Safety and Efficacy of Solitaire Stent Thrombectomy
Individual Patient Data Meta-Analysis of Randomized Trials

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Background and Purpose—Recent positive randomized trials of endovascular therapy for ischemic stroke used predominantly stent retrievers. We pooled data to investigate the efficacy and safety of stent thrombectomy using the Solitaire device in anterior circulation ischemic stroke.

Methods—Patient-level data were pooled from trials in which the Solitaire was the only or the predominant device used in a prespecified meta-analysis (SEER Collaboration): Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME), Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE), Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA), and Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (REVASCAT). The primary outcome was ordinal analysis of modified Rankin Score at 90 days. The primary analysis included all patients in the 4 trials with 2 sensitivity analyses: (1) excluding patients in whom Solitaire was not the first device used and (2) including the 3 Solitaire-only trials (excluding ESCAPE). Secondary outcomes included functional independence (modified Rankin Score 0–2), symptomatic intracerebral hemorrhage, and mortality.

Results—The primary analysis included 787 patients: 401 randomized to endovascular thrombectomy and 386 to standard care, and 82.6% received intravenous thrombolysis. The common odds ratio for modified Rankin Score improvement was 2.7 (2.0–3.5) with no heterogeneity in effect by age, sex, baseline stroke severity, extent of computed tomography changes, site of occlusion, or pretreatment with alteplase. The number needed to treat to reduce disability was 2.5 and for an extra patient to achieve independent outcome was 4.25 (3.29–5.99). Successful revascularization occurred in 77% of patients.
treated with Solitaire device. The rate of symptomatic intracerebral hemorrhage and overall mortality did not differ between treatment groups.

**Conclusions**—Solitaire thrombectomy for large vessel ischemic stroke was safe and highly effective with substantially reduced disability. Benefits were consistent in all prespecified subgroups. (Stroke. 2016;47:798-806. DOI: 10.1161/STROKEAHA.115.012360.)

**Key Words:** endovascular treatment ■ intra-arterial therapy ■ ischemic stroke ■ mechanical thrombectomy ■ meta-analysis ■ randomized controlled trial ■ stent retriever device ■ thrombolysis

The management of ischemic stroke because of large vessel occlusion has been transformed by the publication of 5 positive randomized trials which predominantly used stent retrievers.1–5 These trials have led to highest-level guideline recommendations in the United States,6 Europe,7 and Canada8 supporting mechanical stent thrombectomy within 6 hours of ischemic stroke onset for patients with large vessel stroke because of internal carotid and middle cerebral artery occlusions.

Although each trial was positive in its own right and no major subgroup heterogeneity was observed in the individual trials, the power to detect subgroup effects was low and precision of effect size measures was limited. Further, there was variation in the device and procedural approach used in the trials. Multiple study-level meta-analyses of summary trial data have been published.8–11 However, individual pooled patient data meta-analysis, similar to that performed for intravenous thrombolysis, adds power, improves precision, and allows accurate interrogation of subgroups.12

The trialists have agreed to pool individual patient data to address these outstanding questions. In a separate report, data from all 5 trials is being analyzed to clarify aspects of treatment across diverse device therapies. The purpose of the current report is to examine treatment effects in patients treated specifically with the most common device used in the pivotal trials, the Solitaire stent retriever (Medtronic, Dublin, Ireland).

**Methods**

For this report specifically analyzing the Solitaire device, studies were eligible for the primary analysis if they met the following selection criteria: (1) randomized trial of endovascular thrombectomy added to best medical therapy versus best medical therapy alone, with the Solitaire device used first in all or a majority of the interventions and (2) imaging confirmation of large vessel occlusion before study entry. Four trials met these criteria and were included in the primary analysis (SEER Collaboration): Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME), Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE), Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA), and Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (REVASCAT). The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial was not included because the Solitaire device was used in only a minority of the interventions (but is included in a separately reported, larger analysis not focused on the Solitaire device).

Data from each trial were collated by an independent statistical center which performed analyses according to a prespecified statistical analysis plan (available in the online-only Data Supplement). Commonalities and differences in trial characteristics are summarized in Table I in the online-only Data Supplement. The primary analysis included all patients enrolled in all 4 trials. Two sensitivity analyses were performed: (1) including in the endovascular arm only those patients in whom the first device actually used was Solitaire or would have been Solitaire had a target clot been still present and accessible (Solitaire intention to treat analysis) and (2) including only patients from the 3 trials that universally used Solitaire in the endovascular arm (SWIFT PRIME, EXTEND-IA, and REVASCAT). The primary outcome was degree of disability as assessed on the modified Rankin scale (mRS) at 90 days.

Prespecified subgroup analyses were age (<70 years of age versus ≥70 years and <80 years of age versus ≥80 years), sex (male/female), stroke severity (National Institutes of Health Stroke Scale [NIHSS] ≤15, 16–20, and ≥21), site of intracranial vascular occlusion (internal carotid artery, M1 and M2 middle cerebral artery), presence of tandem cervical carotid occlusion (yes/no), extent of initial early ischemic changes (Alberta Stroke Program Early CT Score [ASPECTS] 0–5, 6–8, and 9–10), administration of alteplase (yes/no), and time from onset to randomization (<5 h and ≥5 h). Onset to randomization dichotomization at 5 h was chosen to approximate the subgroup who could have endovascular treatment commenced within 6 h of onset. In addition, patients treated with alteplase within 3 hours of stroke onset (FDA label for alteplase) were examined.

Prespecified secondary efficacy outcomes were independent functional outcome (mRS 0–2) at 90 days; major early neurologic recovery at 24 h, defined as a reduction in NIHSS from baseline of at least 8 points or reaching 0 to 1; and the rate of successful revascularization at end of endovascular procedure defined as modified Thrombolysis in Cerebral Ischemia (mTICI) 2b/3 representing restoration of blood flow to >50% of the affected territory. For this analysis, final revascularization in ESCAPE patients was reclassified so that all trials used the mTICI scale which demarcates 2b as 50% to 99% restoration of blood flow to the affected territory.13

Safety outcomes examined were symptomatic intracerebral hemorrhage (as defined by the source trial, see Table I in the online-only Data Supplement) and mortality. The rate of radiologically defined parenchymal hematoma was also reported.

The technical efficacy and safety of the Solitaire device was also assessed in all patients in the 4 trials in which Solitaire was actually used as the first device deployed. This as-treated population did not include patients randomized to the endovascular arm who did not receive a device either because they had already reperfused by the time of catheter angiography or navigation to the target occlusion could not be accomplished.

Statistical analysis was performed by the independent statistician who merged the individual trial databases and used SAS v.9.2 (SAS Institute, Cary, NC). The primary outcome was analyzed using mixed methods ordinal logistic regression with mRS categories 5 and 6 merged and study and trial-by-treatment interaction as random effects variables. Because the trials were conducted independently, in different geographic locations and health systems, the statistical analysis plan specified random rather than fixed effects to avoid the assumption of a common effect size among these trials. Unadjusted and adjusted models were analyzed. The adjusted analysis included...
Table 1. Patient and Procedural Characteristics for the Four Trials: SWIFT PRIME, ESCAPE, EXTEND-IA, and REVASCAT

| Characteristic                                      | Control | Intervention |
|----------------------------------------------------|---------|--------------|
| Number                                             | 386     | 401          |
| Age, y, mean (SD)                                   | 67.8 (12.3) | 67.3 (12.7)  |
| Male sex, n (%)                                     | 193 (50.0) | 195 (48.6)   |
| Race, n (%)                                         |         |              |
| White                                              | 347 (89.9) | 357 (89.0)   |
| Black                                              | 14 (3.6)  | 16 (4.5)     |
| Asian                                               | 13 (3.4)  | 11 (2.7)     |
| Other                                               | 12 (3.1)  | 15 (3.7)     |
| NIHSS score, median (interquartile range)           |         |              |
| Serum glucose, mg/dL, mean (SD)                     | 131.8 (48.3) | 128.7 (39.8) |
| Time (min) from stroke onset to hospital arrival, median (interquartile range) | 108 (58–206) | 105 (55–199) |
| Treatment with intravenous alteplase, n (%)         | 327 (84.7) | 323 (80.5)   |
| Time (min) from stroke onset to initiation of alteplase, median (interquartile range) | 120 (89–164) | 114 (86–150) |
| Time from hospital arrival to initiation of intravenous alteplase (door-to-needle), min, median (interquartile range) | 38 (26–57) | 36 (24–54)   |
| Hypertension, n (%)                                 | 259 (67.1) | 254 (63.3)   |
| Diabetes mellitus, n (%)                            | 54 (14.0)  | 48 (12.0)    |
| Current or past tobacco use, n (%)                  | 132 (34.2) | 129 (32.2)   |
| Internal carotid artery (ICA)                       | 66 (17.1)  | 73 (18.2)    |
| First segment of middle cerebral artery (M1)        | 287 (74.4) | 285 (71.1)   |
| Site of vessel occlusion, n (%)                     | 51 (18–123) | 48 (21–109)  |
| Internal carotid artery (M2)                        | 23 (6.0)   | 33 (8.2)     |
| Not recorded                                        | 10 (2.6)   | 10 (2.5)     |
| Second segment of middle cerebral artery (M1)       | 9 (7–10)   | 9 (7–10)     |
| Time (min) from hospital arrival to arterial access, median (interquartile range) | N/A | 225 (157–302) |
| Time (min) from stroke onset to arterial access, median (interquartile range) | N/A | 93 (69–127)   |
| Time (min) from initial imaging to arterial access, median (interquartile range) | N/A | 63 (46–85)    |
| Time (min) from alteplase commencement to arterial access, median (interquartile range) | N/A | 68 (43–103)   |

Table 1. Continued

| Characteristic                                      | Control | Intervention |
|----------------------------------------------------|---------|--------------|
| Time (min) from arterial access to mTICI 2b/3 or completion, median (interquartile range) | N/A | 38 (24–60)   |
| Time (min) from stroke onset to mTICI 2b/3 or completion, median (interquartile range) | N/A | 274 (196–365) |
| Final mTICI, n (%)                                  |         |              |
| 3                                                  | N/A     | 132 (32.9)   |
| 2b                                                 | 153 (38.2) |              |
| 2a                                                 | 62 (15.5)  |              |
| 1                                                  | 6 (1.5)  |              |
| 0                                                  | 19 (4.7)  |              |

*Final mTICI as assessed by individual trial core laboratory. Scale ranges from no flow (0) to normal flow (3). mTICI 2b is restoration of flow to >50% of the affected arterial territory. NIHSS score (standardized neurological examination) ranges from normal (0) to death (42). No statistically significant differences between groups. ASPECTS indicates Alberta Stroke Program Early CT Score; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—intra-Arterial; mTICI, modified Treatment of Cerebral Ischemia; NIHSS, National Institutes of Health Stroke Scale; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset; and SWIFT PRIME, Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment.

7 prespecified covariates: age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS score, and time from onset to randomization. Number needed to treat (NNT) values reflecting concurrent transitions across multiple mRS levels were derived by calculating the geometric mean of the NNT values yielded by the algorithmic joint outcome table method and the permutation test method (combining mRS categories 5 and 6). The secondary dichotomous outcomes were analyzed using binary logistic regression with the same covariates and study and trial-by-treatment interaction as random effects variables. NNT for dichotomous outcomes was calculated as 100/absolute risk reduction. Assessment of time of reperfusion as a predictor of outcome was conducted separately in the intervention group. The adjusted probability of independent outcome in the intervention group that achieved mTICI 2b/3 reperfusion was solved using a hierarchical generalized linear mixed model with study as a random variable and onset-to-reperfusion time. Probabilities were graphed as a function of time with the probability of independent outcome regressed against time using simple linear regression to produce an estimate of effect size for each unit of time delay to treatment.

**Results**

**Characteristics of the Patients**

In total, the primary analytic population included 787 anterior circulation ischemic stroke patients, 401 randomized to stent thrombectomy and 386 to standard care. Of these, 650/787 (82.6%) received intravenous thrombolysis (Table 1). In the first sensitivity analysis, the Solitaire-first intention to treat, the population included 713 patients, 327 randomized to thrombectomy and 386 to standard care. In the second sensitivity analysis, of the 3 Solitaire-only trials, there were 472...
patients, including 236 randomized to endovascular intervention and 236 to standard care (Tables II and III in the online-only Data Supplement).

**Primary Outcome**

In the primary analysis, the common odds ratio (OR) for improvement in ordinal analysis of mRS was 2.4 (1.8–3.0; P=0.0000000001) unadjusted and common OR 2.7 (2.0–3.5; P=0.0000000001) adjusted—an NNT of 2.5 patients to improve at least one level on the mRS (Table II and Figures 1 and 2A). Effects were similar in the 2 sensitivity analyses (Figure 1; Figures I and II and Tables IV and V in the online-only Data Supplement) and in patients who received alteplase within 3 hours of stroke onset (Table VI in the online-only Data Supplement). There was no heterogeneity in effect in subgroup analysis by age, sex, baseline stroke severity, pretreatment thrombolysis, site of intracranial vascular occlusion, time from onset to randomization, or extent of initial noncontrast computed tomography abnormalities, with the exception of the Solitaire as first device population where there was heterogeneity in treatment effect by baseline ASPECTS score, male and female, internal carotid and middle cerebral artery occlusion, and ASPECTS score ≥9.

There was no evidence of a study-by-treatment interaction, indicating homogeneity of effect across all 4 trials (P=0.513).

In the safety analyses, there were no significant differences in symptomatic hemorrhage or mortality overall (Table 2). There was, however, a significant reduction in mortality in the subgroup aged ≥80 in the complete SEER data set (20% versus 40%, adjusted OR 3.7 [1.3–10.6; P=0.01]; Figure 2C) with similar trend in the Solitaire sensitivity population (Figure IIIC in the online-only Data Supplement). Results were similar in those treated with alteplase within 3 hours versus 3 to 4.5 hours after stroke onset (Tables VI–VIII in the online-only Data Supplement).

In the technical efficacy analysis, among patients from all 4 trials harboring persisting occlusions at catheter angiography and actually treated with Solitaire as first device used, the rate of successful recanalization (mTICI 2b/3) was 236/306 (77%). Rates of mRS 0 to 2 increased with each successive category of mTICI (P=0.01 for trend; Table IX in the online-only Data Supplement). There was a small but significant reduction in the proportion of Solitaire-treated patients achieving independent outcome as time from onset to reperfusion increased (Figure 4).

**Secondary Outcomes and Safety**

Benefit was seen in all secondary efficacy outcomes. The NNT to achieve an extra patient with independent outcome (mRS 0–2) was 4.25 (95% confidence interval 3.29–5.99; Table 2). Major early neurological recovery was substantially increased in the Solitaire-treated patients. Findings were similar in the 2 sensitivity analysis populations (Tables IV and V in the online-only Data Supplement). In a simpler fixed effects model, there was no evidence of a study-by-treatment interaction, indicating homogeneity of effect across all 4 trials (P=0.513).

In the safety analyses, there were no significant differences in symptomatic hemorrhage or mortality overall (Table 2). There was, however, a significant reduction in mortality in the subgroup aged ≥80 in the complete SEER data set (20% versus 40%, adjusted OR 3.7 [1.3–10.6; P=0.01]; Figure 2C) with similar trend in the Solitaire sensitivity population (Figure IIIC in the online-only Data Supplement). Results were similar in those treated with alteplase within 3 hours versus 3 to 4.5 hours after stroke onset (Tables VI–VIII in the online-only Data Supplement).

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**Discussion**

This individual patient data meta-analysis has demonstrated robust benefit of Solitaire stent thrombectomy. The degree of benefit conferred is substantial, with 40 of every 100 patients treated having reduced disability as a result of thrombectomy, including 23 patients achieving an independent outcome. No major safety concerns were noted, with no increase in symptomatic hemorrhage or mortality. Benefit was homogeneous across a broad range of patients, including younger and older, male and female, internal carotid and middle cerebral artery...
clot locations, presence or absence of tandem cervical carotid occlusion, milder and more severe deficits, milder and more severe ischemic injury on initial imaging, and in those who received alteplase or were alteplase-ineligible.

Older age has often been used as an exclusion criterion for thrombectomy, and indeed 2 of the 4 trials analyzed had an upper age limit (SWIFT PRIME and REV ASCAT). Nonetheless, in patients with good or independent premorbid function, there was no evidence of reduced treatment effect in the elderly and, moreover, a clinically and statistically significant 20% absolute reduction in mortality in patients aged ≥80 in the SEER trials. There is, therefore, no justification for exclusion from thrombectomy purely on the basis of age in clinical practice.

Initial analyses of Interventional Management of Stroke (IMS-3) and recent combined analysis with MR CLEAN focused on stroke severity (NIHSS ≥ 20) as a key determinant of endovascular treatment benefit.16,17 Our analyses demonstrated at least as great a treatment benefit in those with NIHSS ≤ 15 as in those with NIHSS > 20. Although few patients were enrolled in the recent trials with NIHSS < 6, there is no evidence of treatment effect modification across the available severity spectrum. Treatment of mild stroke will continue to require clinical judgment.18

The preponderance of patients in these trials received intravenous alteplase before endovascular thrombectomy and fibrinolytic treatment was part of the inclusion criteria for EXTEND-IA and SWIFT PRIME. All patients who were alteplase-eligible in the analyzed trials were given alteplase. These data, therefore, support the continued use of alteplase before thrombectomy in all eligible patients. Although there were fewer patients in these trials who were alteplase-ineligible, there was clear benefit of endovascular thrombectomy in these patients not candidates for pretreatment with fibrinolytic agents, confirming the benefits of endovascular thrombectomy in this group.

The crucial effect of time has been emphasized in relation to intravenous thrombolysis12,19 and also applies to endovascular therapies.20,21 In the case of alteplase, time to treatment is the most commonly analyzed metric as time of reperfusion is infrequently documented and may occur several hours post-treatment. The precise quantification of time to reperfusion and the higher frequency of reperfusion with endovascular treatment should allow more detailed understanding of the

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**Figure 1.** Functional outcome (modified Rankin Scale [mRS] at 90 days) in the primary and sensitivity analysis populations. Odds ratios (OR) and 95% confidence intervals (CI) for ordinal analysis of mRS (both unadjusted and adjusted for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, Alberta Stroke Program Early CT Score (ASPECTS), and time from onset to randomization) and for independent functional outcome (mRS 0–2), both unadjusted and adjusted.
relationship of time to outcome. The proportion of patients with favorable imaging decreases over time such that earlier imaging should increase the proportion eligible for treatment and the overall beneficial effect to the stroke population. Our pooled analysis confirmed a time–benefit relationship, with decline in frequency of independent outcome with longer onset to reperfusion times. However, the effect size is small in this analysis, and it is likely that these studies underestimate the importance of time because of selective recruitment of patients with good quality collateral flow or penumbral profiles. The impact of time has previously been shown to be muted in patients with favorable imaging profiles. Accordingly, in clinical practice, it is essential to streamline systems to minimize delays and achieve optimal patient outcomes.

The Solitaire device for stent thrombectomy had an overall rate of successful revascularization (mTICI 2b/3) of 236/306 (77%) across these studies with a low rate of symptomatic hemorrhage. Although further device innovation to improve the rates of complete reperfusion (mTICI 3) on first pass of the device will undoubtedly occur, these results set a clear benchmark for future technological development.

In seeking to characterize the effects of the Solitaire stent retriever, the inclusion of trials in which other endovascular treatments were used has the potential to introduce confounds. We eliminated this concern by confining this analysis to studies that used the Solitaire device in a majority of patients and by performing sensitivity analyses confined to the patients treated with the Solitaire device.

Limitations of this study include the potential heterogeneity in inclusion criteria between studies. However, we found no evidence of a study-by-treatment interaction and analysis at the level of individual patient data minimizes the risk of bias. All of the 4 trials specified that patients were included on the basis of imaging, and treatment was conducted quickly once imaging eligibility had been ascertained. Thus, certain patient groups were not included in the trials in sufficient numbers to draw conclusions regarding efficacy. This particularly applies to those with large ischemic core, defined using ASPECTS, poor collateral grade, or unfavorable penumbral patterns. The point estimate for treatment effect was unfavorable in the small group of patients with baseline ASPECTS 0 to 5. However, benefit was not statistically excluded and may accrue in some of these patients, depending on infarct volume, location, and patient comorbidities. More advanced imaging may improve the reliability of core estimation versus noncontrast computed tomography and provide greater information about infarct topography. This analysis has focused on the endovascular trials using only or predominantly the Solitaire device and does

Figure 2. Distribution of modified Rankin scores (mRS) at 90 days in the primary analysis: SWIFT PRIME, EXTEND-IA, ESCAPE, and REVASCAT. Overall results (A) comparing age dichotomized at 70 years (B), comparing age dichotomized at 80 years (C), comparing those who did or did not receive intravenous alteplase before endovascular stent thrombectomy (D). (Continued)
not provide detailed evidence regarding other endovascular devices or approaches. Further individual patient data meta-analysis in a broader range of endovascular trials is planned.

This analysis confirms the robust treatment benefits of endovascular stent thrombectomy using the Solitaire device in patients with large vessel occlusion ischemic stroke, selected by imaging and treated rapidly within 6 hours of stroke onset. No clinical effect modifiers were identified, indicating that age and stroke severity (within the range included in the trials) should not exclude patients from therapy. Effects in later time windows and in patients with more extensive irreversible brain injury at baseline require further study.

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NeXtGen Biologics, Abbott Vascular, and Pulsar Vascular. He holds stock in Intratech Medical Ltd, Blockade Medical LLC, and Medina Medical Inc. In addition, Dr Levy renders expert legal opinion in his expertise as a neurosurgeon for attorneys. Dr Diener reports honorary board membership for Medtronic. Dr Pereira reports personal fees from Covidien (Medtronic). Dr Jahan has served as a consultant for Stryker and has acted as a consultant for Microvention. The other authors report no conflicts.

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Safety and Efficacy of Solitaire Stent Thrombectomy: Individual Patient Data Meta-Analysis of Randomized Trials

Bruce C.V. Campbell, Michael D. Hill, Marta Rubiera, Bijoy K. Menon, Andrew Demchuk, Geoffrey A. Donnan, Daniel Roy, John Thornton, Laura Dorado, Alain Bonafe, Elad I. Levy, Hans-Christoph Diener, María Hernández-Pérez, Vitor Mendes Pereira, Jordi Blasco, Helena Quesada, Jeremy Rempel, Reza Jahan, Stephen M. Davis, Bruce C. Stouch, Peter J. Mitchell, Tudor G. Jovin, Jeffrey L. Saver and Mayank Goyal

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SUPPLEMENTAL MATERIAL

Individual patient data meta-analysis of randomized trials of Solitaire stent thrombectomy

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Statistical Analysis Plan
| Trial      | Num  | Onset to arterial access window | Age limits | Mean age enrolled | NIHSS limits | Median NIHSS enrolled | Proportion treated with alteplase | Device | Vessel occlusion site | Imaging selection | Gener Anaesthesia | Onset to arterial access (median, min) | Successful revascularization (mTICI 2b/3) | Definition of SICH |
|-----------|------|--------------------------------|------------|------------------|--------------|-----------------------|-----------------------------------|--------|---------------------|------------------|-----------------|---------------------|----------------------------------------|-------------------|
| ESCAPE    | 316  | 12 (84%<6h)                    | ≥18        | 71.0             | ≥6           | 17                    | 72%                               | Any approved (79% stent retriever, 61% Solitaire) | ICA/M1/M1 equivalent (all M2s) | CT+CT A/+/- mCTA collateral scoring +/-CTP | 9%              | 200  | 76%*                | Any ICH judged to cause ≥2 point increase NIHSS |
| EXTEND-IA | 70   | 6                              | ≥18        | 69.4             | No limits    | 15                    | 100%                              | Solitaire | ICA/M1/M2           | CT+CT A+/-CTP | 36%             | 210  | 86%                | PH2/SAH + ≥4 point increase NIHSS |
| SWIFT PRIME | 196  | 6                              | 18-80/85† | 65.7             | 8-30         | 17                    | 100%                              | Solitaire | ICA/M1              | CT+CT A +/-CTP or MRI DWI+MRA +/- PWI | 37%             | 224  | 88%                | Any PH/SAH/IVH + ≥4 point increase NIHSS |
| REVASCAT  | 206  | 8 (90%<6h)                     | 18-80/85† | 66.5             | ≥6           | 17                    | 73%                               | Solitaire | ICA/M1              | CT+CT A +/-CTP | 7%              | 269  | 66%                | PH2 + ≥4 point increase NIHSS |

NIHSS – National Institutes of Health Stroke Scale, mTICI – modified Treatment in Cerebral Ischaemia grading of angiographic reperfusion (2b is >50% reperfusion of the affected territory), ICA – internal carotid artery, MCA – middle cerebral artery: M1 first segment, M2 second segment. CT – non-contrast computer tomography, CTA – CT angiography, mCTA – multiphase CT angiography for collateral scoring, CTP – CT perfusion, MRI – magnetic resonance imaging, MRA – magnetic resonance angiography.

* ESCAPE reported 72% revascularization using Thrombolysis in Cerebral Infarction (TICI) scale where 2b is >66% reperfusion of the affected territory – this was re-scored defining mTICI 2b>50% for this meta-analysis.
† SWIFT PRIME upper limit age 85 at trial start; after 1st 72 patients amended to upper limit age 80.
‡ REVASCAT amended protocol to include 80-85 year olds if CT ASPECTS>8
Table II – Patient and procedural characteristics for sensitivity analysis 1: SWIFT PRIME, EXTEND-IA, REVASCAT and ESCAPE (excluding those in whom a device other than Solitaire was used first)

| Characteristic                                                      | Control                  | Intervention             |
|--------------------------------------------------------------------|--------------------------|--------------------------|
| Number                                                             | 386                      | 327                      |
| Age, yr, mean (SD)                                                 | 67.8 (12.3)              | 66.8 (12.4)              |
| Male sex – no. (%)                                                 | 193 (50.0)               | 156 (47.7)               |
| Race – no. (%)                                                     |                          |                          |
| White                                                              | 347 (89.9)               | 295 (90.2)               |
| Black                                                              | 14 (3.6)                 | 13 (4.0)                 |
| Asian                                                              | 13 (3.4)                 | 5 (1.5)                  |
| Other                                                              | 12 (3.1)                 | 14 (4.3)                 |
| NIHSS score, Median (Inter-quartile range)                         | 17 (12-19)               | 17 (13-19)               |
| Previously diagnosed atrial fibrillation – no. (%)                 | 146 (37.8)               | 114 (34.9)               |
| Hypertension – no. (%)                                             | 259 (67.1)               | 203 (62.1)               |
| Diabetes mellitus – no. (%)                                        | 54 (14.0)                | 43 (13.1)                |
| Current or past tobacco use – no. (%)                              | 132 (34.2)               | 114 (34.9)               |
| Serum glucose – mg/dL – mean (sd)                                  | 131.8 (48.3)             | 128.2 (39.3)             |
| Time (min) from stroke onset to hospital arrival, Median (Inter-quartile range) | 108 (58-206)             | 108 (57-197)             |
| Treatment with intravenous alteplase – no. (%)                     | 327 (84.7)               | 266 (81.3)               |
| Time (min) from stroke onset to initiation of alteplase, Median (Inter-quartile range) | 120 (89-164)             | 117 (90-155)             |
| Time from hospital arrival to initiation of intravenous alteplase (door-to-needle) – min Median (Inter-quartile range) | 38 (26-57)               | 39 (25-55)               |
| Time from initiation of intravenous alteplase to randomization – min Median (Inter-quartile range) | 51 (18-123)              | 50 (22-112)              |
| Site of vessel occlusion – no. (%)                                 |                          |                          |
| Internal carotid artery (ICA)                                      | 66 (17.1)                | 52 (15.9)                |
| First segment of middle cerebral artery (M1)                       | 287 (74.4)               | 237 (72.5)               |
| Second segment of middle cerebral artery (M2)                      | 23 (6.0)                 | 30 (9.2)                 |
| Not recorded                                                       | 10 (2.6)                 | 8 (2.4)                  |
| Non-contrast CT ASPECTS – Median (Inter-quartile range)            | 9 (7-10)                 | 9 (7-10)                 |
| Time (min) from stroke onset to arterial access, median (IQR)      | N/A                      | 235 (164-301)            |
| Time (min) from hospital arrival to arterial access, median (IQR) | N/A | 98 (72-131) |
| Time (min) from initial imaging to arterial access, median (IQR) | N/A | 65 (47-86) |
| Time (min) from alteplase commencement to arterial access, median (IQR) | N/A | 68 (45-102) |
| Time (min) from arterial access to TICI 2b/3 or completion, median (IQR) | N/A | 38 (25-61) |
| Time (min) from stroke onset to mTICI 2b/3 or completion, median (IQR) | N/A | 280 (201-366) |
| Final mTICI – no. (%)* | N/A | |
| 3 | 119 (36.4) |
| 2b | 117 (35.8) |
| 2a | 49 (15.0) |
| 1 | 5 (1.5) |
| 0 | 16 (4.9) |
| Angiogram not performed | 21 (6.4) |

NIHSS - National Institutes of Health Stroke Scale (NIHSS) score (standardized neurological examination) ranges from normal (0) to death (42)
No statistically significant differences between groups

* mTICI: modified Treatment in Cerebral Ischemia classification, as assessed by individual trial core laboratory, i.e. TICI 2b >50%. Scale ranges from no flow (0) to normal flow (3).
**Table III** – Patient and procedural characteristics for sensitivity analysis 2: SWIFT PRIME, EXTEND-IA and REVASCAT (Solitaire only trials)

| Characteristic                                                                 | Control                  | Intervention             |
|-------------------------------------------------------------------------------|--------------------------|--------------------------|
| Number                                                                        | 236                      | 236                      |
| Age, yr, mean (SD)                                                            | 67.3 (10.6)              | 65.8 (12.0)              |
| Male sex – no. (%)                                                            | 122 (51.7)               | 116 (49.2)               |
| Race – no. (%)                                                                |                          |                          |
| White                                                                         | 216 (91.5)               | 213 (90.3)               |
| Black                                                                         | 8 (3.4)                  | 10 (4.2)                 |
| Asian                                                                          | 4 (1.7)                  | 1 (0.4)                  |
| Other                                                                          | 8 (3.4)                  | 12 (5.1)                 |
| NIHSS score, Median (Inter-quartile range)                                    | 17.0 (12-19)             | 17.0 (14-20)             |
| Previously diagnosed atrial fibrillation – no. (%)                            | 86 (36.4)                | 82 (34.7)                |
| Hypertension – no. (%)                                                        | 151 (64.0)               | 149 (63.1)               |
| Diabetes mellitus – no. (%)                                                   | 42 (17.8)                | 36 (15.3)                |
| Current or past tobacco use – no. (%)                                         | 100 (42.4)               | 96 (40.7)                |
| Serum glucose – mg/dL – mean (sd)                                             | 132.5 (45.7)             | 129.3 (40.3)             |
| Time (min) from stroke onset to hospital arrival, Median (Inter-quartile range) | 105 (61-201)             | 100 (57-189)             |
| Treatment with intravenous alteplase – no. (%)                                | 209 (88.6%)              | 203 (86.0%)              |
| Time (min) from stroke onset to initiation of alteplase, Median (Inter-quartile range) | 115 (90-155)             | 118 (90-157)             |
| Time from hospital arrival to initiation of intravenous alteplase (door-to-needle) – min | 40 (31-60)               | 43 (29-56)               |
| Time from initiation of intravenous alteplase to randomization – min Median (Inter-quartile range) | 76 (36-140)              | 59 (29-121)              |
| Site of vessel occlusion – no. (%)                                            |                          |                          |
| Internal carotid artery (ICA)                                                 | 27 (11.4)                | 28 (11.9)                |
| First segment of middle cerebral artery (M1)                                  | 182 (77.1)               | 174 (73.7)               |
| Second segment of middle cerebral artery (M2)                                 | 20 (8.5)                 | 27 (11.4)                |
| Not recorded                                                                   | 7 (3.0)                  | 7 (3.0)                  |
| Non-contrast CT ASPECTS – Median (Inter-quartile range)                       | 8 (7-10)                 | 8 (7-10)                 |
| Time (min) from stroke onset to arterial access, median (IQR)                 | N/A                      | 235 (171-290)            |
| Time (min) from hospital arrival to arterial access, median (IQR)             | N/A                      | 104 (79-137)             |
| Time (min) from initial imaging to arterial access, median (IQR) | N/A | 75 (51-90) |
| Time (min) from alteplase commencement to arterial access, median (IQR) | N/A | 74 (53-103) |
| Time (min) from arterial access to TICI 2b/3 or completion, median (IQR) | N/A | 49 (29-66) |
| Time (min) from stroke onset to mTICI 2b/3 or completion, median (IQR) | N/A | 287 (218-367) |
| Final mTICI – no. (%)* | N/A | 94 (39.8) |
| 3 | 73 (30.9) |
| 2b | 33 (14.0) |
| 2a | 3 (1.3) |
| 1 | 13 (5.5) |
| 0 | 20 (8.5) |
| Angiogram not performed | N/A |

NIHSS - National Institutes of Health Stroke Scale (NIHSS) score (standardized neurological examination) ranges from normal (0) to death (42) No statistically significant differences between groups

* mTICI: modified Treatment in Cerebral Ischemia classification, as assessed by individual trial core laboratory, i.e. TICI 2b >50%. Scale ranges from no flow (0) to normal flow (3).
Table IV – Patient outcomes in the sensitivity analysis 1: SWIFT PRIME, EXTEND-IA, REVASCAT and ESCAPE (excluding those in whom a device other than Solitaire was used first)

| Outcome                                                                 | Control (n=386) | Intervention (n=327) | Adjusted* | Unadjusted |
|-------------------------------------------------------------------------|-----------------|----------------------|-----------|------------|
|                                                                         |                 |                      | Effect size OR (95%CI) | p value | Effect size OR (95%CI) | p value |
| Primary outcome                                                        |                 |                      | p value |           | p value |           |
| Functional outcome at 90 days (Modified Rankin Scale – mRS) Ordinal analysis† – median (IQR) | 4 (2-5) | 2 (1-4) | 2.8 (2.1-3.7) | <0.001 | 2.5 (1.9-3.3) | <0.001 |
| Secondary Outcomes                                                      |                 |                      | p value |           | p value |           |
| Independent functional outcome (mRS0-2)                                 | 119 (30.8) | 182 (55.7) | 3.4 (2.3-5.0) | <0.001 | 2.7 (2.0-3.8) | <0.001 |
| Excellent functional outcome (mRS0-1)                                   | 67 (17.4) | 120 (36.7) | 3.2 (2.2-4.7) | <0.001 | 2.7 (1.9-3.9) | <0.001 |
| Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24h)‡ | 100 (25.9) | 195 (59.6) | 4.9 (3.5-6.9) | <0.001 | 4.2 (3.1-5.8) | <0.001 |
| Safety                                                                  |                 |                      | p value |           | p value |           |
| Death                                                                   | 63 (16.3%) | 41 (12.5%) | 0.71 (0.41 to 1.2) | 0.23 | 0.72 (0.44 to 1.2) | 0.17 |
| Symptomatic intracerebral hemorrhage§                                   | 11 (2.8%) | 8 (2.4%) | 0.70 (0.26 to 1.9) | 0.47 | 0.84 (0.32 to 2.2) | 0.73 |
| Parenchymal hematoma (PH)                                               | 31 (8.0%) | 30 (9.2%) | 1.1 (0.63 to 1.9) | 0.77 | 1.1 (0.58 to 2.2) | 0.70 |

* for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS score, and time from onset to randomization
† Modified Rankin scale (mRS) ranges from normal (0) to death (6). Analysis combined mRS 5 & 6
‡ National Institutes of Health Stroke Scale (NIHSS) score (standardized neurological examination) ranges from normal (0) to death (42), 8 point reduction is highly clinically significant.
§ SICH - Symptomatic intracerebral hemorrhage defined by source trial
Table V – Patient outcomes in the sensitivity analysis 2: SWIFT PRIME, EXTEND-IA and REVASCAT (Solitaire only trials)

| Outcome | Control (n=236) | Intervention (n=236) | Adjusted† | Unadjusted |
|---------|----------------|----------------------|------------|------------|
|         |                |                      | Effect size | Effect size |
|         |                |                      | OR (95%CI) | OR (95%CI) |
|         |                |                      | p value    | p value    |
| **Primary outcome** | | | | |
| Functional outcome at 90 days (Modified Rankin Scale – mRS) | 3.0 (IQR 2-5) | 2.0 (IQR 1-4) | 2.5 (1.8 to 3.5) | <0.0001 | 2.3 (1.6 to 3.1) | <0.0001 |
| **Secondary Outcomes** | | | | |
| Independent functional outcome (mRS0-2) | 76 (32.2%) | 129 (54.7%) | 3.0 (1.9 to 4.5) | <0.0001 | 2.5 (1.7 to 3.6) | <0.0001 |
| Excellent functional outcome (mRS0-1) | 41 (17.4%) | 85 (36.0%) | 2.9 (1.8 to 4.7) | <0.0001 | 2.7 (1.7 to 4.1) | <0.0001 |
| Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24h)‡ | 61 (25.8%) | 141 (59.7%) | 4.9 (3.0 to 8.0) | <0.0001 | 4.3 (2.9 to 6.3) | <0.0001 |
| **Safety** | | | | |
| Death | 35 (14.8%) | 31(13.1%) | 0.82 (0.42 to 1.6) | 0.57 | 0.83 (0.46 to 0.67) | 0.54 |
| Symptomatic intracerebral hemorrhage§ | 7 (3.0%) | 4 (1.7%) | 0.47 (0.13 to 1.7) | 0.26 | 0.44 (0.08 to 2.5) | 0.35 |
| Parenchymal hematoma (PH) | 25 (10.6%) | 23 (9.7%) | 0.84 (0.45 to 1.6) | 0.59 | 0.92 (0.46 to 1.8) | 0.81 |

* for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS score, and time from onset to randomization
† Modified Rankin scale (mRS) ranges from normal (0) to death (6). Analysis combined mRS 5 & 6
‡ National Institutes of Health Stroke Scale (NIHSS) score (standardized neurological examination) ranges from normal (0) to death (42), 8 point reduction is highly clinically significant.
§ SICH - Symptomatic intracerebral hemorrhage defined by source trial
Table VI – Patient outcomes for those treated with alteplase within 0-3 hours of stroke onset (in accordance with US FDA label) versus 3-4.5 hours after stroke onset in the primary analysis: SWIFT PRIME, EXTEND-IA, REVASCAT and ESCAPE (entire SEER dataset)

| Outcome | IV alteplase only (n=264) | IV alteplase + Endovascular (n=280) | Adjusted* | Unadjusted |
|---------|--------------------------|-----------------------------------|------------|------------|
|         |                          |                                   | Effect size (95%CI) | p value    | Effect size (95%CI) | p value |
| Alteplase commenced 0-3h |                          |                                   |              |            |
| **Primary outcome** |                          |                                   |              |            |
| Functional outcome at 90 days (Modified Rankin Scale – mRS) | 3 (2-5) | 2 (1-4) | 2.4 (1.8, 3.3) | <0.001 | 2.3 (1.7, 3.1) | <0.001 |
| Ordinal analysis† – median (IQR) | 88 (33.3) | 158 (64) | 3.0 (2.0, 4.4) | <0.001 | 2.6 (1.8, 3.7) | <0.001 |
| **Secondary Outcomes** |                          |                                   |              |            |
| Independent functional outcome (mRS0-2) | 52 (19.7) | 107 (38.2) | 2.6 (1.7, 3.9) | <0.001 | 2.5(1.7, 3.7) | <0.001 |
| Excellent functional outcome (mRS0-1) | 74 (28.0) | 172 (61.4) | 4.7 (3.1, 7.0) | <0.001 | 4.1 (2.8, 5.9) | <0.001 |
| Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24h)‡ |                          |                                   |              |            |
| **Safety** |                          |                                   |              |            |
| Death | 43 (16.3) | 28 (10.0) | 0.54 (0.25-1.2) | 0.12 | 0.57 (0.34-0.97) | 0.04 |
| Symptomatic intracerebral hemorrhage§ | 8 (3.0) | 8 (2.9) | 0.73 (0.26, 2.1) | 0.56 | 0.92 (0.30, 2.8) | 0.88 |
| Parenchymal hematoma (PH) | 24 (9.1) | 16 (5.7) | 0.54 (0.27, 1.1) | 0.08 | 0.61 (0.31, 1.2) | 0.14 |
| Outcome | IV alteplase only (n=264) | IV alteplase + Endovascular (n=280) | Adjusted | Unadjusted |
|---------|--------------------------|-------------------------------------|----------|------------|
|         |                          |                                     | Effect size (95%CI) | p value | Effect size (95%CI) | p value |
| **Primary outcome** |                          |                                     |          |            |          |            |
| Functional outcome at 90 days (Modified Rankin Scale – mRS) | 4 (3-5) | 3 (2-4) | 3.1 (1.5, 6.5) | 0.003 | 2.8 (1.4, 5.6) | 0.004 |
| **Secondary Outcomes** |                          |                                     |          |            |          |            |
| Independent functional outcome (mRS0-2) | 14 (22.2) | 20 (40.8) | 3.7 (1.3, 10.4) | 0.01 | 2.3 (1.0, 5.3) | 0.05 |
| Excellent functional outcome (mRS0-1) | 8 (12.7) | 12 (24.5) | 2.8 (0.93, 8.3) | 0.07 | 2.1 (0.79, 5.8) | 0.13 |
| Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24h)† | 13 (20.6) | 24 (49.0) | 2.9 (1.2, 7.2) | 0.02 | 3.7 (1.6, 8.5) | 0.003 |
| **Safety** |                          |                                     |          |            |          |            |
| Death | 11 (7.5) | 5 (10.2) | 0.40 (0.10-1.5) | 0.17 | 0.52 (0.16-1.6) | 0.26 |
| Symptomatic intracerebral hemorrhage§ | 2 (3.2) | 1(2.0) | 0.88 (0.05, 16.3) | 0.93 | 0.64 (0.05, 7.4) | 0.72 |
| Parenchymal hematoma (PH) | 6 (9.5) | 9 (18.4) | 1.8 (0.52, 6.4) | 0.34 | 2.1 (0.70, 6.6) | 0.18 |

* adjusted for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS score, and time from onset to randomization
† Modified Rankin scale (mRS) ranges from normal (0) to death (6). Analysis combined mRS 5 & 6
‡ National Institutes of Health Stroke Scale (NIHSS) score (standardized neurological examination) ranges from normal (0) to death (42), 8 point reduction is highly clinically significant.
§ SICH - Symptomatic intracerebral hemorrhage defined by source trial
| Outcome | IV alteplase only (n=264) | IV alteplase + Endovascular (n=229) | Effect size adjusted | Effect size unadjusted |
|---------|--------------------------|--------------------------------------|----------------------|------------------------|
|         |                          |                                      | OR (95%CI)            | p value                |
| Alteplase commenced 0-3h |                          |                                      |                      |                        |
| Primary outcome |                          |                                      |                      |                        |
| Functional outcome at 90 days (Modified Rankin Scale – mRS) | 4 (2-5) | 2 (1-4) | 2.6 (1.8, 3.9) | <0.001 | 2.4 (1.7, 3.3) | <0.001 |
| Secondary Outcomes |                          |                                      |                      |                        |
| Independent functional outcome (mRS0-2) | 88 (33.3) | 134 (58.5) | 3.1 (2.1, 4.7) | <0.001 | 2.7 (1.9, 4.0) | <0.001 |
| Excellent functional outcome (mRS0-1) | 52 (19.7) | 91 (39.7) | 2.8 (1.8, 4.3) | <0.001 | 2.6 (1.8, 4.0) | <0.001 |
| Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24h) | 74 (28.0) | 141 (61.6) | 5.0 (3.3, 7.6) | <0.001 | 4.1 (2.8, 6.0) | <0.001 |
| Safety |                          |                                      |                      |                        |
| Death | 43 (16.3) | 24 (10.5) | 0.57 (0.27, 1.2) | 0.15 | 0.60 (0.32, 1.1) | 0.11 |
| Symptomatic intracerebral hemorrhage | 8 (3.0) | 6 (2.6) | 0.54 (0.14, 2.0) | 0.36 | 0.85 (0.25, 2.8) | 0.79 |
| Parenchymal hematoma (PH) | 24 (9.1) | 14 (6.1) | 0.54 (0.26, 1.1) | 0.09 | 0.63 (0.31, 1.25) | 0.18 |
### Alteplase commenced 3-4.5h

| Outcome                                                                 | IV alteplase only (n=176) | IV alteplase + Endovascular (n=178) | Adjusted | Unadjusted |
|-------------------------------------------------------------------------|----------------------------|--------------------------------------|-----------|------------|
| **Primary outcome**                                                     |                            |                                      | Effect size OR (95%CI) | p value     | Effect size OR(95%CI) | p value     |
| Functional outcome at 90 days (Modified Rankin Scale – mRS)             | 4 (3-5)                    | 3 (2-4)                              | 3.1 (1.4, 6.7)      | 0.006       | 2.9 (1.4, 5.9)      | 0.005       |
| **Secondary Outcomes**                                                  |                            |                                      |                      |             |                      |             |
| Independent functional outcome (mRS0-2)                                 | 14 (22.2)                  | 17 (40.5)                            | 3.9 (1.3, 11.6)     | 0.01        | 2.3 (0.96, 5.4)     | 0.06        |
| Excellent functional outcome (mRS0-1)                                   | 8 (12.7)                   | 10 (23.8)                            | 2.5 (0.81, 7.9)     | 0.11        | 2.1 (0.73, 5.9)     | 0.17        |
| Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24h)‡ | 13 (20.6)                  | 20 (47.6)                            | 2.7 (1.0, 6.9)      | 0.05        | 3.5 (1.5, 8.3)      | 0.005       |
| **Safety**                                                              |                            |                                      |                      |             |                      |             |
| Death                                                                   | 11 (17.5)                  | 5 (11.9)                             | 2.1 (0.55, 8.3)     | 0.27        | 1.6 (0.51, 5.2)     | 0.40        |
| Symptomatic intracerebral hemorrhage§                                    | 2 (3.2)                    | 1 (2.4)                              | 0.99 (0.05, 19.1)   | 0.99        | 0.76 (0.07, 9.0)    | 0.83        |
| Parenchymal hematoma (PH)                                               | 6 (9.5)                    | 9 (21.4)                             | 2.2 (0.61, 7.6)     | 0.23        | 2.6 (0.80, 8.4)     | 0.11        |

* for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS score, and time from onset to randomization

† Modified Rankin scale (mRS) ranges from normal (0) to death (6). Analysis combined mRS 5 & 6

‡ National Institutes of Health Stroke Scale (NIHSS) score (standardized neurological examination) ranges from normal (0) to death (42), 8 point reduction is highly clinically significant.

§ SICH - Symptomatic intracerebral hemorrhage defined by source trial
Table VIII – Patient outcomes for those treated with alteplase within 0-3 hours of stroke onset (in accordance with US FDA label) versus 3-4.5 hours after stroke onset in the sensitivity analysis 2: SWIFT PRIME, EXTEND-IA and REVASCAT (3 Solitaire-only trials)

| Outcome                                                                 | IV alteplase only (n=176) | IV alteplase + Endovascular (n=178) | Adjusted\* | Unadjusted |
|------------------------------------------------------------------------|---------------------------|-------------------------------------|------------|------------|
|                                                                         |   |                                      | Effect size OR (95%CI) | p value    | Effect size OR(95%CI) | p value    |
| **Primary outcome**                                                    |   |                                      | 3 (2-5)     | 2 (1-4)    | 2.3 (1.4, 3.6)        | <0.001     | 2.3 (1.6, 3.3)          | <0.001     |
| Functional outcome at 90 days (Modified Rankin Scale – mRS) Orbinal analysis\† – median (IQR) |   |                                      | 3 (2-5)     | 2 (1-4)    | 2.3 (1.4, 3.6)        | <0.001     | 2.3 (1.6, 3.3)          | <0.001     |
| **Secondary Outcomes**                                                 |   |                                      | 61 (34.7)   | 105 (59%)  | 2.9 (1.8, 4.7)        | <0.001     | 2.6 (1.7, 4.1)          | <0.001     |
| Independent functional outcome (mRS0-2)                                |   |                                      | 61 (34.7)   | 105 (59%)  | 2.9 (1.8, 4.7)        | <0.001     | 2.6 (1.7, 4.1)          | <0.001     |
| Excellent functional outcome (mRS0-1)                                  |   |                                      | 33 (18.8)   | 72 (40.4)  | 2.9 (1.7, 4.8)        | <0.001     | 2.9 (1.8, 4.8)          | <0.001     |
| Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24h)\‡ |   |                                      | 6 (16.7)    | 17 (54.8)  | 6.4 (1.5, 26.9)       | 0.01       | 4.4 (2.8, 6.9)          | <0.001     |
| **Safety**                                                             |   |                                      | 24 (13.6)   | 21 (11.8)  | 0.87 (0.44, 1.7)       | 0.69       | 0.84 (0.45, 1.6)        | 0.59       |
| Death                                                                  |   |                                      | 24 (13.6)   | 21 (11.8)  | 0.87 (0.44, 1.7)       | 0.69       | 0.84 (0.45, 1.6)        | 0.59       |
| Symptomatic intracerebral hemorrhage§                                  |   |                                      | 6 (3.4)     | 4 (2.2)    | 0.57 (0.15, 2.2)       | 0.41       | 0.53 (0.08, 3.6)        | 0.52       |
| Parenchymal hematoma (PH)                                              |   |                                      | 19 (10.8)   | 12 (6.7)   | 0.47 (0.21, 1.1)       | 0.07       | 0.59 (0.28, 1.3)        | 0.18       |
| **Alteplase commenced 3-4.5h** | N=36 | N=31 | Adjusted | Unadjusted |
|-------------------------------|------|------|----------|------------|
| **Outcome**                   |      |      |          |            |
| IV alteplase only (n=176)     |      |      |          |            |
| IV alteplase + Endovascular (n=178) |      |      |          |            |
| **Primary outcome**           |      |      |          |            |
| Functional outcome at 90 days  |      |      |          |            |
| (Modified Rankin Scale – mRS) | 4 (2-5) | 3 (2-4) | 2.6 (0.93, 7.3) | 0.07 | 2.5 (1.0, 6.1) | 0.05 |
| Ordinal analysis† – median (IQR) |      |      |          |            |
| **Secondary Outcomes**        |      |      |          |            |
| Independent functional outcome (mRS0-2) | 9 (25.0) | 13 (41.9) | 4.4 (1.0, 18.8) | 0.05 | 2.1 (0.72, 6.0) | 0.17 |
| Excellent functional outcome (mRS0-1) | 5 (13.9) | 7 (22.6) | 2.1 (0.48, 9.3) | 0.32 | 1.7 (0.48, 6.3) | 0.39 |
| Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24h)‡ | 6 (16.7) | 17 (54.8) | 6.4 (1.5, 26.9) | 0.01 | 6.1 (1.9, 19.1) | 0.003 |
| **Safety**                    |      |      |          |            |
| Death                         | 6 (16.7) | 4 (12.9) | 0.44 (0.05, 3.6) | 0.44 | 0.69 (0.15, 3.2) | 0.63 |
| Symptomatic intracerebral hemorrhage§ | 1 (2.8) | 0 (0) | NA | NA | NA | NA |
| Parenchymal hematoma (PH)     | 5 (13.9) | 6 (19.4) | 1.2 (0.26, 5.8) | 0.79 | 1.5 (0.40, 5.6) | 0.55 |

* for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS score, and time from onset to randomization
† Modified Rankin scale (mRS) ranges from normal (0) to death (6). Analysis combined mRS 5 & 6
‡ National Institutes of Health Stroke Scale (NIHSS) score (standardized neurological examination) ranges from normal (0) to death (42), 8 point reduction is highly clinically significant.
§ SICH - Symptomatic intracerebral hemorrhage defined by source trial
**Table IX** – Rates of mTICI at final angiogram and associated rates of independent outcome in the patients treated with the Solitaire as first device used (n=306), p=0.01 for trend.

| mTICI | mRS 0-2 - n (%)   |
|-------|-------------------|
| 0-1   | 8/21 (38%)        |
| 2a    | 25/49 (51%)       |
| 2b    | 62/117 (53%)      |
| 3     | 77/119 (65%)      |
**Figure I** – Distribution of modified Rankin scores at 90 days in the sensitivity analysis 1: SWIFT PRIME, EXTEND-IA, REVASCAT and ESCAPE (excluding those in whom a device other than Solitaire was used first). Panel A) overall results B) comparing age dichotomized at 70 years C) comparing age dichotomized at 80 years D) comparing those who did or did not receive intravenous alteplase prior to endovascular stent thrombectomy.
### C) Age <80 versus ≥80

#### Modified Rankin Scale Score

|            | Control (N=322) | Intervention (N=274) |
|------------|----------------|----------------------|
| 0          | 9              | 14                   |
| 1          | 10             | 25                   |
| 2          | 15             | 20                   |
| 3          | 18             | 15                   |
| 4          | 22             | 10                   |
| 5          | 14             | 6                    |
| 6          | 12             | 11                   |

### D) Alteplase vs no alteplase treatment

#### Modified Rankin Scale Score

|            | Control (N=323) | Intervention (N=266) |
|------------|----------------|----------------------|
| 0          | 9              | 14                   |
| 1          | 10             | 23                   |
| 2          | 13             | 19                   |
| 3          | 17             | 16                   |
| 4          | 20             | 12                   |
| 5          | 15             | 5                    |
| 6          | 16             | 11                   |

|            | Control (N=55) | Intervention (N=61) |
|------------|----------------|---------------------|
| 0          | 5              | 12                  |
| 1          | 5              | 23                  |
| 2          | 16             | 20                  |
| 3          | 11             | 16                  |
| 4          | 29             | 5                   |
| 5          | 15             | 5                   |
| 6          | 18             | 20                  |
Figure II – Distribution of modified Rankin scores at 90 days in the sensitivity analysis 2: SWIFT PRIME, EXTEND-IA and REVASCAT (Solitaire-only trials). Panel A) overall results B) comparing age dichotomized at 70 years C) comparing age dichotomized at 80 years D) comparing those who did or did not receive intravenous alteplase prior to endovascular thrombectomy.
C) Age <80 versus ≥80

Modified Rankin Scale Score

|       | Control (N=217) | Intervention (N=206) |
|-------|-----------------|----------------------|
|       | 8               | 14                   |
| 0%    | 9               | 24                   |
| 20%   | 16              | 19                   |
| 40%   | 18              | 14                   |
| 60%   | 19              | 10                   |
| 80%   | 15              | 7                    |
| 100%  | 14              | 12                   |

Patients (%)

D) Alteplase vs no alteplase treatment

Modified Rankin Scale Score

|       | Control (N=207) | Alteplase (N=203) |
|-------|-----------------|-------------------|
|       | 9               | 15                |
| 0%    | 9               | 18                |
| 20%   | 15              | 19                |
| 40%   | 18              | 15                |
| 60%   | 19              | 14                |
| 80%   | 15              | 10                |
| 100%  | 14              | 6                 |

Patients (%)

|       | Control (N=24) | No Alteplase (N=33) |
|-------|----------------|---------------------|
|       | 4              | 6                   |
| 0%    | 8              | 18                  |
| 20%   | 13             | 18                  |
| 40%   | 13             | 24                  |
| 60%   | 17             | 9                   |
| 80%   | 21             | 6                   |
| 100%  | 25             | 18                  |

Patients (%)
Figure III – Treatment effect in pre-defined subgroups (Forest plot) for sensitivity analysis 1: SWIFT PRIME, EXTEND-IA, REVASCAT and ESCAPE (excluding those in whom a device other than Solitaire was used first). Odds ratios with 95% confidence intervals, analyses adjusted for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS score, and time from onset to randomization.

|                          | Control n=386 | Intervention n=327 | Odds ratio (95% CI) | Interaction p-value |
|--------------------------|---------------|--------------------|---------------------|---------------------|
| Age                      |               |                    |                     |                     |
| <70y                     | 191           | 179                | 2.61 (1.77, 3.67)   | 0.34                |
| ≥70y                     | 192           | 148                | 3.27 (1.99, 5.36)   | 0.09                |
| <80y                     | 328           | 274                | 2.60 (1.91, 3.54)   | 0.09                |
| ≥80y                     | 55            | 53                 | 4.75 (1.95, 11.58)  |                     |
| Sex                      |               |                    |                     |                     |
| Male                     | 193           | 156                | 2.89 (1.92, 4.34)   | 0.77                |
| Female                   | 191           | 171                | 2.76 (1.86, 4.09)   |                     |
| NIHSS                    |               |                    |                     |                     |
| 0-15                     | 155           | 137                | 3.26 (2.06, 5.14)   | 0.98                |
| 16-20                    | 150           | 125                | 3.16 (1.99, 5.00)   |                     |
| >20                      | 76            | 62                 | 3.67 (1.86, 8.12)   |                     |
| Site of vessel occlusion |               |                    |                     |                     |
| ICA                      | 66            | 52                 | 6.80 (3.12, 14.81)  | 0.09                |
| M1 MCA                   | 287           | 237                | 2.53 (1.83, 3.49)   |                     |
| M2 MCA                   | 23            | 30                 | 1.85 (0.57, 6.06)   |                     |
| Tandem occlusion         |               |                    |                     |                     |
| Tandem                   | 41            | 33                 | 6.04 (2.29, 15.90)  | 0.40                |
| No Tandem                | 345           | 294                | 2.63 (1.95, 3.56)   |                     |
| ASPECTS                  |               |                    |                     |                     |
| 0-5                      | 31            | 20                 | 0.88 (0.24, 3.27)   | 0.03                |
| 6-8                      | 152           | 138                | 2.55 (1.63, 4.00)   |                     |
| 9-10                     | 197           | 160                | 3.40 (2.27, 5.08)   |                     |
| IV thrombolysis          |               |                    |                     |                     |
| Alteplase                | 327           | 266                | 2.65 (1.86, 3.77)   | 0.62                |
| No alteplase             | 59            | 61                 | 3.86 (1.81, 8.21)   |                     |
| Onset to randomization   |               |                    |                     |                     |
| <5h                      | 308           | 269                | 2.95 (2.16, 4.03)   | 0.50                |
| >5h                      | 75            | 58                 | 2.18 (1.06, 4.49)   |                     |
**Figure IV** – Treatment effect in pre-defined subgroups (Forest plot) for sensitivity analysis 2: SWIFT PRIME, EXTEND-IA and REVASCAT. Odds ratios with 95% confidence intervals, analyses adjusted for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS score, and time from onset to randomization.

(Solitaire-only trials)
STATISTICAL ANALYSIS PLAN FOR THE INTEGRATION OF SAFETY AND EFFICACY DATA

PRODUCT UNDER INVESTIGATION:
Solitaire™ FR Revascularization Device

CLINICAL STUDIES FOR INTEGRATION:
EXTEND-IA: EXTENDING THE TIME FOR THROMBOLYSIS IN EMERGENCY NEUROLOGICAL DEFICITS – INTRA-ARTERIAL

ESCAPE: ENDOVASCULAR TREATMENT FOR SMALL CORE ANTERIOR CIRCULATION PROXIMAL OCCLUSION WITH EMPHASIS ON MINIMIZING CT TO RECANALIZATION TIMES

REVASCAT: RANDOMIZED TRIAL OF REVASCULARIZATION WITH SOLITAIRE FR® DEVICE VERSUS BEST MEDICAL THERAPY IN THE TREATMENT OF ACUTE STROKE DUE TO ANTERIOR CIRCULATION LARGE VESSEL OCCLUSION PRESENTING WITHIN 8 HOURS OF SYMPTOM ONSET

SWIFT PRIME: SOLITAIRE™ FR WITH THE INTENTION FOR THROMBECTOMY AS PRIMARY ENDOVASCULAR TREATMENT FOR ACUTE ISCHEMIC STROKE

Statistical Method and Analyses to Support the SEER working group (SWIFT PRIME, ESCAPE, EXTEND IA, REVASCAT)

DATE AND VERSION
November 1, 2015 (Version 1.0)

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| Antonio Davalos (REVASCAT)            | Signature | Date         |
| Dr. Jeff Saver (SWIFT PRIME)          | Signature | Date         |
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### 2. LIST OF ABBREVIATIONS AND DEFINITIONS

| Abbreviation | Abbreviated Term                          | Definition                                                                                                                                 |
|--------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| AAE          | Anticipated Adverse Event                 | Any decline away from the patient’s baseline health, whether related to the investigational device, the procedure or the disease that is predefined in the Investigational Plan, CRFs, and Instructions For Use. |
| ADE          | Adverse Device Effect                     | Any untoward and unintended response to a medical device including insufficiencies or inadequacies in instructions for use or deployment of the device. |
| AE           | Adverse Event                             | Any decline away from the patient’s baseline health. Any decline from the patient’s pre-treatment condition that occurs during the course of the clinical Study, after study enrollment, whether related to the investigational device, the procedure or the disease. Treatment includes all investigational or commercially approved products administered according to the Investigational Plan. |
| AICH         | Asymptomatic Intracranial Hemorrhage      | Any intracranial hemorrhage within 24 hours not meeting the criteria for symptomatic intracranial hemorrhage.                                |
| AIS          | Acute Ischemic Stroke                     | Focal symptoms due to cerebral infarction from an arterial occlusion.                                                                        |
| CEC          | Clinical Events Committee                 | Independent committee responsible for the review and validation of all complications that occur over the course of the Study.              |
| DICOM        | Digital Imaging and Communications in Medicine | The standard foundation for imaging and image management; A global information-technology standard designed to ensure the interoperability of systems used to produce, store, display, process, send, retrieve, query, or print medical images and derived structured documents. |
| DSMB         | Data Safety and Monitoring Board          | An independent data monitoring committee, established by the sponsor, to assess at intervals, the progress of a clinical trial, the safety data and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify or stop a trial. |
| DWI          | Diffusion Weighted Imaging                | Imaging obtained using magnetic resonance sequences that measure diffusion properties of water within tissue.                               |
| eCRF         | Electronic Case Report Form               | An electronic document designed to record all of the protocol requested information to be reported to the sponsor on each study patient. eCRFs are “living documents” in the respect that new information on the patient is continually gathered throughout the study. |
| FR           | Flow Restoration                          | Restore flow through a vessel that is occluded by blood clot.                                                                             |
| GCP          | Good Clinical Practice                    | The regulations enforced in the US by the FDA’s bioresearch monitoring program for medical devices, consisting of 21 CFR 812, -50 and -56. The GCP requirements are also stated in “Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, ICH, April 1996: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported are credible and accurate, and that the rights, integrity and confidentiality of trial patients are protected. |
| Abbreviation | Abbreviated Term                                      | Definition                                                                                                                                                                                                 |
|--------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HIPAA        | Health Insurance Portability and Accountability Act  | Health Insurance Portability and Accountability Act of 1996. Title II of the Act, “Administrative Simplification” refers in large part to federal privacy rules that require health care providers and others to obtain written authorization from patients or their legally authorized representatives before using or disclosing their “Protected Health Information” (PHI) for any purposes other than treatment, billing, quality assurance and education. |
| ICF          | Informed Consent Form                                 | The written, signed and dated document that provides objective evidence of the process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the trial that are relevant to the patient’s decision to participate (21 CFR 50). |
| ICH          | International Conference for Harmonization            | An Organization whose main purpose is to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. |
| IDE          | Investigational Device Exemption                      | An approved IDE permits a device that would otherwise be required to comply with a performance standard or would require a premarket approval to be shipped lawfully for the purpose of conducting investigations of that device (21 CFR 812). |
| I/E          | Inclusion/Exclusion Criteria                          | A list of conditions that would include or exclude a patient from enrolling/participating in a clinical study as outlined in the study protocol.                                                             |
| IEC          | Independent Ethics Committee                          | An independent body, constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human patients involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities and the methods and material to be used in obtaining and documenting informed consent of the trial patients. |
| INR          | International Normalized Ratio                        | Ratio that measures the time it takes for blood to clot and compares it to a reference normal value.                                                                                                           |
| IP           | Investigational Plan                                 | The clinical protocol and associated documents whose required composition is described in 21 CFR 812.25.                                                                                                     |
| IRB          | Institutional Review Board                            | Any board, committee, or other group formally designated by an institution to review biomedical research involving patients and established, operated and functioning in conformance with 21 CFR 56. |
| ISO          | International Organization for Standardization       | International standard-setting body composed of representatives from various national standards organizations.                                                                                               |
| ITT          | Intent-to-Treat                                       | The ITT population includes all patients with data for a given endpoint and are assessed according to randomized assignment regardless of the treatment actually received. |
| IV t-PA      | Intravenous Tissue Plasminogen Activator              | Medical treatment of myocardial infarction with ST-elevation (STEMI), acute ischemic stroke (AIS), acute massive pulmonary embolism, and central venous access devices (CVAD) administered intravenously. t-PA is an enzyme (serine protease) found in endothelial cells that line the blood vessels that converts plasminogen into plasmin, an enzyme responsible for blood clot breakdown. |
| IVRS         | Interactive Voice Response System                     | Accessed by telephone, it is a system that randomly assigns the patient to a treatment arm based on the pre-determined randomization algorithm.                                                               |
| IWRS         | Interactive Web Response System                       | Accessed by internet, it is a system that randomly assigns the patient to a treatment arm based on the pre-determined randomization algorithm.                                                               |
| Abbreviation | Abbreviated Term | Definition |
|--------------|-----------------|------------|
| MedDRA       | Medical Dictionary for Regulatory Activities | Standardized medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorized for sale. Products covered by the scope of MedDRA include pharmaceuticals, vaccines and drug-device combination products. |
| mRS          | Modified Rankin Score | Scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke. 0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 Dead |
| NIHSS        | National Institute of Health Stroke Scale | Method for quantifying neurologic deficits developed by the National Institutes of Health. It is used to assess the severity of a stroke. |
| OC/RDC       | ORACLE Clinical/Remote Data Capture | EDC system that will be deployed to support data collection for this study. |
| PTT          | Partial Thromboplastin Time | Measure of how long it takes for blood to clot. This test is used to determine if a patient has bleeding or clotting problems. |
| PWI          | Perfusion weighted imaging | Imaging obtained using contrast that measures the brain perfusion including vascular transit time, cerebral blood volume, and cerebral blood flow. |
| QALY         | Quality-adjusted life year | A measure that takes into account both the quantity and quality of life generated by healthcare interventions. It is the arithmetic product of life expectancy and a measure of the quality of the remaining life-years. |
| RAPID        | Rapid processing of Perfusion and Diffusion | A system that computes quantitative perfusion maps (cerebral blood volume, CBV; cerebral blood flow, CBF; mean transit time, MTT; and the time until the residue function reaches its peak, T(max)) using deconvolution of tissue and arterial signals. |
| SAE          | Serious Adverse Event | Adverse Event that led to death or serious deterioraion in the health of a patient that resulted in a life threatening illness or injury, permanent impairment of a body structure or a body function, hospitalisation or prolongation of existing hospitalisation, medical or surgical intervention to prevent permanent impairment to a body structure or a body function or is a congenital anomaly/birth defect. |
| Abbreviation | Abbreviated Term | Definition |
|--------------|------------------|------------|
| SICH         | Symptomatic Intracranial Hemorrhage | Any PH1, PH2, RIH, SAH, or IVH associated with a 4 points or more worsening on the NIHSS within 24 hrs. PH1: Hematoma within ischemic field with some mild space-occupying effect but involving ≤ 30% of the infarcted area. PH2: Hematoma within ischemic field with space-occupying effect involving >30% of the infarcted area RIH: Any intraparenchymal hemorrhage remote from the ischemic field IVH: Intraventricular hemorrhage SAH: Subarachnoid hemorrhage |
| TICI         | Thrombolysis in Cerebral Infarction Perfusion Categories | 0 = No perfusion. No antegrade flow beyond the point of occlusion. 1 = Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion 2A = Perfusion of less than half of the vascular distribution of the occluded artery (eg, filling and perfusion through 1 M2 division) 2B = Perfusion of half or greater of the vascular distribution of the occluded artery (eg, filling and perfusion through 2 or more M2 divisions) 3 = Full perfusion with filling of all distal branches |
| UADE         | Unanticipated Adverse Device Effect | Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the Investigational Plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients. |
| ULN          | Upper Limit of Normal | Upper limit within a particular range. |
3. **INTRODUCTION**

This Statistical Analysis Plan (SAP) describes the statistical methods to be used for the analysis of the integrated safety and efficacy data from 4 randomized parallel-design studies where the objective was to treat patients presenting with an acute ischemic stroke. This plan has 5 elements:

- Comparison of the baseline patient-level data across the 4 studies,
- statistical analyses to evaluate safety and efficacy across the 4 studies using the analysis dataset rules from each of the individual studies,
- pooling the statistical evidence across the 4 randomized studies using the analysis dataset rules from each of the individual studies,
- pooling the patient-level data across the 4 randomized studies, generating an integrated database with a common set of analysis dataset rules
- statistical analyses to evaluate safety and efficacy across the 4 studies using the integrated database with a common set of analysis dataset rules

The tabulations and information from this SAP will provide an unbiased examination of the safety and efficacy of mechanical embolectomy relative to medical management alone. The integrated database will also allow examination of the safety and efficacy of mechanical embolectomy with the Solitaire FR device.

These analyses will be presented to the SEER committee for review, publication, and presentation. The approach used for the integration outlined in this document will also generate the requisite information to support the generation of an integrated Clinical Study Report (CSR), including the detailed descriptions of the statistical methodologies to be applied.

The structure and content of this plan provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for medical devices, as well as the Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.

3.1. **Study Design and Enrollment for EXTEND-IA, ESCAPE, REVASCAT AND SWIFT PRIME**

The clinical trial designs and control groups were similar across the 4 studies. The source of the summarized information from each study, along with the information regarding recruitment, was ClinicalTrials.gov.

ESCAPE was a multi-center, randomized, single blind (Outcomes Assessor) parallel design study open to patients ≥18 years of age enrolled within 12 hours of last being seen normal with a baseline NIHSS > 5 at the time of randomization. Several devices were permitted to be used, with the Solitaire stent retriever used in the majority. On the advice of the DSMB, trial recruitment was halted for efficacy and the study was terminated.

EXTEND-IA was a multi-center, randomized, single blind (Outcomes Assessor) parallel design study open to patients ≥18 years of age enrolled within 4.5 hours of stroke onset. Only the
Solitaire stent retriever device was used. On the advice of the DSMB, trial recruitment was halted for efficacy and the study was terminated.

REVASCAT was a multi-center, randomized, single blind (Outcomes Assessor) parallel design study open to patients 18 to 85 years of age presenting within 8 hours of symptom onset consistent with an acute ischemic stroke. Only the Solitaire stent retriever device was used. On the advice of the DSMB, trial recruitment was halted for efficacy and the study was terminated.

SWIFT PRIME was a multi-center, randomized, single blind (Outcomes Assessor) parallel design study open to patients 18-85 years of age. Eligible patients were treated within 6 hours of the onset of stroke symptoms and within 1.5 hours from CTA or MRA to groin puncture and had a baseline NIHSS ≥ 8 and < 30 at the time of randomization. Only the Solitaire stent retriever device was used. This study was completed in January 2015.

Collectively, the primary objective of all 4 studies was the same: to evaluate the hypothesis that mechanical embolectomy is superior to medical management alone in achieving a favorable outcome based on the distribution of the modified Rankin Scale at 90 days in patients presenting with an acute large vessel ischemic stroke.

The methods for assigning patients to either mechanical embolectomy or medical management through randomization were also similar across the 4 studies regarding stratification.

For EXTEND-IA, patients were randomized to receive intra-arterial clot retrieval after IV tPA or IV tPA alone. Patients randomized to treatment were stratified for site of baseline arterial occlusion into one of three groups: Internal carotid artery (ICA), proximal middle cerebral artery (MCA –M1), or distal middle cerebral artery (MCA – M2).

For ESCAPE, patients were randomized to receive intra-arterial clot retrieval after IV tPA or IV tPA alone. The randomization was stratified based on age, baseline stroke severity (NIHSS), initial arterial lesion location, ASPECTS score, and site.

For REVASCAT, patients were randomly assigned in an equal ratio to either mechanical embolectomy or medical management, stratifying on age (≤70 or >70 years), baseline NIHSS (<17 verses >=17), therapeutic window (≤4.5 or >4.5 hours), investigational site and occlusion site (intracranial ICA or M1).

For SWIFT PRIME, patients were randomized to IV tPA alone or IV tPA plus Solitaire. The randomization ratio for mechanical embolectomy or medical management was 1:1 and balanced within investigational sites and by baseline NIHSS severity (≤ 17 versus >17), age (<70 years versus ≥70 years at the time of randomization) and occlusion location (M1 versus all other).

The time to treatment was an important factor for inclusion in each of the 4 studies. For EXTEND-IA, patients were to be enrolled within 6 hours of stroke onset. For ESCAPE, the time to treatment had to be within 12 hours of stroke symptoms, endovascular treatment (groin puncture) within 60 minutes, target CT to first recanalization of 90 minutes. For REVASCAT, the time to treatment had to be within 8 hours of symptom onset. For SWIFT PRIME, the time to treatment had to be within 6 hours of onset of stroke symptoms and within 1.5 hours (90 minutes) from CTA or MRA to groin puncture.
Time Points for Evaluation Across the 4 Studies

The schedule of assessment for each of the 4 randomized studies only fully aligned for the baseline / pre-procedure and 90 day evaluation. The post-randomization evaluations were similar in terms of timing; however, the time windows for evaluation did not completely align. Specifically, the first post-procedure assessment in SWIFT PRIME had a 27 hour +/- 6 hour window (21 to 33 hours post procedure). ESCAPE defines the time point simply as 24 hours or 1 day; it is indeterminate what the exact window was; this will be quantified based on the actual data. REVASCAT had a 22 to 36 hour time window. For integration purposes, all data collected at the ~24 hour post-randomization evaluation will be integrated for the Level 1 presentation and the distributions will be compared across the 4 randomized studies. For the Level 2 presentation of the safety and efficacy results, only evaluations recorded within 21 to 36 hours of randomization will be considered.

Multiple observations for a patient within a time window

If a patient has multiple observations within a time window for the -24 hour post randomization evaluation, the value recorded closest to 24 hours will be used.

Retaining Clinical Center or Site in the Model for Analysis

In each of the 4 multicenter studies, the randomization scheme was balanced intra-center. Within each center, patients were stratified relative to a number of factors. The timing of individual examinations and the time windows are presented below.

| Evaluations   | Pre-Rx | Rx | 2-8 H | D 1 | D 2 | D 3 | D 5 | D 7-10 | D 30 | D 90 |
|---------------|--------|----|-------|-----|-----|-----|-----|--------|------|------|
| ESCAPE        | ●      | ●  | ●     | ●   | ●   | ●   | ●   | ●      | ●    | ●    |
| EXTEND-IA     | ●      | ●  | ●     | ●   | ●   | ●   | ●   | ●      | ●    | ●    |
| REVASCAT      | ●      | ●  | ●     |     | ●   | ●   | ●   | ●      | ●    | ●    |
| SWIFT PRIME   | ●      | ●  | ●     |     | ●   | ●   | ●   | ●      | ●    | ●    |

| Time Windows  | D 1   | D 2   | D 3   | D 5   | D 7-10 | D 30   | D 90   |
|---------------|-------|-------|-------|-------|--------|--------|--------|
| ESCAPE        | 18H-30H | 42H to 54H | D4 to D6 | D25 to D35 | D83 to D97 |
| EXTEND-IA     | 18H-30H | D2 to D4 |       |        |        |        |        |
| REVASCAT      | 22H to 36H | D3 to D7 |       |        |        |        |        |
| SWIFT PRIME   | 21H to 33H |       |       | D7 to D10 | D23 to D37 | D75 to D105 |
|        | MRS     | Pre-Rx | Rx    | 2-8 H | D 1 | D 2 | D 3 | D 5 | D 7-10 | D 30 | D 90 |
|--------|---------|--------|-------|-------|-----|-----|-----|-----|--------|------|------|
| **ESCAPE** |         | ⬤      |       |       | ⬤   |     |     |     | ⬤      | ⬤    |      |
|         |         |        |       |       |     |     |     |     |        |      |      |
|         |         |        |       |       |     |     |     |     |        |      |      |
| **EXTEND-IA** |        | ⬤      |       |       | ⬤   |     |     |     | ⬤      | ⬤    |      |
| **REVASCAT** |        | ⬤      |       |       | ⬤   |     |     | ⬤   | ⬤      | ⬤    |      |
| **SWIFT PRIME** |        | ⬤      |       |       | ⬤   |     |     | ⬤   | ⬤      | ⬤    | ⬤    |

|        | NIHSS   | Pre-Rx | Rx    | 2-8 H | D 1 | D 2 | D 3 | D 5 | D 7-10 | D 30 | D 90 |
|--------|---------|--------|-------|-------|-----|-----|-----|-----|--------|------|------|
| **ESCAPE** |         | ⬤      | ⬤     | ⬤     | ⬤   |     |     |     | ⬤      | ⬤    | ⬤    |
|         |         |        |       |       |     |     |     |     |        |      |      |
| **EXTEND-IA** |        | ⬤      | ⬤     | ⬤     | ⬤   |     |     | ⬤   | ⬤      | ⬤    |      |
| **REVASCAT** |        | ⬤      | ⬤     | ⬤     | ⬤   |     |     | ⬤   | ⬤      | ⬤    |      |
| **SWIFT PRIME** |        | ⬤      | ⬤     | ⬤     | ⬤   |     |     | ⬤   | ⬤      | ⬤    | ⬤    |

|        | BARTHEL | Pre-Rx | Rx    | 2-8 H | D 1 | D 2 | D 3 | D 5 | D 7-10 | D 30 | D 90 |
|--------|---------|--------|-------|-------|-----|-----|-----|-----|--------|------|------|
| **ESCAPE** |         | ⬤      | ⬤     | ⬤     | ⬤   |     |     |     | ⬤      | ⬤    | ⬤    |
|         |         |        |       |       |     |     |     |     |        |      |      |
| **EXTEND-IA** |        | ⬤      | ⬤     | ⬤     | ⬤   |     |     | ⬤   | ⬤      | ⬤    |      |
| **REVASCAT** |        | ⬤      | ⬤     | ⬤     | ⬤   |     |     | ⬤   | ⬤      | ⬤    |      |
| **SWIFT PRIME** |        | ⬤      | ⬤     | ⬤     | ⬤   |     |     | ⬤   | ⬤      | ⬤    | ⬤    |

- **ESCAPE**: 24+/6 hours post-random.
- **EXTEND-IA**: 27+/6 hours post-random.
- **SWIFT PRIME**: 27+/6 hours post-random.
3.2. Selection of the computational Model for Analysis

The selection of a computational model was based on our expectation about whether or not the studies shared a common effect size, and on our research goals in performing the analysis. The use of a fixed-effect model would be appropriate if we believed that the studies are functionally identical, and our goal is to compute the common effect size for the identified population, and not to generalize to other populations. Given the studies were all conducted independently and in different geographic locations, it would be unlikely that all the studies were functionally equivalent. The consensus opinion of the SEER working group was that these studies differed in ways that could impact the outcomes and therefore one should not assume a common effect size. Additionally, the goal of this analysis is to generalize to a range of scenarios. Therefore, if one did make the argument that all the studies used an identical, narrowly defined population, then it would not be possible to extrapolate from this population to others, and the utility of the analysis would be severely limited. We acknowledge the number of studies being analyzed is small and the estimate of the between-studies variance may lack precision.

In summary, a fixed-effect meta-analysis estimates a single effect that is assumed to be common to every study, while a random-effects meta-analysis estimates the mean of a distribution of effects. Study weights are more balanced under the random-effects model than under the fixed-effect model. Large studies are assigned less relative weight and small studies are assigned more relative weight as compared with the fixed-effect model. The standard error of the summary effect and the confidence intervals for the summary effect are wider under the random-effects model than under the fixed-effect model. The selection of a model must be based solely on the question of which model fits the distribution of effect sizes, and takes into account the relevant sources of error; for this reason, we believe the application of a more conservative random effects model is justified.
4. ANALYSIS POPULATIONS

The following populations will be considered for the integration and presentation of the data:

Enrolled Population
The *Enrolled Population* includes all consented patients in each of the 4 studies who were randomized, independent of the administration of tPA or the outcome of the procedure. The randomized groups for comparison will be referred to as the *Standard of Care Plus Thrombectomy* and *Standard of Care Alone*. In the analysis tables, the *Standard of Care Plus Thrombectomy* will be referred to as the *Device Group*; *Standard of Care Alone* will be referred to as the *Control Group*.

The primary analysis will be performed in the 3 trials that used only the Solitaire device (SWIFT PRIME, EXTEND-IA and REVASCAT). Two sensitivity analyses will be performed including additional data from the ESCAPE trial 1) including only those patients from the endovascular arm in which the first device actually used was Solitaire or would have been used had a target clot been still present and accessible (Solitaire intention to treat analysis), and 2) including all patients in the endovascular arm, whether or not Solitaire was used first (4 trial analysis).

Addendum 30-Dec-2015 – in response to journal reviewer’s suggestion, the primary analysis was changed to be the full four trial dataset and the 3 trial analysis was instead presented as the second sensitivity analysis.

IV tPA Treated Within 3-Hours Population (in accordance with FDA label for alteplase)
The *IV tPA Treated Within 3-Hours Population* includes all consented patients in each of the 3 populations studied who were administered IV tPA within 3 hours of the stroke symptom onset.
5. BASELINE INFORMATION

The demographic, physical characteristic, neurologic history and pre-procedure imaging data will be evaluated to assess the magnitude of the differences in the patients enrolled in the 4 studies. Probability values to evaluate the differences will be considered significant if the value is <0.05. The description presented below describes the method of summarization and comparison of the following factors:

- Age (years)
- Sex
- Race
- NIHSS (Baseline) Score
- Previously Diagnosed Atrial Fibrillation
- Hypertension
- Diabetes Mellitus
- Current or Past Tobacco Use
- Serum Glucose (mg/dL)
- Site of Vessel Occlusion
- Non-Contrast CT ASPECTS

5.1. Evaluation and Integration of the Baseline Demographic Data for EXTEND-IA, ESCAPE, REVASCAT AND SWIFT PRIME

All enrolled patients from the 4 studies will be summarized with respect to age at entry into the study, Sex, ethnicity, and race. Age will be calculated as [Date of Informed Consent – Date of Birth] / 365.25 rounded down to the nearest integer. Age will be reported in years (yr) and summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (i.e., minimum and maximum values) and compared between the randomized treatment assignments using a mixed model specifying the distribution as continuous with study and study-by-treatment as random effects. Patients with missing data that cannot be resolved will not be included in the tabulation and excluded from the summary statistics. The number and percent of patients ≤70 and > 70 and ≤80 and >80 years of age at the time of enrollment will be presented by randomized treatment assignment and study, and independent of study using counts and percentages. The proportion of patients in each mutually-exclusive category will be compared between the randomized groups using a mixed model specifying the distribution as binomial with study and study-by-treatment as random effects. Results will also be generated for the IV tPA Treated Population (Tables 1a) and the IV tPA Treated Within 3-Hours Population (Tables 1b).
5.2. Evaluation and Integration of the Baseline Physical Characteristic Data for EXTEND-IA, ESCAPE, REVASCAT AND SWIFT PRIME

All enrolled patients from the 4 studies will be presented in Table 2.0 entitled *Summary of Physical Characteristics Recorded at Baseline* (Enrolled Population). This table will summarize the physical characteristic data by study with respect to height (inches), weight (lbs.), BMI, and Pre-stroke mRS. Height, weight, BMI, and pre-stroke mRS will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (*i.e.*, minimum and maximum values) and compared between the randomized treatment assignments using a mixed model specifying the distribution as continuous with study and study-by-treatment as random effects. Patients with missing data that cannot be resolved will not be included in the tabulation and excluded from the summary statistics.
6. **TPA AND MECHANICAL THROMBECTOMY INFORMATION**

Patients will be classified as having received tPA (Yes or No) and if they underwent mechanical thrombectomy (Yes or No). Specific information regarding the time to administration of tPA and the thrombectomy procedure will also be used in the logistic and random-effect models.

6.1. **Evaluation of the Time to Specific Events**

- Time (minutes) from Stroke Onset to Hospital Arrival
- Treatment with Intravenous Alteplase
- Time (minutes) from Stroke Onset to Treatment with Intravenous Alteplase
- Time (minutes) from Hospital Arrival to Treatment with Intravenous Alteplase
- Time (minutes) from Treatment with Intravenous Alteplase to Randomization
- Time (minutes) from Stroke Onset to Arterial Access
- Time (minutes) from Hospital Arrival to Arterial Access
- Time (minutes) from Initial Imaging to Arterial Access
- Time (minutes) from Treatment with Intravenous Alteplase to Arterial Access
- Time (minutes) from Arterial Access to mTICI 2b/3 or Completion
- Time (minutes) from Stroke Onset to mTICI 2b/3 or Completion

Individual times will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (i.e., minimum and maximum values) and compared between the randomized treatment assignments using a mixed model specifying the distribution as continuous with study and study-by-treatment as random effects. Patients with missing data that cannot be resolved will not be included in the tabulation and excluded from the summary statistics.
7. SAFETY INFORMATION

The assessment of safety will be based on adverse events reported within 90 days of randomization and the incidence of symptomatic ICH (intracranial hemorrhage) within 21 to 36 hours of randomization.

7.1. Assessment of the Safety Data for EXTEND-IA, ESCAPE, REVASCAT AND SWIFT PRIME

The incidence of symptomatic ICH will be defined in accordance with the definitions used in each trial.

Adverse events will be presented according to 3 time intervals: peri-procedural adverse events, adverse events reported within 30 days of randomization, and adverse events within 90 days of randomization. *Peri-procedural adverse events* are events that occur during the thrombectomy procedure.

An adverse event is defined as any decline away from the patient’s baseline health. Any decline from the patient’s pre-treatment condition that occurs during the course of the clinical Study, after starting treatment, whether related to the investigational device, the procedure or the disease. A serious adverse event is an event that leads to death, fetal distress, fetal death or a congenital abnormality or birth defect, and serious deterioration in the health of a patient that resulted in a life-threatening illness or injury such as a permanent impairment of a body structure or a body function, requiring in-patient hospitalization or prolongation of existing hospitalization, results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function. Treatment includes all investigative or commercially approved products administered according to the Investigational Plan from each of the 4 studies. The following information regarding each adverse event includes the date and time of onset and resolution (duration), intensity, whether it was serious, any required treatment or action taken, outcome, relationship to the investigational procedure or tPA, and whether the adverse event caused withdrawal from the study.

**Mild:** Patient is aware of event or symptom but event/symptom is easily tolerated.

**Moderate:** Patient experiences sufficient discomfort to interfere with or reduce their usual level of activity.

**Severe:** Significant impairment of functioning; patient is unable to carry out usual activities.

The relationship of the adverse events across the studies were defined using different scales.

For SWIFT PRIME, there were 9 coded categories:
1 = IV t-PA Related,
2 = Device Related: Solitaire,
3 = Device Related: Ancillary,
4 = Device Related: Unknown,
5 = Procedure/Treatment Related,
6 = Study Disease Related,
7 = Concomitant Disease,
8=Unknown, and
9=Other.

For ESCAPE, there were 5 coded categories for relationship to the *investigational product*:
1=Not related,
2=Unlikely,
3=Possible,
4=Probable,
5=Definite

For ESCAPE, there were 2 categories for relationship to the endovascular procedure; yes or no.

For REVASCAT, *relationship* to the *investigational device or procedure* was collected using the following 5 categories:
1=Definitive
2=Probable
3=Possible
4=Conditional
5=Not related

For EXTEND-IA, *relationship* to the *investigational device* was collected using the following 5 categories:
1=Not related,
2=Unlikely,
3=Possible,
4=Probable,
5=Definite
8. EFFICACY AND SAFETY INFORMATION

There are 7 outcomes that will be summarized using the integrated data from the 4 studies in the primary and two sensitivity analysis populations described above. The primary outcome is ordinal analysis of the mRS at 90 days. Secondary outcomes are functional independence (mRS ≤ 2 at 90 days), excellent functional outcome (mRS 0-1), the proportion of patients with a reduction in NIHSS between baseline and 21-36 hours of ≥8 points or reaching 0-1, death due to any cause at 90 days, symptomatic intracerebral hemorrhage and parenchymal hematoma.

8.1. Evaluation of the 90-Day mRS Data for EXTEND-IA, ESCAPE, REVASCAT AND SWIFT PRIME

The mRS is a well-accepted and defined scoring system for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke using a 0-6 multinomial ordinal scale:

0  No symptoms at all
1  No significant disability despite symptoms; able to carry out all usual duties and activities
2  Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3  Moderate disability; requiring some help, but able to walk without assistance
4  Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5  Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6  Dead

The statistical hypothesis on Rankin shift is that the distribution of mRS in patients randomized to the treatment (Standard of Care plus Embolectomy) will be more favorable than the distribution in the control group (Standard of Care alone). For this purpose, the entire distribution 0 to 6 of mRS values will be considered except that categories 5 and 6 are collapsed into a single group.

The null and alternative hypotheses to be tested appear below:

\[ H_0: \pi_t = \pi_c \]
\[ H_a: \pi_t < \pi_c, \]

where \( \pi_t \) is the central tendency of the mRS distribution at the 90-day follow-up visit in the treatment group, and \( \pi_c \) is the corresponding value in the control group, with lower values indicating better outcomes.

A random-effects generalized linear model for independent data by maximum likelihood that allows for subject-specific (conditional) and population-averaged (marginal) inference (PROC GLIMMIX) will also be generated, incorporating predictive factors and stratification variables specified in the randomization as covariates: NIHSS recorded at baseline, age, sex, time to tPA,
occlusion location, time from onset to randomization and baseline ASPECTS score. The SAS code used to conduct the adjusted analysis is presented below.

```sas
proc glimmix data=MASTER_001 method=laplace;
   class SEX OCC_SITE TPA_YN TREAT_N STUDY;
   model MRSD90 = AGE_N SEX NIHSS_BL ASPECTS OCC_SITE TPA_YN TREAT_N SYM_RAND_MIN / dist=multinomial link=cumlogit ddfm=residual solution cl or;
   random STUDY STUDY * TREAT_N / solution;
run;
```

The SAS code used to conduct the unadjusted analysis is presented below.

```sas
proc glimmix data=MASTER_001 method=laplace;
   class TREAT_N STUDY;
   model MRSD90 = TREAT_N / dist=multinomial link=cumlogit ddfm=residual solution cl or;
   random STUDY TREAT_N*STUDY / solution;
run;
```

The number needed to treat (NNT) to achieve an improvement by at least one level in the mRS will be calculated as the average of the algorithmic joint outcome table and the permutation method.

Separate sub-group analyses will be prepared to examine factors that may have influenced the 90-day mRS scores. Factors include: age (<70 years of age vs ≥70 years and <80 years of age vs ≥80 years), sex (male/female), stroke severity (≤15, 16-20, ≥21), site of intracranial vascular occlusion (ICA, M1, M2), presence of tandem cervical carotid occlusion (yes/no), extent of initial early infarct signs (ASPECTS 0-5, 6-8, 9-10), administration of alteplase (yes/no) and time from onset to randomization (<5h, ≥5h). Onset to randomization dichotomization at 5h was chosen to approximate the subgroup who could have endovascular treatment commenced within 6h of onset.

**8.2. Evaluation of the 90-Day Mortality Data for EXTEND-IA, ESCAPE, REVASCAT AND SWIFT PRIME**

The incidence of 90-day mortality will be compared across studies and between the randomized treatment groups.
8.3. Evaluation of Functional Independence at 90-Days for EXTEND-IA, ESCAPE, REVASCAT AND SWIFT PRIME

Functional independence as defined by a modified Rankin Scale (mRS) score ≤ 2 at 90 days will be compared across the studies and between the randomized treatment groups. The SAS code used to conduct the adjusted analysis is presented below.

```sas
proc glimmix data=MASTER_001 METHOD=RSPL;
   class SEX OCC_SITE TPA_YN TREAT_N S TUDY;
   model MRSD90=AGE_N SEX NIHSS_BL ASPECTS OCC_SITE TPA_YN SYM_RAND_MIN TREAT_N / DIST=binary ddfm=residual link=logit cl or ODDSRATIO;
   random STUDY STUDY*TREAT_N / solution;
run;
```

The SAS code used to conduct the unadjusted analysis is presented below.

```sas
proc glimmix data=MASTER_001 METHOD=RSPL;
   class TREAT_N STUDY;
   model MRSD90 = TREAT_N / DIST=binary ddfm=residual link=logit cl or ODDSRATIO;
   random STUDY STUDY*TREAT_N / solution;
run;
```

8.4. Evaluation of the Changes from Baseline in NIHSS at 90-Days for EXTEND-IA, ESCAPE, REVASCAT AND SWIFT PRIME

The changes in the NIH Stroke Scale score from baseline to 21 to 36 hours after randomization will be compared among the studies and between the randomized treatment groups. Results will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, range (i.e., minimum and maximum values) and compared between the randomized treatment assignments using a mixed model specifying the distribution as continuous with study and study-by-treatment as random effects. Patients with missing data that cannot be resolved will not be included in the tabulation and excluded from the summary statistics.

8.5. Evaluation of the effect of time from onset to reperfusion in the patients who achieved successful endovascular revascularization

A limited assessment of time as a predictor of outcome will be conducted in the intervention group. The adjusted probability of independent outcome in the intervention group that achieved mTICI 2b/3 reperfusion will be solved using an hierarchical generalized linear model with study as a grouping variable and onset-to-reperfusion time. Probabilities will be graphed as a function of time with the probability of independent outcome regressed against time using simple linear regression to produce an estimate of effect size for delay to treatment.
背景および目的：虚血性脳卒中の血管内治療を支持する
最新の無作為化試験は，主にステントリトリーバーを使用
したものですのである。そこで，前向き虚血性脳卒中で
Solitaire デバイスによるステント血栓除去術の有効性と
安全性を調査するためデータを統合した。
方法：既存のメタ解析（SEER Collaboration）] Solitaire
FR With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME).
Endovascular Treatment for Small Core and Anterior
Circulation Proximal Occlusion With Emphasis on
Minimizing CT to Recanalization Times (ESCAPE).
Extending the Time for Thrombolyis in Emergency
Neurological Deficits—intra-Arterial (EXTEND-IA),
Randomized Trial of Revascularization With Solitaire
FR Device Versus Best Medical Therapy in the
Treatment of Acute Stroke Due to Anterior Circulation
Large Vessel Occlusion Presenting Within Eight Hours
of Symptom Onset (REVASCAT) ]で，Solitaire のみ
または Solitaire を主なデバイスとして使用した試験から
患者レベルのデータを集積した。主要評価項目は 90 日目の
改善 mRS の順位解析とした。主要解析では 4 試験の患者
全員を対象として，(1) 最初に Solitaire デバイスを使用しなかった患者を除く程度分析と，(2) Solitaire のみを使用
した 3 試験（ESCAPE を除く）の程度分析を実施した。
二重評価項目は身体機能の自立性（mRS 0 ～ 2），症候性
脳内出血，死亡率とした。
結果：主要解析は 787 例の患者を対象とした。401 例が血管
内血栓除去術，386 例が標準的治療に押しつけられた患者
で，82.6%が静脈内血栓溶解療法を行った。mRS 改善
の共通オッズ比は 2.7（2.0 ～ 3.5）であり，年齢，性別，ベー
スラインの脳卒中重症度，CT 変化の程度，閉塞部位，ア
ルテプラーゼの先行投与による効果の不均一性はみられ
なかった。機能障害の減少に必要な治療患者数は 2.5，自
立の転帰を達成した患者を 1 人増やすために必要な治療
患者数は 4.25（3.29 ～ 5.09）であった。Solitaire デバイ
スで治療した患者の再開通率は 77%であった。治療群に
おける症候性脳内出血例および全死亡率の差は認められな
かった。
結論：大血管性虚血性脳卒中に対する Solitaire による血
栓除去術は，機能障害の大幅な減少につながる，安全で
非常に有効な治療法である。既存のサブグループすべ
てにおいて，利益は一貫していた。
大血管の閉塞による虚血性脳卒中を伴う症例は、ステント型血栓除去デバイス（ステントリトリーパー）を使用し良好な成績をもたらすことが示された。これらの症例においても、内頸動脈および中大動脈の閉塞による大脳性虚血性脳卒中患者に対する適応である。従来の治療法では、血管内内視鏡的治療や従来型のデバイスが使用され、虚血性脳卒中発症2年後から6時間以内の機械的ステント血栓除去術の有効性が示されている。

各症例体幹は問題なく、各症例のサブグループに大きな不均一性は認められなかった。サブグループ効果の検出力が弱く、効果量の評価も難しかった。また、被験者数の多さおよび治療法の多様性が問題となった。要約試験データを使用した、試験レベルのメタ解析がいくつか発表されている。しかし、患者個人のデータをフェードするメタ解析では静脈内血栓除去法で実施された解析と同様、検出力が低め、精度を改善し、正確なサブグループの調整が可能であると示された。

今後、以上の未解決の問題に対応するため、各患者データを統合することで有意の結果を得ることが求められる。多様なデバイスを使用した治療の多角的側面を明らかにする解析も、全ての試験のデータで実施しており、本論文は別に報告した。本報告では、特に重要な試験で最も使用されているデバイスのSolitaireステントリトリーパー（Medtronic、アイルランド、ダブリン）で治療した患者で、その治療効果を検討する

【方 法】

特にSolitaireデバイスについて解析を報告するため、以下の選択基準に一致する試験を主要解析の対象とした。

(1)血管内内訳血栓除去手術（STENT）は、脳卒中病態を考慮し、最適な薬物治療のみを比較した無作為化試験であり、(2)試験開始前に画像検査で大血管の閉塞を確認している。

上記の基準を満たし主要解析の対象となった4試験（SEER Collaboration）は、Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment（SWIFT PRIME）、Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times（ESCAPE）、Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial（EXTEND-IA）、Randomized Trial of Recanalization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset（REVASCAT）であった。

Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands（MR CLEAN）試験は、Solitaireデバイスが少数の血管内治療に使用されたため除外した（本論文は別に報告した）。Solitaireデバイス中心ではない大規模解析には含まれていない）。

各試験のデータは第三者の統計センターで照合し、そこで事前に設定した統計解析計画（オンラインデータ補遺に記載）に沿って解析が実施された。試験の特徴の共通点と相違点はオンラインデータ計画書を参照することとした。

(1)実際にはSolitaireを最初に使用した場合、Solitaireを使用に予定していた血管内治療群の患者で、またアクセスポリなどが実施された患者（Solitaire intention-to-treat解析）と、(2)血管内治療群すべてにSolitaireを使用した3試験（SWIFT PRIME、EXTEND-IA、REVASCAT）の患者で、精度分析を実施した。主要評価項目は90日目の改善mRSで評価した機能障害度とした。

事前に設定したサブグループ解析は、年齢（50歳未満vs. 70歳以上80歳未満vs. 80歳以上）、性別（男性/女性）、脳卒中重症度（NIHSS ≤15, 16 - 20, ≥21）、頭蓋内血管障害部位（内頸動脈、中大動脈、外頸動脈）、頭部血管障害のtandem lesionの有無（あり/なし）、初期の虚血性変化の程度（Alberta Stroke Program Early CT Score（ASPECTS）0～5, 6～8, 9～10）、アルテプラーゼの投与（あり/なし）、発症から無作為化手術までの時間（5時間未満および5時間以上）であった。発症後5時間以内に血管内治療を開始することができたサブグループをまとめるため、発症から無作為化されての区切りは5時間とした。また、脳卒中発症後5時間以内（FDAのアルテプラーゼ添付文書通り）にアルテプラーゼを投与した患者を検討した。

事前に設定した有効性の副次評価項目は、90日目の機能的自立の転帰（mRS 0～2）、24時間での主要神経症状の早期回復（NIHSSスコアラインから8点以上低下またはNIHSSが0～1）、血管内内訳血栓除去時の再開通率（改変Treatment in Cerebral Ischemia（mTICI））分類で50%を超える閉塞動脈支配領域で血流が回復した件数を表す2b/3に該当」とした。この解析のため、閉塞動脈支配領域の50～99%の血流回復を2bに区分するmTICI分類をすべての試験が使用したことになるよう、ESCAPE患者の再開通成績を再分類した。

安全性の評価項目は、症候性脳内出血（原試験の定義

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による。オンラインデータ補遺表Ⅰ参照）と死亡率とした。
X線画像で判断した脳実質内血腫の率も報告した。

Solitaire デバイスの技術的有効性および安全性、最初の投入デバイスとしてSolitaireを実際に使用した4}
試験の患者すべてで評価した。この目的通りに治療を受けた集団には、血管内治療群に割り付けられているが
カテーテル血管造影の時点ですでに再灌流していない患者
や、標的とする閉塞へのナビゲーションが失敗したため
デバイスが使用されなかった患者は含まれていない。

統計解析は、第三者の統計専門家が各試験データベース
を統合し、SAS v.9.2（SAS Institute, ソースカロライ
ナ州キャリ）を使用して実行した。主要評価項目は、
カテゴリー5と6を合わせたmRS 分類および試験にラン
ダム効果の変数として試験×治療の交互作用を取り
混ぜた順序ロジスティック回帰で解析した。試験は地理
的に異なる場所、異なる医療体制のもとで別々に実施
されたため、統計解析計画では固定効果ではなくランダム
効果を指定し、試験×治療の効果量があると仮定しない
ようにした。解析は未調整のモデルと調整モデルで実
行した。調整済みモデルの解析には、事前に設定した7
つの共変量（年齢、性別、ベースラインの脳卒中重症度、
閉塞部位、アルテプラーゼの静脈内投与、ASPECTS ス
コア、発症から無作為割付けまでの時間）を取り入れ
た。複数のmRSレベル間の同時移行を反映させた治療必要
例数（NNT）の値は、算法的 joint outcome table 法
および並べ替え検定法（mRS カテゴリー5と6の結合）
で求めた NNT 値の幾何平均を計算することにより導き
出した11,13,15。2 値型データの二次評価項目は、試験×治
療の交互作用をランダム効果の変数とし、同じ共変量と
試験を入れた二項ロジスティック回帰で解析した。2 値
型データの転帰を扱う場合のNNT は100／絶対リスク
の低下で計算した。血管内治療群で転帰の予測因子とし
て再灌流が起こった時間の評価を別に実施した。mTICI
2b/3の再灌流率を達成した血管内治療群の自立の転帰の
確率（調整後）は、試験をランダム効果の変数として
発症から再灌流までの時間を入力した階層型の一般化線形
混合モデルで算出した。確率を時間間数でグラフ化し、自
立の転帰の確率と時間の単純な線形回帰分析により、治
療が遅れた時間単位の効果量推定値を算出した。

結果

患者の特徴

合計で前方循環系の虚血性脳卒中患者787例が主要解
析集団となった。ステント血栓除去術には401例、標
準的治療には386例が割り付けられた。787例中650
例（82.6％）が静脈内血栓溶解療法を行った（表1）。
1つの目的感度分析でSolitaireを最初のデバイスにした
intention-to-treat 集団は713例で、血栓除去術は327
例、標準的治療は386例であった。2つの目的感度分析
の患者は、3つのSolitaire単独試験で血管内治療に割り
付けられた236例と標準的治療に割り付けられた236
例を含む472例であった（オンラインデータ補遺表II
およびIII）。

主要評価項目

主要解析としてmRSの順序解析を実行したところ、
改善の共通オッズ比（OR）は未調整で2.4（1.8 ～ 3.0,
P = 0.0000000001）、調和で2.7（2.0 ～ 3.5, P <
0.0000000001）であり、mRSを1段階以上改善するた
めのNNTは2.5人であった（表1、図1および2A）。2
つの感度分析（図1およびオンラインデータ補遺表I、
図II、表IV、表V）および脳卒中発症後3時間以内に
アルテプラーゼを投与した患者（オンラインデータ補
遺表Ⅵ）で効果は同程度であった。年齢、性別、ベー
ースラインの脳卒中重症度、血栓溶解薬の投与歴、頭蓋
内血管の閉塞部位、発症から無作為割付けまでの時間、
初期の非進影CT画の異常の程度によるサブグループ
の効果の差は認められなかったが、最初のデバイス
としてSolitaireを使用した集団だけはベースライン
のASPECTS スコアによる治療効果の差が認められ、
P = 0.02であった（図2B、2C、3）。2つの感度分析
集団の結果はほぼ同じであった（オンラインデータ補遺
表ⅢおよびIV）。

副次評価項目および安全性

すべての有効性の副次評価項目で利益が認められた。
自立の転帰を達成した患者（mRS 0 ～ 2）を1人者やす
ためのNNTは4.25人であった（95%信頼区間3.29 ～
5.99、表2）。Solitaire治療患者では主要神経症状の早
期回復例が大幅に増加した。2つの感度分析集団の結果
はほぼ同じであった（オンラインデータ補遺表IIおよび
V）。単純な固定効果モデルで試験×治療の交互作用
のエビデンスは認められず、全4試験の効果の均一性が
示された（P = 0.513）。

安全性の解析で、全般に噴射性出血および死亡率有意
差はなかった（表2）、しかし、完全なSEERデータセッ
トでは80歳以上のサブグループの死亡率が有意に低下
し[20% vs. 40%，調整OR 3.7 （1.3 ～ 10.6, P = 0.01)
、図2C]。Solitaire 感度分析集団も同様の傾向であった
（オンラインデータ補遺表IIIC）。脳卒中発症後3時間
以内にアルテプラーゼを投与した患者と3 ～ 4.5 時間
表1 4試験の患者および治療手順の特徴：SWIFT PRIME, ESCAPE, EXTEND-A, REVASCAT

| 特徴                      | 対照 | 血管内治療 |
|---------------------------|------|----------|
| 患者数                    | 386  | 401      |
| 年齢、歳、平均（SD）       | 67.8 (12.3) | 67.3 (12.7) |
| 男性、n (%)               | 193 (50.0)  | 195 (48.6) |
| 人種、n (%)               | 13 (3.4)    | 11 (2.7)  |
| アジア系                  | 12 (3.1)    | 15 (3.7)  |
| NHSS スコア、中央値（四分位範囲） | 17 (12-19)  | 17 (13-20) |
| 心房細動の診断確率、n (%) | 146 (37.8)  | 143 (35.7) |
| 高血圧、n (%)             | 259 (67.1)  | 254 (63.3) |
| 糖尿病、n (%)             | 54 (14.0)   | 48 (12.0)  |
| 呼吸数または元呼吸数、n (%)| 132 (34.2)  | 129 (32.2) |
| 血清Ct、mg/dL、平均（SD） | 131.8 (48.3) | 128.7 (39.8) |
| 脳卒中発症からカテーテル到着までの時間（分）、中央値（四分位範囲） | 108 (58-206) | 105 (55-199) |
| アルテフライザーの静脈内投与、n (%) | 327 (84.7)  | 323 (80.5) |
| 脳卒中発症からアルテフライザー開始までの時間（分）、中央値（四分位範囲） | 120 (89-164) | 114 (86-150) |
|  |

表1 続き

| 特徴                      | 対照 | 血管内治療 |
|---------------------------|------|----------|
| 最終的な mTICI、n (%)     | 3    | 132 (32.9) |
| 2b                        | 153 (38.2) |
| 2a                        | 62 (15.5)  |
| 1                         | 6 (1.5)  |
| 0                         | 19 (4.7)  |
| 血管造影を実施せず         | 29 (7.2)  |

mTICIは各試験の中心検査機関で評価した結果である。分類の範囲は血管にない（0）～正常血管（5）である。mTICI 2b は 50% を超える緊密な動脈内洗浄領域で血流が回復したことを示す。NHSS スコア（標準化された神経学的検査）の範囲は正常（0）～死亡（42）である。群間に統計学的な有意差はない。

ASPECTS： Alberta Stroke Program Early CT Score, ESCAPE：Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times, EXTEND-A：Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial, mTICI：modified Treatment in Cerebral Ischemia, NHSS：National Institute of Neurological Stroke, REVASCAT：Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset, SWIFT PRIME：Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment。

に投与した患者の結果にほとんど差はなかった（オンラインデータ補遺 表 VI ～ VIII）。

技術的有効性の解析で、カテーテル血管造影の時点で閉塞が続いていたため実際に Solitaire を最初のデバイスとして使用した全 4 試験の患者の再開通 (mTICI 2b/3) 率は 77% （306 例中 236 例）であった。mRS 0 ～2 の達成率は mTICI の各段階で連続的に上昇した（傾向の P = 0.01, オンラインデータ補遺 表 IX）。発症から再灌流までの時間と延びると同時に、自立の転帰を達成した Solitaire 治療患者の割合はわずかに減少したが、有意であった（図 4）。

考 察

患者個人のデータを使用した本メタ解析により、Solitaire によるステント血栓除去術が実験室に有益であることが証明された。Solitaire がもたらす利益はかなり大きく、治療患者 100 人中 40 人で血栓除去術後の機能障害が軽減し、うち 23 人の転帰は自立に至った。重大な安全性の問題もなく、症候性出血や死亡率の増加はみられなかった。若年者、高齢者、男女を問わず、また血栓の部位が内頸動脈か中大頸動脈か、頸部頭動脈閉塞の tandem lesion があるか否か、欠損が軽度か重度か、初期検査画像の血流性損傷が軽度か重度か、アルテフライザーを投与したかアルテフライザー不適応かに関係なく、幅広い患者に均一の利益が認められた。

高齢は血栓除去術の除外基準にあげられることが多く、実際に解析した 4 試験中 2 試験に年齢の上限があっ
表2 主要解析の評価項目：SWIFT PRIME, ESCAPE, EXTEND-IA, REVASCAT

| 評価項目 | 対照 (n = 386) | 血管内治療 (n = 401) | 調整* | 未調整 | P値 |
|----------|---------------|----------------------|-------|--------|-----|
| 主要評価項目 | 90日目の機能的転帰（mRS） | 2 (1-4) | 2.7 (2.0-3.5) | < 0.0001 | 2.4 (1.8-3.0) | < 0.0001 |
| 副次評価項目 | 機能的自立の転帰 (mRS 0〜2) | 119 (31.5%) | 216 (54.0%) | 3.1 (2.2-4.4) | < 0.0001 | 2.6 (1.9-3.5) | < 0.0001 |
| 良好な機能的転帰 (mRS 0〜1) | 67 (17.7%) | 143 (35.8%) | 3.0 (2.1-4.3) | < 0.0001 | 2.6 (1.9-3.7) | < 0.0001 |
| 神経症状の早期改善 (24時間で NIHSS が8点以下) | 100 (25.9%) | 240 (59.9%) | 4.8 (3.5-6.7) | < 0.0001 | 4.3 (3.1-5.8) | < 0.0001 |

安全性
| 項目 | 対照 (n = 386) | 血管内治療 (n = 401) | P値 |
|-------|---------------|----------------------|-----|
| 死亡 | 63 (16.3%) | 48 (12.0%) | 0.64 (0.35-1.2) | 0.16 | 0.69 (0.43-1.1) | 0.12 |
| 症状性脳内出血 | 11 (2.8%) | 10 (2.5%) | 0.76 (0.31-1.9) | 0.58 | 0.87 (0.36-2.1) | 0.76 |
| 脳実質内血腫（PH） | 31 (8.0%) | 32 (8.0%) | 0.96 (0.56-1.6) | 0.89 | 1.0 (0.57-1.8) | 0.96 |

CI：信頼区間，CT：コンピュータ断層撮影法，ESCAPE：Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times，EXTEND-IA：Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial，IQR：四分位間距離，mRS：modified Rankin Scale，REVASCAT：Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset，SWIFT PRIME：Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment。

※年齢，性別，ベースラインの脳卒中重症度，閉塞部位，アルテプラーゼの静脈内投与，Alberta Stroke Program Early CT Score (ASPECTS)，発症から無作為割付けまでの時間について調整した。

†mRSの範囲は正常 (0)〜死亡 (6) の間である。解析ではmRS 5と6を統合した。

‡JCI（日本脳卒中共同研究） NIHSS スコア (標準化された神経学的検査) の範囲は正常 (0)〜死亡 (42) であり，8点の低下は臨床的に大きな意味がある。

§SICH：症状性脳内出血の定義は原試験の定義による。

![Figure 1](image.png)

主要解析および感度解析ビスケットの機能的転帰（90日目の改変mRS）。mRSの順序解析 [未調整および年齢，性別，ベースラインの脳卒中重症度，閉塞部位，アルテプラーゼの静脈内投与，Alberta Stroke Program Early CT Score (ASPECTS)。発症から無作為割付けまでの時間について調整後] との，機能的自立の転帰 (mRS 0〜2, 未調整および調整後) のオッズ比（OR）および95%信頼区間に。
た（SWIFT PRIME と REVASCAT）。しかし発症前の機能に問題がなく自立していた場合、高齢者でも治療効果の低下は確認されていない。また、SEER 試験の 80 歳以上の患者で臨床的および統計学的に有意な 20％の絶対的死亡率低下が認められている。したがって、実際の診療では単に年齢で血栓除去術の対象者から外すことは妥当でない。

Interventional Management of Stroke（IMS-3）の一次解析および最近実施された MR CLEAN との複合解析は、血管内治療の利益を決定する重要な因子として脳卒中重症度（NIHSS ≥ 20）に焦点を当てていた16,17。本解析は、NIHSS ≤ 15 の患者に少なくとも NIHSS > 20 の患者と同程度の治療効果があることを示した。最近の試験に NIHSS < 6 の患者はほとんど登録していなかったが、既存の重症度の範囲で治療効果の変動は確認されていない。軽度の脳卒中の治療は引き続き臨床判断が求められるであろう18。

血管内血栓除去術の前に試験患者の多くアルテプラーゼの静脈内投与を受けており、線維素溶解療法は EXTEND-IA および SWIFT PRIME の選択基準の一部であった。解析した試験のアルテプラーゼ適応患者にはすべてアルテプラーゼが投与された。したがって、適格な場合は血栓除去術の前にアルテプラーゼを後継使用することが推奨される。これらの試験でアルテプラーゼが適さない患者の数は少なかったが、線維素溶解療法の先行投与が考慮されない患者でも血管内血栓除去術の明らかに利益が認められ、この患者群にも血管内血栓除去術が有効であることが確認された。

静脈内血栓溶解療法が時間の決定的影響を与えることはかねてより強調されてきたが19,20。血管内治療にも当てはまる20,21。アルテプラーゼの場合、再灌流が起こった時刻がほとんど記録されず、投与から数時間後に再灌流が起こることもあるため、治療までの時間が最もよく解析される測定単位となる。再灌流までの時間を正確に定量化し、血管内治療で再灌流率を上げることが、時間と再灌流の関係を深く理解することにつながる。早期の画像検査により治療に適した患者の割合および脳卒中の患者群全体に対する効果は増大するが22。時間とともに画像検査の範囲は広がる傾向を示す。本研究の統合解析により時間と利便の関係が確認され、発症から再灌流までの時間が長引くほど自立に至る確率が低下した。しかし本解析における効果量は小さかった。これらの観点は患者の状態を適切に判断したため、時間の重要性に対する評価が低いようにある。画像検査の成果が良好な患者の場合、時間の影響は軽減することが以前明らかにされた23。よって，
表1

| 年齢   | 対照  | 血管内治療  | オッズ比 (95%CI) | 交互作用 |
|--------|-------|------------|----------------|---------|
|        | n=386 | n=401      |                |         |
| <70歳  | 191   | 212        | 2.45 (1.68, 3.56) | 0.39    |
| ≥70歳  | 192   | 189        | 3.16 (2.05, 4.86) | 0.06    |
| ≥80歳  | 55    | 74         | 2.57 (1.90, 3.50) | 0.17    |

| 性別   | 対照  | 血管内治療  | オッズ比 (95%CI) | 交互作用 |
|--------|-------|------------|----------------|---------|
|        | n=191 | n=195      |                |         |
| 女性   | 191   | 206        | 2.56 (1.76, 3.72) | 0.91    |
| 男性   | 193   | 195        | 2.80 (1.91, 4.11) |         |

| NIHSS  | 対照  | 血管内治療  | オッズ比 (95%CI) | 交互作用 |
|--------|-------|------------|----------------|---------|
|        | n=66  | n=73       |                |         |
| 0-15   | 155   | 163        | 2.84 (1.85, 4.38) | 0.72    |
| 16-20  | 150   | 149        | 3.05 (1.97, 4.73) |         |
| ＞20    | 76    | 86         | 3.25 (1.66, 6.35) |         |

| 血管閉塞部位 | 対照  | 血管内治療  | オッズ比 (95%CI) | 交互作用 |
|-------------|-------|------------|----------------|---------|
| ICA         | 66    | 73         | 5.23 (2.60, 10.53) | 0.18    |
| M1 MCA      | 287   | 285        | 2.41 (1.77, 3.28) |         |
| M2 MCA      | 23    | 33         | 1.77 (0.55, 5.65) |         |

| 動脈閉塞のtandem lesion | 対照  | 血管内治療  | オッズ比 (95%CI) | 交互作用 |
|-------------------------|-------|------------|----------------|---------|
| あり                     | 41    | 43         | 4.38 (1.82, 10.52) | 0.48    |
| なし                     | 345   | 358        | 2.53 (1.91, 3.36) |         |

| ASPECTS  | 対照  | 血管内治療  | オッズ比 (95%CI) | 交互作用 |
|----------|-------|------------|----------------|---------|
| 0-5      | 31    | 22         | 0.86 (0.23, 3.18) | 0.07    |
| 6-8      | 152   | 161        | 2.53 (1.65, 3.86) |         |
| 9-10     | 197   | 205        | 3.07 (2.12, 4.47) |         |

| 静脈内血栓治癒法 | 対照  | 血管内治療  | オッズ比 (95%CI) | 交互作用 |
|-----------------|-------|------------|----------------|---------|
| アルテプラーゼあり| 327   | 323        | 2.50 (1.87, 3.35) | 0.68    |
| アルテプラーゼなし| 59    | 78         | 3.30 (1.65, 6.63) |         |

| 発症から無作為割付けまでの時間 | 対照  | 血管内治療  | オッズ比 (95%CI) | 交互作用 |
|-------------------------------|-------|------------|----------------|---------|
| ＜5時間                        | 308   | 326        | 2.76 (2.05, 3.72) | 0.47    |
| ＞5時間                        | 75    | 75         | 2.00 (1.04, 3.84) |         |

図3
事前に設定されているサブグループにおける治療効果（フォレストプロット）。年齢、性別、ベースラインの脳卒中重症度、閉塞部位、アルテプラーゼの静脈内投与、頸部動脈閉塞のtandem lesion、Alberta Stroke Program Early CT Score（ASPECTS）、発症から無作為割付けまでの時間について調整した解析。CI：信頼区間、ICA：内頸動脈、MCA：中大脳動脈、NIHSS：米国国立衛生研究所腦卒中スケール。

実際の診療では体制を合理化して遅延の発生を避け、最適な転帰の達成を目指ることが重要である。

当該試験においてSolitaireデバイスをステント血栓除去術に使用した場合の全再開通（mTICI 2b/3）率は77%（306例中236例）であり、症状性出血率は低い。デバイスに改良が加えられ1回目的デバイス通過で完全に再灌流する（mTICI 3）率が向上することに疑いの余地はないが、その結果は将来的の技術的進歩の明確な基準点となる。

Solitaireステントリトリーバーの効果の特性を明らかにする場合、他の血管内治療を行った試験を組み入れると、交絡を招くおそれがある。本解析は大多数の患者にSolitaireデバイスを使用した試験に限定し、さらにSolitaireデバイスの治療患者のみで度数分析を実施することにより、この問題を解消した。

本研究の限界として、試験間の選択基準が同じでないことがある。しかし試験X治療の交互作用は認められず、患者個体レベルのデータを解析することによりバイアスのリスクは最小限に抑えられる。4試験はいずれも画像検査に基づいて患者を選択し、画像で適格性が確認された真直ちに治療を行うことが定められていた。よって、特定の患者群については登録数が有効性の結論を出
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