Endovascular Treatment in the DEFUSE 3 Study

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Background and Purpose—Endovascular therapy in an extended time window has been shown to be beneficial in selected patients. This study correlated angiographic outcomes of patients randomized to endovascular therapy with clinical and imaging outcomes in the DEFUSE 3 study (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3).

Methods—Angiograms were assessed for the primary arterial occlusive lesion and the modified Thrombolysis in Cerebral Infarction (TICI) score at baseline and the final modified TICI score. Clinical outcomes were assessed using an ordinal analysis of 90-day modified Rankin Scale and a dichotomous analysis for functional independence (modified Rankin Scale score of 0–2). TICI scores were correlated with outcome, types of device used for thrombectomy, and 24-hour follow-up imaging.

Results—TICI 2B-3 reperfusion was achieved in 70 of 92 patients (76%). TICI 2B-3 reperfusion showed a more favorable distribution of Rankin Scale scores compared with TICI 0-2A; odds ratio, 2.77; 95% confidence interval, 1.17–6.56; *P*=0.019. Good functional outcome (90-day modified Rankin Scale score of 0–2) increased with better TICI scores (*P*=0.0028). There was less disability comparing TICI 3 patients to TICI 2B patients (*P*=0.037). Successful reperfusion (TICI 2B-3) was independent of the device used, the site of occlusion (internal carotid artery or M1) or adjunctive use of carotid angioplasty and stenting. Significantly less infarct growth at 24 hours was seen in TICI 3 patients compared with TICI 0-2A (*P*=0.0015) and TICI 2B (*P*=0.0002) patients.

Conclusions—Thrombectomy in an extended time window demonstrates similar rates of TICI 2B-3 reperfusion to earlier time window studies. Successful reperfusion was independent of the device used, the site of occlusion or adjunctive use of carotid angioplasty and stenting. TICI 3 reperfusion was more likely to result in low rates of infarct growth at 24 hours and good functional outcome at 90 days.

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Endovascular thrombectomy improves outcome for acute ischemic stroke patients with large artery anterior circulation strokes, when performed within 6 hours of stroke onset.[1] Recently, 2 trials demonstrated benefit extended to 16 to 24 hours after last seen well in selected patients.[2,3] The DEFUSE 3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) was a randomized study comparing medical therapy to endovascular treatment plus medical therapy 6 to 16 hours after last known well.[3]

DEFUSE 3 used Food and Drug Administration (FDA) cleared thrombectomy devices for use in an 8-hour time window. Data from randomized studies before DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 provide limited information about the effectiveness of these devices beyond 6 hours.[4] In addition, data from DEFUSE 3 offer an opportunity to correlate angiographic findings before and after endovascular treatment with baseline and follow-up noninvasive imaging. This study correlates the angiographic findings at endovascular treatment with clinical outcome, device choice, and noninvasive imaging.

Methods

The study protocol was previously described.[5] DEFUSE 3 was a multicenter, prospective, randomized trial enrolling patients for

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endovascular therapy 6 to 16 hours after last known well. Subjects were randomized 1:1 to endovascular therapy plus medical therapy versus medical therapy alone. Ethics approval was obtained from the local institutional review board at each center, and written informed consent was obtained from patients. The study was halted in May 2017, when an early interim analysis demonstrated efficacy according to the prespecified efficacy boundary with 182 patients randomized, 92 to endovascular treatment and 90 to medical treatment. Anonymized data from the DEFUSE 3 study will be made publicly available at the National Institutes of Health repository for open data.

Imaging eligibility was determined by either computed tomographic (CT) perfusion or magnetic resonance (MR) perfusion-diffusion studies showing a Target Mismatch Profile, previously described.[5] Mismatch between core and salvageable ischemic tissue (penumbra) was determined from CT or MR using a previously described automated processing system (RAPID, iSchemaView, Menlo Park, CA—versions 4.51 and 4.6).[6,7] Patients also had baseline MR angiography or CT angiography to confirm an intracranial internal carotid artery (ICA) or middle cerebral artery (MCA) M1 occlusion.

Endovascular Therapy

Interventionalists were preapproved based on training and post-training experience as previously described.[3] Interventionalists could use any FDA-approved device for thrombectomy (approved for use within an 8-hour window after stroke onset and used in the DEFUSE 3 study with an FDA investigational device exemption). The devices used were the Trevo Retriever (Stryker Neurovascular, Fremont, CA), the Solitaire Revascularization Device (Medtronic, Irvine, CA), Covidien MindFrame Capture Revascularization Device (Medtronic), and the Penumbra Suction Thrombectomy system (Penumbra, Alameda, CA).

The interventionalist could use any device or combination of devices in the ICA or MCA M1 segment. They could also use the devices to remove thrombus from MCA M2 segments. If the interventionalists encountered severe common or proximal ICA stenosis or occlusion, they could also perform angioplasty or stenting with FDA-approved devices. Adjuvant intraarterial thrombolytic agents were prohibited in DEFUSE 3.

Outcome Measures

The modified Rankin Scale (mRS) was determined at day 90. An ordinal analysis of mRS scores was performed, and functional independence at day 90, defined as an mRS score of 0 to 2, was also determined.

Follow-up imaging was performed at 24 (±6) hours with MR imaging (CT was allowed if MR was not possible). This was used to determine (1) lesion growth between baseline and 24 hours; (2) successful reperfusion, (>90% Tmax>6 s lesion volume reduction); and (3) recanalization on CT angiography/MR angiography. Baseline and follow-up MR imaging and CT images were assessed by core laboratory readers blinded to randomization assignment.

Angiographic Assessment

Sites were asked to provide a baseline pretreatment angiogram and a final post-treatment angiogram of the involved carotid circulation. Angiographic studies were assessed at baseline for the primary arterial occlusive lesion and the modified Thrombolysis in Cerebral Infarction (TICI) score.[8] The final angiogram was assessed for the modified TICI score. A lateral projection was available for the final angiogram in 90 cases. In the 2 cases where this was not available, the primary arterial occlusive lesion had not been reperfused and the TICI score was 0. The endovascular procedure was deemed successful if the final angiogram demonstrated a modified TICI score of 2b (50%–99% reperfusion) or 3 (complete reperfusion). Angiographic studies were evaluated by 2 independent raters at the core laboratory at Stanford and, in cases of disagreement, a consensus reading was used.

Statistical Analysis

Recanalization categories were compared with respect to the 90-day mRS distribution via Wilcoxon rank-sum test, and the effect of reperfusion is estimated via the proportional odds model. Univariate association between categorical variables was assessed using χ^2 test. Gradual change in the good functional outcome rates, recanalization, and reperfusion across levels of TICI reperfusion were assessed by the Cochran-Armitage test. Exact tests were used when cell counts were <5 for categorical variables. Infarct growth between levels of TICI reperfusion was compared by Wilcoxon rank-sum test.

All statistical tests were 2-sided and conducted using level of significance 0.05. Statistical analysis was done with SAS version 9.4.

Results

Baseline clinical and noninvasive imaging data for the 92 patients randomized to endovascular therapy are presented in Table I in the online-only Data Supplement. Baseline angiograms showed that 35 patients (38%) had ICA common carotid artery occlusions, 54 (59%) had MCA M1 occlusions, 2 (2%) had MCA M2 occlusions, and 1 patient (1%) had no occlusion. Baseline TICI scores of 0 to 1 were present in 90 patients, 1 patient was TICI 2A and 1 TICI 3. The final angiogram showed TICI 2B-3 reperfusion in 70 patients (76%), with 52 (57%) TICI 2B and 18 (20%) TICI 3. In addition, 10 patients (11%) were TICI 0 and 12 (13%) were TICI 2A. The TICI 2B-3 rates were similar when the arterial occlusive lesion was the carotid artery (74%) versus the MCA M1 (76%). The 2 readers TICI scoring agreed in 85 of 92=92% (95% confidence interval, 85–96), with a κ of 0.87 (95% confidence interval, 0.78–0.97).

Figure shows the 90-day mRS score distribution stratified by TICI scores. There was a more favorable distribution of scores (less disability) comparing TICI 2B-3 patients to TICI 0-2A patients; odds ratio, 2.77; 95% confidence interval, 1.17–6.56; P=0.019 (Figure [A]). There was less disability comparing TICI 3 patients to TICI 2B patients (P=0.037). However, there was not a significant difference in disability comparing TICI 2B patients to TICI 0-2A patients (P=0.07; Figure [B]). Table shows the rates of good functional outcome (90-day mRS score of 0–2) by TICI score, which consistently increased with better TICI scores (P=0.0028). TICI score was an independent predictor of good functional outcome (P=0.006, for TICI 0-2A, 2B, 3), and there was no interaction found between TICI score and age (P=0.956) or baseline NIHSS (National Institutes of Health Stroke Scale) score (P=0.384).

Table II in the online-only Data Supplement shows the recanalization, reperfusion, and infarct growth rates at 24-hour follow-up imaging stratified by TICI score. Rates of recanalization significantly increased across higher TICI scores (P=0.0004) as did rates of successful reperfusion (P<0.0001). The decline in infarct growth, however, was not found to be gradual across TICI scores. Although there was no difference between TICI 0-2A and 2B (P=0.887), infarct growth was attenuated with TICI 3 reperfusion compared with TICI 0-2A (P=0.0015) and TICI 2B (P=0.0002).

Ninety of 92 patients (98%) randomized to endovascular therapy had an intervention. Eighty-eight had attempted thrombectomy, 87 with approved devices, and 1 with placement of a self-expanding stent. Two patients had ICA stenting alone without subsequent thrombectomy. Eleven of 88 patients with attempted thrombectomy also had extracranial carotid angioplasty or stenting. Two patients with cervical carotid occlusions (common carotid artery and ICA) had no intervention

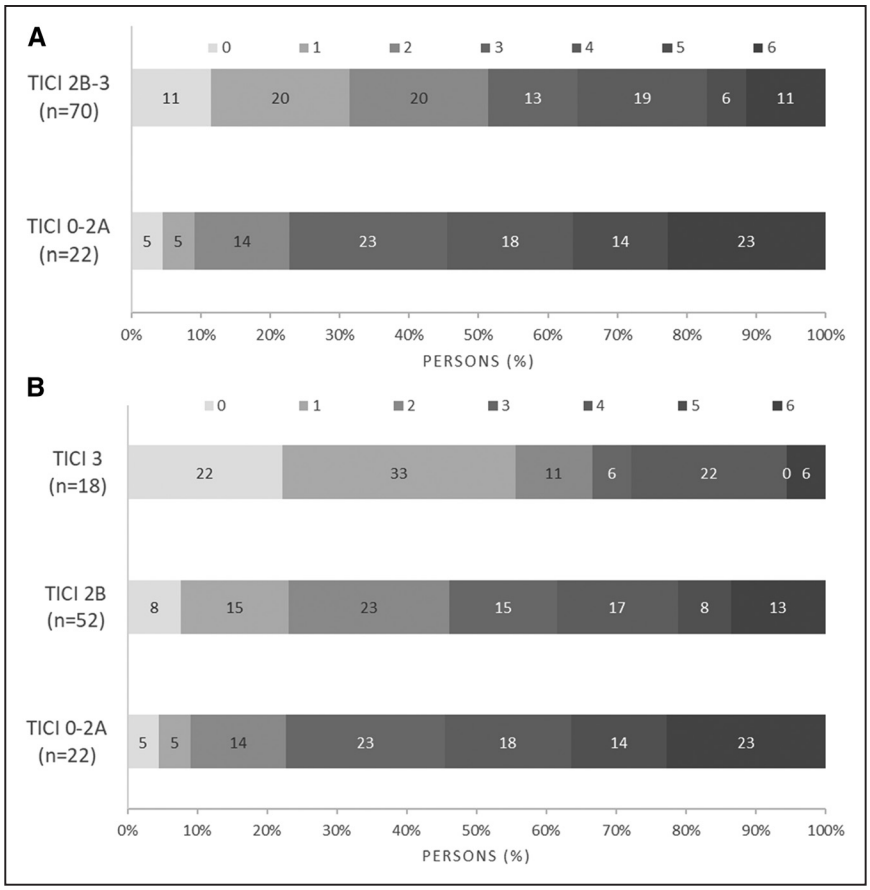

Figure. Rankin Scale scores stratified by final Thrombolysis in Cerebral Infarction (TICI). **A**, Ninety-day modified Rankin Scale (mRS) distribution stratified by TICI scores 0-2A, 2B-3. **B**, Ninety-day mRS distribution stratified by TICI scores 0-2A, 2B, and 3.

because the endovascular therapist felt that treatment was not feasible. Table III in the online-only Data Supplement displays the angiographic and clinical results when aspiration or stent retrievers were used as first-line therapy. There were no differences in successful reperfusion (TICI 2B-3) or good functional outcome between the 2 groups; however, treatment with the alternative therapy was used more frequently when aspiration was used first. There were 5 protocol violations and 2 device-related complications (described in the online-only Data Supplement).

Eleven patients with carotid angioplasty or stenting and attempted thrombectomy did not have significantly different TICI 2B-3 rates (82%, 9/11) or rates of good functional outcome (45%, 5/11) when compared with the 76 patients who were treated solely with approved thrombectomy devices (TICI 2B-3 76%, 58/76, P=0.73; good functional outcome 45%, 34/76, P=1.0). Two other patients who underwent carotid stenting without thrombectomy had mRS scores of 2 and 5 at 90 days.

Interventionalists performed 2.3±1.5 (mean±SD) passes in the thrombectomy patients. The rates of good functional outcome at 90 days (mRS score of 0–2) were similar for patients treated with 1 pass (50%, 16/32) or 2 passes (56%, 14/25) and were significantly higher than those patients treated with ≥3 passes (27%, 8/30; P=0.024).

Discussion

Successful reperfusion (TICI 2B-3) was achieved in 76% of the patients treated in this extended time window using FDA-approved thrombectomy devices. This rate is similar to the HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) meta-analysis of earlier time window trials (71%) and the recently reported DAWN trial (84%).[1,2] There was no difference in the TICI 2B-3 rates achieved if the first-line device was a suction thrombectomy catheter or a stent retriever, consistent with the results of an earlier time window trial, which also showed comparable TICI 2B-3 rates for the 2 techniques.[9] In our study, interventionalists did switch to the alternative device more frequently when they started with a suction thrombectomy catheter. DEFUSE 3 allowed interventionalists to perform angioplasty and stenting of the cervical carotid artery. This added procedure did not adversely affect TICI 2B-3 rates or outcomes when compared with patients treated solely with thrombectomy devices.

TICI 2-3 reperfusion has been used as a standard for FDA thrombectomy device approval studies evaluating devices in an earlier time window,[10,11] and TICI 2B-3 reperfusion has

Table. TICI Score Versus Good Functional Outcome

TICI Score	mRS Score of 0–2; N (%)
0 (n=10)	1 (10)
2A (n=12)	4 (33)
2B (n=52)	24 (46)
3 (n=18)	12 (67)

mRS indicates modified Rankin Scale; and TICI, Thrombolysis in Cerebral Infarction.

been considered a benchmark for successful reperfusion in other randomized trials.[1] TICI 2B-3 reperfusion has also been identified in a consensus statement as successful reperfusion.[8] Our results show the degree of TICI reperfusion was an independent predictor of good outcome and TICI 3 reperfusion results in better clinical outcomes than TICI 2B. Similarly, TICI 3 reperfusion has been shown in an earlier time window retrospective study to have significantly better outcomes when compared with TICI 2B reperfusion.[12] These differences in clinical outcome between TICI 2B and TICI 3 are supported by our finding that TICI 3 reperfusers had significantly less infarct growth on follow-up imaging (median, 5 mL; interquartile range, 1–15) when compared with TICI 2B patients (median, 32 mL; interquartile range, 14–103). The infarct growth measurement at 24 hours may not represent the full size of the eventual infarct as there is evidence that final infarct volume is not realized for several days in tissue that is not reperfused.[13] However, the values we measured suggest that TICI 3 reperfusion freezes the infarct size when compared with TICI 2B. These results suggest the potential importance of striving for full TICI 3 reperfusion.

These results also suggest the ability to reperfuse large arteries with current devices is not adversely affected by treatment in an extended time window. Several factors have been postulated to influence the ability to reperfuse large artery occlusions in acute ischemic stroke, including collateral status.[14,15] Patients with good collaterals have been shown to have higher rates of reperfusion.[14,15] DEFUSE 3 selected patients with a good collateral status by using a mismatch profile yielding relatively small cores in an extended time window. An important limitation of the present study is the limited sample size for analysis.

In conclusion, endovascular treatment with FDA-approved devices in an extended time window yielded similar rates of TICI 2B-3 reperfusion to earlier time window studies. Rates of good reperfusion were independent of the device used, the site of occlusion or adjunctive use of carotid angioplasty and stenting. TICI 3 reperfusion was associated with less infarct growth at 24 hours and a higher rate of good functional outcome at 90 days.

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Disclosures

Dr Marks has stock in Thrombx Medical. Dr Heit is a consultant in Medtronic. Dr Christensen has stock and is a consultant in IschemiaView. Dr Derdeyn is a scientific advisory board and has stock options in Pulse Therapeutics; and receives honorarium from Bayer. Dr Rasmussen is Modest in Stryker Neurovascular, Medtronic Neurovascular, Neurvive Medical, Neurvana Medical, Boston Scientific, and Perflow; and is Significant in Mehana Medical. Dr Zaidat is a consultant in Stryker, Penumbra, Neuravi, and Medtronic. Dr Yeatts is a consultant in Genentech. Dr Albers has stock in iSchemaView; and is a consultant in iSchemaView and Medtronic. The other authors report no conflicts.

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