Early Trajectory of Stroke Severity Predicts Long-Term Functional Outcomes in Ischemic Stroke Subjects

Results From the ESCAPE Trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times)

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Background and Purpose—The trajectory of neurological improvement after stroke treatment is clinically likely to be an important prognostic signal. We compared the accuracy of early longitudinal National Institutes of Health Stroke Scale (NIHSS) measurement versus other early markers of stroke severity post treatment in predicting subjects’ 90-day stroke outcome.

Methods—Data are from the Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times). Stroke severity was assessed at baseline, 1, 2, 5, 30, and 90 days. Subjects’ functional outcome was assessed using the modified Rankin Scale at baseline, 30 days, and 90 days. Group-based trajectory model was used to identify distinct subgroups of longitudinal trajectories of NIHSS measured over the first 2, 5, and 30 days. The accuracy of baseline NIHSS, infarct volume, 24-hour change in NIHSS, infarct volume, and disease severity trajectory subgroups in predicting 90-day stroke outcome were assessed using logistic regression analysis.

Results—Group-based trajectory model of the 2-day longitudinal NIHSS data revealed 3 distinct subgroups of NIHSS trajectories—large improvement (41.6%), minimal improvement (31.1%), and no improvement (27.3%) subgroups. Individuals in the large improvement group were more likely were more likely to exhibit good outcomes after 90 days than those in the minimal improvement or no improvement subgroup. Among candidate predictors, the 2-day trajectory subgroup variable was the most accurate in predicting 90-day modified Rankin Scale at 84.5%.

Conclusions—Early trajectory of neurological improvement defined by 2-day longitudinal NIHSS data predicts functional outcomes with greater accuracy than other common variables.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01778335.

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Key Words: National Institutes of Health (U.S.) ■ prognosis ■ stroke ■ thrombolytic therapy ■ tomography, x-ray computed tomography

See related article, p 6.

Initial stroke severity is a primary determinant of clinical outcome among subjects with acute ischemic stroke. Several measures of stroke severity have been developed and include the National Institutes of Health Stroke Scale (NIHSS) scale,1,2 the Canadian Neurological Scale,3 Scandinavian Stroke Scale,4,5 and the European Stroke Scale6 among others. Although baseline measures of stroke severity are always reported and represent the best pretreatment measure to
predict outcome, other markers of stroke severity that include post-treatment information may be better predictors of clinical and functional outcomes. For example, change in NIHSS, infarct volume, and 24-hour NIHSS have been shown to be the strongest predictors of subjects’ 90-day stroke outcomes.\(^7\)\(^-\)\(^9\) Repeated assessments of stroke severity are routinely collected in stroke research studies providing an opportunity to assess longitudinal data on subjects’ postdischarge functional outcomes.

We investigated the prognostic utility of the trajectory of stroke severity change using repeat assessments of stroke severity within 48 hours of stroke symptom onset in predicting subjects’ 90-day functional outcome defined by the modified Rankin Scale (mRS) score. Specifically, we compare the predictive performance of several early markers of stroke severity, including 24-hour NIHSS, change in NIHSS from baseline to 24 hours, and latent NIHSS trajectories in predicting 90-day functional outcomes in subjects enrolled in the ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times).

**Study Design**

The ESCAPE trial was an investigator initiated multicenter, prospective, randomized, open-label controlled trial with blinded endpoint assessment (PROBE) design assessing the additional benefit of modern endovascular treatment when compared with guideline-based standard of care. Participants were assigned, in a 1:1 ratio, to receive endovascular treatment plus guideline-based care (intervention group) or guideline-based care alone (control group). The trial screened subjects fulfilling clinical eligibility criteria if they presented within 12 hours of stroke symptom onset and then included them only if they met neurovascular imaging criteria. All subjects had standard assessment for demographics, medical history, previous medications, baseline laboratory tests, and stroke severity (defined by the NIHSS score). The trial enrolled 316 subjects with 165 subjects randomized to intervention arm and 150 subjects randomized to control arm, and 1 excluded due to improper consent procedures. After randomization, NIHSS was assessed within the first 8 hours, at 24 hours, 48 hours, 5 days, 30 days, and 90 days. The primary outcome was the mRS at 90 days after randomization.\(^10\)\(^,\)\(^11\)

Group-based trajectory modeling (GBTM) was used to identify subject subgroups with distinct longitudinal trajectories of stroke severity, as measured by the NIHSS over a 48-hour, 5-day, and 30-day period after randomization. GBTM is a flexible methodology that models heterogeneity in longitudinal trajectory of individuals, while identifying latent (ie, unobserved) subgroups of individuals with the similar longitudinal trajectories. GBTM estimates subject-specific posterior probability of belonging to different latent subgroups. This methodology simultaneously implements several regression models through maximization of a likelihood that combines the information from all models. Specifically, the probability of belonging to each potential adherence group is modeled as a simple multinomial logistic regression with no predictors (only an intercept for each group). Within each subgroup, stroke severity is modeled as a smooth function of time using up to a fourth-order polynomial. Therefore, the model assumes that repeated observations on the same individual are independent conditional on trajectory group, meaning that the within-person correlation structure is explained completely by the estimated trajectory curve for each person’s group. The output of a group-based trajectory model includes estimated probabilities of group membership for each individual and each group and an estimated trajectory curve over time for each group.\(^12\)\(^-\)\(^16\)

Model selection involved the iterative process of estimating the number of trajectory groups, average probability of group membership, and the shape/order of each trajectory group using both statistical and nonstatistical considerations. Specifically, model selection begins with one quartic group, and more groups were added only if a better fit was detected using the above criteria. In addition, only the polynomial terms (quartic, cubic, or quadratic) with significant coefficients were kept before adding additional groups, but the linear terms were retained whether they were significant. The selected model is considered to be adequate if the average of the posterior probabilities of group membership for individuals assigned to each group exceed 0.7. Measures of goodness-of-fit of the GBTM are generally based on information-theoretical approaches such as the Akaike Information Criterion and Bayesian Information Criterion, with smaller values of AIC, and Bayesian Information Criterion indicating better model fit. Descriptive statistics, including means, SD, percentages, are used to summarize subject demographic, clinical, and imaging characteristics by the identified trajectory subgroups. Fisher exact test was used to assess the differences in categorical subjects’ characteristics across the 3 trajectory subgroups, whereas ANOVA was used to assess the differences in continuous subject characteristics across trajectory subgroups.

The prognostic value of the trajectory subgroups and other markers of stroke severity in predicting 90-day mRS was assessed using logistic regression analysis. Specifically, a logistic regression model\(^17\) was used assess the predictive accuracy of trajectory subgroups, baseline NIHSS, NIHSS at 24 hours, change in NIHSS between baseline and 24 hours, and infarct volume in predicting 90-day stroke outcomes with and without adjustment for other baseline characteristics including age, sex, Alberta Stroke Program Early CT Score, baseline occlusion, and intravenous alteplase. The presence of multicollinearity among the covariates was evaluated using the criterion of a variance inflation factor. For each model, odds ratios with 95% confidence intervals were used to describe the effect size of each predictor, whereas the area under the receiver operating characteristic curve (AUC) was used as a measure of predictive accuracy of the logistic regression prediction model. The Hosmer–Lemeshow test\(^17\) was used to assess the goodness-of-fit and calibration of the logistic regression models. All analyses were conducted in SAS 9.4.\(^18\)

**Results**

There were 4 repeated assessments of NIHSS over 48 hours and 6 repeated measurements over 30 days post randomization.
The GBTM of the 48-hour longitudinal NIHSS data revealed 3 distinct subgroups of subjects. Specifically, 41.6% of the subjects had consistently large improvement, 31.1% of the subjects had minimal improvement, whereas 27.3% had no improvement in NIHSS over the 48-hour period (Figure 1). Each trajectory subgroup had an average posterior probability of >0.9 indicating excellent grouping. When the 5- and 30-day NIHSS longitudinal data were used, the GBTM revealed similar number of distinct trajectory groups (Figures 2 and 3).

Table 1 describes the demographic, clinical, and imaging characteristics of subjects in each of the three trajectory subgroups. Subjects in the large improvement subgroup were likely to be younger with lower baseline NIHSS, who mostly received endovascular treatment and intravenous alteplase. There were no significant differences among subjects in the trajectory subgroups with respect to sex, smoking status, hypertension, diabetes mellitus, use of general anesthesia, and work flow times.

Table 2 describes the univariate contribution of baseline NIHSS, infarct volume, delta NIHSS, 24-hour NIHSS, and trajectory grouping variable in predicting 90-day mRS. Specifically, we found that baseline NIHSS (model 1) was least discriminative predictive of 90-day mRS (AUC=66.6%). Final infarct volume (model 2) had the second least discriminatory power in predicting 90-day mRS (AUC=73.1%), whereas 2- and 5-day trajectory grouping variables (models 5 and 6) were most discriminative (but not different between them) in predicting 90-day mRS (AUC=84.5% and 85.8%), respectively.

Although the 24-hour NIHSS score and change in 24-hour NIHSS had slightly lower AUCs than trajectory group variable, the 95% confidence intervals for the AUCs of these markers of stroke severity overlapped, suggesting that there are no significant differences in predictive performance of these markers of stroke severity in predicting 90-day mRS. An examination of the results predictive performance of these markers for the 5- and 30-day longitudinal NIHSS data revealed that there is a negligible improvement in the predictive performance of the trajectory variable when compared with the trajectory grouping variable derived from the 48-hour data.

Table 3 describes the results from the multiple logistic regression analyses of the relationship between early clinical prognostic markers and 90-day stroke outcomes after adjusting for subjects’ baseline characteristics such as sex, age, Alberta Stroke Program Early CT Score, type of treatment received, and baseline occlusions (ie, models 1–6). For each model, the variance inflation factor was <4, indicating that there was no evidence of multicollinearity among all the explanatory variables. Overall, all models had high discriminatory performance in predicting mRS after adjusting for subjects’ baseline characteristics. Although there was ≈10% improvement in the predictive performance of baseline NIHSS (≈10% increase in AUC) after adjusting for baseline...
characteristics, there was negligible improvement in predictive performance of change in NIHSS (model 3*), NIHSS at 24 hours (model 4*), and trajectory grouping variable in predicting 90-day mRS (models 5* and 6*). The model with baseline NIHSS had the smallest predictive accuracy. Greater discriminatory power was observed for models using a post-baseline marker of stroke severity concomitant with a smaller marginal effect of treatment in predicting 90-day mRS. For

<table>
<thead>
<tr>
<th>Variable</th>
<th>Large Improvement (n=135)</th>
<th>Minimum Improvement (n=113)</th>
<th>No Improvement (n=67)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.1 (19.5)</td>
<td>73.1 (19.7)</td>
<td>73.5 (21.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>69 (51.5)</td>
<td>62 (54.9)</td>
<td>34 (50.8)</td>
<td>0.80</td>
</tr>
<tr>
<td>Baseline occlusions (ICA)</td>
<td>21 (15.6)</td>
<td>31 (27.4)</td>
<td>32 (47.8)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; ED, emergency department; ICA, internal carotid artery; IQR, interquartile range; IV, intravenous; IV-IA, intravenous-intra-arterial; NIHSS, National Institutes of Health Stroke Severity; and IPA, tissue-type plasminogen activator.
example, the model with baseline NIHSS (model 1*) had the smallest predictive accuracy, but showed the largest treatment effect size (odds ratio, 3.38; \( P < 0.01 \)). In contrast, the model with 2-day trajectory subgroup variable as a marker of stroke severity (model 5*) had the highest predictive accuracy (AUC=88.5%) but the smallest treatment effect size (odds ratio, 2.04; \( P < 0.05 \)).

**Discussion**

Early postbaseline markers of stroke severity in the first 48 hours can accurately predict subject outcomes among those treated with endovascular therapy. We show that latent trajectory subgroups based on longitudinal NIHSS scores collected during the first 48 hours are better predictors of 90-day outcome than other markers of stroke severity.

A critical distinction in comparing trajectory groups to baseline measures of severity is that the trajectory group necessarily includes the impact of the treatment effect in influencing trajectories of stroke severity because trajectory groups include data derived after randomization and treatment. The identification of the 48-hour trajectory, incorporating just 4 measures (baseline, 2–8 hours, 24 hours, 48 hours) as the most powerful predictor of outcome is directly relevant to quality improvement measurement strategies in stroke and to future trials of acute stroke therapy. The results are consistent with the findings of the NINDS tPA Study (National Institutes of Neurological Disorders and Stroke Tissue Plasminogen Activator) group that identified the binary outcome of NIHSS 0 to 2 at 24 hours as the most powerful predictor of intravenous alteplase treatment effect.8

Although the predictive performance of 5- and 30-day repeated assessments of stroke severity were also investigated, the improvement in predictive power of the repeated assessments beyond the first 48 hours were negligible. Although it has been established that rapid treatment of stroke subjects often yields good clinical outcomes, early

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**Table 3. Adjusted Effects (Odds Ratio [95% CI]) of Markers of Stroke Severity in Predicting Patients’ 90-Day Modified Rankin Scale Outcomes**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female vs male)</td>
<td>1.22 [0.73–2.06]</td>
<td>1.53 [0.88–2.64]</td>
<td>1.39 [0.79–2.43]</td>
<td>1.37 [0.75–2.50]</td>
<td>1.46 [0.78–2.76]</td>
<td>1.46 [0.78–2.76]</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.96 [0.94–0.98]*</td>
<td>0.95 [0.93–0.97]*</td>
<td>0.95 [0.93–0.97]*</td>
<td>0.96 [0.94–0.98]*</td>
<td>0.97 [0.95–0.99]*</td>
<td>0.97 [0.95–0.99]*</td>
</tr>
<tr>
<td>Treatment (treatment vs control)</td>
<td>3.38 [1.99–5.73]*</td>
<td>2.47 [1.42–4.29]*</td>
<td>2.55 [1.44–4.50]*</td>
<td>2.75 [1.50–5.04]*</td>
<td>2.04 [1.10–3.79]*</td>
<td>1.84 [0.97–3.49]</td>
</tr>
<tr>
<td>Intravenous alteplase (yes vs no)</td>
<td>0.80 [0.44–1.44]</td>
<td>0.90 [0.49–1.64]</td>
<td>0.61 [0.32–1.15]</td>
<td>0.55 [0.27–1.11]</td>
<td>0.56 [0.27–1.15]</td>
<td>0.53 [0.25–1.12]</td>
</tr>
<tr>
<td>Baseline occlusion (MCA vs ICA)</td>
<td>1.44 [0.78–2.68]</td>
<td>1.23 [0.64–2.36]</td>
<td>1.63 [0.85–3.13]</td>
<td>0.88 [0.42–1.81]</td>
<td>0.71 [0.33–1.51]</td>
<td>0.68 [0.31–1.51]</td>
</tr>
<tr>
<td>ASPECTS (0–5 ref)</td>
<td>6–7</td>
<td>0.80 [0.13–5.14]</td>
<td>0.75 [0.11–5.33]</td>
<td>0.67 [0.11–4.00]</td>
<td>0.29 [0.04–1.91]</td>
<td>0.43 [0.06–3.37]</td>
</tr>
<tr>
<td>8–10</td>
<td>1.59 [0.29–8.85]</td>
<td>0.78 [0.13–4.88]</td>
<td>1.23 [0.24–6.27]</td>
<td>0.48 [0.09–2.65]</td>
<td>0.47 [0.07–3.17]</td>
<td>0.44 [0.06–3.45]</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>0.91 [0.87–0.96]*</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Infarct volume</td>
<td>…</td>
<td>0.98 [0.97–0.99]*</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>( \Delta )NIHSS</td>
<td>…</td>
<td>…</td>
<td>0.85 [0.81–0.90]*</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>NIHSS at 24 h</td>
<td>…</td>
<td>…</td>
<td>0.83 [0.78–0.87]*</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>2-d trajectory group 2 vs group 1</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>0.10 [0.05–0.19]*</td>
<td>…</td>
</tr>
<tr>
<td>5-d trajectory group 2 vs group 1</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>0.01 [&lt;0.01–0.04]*</td>
<td>…</td>
</tr>
<tr>
<td>Predictive accuracy (AUC%–95% CI)</td>
<td>76.6 [77.0–86.4]</td>
<td>81.7 [77.0–86.4]</td>
<td>82.4 [77.6–87.1]</td>
<td>85.8 [81.5–90.1]</td>
<td>88.6 [85.0–92.2]</td>
<td>89.4 [85.9–92.9]</td>
</tr>
<tr>
<td>Hosmer–Lemeshow test statistic</td>
<td>0.73</td>
<td>0.51</td>
<td>0.17</td>
<td>0.57</td>
<td>0.85</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Model 1 is logistic regression with baseline NIHSS as predictor; model 2 is logistic regression with infarct volume as predictor; model 3 is logistic regression with \( \Delta \)NIHSS as predictor; model 4 is logistic regression with NIHSS at 24 hours as predictor; model 5 is logistic regression with 2-day trajectory grouping variable as predictor; model 6 is logistic regression with 5-day trajectory grouping variable as predictor. ASPECTS indicates Alberta Stroke Program Early CT Score; AUC, area under the receiver operating characteristic; CI, confidence interval; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Severity Scale.

\*P<0.05.
repeat assessment of stroke severity can be useful for developing appropriate prognostic risk determination tools that aid clinical decision making after stroke treatment. This technique may be considered for single acute treatments and potentially as a surrogate outcome in acute ischemic stroke trials.

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Disclosures
Drs Hill, Goyal, and Demchuk report grants from Medtronic LLC (Covidien) as described above for the ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times). Drs Hill and Demchuk report support from the Heart & Stroke Foundation of Alberta that was used for the ESCAPE trial. The other authors report no conflicts.

References
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In the article by Sajobi et al, “Early Trajectory of Stroke Severity Predicts Long-Term Functional Outcomes in Ischemic Stroke Subjects: Results From the ESCAPE Trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times),” which published online ahead of print December 6, 2016, and appeared in the January 2017 issue of the journal (Stroke. 2017;48:105–110. DOI: 10.1161/STROKEAHA.116.014456), a correction is needed.

On page 105, Dr William’s affiliation, “Royal College of Physicians in Ireland and Beaumont Hospital, Dublin, Ireland,” has been changed to read “Royal College of Surgeons in Ireland and Beaumont Hospital, Dublin, Ireland.”

This correction has been made to the current online version of the article, which is available at http://stroke.ahajournals.org/content/48/1/105.