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Endovascular Therapy is Effective and Safe for Patients with Severe Ischemic Stroke: Pooled Analysis of IMS III and MR CLEAN Data

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

IMS III: the Departments of Neurology and Rehabilitation Medicine and Radiology, University of Cincinnati Neuroscience Institute, University of Cincinnati Academic Health Center, Cincinnati (J.P.B., P.K., J.S., J.C., T.A.T.); the Department of Public Health Sciences (Y.Y.P., L.D.F.) and the Division of Emergency Medicine (E.C.J.), Medical University of South Carolina, Charleston; Calgary Stroke Program, Seaman Family MR Research Centre, Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada (A.M.D., M.D.H., M.G., K.J.R.); the Stroke Institute, University of Pittsburgh Medical Center, Pittsburgh (T.G.J.); Melbourne Brain Centre, Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia (B.Y.); the Department of Neuroradiology, Dresden University Stroke Center, University Hospital, Dresden, Germany (R.v.K.); the Neurovascular Unit, Department of Neurology, Hospital Universitari Vall d'Hebron, Barcelona, Spain (C.A.M.); the Department of Neurology, University Medical Center Utrecht and the Rudolph Magnus Institute of Neurosciences, Utrecht, and the St. Antonius Hospital, Nieuwegein — both in the Netherlands (W.J.S.); Department of Neurology and Stroke Center, Lariboisière Hospital, Paris (M.M.); The George Institute for Global Health, University of Sydney and Royal Prince Alfred Hospital, Sydney, Australia (CSA); the Department of Radiology (O.A.B., C.B.M.) and Neurology (Y.B.R.), Academic Medical Center, Amsterdam, the Netherlands; the Department of Neurology (D.W.D., B.R.), Radiology (A.v.L.), and Public Health (H.F.L.), Erasmus MC University Medical Center, Rotterdam, the Netherlands; the Department of Radiology (W.H.Z.) and Neurology (R.J.O), Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, the Netherlands.

Corresponding Author: Joseph P. Broderick, MD, University of Cincinnati Neuroscience Institute, Department of Neurology, 260 Stetson St, Suite 2300, PO Box 670525, Cincinnati, OH, 45267-0525. Telephone number: (513) 919-5404. Fax number (513) 558-4887. joseph.broderick@uc.edu.

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Abstract

Background and Purpose—We assessed the effect of endovascular treatment in acute ischemic stroke patients with severe neurological deficit (NIHSS ≥ 20) following a pre-specified analysis plan.

Methods—The pooled analysis of the IMS III and MR CLEAN trial included participants with an NIHSS ≥ 20 prior to intravenous (IV) t-PA treatment (IMS III) or randomization (MR CLEAN) who were treated with IV t-PA ≤ 3 hours of stroke onset. Our hypothesis was that participants with severe stroke randomized to endovascular therapy following IV t-PA would have improved 90-day outcome (distribution of modified Rankin scale [mRS] scores), as compared to those who received IV t-PA alone.

Results—Among 342 participants in the pooled analysis (194 from IMS III, 148 from MR CLEAN), an ordinal logistic regression model showed that the endovascular group had superior 90-day outcome compared to the IV t-PA group (adjusted odds ratio [aOR] 1.78; 95% confidence interval [CI] 1.20-2.66). In the logistic regression model of the dichotomous outcome (mRS 0-2, or ‘functional independence’), the endovascular group had superior outcomes (aOR 1.97; 95% CI 1.09-3.56). Functional independence (mRS ≤ 2) at 90 days was 25% in the endovascular group as compared to 14% in the IV t-PA group.

Conclusions—Endovascular therapy following IV t-PA within 3 hours of symptom onset improves functional outcome at 90 days after severe ischemic stroke.

Keywords

acute stroke; endovascular; t-PA

Introduction

The main purpose of the Interventional Management of Stroke phase III (IMS III) Trial was to evaluate the “approach” of intravenous (IV) tissue plasminogen activator (t-PA) followed by protocol-approved endovascular treatment (heretofore referred to as the endovascular group) relative to IV t-PA 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 (≥ 20) National Institutes of Health stroke scale (NIHSS) scores and those with major arterial occlusions on pre-treatment 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 two trials after the MR CLEAN results had been published in December, 2014.³ Based on pilot observations from a pre-IMS registry, IMS I and II, IMS III investigators pre-specified 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) since most such patients have occlusion of a major intracranial artery and the greatest volume of ischemic brain at risk.⁴⁻⁶ Finally, while the 90-day modified Rankin Scale (mRS) was the

primary outcome of IMS III, the trial was designed to follow subjects out to 12 months, and the subgroup of subjects with an NIHSS ≥ 20 randomized to endovascular therapy, had better functional outcomes and quality of life over a year as compared to those treated with IV t-PA alone.⁷ In MR CLEAN, a subgroup analysis of tertiles of NIHSS score was pre-specified, because effect modification by initial stroke severity was expected.⁸ Herein, we present pooled analyses of the trials examining the more severe AIS subject subgroup who were first treated with IV t-PA 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} The trials are registered in [Clinicaltrials.gov](https://clinicaltrials.gov) (IMS III - registration number - NCT00359424) and Current Controlled Trials (MR CLEAN - registration number: ISRCTN10888758 / Netherlands Trial Register: NTR1804). Informed consent was obtained from the patient or a legal representative prior to enrollment for both trials.

The primary hypothesis to be addressed by this pooled analysis was that endovascular therapy following IV t-PA within 6 hours of stroke onset, as compared to treatment with IV t-PA 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 two trials are provided in Table 1, and detailed inclusion and exclusion criteria for the two trials are shown in the Appendix - Supplemental Tables I and II. However, the current pooled analysis included all subjects of both trials treated with IV t-PA within 3 hours of onset with an NIHSS ≥ 20 . For IMS III, this criterion included patients with an NIHSS ≥ 20 just prior to treatment with t-PA; for MR CLEAN, this included patients with an NIHSS ≥ 20 just prior to randomization and which occurred after t-PA therapy.

Treatments

All participants in MR CLEAN treated with IV t-PA received the standard dose (0.9 mg per kilogram), with 10% as bolus and the remainder infused over a 1-hour period (maximum dose, 90 mg). In IMS III, the 176 participants in the first four protocol versions of IMS III Trial had the IV t-PA infusion stopped after 40 minutes of infusion. In last protocol version of IMS III, the remaining 18 participants were treated with the standard dose of IV t-PA over 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 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 up to 22 mg of t-PA through the EKOS Micro-Infusion Catheter [EKOS], or a standard microcatheter). However, only a few subjects in IMS III near the completion of the trial were treated with a stent retriever. In IMS III, the angiographic procedure had to begin within 5 hours of stroke onset and be completed within 7 hours of stroke onset.

For MR CLEAN, the use of alteplase or urokinase for intraarterial thrombolysis was allowed with a maximum dose of 90 mg of IV t-PA or 1,200,000 IU of urokinase. The dose was restricted to 30 mg of t-PA or 400,000 IU of urokinase if IV t-PA was given. Mechanical treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent.³ However, a retrievable stent was used in almost all subjects.

Outcome measures

The primary outcome measure was the mRS at 90 days. The mRS is a measure of disability, which ranges from 0 (no symptoms) to 5 (severe disability and bedridden) and 6 (death).¹⁰ The mRS was determined by a study investigator who was mRS-certified and blinded to the treatment assignment. For IMS III, 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 MR CLEAN, the mRS 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 by vascular neurologists who were blinded for the treatment-group assignments.

Secondary outcomes at 90 days included the Barthel Index (BI)¹¹ and the EQ-5D-3L (formerly known as EuroQol) health-related quality-of-life (HRQoL) measure, which were obtained either from the subject or a proxy. The BI is an ordinal scale for measuring 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, anxiety/depression).¹² In the MR CLEAN trial, symptomatic intracranial hemorrhage (sICH) was reported by the local investigator and defined as neurologic deterioration (4 points increase in NIHSS from baseline) with ICH confirmed on imaging. For IMS III, sICH was defined as an ICH temporally related to a decline in neurological status as well as new or worsening neurologic symptoms *in the judgment of the clinical investigator* and which may warrant medical intervention (4 points increase in NIHSS from baseline was used as a guide to investigators).

Statistical Analyses

The primary analysis of the 90-day (mRS) used an ordinal regression model with pre-specified covariates (NIHSS, age, previous stroke, diabetes and atrial fibrillation) and study. Secondary analysis of dichotomized mRS (0-2 vs 3-6) used logistic regression as above. Because MR CLEAN defined NIHSS at time of randomization (often several hours after start of IV t-PA), we also performed an exploratory pooled analysis of mRS outcomes using those subjects in IMS III who had an NIHSS ≥ 20 at 40 minutes after commencement of IV t-PA to better approximate the MR CLEAN study population. For the secondary endpoint of

the Barthel Index, we compared the proportion of participants with a BI score of 95-100 using a logistic regression model with covariates as above (IMS III pre-specified 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 two 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 symptomatic intracranial hemorrhage in the two 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 two trials and pooled cohort. The IMS III cohort was older with a greater proportion of females, prior stroke, diabetes mellitus, and atrial fibrillation, and a shorter time from symptom onset to randomization.

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

BI scores were available in 266/342 (78%) of the subjects. Logistic regression model of dichotomous BI of 95-100 was in favor of the endovascular group (OR 1.64, 95% CI 1.00-2.68; aOR 1.80, 95% CI 1.07-3.03). For EQ-5D-3L, available in 330/342 (96%) subjects, linear regression according to MR CLEAN statistical analysis plan showed an unadjusted regression coefficient of 0.09 (95% CI 0.01 to 0.18; $P=0.023$) and an adjusted regression coefficient of 0.10 (95% CI 0.02 to 0.18) ($P=0.012$). The thrombolysis in cerebral infarction (TICI) 2b3 reperfusion score for the IMS III cohort was 42/109 (39%), for MR CLEAN was 31/53 (58%) and for the pooled cohort was 73/162 (45%). The proportion of sICH in the endovascular group ($N=16$; 8.4%) was not significantly different from that in the IV t-PA only group ($N=12$; 8.0%), adjusting for study.

In the exploratory pooled analysis of those IMS III participants with an NIHSS ≥ 20 at 40 minutes after the start of t-PA, there were 39 endovascular participants and 9 IV t-PA participants missing the 40 min NIHSS out of 656 subjects. In addition, 68 participants who had an NIHSS ≥ 20 prior to IV t-PA had improved to an NIHSS <20 at 40 minutes; 16 subjects who had an NIHSS <20 prior to IV t-PA had worsened to an NIHSS ≥ 20 at 40 minutes. Figure 2 shows the change from pre-treatment to 40 minute NIHSS. Thus, 142 IMS III participants with an NIHSS ≥ 20 at 40 minutes after the start of IV t-PA were available for the exploratory pooled analysis. In the ordinal logistic regression model, the endovascular group once again had superior outcomes as compared to the IV t-PA group

(OR 1.75, 95%CI 1.16-2.66; 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. aOR 2.70, 95%CI 1.34-5.43). Since the study-by-treatment interaction term was not significant in the unadjusted or adjusted models of mRS 0-2, 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 two trials, this pooled analysis of subjects with severe acute ischemic stroke (NIHSS ≥ 20) demonstrates the benefit of endovascular therapy after IV t-PA as compared to IV t-PA alone with both ordinal and dichotomous analyses of the mRS. Endovascular therapy after IV t-PA improved outcome to the extent that about 1 in 4 subjects are functionally independent at 3 months, as compared to IV t-PA alone where only about 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 CT angiography whereas no benefit was seen in IMS III for subjects with moderately severe stroke. Advances in endovascular technology with better reperfusion rates (TICI 2b-3 in 58% in MR CLEAN vs 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 two trials is also explained by a substantial but unknown proportion of subjects in IMS III who didn't have a documented large artery occlusion, since only 47% of IMS III participants had a pre-treatment CTA.²

Previous studies have demonstrated that subjects with an NIHSS ≥ 20 almost always have a large artery occlusion by vascular imaging, even after IV t-PA.^{9,14-16} Of 89 IMS III participants with an NIHSS ≥ 20 and CTA prior to treatment with IV t-PA, only one had no documented major arterial occlusion on CTA and this person had an M2 occlusion on subsequent intra-arterial angiography. Of 217 IMS III participants with an NIHSS < 20 and CTA prior to treatment with IV t-PA, 23 had no major documented occlusion, and of these, one had an M2 and one had an M3 occlusion at intra-arterial angiography. The importance of documentation of a major arterial occlusion prior to enrollment in an endovascular trial is also reflected in a post-hoc analysis of IMS III which demonstrated benefit for endovascular therapy in participants with an intracranial occlusion by baseline CTA and which included all levels of the NIHSS.²

Improvement in the NIHSS between baseline and 40 minutes after t-PA infusion in IMS III demonstrates the early effect of IV t-PA 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 like MR CLEAN, which randomized patients with a substantial delay after start of IV t-PA, may exclude patients who are most likely to reperfuse early with t-PA and include patients with poorer

collateral flow, more resistance to reperfusion, and larger ischemic cores.^{17,18} The remaining patients with no improvement and persistent occlusions will be a group with a lower likelihood of good outcomes since the time to reperfusion with endovascular therapy will be longer. The rate of mRS of 0-1 at 3 months for patients with an NIHSS ≥ 20 in IMS III was 10.6% vs. 4.8% in MR CLEAN, despite superior technology and reperfusion rates in MR CLEAN. These data highlight the potentially large differences in trial population that may result from a small change in definitions (time to start of IV t-PA vs. time to randomization several hours later). Future trials that plan to compare endovascular therapy alone without prior IV t-PA to endovascular therapy after IV t-PA, as has been done in trials of acute myocardial infarction, will have to account for the benefit of IV t-PA, particularly when it is started very rapidly.

Recent endovascular trials^{3,19-22} 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. While 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,^{23,24} the time to intervene may be short for many patients with large areas of severely ischemic brain.²⁵ Imaging selection is one method to identify those stroke patients who are most likely to benefit from endovascular therapy, particularly in time windows beyond 6 hours from onset.²⁶ Another way to improve outcomes in stroke patients is to optimize initial triage of stroke patients 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.²⁶ 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 two 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 are remarkably consistent regarding 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 IV t-PA/endovascular versus IV t-PA alone.²⁷ 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Distribution of 90-Day Outcomes for IMS III, MR CLEAN, and Pooled Cohorts

Figure 2.
Distribution of NIHSS Change from Pretreatment NIHSS to 40-minutes NIHSS in IMS III
(positive change indicates increase in NIHSS score / decline in clinical status)

Table 1**Key Differences Between IMS III and MR CLEAN Trials**

	IMS III	MR CLEAN
Study time period	2006-2012	2010-2014
Countries of study enrollment	U.S., Canada, Australia, Germany, Spain, France, Netherlands	The Netherlands
Time window from stroke onset to treatment	3 hours to start of IV t-PA	6 hours to start of endovascular therapy or standard therapy (89% treated with IV t-PA out to 4 ½ hours)
Use of vascular imaging prior to enrollment	Encouraged and data collected, not required	Required
Demonstration of large intracranial arterial occlusion on vascular imaging	Presence of major arterial occlusion required only if NIHSS 8-9	Required demonstration of major arterial occlusion on vascular imaging
NIHSS eligibility	10, or 8-9 with demonstration of major arterial occlusion on vascular imaging	2
Decision process for randomization	Decision made by treating physician investigator within 40 minutes of IV t-PA initiation	Pragmatic design in which treating physician(s) randomized to insure endovascular treatment within 6 hours from stroke onset
Age (years)	18-82	18 years, no upper age limit
Dose of IV t-PA in endovascular arm (mg/kg)	0.9 mg/kg with 10% bolus, infusion stopped at 40 minutes. Last protocol modification used entire infusion over 60 minutes	0.9 mg/kg over 1 hour, 10% as a bolus
Endovascular treatment	<10 total stent retrievers, earlier endovascular technology and intra-arterial t-PA	82% stent retrievers, intra-arterial thrombolytic allowed.

Table 2

Baseline Variables in the IMS III, MR CLEAN, and Pooled Cohorts

	IMS III n=194		MR CLEAN n=148		Pooled n=342	
	Endovascular N=127	Control N=67	Endovascular N=64	Control N=84	Endovascular N=191	Control N=151
Age (med, IQR)	72 (60-77)	73 (63-78)	67 (52-79)	66 (60-76)	71 (59-77)	69 (60-77)
Male sex (n, %)	66 (52%)	33 (49%)	37 (58%)	56 (67%)	103 (54%)	89 (59%)
NIHSS ¹ (med, IQR)	23 (21-25)	22 (21-45)	22 (21-25)	23 (21-25)	23 (21-25)	23 (21-25)
ASPECTS ² Score (med, IQR)	7 (5-9)	8 (5-10)	8 (7-9)	9 (6-10)	8 (6-9)	9 (6-10)
Previous stroke (n, %)	17 (13%)	13 (19%)	4 (6%)	6 (7%)	21 (11%)	19 (13%)
Diabetes Mellitus (n, %)	30 (24%)	16 (24%)	11 (17%)	11 (13%)	41 (21%)	27 (18%)
Atrial fibrillation (n, %)	59 (46%)	25 (37%)	18 (28%)	17 (20%)	77 (40%)	42 (28%)
Time from onset to randomization, min (med, IQR)	137 (117-172)	132 (113-165)	197 (166-241)	186 (138-247)	153 (125-192)	153 (123-205)
Time from onset to EVT ³ , min (med, IQR)	255 (210-290)		255 (215-304)		255 (213-299)	
Time from onset to IV t-PA, min (med, IQR)	115 (96-141)	115 (92-139)	75 (61-105)	75 (64-98)	105 (77-130)	90 (71-122)

¹ 1 IMS III Endovascular subject missing² Alberta Stroke Program Early CT score (ASPECTS)¹³; 1 MR CLEAN Control subject missing, 1 IMS III Endovascular subject missing³ EVT – endovascular therapy; 7 MR CLEAN Endovascular subjects missing, 20 IMS III Endovascular subjects missing