Original Investigation

Endovascular Stroke Treatment Outcomes After Patient Selection Based on Magnetic Resonance Imaging and Clinical Criteria

Thabele M. Leslie-Mazwi, MD; Joshua A. Hirsch, MD; Guido J. Falcone, MD, MPH; Pamela W. Schaefer, MD; Michael H. Lev, MD; James D. Rabinov, MD; Natalia S. Rost, MD, MPH; Lee Schwamm, MD; R. Gilberto González, MD

IMPORTANCE Which imaging modality is optimal to select patients for endovascular stroke treatment remains unclear.

OBJECTIVE To evaluate the effectiveness of specific magnetic resonance imaging (MRI) and clinical criteria in the selection of patients with acute ischemic stroke for thrombectomy.

DESIGN, SETTING, AND PARTICIPANTS In this observational, single-center, prospective cohort study, we studied 72 patients with middle cerebral artery or terminal internal carotid artery occlusion using computed tomographic angiography, followed by core infarct volume determination by diffusion weighted MRI, who underwent thrombectomy after meeting institutional criteria from January 1, 2012, through December 31, 2014. In this period, 31 patients with similar ischemic strokes underwent endovascular treatment without MRI and are categorized as computed tomography only and considered in a secondary analysis.

INTERVENTIONS Patients were prospectively classified as likely to benefit (LTB) or uncertain to benefit (UTB) using diffusion-weighted imaging lesion volume and clinical criteria (age, National Institutes of Health Stroke Scale score, time from onset, baseline modified Rankin Scale [mRS] score, life expectancy).

MAIN OUTCOMES AND MEASURES The 90-day mRS score, with favorable defined as a 90-day mRS score of 2 or less.

RESULTS Forty patients were prospectively classified as LTB and 32 as UTB. Reperfusion (71 of 103 patients) and prospective categorization as LTB (40 of 103 patients) were associated with favorable outcomes ($P < .001$ and $P < .005$, respectively). Successful reperfusion positively affected the distribution of mRS scores of the LTB cohort ($P < .001$). Reperfusion was achieved in 27 LTB patients (67.5%) and 24 UTB patients (75.0%) ($P = .86$). Favorable outcomes were obtained in 21 (52.5%) and 8 (25.0%) of LTB and UTB patients who were treated, respectively ($P = .02$). Favorable outcomes were observed in 20 of the 27 LTB patients (74.1%) who had successful reperfusion compared with 8 of the 24 UTB patients (33.3%) who had successful reperfusion ($P = .004$). The ratio of treated to screened patients was 1:3.

CONCLUSIONS AND RELEVANCE Prospective classification as LTB by MRI and clinical criteria is associated with likelihood of favorable outcome after thrombectomy, particularly if reperfusion is successful. Selection of patients using MRI compares favorably with selection using computed tomographic techniques with the distinction that a higher proportion of screened patients were treated.

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The effectiveness of mechanical thrombectomy for treating major ischemic strokes has been demonstrated in recent randomized clinical trials. The next challenge is to incorporate thrombectomy in the routine care of individual patients. The trials were successful largely because of the use of third-generation thrombectomy devices and the application of advanced imaging for patient selection. Imaging was used to recognize treatable occlusions and to identify patients most likely to have a favorable clinical outcome through the direct or indirect identification of small ischemic cores. We describe the results of a prospective, observational study that is distinct from the recent trials in that the imaging used included diffusion magnetic resonance imaging (MRI). Diffusion-weighted imaging (DWI) is the most precise method to estimate the size of the early ischemic core and thus may represent the most reliable approach for making a thrombectomy treatment decision in an individual patient.

Classification Criteria

Likely to Benefit
All the following criteria had to be met for the likely to benefit (LTB) group: (1) age younger than 80 years, (2) time from stroke onset or last seen well to groin puncture of less than 6 hours, (3) premorbid baseline mRS score of 0 or less and life expectancy greater than 12 months, and (4) DWI volume less than 70 mL.

Uncertain to Benefit
One or more of the following criteria had to be met for the uncertain to benefit (UTB) group: (1) age of 80 years or older, (2) time from stroke onset or last seen well to groin puncture of 6 to 8 hours, (3) premorbid baseline mRS score of 2 to 3 and a life expectancy greater than 6 months, and (4) DWI volume of 70 to 100 mL.

Unlikely to Benefit Cohort
Patients in the CT-only cohort did not undergo MRI because they were unable to (pacemakers, metallic implants, or foreign bodies) or because they presented very early (eg, in-house strokes) with reassuring CT findings, specifically no evidence of a large infarct on the head CT or a malignant collateral pattern on CTA (complete absence of visualized collateral vessels).

Imaging
Both CT and CTA were performed using multidetector scanners (GE Medical Systems). The CTA was performed from vertex to aortic arch after injection of 65 to 140 mL of a nonionic contrast agent (Isovue; Bracco Diagnostics) at 3 to 4 mL/s. Median parameters were a 1.25-mm section thickness and 220-mm reconstruction diameter.

The MRI included DWI for all with fluid-attenuated inversion recovery and gradient echo in a subset. The DWI median values were as follows: field of view, 220 mm; number of sections, 25; thickness, 5 mm; gap, 1 mm; repetition time, 5 seconds; echo time, 85.3 milliseconds; acquisition matrix, 128 × 128; and b = 0 s/mm² and 1000 s/mm² in at least 6 diffusion-gradient directions. Isotropic DWI and apparent diffusion coefficient maps were calculated. The DWI volume was estimated using the ABC/2 method at the MRI scanner.

Procedural Details
All patients were treated on an emergency basis, monitored by an anesthesia team with the patients under sedation, except for 39 patients, most of whom arrived at our facility intubated. No patients required intubation during the procedure. Procedures were performed using biplane angiography. A 7F Cook Shuttle sheath (Cook Medical) was the usual guide catheter. Stent retrievers were used in 72 cases (70%), and in 47 patients (45%) the de...
vice was pulled into a large-bore intermediate catheter. Six patients were treated with the Trevo device (Stryker Neurovascular), and the rest were treated with Solitaire (Covidien Neurovascular). The remaining cases involved earlier-generation devices (9 cases, early in the study period), use of aspiration alone (particularly a direct aspiration first pass technique), or a combination of techniques. Final biplanar angiography was used to grade the angiographic result. All patients were admitted to the neurologic intensive care unit, with additional head imaging at 24 hours.

Reperfusion Assessment
Reperfusion was graded using the modified Thrombolysis in Cerebral Infarction (mTICI) scale. A distinct mTICI grading, typically by a different neuroendovascular specialist, was additionally performed, with differences adjudicated among the operators. Successful reperfusion was defined as an mTICI score of 2b/3 on final intracranial angiogram.

Outcome Measures
The primary outcome measure was the 3-month mRS score, which was obtained through physician telephone interview or by direct neurology clinic evaluation. A standard form was completed from which the mRS score was calculated. In 3 patients, a 90-day mRS score was not available; their score was calculated based only on medical record notes (all had poor outcomes). Both dichotomized (mRS scores of 0-2 vs 3-6) and shift analyses were used. Additional measures included rates of mortality and hemorrhage.

Statistical Analysis
Descriptive statistics are presented as number (percentage) for discrete variables and mean (SD) or median (interquartile range) for continuous variables as appropriate (Table 1). The 3-month mRS score was modeled as a dichotomous variable (scores of 0-2 vs 3-6) in the primary analysis and a discrete 6-bin variable in the secondary analyses. The main exposure of interest in the study was the LTB status (yes or no), prospectively ascertained in patients undergoing MRI. Other modeling strategies were explored in secondary analyses. All variables that were relevant for the present study had less than 5% missing data.

Univariable, unadjusted associations between 90-day mRS and covariates were explored using regression analysis with only 1 predictor at a time; tested variables were sex, age, admission NIHSS score, baseline mRS score greater than 1, admission glucose level, history of diabetes mellitus, admission systolic blood pressure, history of hypertension, presence of atrial fibrillation, and time from stroke onset to beginning of intervention. For the primary analysis, multivariable logistic regression was subsequently used to assess the association between the patients classified by MRI as LTB and clinical outcome after adjusting for potential confounders. Model building proceeded as follows; variables with unadjusted P < .10 were included in the model, variables that changed to P > .10 in the multivariable model were removed, all variables excluded in prior steps were reintroduced one at a time, and those with P < .10 were kept in the model.

Sensitivity analyses were implemented on the results obtained in the primary analysis. We reanalyzed data keeping the 90-day mRS score as a 7-bin variable and implementing shift analysis by means of ordinal logistic regression. The proportional odds assumption was tested for the ordinal logistic regression. Model building proceeded as described for logistic regression in the primary analysis. We also explored the effect of forcing variables other than age and sex that could be important for biological or clinical reasons.

Secondary analyses were also undertaken to compare the 2 MRI groups prospectively classified as LTB and UTB with patients selected by CT only. An exploratory analysis evaluated patients who were assessed for possible intervention but not treated. This analysis included LTB (treated), UTB (treated), CT only (treated), untreated with no target occlusion or improving symptoms, and untreated with large core or other exclusion factor. For these secondary and exploratory analyses, univariable and multivariable assessments proceeded as described for the primary and sensitivity analyses. All analyses were performed using MedCalc software, version 15.2.2, and STATA software, version 13 (StataCorp).

Results
Study Population
A total of 103 consecutive patients met the inclusion criteria. Of these, 72 had MRI evaluations; 40 were prospectively classified as LTB and 32 as UTB. For the UTB classification, 17 pa-
patients were 80 years or older, 10 had intervention that began 6 to 8 hours after ictus, 3 had baseline mRS scores greater than 2, and 2 had DWI volumes of 70 to 100 mL. In this period, 31 patients with similar ischemic strokes underwent endovascular treatment without undergoing MRI. Details are listed in Table 1 and considered in a secondary analysis.

Clinical and procedural characteristics are listed in Table 1, and outcomes are listed in Table 2. The primary outcome measure was favorable 90-day functional outcomes (mRS scores of 0–2). No association of outcome and intravenous tissue plasminogen activator administration was found. Seventy-two patients underwent MRI and prospective classification as LTB or UTB before intervention. Univariable regression analysis of covariates in these patients with respect to 90-day functional outcomes was performed, revealing statistically significant associations between 90-day outcomes and successful reperfusion (mTICI scale score of 2b/3), LTB classification, history of diabetes, history of hypertension, and time to intervention.

After multivariable logistic regression, the following remained significant: successful reperfusion (71 of 103 patients, \( P < .001 \)), LTB classification (40 of 103 patients, \( P = .005 \)), and history of diabetes (27 of 103 patients, \( P = .004 \)). The adjusted odds ratios (95% CIs) were 77.0 (7.5–794.0) for a favorable outcome for successful reperfusion, 8.0 (1.9–34.0) for LTB classification, and 0.09 (0.02–0.46) for history of diabetes. To identify significant differences between the LTB and UTB cohorts, univariable logistic regression was performed for each of the covariates, and significant differences were detected for age, time to intervention, and LTB classification. Multivariable logistic regression that included these factors resulted in only LTB classification remaining significant (\( P = .02 \)).

An ordinal logistic regression model for the LTB and UTB groups was separately established to test whether successful reperfusion was associated with a favorable outcome with history of diabetes as a covariate. Reperfusion was a significant predictor of a shift toward good outcome (\( P < .001 \)) in the LTB group but not in the UTB group (\( P = .13 \)) adjusted for diabetes status. There was a significant interaction between reperfusion and LTB status; LTB patients who underwent reperfusion were more likely to have shift to lower mRS scores (\( P = .048 \)). The association of reperfusion to functional outcome score distribution is illustrated in the Figure. The Figure displays 90-day mRS scores for LTB patients and the effect of reperfusion. Successful reperfusion was achieved in 27 LTB patients (67.5%) and 24 UTB patients (75.0%) (\( P = .86 \)). Favorable outcomes occurred in 21 (52.5%) and 8 (25.0%) of LTB and UTB patients, respectively (\( P = .02 \); Fisher exact test). Considering the effect of successful intervention, favorable outcomes were observed in 20 of 27 LTB patients (74.1%) who underwent successful reperfusion compared with 8 of 24 UTB patients (33.3%) who underwent successful reperfusion (\( P = .004 \); Fisher exact test).

Failure of reperfusion was associated with poor patient outcomes, with mRS scores of 0 to 2 occurring in only 1 of 13 LTB patients and 0 of 8 UTB patients. The mortality rate was 7% in LTB patients after reperfusion compared with 38% in those without. In the UTB group, the mortality rates were approximately 25% irrespective of successful reperfusion. There were no significant differences in the symptomatic and asymptomatic hemorrhage rates.

Thirty-one patients underwent endovascular intervention without undergoing MRI. Details are listed in Table 1 and Table 2. There were no outcome differences between the CT-only and UTB cohorts, but there were significantly more favorable outcomes in the LTB cohort compared with the CT-only cohort (52.5% compared to 29.0%, \( P = .04 \)). Univariable logistic regression assessed covariates between groups. Age was significantly different (median 66 years for LTB, 80 years for UTB, and 67 years for CT only, \( P = .01 \)). There were no significant differences in rate of reperfusion, admission NIHSS score, and time to intervention. Multivariable logistic regression analysis that included age and LTB classification as covariates resulted in only LTB classification remaining significant (\( P = .01 \)).

For the first 20 months of this study, 191 patients were screened for endovascular stroke therapy based on presentation at less than 8 hours from onset and NIHSS score greater than 8, with 134 not receiving therapy. Of these, 131 had available mRS follow-up (Table 3). The 3 most common reasons for not pursuing endovascular treatment were no endovascular target (no persistent occlusion after intravenous tissue plas-
Discussion

Patients with acute stroke and occlusions of the terminal internal carotid artery or proximal middle cerebral artery classified as LTB using MRI and clinical criteria have a high likelihood of favorable outcomes when endovascular intervention restores cerebral perfusion. Failure to achieve reperfusion portends poor outcomes regardless of classification. This study complements recent trials by demonstrating clinical efficacy using third-generation devices but differs from them by using diffusion MRI in selecting patients. An additional distinguishing feature is that a higher proportion of screened patients were treated compared with available data from recent trials. The high treated to screened ratio supports the hypothesis that higher precision in ischemic core measurement provides a more refined approach to patient selection and may be the best approach for identifying individual patients for endovascular treatment under routine clinical conditions.

The appeal of MRI in acute stroke is the ability of diffusion imaging to define the ischemic core more precisely than other methods. We established prospective patient classification for preprocedural prognostication based on systematic review of our acute stroke outcomes and the published literature. Patients with a clinical deficit and small core infarct despite a proximal vessel occlusion must have an excellent collateral circulation. A threshold DWI volume of less than 70 mL has been used by the Cleveland Clinic to improve outcomes in patients with acute stroke treated endovascularly and was effectively used in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 trial. It bears emphasis that DWI volumes were calculated at acquisition by

Table 3. Outcomes of All Patients Evaluated for Endovascular Therapy During First 20 Months of Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treated, LTB (n = 24)</th>
<th>Treated, UTB (n = 18)</th>
<th>Treated, CT Only (n = 18)</th>
<th>Untreated With No Target Occlusion or Improving Symptoms (n = 73)</th>
<th>Untreated With Large Core or Other Exclusion Factor (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome (mRS scores of 0-2)</td>
<td>13 (54.2)</td>
<td>3 (16.6)</td>
<td>3 (16.6)</td>
<td>36 (49.3)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Unfavorable outcome (mRS score &gt;2)</td>
<td>11 (45.8)</td>
<td>15 (83.3)</td>
<td>15 (83.3)</td>
<td>37 (50.7)</td>
<td>56 (96.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; LTB, likely to benefit; mRS, modified Rankin Scale; UTB, uncertain to benefit.

Table 4. Comparison of Current Data Set With Recently Published Endovascular Trials

<table>
<thead>
<tr>
<th>Study Population</th>
<th>No. of Patients</th>
<th>Baseline NIHSS Score, Median (IQR)</th>
<th>Median Time From Onset to Puncture, min</th>
<th>Stent-retriever Use, %a</th>
<th>mTICI Score of 2b/3, %b</th>
<th>mRS Score of 0-2, %c</th>
<th>90-Day Mortality, %</th>
<th>Approximate Ratio of Patients Treated to Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTB</td>
<td>40</td>
<td>16.5 (3.4)a</td>
<td>244.6</td>
<td>68</td>
<td>53</td>
<td>18</td>
<td>1:3</td>
<td></td>
</tr>
<tr>
<td>UTB</td>
<td>32</td>
<td>16.4 (3.9)b</td>
<td>309.5</td>
<td>75</td>
<td>25</td>
<td>25</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td>CT only</td>
<td>31</td>
<td>16.9 (4.7)b</td>
<td>231.8</td>
<td>65</td>
<td>29</td>
<td>26</td>
<td>1:3</td>
<td></td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>233</td>
<td>17 (14-21)</td>
<td>260</td>
<td>82</td>
<td>59</td>
<td>32</td>
<td>18</td>
<td>Not reported</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>35</td>
<td>17 (13-20)</td>
<td>210</td>
<td>100</td>
<td>86</td>
<td>71</td>
<td>9</td>
<td>1:14</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>165</td>
<td>16 (13-20)</td>
<td>211a</td>
<td>86</td>
<td>72</td>
<td>53</td>
<td>10.4</td>
<td>Not reported</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>98</td>
<td>17 (13-20)</td>
<td>224</td>
<td>100</td>
<td>88</td>
<td>60</td>
<td>9</td>
<td>1:7.5</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>103</td>
<td>17 (14-20)</td>
<td>269</td>
<td>100</td>
<td>66</td>
<td>44</td>
<td>18.4</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mTICI, modified Thrombolysis in Cerebral Infarction; REVASCAT, Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT-PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment.

a Not all data are provided in both number and percentage form for all these trials; therefore, only percentages are reported here.

b Data presented as mean (SD).

c Estimation based on reported 241-minute median time from onset to first reperfusion and 30-minute median time from groin puncture to first reperfusion.
the treating teams using the ABC/2 method, without special image analysis software.

**Comparison With Recent Trials**

Table 4 compares variables and findings of this study with recently published endovascular trials.1–5 Our LTB cohort compares favorably with the populations in the Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial (EXTEND-IA), Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE), and Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trials, which most closely resemble our selection criteria. The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN) in the Netherlands1 and the Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours trial (REVASCAT)4 found favorable outcomes (mRS scores of 0–2) in approximately 33% and 44% of treated patients presenting with a persistent occlusion despite receiving intravenous tissue plasminogen activator. The ESCAPE, EXTEND-IA, and SWIFT PRIME trials had higher rates of favorable outcomes, from 53% to 71%. These 3 trials selected patients with small ischemic cores using advanced imaging beyond identifying an occlusion by CTA. We applied diffusion MRI for the same purpose and screened 3 patients for each patient treated, whereas in EXTEND-IA and SWIFT PRIME a mean of 14 and 7.5 patients, respectively, were screened to select a patient for treatment. The outcomes of the clinical trials and our prospective observational study suggest that there is a trade-off between maximizing the favorable outcome rate with endovascular treatment and the selection rate of those patients. We found a 52.5% favorable outcome rate in the LTB group, but the rate was 25.0% and 29.0% for the UTB and CT-only groups. Thus, the overall rate of favorable outcomes was 36.9% when treating 1 of every 3 patients screened. This may be close to the optimal trade-off with current treatment technology.

**Consequences of Failed Reperfusion and Presence of Large Core Infarct**

Failed reperfusion despite attempted thrombectomy is a strong signal of probable poor outcome. Considering all patients, only 2 of 32 in whom endovascular intervention was unsuccessful were functionally independent at 90 days. Failed reperfusion is incompletely understood and may relate to clot factors (eg, density, adherence, fragmentation, poor device integration) or patient factors (eg, anatomy). A similarly bleak prognosis was found in the 39 patients who did not undergo intervention because a large core infarct was identified by MRI or CT: none had favorable 90-day outcomes.

**Time and Physiologic Findings**

No significant association between time and outcomes existed, despite approximately 30 additional minutes to obtain MRI compared with CT and CTA only. This finding implicates individual physiologic findings as having a greater effect on determining outcome in patients undergoing thrombectomy. Cross-sectional studies17,18 of patients with proximal anterior circulation occlusions found that most have small (<70 mL) core infarcts even up to 24 hours after stroke onset or diffusion lesion stability despite persistent arterial occlusion. These observations of excellent collateral circulation that is less time dependent are supported by the work of Al-Ali et al19 and by Abou-Chebl,20 who found that comparable groups of patients with stroke with mean time to intervention of 3.4 vs 18.6 hours had similar outcomes.

**Limitations**

Our work has limitations inherent to its design as a single-center, prospective, nonrandomized, observational study. Most important, there is no randomized control group, so the benefit of the approach taken here cannot be quantified.

**Conclusions**

As thrombectomy moves from clinical trials to routine clinical use, a critical question is how to best assess the probability of success in an individual. Patients prospectively classified as LTB based on diffusion MRI and clinical criteria (including age and time from onset) have a likelihood of favorable outcome after successful thrombectomy similar to that found in recent trials but with the distinction that MRI use in a clinical setting produced a higher treated to screened ratio. A randomized clinical trial evaluating selection techniques is warranted.


