Twelve-Month Clinical and Quality-of-Life Outcomes in the Interventional Management of Stroke III Trial

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Background and Purpose—Randomized trials have indicated a benefit for endovascular therapy in appropriately selected stroke patients at 3 months, but data regarding outcomes at 12 months are currently lacking.

Methods—We compared functional and quality-of-life outcomes at 12 months overall and by stroke severity in stroke patients treated with intravenous tissue-type plasminogen activator followed by endovascular treatment as compared with intravenous tissue-type plasminogen activator alone in the Interventional Management of Stroke III Trial. The key outcome measures were a modified Rankin Scale score ≤2 (functional independence) and the Euro-QoL EQ-5D, a health-related quality-of-life measure.

Results—656 subjects with moderate-to-severe stroke (National Institutes of Health Stroke Scale ≥6) were enrolled at 58 centers in the United States (41 sites), Canada (7), Australia (4), and Europe (6). There was an interaction between treatment group and stroke severity in the repeated measures analysis of modified Rankin Scale ≤2 outcome (P=0.039). In the 204 participants with severe stroke (National Institutes of Health Stroke Scale ≥20), a greater proportion of the endovascular group had a modified Rankin Scale ≤2 (32.5%) at 12 months as compared with the intravenous tissue-type plasminogen activator group (18.6%, P=0.037); no difference was seen for the 452 participants with moderately severe strokes (55.6% versus 57.7%). In participants with severe stroke, the endovascular group had 35.2 (95% confidence interval: 2.1, 73.3) more quality-adjusted-days over 12 months as compared with intravenous tissue-type plasminogen activator alone.

Conclusions—Endovascular therapy improves functional outcome and health-related quality-of-life at 12 months after severe ischemic stroke.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00359424. (Stroke. 2015;46:1321-1327. DOI: 10.1161/STROKEAHA.115.009180.)

Key Words: acute stroke ■ endovascular procedures ■ randomized trial ■ tPA

The main purpose of the Interventional Management of Stroke Phase III (IMS III) Trial1 was to evaluate the approach of intravenous tissue-type plasminogen activator (tPA) 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. The trial was terminated for futility when 656 participants had been enrolled; details of the primary outcome have been published.1 In the predefined severity subgroups, the distribution of functional outcomes at 3 months neared statistical significance in participants with severe stroke, in favor of the endovascular group, but there was no difference in functional outcomes for participants with moderately severe stroke.

The IMS III trial was also designed to examine outcomes over 12 months of follow-up as a secondary objective. We present 12-month functional and health-related quality-of-life outcomes for participants overall and by stroke severity.

Methods

Trial Design

The IMS III Trial was a Phase III, randomized, parallel-arm, open-label clinical trial with blinded outcome evaluation in which intravenous tPA was started within 3 hours of symptom onset in both treatment groups. Detailed methodology for the IMS III Trial, the 3-month outcomes, and the study protocol have been published.1–3 The trial was registered in Clinicaltrials.gov (registration number: NCT00359424).

The design, analysis, and data collection for the IMS III trial, as well as the writing of the article, were performed by members of the Executive Committee and Site Investigators (Materials in the online-only Data Supplement) who vouch for the accuracy and completeness of the presented data and for the fidelity of this report to the study protocol.

Participants

A maximum of 900 participants with moderate-to-severe ischemic stroke between ages 18 and 82 were to be randomized from 58 centers in North America, Australia, and Europe. Moderate-to-severe ischemic stroke was initially defined as National Institutes of Health Stroke Scale (NIHSS) score ≥20; on approval of Amendment 3, the protocol allowed enrollment of patients with NIHSS of 8–9 if they had computed tomography angiography (CTA) evidence of an occlusion of the first segment of the middle cerebral artery (M1), internal carotid artery, or basilar artery at institutions where baseline CTA imaging is standard of care for acute stroke patients. The protocol required intravenous tPA infusion initiation within 3 hours of symptom onset.

Informed consent was obtained from the patient or a legal representative before enrollment. Detailed inclusion and exclusion criteria are shown in Table I in the online-only Data Supplement.

Treatments

All participants began receiving a standard dose of intravenous tPA (0.9 mg per kilogram), with 10% as bolus and the remainder infused over a 1-hour period (maximum dose, 90 mg). Throughout the trial, randomization was required within 40 minutes of initiation of the infusion. The participants randomized to intravenous tPA alone received the remainder of the standard dose. Participants randomized to the endovascular group before the fifth protocol version had intravenous tPA discontinued at 40 minutes; beginning with the fifth protocol version, participants received the remainder of the standard intravenous tPA dose over 1 hour.1 The endovascular group underwent angiography as soon as possible, either at the hospital initiating treatment or after transfer to another participating hospital. Participants who had no 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 (ie, thrombectomy with the Merci Retriever [Concentric Medical], Penumbra System [Penumbra], or Solitaire FR Revascularization Device [Covidien], or endovascular infusion of tPA through the EKOS Micro-Infusion Catheter [EKOS], or a standard microcatheter). The angiographic procedure had to begin within 5 hours of stroke onset and be completed within 7 hours of stroke onset. Heparin infusion was started intravenously with a 2000-U bolus followed by an infusion of 450 U per hour during endovascular therapy and was discontinued at the end of the procedure.

Primary Study Outcome Measure and QOL Measure

The primary outcome measure was independent functional outcome, defined by a modified Rankin Scale (mRS) ≤2 at 3 months. The mRS is a measure of disability, which ranges from 0 (no symptoms) to 5 (severe disability and bedridden) and 6 (death).4 The mRS was also obtained at 1, 6, 9, and 12 months postrandomization. The mRS was determined by a study investigator who was mRS-certified and blinded to the treatment assignment. The mRS assessment at 3 months was performed in person, except in a few instances where in-person assessment was not possible, whereas those at 1, 6, 9, and 12 months were conducted by phone.

The health-related quality-of-life measure used for the IMS III Trial was EQ-5D (formerly known as EuroQol). The EQ-5D-3L was obtained from both the subject and proxy at 5 days, 3, 6, 9, and 12 months.5,6 The EQ-5D-3L comprised 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 3 levels: no problems; slight or moderate problems; and extreme problems. Participants received the certified EQ-5D-3L instruments in their native languages. The EQ-5D-3L assessment at 5 days and 3 months was conducted in person when possible, whereas assessments at 1, 6, 9, and 12 months were done by phone.

Subject responses to the EQ-5D-3L instrument were transformed to utility weights using the Shaw (2005) approach for US populations recommended by the Agency for Healthcare Research and Quality.7 The subject responses were used when available; proxy responses were used when subject responses were missing to minimize systematic bias when the EQ-5D-3L is used in follow-up studies of stroke patients.8 Where responses from both subject and proxies were missing for the first time of EQ-5D-3L data collection (at 5 days after randomization or hospital discharge), utility weights were imputed based on mean observed NIHSS score for the subject’s stroke severity category levels: ≤19 or ≥20 to reflect baseline severity. Quality-adjusted days (QADs) in the study were estimated for the 12 months (365 days) post stroke using linear interpolation between measurements and calculating area under the curve.9 The subject responses were used when available; proxy responses were used when subject responses were missing to minimize systematic bias when the EQ-5D-3L is used in follow-up studies of stroke patients.8 Where responses from both subject and proxies were missing for the first time of EQ-5D-3L data collection (at 5 days after randomization or hospital discharge), utility weights were imputed based on mean observed NIHSS score for the subject’s stroke severity category levels: ≤19 or ≥20 to reflect baseline severity.

Statistical Analyses

Participants were randomly assigned in a 2:1 ratio to endovascular therapy or intravenous tPA alone with the use of an Internet-based, computerized algorithm of minimization and the biased-coin method, which accounted for 2 factors: clinical center and baseline NIHSS strata (scores of 8–19 versus ≥20). Repeated measures analysis of the mRS (both dichotomized as 0–2 [favorable] versus 3–6 [unfavorable]}
and as full ordinal scale) was performed adjusting for the stroke severity cohort, age, and time from stroke onset to initiation of intravenous tPA. The generalized linear mixed effects model with logit link (for dichotomized mRS) or cumulative logit link (for ordinal mRS) was used. The statistically significant quadratic term for time was included to better fit the curvilinear profile of the longitudinal data. Odds ratios were estimated from individual models fit to each stroke severity subgroup. The mixed effects model uses all available data on each subject to estimate overall treatment effects and time-specific treatment effects. SAS v9.3 procedures, GENMOD and GLIMMIX, were used for the repeated measures analyses. The total number of QADs for the 2 treatment groups over the 12-month follow-up was calculated overall and for each severity cohort. The QADs for the 2 groups were compared using the linear regression adjusting for prestroke mRS and age.

Results
A total of 656 participants were randomized (434 participants to endovascular therapy and 222 to intravenous tPA alone) at 58 study centers between August 25, 2006, and April 17, 2012, in the United States (41 sites), Canada (7), Australia (4), and Europe (6). Table II in the online-only Data Supplement shows the numbers of available mRS and EQ-5D-3L measures by treatment group at each time point. The Spearman correlation coefficients between ordinal mRS and utility score ranged from −0.87 to −0.91 overall. All observed correlation coefficients were significantly different from 0 (P<0.0001).

Figure 1 presents the unadjusted percent favorable mRS outcome (0–2) over time by treatment group and stroke severity cohort. An interaction effect between treatment and cohort was significant in the dichotomized mRS model (P=0.039), but was not significant in the ordinal mRS model (P=0.35). In the moderately severe stroke cohort, the 2% difference at 3 months between the treatment groups remained steady. In contrast, the difference between treatment groups in the severe stroke cohort increased after 3 months in favor of the endovascular treatment group, with the 12-month unadjusted difference being significant (P=0.037). Figure 2 illustrates the distribution of the ordinal mRS scores at each time point by the stroke severity cohort. As in the case of the dichotomized mRS, the mRS score distribution in the moderately severe cohort was similar between the treatment groups for each time point, whereas for the severe stroke cohort, the distributions were different, particularly in the 9 month assessment (P=0.045). Figure 3 displays the unadjusted and adjusted (for baseline NIHSS cohort, age, and time from symptom onset to intravenous tPA initiation) repeated measures analyses for the dichotomized mRS and ordinal mRS. The analysis of the longitudinal dichotomous mRS confirms the trend in Figure 1. Although the treatment group difference over time in the moderately severe stroke cohort was not significant, the odds of favorable outcome over the 12-month period in the endovascular group in the severe cohort was more than twice that of the intravenous tPA alone group in unadjusted (P=0.026) as well as adjusted analyses (P=0.028). A similar trend was observed in the repeated measures analysis of the ordinal mRS, although the estimated magnitude of the effect is imprecise as evidenced by the wide confidence interval (common OR, 95% confidence interval: 7.97, 0.76–83.86 unadjusted and 10.15, 1.06–97.37 adjusted).

Figure 4 presents the unadjusted and adjusted repeated measures analysis for prespecified subgroups in participants with severe stroke: age (18–65, ≥66 years), time from symptom onset to treatment with intravenous tPA (≤2 hours, >2 hours), baseline Alberta Stroke Program Early CT score (ASPECTS) score (0–7, 8–10), and presence of occlusion of the internal carotid artery, first part of the middle cerebral artery, or basilar

![Figure 1. Proportion of mRS 0–2 over time by stroke severity cohort. IV indicates intravenous; mRS, modified Rankin Scale; and tPA, tissue-type plasminogen activator. *Endovascular therapy significantly better than IV tPA, P≤0.05.](http://stroke.ahajournals.org/content/early/2017/07/07/STROKEAHA.117.022781/DataSupplement/figure1)
artery on baseline CTA. ASPECTS allows for the systematic assessment of 10 regions of the brain with the use of CT, with a score of 1 indicating a normal region and 0 indicating a region showing signs of ischemia; total scores range from 10 (no evidence of early ischemia) to 0 (all 10 regions in the hemisphere show early ischemic changes). The point estimates in favor of

![Figure 2. Distribution of mRS scores by time of assessment by stroke severity cohort. IV indicates intravenous; mRS, modified Rankin Scale; and tPA, tissue-type plasminogen activator.](image)

![Figure 3. Unadjusted* and adjusted† common odds ratio (95% CI) from repeated measures analysis of the mRS 0–2 and ordinal mRS, overall and by stroke severity. IV indicates intravenous; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator. *Model includes time and treatment covariates. †Model includes time, treatment, NIHSS cohort, time from onset to IV tPA initiation, and age covariates.](image)
the endovascular group were consistent across all subgroups. Figures I–IV in the online-only Data Supplement illustrate the proportion of mRS 0–2 over time in the severe stroke cohort by these prespecified subgroups for participants with severe stroke. Participants with severe stroke in the endovascular group had a significantly greater number of QADs, whereas there was no significant difference for participants with moderately severe strokes (Table).

Discussion

The IMS III trial was stopped early because of futility, according to the prespecified rules, and failed to show an overall benefit in functional outcome at 3 months with the use of additional endovascular therapy, as compared with the standard therapy of intravenous tPA alone. The safety profiles were similar in the 2 treatment groups. However, the results over 12 months presented here suggest that participants with severe strokes who are treated with intravenous tPA within 3 hours of onset may benefit from additional endovascular therapy in terms of functional outcome and HQQoL as compared with those treated with intravenous tPA alone. In participants with severe stroke, the absolute difference in functional outcome at 12 months in favor of endovascular therapy as compared with intravenous tPA (14%) is similar to the benefit of intravenous tPA as compared with placebo in the original National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Trial (11% to 13%)\(^1\) which led to tPA as the only FDA-approved treatment for acute ischemic stroke. We had designed a stratified analysis for the IMS III Trial hypothesizing that the benefit of endovascular therapy would be greater in participants with severe stroke, based on prior pilot trials of endovascular therapy.\(^2,14\) Conversely, however, we demonstrated no difference in functional outcome or health-related quality-of-life in those with moderately severe strokes at 12 months.

This observed benefit for endovascular therapy for patients with severe stroke is supported by the MR CLEAN, ESCAPE, EXTEND IA, and SWIFT PRIME Trials, which also demonstrated effectiveness for endovascular therapy in participants with moderately severe strokes (personal communication—Jeff Saver—SWIFT PRIME results and presentation).\(^15–17\) All of these trials used the stent-retrievers in the overwhelming majority of study participants as compared with only a handful of participants in IMS III. Use of intravenous tPA in these trials as standard therapy included 100% of participants in EXTEND IA and SWIFT PRIME, 89% in MR CLEAN, and 74% in ESCAPE. Although the inclusion criteria of the 4 trials varied, one consistent criterion for every trial was the presence of documented major arterial occlusion before randomization. When IMS III began, only a small percentage of centers used baseline vascular imaging as part of the assessment for acute stroke.\(^18\) It was for this reason that the NIHSS was used as a surrogate, although imperfect marker for large artery occlusion. This situation changed rapidly during the course of IMS III with increasing use of CTA before treatment with tPA. Previous studies comparing the NIHSS and presence of major arterial occlusions have demonstrated that patients with an NIHSS ≥20

Table. Estimated* Mean (95% CI) Quality-Adjusted Days (QADs) From the Stroke Date to the 12 Months Follow-Up or Time of Death or Drop-Out for Participants by Baseline Stroke Severity

<table>
<thead>
<tr>
<th>Baseline Stroke Severity</th>
<th>IV tPA and Endovasc., N=285</th>
<th>IV tPA Alone, N=143</th>
<th>Mean (95% CI) Difference in Days</th>
<th>IV tPA and Endovasc., N=130</th>
<th>IV tPA Alone, N=71</th>
<th>Mean (95% CI) Difference in Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality-adjusted days</td>
<td>212.6</td>
<td>211.1</td>
<td>1.5 (−22.5, 22.3)</td>
<td>145.8</td>
<td>110.6</td>
<td>35.2 (0.6, 67.4)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; IV, intravenous; and tPA, tissue-type plasminogen activator.

*Multivariable model controlling for age and baseline mRS.
almost all have a larger arterial occlusion by vascular imaging, even after intravenous tPA. Of those participants in IMS III with an NIHSS ≥20 and CTA before treatment with intravenous tPA, only one patient had no documented major arterial occlusion on pretreatment CTA, and this person had an M2 occlusion on subsequent intra-arterial angiography. In contrast, of those subjects in IMS III with an NIHSS <20 and CTA before treatment with intravenous tPA, 23 enrolled participants 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 before enrollment in an endovascular trial is also reflected in the IMS III post hoc analysis, which demonstrated benefit for endovascular therapy in participants with an intracranial occlusion by baseline CTA, which included all levels of NIHSS. Thus, the inability to demonstrate a major arterial occlusion before enrollment in IMS III in those patients with an NIHSS <20 is one major explanation for lack of benefit in IMS III, particularly because IMS III and the other endovascular trials were consistent in their outcomes for the subgroup of patients with an NIHSS ≥20, even with differences in the use of endovascular technology and other patient selection criteria.

IMS III participants with an NIHSS score ≥20 not only have large artery occlusions, but also have large areas of ischemic brain, some of which is potentially salvageable with timely reperfusion. The NIHSS estimates the volume of brain with ischemia severe enough to cause brain dysfunction. In this respect, it provides similar information to a brain perfusion study. However, the NIHSS does not provide an estimate of brain with low perfusion values or diffusion-positive magnetic resonance images consistent with likely irreversible ischemia or an ischemic core. Thus, its estimation of potentially salvageable brain has the greatest utility when the assessment is done close to the onset of stroke symptoms and in the setting of successful early reperfusion.

Our study indicates that participants with severe stroke may have functional recovery that continues after 3 months and that differences between 2 treatment approaches may accumulate beyond 3 months, the traditional time-point for primary outcome measures in Phase III acute stroke trials.

Recently, the MISTIE II Trial, a randomized minimally invasive surgery trial of intracerebral hemorrhage, also found that the differences in outcome between the active and standard therapy arms became greater over the course of 12 months as the result of blood clot aspiration. The most severely affected patients with ischemic stroke are highly likely to benefit from the addition of endovascular therapy after intravenous tPA.

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SUPPLEMENTAL MATERIAL

Twelve-month Clinical and Quality of Life Outcomes in the Interventional Management of Stroke III Trial
SUPPLEMENTAL MATERIALS

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NINDS ADMINISTRATION: S. Janis, W. Galpern.
Supplemental Figure Ia-b: Proportion of mRS 0-2 over Time for Age Subgroups:

a.

Severe Stroke Cohort & Age Group 18-65
Percent mRS 0-2 by Treatment

b.

Severe Stroke Cohort & Age Group 66+
Percent mRS 0-2 by Treatment

* Endovascular therapy significantly better than IV tPA, \( \alpha=0.05 \)
Supplemental Figure IIa-b: Proportion of mRS 0-2 over Time for Time to IV t-PA Treatment Subgroups:

a.

b.

* Endovascular therapy significantly better than IV t-PA, p ≤ 0.05
Supplemental Figure IIIa-b: Proportion of mRS 0-2 over Time for Time by ASPECTS Subgroups:

a.

Severe Stroke Cohort & ASPECTS 0-7
Percent mRS 0-2 by Treatment

* Endovascular therapy significantly better than IV tPA, p < 0.05

b.

Severe Stroke Cohort & ASPECTS 8-10
Percent mRS 0-2 by Treatment
Supplemental Figure IV: Proportion of mRS 0-2 over Time for ICA/M1/Basilar Subgroup

Severe Stroke Cohort & ICA/M1/basilar occlusion
Percent mRS 0-2 by Treatment

*Endovascular therapy significantly better than IV tPA, p ≤ 0.05

*ICA – internal carotid artery, M1- first division of middle cerebral artery
Supplemental Table I: Inclusion and Exclusion Criteria

Clinical Inclusion Criteria

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

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

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

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

Clinical Exclusion Criteria

• History of stroke in the past 3 months.

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

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

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

• Presumed septic embolus, or suspicion of bacterial endocarditis.

• Presumed pericarditis including pericarditis after acute myocardial infarction.

• Suspicion of aortic dissection.

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

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

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

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

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

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

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

• Individual legally empowered in the state where the consent is obtained) cannot provide
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 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.
## Supplemental Table II: Available mRS and EQ-5D utility score by Time Point and by Baseline NIHSS Cohort

### a. All Randomized Participants (N=656)

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<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
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* Participants whose mRS values were missing because death occurred prior to the corresponding visit were imputed with a score of 6.

† Combines subject responses (imputed if subject died) and proxy’s response if the subject was unable to provide responses.

‡ Scores on the modified Rankin Scale range from 0-6 with 0 (indicating no symptoms), 1 no clinically significant disability (able to carry out all normal activities despite the presence of symptoms), 2 slight disability (able to attend to own affairs but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance or walk without assistance), 5 severe disability (requires constant nursing care and attention, bedridden, and incontinent), 6 death.

### b. Baseline NIHSS 8-19 Cohort (N=452)

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### c. Baseline NIHSS ≥ 20 Cohort (N=204)

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* Participants whose mRS values were missing because death occurred prior to the corresponding visit were imputed with a score of 6.

† Combines subject responses (imputed if subject died) and proxy’s response if the subject was unable to provide responses.

‡ Scores on the modified Rankin Scale range from 0-6 with 0 (indicating no symptoms), 1 no clinically significant disability (able to carry out all normal activities despite the presence of symptoms), 2 slight disability (able to attend to own affairs but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance or walk without assistance), 5 severe disability (requires constant nursing care and attention, bedridden, and incontinent), 6 death.