Predictive Value of RAPID Assessed Perfusion Thresholds on Final Infarct Volume in SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment)

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Background and Purpose—Computed tomography perfusion imaging can estimate the size of the ischemic core, which can be used for the selection of patients for endovascular therapy. The relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) thresholds chosen to identify ischemic core influence the accuracy of prediction. We aimed to analyze the accuracy of various rCBV and rCBF thresholds for predicting the 27-hour infarct volume using RAPID automated analysis software from the SWIFT PRIME trial (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) data.

Methods—Patients from the SWIFT PRIME study who achieved complete reperfusion based on time until the residue function reached its peak >6 s perfusion maps obtained at 27 hours were included. Patients from both the intravenous tissue-type plasminogen activator only and endovascular groups were included in analysis. Final infarct volume was determined on magnetic resonance imaging (fluid-attenuated inversion recovery images) or computed tomography scans obtained 27 hours after symptom onset. The predicted ischemic core volumes on rCBV and rCBF maps using thresholds ranging between 0.2 and 0.8 were compared with the actual infarct volume to determine the most accurate thresholds.

Results—Among the 47 subjects, the following baseline computed tomography perfusion thresholds most accurately predicted the actual 27-hour infarct volume: rCBV=0.32, median absolute error (MAE)=9 mL; rCBV=0.34, MAE=9 mL; rCBF=0.30, MAE=8.8 mL; rCBF=0.32, MAE=7 mL; and rCBF=0.34, MAE=7.3.

Conclusions—Brain regions with rCBF 0.30 to 0.34 or rCBV 0.32 to 0.34 thresholds provided the most accurate prediction of infarct volume in patients who achieved complete reperfusion with MAEs of ≤9 mL.

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

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Key Words: brain ■ cerebral blood volume ■ perfusion imaging ■ reperfusion ■ stroke

The SWIFT PRIME trial (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) demonstrated improved functional outcomes in patients with anterior circulation acute ischemic stroke who underwent mechanical thrombectomy with the Solitaire stent retriever in addition to intravenous tissue-type plasminogen activator (tPA), in comparison to intravenous tPA alone.[1] The trial primarily used advanced perfusion imaging with automatic image postprocessing software to identify patients with a favorable target mismatch perfusion profile before randomization. In patients who achieved successful reperfusion, ischemic core volumes on baseline perfusion imaging were shown to accurately predict final infarct volumes when measured with computed tomography (CT) or magnetic resonance imaging (MRI) at 27 hours.[2]

CT perfusion (CTP) was the primary baseline imaging modality in patients who underwent randomization in SWIFT

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PRIME. Per its trial protocol, ischemic core was identified as tissue with >70% reduction in cerebral blood flow (CBF), when compared with normally perfused tissue (termed as a relative CBF [rCBF]). The optimal CTP parameters that most accurately identify the infarct core in patients with large vessel occlusion strokes remain to be determined. Studies have tested a variety of perfusion-based thresholds to identify CTP parameters that best correlate with final infarct volume.[3–6] The purpose of our study was to analyze the accuracy of different thresholds for predicting final infarct volume using the SWIFT PRIME trial data.

Methods

Study Design

The methodology and final results of the SWIFT PRIME trial have been previously published.[1,7] Briefly, patients with anterior circulation stroke who received intravenous tPA therapy were randomly assigned for endovascular thrombectomy with the Solitaire stent retriever within 6 hours after symptom onset (endovascular arm) or intravenous tPA alone (control arm). Imaging selection of patients for the trial used target mismatch criteria using CTP or MR perfusion imaging with fully automated processing software RAPID (iSchemaView, Menlo Park, CA). After enrolling 71 patients, protocol revision allowed further randomization of patients without advanced perfusion imaging (based on CT or MRI Alberta Stroke Program Early CT score alone); however, most participating sites continued to use perfusion imaging for patients screening and study enrollment. RAPID performed quantitative analysis of following perfusion maps: cerebral blood volume (CBV), CBF, mean transit time, and the time until the residue function reached its peak (Tmax; which is similar to time-to-peak parameter).

Image Processing and Analysis

CTP-based inclusion criteria for SWIFT PRIME were the following: ischemic core lesion volume ≤50 mL, Tmax >10 s, lesion volume ≤100 mL, mismatch volume ≥15 mL, and mismatch ratio >1.8. Ischemic core was defined as an area with >70% reduction in CBF (rCBF<0.3) in comparison to the mean CBF of normally perfused brain parenchyma.

Repeat perfusion imaging with measurement of Tmax volume >6 s at 27 hours was performed to assess the degree reperfusion. The percentage of reperfusion at 27 hours was calculated as the difference between baseline and 27-hour hypoperfusion volumes divided by the baseline hypoperfusion volume. Patients were included in our analysis if they had complete (defined as 100%) reperfusion at 27 hours. Figure 1 illustrates an example of a case with 100% reperfusion. Patients from both the tPA only and endovascular groups were included. Relative CBV (rCBV) and rCBF thresholds ranging between 0.2 and 0.8 were applied using the same software (RAPID), to identify which thresholds were most accurate for predicting the final 27-hour infarct volume. Median absolute errors (MAEs) for rCBV and rCBF thresholds were calculated based on infarct growth values, which were defined as 27-hour infarct volume minus the baseline ischemic core volume. MRI fluid-attenuated inversion recovery or noncontrast CT was performed at 27 hours to measure the final infarct volume. Regions of hemorrhage were not included in final volume. The assessments were made by the SWIFT PRIME core laboratory, which was blinded to the type of treatment.

Statistical Analysis

Standard summary statistics were tabulated for all variables analyzed, including means, SDs, medians, and ranges for continuous variables and frequency distributions for binary or categorical variables. Correlation and regression analyses were performed to compare infarct volumes at baseline versus 27 hours postrandomization, and results summarized with scatterplots and Bland–Altman analysis. Correlations were computed using Spearman nonparametric rho, and regressions were conducted under standard least-squares methods. All statistical analyses were performed in R, version 3.2 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

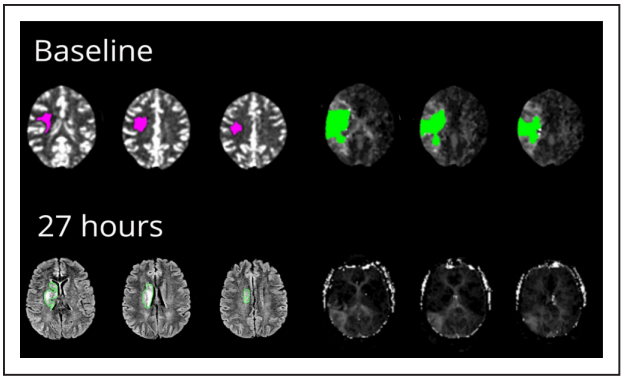

Figure 1. An example of a case with complete (100%) reperfusion. In this case of the right middle cerebral artery occlusion, the patient was randomized to the Solitaire group and Thrombolysis in Cerebral Infarction (TICI) 3 reperfusion was obtained 4 h after symptom onset. Note the close correspondence between the size and location of the ischemic core lesion at baseline (pink) and the subacute infarct seen on fluid-attenuated inversion recovery at 27 h (outlined in green in the **lower left**). The solid green lesion at baseline (**upper right**) is the Tmax >6 perfusion lesion. This lesion is completely reperfused on the 27-h scan (**bottom right**).

Results

In SWIFT PRIME, 88 patients had CTP at both baseline and 27-hour follow-up imaging. Forty-seven patients achieved 100% reperfusion based on Tmax >6 s perfusion maps obtained at 27 hours, 34 patients from the endovascular arm, and 13 patients from the intravenous tPA only arm. The baseline characteristics of these 47 patients are summarized in Table. The median time from stroke onset to baseline perfusion imaging within our study cohort was 114 minutes. Median National Institutes of Health Stroke Scale was 16, and mean age was 65.1±13.1. The median 27-hour infarct volume was 14.1 mL (interquartile range, 3.8–39.1). Two patients developed parenchymal hematoma type 1, and 1 patient developed parenchymal hematoma type 2.

Difference between the 27-hour final infarct volumes and predicted infarct and MAEs for the different rCBV and rCBF thresholds that we tested with RAPID is shown in Figure 2 and Table I in the online-only Data Supplement. The following CBV thresholds most accurately predicted the 27-hour infarct volume: rCBV=0.32, MAE=9 mL; and rCBV=0.34, MAE=9 mL. The following CBF thresholds most accurately predicted the 27-hour infarct volume: rCBF=0.30, MAE=8.8 mL; rCBF=0.32, MAE=7 mL; and rCBF=0.34, MAE=7.3. Figures 3 through 5 show correlation between predicted and final infarct core volumes for the rCBV and rCBF thresholds with the lowest MAE. Correlation of these thresholds between the baseline ischemic core volume and the 27-hour Tmax >6-s volume (predicted 27-hour volume) with the actual 27-hour infarct volume were as follows: rCBV=0.32, r=0.54, P<0.001; rCBV=0.34; r=0.52, P<0.001; rCBF=0.30, r=0.61, P<0.001; rCBF=0.32, r=0.62, P<0.001; and rCBF=0.34, r=0.62, P<0.001).

Table. Clinical Characteristics at Outcomes of the Patients Who Achieved Complete (100%) Reperfusion at 27 Hours

Characteristic	All, n=47	Control Arm (IV tPA Only), n=13	Endovascular Arm (IV tPA+Solitaire), n=34
Age, mean±SD, [median] (IQR)	65.1±13.1 (47) [68] (57–75)	68.8±13.8 (13) [73] (68–75)	63.7±12.7 (34) [65] (56–74)
Male sex, %	46.8% (22/47)	15.4% (2/13)	58.8% (20/34)
Baseline NIHSS score, mean±SD, [median] (IQR)	16.1±4.7 (47) [16] (12–18)	16.4±4.5 (13) [16] (14–19)	16.0±4.9 (34) [16] (12–18)
Baseline ASPECTS, mean±SD, [median] (IQR)	9.0±1.1 (47) [9] (8–10)	9.2±0.7 (13) [9] (9–10)	8.9±1.2 (34) [9] (8–10)
Site of occlusion			
ICA	7.0% (3/43)	0.0% (0/13)	10.0% (3/30)
M1	74.4% (32/43)	84.6% (11/13)	70.0% (21/30)
M2	18.6% (8/43)	15.4% (2/13)	20.0% (6/30)
Time from stroke onset to IV tPA, min, mean±SD, [median] (IQR)	122.7±49.2 (47) [121] (46–246)	124.8±58.9 (13) [128] (55–246)	121.9±45.9 (34) [121] (46–231)
Time from stroke onset to baseline perfusion imaging, min, mean±SD, [median] (IQR)	144.1±80.0 (47) [114] (76–220)	140.2±76.1 (13) [117] (65–217)	145.6±82.5 (34) [108] (77–228)
Time from stroke onset to groin puncture, min, mean±SD, [median] (IQR)	208.5±73.0 (34) [191] (155–269)	…	208.5±73.0 (34) [191] (155–269)
Time from stroke onset to recanalization, min, mean±SD, [median] (IQR)	246.8±75.3 (29) [232] (186–296)	…	246.8±75.3 (29) [232] (186–296)
Baseline perfusion lesion volume (Tmax>6), mean±SD, [median] (IQR)	114.5±63.6 (47) [119] (64–149)	133.5±71.2 (13) [131] (87–162)	107.2±60.0 (34) [98] (53–146)
Posttreatment recanalization			
TICI 0		…	3.4% (1/29)
TICI 1		…	0% (0/29)
TICI 2a		…	10.3% (3/29)
TICI 2b		…	6.9% (2/29)
TICI 3		…	79.3% (23/29)
Infarct volume at 27 h, mean±SD, [median] (IQR)	27.2±32.7 (47) [14.1] (3.8–39.1)	23.0±24.2 (13) [11.2] (6.9–36.2)	28.8±35.6 (34) [14.5] (3.8–39.1)
mRS 0–2 at 90 d, %	71.7% (33/46)	58.3% (7/12)	76.5% (26/34)

ASPECTS indicates Alberta Stroke Program Early CT score; ICA, internal carotid artery; IQR, interquartile range; IV, intravenous; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction; and tPA, tissue-type plasminogen activator.

Discussion

The objective of using perfusion imaging when selecting patients for thrombectomy is to identify the population that is most likely to demonstrate clinical recovery with minimal chance of reperfusion injury. The ischemic core represents infarcted tissue with no potential for recovery even if complete reperfusion is achieved.[8–10] In SWIFT PRIME, successful reperfusion was defined as ≥90% reperfusion at 27 hours, which was achieved in 53 (83%) patients from the interventional group and 21 (40%) patients from intravenous tPA only group. For this study, we only selected cases that achieved 100% reperfusion at 27 hours to reduce the effect of infarct growth in cases with 90% to 99% reperfusion. If reperfusion occurs soon after imaging, the final infarct volume should be similar to the baseline ischemic core volume. The SWIFT PRIME data provide a unique database to assess the optimal thresholds for defining the ischemic core on CTP.

In SWIFT PRIME, an rCBF threshold of 0.3 was preselected to define the ischemic core on baseline CTP imaging. This selection was based on the analysis of the median absolute differences between CTP lesion volumes and MRI diffusion weighted imaging lesion volumes in patients who were scanned with both CTP and MRI.[11] In this pooled data set of 103 patients, both imaging studies were performed within a very brief time period (median time between completion of CT and start of MRI was 36 minutes). Determining which perfusion parameters can most accurately identify the true ischemic core is of critical importance; studies have demonstrated ischemic core size to be a powerful predictor for the development of parenchymal hematomas and clinical outcome in patients with acute stroke.[12–15]

Overestimation of the core could result in unwarranted exclusion of patients who could benefit from reperfusion. On the other hand, underestimation of the true core size could

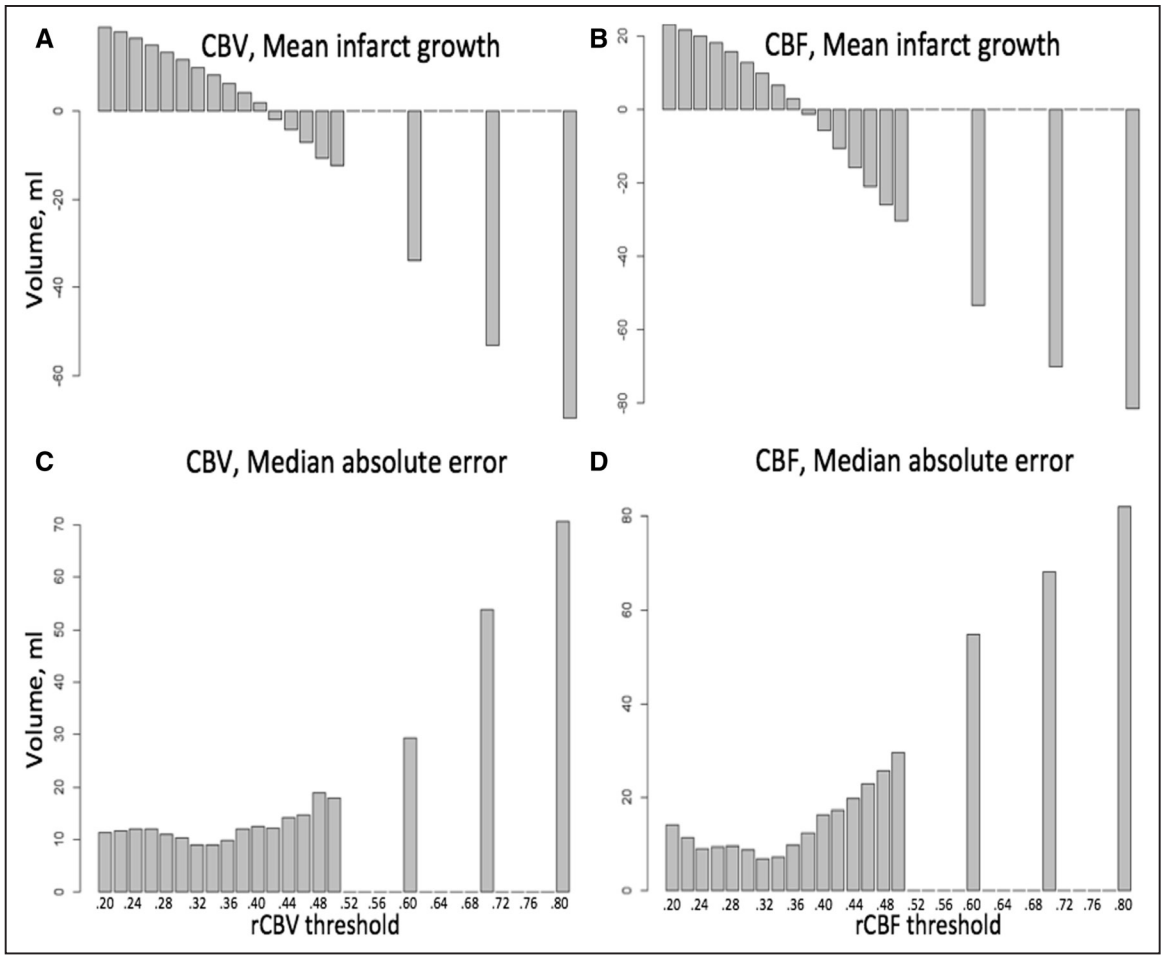

Figure 2. Graphic representation of accuracy of relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) thresholds. A range of thresholds tested was from 0.2 to 0.8 (*x* axis). Mean difference between the 27-h infarct and the predicted infarct volumes for (**A**) CBV and (**B**) CBF, and median absolute errors for (**C**) CBV and (**D**) CBF were calculated. Negative values of the mean difference indicate that the final infarct volume at 27 h was smaller than the predicted one.

increase the risk of hemorrhagic complications and decrease the likelihood of good clinical outcome after revascularization. As the optimal rCBF or rCBV threshold for determining core is likely to vary for patient to patient and, therefore, choosing a threshold that favors underestimation rather than overestimation of ischemic core is considered preferable, to help ensure an eligible patient is not excluded from receiving potentially viable treatments. Recent endovascular stroke trials (MR CLEAN [Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands],[16] ESCAPE [Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke],[17] SWIFT PRIME,[1] EXTEND-IA [Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial],[18] and REVASCAT [Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours][19]) showed strong evidence in support of modern thrombectomy therapies in patients with acute stroke, which were proven to be safe and highly effective in reducing neurological deficits. Excluding patients from these procedures because of overestimation of ischemic core would deprive them from a chance of regaining their neurological function.

This study validates the originally proposed rCBF value of 0.3 which was used in the SWIFT PRIME trial to identify ischemic core. This threshold produced a small MAE and resulted in very few cases of core overcall (n=11; median core overcall was 8.8 mL); threshold generated ischemic core lesions that were typically slightly smaller than the 27-hour infarct volume. An alternative threshold of rCBV is 0.32 (MAE=9 mL). This threshold had a similar MAE to rCBF 0.3 but a slightly lower correlation coefficient and a larger median core overcall (n=13; median core overcall=12.0 mL).

When the predictability of different thresholds was tested for the 2 arms of SWIFT PRIME separately, we observed higher variability in the correlation between the baseline and final core volumes in the intravenous tPA only group. This could be explained by a relatively small sample size of this group (n=13), as well as by the pharmacological effect of tPA which, unlike stent retriever thrombectomy, does not typically provide immediate recanalization of the occluded segment, permitting time for further infarct growth.[20]

Limitations of the study include the fact that complete reperfusion was assessed at 27 hours. An earlier assessment would have allowed exclusion of patients with longer imaging

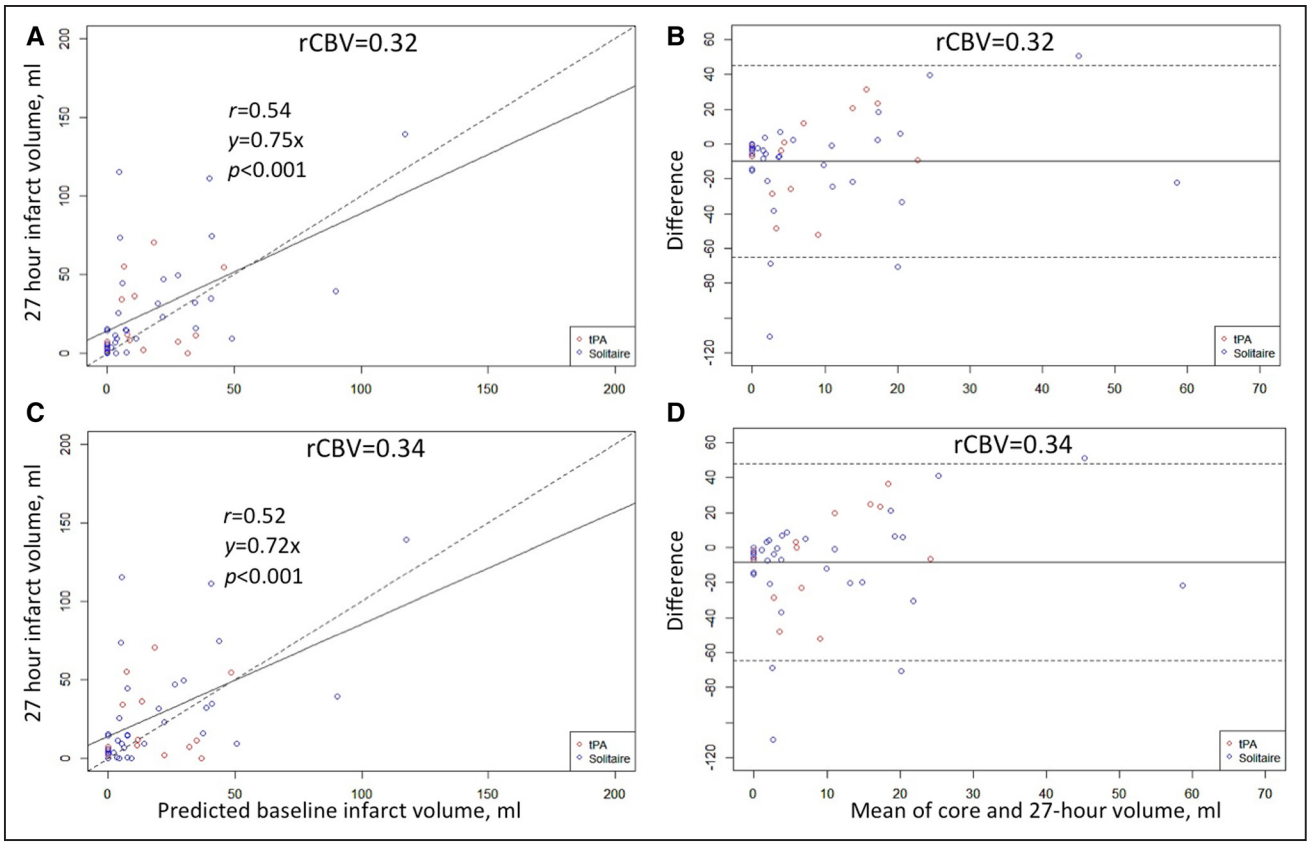

Figure 3. Graphic representation of correlation between predicted and final infarct core volumes for the relative cerebral blood volume (rCBV) thresholds with the lowest median absolute error. **A** and **C**, Scatter plots for rCBV thresholds 0.32 and 0.34. Dotted line represents the reference line of 100% correlation. *x* axis represents the predicted baseline volume of ischemic core. *y* axis values represent final infarct core volume measured at 27 h. **B** and **D**, Bland–Altman plots for rCBV thresholds 0.32 and 0.34. *x* axis represents the mean of the baseline core and the 27-h infarct volume. *y* axis indicates difference between predicted and final infarct core volumes. A black horizontal line represents mean infarct growth, and dotted lines indicate 95% confidence interval.

to reperfusion times and would have potentially improved the accuracy of predicting the ischemic core. Even in the endovascular group, reperfusion typically did not occur for at least 60 minutes after imaging was obtained. Therefore, infarct growth between the time of imaging and reperfusion likely reduced the agreement between infarct core volumes and final infarct size. In SWIFT PRIME, the median time between baseline imaging and establishing successful endovascular reperfusion was 100 minutes. Previous analysis of the trial's data showed a trend toward a lower median infarct growth (12 mL) in patients who achieved faster Thrombolysis in Cerebral Infarction 2b/3 reperfusion, than patients who were reperfusion at or later time than 100 minutes from baseline imaging (15 mL infarct growth), but the difference did not reach statistical significance (P=0.42).[2]

Three patients had hemorrhagic transformation of the ischemic core region after reperfusion; this led to an increase in the size of the infarct volume because it is not possible to separate the region of hemorrhage from the infarction.[2] In addition, vasogenic edema can further contribute to overestimation of the true infarct volume at 27 hours. These factors, which all contribute to the final infarct being larger than the baseline ischemic core, favor choosing an ischemic core threshold that yields core volumes that are smaller than the observed 27-hour final infarct volumes. Finally, patients with a predicted baseline ischemic core of >50 mL were excluded from SWIFT PRIME. Additional studies are needed to confirm that similar rCBF and rCBV thresholds provide accurate prediction of final infarct volume in patients with larger baseline core values.

Conclusions

Our study showed that brain regions with rCBF 0.30 to 0.34 or rCBV 0.32 to 0.34 thresholds provided the most accurate prediction of infarct volume in patients who achieved complete reperfusion with MAEs of <10 mL.

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Disclosures

Dr Levy serves as a scientific consultant to Medtronic; has shareholder/ownership interest with Intratech Medical Ltd and Blockade Medical LLC; has received fees from Abbott for carotid training; and has served as an expert witness for Renders Medical/Legal opinion. Dr Saver serves as a scientific consultant about trial design and conduct for Covidien and Stryker and is an employee of the University of California, which holds a patent on retriever devices

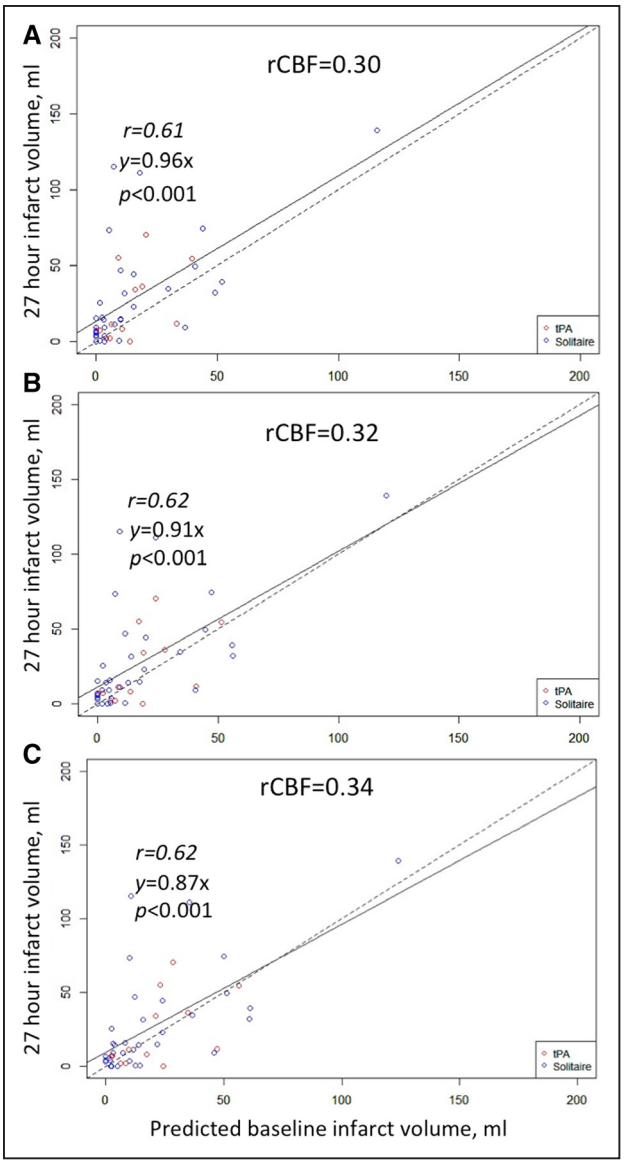

Figure 4. Graphic representation of correlation between predicted and final infarct core volumes for the relative cerebral blood flow (rCBF) thresholds with the lowest median absolute error. Scatter plots for rCBF thresholds 0.30 (**A**), 0.32 (**B**), and 0.34 (**C**).

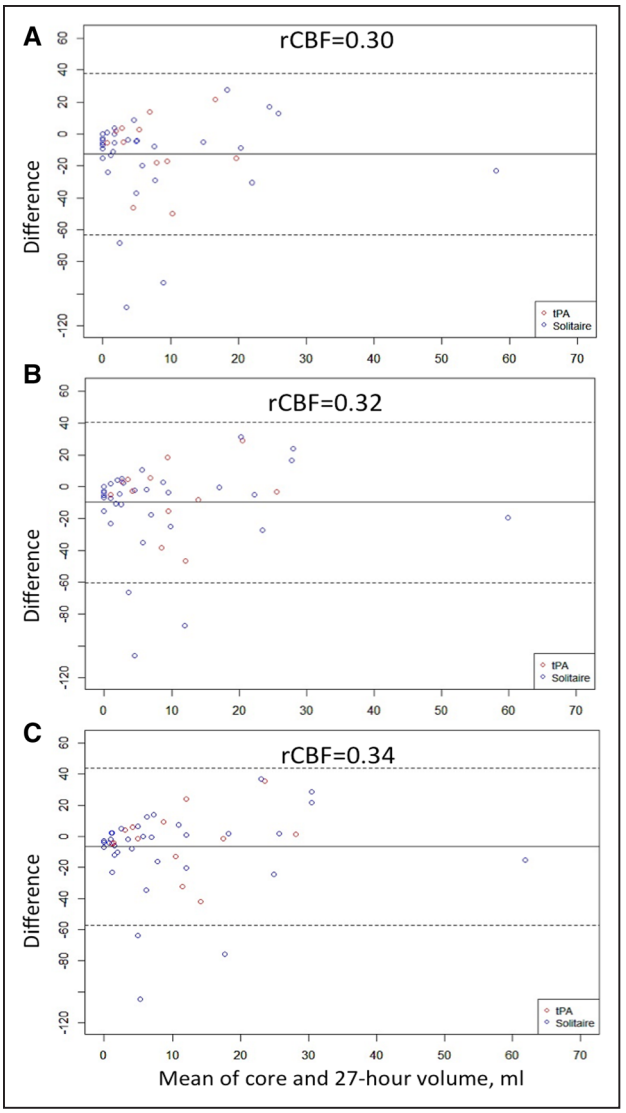

Figure 5. Graphic representation of correlation between predicted and final infarct core volumes for the relative cerebral blood flow (rCBF) thresholds with the lowest median absolute error. Bland–Altman plots for rCBF thresholds 0.30 (**A**), 0.32 (**B**), and 0.34 (**C**).

for stroke. Dr Siddiqui has financial interests in Hotspur, Intratech Medical, StimSox, Valor Medical Blockage Medical, Lazarus Effect, Pulsar Vascular, and Medina Medical, Inc; has served as a scientific consultant to Medtronic, Codman and Shurtleff, Inc, GuidePoint Global Consulting, Penumbra, Stryker, Pulsar Vascular, Microvention, Lazarus Effect, Blockade Medical, and Reverse Medical; is part of the Speakers' bureaus at Codman and Shurtleff, Inc; is on the advisory board for Medtronic Neurovascular, Codman and Shurtleff, Inc, Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL), and Medina Medical, Inc; and has received an honoraria from Abbott Vascular and Codman and Shurtleff, Inc for physician training and Penumbra, Inc. Dr Goyal served as a consultant to Medtronic for design and conduct of the SWIFT PRIME trial; has also received honoraria from Medtronic/Covidien for speaking and teaching engagements; and was also one of the Principal Investigators for the ESCAPE trial. The ESCAPE trial was partially funded by Covidien through an unrestricted research grant to the University of Calgary. Dr Bonafé has been a consultant for Covidien and has a licensing agreement with GE. Dr Cognard has been a consultant for Medtronic, Sequent, Codman, Microvention, and Stryker. Dr Jahan has been a consultant and speaker for Covidien. Dr Albers has an equity interest and is a consultant for iSchemaView, which provided the RAPID software and Core Laboratory services for the SWIFT PRIME study and has been a consultant for Covidien. The other author reports no conflicts.

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