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 Khatr, 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 Carrozella, RN, BA, RT (R); Karla J. Ryckbost, 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.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00359424 (IMS III) and ISRCTN10888758 (MR CLEAN). (Stroke. 2015;46:3416-3422. DOI: 10.1161/STROKEAHA.115.011397.)

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 (heretofore 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 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 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. 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 within 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 repertusion interventions. Those participants with a treatable vascular occlusion received endovascular intervention chosen by the site neurointerventionalist. 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 1 200 000 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.10 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 mRS 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 assignments.
Secondary outcomes at 90 days included the Barthel index (BI) 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). In the MR CLEAN trial, symptomatic intracranial hemorrhage (sICH) was reported by the local investigator and 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 with ICH confirmed on imaging. For the IMS III trial, sICH was defined as an ICH score of 8–9 or with demonstration of major arterial occlusion on vascular imaging ≥2.

**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], 1.15–2.35; and adjusted OR [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 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).
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 before intravenous tPA had improved to 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.²

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.⁵,¹⁴–¹⁶ 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.³
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.
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.

Acknowledgments
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.

Sources of Funding
The Interventional Management of Stroke III (IMS III) trial was funded by National Institutes of Health/National Institute of Neurological Disorders and Stroke grant numbers: University of Cincinnati (U01NS052220) and Medical University of South Carolina (U01NS054630 and U01NS077304). Genentech Inc supplied study drug used for intra-arterial tissue-type plasminogen activator treatment in the Endovascular group. EKOS Corp, Concentric Inc, and Cordis Neurovascular Inc supplied study catheters during Protocol Versions 1 to 3. In the United States, IMS III investigator meeting support was provided in part by Genentech Inc, EKOS Corp, and Concentric Inc. In Europe, IMS III investigator meeting support was provided in part by Boehringer Ingelheim. The Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial was funded by the Dutch Heart Foundation and through unrestricted grants from AngioloCare BV, Covidien/EV3R, MEDAC GmbH/LAMEPRO, and Penumbra Inc.

Disclosures
Interventional Management of Stroke III (IMS III): J.P. Broderick received research monies to Department of Neurology from Genentech for A Study of the Efficacy and Safety of Activase (Alteplase) in Patients With Mild Stroke (PRISMS) trial and travel fee to Australian stroke conference from by Boehringer Ingelheim. Y. Palesch received research monies to her department for her role as a Data and Safety Monitoring Board (DSMB) member for the Biogen and Braintree trials. A. Demchuck received honoraria for CME and unrestricted grant to support the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial from Covidien. S. Yeatts research monies from Genentech for statistical role in the PRISMS trial. P. Khatri’s Department of Neurology received research support from Genentech, Inc for her role as lead principal investigator (PI) of the PRISMS trial, Penumbra, Inc for her role as neurology PI of the Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY) trial, and Biogen, Inc for her role as a DSMB member; royalties from UpToDate, Inc. M. Goyal is a consultant for Covidien for teaching engagements and for design and conduct of the Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) Trial; received partial funding for the ESCAPE trial from Covidien through an unrestricted grant to the institution. M. Mazighi received funding for travel from Covidien, Boehringer Ingelheim, and Bayer. B. Yan received research funding from Codman (Johnson Johnson), speaker’s honorarium from Stryker and from Biosense, and an educational grant from Bayer. R. von Kummer received personal fees from Lundbeck, Penumbra, Covidien, and Synarc. M. Hill received consulting fees from the VenaLabs Group; grant support from Covidien and Hoffmann-La Roche Canada; lecture fees from Hoffmann-La Roche Canada, Servier Canada, and Bristol-Myers Squibb Canada; stock ownership in Calgary Scientific; financial support from Heart and Stroke Foundation of Alberta, Northwest Territories, and Nunavut and Alberta Innovates-Health Solutions. E. Jauch received research monies to the Division of Emergency Medicine from Penumbra, Covidien, and Stryker for POSITIVE Stroke Clinical Trial, and from Genentech for the PRISMS trial. T. Jovin is a consultant and has stock ownership from Silk Road Medical. C. Anderson received speaker fees from Covidien. S. Engelter received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim, and Pfizer, is a scientific advisory board member for Bayer, Boehringer Ingelheim, BMS/Pfizer, and Covidien and on the editorial board of Stroke; received Science Funds of the University Hospital Basel, the Swiss Heart Foundation, and Swiss National Science Foundation. T. Tomsick received research monies to the Department of Radiology from Genentech for the PRISMS trial. Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands (MR CLEAN): C.B.L.M. Majoie’s institution received fees for his role as a consultant for Stryker (speakers bureau/lecture fees). The other authors report no conflicts.

References
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


*Stroke*. 2015;46:3416-3422; originally published online October 20, 2015; doi: 10.1161/STROKEAHA.115.011397

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/12/3416

An erratum has been published regarding this article. Please see the attached page for:
/content/47/1/e21.full.pdf

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/

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.
SUPPLEMENTAL MATERIAL

Pooled Analyses of IMS III and MR CLEAN
SUPPLEMENTAL MATERIALS
TABLE OF CONTENTS
  1) Acknowledgements-List of Investigators and Administrative Staffs..................pp. 1-6
  2) Supplemental Table I: Inclusion and Exclusion Criteria IMS III..........................pp.7-8
  4) Supplemental Table II: Inclusion and Exclusion Criteria MR CLEAN................. p. 9
LIST OF INVESTIGATORS AND ADMINISTRATIVE STAFFS

ENROLLING CLINICAL CENTERS: University of Cincinnati College of Medicine (72 subjects) J. Broderick, T. Tomisk; 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. Demaerschalk, 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. Tayal, A. Ku; Dresden University of Technology (17), U. Bodechel, 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, JA. 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. Radvany; 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. Showknee; 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. Dippel; Aad van der Lugt; Charles B.L.M. Majoie; Yvo B.W.E.M. Roos; Robert J. van Oostenbrugge; Wim H. van Zwam; Olvert A. Berkhemer; Puck S.S. Fransen; Debbie Beumer; Lucie A. van den Berg

Local principal investigators
Wouter J. Schonewille; Jan Albert Vos; Charles B.L.M. Majoie; Yvo B.W.E.M. Roos; Paul J. Nederkoorn; Marieke J.H. Wermer; Marianne A.A. van Walderveen; Robert J. van Oostenbrugge; Wim H. van Zwam; Julie Staals; Jeanette Hofmeijer; Jacques A. van Oostayen; Geert J. Lycklama à Nijeholt; Jelis Boiten; Diederik W.J. Dippel; Patrick A. Brouwer; Bart J. Emmer; Sebastiaan F. de Bruijn; Lucas C. van Dijk; L. Jaap Kappelle; Rob H. Lo; Ewoud J. van Dijk; Joost de Vries; Paul L.M. de Kort; Jan S.P. van den Berg; Boudewijn A.A.M. van Hasselt; Leo A.M. Aerden; René J. Dallinga; Marieke C. Visser; Joseph C.J. Bot; Patrick C. Vroomen; Omid Eshghi; Tobien H.C.M.L. Schreuder; Roel J.J. Heijboer; Koos Keizer; Alexander V. Tiellieb; Heleen M. den Hertog; Dick G. Gerrits; Renske M. van den Berg-Vos; Giorgos B. Karas

Imaging assessment committee
Charles B.L.M. Majoie (chair); Wim H. van Zwam; Aad van der Lugt; Geert J. Lycklama à Nijeholt; Marianne A.A. van Walderveen; Joseph C.J. Bot; Henk A. Marquering; Ludo F. Beenen; Marieke E.S. Sprengers; Sjoerd F.M. Jenniskens; René van den Berg; Olvert A. Berkhemer; Albert J. Yoo

Outcome assessment committee
Yvo B.W.E.M. Roos (chair); Peter J. Koudstaal; Jelis Boiten; Ewoud J. van Dijk

Adverse event committee
Robert J. van Oostenbrugge (chair); Marieke J.H. Wermer; H. Zwenneke Flach

Trial statisticians
Ewout W. Steyerberg; Hester F. Lingsma

Data monitoring committee
Martin M. Brown (Chair); Thomas Liebig; Theo Stijnen; Hester F. Lingsma

Advisory board:
Tommy Andersson; Heinrich P. Mattle; Nils Wahlgren; Peter J. Koudstaal

Research nurses / local trial coordinators
Esther van der Heijden; Nazihza Ghannouti; Nadine Fleitour; Imke Hooijenga; Annemieke Lindel-Velema; Corina Puppels; Wilma Pellikkaan; Kirsten Janssen; Nicole Aaldering; Marjan Elfrink; Joke de Mens; Annet Geerlings; Gina van Vemde; Ans de Ridder; Paut Greebe; José de Bont-Stikkelbroeck; Willy Struijk; Tiny Simons; Gert Messchendorp; Friedus van der Minne; Hester Bongenaar; Karin Bodde

PhD / Medical students:
Silvan Licher; Nikki Boodt; Adriaan Ros; Esmee Venema; Ilse Slokkers; Raymie-Jayce Ganpat; Maxim Mulder; Nawid Saiedie; Alis Heshmatollah; Stefanie Schipperen; Stefan Vinken; Tiemen van Boxtel; Jeroen Koets; Merel Boers; Emilie Santos; Jordi Borst
List of affiliations
Department of Neurology¹, Radiology², Public Health⁴¹, Erasmus MC University Medical Center; Department of Radiology³, Neurology⁴, Biomedical Engineering and Physics³⁸, Academic Medical Center, Amsterdam; Department of Neurology⁶, Radiology⁶, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM); Department of Neurology⁷, Radiology⁸, Sint Antonius Hospital, Nieuwegein; Department of Neurology⁹, Radiology¹⁰, Medical Statistics and Bioinformatics⁴⁴, Leiden University Medical Center; Department of Neurology¹¹, Radiology¹², Rijnstate Hospital, Arnhem; Department of Radiology¹³, Neurology¹⁴, MC Haaglanden, the Hague; Department of Neurology¹⁵, Radiology¹⁶, HAGA Hospital, the Hague; Department of Neurology¹⁷, Radiology¹⁸, University Medical Center Utrecht; Department of Neurology¹⁹, Neurosurgery²⁰, Radiology²⁰, Radboud University Medical Center, Nijmegen; Department of Neurology²¹, Sint Elisabeth Hospital, Tilburg; Department of Neurology²², Radiology²³, Isala Klinieken, Zwolle; Department of Neurology²⁴, Radiology²⁵, Reinier de Graaf Gasthuis, Delft; Department of Neurology²⁶, Radiology²⁷, VU Medical Center, Amsterdam; Department of Neurology²⁸, Radiology²⁹, University Medical Center Groningen, the Netherlands; Department of Neurology³⁰, Radiology³¹, Atrium Medical Center, Heerlen; Department of Neurology³², Radiology³³, Catharina Hospital, Eindhoven; Department of Neurology³⁴, Radiology³⁵, Medical Spectrum Twente, Enschede; Department of Neurology³⁶, Radiology³⁷, Sint Lucas Andreas Hospital, Amsterdam; all in the Netherlands
Department of Radiology³⁸, Texas Stroke Institute, Texas, United States of America; UCL Institute of Neurology⁴², National Hospital for Neurology and Neurosurgery, London, United Kingdom; Med. Fakultät⁴³, Uniklinik Köln, Germany; Department of Radiology⁴⁵, Neurology⁴⁶, Karolinska University Hospital, Stockholm, Sweden; Department of Neurology⁴⁷, 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.

• Susicion 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
consent, randomization and entry into the study could not proceed.

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.

• 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

International Management of Stroke III とオランダのMR CLEAN 試験の統合解析

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 1 ; Olvert A. Berkhemer, MD 3 ; Yuko Y. Palesch, PhD 2 , et al.

1 Departments of Neurology and Rehabilitation Medicine and Radiology, University of Cincinnati Neuroscience Institute, University of Cincinnati Academic Health Center, Cincinnati, OH; 2 Department of Public Health Sciences, Medical University of South Carolina, Charleston; and 3 Department of Radiology, Academic Medical Center, Amsterdam, the Netherlands.

Background and Purpose: We performed a pooled analysis of the Interventional Management of Stroke III (IMS III) and Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke (MR CLEAN) trials to compare the outcomes of treatment in patients with severe ischemic stroke. IMS III was a randomized, double-blind trial of aspirin and placebo in patients with severe stroke. MR CLEAN was a randomized, double-blind trial of endovascular treatment versus medical therapy in patients with acute ischemic stroke of less than 6 hours' duration.

Methods: We used a common analysis platform to compare patients treated with intravenous thrombolysis (IVT) who had a National Institutes of Health Stroke Scale (NIHSS) score of 20 or more at baseline and a Rankin score of 5 or worse at 90 days. The primary end point was the modified Rankin scale (mRS) score at 90 days.

Results: A total of 342 patients (194 in IMS III and 148 in MR CLEAN) were included in the analysis. The median NIHSS score at baseline was 27 (interquartile range, 18-34). The rate of favorable outcomes (mRS score of 0-2) at 90 days was 30% in the IMS III group and 37% in the MR CLEAN group.

Conclusions: The 90-day functional outcomes were similar in the two treatment groups. The results of this pooled analysis suggest that endovascular treatment is a viable and effective option for patients with severe ischemic stroke.

Stroke 2015; 46: 3416-3422. DOI: 10.1161/STROKEAHA.115.011397.

Table 1: Comparison of Functional Outcomes at 90 Days

<table>
<thead>
<tr>
<th>Treatment</th>
<th>mRS Score Distribution (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>IMS III</td>
<td>36%</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>24%</td>
</tr>
</tbody>
</table>

*In the IMS III trial, the NIHSS score was used to determine eligibility. In the MR CLEAN trial, the mRS score was used to determine eligibility.

Figure 1: Bar chart showing the distribution of functional outcomes at 90 days.