Endovascular Therapy Is Effective and Safe for Patients With Severe Ischemic Stroke

Pooled Analysis of Interventional Management of Stroke III and Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands Data

Joseph P. Broderick, MD; Olvert A. Berkhemer, MD; Yuko Y. Palesch, PhD; Diedrik W.J. Dippel, MD, PhD; Lydia D. Foster, MS; Yvo B.W.E.M. Roos, MD, PhD; Aad van der Lugt, MD, PhD; Thomas A. Tomsick, MD; Charles B.L.M. Majoie, MD, PhD; Wim H. van Zwan, MD, PhD; Andrew M. Demchuk, MD; Robert J. van Oostenbrugge, MD, PhD; Pooja Khatri, MD; Hester F. Lingsma, PhD; Michael D. Hill, MD; Bob Roozenbeek, MD, PhD; Edward C. Jauch, MD; Tudor G. Jovin, MD; Bernard Yan, MD; Rüdiger von Kummer, Dr. Med; Carlos A. Molina, MD; Mayank Goyal, MD; Wouter J. Schonewille, MD, PhD; Mikael Mazighi, MD, PhD; Stefan T. Engelter, MD; Craig S. Anderson, MD, PhD; Judith Spilker, RN, BSN; Janice Carrozzella, RN, BA, RT (R); Karla J. Ryckborst, RN, BN; L. Scott Janis, PhD; Kit N. Simpson, PhD; for the IMS III and MR CLEAN Investigators

Background and Purpose—We assessed the effect of endovascular treatment in acute ischemic stroke patients with severe neurological deficit (National Institutes of Health Stroke Scale score, ≥20) after a prespecified analysis plan.

Methods—The pooled analysis of the Interventional Management of Stroke III (IMS III) and Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trials included participants with an National Institutes of Health Stroke Scale score of ≥20 before intravenous tissue-type plasminogen activator (tPA) treatment (IMS III) or randomization (MR CLEAN) who were treated with intravenous tPA ≤3 hours of stroke onset. Our hypothesis was that participants with severe stroke randomized to endovascular therapy after intravenous tPA would have improved 90-day outcome (distribution of modified Rankin Scale scores), when compared with those who received intravenous tPA alone.

Results—Among 342 participants in the pooled analysis (194 from IMS III and 148 from MR CLEAN), an ordinal logistic regression model showed that the endovascular group had superior 90-day outcome compared with the intravenous tPA group (adjusted odds ratio, 1.78; 95% confidence interval, 1.20–2.66). In the logistic regression model of the dichotomous outcome (modified Rankin Scale score, 0–2, or functional independence), the endovascular group had superior outcomes (adjusted odds ratio, 1.97; 95% confidence interval, 1.09–3.56). Functional independence (modified Rankin Scale score, ≤2) at 90 days was 25% in the endovascular group when compared with 14% in the intravenous tPA group.
Conclusions—Endovascular therapy after intravenous tPA within 3 hours of symptom onset improves functional outcome at 90 days after severe ischemic stroke.

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Key Words: clinical trial ▪ endovascular procedures ▪ stroke ▪ tissue-type plasminogen activator

The main purpose of the Interventional Management of Stroke III (IMS III) trial was to evaluate the approach of intravenous tissue-type plasminogen activator (tPA) treatment followed by protocol-approved endovascular treatment (hereafter referred to as the endovascular group) relative to intravenous tPA alone in affecting good clinical outcome at 3 months after ischemic stroke.1 Although the IMS III trial was stopped for overall futility in April 2012 after 656 participants had been enrolled, there was emerging evidence of potential benefit in those participants with high National Institutes of Health Stroke Scale (NIHSS) scores (≥20) and those with major arterial occlusions on pretreatment computed tomographic angiography (CTA).2 As the Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands (MR CLEAN) was nearing completion of enrollment and follow-up in the spring of 2014, the IMS III and MR CLEAN investigators identified these subgroups as targets for a pooled analysis of the 2 trials after the IMS III and MR CLEAN investigators identified these subgroups as targets for a pooled analysis of the 2 trials after the MR CLEAN results had been published in December 2014.3 On the basis of pilot observations from a pre-IMS registry, IMS I, II, and III investigators prespecified a stratified analysis for the primary outcome, hypothesizing that the efficacy of endovascular therapy would be greater in participants with more severe stroke (NIHSS score, ≥20) because most such patients have occlusion of a major intracranial artery and the greatest volume of ischemic brain at risk.4–6 Finally, although the 90-day modified Rankin Scale (mRS) score at 90 days was the primary outcome of IMS III, the trial was designed to follow-up subjects for 12 months, and the subgroup of subjects with an NIHSS score ≥20 randomized to endovascular therapy had better functional outcomes and quality of life over a year when compared with those treated with intravenous tPA alone.7 In the MR CLEAN trial, a subgroup analysis of tertiles of NIHSS score was prespecified because effect modification by initial stroke severity was expected.8 Herein, we present pooled analyses of the trials examining the more severe acute ischemic stroke subject subgroup who were first treated with intravenous tPA within 3 hours of onset.

Methods

Trial Design

Both the IMS III and MR CLEAN trials were phase III, randomized, parallel arm, open-label clinical trials with blinded outcome evaluation, the details of which are outlined elsewhere.1,5,6,11,12,15,16 Informed consent was obtained from the patient or a legal representative before enrollment for both trials.

The primary hypothesis to be addressed by this pooled analysis was that endovascular therapy after intravenous tPA with 6 hours of stroke onset when compared with treatment with intravenous tPA alone would be associated with improved 90-day outcome, as measured by the distribution of outcomes on the mRS.1 Key differences in inclusion criteria, study design, and treatments between the 2 trials are provided in Table 1, and detailed inclusion and exclusion criteria for the 2 trials are shown in the Appendix—Tables I and II in the online-only Data Supplement. However, the current pooled analysis included all subjects of both trials treated with intravenous tPA within 3 hours of onset with an NIHSS score of ≥20. For the IMS III trial, this criterion included patients with an NIHSS score ≥20 just before treatment with tPA; for the MR CLEAN trial, this included patients with an NIHSS score of ≥20 just before randomization that occurred after tPA therapy.

Treatments

All participants in the MR CLEAN trial treated with intravenous tPA received the standard dose (0.9 mg/kg), with 10% as bolus and the remainder infused over a 1-hour period (maximum dose, 90 mg). In the IMS III trial, the 176 participants in the first 4 protocol versions of IMS III trial had the intravenous tPA infusion stopped after 40 minutes of infusion. In the last protocol version of IMS III, the remaining 18 participants were treated with the standard dose of intravenous tPA for 1 hour.9

The endovascular group in both trials underwent angiography as soon as possible, either at the hospital initiating treatment or after transfer to another participating hospital. Participants without evidence of a treatable occlusion received no additional reperfusion interventions. Those participants with a treatable vascular occlusion received endovascular intervention chosen by the site neurointerventionist. For the IMS III trial, this included thrombectomy with the Merci Retriever (Concentric Medical), Penumbra System (Penumbra), or Solitaire FR Revascularization Device (Covidien) or endovascular infusion of ≤22 mg of tPA through the EKOS Micro-Infusion Catheter (EKOS) or a standard microcatheter. However, only a few subjects in the IMS III trial near the completion of the trial were treated with a stent retriever. In the IMS III trial, the angiographic procedure had to begin within 5 hours of stroke onset and be completed within 7 hours of stroke onset.

For the MR CLEAN trial, the use of alteplase or urokinase for intra-arterial thrombolysis was allowed with a maximum dose of 90 mg of intravenous tPA or 1200 000 IU of urokinase. The dose was restricted to 30 mg of tPA or 400 000 IU of urokinase if intravenous tPA was given. Mechanical treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent.11 However, a retrievable stent was used in almost all subjects.

Outcome Measures

The primary outcome measure was the mRS score at 90 days. The mRS score is a measure of disability, which ranges from 0 (no symptoms) to 5 (severe disability and bedridden) and 6 (death).10 The mRS score was determined by a study investigator who was tPA certified and blinded to the treatment assignment. For the IMS III trial, the mRS assessment at 90 days was performed in person, except in a few instances where in-person assessment was not possible, and the assessment was conducted by phone. For the MR CLEAN trial, the mRS score was determined by a phone assessment performed by an experienced investigator who was blinded to treatment allocation. This interview generated masked reports for the assessment of the mRS score by vascular neurologists who were blinded for the treatment-group assignment.
Secondary outcomes at 90 days included the Barthel index (BI)\(^1\) and the EQ-5D-3L (formerly known as EuroQol) health-related quality-of-life measure, which were obtained either from the subject or a proxy. The BI is an ordinal scale for measuring the performance of activities of daily living, with scores ranging from 0 to 100 (0 indicating severe disability and 95 or 100 indicating no disability). The EQ-5D-3L comprises 3 levels of assessment (no problems, slight or moderate problems, and extreme problems) across 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).\(^2\) In the MR CLEAN trial, symptomatic intracranial hemorrhage (sICH) was reported by the local investigator and defined as neurological deterioration (≥4-point increase in NIHSS score from baseline) with ICH confirmed on imaging. For the IMS III trial, sICH was defined as an ICH temporally related to a decline in neurological status and new or worsening neurological symptoms in the judgment of the clinical investigator that may warrant medical intervention (≥4-point increase in NIHSS score from baseline was used as a guide to investigators).

### Statistical Analyses

The primary analysis of the 90-day outcome (mRS) used an ordinal regression model with prespecified covariates (NIHSS, age, previous stroke, diabetes mellitus, and atrial fibrillation) and study. Secondary analysis of dichotomized mRS scores (0–2 versus 3–6) used logistic regression as above. Because MR CLEAN defined NIHSS at the time of randomization (often several hours after start of intravenous tPA), we also performed an exploratory pooled analysis of mRS outcomes using those subjects in the IMS III trial who had an NIHSS score of ≥20 at 40 minutes after commencement of intravenous tPA to better approximate the MR CLEAN study population. For the secondary end point of the BI, we compared the proportion of participants with a BI score of 95 to 100 using a logistic regression model with covariates as above (IMS III prespecified approach). Missing mRS and BI assessments were imputed as unfavorable for dichotomized outcomes and excluded for the ordinal mRS outcome. For the EuroQOL-5D, we compared the mean EuroQOL score at 90 days between the 2 treatment groups (MR CLEAN prespecified approach). EuroQOL-5D index value was calculated to conform to the American standard, and missing assessments were excluded from the analysis. Comparison of the proportion of sICH in the 2 treatment groups was done using the Cochran–Mantel–Haenszel test, adjusting for study.

### Results

A total of 342 participants were included in the pooled analysis (194, IMS III; 148, MR CLEAN). Table 2 shows the distribution of baseline variables for the 2 trials and pooled cohort. The IMS III cohort was older with a greater proportion of women, previous stroke, diabetes mellitus, and atrial fibrillation and a shorter time from symptom onset to randomization.

mRS scores were available in 341 of 342 subjects. In the ordinal logistic regression model, the endovascular group had superior 90-day outcome when compared with the intravenous tPA group (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.12–2.42 and adjusted OR [aOR], 1.78; 95% CI, 1.20–2.66; Figure 1). In the logistic regression model of dichotomous outcome, mRS score of 0 to 2 or functional independence, the endovascular group also had superior outcomes (OR, 2.02; 95% CI, 1.15–3.56 and aOR, 1.97; 95% CI, 1.09–3.56). Functional independence (mRS score, ≤2) at 90 days was 25% in the endovascular group when compared with 14% in the intravenous tPA group (Figure 1).

BI scores were available in 266 of 342 subjects (78%). Logistic regression model of dichotomous BI scores of 95 to 100 was in favor of the endovascular group (OR, 1.64; 95% CI, 1.00–2.68 and aOR, 1.80; 95% CI, 1.07–3.03). For EQ-5D-3L, available in 330 of 342 (96%) subjects, linear regression according to MR CLEAN statistical analysis plan showed an unadjusted regression coefficient of 0.09 (95% CI, 0.01–0.18; \(P=0.023\)) and an adjusted regression coefficient of 0.10 (95% CI, 0.02–0.18; \(P=0.012\)). The thrombolysis in cerebral infarction 2b reperfusion score for the IMS III cohort was 42 of 109 (39%), for MR CLEAN was 31 of 53 (58%), and for the pooled cohort was 73 of 162 (45%). The proportion of sICH in the endovascular group (n=16; 8.4%) was not significantly different from that in the intravenous tPA only group (n=12; 8.0%), adjusting for study.

### Table 1. Key Differences Between IMS III and MR CLEAN Trials

<table>
<thead>
<tr>
<th>Study time period</th>
<th>IMS III</th>
<th>MR CLEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries of study enrollment</td>
<td>United States, Canada, Australia, Germany, Spain, France, Netherlands</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Time window from stroke onset to treatment</td>
<td>≤3 h to the start of IV tPA</td>
<td>≤6 h to the start of endovascular therapy or standard therapy (99% treated with IV tPA out to 4.5 h)</td>
</tr>
<tr>
<td>Use of vascular imaging before enrollment</td>
<td>Encouraged and data collected not required</td>
<td>Required</td>
</tr>
<tr>
<td>Demonstration of large intracranial arterial occlusion on vascular imaging</td>
<td>Presence of major arterial occlusion required only if NIHSS score is 8–9</td>
<td>Required demonstration of major arterial occlusion on vascular imaging</td>
</tr>
<tr>
<td>NIHSS eligibility</td>
<td>≥10, or 8–9 with demonstration of major arterial occlusion on vascular imaging</td>
<td>≥2</td>
</tr>
<tr>
<td>Decision process for randomization</td>
<td>Decision made by treating physician investigator within 40 min of IV tPA initiation</td>
<td>Pragmatic design in which treating physician(s) randomized to insure endovascular treatment within 6 h from stroke onset</td>
</tr>
<tr>
<td>Age, y</td>
<td>18–82</td>
<td>18 y, no upper age limit</td>
</tr>
<tr>
<td>Dose of IV tPA in endovascular arm, mg/kg</td>
<td>0.9 mg/kg with 10% bolus, infusion stopped at 40 min; last protocol modification used entire infusion for 60 min</td>
<td>0.9 mg/kg for 1 h, 10% as a bolus</td>
</tr>
<tr>
<td>Endovascular treatment</td>
<td>&lt;10 total stent retrievers, earlier endovascular technology and intra-arterial tPA</td>
<td>82% stent retrievers, intra-arterial thrombolytic allowed</td>
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</table>

IMS III indicates Interventional Management of Stroke III; IV, intravenous; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.
In the exploratory pooled analysis of those IMS III participants with an NIHSS score of ≥20 at 40 minutes after the start of tPA, there were 39 endovascular participants and 9 intravenous tPA participants missing the 40-minute NIHSS score of 656 subjects. In addition, 68 participants who had an NIHSS score of ≥20 before intravenous tPA had improved to an NIHSS score of <20 at 40 minutes; 16 subjects who had an NIHSS score of <20 before intravenous tPA had worsened to an NIHSS score of ≥20 at 40 minutes. Figure 2 shows the change from pretreatment to 40 minute NIHSS. Thus, 142 IMS III participants with an NIHSS score of ≥20 at 40 minutes after the start of intravenous tPA were available for the exploratory pooled analysis. In the ordinal logistic regression model, the endovascular group once again had superior outcomes when compared with the intravenous tPA group (OR, 1.75; 95% CI, 1.16–2.66 and aOR, 2.04; 95% CI, 1.32–3.16). In the logistic regression model of dichotomous mRS outcome, the endovascular group had superior outcomes (OR, 2.52; 95% CI, 1.30–4.93 and aOR, 2.70; 95% CI, 1.34–5.43). Because the study-by-treatment interaction term was not significant in the unadjusted or adjusted models of mRS score of 0 to 2, both in the original or exploratory pooled populations, there was insufficient evidence for a differential treatment effect between studies.

Discussion

Despite differences in study design and endovascular technology used in the 2 trials, this pooled analysis of subjects with severe acute ischemic stroke (NIHSS score, ≥20) demonstrates the benefit of endovascular therapy after intravenous tPA when compared with intravenous tPA alone with both ordinal and dichotomous analyses of the mRS. Endovascular therapy after intravenous tPA improved outcome to the extent that 1 in 4 subjects is functionally independent at 3 months when compared with intravenous tPA alone where only 1 in 10 achieved the same level of recovery. These effects were seen without any statistically significant increase in mortality or sICH for endovascular therapy.

MR CLEAN demonstrated significant benefit for endovascular therapy for both severe and moderately severe ischemic stroke in subjects with documented occlusion by CTA, whereas no benefit was seen in the IMS III trial for subjects with moderately severe stroke. Advances in endovascular technology with better reperfusion rates (thrombolysis in cerebral infarction 2b3 in 58% in MR CLEAN versus 39% in IMS III) contribute to the discrepancy between IMS III and MR CLEAN for subjects with moderately severe stroke. However, the difference between the 2 trials is also explained by a substantial but unknown proportion of subjects in the IMS III trial who did not have a documented large-artery occlusion because only 47% of IMS III participants had a pretreatment CTA.

Previous studies have demonstrated that subjects with an NIHSS score of ≥20 almost always have a large-artery occlusion by vascular imaging, even after intravenous tPA. Of 89 IMS III participants with an NIHSS score of ≥20 and CTA before treatment with intravenous tPA, only 1 had no documented major arterial occlusion on CTA, and this participant had an M2 occlusion on subsequent intra-arterial angiography. Of 217 IMS III participants with an NIHSS score of <20 and CTA before treatment with intravenous tPA, 23 had no major documented occlusion, and of these, 1 had an M2 and 1 had an M3 occlusion at intra-arterial angiography. The importance of documentation of a major arterial occlusion before enrollment in an endovascular trial is also reflected in a post hoc analysis of IMS III that demonstrated benefit for endovascular therapy in participants with an intracranial occlusion by baseline CTA and that included all levels of the NIHSS.

<table>
<thead>
<tr>
<th>Table 2. Baseline Variables in the IMS III, MR CLEAN, and Pooled Cohorts</th>
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<tr>
<td><strong>IMIS III, n=194</strong></td>
</tr>
<tr>
<td><strong>Endovascular, n=127</strong></td>
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<tr>
<td><strong>Control, n=67</strong></td>
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<tr>
<td><strong>Age (median, IQR)</strong></td>
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<tr>
<td><strong>Control, n=67</strong></td>
</tr>
<tr>
<td><strong>Male sex, n (%)</strong></td>
</tr>
<tr>
<td><strong>Control, n=67</strong></td>
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<tr>
<td><strong>NIHSS score (median, IQR)</strong></td>
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<tr>
<td><strong>Control, n=67</strong></td>
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<tr>
<td><strong>ASPECTS score (median, IQR)</strong></td>
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<tr>
<td><strong>Control, n=67</strong></td>
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<tr>
<td><strong>Previous stroke, n (%)</strong></td>
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<tr>
<td><strong>Control, n=67</strong></td>
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<tr>
<td><strong>Diabetes mellitus, n (%)</strong></td>
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<tr>
<td><strong>Control, n=67</strong></td>
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<tr>
<td><strong>Atrial fibrillation, n (%)</strong></td>
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<tr>
<td><strong>Control, n=67</strong></td>
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<tr>
<td><strong>Time from onset to randomization, min (median, IQR)</strong></td>
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<tr>
<td><strong>Control, n=67</strong></td>
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<tr>
<td><strong>Time from onset to EVT, min (median, IQR)</strong></td>
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<tr>
<td><strong>Control, n=67</strong></td>
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<tr>
<td><strong>Time from onset to IV tPA, min (median, IQR)</strong></td>
</tr>
<tr>
<td><strong>Control, n=67</strong></td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT score; EVT, endovascular therapy; IMS III, Interventional Management of Stroke III; IQR, interquartile range; IV, intravenous; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands; and NIHSS, National Institutes of Health Stroke Scale.

*1 IMS III endovascular subject missing.
†1 MR CLEAN control subject missing and 1 IMS III endovascular subject missing.
‡7 MR CLEAN endovascular subjects missing and 20 IMS III endovascular subjects missing.
Improvement in the NIHSS score between baseline and 40 minutes after tPA infusion in the IMS III trial demonstrates the early effect of intravenous tPA on some subjects with larger-artery occlusions and severe stroke. This observation emphasizes the importance of starting a reperfusion therapy, whether medical or mechanical as quickly as possible. Endovascular trials, such as MR CLEAN, which randomized patients with a substantial delay after the start of intravenous tPA, may exclude patients who are most likely to reperfuse early with tPA and include patients with poorer collateral flow, more resistance to reperfusion, and larger ischemic cores. The remaining patients with no improvement and persistent occlusions will be a group with a lower likelihood of good outcomes because the time to reperfusion with endovascular therapy will be longer. The rate of mRS score of 0 to 1 at 3 months for patients with an NIHSS score of ≥20 in the IMS III trial was 10.6% versus 4.8% in the MR CLEAN trial, despite superior technology and reperfusion rates in the MR CLEAN trial. These data highlight the potentially large differences in trial population that may result from a small change in definitions (time to start of intravenous tPA versus time to randomization several hours later). Future trials that plan to compare endovascular therapy alone without previous intravenous tPA to endovascular therapy after intravenous tPA, as has been done in trials of acute myocardial infarction, will have to account for the benefit of intravenous tPA, particularly when it is started rapidly.

Recent endovascular trials not only represent a major step forward for acute ischemic stroke therapy but also demonstrate the poor outcome in many patients with severe stroke, even after endovascular therapy. Only one quarter of subjects in this pooled analysis of those subjects with the most severe strokes were functionally independent at 3 months. Although an earlier time from onset to endovascular reperfusion has been clearly demonstrated to be associated with improved outcomes for patients with ischemic strokes with large-artery occlusions, the time to intervene may be short for many patients with large areas of severely ischemic brain. Imaging selection is one method to identify those patients with stroke who are most likely to benefit from endovascular therapy, particularly in time windows beyond 6 hours from onset. Another way to improve outcomes in patients with stroke is to optimize initial triage of patients with stroke by prehospital personnel who are most likely to have large-artery occlusion and transport them directly to the best location to minimize the time to start of the most appropriate reperfusion therapy. This will be a major task for stroke systems of care over the coming years.

Figure 1. Distribution of 90-day outcomes for Interventional Management of Stroke III (IMS III), Multi-center Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands (MR CLEAN), and pooled cohorts. mRS indicates modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.
This is the first published pooled analysis in the era of randomized endovascular trials. Such a process allows for careful review of data by all participants, a prespecified statistical approach, and a more detailed and nuanced discussion of potential differences in the 2 trials by the investigators themselves. Despite some heterogeneity in design and technology, the data in this subgroup of subjects from IMS III and MR CLEAN trials are remarkably consistent on the benefit and safety of endovascular therapy. Heterogeneity in study populations, particularly selection by imaging, is also an issue for the pooled analysis of endovascular trials, which is underway. The Thrombectomy and tPA (TREAT) analysis will use retrospective subject-level pooled analysis of randomized trials testing combined intravenous tPA/endovascular versus intravenous tPA alone. Such large pooled analyses will be able to better delineate the benefit of endovascular therapy among subgroups of patients as selected by imaging criteria, time to treatment, stroke severity, and other patient characteristics.

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J.P. Broderick, Y.Y. Palesch, L.D. Foster, S.D. Yeatts, K.N. Simpson, O.A. Berkhemer, D.W.J. Dippel, and Y. B.W.E.M. Roos were responsible for the analyses used in this article. Y.Y. Palesch, L.D. Foster, J.P. Broderick, O.A. Berkhemer, D.W.J. Dippel, and Yvo B.W.E.M. Roos had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**References**


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On page 3416, in the author byline, “IMS II,” has been changed to read “IMS III” investigators.

The publisher regrets the error.

This correction has been made to the online version of the article, which is available at http://stroke.ahajournals.org/content/46/12/3416.

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LIST OF INVESTIGATORS AND ADMINISTRATIVE STAFFS

ENROLLING CLINICAL CENTERS: University of Cincinnati College of Medicine (72 subjects) J. Broderick, T. Tomick; University of Pittsburgh Medical Center (46) L Wechsler, T. Jovin; Calgary Health Region/Foothills Medical Centre (44) A. Demchuk, M. Goyal; Toronto Western Hospital (29) F. Silver, K. Murphy; Hospital Vall d’Hebron (28) C. Molina, M. Ribo; Royal Melbourne Hospital (27) B. Yan, P. Mitchell; Mayo Clinic Arizona (26) B. Damaerschalk, B. Chong; Oregon Health Sciences University, Oregon Stroke Center (24) W. Clark, S. Barnwell; Riverside Methodist Hospital (24) R. Budzik; Alexian Brothers Hospital Network (23) T. Malisch; Froedtert Hospital/ Medical College of Wisconsin (23) O. Zaidat; Colorado Neurological Institute/Swedish Medical Center (21) C. Fanale, D. Frei; Allegheny General Hospital (18) A. Taylor, A. Ku; Dresden University of Technology (17), U. Bodchetel, R. von Kummer; Ruan Neurology /Mercy Medical Center, (16) M Jacoby, W. Young; Lehigh Valley Hospital (15) Y. Isayev, D. Shaff; UCLA Medical Center (14) S. Starkman, F. Vinuela; University of Louisville (11) A. Abou-Chebl; Martin Luther University (10) K. Wartenberg, K. Stock; Royal Prince Alfred Hospital (10) C. Anderson, G. Parker; Abington Memorial Hospital (9) Q. Shah; Vancouver General Hospital (9) A. Woolfenden, G. Redekop; Henry Ford Hospital (8) C. Lewandowski, W. Sanders; University of Virginia Health System (8) E. Clarke Haley, A. Evans; Washington University (8) P. Panagos, C. Derdeyn; Hoag Memorial Hospital Presbyterian (7) D. Brown, M. Brandt-Zawadzki; Morton Plant Mease Health Care (7) A. Arora, E. Lopez De Valle; PENN State M.S. Hershey Medical Center (7) K. Cockroft; University of Miami Miller School of Medicine/Jackson Memorial Hospital (7) D. Yavagal; Lahey Clinic Medical Center (6) In Sup Choi; Mission Hospitals/Mission Neurology Services (6) A. Schneider, J. Short; Monash Medical Centre (6) T. Phan, W. Chong; University of North Carolina (5) D. Huang, S. Solander; University of Texas Medical School at Houston (5), J. Grotta, P. Chen; Upstate Medical University (5) Z. El Zammar, E. Deshaies; Bichat Stroke Centre and Paris Diderot University (4) P. Amarenco, M. Mazighi; Medical University of South Carolina (4) E. Jauch, A. Turk; Ottawa Hospital-Civic Campus (4) G. Stotts, C. Lum; Park Nicollet Institute (4) S. Hanson, M. Madison; Trillium Health Care (4) D. Selchen, D. Rosso; Chattanooga Ctr. for Neurological Res (3) T. Delvin, B. Baxter; Jewish Hospital Louisville (3) J. Gebel, R. Paulson; Nevada Neuroscience Institute Research Foundation (3) S. Selco, L. Blake; St. Antonius Hospital (3) W. Schonewille, J.A. Vos; Stroke Center at Hartford (3) L. Abbott, G. Spiegel; University of Montreal Notre Dame Hospital (3) A. Poppe, J. Raymond; Barrow Neurology Clinics at St. Joseph’s Hospital and Med. Ctr. (2), J. Frey, F. Albuquerque; Cleveland Clinic (2) D. Krieger, T. Masaryk; Michigan State University Sparrow Hospital (2), S. Hussain; Sunnybrook Health Sciences Centre (2) R. Swartz, P. Howard; University Hospitals Case Medical Center (2) R. Tarr; Rhode Island Hospitals (1) P. Panagos, R. Haas; Hospital Universitari Germans Trias i Pujol (1) A. Davalos, P. Bermejo; Johns Hopkins University (1) V. Urrutia, M. Radvary; Massachusetts General Hospital (1) L. Schwamm, R. Nogueira; St. Vincent’s Hospital (1) R. Markus, R. Parkinson; University Medical Center at Brackenridge & Seton Medical Center (1) J. Neal Rutledge; William Beaumont Hospital (1) C. Kazmierczak.

NON ENROLLING SITES: Intercoastal Medical Group/Sarasota Memorial Hospital-M. Concha, N. Razack; University of Rochester Medical Center-C. Benesch, B. Jahromi; St. Louis University-R. Edgell, N. Vora; Reading Hospital and Medical Center-R. Chavali; Methodist Research Institute/Clarian Health Partners-J. Scott; Central DuPage Hospital-H. Shownkee; QEII Health Sciences Centre, Dalhousie University-S. Phillips, E. Versnick; Hospital of the
University of Pennsylvania- S. Kasner, R. Hurs; University of Alberta Stroke Program- A. Shuaib, D. Emery; Sutter Medical Facility of Sacramento-B. Varjavand, R. Atkinson; St. John Providence Medical Center-R. Fessler; University of Freiburg- W. Niesen, C. Hader, Ernst Moritz; Arndt University-A. Khaw, S. Langner; University of Basel- P. Lyrer, C. Stippich.


CORPORATE PARTNERS: Genentech, Inc., Codman Neurovascular (a business unit of Codman & Surtleff, Inc.), EKOS Corporation, Concentric Medical Inc. (a wholly owned 5 subsidiary of Stryker Neurovascular), Penumbra, Inc, ev3 Neurovascular (division of Tyco Healthcare Group d/b/a/ Covidien).

NINDS ADMINISTRATION: S. Janis, W. Galpern.
MR CLEAN

Executive committee
Diederik W.J. Dippel1; Aad van der Lugt2; Charles B.L.M. Majoie3; Yvo B.W.E.M. Roos4; Robert J. van Oostenbrugge5; Wim H. van Zwam6; Olvert A. Berkhemer1,3; Puck S.S. Fransen1,2; Debbie Beumer1,5; Lucie A. van den Berg4

Local principal investigators
Wouter J. Schonewille7; Jan Albert Vos8; Charles B.L.M. Majoie3; Yvo B.W.E.M. Roos4; Paul J. Nederkoorn4; Marieke J.H. Wermer9; Marianne A.A. van Walderveen10; Robert J. van Oostenbrugge5; Wim H. van Zwam6; Julie Staals5; Jeannette Hofmeijer11; Jacques A. van Oostayen12; Geert J. Lycklama à Nijeholt13; Jelis Boiten14; Diederik W.J. Dippel1; Patrick A. Brouwer2; Bart J. Emmer2; Sebastiaan F. de Bruijn15; Lukas C. van Dijk16; L. Jaap Kappelle17; Rob H. Lo18; Ewoud J. van Dijk19; Joost de Vries20; Paul L.M. de Kort21; Jan S.P. van den Berg22; Boudewijn A.A.M. van Hasselt23; Leo A.M. Aerden24; René J. Dallinga25; Marieke C. Visser26; Joseph C.J. Bot27; Patrick C. Vroomen28; Omid Eshghi29; Tobien H.C.M.L. Schreuder30; Roel J.J. Heijboer31; Koos Keizer32; Alexander V. Tiellebeek33; Heleen M. den Hertog34; Dick G. Gerrits35; Renske M. van den Berg-Vos36; Giorgos B. Karas37

Imaging assessment committee
Charles B.L.M. Majoie3 (chair); Wim H. van Zwam6; Aan van der Lugt2; Geert J. Lycklama à Nijeholt13; Marianne A.A. van Walderveen10; Joseph C.J. Bot27; Henk A. Marquering38; Ludo F. Beenen9; Marieke E.S. Sprengers5; Sjoerd F.M. Jenniskens39; René van den Berg3; Olvert A. Berkhemer1,3; Albert J. Yoo40

Outcome assessment committee
Yvo B.W.E.M. Roos4 (chair); Peter J. Koudstaal1; Jelis Boiten; Ewoud J. van Dijk19

Adverse event committee
Robert J. van Oostenbrugge5 (chair); Marieke J.H. Wermer9; H. Zwenneke Flach23

Trial statisticians
Ewout W. Steyerberg41; Hester F. Lingsma41

Data monitoring committee
Martin M. Brown42 (Chair); Thomas Liebig43; Theo Stijnen44; Hester F. Lingsma41

Advisory board:
Tommy Andersson45; Heinrich P. Mattle46; Nils Wahlgren47; Peter J. Koudstaal1

Research nurses / local trial coordinators
Esther van der Heijden1; Naziha Ghannouti1; Nadine Fleitour4; Imke Hooijenga4; Annemieke Lindel-Velema5; Corina Puppels7; Wilma Pellikaan7; Kirsten Janssen9; Nicole Aaldering11; Marjan Elfrink11; Joke de Menis14; Annet Geerlings19; Gina van Vemde22; Ans de Ridder17; Pau Greebe17; José de Bont-Stikkelbroeck21; Willy Struijk15; Tiny Simons30; Gert Messchendorp28; Friedus van der Minne28; Hester Bongenaar32; Karin Bodde26.

PhD / Medical students:
Silvan Licher1; Nikki Boodt; Adriaan Ros1; Esmee Venema1; Ilse Slokkers1; Raymie-Jayce Ganpat1; Maxim Mulder1; Nawid Saiedie1; Alis Heshmatollah1; Stefanie Schipperen1; Stefan Vinken1; Tiemen van Boxtel1; Jeroen Koets1; Merel Boers38; Emilie Santos23,38; Jordi Borst3; Ivo...
Jansen; Manon Kappelhof; Marit Lucas; Ralph Geuskens; Renan Sales Barros; Roeland Dobbe; Marloes Csizmadia

List of affiliations
Department of Neurology, Radiology, Public Health, Erasmus MC University Medical Center; Department of Radiology, Neurology, Biomedical Engineering and Physics, Academic Medical Center, Amsterdam; Department of Neurology, Radiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM); Department of Neurology, Radiology, Sint Antonius Hospital, Nieuwegein; Department of Neurology, Radiology, Medical Statistics and Bioinformatics, Leiden University Medical Center; Department of Neurology, Radiology, Rijnstate Hospital, Arnhem; Department of Radiology, MC Haaglanden, the Hague; Department of Neurology, Radiology, HAGA Hospital, the Hague; Department of Neurology, Radiology, University Medical Center Utrecht; Department of Neurology, Neurosurgery, Radboud University Medical Center, Nijmegen; Department of Neurology, Sint Elisabeth Hospital, Tilburg; Department of Neurology, Radiology, Isala Klinieken, Zwolle; Department of Neurology, Radiology, Reinier de Graaf Gasthuis, Delft; Department of Neurology, Radiology, VU Medical Center, Amsterdam; Department of Neurology, Radiology, University Medical Center Groningen, the Netherlands; Department of Neurology, Radiology, Atrium Medical Center, Heerlen; Department of Neurology, Radiology, Catharina Hospital, Eindhoven; Department of Neurology, Radiology, Medical Spectrum Twente, Enschede; Department of Neurology, Radiology, Sint Lucas Andreas Hospital, Amsterdam; all in the Netherlands
Department of Radiology, Texas Stroke Institute, Texas, United States of America; UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, London, United Kingdom; Med. Fakultät, Uniklinik Köln, Germany; Department of Radiology, Neurology, Karolinska University Hospital, Stockholm, Sweden; Department of Neurology, University Hospital of Bern, Switzerland
IMS III - Supplemental Table I: Inclusion and Exclusion Criteria

Clinical Inclusion Criteria

• Age: 18 through 82 years (i.e., candidates must have had their 18th birthday, but not had their 83rd birthday).

• Initiation of IV t-PA within 3 hours of onset of stroke symptoms. Time of onset is defined as the last time when the patient was witnessed to be at baseline (i.e., subjects who have stroke symptoms upon awakening will be considered to have their onset at beginning of sleep).

• An NIHSSS ≥ 10 at the time that IV t-PA is begun or an NIHSSS >7 and <10 with an occlusion seen in M1, ICA or basilar artery on CTA at institutions where baseline CTA imaging is standard of care for acute stroke patients.

• Investigator verification that the subject has received/ is receiving the correct IV t-PA dose for the estimated weight prior to randomization

Clinical Exclusion Criteria

• History of stroke in the past 3 months.

• Previous intra-cranial hemorrhage, neoplasm, subarachnoid hemorrhage, or arteriovenous malformation.

• Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT scan is normal.

• Hypertension at time of treatment; systolic BP > 185 or diastolic > 110 mm Hg; or aggressive measures to lower blood pressure to below these limits are needed.

• Presumed septic embolus, or suspicion of bacterial endocarditis.

• Presumed pericarditis including pericarditis after acute myocardial infarction.

• Suspicion of aortic dissection.

• Recent (within 30 days) surgery or biopsy of parenchymal organ.

• Recent (within 30 days) trauma, with internal injuries or ulcerative wounds.

• Recent (within 90 days) severe head trauma or head trauma with loss of consciousness.

• Any active or recent (within 30 days) hemorrhage.

• Recent (within 30 days) trauma, with internal injuries or ulcerative wounds.

• Recent (within 90 days) severe head trauma or head trauma with loss of consciousness.

• Any active or recent (within 30 days) hemorrhage.

• Individual legally empowered in the state where the consent is obtained) cannot provide
Imaging Exclusion Criteria

- High density lesion consistent with hemorrhage of any degree.
- Significant mass effect with midline shift.
- Large (more than 1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline imaging. An ASPECTS of < 4 can be used as a guideline when evaluating >1/3 region of territory involvement. Sulcal effacement and/or loss of grey-white differentiation alone are not contraindications for treatment.
- CT evidence of intraparenchymal tumor.
- Baseline CTA without evidence of an arterial occlusion (Amendment 5 only). NOTE: The trial did not require baseline CTA imaging, if CTA was routinely performed prior to IV t-PA, information from the CTA was to be used to satisfy this exclusion.

Guidelines for Interpretation of the Inclusion/Exclusion Criteria

The following guidelines apply to the inclusion exclusion and imaging criteria noted above.

- Subjects with no other exclusion criteria that experience unavoidable delay in start of IV t-PA could be included in the trial up to 15 minutes beyond the 3 hour onset of stroke symptoms. This was not considered as a protocol violation.
- The “correction” of baseline glucose or coagulation laboratory values to meet exclusion criteria was not allowed.
- Subjects who have taken Clopidogrel within the last 24 hours from screening for the trial were not excluded.
- Subjects who received low molecular weight heparins (such as Dalteparin, Enoxaparin, Tinzaparin) as DVT prophylaxis or in full dose within the last 24 hours from screening for the trial were excluded.
- Subject who have received GP IIb/IIIa Inhibitors within the within the past 2 weeks from screening for the trial were excluded.
- The preferred baseline imaging modality was CT scan. However, at sites where MR imaging was the standard baseline imaging and the performance of a CT scan will necessitate a delay in treatment a MRI was acceptable with prior approval from the UCCIAC.
- The performance of a CTA was not required or recommended prior to enrollment; however CTA at baseline could be performed at centers where it is standard of care for all acute strokes with prior approval from the UCCIAC.
MR CLEAN - Supplemental Table II: Inclusion and Exclusion Criteria

**Inclusion Criteria**

- Patients aged 18 years or older with acute ischemic stroke and a symptomatic anterior proximal artery occlusion, which can be treated within 6 hours after stroke onset, are eligible for participation in this trial.

- General inclusion criteria are: a clinical diagnosis of acute stroke with a deficit on the NIHSS of at least 2 points, CT or MRI ruling out intracranial hemorrhage, occlusion of distal intracranial carotid artery or middle (M1 or M2) or anterior cerebral artery (A1) demonstrated with CT angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA), the possibility to start treatment within 6 hours of onset, aged 18 years or over and informed consent given in writing.

**Exclusion Criteria**

- We use three sets of exclusion criteria: general exclusion criteria for IAT, a specific exclusion criterion for mechanical treatment and specific exclusion criteria for intra-arterial thrombolysis.

- General exclusion criteria are: arterial blood pressure exceeding 185/110 mmHg, blood glucose less than 2.7 or over 22.2 mmol/L, treatment with IV thrombolysis in a dose exceeding 0.9 mg/kg or 90 mg or treatment with IV thrombolysis despite contraindications, and, finally, cerebral infarction in the distribution of the relevant occluded artery in the previous 6 weeks.

- A specific exclusion criterion for intended mechanical thrombectomy is laboratory evidence of coagulation abnormalities (that is, platelet count <40 × 10^9/L, activated partial Thromboplastin time (APTT) >50 seconds or International normalized ratio (INR) >3.0).

- Specific exclusion criteria for intended intra-arterial thrombolysis are: a history of cerebral hemorrhage, severe head injury (contusion) in the previous 4 weeks and clinical laboratory evidence of coagulation abnormalities, (that is, platelet count <90 × 10^9/L, APTT >50 seconds or INR >1.7), or treatment with oral thrombin or factor X antagonists.

- These hierarchically ordered exclusion criteria make it possible that patients with contraindications for IV or IAT with alteplase but no contraindication for mechanical thrombectomy are included in the study. Also, patients who cannot be treated within the 4.5-hour time window may still be included in the trial. Enrollment was not limited according to the Alberta Stroke Program Early CT Score (ASPECTS) or extension of early signs of infarction at baseline.
Abstract

Background and Purpose: Stroke Management in Stroke III and the Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trials found no difference in outcomes between endovascular treatment and best medical care. The present study aimed to determine the optimal timing for endovascular therapy among patients with severe ischemic stroke.

Methods: This study included 342 patients treated with endovascular therapy within 24 hours of symptom onset in the MR CLEAN trial. The time from symptom onset to groin puncture was divided into three groups: ≤6 hours, 6–12 hours, and >12 hours. The primary outcome was a modified Rankin Scale (mRS) score of 0–2 at 90 days.

Results: Among patients treated within 6 hours, the proportion of patients with an mRS score of ≤2 was significantly higher in the <6-hour group compared to the 6–12-hour group (81.8% vs. 68.9%, p = 0.009). In the 6–12-hour group, the proportion was significantly lower compared to the >12-hour group (74.6% vs. 68.9%, p = 0.001). There was no significant difference between the >12-hour group and the <6-hour group (74.6% vs. 81.8%, p = 0.209).

Conclusions: Endovascular therapy is most effective when performed within 6 hours of symptom onset.