ORIGINAL ARTICLE

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

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ABSTRACT

BACKGROUND

In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion, intraarterial treatment is highly effective for emergency revascularization. However, proof of a beneficial effect on functional outcome is lacking.

METHODS

We randomly assigned eligible patients to either intraarterial treatment plus usual care or usual care alone. Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation that was confirmed on vessel imaging and that could be treated intraarterially within 6 hours after symptom onset. The primary outcome was the modified Rankin scale score at 90 days; this categorical scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). The treatment effect was estimated with ordinal logistic regression as a common odds ratio, adjusted for prespecified prognostic factors. The adjusted common odds ratio measured the likelihood that intraarterial treatment would lead to lower modified Rankin scores, as compared with usual care alone (shift analysis).

RESULTS

We enrolled 500 patients at 16 medical centers in the Netherlands (233 assigned to intraarterial treatment and 267 to usual care alone). The mean age was 65 years (range, 23 to 96), and 445 patients (89.0%) were treated with intravenous alteplase before randomization. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intraarterial treatment. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence (modified Rankin score, 0 to 2) in favor of the intervention (32.6% vs. 19.1%). There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage.

CONCLUSIONS

In patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe. (Funded by the Dutch Heart Foundation and others; MR CLEAN Netherlands Trial Registry number, NTR1804, and Current Controlled Trials number, ISRCTN10888758.)

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This article was published on December 17, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1411587

Intravenous alteplase administered within 4.5 hours after symptom onset is the only reperfusion therapy with proven efficacy in patients with acute ischemic stroke.[1] However, well-recognized limitations of this therapy include the narrow therapeutic time window and contraindications such as recent surgery, coagulation abnormalities, and a history of intracranial hemorrhage.[2] Moreover, intravenous alteplase appears to be much less effective at opening proximal occlusions of the major intracranial arteries, which account for more than one third of cases of acute anterior-circulation stroke.[3,4] Early recanalization after intravenous alteplase is seen in only about one third of patients with an occlusion of the internal-carotid-artery terminus,[5] and the prognosis without revascularization is generally poor for such patients.[6] For these reasons, intraarterial treatment is regarded as a potentially important component of the therapeutic armamentarium.

A Quick Take is available at NEJM.org

Intraarterial therapy can be broadly divided into chemical dissolution of clots with locally delivered thrombolytic agents and clot retrieval or thrombectomy with mechanical devices. Although early randomized trials and subsequent meta-analyses[7] showed a benefit of treatment with prourokinase[8,9] or urokinase,[10] their results are not directly applicable to current decision making about treatment because the control groups did not include intravenous alteplase, and mechanical approaches have largely replaced locally applied thrombolytic agents as first-line therapy.[11]

The neutral results of the recent randomized, controlled trials of intraarterial treatment have contributed to uncertainty regarding the efficacy of the catheter-based approach.[12-14] Numerous questions have been raised concerning the design and conduct of these trials, including a relatively long interval before intraarterial treatment, the absence of pretreatment vascular imaging to confirm a proximal intracranial occlusion, and the limited use of third-generation mechanical thrombectomy devices such as retrievable stents. In the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), we assessed whether intraarterial treatment plus usual care would be more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation that could be treated intraarterially within 6 hours after symptom onset.

METHODS

STUDY DESIGN

MR CLEAN was a pragmatic, phase 3, multicenter clinical trial with randomized treatment-group assignments, open-label treatment, and blinded end-point evaluation. Intraarterial treatment (intraarterial thrombolysis, mechanical treatment, or both) plus usual care (which could include intravenous administration of alteplase) was compared with usual care alone (control group) in patients with acute ischemic stroke and a proximal intracranial arterial occlusion of the anterior circulation that was confirmed on vessel imaging.

The study protocol (available with the full text of this article at NEJM.org) was approved by a central medical ethics committee and the research board of each participating center. All patients or their legal representatives provided written informed consent before randomization.

Members of the executive committee and the local investigators designed the study, collected and analyzed the data, wrote the manuscript, and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol. The study sponsors were not involved in the study design, study conduct, protocol review, or manuscript preparation or review.

PATIENTS AND PARTICIPATING CENTERS

The study was conducted at 16 centers in the Netherlands. Patients were 18 years of age or older (no upper age limit) with acute ischemic stroke caused by an intracranial occlusion in the anterior circulation artery. Initiation of intraarterial treatment had to be possible within 6 hours after stroke onset. Eligible patients had an occlusion of the distal intracranial carotid artery, middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2), established with computed tomographic (CT) angiography (CTA), magnetic resonance angiography (MRA), or digital-subtraction angiography (DSA), and a score of 2 or higher on the National Institutes of Health Stroke Scale (NIHSS; range, 0 to 42, with higher scores indicating more severe neurologic deficits). Inclusion of patients with an additional extracranial internal-carotid-artery occlusion or dissection was left to the judgment of the treating physician. Detailed inclusion and exclusion criteria are listed in the

study protocol. We did not keep a log of patients who were screened for eligibility.

RANDOMIZATION

The randomization procedure was Web-based, with the use of permuted blocks. We stratified randomization according to medical center, use of intravenous alteplase (yes or no), planned treatment method (mechanical or other), and stroke severity (NIHSS score of ≤14 or >14).

INTERVENTION

Intraarterial treatment consisted of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both. The method of intraarterial treatment was left to the discretion of the local interventionist.

The use of alteplase or urokinase for intraarterial thrombolysis was allowed in this trial, with a maximum dose of 90 mg of alteplase or 1,200,000 IU of urokinase. The dose was restricted to 30 mg of alteplase or 400,000 IU of urokinase if intravenous alteplase was given. Mechanical treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent.

Only devices that had received U.S. Food and Drug Administration approval or a Conformité Européenne (CE) marking and were approved by the steering committee could be used in the trial. One or more members of each intervention team had to have completed at least five full procedures with a particular type of device.[15]

OUTCOME AND SAFETY MEASURES

The primary outcome was the score on the modified Rankin scale at 90 days. The modified Rankin scale is a 7-point scale ranging from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence.[16]

Secondary outcomes included the NIHSS score at 24 hours and at 5 to 7 days or discharge if earlier, activities of daily living measured with the Barthel index, and the health-related quality of life measured with the EuroQol Group 5-Dimension Self-Report Questionnaire at 90 days.[17,18] We examined the following prespecified dichotomizations of the modified Rankin score: 0 or 1 versus 2 to 6, 0 to 2 versus 3 to 6, and 0 to 3 versus 4 to 6. Imaging outcomes included arterial recanalization measured with CTA or MRA at 24 hours and the final infarct volume on noncontrast CT at 5 to 7 days.

Safety variables included hemorrhagic complications, progression of ischemic stroke, new ischemic stroke into a different vascular territory, and death. If neurologic deterioration developed, additional neuroimaging was required. Symptomatic intracranial hemorrhage was defined as neurologic deterioration (an increase of 4 or more points in the score on the NIHSS) and evidence of intracranial hemorrhage on imaging studies. Local neurologists were aware of the treatment-group assignments and reported serious adverse events through our Web-based database or by fax or e-mail.

CLINICAL AND RADIOLOGIC ASSESSMENT

All patients underwent clinical assessment (including determination of the NIHSS score) at baseline, after 24 hours, and at 5 to 7 days or at discharge if earlier. A single experienced trial investigator, who was unaware of the treatment-group assignments, conducted the follow-up interviews at 90 days by telephone with the patient, proxy, or health care provider. This interview provided reports for the assessment of the modified Rankin score by reviewers who remained unaware of the treatment-group assignments.[16-18]

The imaging committee evaluated the findings on baseline noncontrast CT for the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with 1 point subtracted for any evidence of early ischemic change in each defined region on the CT scan),[19] baseline vessel imaging (CTA, MRA, or DSA) for the location of the occlusion, and follow-up CTA or MRA at 24 hours for vessel recanalization. Recanalization was classified as complete or not complete and was further evaluated with the use of the modified Arterial Occlusive Lesion score (see the Supplementary Appendix, available at NEJM.org, for details about scales).[20,21] Follow-up CT scans obtained at 5 days were assessed for the presence of intracranial hemorrhage.[22] All neuroimaging studies were evaluated by two neuroradiologists who were unaware of the treatment-group assignments. The final infarct volume on the follow-up CT scan was assessed with the use of an automated, validated algorithm.[23] An independent core laboratory assessed angiographic outcomes on DSA imaging, using the modified Thrombolysis in Cerebral Infarction

(TICI) score, which ranges from 0 (no reperfusion) to 3 (complete reperfusion).[21]

STATISTICAL ANALYSIS

All analyses were based on the intention-to-treat principle. The primary effect variable was the adjusted common odds ratio for a shift in the direction of a better outcome on the modified Rankin scale; this ratio was estimated with multivariable ordinal logistic regression.[24] We calculated an adjusted odds ratio for all possible cutoff values on the modified Rankin scale to assess the consistency of effect and the plausibility of proportionality of the odds ratio. The adjusted common odds ratio and all secondary effect variables were adjusted for potential imbalances in the following major prognostic variables between the intervention group and the control group: age; stroke severity (NIHSS score) at baseline; 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).[25] We imputed missing values of baseline variables that were used to adjust the regression models of treatment effect on primary and secondary outcomes with mean or mode, as applicable. No outcomes were imputed, except for single missing values of items on the NIHSS at 24 hours and at 5 to 7 days or discharge. Patients who died were not assigned NIHSS scores and were not included in analyses of such scores.

The adjusted and unadjusted common odds ratios are reported with 95% confidence intervals to indicate statistical precision. Binary outcomes were analyzed with logistic regression and are reported as adjusted and unadjusted odds ratios with 95% confidence intervals. All P values are two-sided.

Treatment-effect modification was explored in prespecified subgroups of patients, defined by NIHSS score (2 to 15, 16 to 19, or ≥20), age (≥80 years or <80 years), occlusion of the internal-carotid-artery terminus (yes or no), additional extracranial internal-carotid-artery occlusion (yes or no), time from stroke onset to randomization (≤120 minutes or >120 minutes), and ASPECTS (0 to 4, 5 to 7, or 8 to 10). The statistical significance of possible differences between subgroups in the treatment effect was tested with interaction terms. No adjustments for multiple tests were made. All analyses were performed with the use of the Stata/SE statistical package, version 13.1 (StataCorp).

Assuming a 10% crossover rate,[26] we calculated that a sample of 500 patients (250 patients in each group) would yield a power of 82%, at a significance level of 0.05, to detect a treatment effect that resulted in an absolute increase of 10 percentage points in the proportion of patients with a modified Rankin score of 0 to 3 in the intervention group as compared with the proportion in the control group.

RESULTS

RANDOMIZATION AND BASELINE CHARACTERISTICS

Between December 2010 and March 2014, a total of 502 patients underwent randomization in 16 Dutch centers. 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.

The mean age of the 500 study participants was 65 years (range, 23 to 96); 292 participants (58.4%) were men. Risk factors for a poor outcome, clinical risk factors for stroke, and aspects of prerandomization treatment were evenly distributed between the two treatment groups (Table 1, and Table S1 in the Supplementary Appendix).

TREATMENT ASSIGNMENTS AND CROSSOVERS

In total, 233 patients (46.6%) were assigned to the intervention group and 267 patients (53.4%) were assigned to the control group. One patient received intraarterial treatment after being assigned to the control group. Intraarterial treatment was never initiated in 17 patients (7.3%) assigned to the intervention group (Fig. S1 in the Supplementary Appendix).

INTERVENTION DETAILS

Actual intraarterial therapy (with or without mechanical thrombectomy) was performed in 196 of the 233 patients in the intervention group (84.1%). In 88 patients (37.8%), general anesthesia was used. A simultaneous second revascularization procedure (acute cervical carotid stenting) was performed in 30 patients (12.9%).

Mechanical treatment was performed in 195 of the 233 patients (83.7%). Retrievable stents were used in 190 patients (81.5%), and other devices were used in 5 patients (2.1%) (Table S2 in the Supplementary Appendix). Additional intraarterial thrombolytic agents were given to 24 patients (10.3%).

Intraarterial thrombolytic agents were used as monotherapy in 1 of the 233 patients (0.4%).

Table 1. Baseline Characteristics of the 500 Patients.*

Characteristic	Intervention (N=233)	Control (N=267)
Age — yr		
Median	65.8	65.7
Interquartile range	54.5–76.0	55.5–76.4
Male sex — no. (%)	135 (57.9)	157 (58.8)
NIHSS score†		
Median (interquartile range)	17 (14–21)	18 (14–22)
Range	3–30	4–38
Location of stroke in left hemisphere — no. (%)	116 (49.8)	153 (57.3)
History of ischemic stroke — no. (%)	29 (12.4)	25 (9.4)
Atrial fibrillation — no. (%)	66 (28.3)	69 (25.8)
Diabetes mellitus — no. (%)	34 (14.6)	34 (12.7)
Prestroke modified Rankin scale score — no. (%)‡		
0	190 (81.5)	214 (80.1)
1	21 (9.0)	29 (10.9)
2	12 (5.2)	13 (4.9)
<2	10 (4.3)	11 (4.1)
Systolic blood pressure — mm Hg§	146±26.0	145±24.4
Treatment with IV alteplase — no. (%)	203 (87.1)	242 (90.6)
Time from stroke onset to start of IV alteplase — min		
Median	85	87
Interquartile range	67–110	65–116
ASPECTS — median (interquartile range)¶	9 (7–10)	9 (8–10)
Intracranial arterial occlusion — no./total no. (%)‖		
Intracranial ICA	1/233 (0.4)	3/266 (1.1)
ICA with involvement of the M1 middle cerebral artery segment	59/233 (25.3)	75/266 (28.2)
M1 middle cerebral artery segment	154/233 (66.1)	165/266 (62.0)
M2 middle cerebral artery segment	18/233 (7.7)	21/266 (7.9)
A1 or A2 anterior cerebral artery segment	1/233 (0.4)	2/266 (0.8)
Extracranial ICA occlusion — no./total no. (%)‖**	75/233 (32.2)	70/266 (26.3)
Time from stroke onset to randomization — min††		
Median	204	196
Interquartile range	152–251	149–266
Time from stroke onset to groin puncture — min		
Median	260	NA
Interquartile range	210–313	

* The intervention group was assigned to intraarterial treatment plus usual care, and the control group was assigned to usual care alone. Plus–minus values are means ±SD. ICA denotes internal carotid artery, 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. The NIHSS is a 15-item scale, and values for 30 of the 7500 items were missing (0.4%). The highest number of missing items for a single patient was 6.

‡ Scores on the modified Rankin scale of functional disability range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence.

§ Data on systolic blood pressure at baseline were missing for one patient assigned to the control group.

¶ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a measure of the extent of stroke. Scores ranges 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.

‖ Vessel imaging was not performed in one patient in the control group, so the level of occlusion was not known.

** Extracranial ICA occlusions were reported by local investigators.

†† Data were missing for two patients in the intervention group.

No intervention was given in 37 patients (15.9%) (Fig. S1 in the Supplementary Appendix).

PRIMARY OUTCOME

Data on the primary outcome (the score on the modified Rankin scale at 90 days) were complete. There was a shift in the distribution of the primary-outcome scores in favor of the intervention. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30) (Table 2). The shift toward better outcomes in favor of the intervention was consistent for all categories of the modified Rankin scale, except for death (Fig. 1). The absolute between-group difference in the proportion of patients who were functionally independent (modified Rankin score,

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

Outcome	Intervention (N=233)	Control (N=267)	Effect Variable	Unadjusted Value (95% CI)	Adjusted Value (95% CI)†
Primary outcome: modified Rankin scale score at 90 days — median (interquartile range)	3 (2 to 5)	4 (3 to 5)	Common odds ratio	1.66 (1.21 to 2.28)	1.67 (1.21 to 2.30)
Secondary outcomes					
Clinical outcomes					
Modified Rankin score of 0 or 1 at 90 days — no. (%)	27 (11.6)	16 (6.0)	Odds ratio	2.06 (1.08 to 3.92)	2.07 (1.07 to 4.02)
Modified Rankin score of 0–2 at 90 days — no. (%)	76 (32.6)	51 (19.1)	Odds ratio	2.05 (1.36 to 3.09)	2.16 (1.39 to 3.38)
Modified Rankin score of 0–3 at 90 days — no. (%)	119 (51.1)	95 (35.6)	Odds ratio	1.89 (1.32 to 2.71)	2.03 (1.36 to 3.03)
NIHSS score after 24 hr — median (interquartile range)‡	13 (6 to 20)	16 (12 to 21)	Beta	2.6 (1.2 to 4.1)	2.3 (1.0 to 3.5)
NIHSS score at 5–7 days or discharge — median (interquartile range)§	8 (2 to 17)	14 (7 to 18)	Beta	3.2 (1.7 to 4.7)	2.9 (1.5 to 4.3)
Barthel index of 19 or 20 at 90 days — no./total no. (%)¶	99/215 (46.0)	73/245 (29.8)	Odds ratio	2.0 (1.3 to 2.9)	2.1 (1.4 to 3.2)
EQ-5D score at 90 days — median (interquartile range)‖	0.69 (0.33 to 0.85)	0.66 (0.30 to 0.81)	Beta	0.08 (0.00 to 0.15)	0.06 (–0.01 to 0.13)
Imaging outcomes					
No intracranial occlusion on follow-up CT angiography — no./total no. (%)**	141/187 (75.4)	68/207 (32.9)	Odds ratio	6.27 (4.03 to 9.74)	6.88 (4.34 to 10.94)
Final infarct volume on CT††					
Patients evaluated — no. (%)	138 (59.2)	160 (59.9)			
Median (interquartile range) — ml	49 (22 to 96)	79 (34 to 125)	Beta	20 (3 to 36)	19 (3 to 34)

* CT denotes computed tomography.
† Values were adjusted for age; NIHSS score at baseline; 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).
‡ The NIHSS score was determined for survivors only. The score was not available for 20 patients: 12 died before assessment was finished, and 8 had missing scores.
§ The NIHSS score was determined for survivors only. The score was not available for 74 patients: 56 died before assessment was finished, and 18 had missing scores.
¶ The Barthel index is an ordinal scale for measuring performance of activities of daily living. Scores ranges from 0 to 20, with 0 indicating severe disability and 19 or 20 indicating no disability that interferes with daily activities.
‖ The EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) is a standardized instrument for the measurement of health status. Scores range from –0.33 to 1.00, with higher scores indicating a better quality of life.
** Data for follow-up CT angiography were not available for 106 patients owing to imminent death or death (24 patients), decreased kidney function (13 patients), insufficient scan quality (5 patients), and other reasons (64 patients).
†† Data for final infarct volume on noncontrast CT (performed at 3 to 9 days) were missing for 202 patients because of death (52 patients), hemicraniectomy (21 patients), technical errors with automated assessment (14 patients), or insufficient scan quality (5 patients) or because CT was not performed for reasons other than death (110 patients).

0 to 2) was 13.5 percentage points (95% CI, 5.9 to 21.2) in favor of the intervention (32.6% vs. 19.1%), with an adjusted odds ratio of 2.16 (95% CI, 1.39 to 3.38) (Table 2).

SECONDARY OUTCOMES

All clinical and imaging secondary outcomes favored the intervention (Table 2, and Table S3 in the Supplementary Appendix). The NIHSS score after 5 to 7 days was, on average, 2.9 points (95% CI, 1.5 to 4.3) lower in the intervention group than in the control group.

Data on recanalization after 24 hours, assessed by means of CTA, were available for 394 patients. An absence of residual occlusion at the target site was more common in the intervention group (141 of 187 patients [75.4%]) than in the control group (68 of 207 patients [32.9%]) (Table 2). Data on infarct volume were available for 298 of 500 patients; the between-group difference in volume (19 ml; 95% CI, 3 to 34) favored the intervention group (Table 2). Good reperfusion (modified TICI score, 2b or 3) was achieved in 115 of 196 patients (58.7%) in the intervention group (Table S4 in the Supplementary Appendix).

SAFETY

There was no significant between-group difference in the occurrence of serious adverse events during the 90-day follow-up period (P=0.31) (Table 3). However, 13 of the 233 patients (5.6%) in the intervention group had clinical signs of a new ischemic stroke in a different vascular territory within 90 days, whereas only 1 of the 267 patients (0.4%) in the control group did so. There was no significant difference in mortality at 7, 30, or 90 days of follow-up.

Procedure-related complications in the intervention group included embolization into new territories outside the target downstream territory of the occluded vessel in 20 of the 233 patients (8.6%), procedure-related vessel dissections in 4 patients (1.7%), and vessel perforations in 2 patients (0.9%).

SUBGROUP ANALYSES

There were no significant interactions between subgroups and treatment effect. The treatment effect remained consistent in all predefined subgroups, including those based on age (<80 years or ≥80 years), NIHSS score (2 to 15, 16 to 19, or ≥20), and ASPECTS (0 to 4, 5 to 7, or 8 to 10) (Fig. S2 in the Supplementary Appendix). The point estimate for treatment effect in the subgroup with ASPECTS of 0 to 4 was close to unity but with a wide confidence interval (adjusted common odds ratio, 1.09; 95% CI, 0.14 to 8.46).

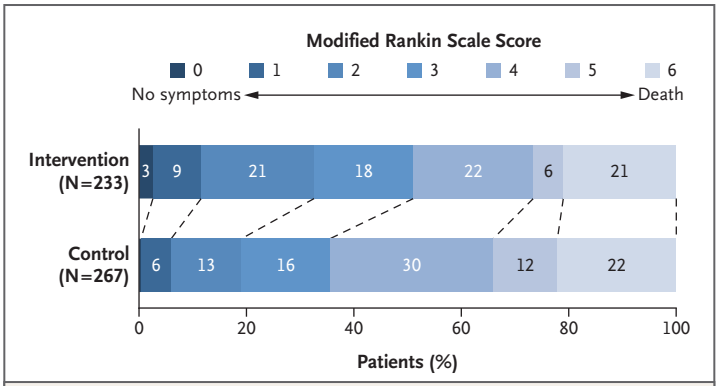

Figure 1. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.

Shown is the distribution of scores on the modified Rankin scale. 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 unable to walk unassisted), 5 severe disability (patient requires constant nursing care and attention), and 6 death. There was a significant difference between the intervention group and the control group in the overall distribution of scores in an analysis with univariable ordinal regression (common odds ratio, 1.66; 95% CI, 1.21 to 2.28), as well as after adjustment of the treatment effect for age; National Institutes of Health Stroke Scale score at baseline; 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) in an analysis with multivariable regression (adjusted common odds ratio, 1.67; 95% CI, 1.21 to 2.30). In the control group, only 1 patient (0.4%) had a modified Rankin score of 0.

DISCUSSION

Our results show that patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation have a benefit with respect to functional recovery when intraarterial treatment is administered within 6 hours after stroke onset. This treatment leads to a clinically significant increase in functional independence in daily life by 3 months, without an increase in mortality.

Our findings stand in clear distinction to those of recent randomized, controlled trials that failed to show a benefit of intraarterial treatment.[12,13] Approximately 90% of patients in each treatment group of MR CLEAN received intravenous al-

Table 3. Safety Variables and Serious Adverse Events within 90 Days after Randomization.

Variable	Intervention (N=233)	Control (N=267)
	no. of patients (%)	
Safety variables		
Death		
Within 7 days	27 (11.6)	33 (12.4)
Within 30 days	44 (18.9)	49 (18.4)
Hemicraniectomy	14 (6.0)	13 (4.9)
Serious adverse events*		
Any serious adverse event	110 (47.2)	113 (42.3)
Symptomatic intracerebral hemorrhage		
Any type	18 (7.7)	17 (6.4)
Parenchymal hematoma†		
Type 1	0	2 (0.7)
Type 2	14 (6.0)	14 (5.2)
Hemorrhagic infarction‡		
Type 1	1 (0.4)	0
Type 2	1 (0.4)	1 (0.4)
Subarachnoid hemorrhage	2 (0.9)	0
New ischemic stroke in a different vascular territory§	13 (5.6)	1 (0.4)
Progressive ischemic stroke	46 (19.7)	47 (17.6)
Pneumonia	25 (10.7)	41 (15.4)
Other infection	16 (6.9)	9 (3.4)
Cardiac ischemia	1 (0.4)	4 (1.5)
Extracranial hemorrhage	0	2 (0.7)
Allergic reaction	1 (0.4)	0
Other complication	22 (9.4)	33 (12.4)

* Only first events of a type are listed. Patients having multiple events of one type were counted once.
† For parenchymal hematoma, type 1 was defined by one or more blood clots in 30% or less of the infarcted area with a mild space-occupying effect, and type 2 was defined by blood clots in more than 30% of the infarcted area with a clinically significant space-occupying effect.
‡ For hemorrhagic infarction, type 1 was defined by small petechiae along the margins of the infarction, and type 2 was defined by more confluent petechiae within the infarction area.
§ P<0.001.

teplase, making our cohort similar to that in the Interventional Management of Stroke (IMS) III trial, in which intravenous alteplase alone was compared with intravenous alteplase plus intra-arterial treatment.[12] However, in the IMS III trial, patients had to be enrolled and undergo randomization within 40 minutes after the start of intravenous alteplase. This requirement may have led to the inclusion of more patients who had a favorable response to intravenous alteplase than in MR CLEAN, which had a median time from the start of intravenous alteplase to randomization that was considerably longer than the maximum time in the IMS III trial. It is likely that intraarterial treatment will not alter the natural history of acute ischemic stroke in the absence of a proximal arterial occlusion. Unlike the IMS III trial and the Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) trial,[13] MR CLEAN required a radiologically proven intracranial occlusion for study eligibility. When the IMS III trial was designed, the availability of CTA was still limited, and the presence of a proximal arterial occlusion was therefore uncertain in a subgroup of patients in that trial (47% of the study population).[12]

Our study benefited from the widespread availability of retrievable stents, which were used in 82% of the patients in the intervention group. These devices were recently shown to be superior to the first-generation Merci device for both revascularization and clinical outcomes.[27,28]

Previous trials have been criticized because investigators could have treated many patients outside the trials. This was reflected in the low recruitment rates in the IMS III trial and the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial,[14] which had an average enrollment of 1 to 2 patients per center per year. In contrast, all stroke centers in the Netherlands that provided intraarterial treatment during the execution of MR CLEAN participated in the trial, and from 2013 onward, reimbursement by insurance companies required participation in a trial.

Our trial had several limitations. First, randomization was slightly unbalanced, resulting in more patients in the control group than in the intervention group. This imbalance was the result of block size and multiple stratifications.

Second, the reperfusion rate in MR CLEAN (modified TICI score of 2b or 3, 58.7%) was relatively low as compared with the rates in recent case series, which were 80% or higher.[29,30] However, the rate of a modified TICI score of 2b or 3 in the IMS III trial was 23 to 44%, depending on the location of the occlusion. The two recently published phase 2 trials of retrievable stents showed reperfusion rates of 61% and 86%, but these rates were based on end points

of a modified TICI score of 2a to 3 and a Thrombolysis in Myocardial Ischemia score of 2 or 3, respectively.[27,28] Differentiation between a modified TICI score of 2a and a score of 2b or 3 is difficult when lateral DSA images are not available. This applied to 15 patients in MR CLEAN, who were subsequently given a modified TICI score of 2a. This may have led to an underestimation of the actual reperfusion rate among patients with a modified TICI score of 2b or 3.

Third, despite the positive result of this trial, almost 9% of the patients in the intervention group had embolization into new vascular territories on DSA. A total of 30 patients (13%) assigned to intraarterial treatment also underwent a simultaneous second revascularization procedure (acute cervical carotid stenting), and this complexity needs to be considered when interpreting our trial results.

Fourth, a relatively low proportion of patients in the control group had a modified Rankin score of 0 to 2 at the 90-day follow-up assessment. This may be explained by our broad inclusion criteria, which allowed contraindications for intravenous alteplase, nonresponse to intravenous alteplase, octogenarians and even nonagenarians, and patients with extracranial internal-carotid-artery occlusions or dissections. Taken together, this resulted in a population with a relatively poor prognosis at baseline. The advantage is a wide generalizability of our results.

Finally, although the outcome assessment was blinded, patients were aware of the treatment-group assignments, and this might have influenced their opinions about their health and functional condition. However, modified Rankin scores at 90 days were based on assessment by reviewers who were unaware of the treatment-group assignments, to avoid biased assessments, and the results of blinded assessments of neuroimaging corroborated our findings.

In conclusion, we found that intraarterial treatment in patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation was effective and safe when administered within 6 hours after stroke onset.

Supported by the Dutch Heart Foundation and by unrestricted grants from AngioCare Covidien/ev3, Medac/Lamepro, and Penumbra.

Dr. Yoo reports receiving grant support from Penumbra; Dr. Brouwer, lecture fees and fees for trial management from Stryker, lecture fees and fees for proctoring from BALT, lecture fees from Toshiba, teaching fees and fees for research and development from Codman/DePuy Synthes, and teaching fees from Sequent Medical; Dr. de Vries, consulting fees from Stryker and grant support from Covidien/ev3; and Dr. René van den Berg, consulting fees from Codman/DePuy Synthes. No other potential conflict of interest relevant to this article was reported.

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

APPENDIX

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