and were more likely to have been assigned to the control group, and therefore, selection bias may have been introduced. However, a sensitivity analysis in which missing outcomes were imputed by means of model-based multiple imputation showed results that were similar to those of the main analysis of the primary outcome, which suggests a limited effect of bias.

In conclusion, the beneficial effect of endovascular treatment in patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation was sustained during the course of at least 2 years.

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