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

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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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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 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]. 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 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 ≤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.[3] 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.

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	United States, Canada, Australia, Germany, Spain, France, Netherlands	The Netherlands
Time window from stroke onset to treatment	≤3 h to the start of IV tPA	≤6 h to the start of endovascular therapy or standard therapy (89% treated with IV tPA out to 4.5 h)
Use of vascular imaging before 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 score is 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 min of IV tPA initiation	Pragmatic design in which treating physician(s) randomized to insure endovascular treatment within 6 h from stroke onset
Age, y	18–82	18 y, no upper age limit
Dose of IV tPA in endovascular arm, mg/kg	0.9 mg/kg with 10% bolus, infusion stopped at 40 min; last protocol modification used entire infusion for 60 min	0.9 mg/kg for 1 h, 10% as a bolus
Endovascular treatment	<10 total stent retrievers, earlier endovascular technology and intra-arterial tPA	82% stent retrievers, intra-arterial thrombolytic allowed

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.

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 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).[12] 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 2b3 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 2. Baseline Variables in the IMS III, MR CLEAN, and Pooled Cohorts

	IMS III, n=194		MR CLEAN, n=148		Pooled Cohort, n=342	
	Endovascular, n=127	Control, n=67	Endovascular, n=64	Control, n=84	Endovascular, n=191	Control, n=151
Age (median, 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 score (median, IQR)*	23 (21–25)	22 (21–45)	22 (21–25)	23 (21–25)	23 (21–25)	23 (21–25)
ASPECTS[13] score (median, 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 (median, IQR)	137 (117–172)	132 (113–165)	197 (166–241)	186 (138–247)	153 (125–192)	153 (123–205)
Time from onset to EVT, min (median, IQR)‡	255 (210–290)		255 (215–304)		255 (213–299)	
Time from onset to IV tPA, min (median, IQR)	115 (96–141)	115 (92–139)	75 (61–105)	75 (64–98)	105 (77–130)	90 (71–122)

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.

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.[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.[9,14–16] 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.[2]
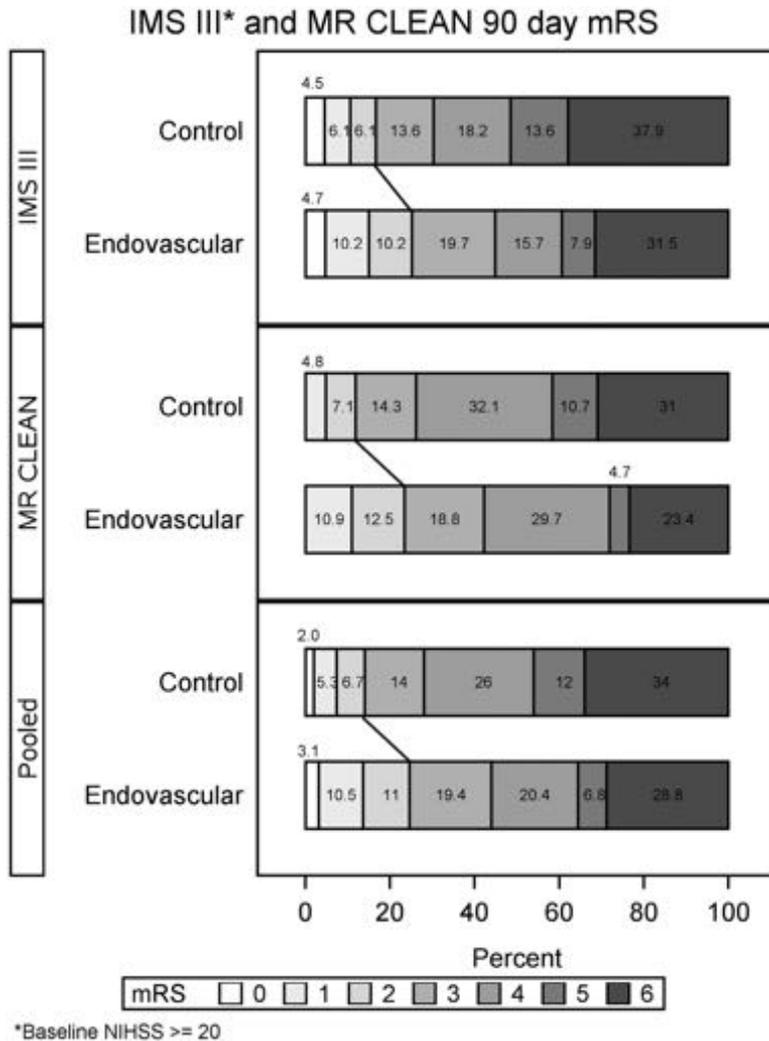
IMS III* and MR CLEAN 90 day mRS

Figure 1. Distribution of 90-day outcomes for Interventional Management of Stroke III (IMS III), Multicenter 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.

*Baseline NIHSS >= 20

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.[17,18] 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[3,19–22] 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,[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 patients with stroke 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 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.[26] This will be a major task for stroke systems of care over the coming years.
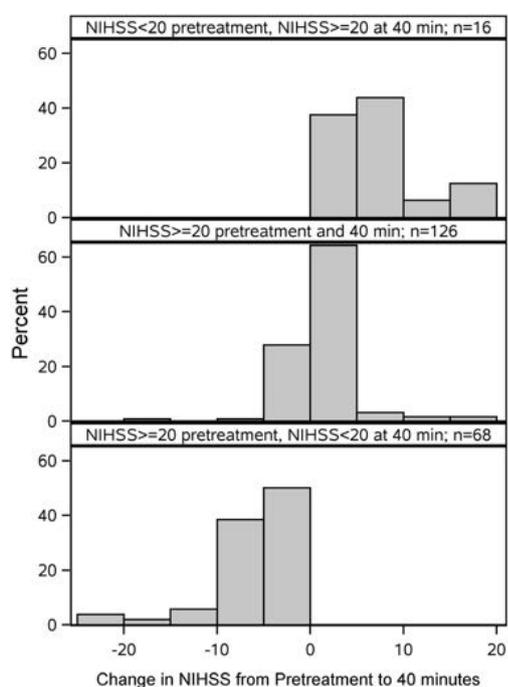
Figure 2. Distribution of National Institutes of Health Stroke Scale (NIHSS) score change from pretreatment NIHSS to 40-minute NIHSS in Interventional Management of Stroke III (IMS III; positive change indicates increase in NIHSS score/decline in clinical status).

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.[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.

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Disclosures

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