ORIGINAL ARTICLE

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

Jeffrey L. Saver, M.D., Mayank Goyal, M.D., Alain Bonafe, M.D., Hans-Christoph Diener, M.D., Ph.D., Elad I. Levy, M.D., Vitor M. Pereira, M.D., Gregory W. Albers, M.D., Christophe Cognard, M.D., David J. Cohen, M.D., Werner Hacke, M.D., Ph.D., Olav Jansen, M.D., Ph.D., Tudor G. Jovin, M.D., Heinrich P. Mattle, M.D., Raul G. Nogueira, M.D., Adnan H. Siddiqui, M.D., Ph.D., Dileep R. Yavagal, M.D., Blaise W. Baxter, M.D., Thomas G. Devlin, M.D., Ph.D., Demetrius K. Lopes, M.D., Vivek K. Reddy, M.D., Richard du Mesnil de Rochemont, M.D., Oliver C. Singer, M.D., and Reza Jahan, M.D., for the SWIFT PRIME Investigators*

ABSTRACT

BACKGROUND

Among patients with acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, less than 40% regain functional independence when treated with intravenous tissue plasminogen activator (t-PA) alone. Thrombectomy with the use of a stent retriever, in addition to intravenous t-PA, increases reperfusion rates and may improve long-term functional outcome.

METHODS

We randomly assigned eligible patients with stroke who were receiving or had received intravenous t-PA to continue with t-PA alone (control group) or to undergo endovascular thrombectomy with the use of a stent retriever within 6 hours after symptom onset (intervention group). Patients had confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischemic-core lesions. The primary outcome was the severity of global disability at 90 days, as assessed by means of the modified Rankin scale (with scores ranging from 0 [no symptoms] to 6 [death]).

RESULTS

The study was stopped early because of efficacy. At 39 centers, 196 patients underwent randomization (98 patients in each group). In the intervention group, the median time from qualifying imaging to groin puncture was 57 minutes, and the rate of substantial reperfusion at the end of the procedure was 88%. Thrombectomy with the stent retriever plus intravenous t-PA reduced disability at 90 days over the entire range of scores on the modified Rankin scale ($P<0.001$). The rate of functional independence (modified Rankin scale score, 0 to 2) was higher in the intervention group than in the control group (60% vs. 35%, $P<0.001$). There were no significant between-group differences in 90-day mortality (9% vs. 12%, $P=0.50$) or symptomatic intracranial hemorrhage (0% vs. 3%, $P=0.12$).

CONCLUSIONS

In patients receiving intravenous t-PA for acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, thrombectomy with a stent retriever within 6 hours after onset improved functional outcomes at 90 days. (Funded by Covidien; SWIFT PRIME ClinicalTrials.gov number, NCT01657461.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Saver at the UCLA Stroke Center, 710 Westwood Plaza, Los Angeles, CA 90095, or at jsaver@mednet.ucla.edu.

Drs. Saver and Goyal contributed equally to this article.

*A complete list of investigators in the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial is provided in the Supplementary Appendix, available at NEJM.org.

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Intravenous tissue plasminogen activator (t-PA) administered within 4.5 hours after the onset of acute ischemic stroke improves outcomes.[1-3] However, intravenous t-PA has multiple constraints, including unresponsiveness of large thrombi to rapid enzymatic digestion, a narrow time window for administration, and the risk of cerebral and systemic hemorrhage. Among patients with occlusions of the intracranial internal carotid artery or the first segment of the middle cerebral artery (or both), intravenous t-PA results in early reperfusion in only 13 to 50%.[4-7]

Neurovascular thrombectomy is a reperfusion strategy that is distinct from pharmacologic fibrinolysis. Endovascular mechanical treatments can remove large, proximal clots rapidly and result in higher rates of reperfusion than intravenous t-PA alone. Three initial trials of endovascular therapies did not show a benefit for thrombectomy over intravenous t-PA or supportive medical care, but they were limited by the use of intraarterial delivery of t-PA or the use of early-generation devices with modest reperfusion efficacy (or both), the failure of two trials to use vessel imaging to confirm the presence of an appropriate target occlusion, and the slow initiation of endovascular intervention.[8-10]

The Solitaire revascularization device (Covidien) is a self-expanding stent used to retrieve thrombi and restore blood flow. In multicenter registries and one randomized trial, this stent retriever, as compared with early-generation mechanical thrombectomy devices, was associated with faster and more frequent reperfusion, reduced intracranial hemorrhage, and improved disability outcome.[11-15]

We performed the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial to establish the efficacy and safety of rapid neurovascular thrombectomy with the stent retriever in conjunction with intravenous t-PA versus intravenous t-PA alone in patients with acute ischemic stroke. This trial was among several contemporaneous trials launched worldwide to test new-generation strategies for mechanical thrombectomy.[16-18] Our trial was conducted in multiple countries and health systems as a registration trial capable of supporting expansion of regulatory labeling. We used a uniform device procedure in the intervention group and tested intracranial neurovascular thrombectomy alone rather than in combination with cervical stenting.

Methods

Trial Design

In this international, multicenter, prospective, randomized, open clinical trial, we compared intravenous t-PA followed by neurovascular thrombectomy with the use of a stent retriever with intravenous t-PA alone in patients with acute ischemic stroke. All the patients had confirmed occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both on vessel imaging and an absence of large ischemic-core lesions. Patients were randomly assigned in a 1:1 ratio to one of two treatment groups: intravenous t-PA plus stent retriever (intervention group) or intravenous t-PA alone (control group). Using a minimization algorithm, we balanced the numbers of patients in the two treatment groups with respect to four factors: investigational site, baseline severity according to the National Institutes of Health Stroke Scale (NIHSS) score (≤17 vs. >17, on a scale of 0 to 42, with higher scores indicating greater severity), age (<70 years vs. ≥70 years), and occlusion location (middle cerebral artery vs. internal carotid artery).

Details of the study design have been published previously.[19] The study was conducted and reported with fidelity to the study protocol, available with the full text of this article at NEJM.org. (An overview of the study procedure is provided in Fig. S1 in the Supplementary Appendix, available at NEJM.org.)

The trial was approved by the institutional review board at each site. Enrolled patients provided written informed consent, or at select sites, there was an exception from explicit informed consent in emergency circumstances.

The trial was funded by Covidien and designed and led by a steering committee that included academic investigators and representatives of the sponsor. The site investigators gathered the data, with monitoring and database maintenance performed by the sponsor. The first and subsequent drafts of the manuscript were written by the first and second authors, incorporating input from all the authors. The academic authors had unrestricted access to the data, performed the data analysis with the primary and the independent study statisticians, and attest to the integrity of the trial and the completeness and accuracy of the reported data. The trial was monitored by an independent data and safety monitoring board.

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PATIENTS AND PARTICIPATING CENTERS

The study was performed at 39 centers in the United States and Europe. All study centers were required to have performed at least 40 mechanical-thrombectomy procedures, including at least 20 procedures with the Solitaire stent retriever, annually. Entry criteria selected patients who had acute ischemic stroke with moderate-to-severe neurologic deficits; had imaging-confirmed occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both; met the imaging eligibility requirements; were receiving or had received intravenous t-PA; and were able to undergo initiation of endovascular treatment within 6 hours after the time that they were last known to be well before the onset of acute stroke symptoms. Qualifying imaging had to be performed at a study hospital; imaging was repeated for patients who were transferred from outside hospitals. Detailed study inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix.

To identify patients with salvageable tissue, at trial launch the entry criteria regarding imaging selection required patients to have a target-mismatch penumbral profile, with a small core of tissue that was likely to be irreversibly injured and a large region of hypoperfused tissue that was likely to be salvageable. Penumbral imaging analysis was performed with the use of RAPID (iSchemaView), an operator-independent image-postprocessing system.[20] After the enrollment of the first 71 patients, these criteria were revised to use a small-to-moderate core-infarct strategy (Table S1 in the Supplementary Appendix) to accommodate study sites with limited perfusion-imaging capability and to ensure accelerated treatment delivery. Study sites with advanced imaging capability were still encouraged to obtain penumbral imaging and to exclude patients who did not meet the target-mismatch profile.

INTERVENTION

In the intervention group, neurovascular thrombectomy was performed with the use of the Solitaire FR (Flow Restoration) or Solitaire 2 device. Concomitant stenting of the cervical internal carotid artery was not permitted, although angioplasty could be performed to permit intracranial access.

A studywide continuous quality-improvement program emphasized the speed and quality of the neurointerventional workflow, including rapid patient transfer to the neuroangiography suite and procedure performance. The study target for the time from qualifying imaging to groin puncture was within 70 minutes.

OUTCOME MEASURES

The primary study-outcome measure was disability at 90 days, as assessed by means of the modified Rankin scale, a global measure of disability on a seven-level scale, with scores ranging from 0 (no symptoms) to 6 (death) (Fig. 1). (Details on the use of this scale are provided in the Supplementary Appendix.)

Secondary clinical efficacy outcomes were the rate of death at 90 days, the rate of functional independence (modified Rankin scale score, ≤2) at 90 days, and the change in the NIHSS score at 27 hours after randomization. The technical efficacy outcomes regarding revascularization were substantial reperfusion, as assessed by means of catheter angiography in the intervention group and defined as a modified Thrombolysis in Ce-

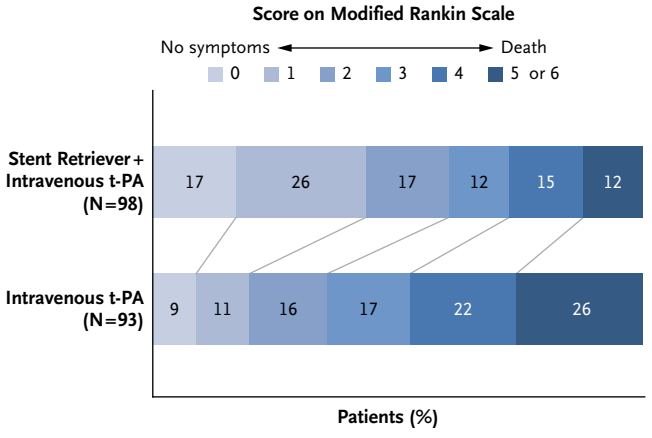


Figure 1. Functional Outcomes at 90 Days, According to the Score on the Modified Rankin Scale.

Shown are the 90-day scores on the modified Rankin scale for the patients in the two treatment groups. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability (able to carry out all usual activities, despite some symptoms), 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention, bedridden, and incontinent), and 6 death. Persons with a score of 0, 1, or 2 are considered to be independent in daily function. Neurovascular thrombectomy with the use of a stent retriever was associated with a significant shift in the distribution of scores toward lesser disability ($P<0.001$ by the Cochran–Mantel–Haenszel test), including an absolute increase of 25 percentage points in the proportion of patients who were functionally independent at 90 days ($P<0.001$). The term t-PA denotes tissue plasminogen activator.

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rebral Infarction score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion)[21]; and successful reperfusion at 27 hours in the two study groups, which was defined as reperfusion of 90% or more of the initial perfusion-lesion volume, as assessed by means of perfusion imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) at 27 hours after randomization. Prespecified safety outcomes were all serious adverse events through study completion and symptomatic intracranial hemorrhage at 27 hours after randomization.

CLINICAL AND RADIOLOGIC ASSESSMENT

Clinical assessments were performed at baseline, 27 hours after randomization, 7 to 10 days (or at discharge if earlier), 30 days, and 90 days. Clinical evaluations included the score on the modified Rankin scale for assessing global disability and the NIHSS score for assessing neurologic deficit. Entry and outcome neurovascular images were assessed in a blinded manner by staff at the core imaging laboratories (iSchemaView for penumbral and volumetric imaging and Synarc for parenchymal and angiographic imaging).

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Intravenous t-PA Alone (N=98)	Stent Retriever plus Intravenous t-PA (N=98)
Age — yr	66.3±11.3	65.0±12.5
Male sex — no./total no. (%)	45/96 (47)	54/98 (55)
Race — no./total no. (%)†		
White	83/92 (90)	79/90 (88)
Black	8/92 (9)	10/90 (11)
Asian or other	1/92 (1)	1/90 (1)
Hispanic ethnic group — no. (%)†	7/92 (8)	8/90 (9)
NIHSS score‡		
Median	17	17
Interquartile range	13–19	13–20
Prestroke score of 0 or 1 on modified Rankin scale — no./total no. (%)§	93/94 (99)	96/98 (98)
Medical history — no./total no. (%)		
Hypertension	56/97 (58)	66/98 (67)
Diabetes mellitus	15/97 (15)	12/98 (12)
Current or past tobacco use	39/93 (42)	41/96 (43)
Atrial fibrillation	38/97 (39)	35/98 (36)
Myocardial infarction	11/97 (11)	8/98 (8)
Serum glucose — mg/dl¶	131±47	131±46
Administration of intravenous t-PA at outside hospital — no./total no. (%)	35/94 (37)	31/98 (32)
Interval from symptom onset to start of intravenous t-PA — min		
Median	117	110.5
Interquartile range	80–155	85–156
Parenchymal imaging variable		
ASPECTS value‖		
Median	9	9
Interquartile range	8–10	7–10
Penumbral imaging performed — no./total no. (%)	75/97 (77)	83/98 (85)
Target-mismatch profile — no./total no. (%)**	64/75 (85)	69/83 (83)

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Table 1 (Continued.)

Characteristic	Intravenous t-PA Alone (N=98)	Stent Retriever plus Intravenous t-PA (N=98)
Site of intracranial-artery occlusion — no./total no. (%)		
Internal carotid artery	15/94 (16)	17/93 (18)
Middle cerebral artery		
First segment	72/94 (77)	62/93 (67)
Second segment††	6/94 (6)	13/93 (14)
Process time — min		
Stroke onset to randomization		
Median	188	190.5
Interquartile range	130–268	141–249
Stroke onset to groin puncture		
Median	NA	224
Interquartile range	NA	165–275
Stroke onset to first deployment of stent retriever		
Median	NA	252
Interquartile range	NA	190–300
Arrival in emergency department to groin puncture		
Median	NA	90
Interquartile range	NA	69–120
Qualifying image to groin puncture		
Median	NA	57
Interquartile range	NA	40–80

* Plus–minus values are means ±SD. There were no significant differences between the two groups. One patient in the group that received intravenous tissue plasminogen activator (t-PA) alone requested the deletion of all data. Three additional patients in the group that received intravenous t-PA alone (1 patient who died and 2 who withdrew) are missing some baseline data owing to early study exit, including data on the prestroke modified Rankin Scale score, the hospital site of intravenous t-PA administration, and site of intracranial-artery occlusion for all 3 patients, and data on sex, race, and ethnic group for 1. Data on race and ethnic group were missing for all 13 patients in France owing to national regulations. Data regarding the location of the arterial occlusion were missing for 7 patients because the core laboratory considered that imaging could not be assessed with complete reliability. Two patients were deemed by the core laboratory to not have occlusions in the internal carotid artery or the first or second segment of the middle cerebral artery. A total of 37 patients did not have baseline penumbral imaging performed, after a protocol amendment making penumbral imaging optional. Data regarding additional baseline characteristics are shown in Table S4 in the Supplementary Appendix. NA denotes not applicable.

† Race and ethnic group were self-reported.

‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficit.

§ Scores on the modified Rankin scale for the assessment of global disability range from 0 (no symptoms) to 6 (death).

¶ To convert the values for glucose to millimoles per liter, multiply by 0.05551.

‖ The Alberta Stroke Program Early CT Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller infarct core.

** The target-mismatch profile was defined as meeting the following criteria as assessed on CT perfusion or diffusion imaging and perfusion MRI: the core infarct lesion measured 50 ml or less, the volume of tissue with a time to maximum delay of more than 10 seconds was 100 ml or less, and the mismatch volume was at least 15 ml and the mismatch ratio was more than 1.8:1.0.

†† These occlusions were classified as first-segment occlusions by the treating site at the time of study entry but as second-segment occlusions by the core imaging laboratory.

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STATISTICAL ANALYSIS

For the primary outcome, we analyzed the score on the modified Rankin scale at 90 days using simultaneous success criteria of the overall distribution of the score (shift in disability levels) and the proportion of patients who were functionally independent. Both criteria needed to be met in order for the study to be declared positive. The statistical hypothesis on the scale shift was that the distribution over the entire range of scores (except for scores of 5 or 6, which were collapsed into a single group) among patients in the intervention group would be more favorable than the distribution in the control group, as analyzed by means of the Cochran–Mantel–Haenszel test.

A simultaneous requirement for success was that the difference in the proportion of patients with a score of 0 to 2 nominally meet a prespecified minimum, which varied according to the final sample size at trial discontinuation or completion, with a larger benefit required with a smaller sample size (Table S2 in the Supplementary Appendix). Missing final scores on the modified Rankin scale were handled with the use of the last-observation-carried-forward approach when a score was available from the 30-day visit or the visit at 7 to 10 days. Power and sample size were determined with the use of the dual success criteria, incorporating a group sequential-analysis plan with five interim analyses for efficacy, futility, and safety. (Details are provided in Table S2 in the Supplementary Appendix and in the full statistical analysis plan in the protocol.)

After the preliminary results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) and the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial were reported,[16,18] our data and safety monitoring board recommended holding enrollment, and the first interim efficacy analysis was performed slightly early (including 196 rather than 200 patients). In February 2015, the study was halted when the interim efficacy analysis showed that the prespecified stopping-criteria boundary for efficacy had been crossed. A test to determine whether the data across clinical sites could be pooled showed no evidence of heterogeneity of treatment effect ($P=0.73$ by the Breslow–Day test), so pooled study results are presented. All P values are two-sided.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From December 2012 through November 2014, 196 patients underwent randomization (98 in each group) at 39 centers in the United States and Europe. Reasons for exclusion are listed in Table S3 in the Supplementary Appendix.

The demographic and clinical characteristics of the two treatment groups at baseline were well balanced (Table 1, and Table S4 in the Supplementary Appendix). Figure S2 in the Supplementary Appendix shows the enrollment and follow-up of patients in the trial.

INTERVENTION

In the intervention group, the time from symptom onset to groin puncture was 224 minutes (interquartile range, 165 to 275), the time from the start of intravenous t-PA to groin puncture was 77 minutes (interquartile range, 50 to 142), and the time from study-qualifying brain imaging to groin puncture was 57 minutes (interquartile range, 40 to 80). In the intervention group, the stent retriever was deployed in 87 patients (89%); the reasons for nondeployment are listed in Table S5 in the Supplementary Appendix. Among these 87 patients, the median time from groin puncture to first deployment of the stent retriever was 24 minutes (interquartile range, 18 to 33). General anesthesia was used in 36 patients (37%) in the intervention group.

PRIMARY OUTCOME

Treatment with thrombectomy with the use of the stent retriever met both of the simultaneous success criteria. Thrombectomy treatment was associated with a favorable shift in the distribution of global disability scores on the modified Rankin scale at 90 days ($P<0.001$ by the Cochran–Mantel–Haenszel test, which was lower than the P value of 0.01 that was specified for early stopping; number needed to treat for one additional patient to have a less-disabled outcome, 2.6). The shift toward better outcomes was consistent in direction across all the score levels of the modified Rankin scale (Fig. 1). The proportion of patients who were functionally independent (modified Rankin scale score, ≤2) at 90 days was

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higher in the intervention group than in the control group, with an absolute difference of 25 percentage points, which exceeded the 12-percentage-point boundary that was prespecified for early stopping. Results remained significant in sensitivity analyses that used multiple imputation and worst-case and best-case scenarios to account for missing data (Table S6 in the Supplementary Appendix) and in analyses that were adjusted for imbalances in baseline prognostic features (Table S7 and Fig. S3 in the Supplementary Appendix).

SECONDARY OUTCOMES

Prespecified secondary clinical efficacy outcomes and technical efficacy outcomes regarding revascularization are shown in Table 2; additional prespecified and post hoc outcomes are shown in Tables S10 and S13 in the Supplementary Appendix. The proportion of outcomes indicating functional independence at 90 days was significantly higher in the intervention group than in the control group, with an absolute difference of 25 percentage points (95% confidence interval [CI], 11 to 38) and a risk ratio of 1.70 (95% CI, 1.23 to 2.33; P<0.001; number needed to treat for one additional patient to be functionally independent, 4.0). Mortality at 90 days did not differ significantly between the intervention group and the control group (9% and 12%, respectively; P=0.50).

In the intervention group, substantial reperfusion (50 to 99%) or complete reperfusion (100%) at the end of the procedure occurred in 73 of the 83 patients (88%) who underwent placement of the stent retriever (Table S9 in the Supplementary Appendix). A total of 4 additional patients who

Table 2. Primary and Secondary Outcomes.*

Outcome	Intravenous t-PA Alone (N=98)	Stent Retriever plus Intravenous t-PA (N=98)	Risk Ratio (95% CI)	P Value
Primary outcome: score on modified Rankin scale at 90 days†				<0.001
No. of patients with data	93	98		
Median score	3	2		
Interquartile range	2–5	1–4		
Secondary outcomes				
Clinical efficacy outcome				
Functional independence at 90 days — no./total no. (%)‡	33/93 (35)	59/98 (60)	1.70 (1.23–2.33)	<0.001
Change in NIHSS score at 27 hr				
No. of patients with data	92	97		
Mean change	−3.9±6.2	−8.5±7.1		<0.001
Death at 90 days — no./total no. (%)§	12/97 (12)	9/98 (9)	0.74 (0.33–1.68)	0.50
Revascularization outcome¶				
Substantial reperfusion immediately after thrombectomy — no./total no. (%)	NA	73/83 (88)	NA	NA
Successful reperfusion at 27 hr — no./total no. (%)	21/52 (40)	53/64 (83)	2.05 (1.45–2.91)	<0.001

* Plus–minus values are means ±SD. CI denotes confidence interval, and NA not applicable.
† Shown are the results of the prespecified Cochran–Mantel–Haenszel test for the shift in disability score. Similar results were found in the analysis of the common odds ratio (odds ratio, 2.63; 95% CI, 1.57 to 4.40; P<0.001).
‡ Functional independence was defined as a score of 0, 1, or 2 on the modified Rankin scale.
§ One patient in the group that received intravenous t-PA alone requested the deletion of all data, including vital status.
¶ Substantial reperfusion was defined as reperfusion of at least 50% and a modified Thrombolysis in Cerebral Infarction score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion). Successful reperfusion was defined as reperfusion of at least 90%, as assessed with the use of perfusion CT or MRI. Data on successful reperfusion were not obtained for all the patients after the adoption of the protocol amendment making penumbral imaging optional.

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underwent the intervention did not have a final angiogram that could be assessed. Successful reperfusion (≥90%) at 27 hours, assessed by means of perfusion CT or MRI, was more frequent in the intervention group than in the control group (53 of 64 patients [83%] vs. 21 of 52 [40%], P<0.001).

SAFETY

The rates of serious adverse events (36% in the intervention group and 31% in the control group, P=0.54) and symptomatic intracranial hemorrhage (0% and 3%, respectively; P=0.12) did not differ significantly between the treatment groups (Table 3, and Table S11 in the Supplementary Appendix). There was no significant between-group difference in the rate of all intracranial hemorrhage subtypes that were assessed radiologically, but there were numerically more subarachnoid hemorrhages in the intervention group than in the control group (four patients and one patient, respectively; P=0.37). No serious adverse events and seven nonserious adverse events were adjudicated to be device-related (Table S12 in the Supplementary Appendix).

SUBGROUP ANALYSES

Within the constraints of the study sample size, no evidence of heterogeneity of treatment effect was detected in any of the eight prespecified subgroups (Fig. 2, and Fig. S4 in the Supplementary Appendix). The benefit of thrombectomy with the stent retriever plus intravenous t-PA over intravenous t-PA alone was also observed in the prespecified subgroup of patients who received intravenous t-PA within 3 hours after symptom onset (P<0.001) (Table S8 in the Supplementary Appendix).

DISCUSSION

Our study showed that in patients with acute ischemic stroke with confirmed large-vessel occlusions of the anterior circulation who were treated with intravenous t-PA, treatment with the stent retriever within 6 hours after symptom onset improved functional outcomes at 90 days. For every 2.6 patients who were treated, 1 additional patient had an improved disability outcome; for every 4.0 patients who were treated, 1 additional patient was functionally independent at 90-day follow-up.

These findings confirm and extend those of recent trials.[16-18] Our trial emphasized speedy endovascular therapy in patients selected by means of imaging, similar to the protocol used in the ESCAPE trial,[18] and achieved onset-to-reperfusion

Table 3. Safety Outcomes.*

Outcome	Intravenous t-PA Alone (N=97)	Stent Retriever plus Intravenous t-PA (N=98)	Risk Ratio (95% CI)	P Value
	no. of patients (%)			
Primary safety outcomes				
Any serious adverse event at 90 days†	30 (31)	35 (36)	1.15 (0.78–1.72)	0.54
Symptomatic intracranial hemorrhage at 27 hr	3 (3)	0	0.00 (NA)	0.12
Additional safety outcomes at 27 hr				
Parenchymal hematoma	7 (7)	5 (5)	0.71 (0.23–2.15)	0.57
Type 1	3 (3)	4 (4)	1.32 (0.30–5.74)	1.00
Type 2	4 (4)	1 (1)	0.25 (0.03–2.17)	0.21
Subarachnoid hemorrhage	1 (1)	4 (4)	3.96 (0.45–34.79)	0.37

* NA denotes not applicable.

† A serious adverse event was an adverse event that led to death, a life-threatening illness or injury, permanent impairment of a body structure or a body function, inpatient or prolonged hospitalization, medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function, or fetal distress, fetal death or a congenital anomaly or birth defect. Serious adverse events that are classified according to organ system are shown in Table S11 in the Supplementary Appendix. None of the serious adverse events were adjudicated by the clinical-events committee to be device-related. Nonserious adverse events that were deemed to be device-related are shown in Table S12 in the Supplementary Appendix.

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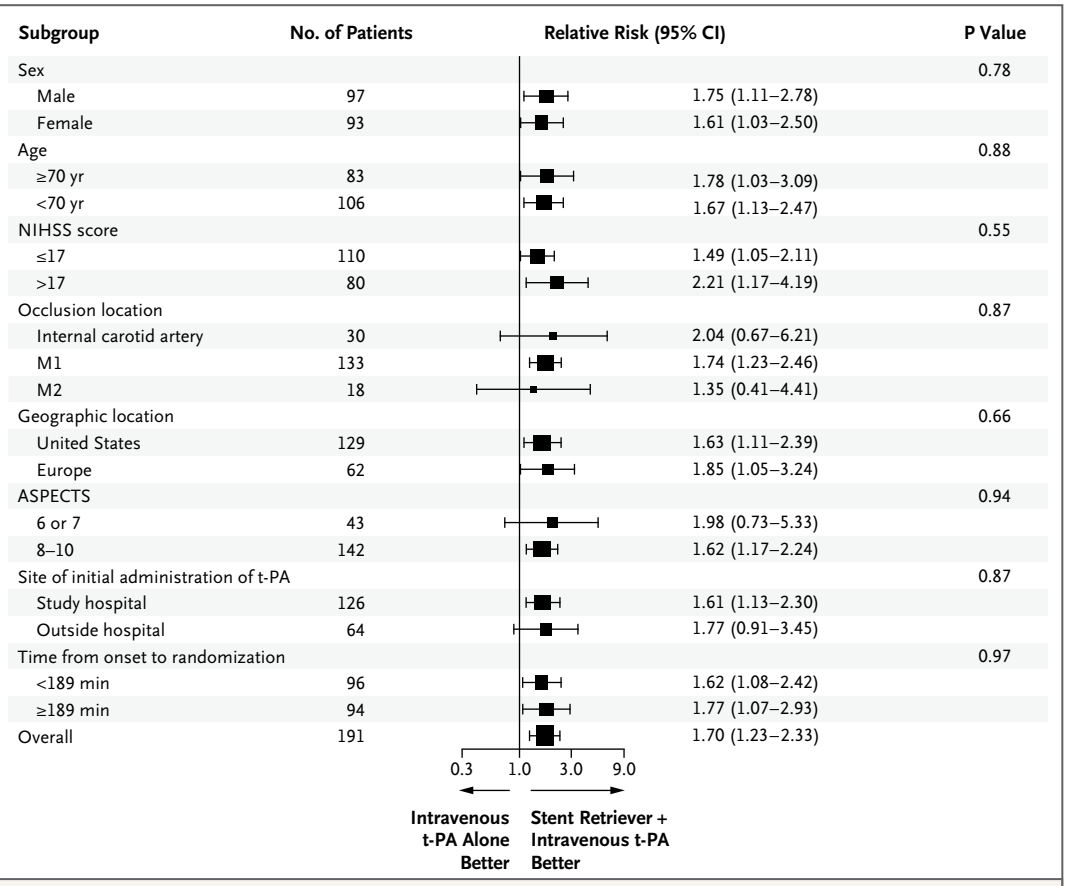


Figure 2. Analysis of Functional Independence at 90 Days in Prespecified Subgroups.

Functional independence was defined as a score on the modified Rankin scale of 0, 1, or 2. P values were based on the Breslow–Day test for homogeneous odds ratios across subgroups. Squares indicate point estimates for treatment effects, and the size of the square is proportional to the precision of the estimate. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits. The threshold of 17 was the threshold used in stratifying randomization. The Alberta Stroke Program Early CT Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller infarct core; a score of 6 or 7 indicates moderate infarct core, and a score of 8 or higher small infarct core. For the time from stroke onset to randomization, the median value was prespecified as the cutoff point for analysis and was found to be 189 minutes. M1 denotes first segment of the middle cerebral artery, and M2 second segment of middle cerebral artery.

times that were faster than those in MR CLEAN[16] and in studies of early-generation interventions.[8-10] The median time from arrival in the emergency department to groin puncture of 90 minutes was faster than the 120-minute target that is recommended in current multisociety guidelines.[22] In our trial, study sites were provided with a prespecified efficiency target of performing groin puncture within 70 minutes after qualifying imaging, and continuous central review encouraged rapid workflow. For patients with intravenous t-PA that was initiated at study centers, groin puncture and stent-retriever deployment could take place while t-PA was infusing.

Several aspects of the treatment and treatment response were distinctive in our study. The rate of substantial or complete reperfusion (88%) among patients undergoing intracranial intervention was higher in this trial than in previous trials. The high reperfusion rate is probably due in part to the more homogeneous patient population (more occlusions in the first segment of the middle cerebral artery and fewer intracranial or cervical occlusions of the internal carotid artery) and the more homogeneous intervention (an ef-

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fective stent retriever and no other device classes and no intraarterial fibrinolytic agent) in this trial than in earlier trials. The frequency of functional independence in the intervention group was high in our trial (60%) and was greater than that observed in MR CLEAN (33%) and similar to that observed in the ESCAPE trial (53%) and the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND IA) trial (71%).[17] The high frequency of this outcome probably reflects the earlier start of the intervention,[23-26] the exclusion of patients with large core infarcts on the basis of imaging,[27,28] and the greater reperfusion rate in our trial, as compared with the other trials.

No significant differences in treatment effect were detected across all the prespecified subgroups, including such factors as age, sex, degree of neurologic deficit, site of occlusion, and size of infarct core on qualifying imaging, although the moderate sample size limited the power of this analysis. We also performed a prespecified analysis comparing patients who received intravenous t-PA at an outside hospital and were transferred to a study center for thrombectomy with those who received both the intravenous t-PA and the endovascular intervention at the study center. One third of the patients were treated with intravenous t-PA at an outside hospital. These patients had less favorable outcomes overall; however, their relative benefit from endovascular therapy did not differ significantly from that observed in patients who received intravenous t-PA at the study site (Fig. 2, and Fig. S4 in the Supplementary Appendix).

The rates of serious adverse events did not differ significantly between the study groups overall or within major organ categories, and no device-specific serious adverse events were observed. The most common nonserious device-specific adverse event was transient, intraprocedural vasospasm without clinical sequelae. Rates of symptomatic hemorrhage were low and did not differ significantly between the two treatment groups. Subarachnoid hemorrhage and intracerebral hematomas as assessed radiologically were also uncommon.

Our study has several limitations. First, we studied a homogeneous cohort of patients treated with intravenous t-PA; additional trials are needed to delineate the effects of stent-retriever therapy in other populations of patients with acute ischemic stroke, including those who are ineligible for intravenous t-PA, those who present more than 6 hours after symptom onset (including those who awaken after having had a stroke), and those with occlusions in the second segment of the middle cerebral artery or the posterior circulation. Second, study conduct included a continuous quality-improvement program to improve endovascular workflow efficiency at the participating sites. Implementation of similar quality-improvement programs in routine care settings,[29] as has been done on a broad scale for intravenous t-PA,[30] would be required to ensure similar stent-retriever outcomes in regular practice. Finally, all the enrolling sites were tertiary care centers with established stroke-intervention programs staffed by experienced neurointerventionalists. These results may not be generalizable to clinical sites without requisite neurointerventional expertise.

In conclusion, we found that in patients with acute ischemic stroke due to large-vessel occlusion who had small or moderate ischemic cores, emergency neurovascular thrombectomy with the stent retriever was safe and effective in achieving reperfusion and substantially reduced the degree of disability and increased the proportion of patients with functional independence 3 months after stroke.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine (J.L.S.), and the Division of Interventional Neuroradiology (R.J.), University of California, Los Angeles (UCLA), Los Angeles, and the Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford (G.W.A.) — both in California; the Departments of Radiology and Clinical Neurosciences, University of Calgary, Calgary, AB (M.G.), and the Division of Neuroradiology and Division of Neurosurgery, Departments of Medical Imaging and Surgery, Toronto Western Hospital, University Health Network, University of Toronto, Toronto (V.M.P.) — both in Canada; the Department of Neuroradiology, Hôpital Gui-de-Chauliac, Montpellier (A.B.), and the Department of Diagnostic and Therapeutic Neuroradiology, University Hospital of Toulouse, Toulouse (C.C.) — both in France; the Department of Neurology, University Hospital of University Duisburg–Essen, Essen (H.-C.D.), the Department of Neurology, University of Heidelberg, Heidelberg (W.H.), the Department of Radiology and Neuroradiology, Christian–Albrechts–University Kiel, Kiel (O.J.), and the Institute of Neuroradiology (R.M.R.) and Department of Neurology (O.C.S.), Klini-

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