

Efficacy of Stent-Retriever Thrombectomy in Magnetic Resonance Imaging Versus Computed Tomographic Perfusion–Selected Patients in SWIFT PRIME Trial (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke)

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Background and Purpose—The majority of patients enrolled in SWIFT PRIME trial (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) had computed tomographic perfusion (CTP) imaging before randomization; 34 patients were randomized after magnetic resonance imaging (MRI).

Methods—Patients with middle cerebral artery and distal carotid occlusions were randomized to treatment with tPA (tissue-type plasminogen activator) alone or tPA+stentriever thrombectomy. The primary outcome was the distribution of the modified Rankin Scale score at 90 days. Patients with the target mismatch profile for enrollment were identified on MRI and CTP.

Results—MRI selection was performed in 34 patients; CTP in 139 patients. Baseline National Institutes of Health Stroke Scale score was 17 in both groups. Target mismatch profile was present in 95% (MRI) versus 83% (CTP). A higher percentage of the MRI group was transferred from an outside hospital ($P=0.02$), and therefore, the time from stroke onset to randomization was longer in the MRI group ($P=0.003$). Time from emergency room arrival to randomization did not differ in CTP versus MRI-selected patients. Baseline ischemic core volumes were similar in both groups. Reperfusion rates ($>90\%$ /TICI [Thrombolysis in Cerebral Infarction] score 3) did not differ in the stentriever-treated patients in the MRI versus CTP groups. The primary efficacy analysis (90-day mRS score) demonstrated a statistically significant benefit in both subgroups (MRI, $P=0.02$; CTP, $P=0.01$). Infarct growth was reduced in the stentriever-treated group in both MRI and CTP groups.

Conclusions—Time to randomization was significantly longer in MRI-selected patients; however, site arrival to randomization times were not prolonged, and the benefits of endovascular therapy were similar.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01657461.

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Key Words: brain ischemia ■ cerebrovascular disorders ■ magnetic resonance imaging ■ patient selection ■ stroke ■ thrombectomy

Neuroimaging plays a critical role in the selection of stroke patients for reperfusion therapies. Computed tomography (CT) and magnetic resonance imaging (MRI) are used widely, although their respective roles remain controversial. Numerous imaging-based biomarkers have been used to screen patients with acute stroke. The target mismatch profile, defined as an ischemic core <70 mL associated with

larger region of hypoperfused tissue, has a strong association with favorable outcome in patients who achieve early reperfusion.¹⁻⁴ Both CT perfusion (CTP) and MRI with diffusion-weighted imaging and perfusion imaging can identify the target mismatch profile.⁵ Ischemic core volume, hypoperfused volume, and the resultant mismatch volume are assessed on baseline imaging.⁶⁻¹⁰ The degree of reperfusion, infarct

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volume, and infarct growth are assessed at follow-up and are correlated with clinical outcomes.^{11–13}

Recent endovascular trials have shown the superiority of endovascular therapy plus intravenous tPA (tissue-type plasminogen activator) compared with intravenous tPA alone in patients with large vessel intracranial occlusions selected primarily with CT-based approaches.^{14–18} Studies that used both MRI and CT to select patients provide a unique opportunity to compare these screening modalities. There are no randomized controlled trials comparing MRI to CT for selection of candidates for either intravenous tPA or endovascular therapy. There are, however, many centers that use MRI as the routine screening modality in the acute stroke populations.¹⁹ SWIFT PRIME trial (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) compared tPA alone with tPA plus endovascular therapy and reported substantially improved outcomes in the endovascular arm of the study.¹⁸ The SWIFT PRIME protocol allowed individual centers to use either CT or MRI to select patients. The aim of the present study was to compare the clinical and imaging outcomes in SWIFT PRIME patients who were selected by diffusion/perfusion MRI versus CTP.

Methods

Trial Design

The present work is a substudy of the SWIFT PRIME clinical trial. Details of this international, multicenter, prospective, randomized, blinded end point trial have been published previously.^{18,20}

This study compares outcomes in ischemic stroke patients enrolled in SWIFT PRIME trial, who were selected with CTP versus MRI diffusion-weighted imaging and perfusion. All patients were randomized to treatment with either intravenous tPA followed by endovascular stentriever thrombectomy versus intravenous tPA alone.

Ethical Approval

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

Population

The protocol required an occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both on CTA or MRA vessel imaging and an absence of large ischemic core lesions. The same automated software (RAPID) was used to identify patients with the target mismatch profile on both CT perfusion and MRI.

Clinical and Radiological Assessment

Clinical Assessment

Clinical assessments were performed at baseline, including the National Institutes of Health Stroke Scale score for assessing neurological deficit. Scores on the National Institutes of Health Stroke Scale range from 0 to 42, with higher scores indicating more severe neurological deficit.

The primary outcome measure was disability at 90 days, assessed using the modified Rankin Scale (mRS) score, ranging from 0 (no symptoms) to 6 (death).

The secondary clinical efficacy outcome was the rate of functional independence, defined as a score of 0, 1, or 2 on the mRS evaluated 90 days after randomization.

Radiological Assessment

Radiological assessments were performed at baseline and 27 hours after randomization based on a central core laboratory reading.

Penumbral Imaging

Volumetric assessments of the ischemic core and the hypoperfused territory were performed at the study sites using the RAPID software (iSchemaView, Menlo Park, CA), an operator-independent image postprocessing system.²¹

During the initial phase of SWIFT PRIME, the inclusion criteria required all patients to meet criteria for the target mismatch profile. After the initial 71 patients were enrolled, the protocol was amended, and perfusion imaging became optional; however, sites were encouraged to continue to follow the target mismatch criteria for patient selection, and 85% of the enrolled patients had target mismatch.

The target-mismatch penumbral profile was defined as meeting the following criteria as assessed on CTP or diffusion-weighted imaging and perfusion-weighted imaging. The core infarct lesion measured ≤ 50 mL, the volume of tissue with a time to maximum delay of >10 seconds was ≤ 100 mL, and the mismatch volume was at least 15 mL, and the mismatch ratio was $>1.8/1.0$.

The secondary radiological efficacy outcomes included revascularization, 27-hour infarct volume, and infarct growth.

Revascularization

The technical efficacy outcome regarding revascularization was set as follows.

Endovascular reperfusion was defined as a modified Thrombolysis in Cerebral Infarction score of 2b (50%–99% reperfusion) or 3 (complete reperfusion) during the procedure. Reperfusion was assessed in both the endovascular and the tPA-alone groups at 27 hours. Successful reperfusion at 27 hours was defined as reperfusion of $\geq 90\%$ of the initial perfusion lesion volume ($T_{max} > 6$ seconds). Percentage reperfusion was calculated as the difference between baseline $T_{max} > 6$ seconds lesion volume and the 27-hour $T_{max} > 6$ seconds volume divided by the baseline $T_{max} > 6$ seconds volume.

Twenty-Seven-Hour Infarct Volume

The 27-hour infarct volume was determined by manually outlining the 27-hour ischemic lesion on the fluid-attenuated inversion recovery sequence if a 27-hour MRI was performed. If MRI was not performed, the subacute hypodense lesion was outlined on a 27-hour noncontrast CT scan.

Infarct growth was evaluated by subtracting baseline infarct core volume from the 27-hour infarct volume.

Workflow Times

Time from emergency room arrival to randomization was recorded, as well as time from stroke onset to randomization.

Statistical Analysis

The primary end point, the mRS score at 90 days, was analyzed using the Cochran–Mantel–Haenszel test. In general, baseline characteristics and study outcomes are reported with means and SDs or medians and interquartile ranges for continuous outcomes and frequency distributions for binary and categorical outcomes. Statistical tests comparing subgroups were performed using *t* tests or Wilcoxon rank-sum test for continuous outcomes, Fisher exact test for binary outcomes, and Pearson χ^2 test for multinomial categorical outcomes. All *P* values reported are 2-sided, with values <0.05 deemed statistically significant.

Results

Characteristics of the Patients

One hundred and seventy-three patients with acute stroke were included in this substudy (Table 1). MRI-based selection was performed in 34 patients (19.7%) and CTP-based selection in

Table 1. Clinical and Radiological Characteristics of the Patients

		CT Perfusion (n=139)	MRI Perfusion (n=34)	P Value
Characteristics of the patients				
Age, y	Median	68	71	0.08
	Interquartile range	59–75	64–77	
Transferred to study site from an outside hospital		34.8% (48/138)	58.8% (20/34)	0.02
Male sex		54.7% (76/139)	26.5% (9/34)	0.004
Clinical assessment at baseline				
NIHSS at baseline	Median	17	17	0.46
	Interquartile range	13–19	13–21	
Radiological assessment at baseline				
ASPECTS at baseline	Median	9	8	<0.001
	Interquartile range	8–10	7–9	
Core infarct volume, mL	Median	4.5	7	0.40
	Interquartile range	0–16	3–12	
Perfusion lesion volume at baseline, mL	Median	132.5	96.5	0.01
	Interquartile range	75–161	66–110	
Target mismatch profile		83.3% (105/126)	95.0% (19/20)	0.31
Occlusion location				0.32
ICA		12.8% (17/133)	22.6% (7/31)	
M1		75.9% (101/133)	71.0% (22/31)	
M2		11.3% (15/133)	6.5% (2/31)	
Processing times				
Time from emergency room arrival to randomization, min	Median	67.0	68.5	0.61
	Interquartile range	48.0–95.0	43.0–112.0	
Time from stroke onset to randomization, min	Median	179.0	235.5	0.003
	Interquartile range	129.0–261.0	194.0–268.0	

Continuous variables presented as median (n), (Q1–Q3), and group comparisons evaluated with the Wilcoxon rank-sum test. Categorical data are presented as % (n/N), and group comparisons evaluated with Fisher exact test. ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; and NIHSS, National Institutes of Health Stroke Scale.

139 patients (80.3%). Median age was 71 years (64–77) in the MRI group and 68 years (59–75) in the CTP group ($P=0.078$).

Clinical and Radiological Assessment

Clinical Assessment at Baseline

At baseline, National Institutes of Health Stroke Scale score was 17 in both groups (MRI group: 17 [13–21] and CTP group: 17 [13–19]; $P=0.46$). The baseline ASPECTS (Alberta Stroke Program Early CT Score) score was lower in the MRI group: 8 (7–9) versus 9 (8–10) in the CTP group ($P<0.001$).

Radiological Assessment at Baseline

Baseline ischemic core volumes were not significantly different between the MRI and the CTP groups ($P=0.40$).

The baseline volume of hypoperfused territory was smaller in the MRI versus CT groups: 97 mL (66–110) versus 133 mL (75–161; $P=0.01$).

The target mismatch profile was observed in 19 out of 20 patients (95.0%) in the MRI group and 105 out of 126 patients (83.3%) in the CTP group ($P=0.31$).

Workflow Times

All patients were treated with tPA within 4.5 hours of stroke onset.

Time from emergency room arrival to randomization was 68.5 (43.0–112.0) in the MRI group and 67.0 (48.0–95.0) in the CTP group ($P=0.61$).

Patients were transferred to study site from an outside hospital in 58.8% (20 of 34) in the MRI group versus 34.8% (48 of 138) in the CTP group ($P=0.004$). Consequently, time from stroke onset to randomization was longer in the MRI group: 235.5 minutes (194.0–268.0) versus 179.0 minutes (129.0–261.0) in the CTP group ($P=0.003$).

Outcome Measures

Primary and secondary outcome measures are reported in Table 2. The mRS score results did not differ in MRI versus CTP groups ($P=0.8$). The rate of functional independence was the same in the MRI and CTP groups ($P=1.0$). The secondary radiological efficacy outcomes including revascularization, 27-hour infarct volume, and infarct growth also did not differ (respectively $P=0.37$, $P=0.43$, and $P=0.28$).

Table 2. Primary and Secondary Outcomes

		CT Perfusion (n=139)	MRI Perfusion (n=34)	P Value
Primary clinical outcome				
Modified Rankin Scale at 90 days	Median	2	2.5	0.85
	Interquartile range	1–4	1–4	
Secondary outcome measures				
Functional independence		50.7%	50.0%	1.00
Revascularization (reperfusion or TICI 2b/3)		69.7%	60.7%	0.37
Infarct volume at 27 h, mL	Median	33.1	39.05	0.43
	Interquartile range	12.95–78.1	15.8–93.5	
Absolute infarct growth, mL	Median	21.7	25.65	0.28
	Interquartile range	7.4–60.8	12.8–78.2	

Continuous variables presented as median (n), (Q1–Q3), and group comparisons evaluated with the Wilcoxon rank-sum test. Categorical data are presented as % (n/N) and group comparisons evaluated with Fisher exact test. CT indicates computed tomography; and TICI, Thrombolysis in Cerebral Infarction.

Comparison of Intravenous tPA Alone Versus Endovascular Therapy Plus Intravenous tPA Subgroups

Comparing the outcomes for the study's primary and secondary efficacy analyses showed similar results in both the CTP and MRI-selected subgroups (Table 3).

The primary efficacy analysis (distribution of mRS score at 90 days) demonstrated a statistically significant benefit in both the MRI ($P=0.022$) and CTP groups ($P=0.014$) favoring thrombectomy plus intravenous tPA over the intravenous tPA alone.

Among MRI-selected patients, mRS score 0 to 2 at 90 days occurred in 63% of the thrombectomy group versus 33% of the tPA alone group (absolute risk reduction 30%; $P=0.17$). Among CTP-selected patients, mRS score 0 to 2 at 90 days occurred in 60% of the thrombectomy group versus 40% of the tPA alone group (absolute risk reduction 20%; $P=0.025$).

In the MRI group, there was a trend toward lower absolute infarct growth (17 mL versus 50 mL; $P=0.089$) in the stentriever group compared with tPA alone that was similar in magnitude to the reduction observed in the CTP group (14 versus 27 mL; $P=0.047$).

Successful reperfusion at 27 hours was more common in the endovascular subgroups, irrespective of selection modality (MRI, $P<0.001$ and CT, $P<0.001$).

Discussion

Main Findings

The key findings of this substudy are that the primary efficacy outcome was statically significant in both the MRI- and CTP-selected subgroups of SWIFT PRIME. The positive outcome

in the MRI group is remarkable considering the small sample size of this subgroup. Despite that fact that MRI-selected patients in SWIFT PRIME were slightly older and treated longer after symptom onset, there were no significant differences in either clinical or imaging outcomes compared with the CTP-selected patients. The longer time from symptom onset to randomization in the MRI-selected group occurred primarily because of transfer delays because a larger percentage of the MRI patients were transferred to the study sites from outside hospitals. The time between arrival at the study site and randomization were nearly identical for both the MRI and CTP groups.

CT and MRI Selection for Thrombectomy

MRI-selected patients demonstrated a statistically significant benefit on the primary efficacy end point, and reductions in infarct growth in the MRI subgroup were also comparable to those seen in the CTP subgroup.

Numerous studies suggest that MRI is more accurate for estimating the ischemic core.^{22,23} Yet, acute CT scanning is more accessible than MRI in most stroke centers and is the most common imaging modality used to evaluate patients with acute ischemic stroke. CT perfusion techniques provide an elegant alternative to diffusion-weighted imaging to estimate the ischemic core, with good specificity.^{24–26} The results reported here confirm these previous findings in the context of a randomized, multicenter study.

Processing Times

A higher percentage of the MRI group was transferred from an outside hospital in the MRI group. Transfer delays account for the longer time from stroke onset to randomization in the MRI group (236 minutes versus 179 minutes in the CTP group). However, irrespective of the additional time, patients with the target mismatch profile on MRI had a high rate of independent functional outcome (60%), which is comparable with previous series of MRI-selected target mismatch patients who achieved endovascular reperfusion.³

Early and complete recanalization is also associated with lower mortality and better functional outcome.^{27,28} In SWIFT PRIME trial, recanalization and reperfusion were achieved in a high percentage of the endovascular patients selected with either MRI or CTP.

MR Versus CT Acquisition Times

MRI studies typically have longer acquisition times than CT studies.^{1,29–31} Interestingly, patients in the MRI group in SWIFT PRIME trial had similar time from emergency room arrival to randomization when compared with the CT perfusion group in the present study. Several factors may contribute to this finding. Workflow is often faster in transfer patients because the receiving center can prepare for the patient's arrival (clear the scanner, stroke team waiting in the emergency room, etc). In addition, new MRI protocols have substantially reduced scanning times.

Limitations of the Study

The primary objective of SWIFT PRIME study was to compare functional outcomes in ischemic stroke patients treated

Table 3. Comparison of Intravenous tPA and Stent Retriever Plus Intravenous tPA Subgroups

	CT Perfusion Group			MRI Perfusion Group			
	Intravenous tPA	Intravenous tPA+Thrombectomy	P Value	Intravenous tPA	Intravenous tPA+Thrombectomy	P Value	
Age, y	68	67	0.354	71	71	0.688	
	60–75	56–74		64–77	63–81		
Assessment at baseline							
NIHSS at baseline	Median	17	16	0.802	16	19	0.251
	Interquartile range	13–19	13–19		13–19	13–22	
ASPECTS at baseline	Median	9	9	0.824	8	8	0.944
	Interquartile range	8–10	8–10		6–9	7–9	
Core infarct volume, mL	Median	6	4	0.674	7	7	0.651
	Interquartile range	0–17	0–16		3–14	2–12	
Perfusion lesion volume at baseline, mL	Median	136	125	0.203	96	97	0.532
	Interquartile range	79–167	68–151		73–125	58–108	
Primary clinical outcome							
mRS score at 90 d	Median	3	2	0.014	4	2	0.022
	Interquartile range	2–4	1–4		2–5	1–3	
Secondary outcome measures							
Functional independence		39.7%	60.3%	0.025	33.3%	63.2%	0.166
Infarct volume at 27 h, mL	Median	35.15	31.8	0.284	61.2	24	0.052
	Interquartile range	18.55–85.5	9.15–73.95		24.5–104.1	10.5–55.3	
Absolute infarct growth, mL	Median	27.2	14.25	0.047	50.4	17.4	0.089
	Interquartile range	12.9–76.4	4.9–57.2		21.5–95.1	7.5–50.8	
Reperfusion or TIC1 3		47.5%	84.7%	<0.001	16.7%	93.8%	<0.001

Continuous variables presented as median (n), (Q1–Q3), and group comparisons evaluated with the Wilcoxon rank-sum test. Categorical data are presented as % (n/N) and group comparisons evaluated with Fisher exact test. ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIC1, Thrombolysis in Cerebral Infarction score; and tPA, tissue-type plasminogen activator.

with intravenous tPA followed by neurovascular thrombectomy with a stent retriever or intravenous tPA alone. Therefore, because imaging modality (CT versus MRI) was not randomized, there were some imbalances in baseline characteristics between the CTP and MRI subgroups. Considering the greater availability of CT versus MRI scanners, the observed disparity in the number of patients in each group was expected and confirms that most stroke patients continue to have limited access to acute MRI scans. Because most hospitals have an easy access to CT and less so for MRI, CTP is an appropriate tool for the majority of patients experiencing acute ischemic stroke.

The small sample-sized MRI subgroup (n=34), with correspondingly wide confidence intervals, may raise concerns with a possible type II error. The fact that the CT subgroup (n=139) was considerably larger adds power to statistical analyses comparing results across the 2 subgroups, although the chance of a type II error is always present regardless of sample size.

The use of advanced imaging to select patients for endovascular therapy in the sub 6-hour window is controversial given that some of the recent randomized trials (MR CLEAN^{14,32} and THRACE³³) demonstrated efficacy without advanced

imaging. The similarity of outcomes despite later treatment time in the SWIFT PRIME MR subgroup provides support for target mismatch selection.

The persistent benefit of thrombectomy, even in patients with longer times from symptom onset to randomization in the MRI-selected group, suggests that MRI may be a favorable modality for evaluating patients who present at extended time windows. This hypothesis requires assessment in large randomized studies.

Conclusions

Time to randomization in the SWIFT PRIME trial was significantly longer in MRI-selected patients; however, this time delay did not seem to impact the clinical response to endovascular therapy. The benefits of endovascular therapy in the MRI-selected subgroup were comparable to those seen in the CT perfusion subgroup.

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