Intra-Arterial Therapy and Post-Treatment Infarct Volumes Insights From the ESCAPE Randomized Controlled Trial

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- *Methods*—The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial was a multicenter randomized open-label trial with blinded outcome evaluation. Among 315 enrolled subjects (endovascular treatment n=165; control n=150), 314 subject's infarct volumes at 24 to 48 hours on magnetic resonance imaging (n=254) or computed tomography (n=60) were measured. Posttreatment infarct volumes were compared by treatment assignment and recanalization/reperfusion status. Appropriate statistical models were used to assess relationship between baseline clinical and imaging variables, post-treatment infarct volume, and functional status at 90 days (modified Rankin Scale).
- **Results**—Median post-treatment infarct volume in all subjects was 21 mL (interquartile range =65 mL), in the intervention arm, 15.5 mL (interquartile range =41.5 mL), and in the control arm, 33.5 mL (interquartile range =84 mL; P<0.01). Baseline National Institute of Health Stroke Scale (P<0.01), site of occlusion (P<0.01), baseline noncontrast computed tomographic scan Alberta Stroke Program Early CT score (ASPECTS) (P<0.01), and recanalization (P<0.01) were independently associated with post-treatment infarct volume, whereas age, sex, treatment type, intravenous alteplase, and time from onset to randomization were not (P>0.05). Post-treatment infarct volume (P<0.01) and delta National Institute of Health Stroke Scale (P<0.01) were independently associated with 90-day modified Rankin Scale, whereas laterality (left versus right) was not.
- *Conclusions*—These results support the primary results of the ESCAPE trial and show that the biological underpinning of the success of endovascular therapy is a reduction in infarct volume.
- Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01778335.

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Key Words: cerebrovascular disease/stroke ■ infarct size ■ ischemic stroke ■ management ■ modified Rankin Scale ■ stroke

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Background and Purpose—The goal of reperfusion therapy in acute ischemic stroke is to limit brain infarction. The objective of this study was to investigate whether the beneficial effect of endovascular treatment on functional outcome could be explained by a reduction in post-treatment infarct volume.

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Everything that we think, plan, or do comes from within the human brain. Our language, our arts and culture, the meaning of being human are all products of the human brain. The drugs, devices, and techniques we have developed for acute ischemic stroke therapy are aimed at saving the human brain from death. Clinical trials in ischemic stroke test if these therapies are capable of reducing damage to the brain.

An ability to speak, listen, and understand; to move, walk, or run; to see and interact with the world around us are all examples of brain functions. Clinical trials use ordinal scales like the modified Rankin Scale (mRS), the National Institute of Health Stroke Scale (NIHSS), or the Barthel index to quantify these functions.^{1–3} Understandably, none of these scales ever capture the entirety of functions and capabilities of the human brain. Therefore, it is important for stroke therapies being tested within clinical trials to also be able to show that they save brain tissue.

Using a detailed post hoc analysis of the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial data, we analyze whether endovascular therapy administered to subjects with acute ischemic stroke and proximal anterior circulation occlusion is capable of saving brain tissue when compared with standard care (intravenous alteplase or best medical therapy).⁴ We also analyze clinical and imaging variables at baseline associated with post-treatment infarct volume (measured at 24–48 hours from stroke symptom onset). Finally, we analyze the relationship between post-treatment infarct volume and the subject's functional ability at 90 days as captured by the mRS (the primary outcome in the ESCAPE trial).

Methods

The ESCAPE trial was an investigator-initiated multicenter randomized controlled trial assessing the additional benefit of modern endovascular treatment when compared with guideline-based standard of care. 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 prespecified neurovascular imaging criteria. The trial enrolled 316 subjects from 22 sites across 3 continents between February 2013 and October 2014, with one subject excluded for improper consent procedures.^{4,5}

All subjects enrolled in the trial had follow-up imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) at 24 to 48 hours from stroke symptom onset. Magnetic resonance diffusionweighted imaging was the modality of choice for measurement of posttreatment infarct volume. If magnetic resonance diffusion-weighted imaging was not available, a noncontrast computed tomographic scan (NCCT) was chosen for measurement. An expert (Dr Al-Ajlan) used Quantomo (Cybertrial Inc, Calgary)⁶ to delineate infarct and measure post-treatment infarct volumes (in milliliters) while being blinded to all other clinical and imaging information. Manual adjustments to delineate infarct boundaries were performed where necessary. If the infarct showed hemorrhagic conversion, the hemorrhage regions were incorporated within the boundaries of infarct. Early recanalization was defined using Thrombolysis in Cerebral Infarction (TICI) Score (2b or 3) on conventional angiography in the intervention arm and using the modified arterial occlusive lesion grade (2 or 3) on 2- to 8-hour CT angiography among subjects in the control arm of the trial.7

Statistical Analyses

Because post-treatment infarct volume had a non-normal distribution, we used the Wilcoxon Rank-Sum test to look for differences in the distribution of volumes between treatment and control and between subjects achieving and not achieving early recanalization. We used generalized linear regression to model the association between treatment and post-treatment infarct volume, adjusting for prespecified variables (age, sex, baseline NIHSS, baseline Alberta Stroke Program Early CT score [ASPECTS] on NCCT), baseline site of occlusion (internal carotid artery versus M1 middle cerebral artery), intravenous alteplase (yes versus no), early recanalization status, and time from stroke onset to randomization. A cube root transformation of posttreatment infarct volume best satisfied the assumptions of this model (normality of residuals and homoscedasticity) and was used for this analysis. Because collateral status on baseline CT angiography was collinear with baseline ASPECTS (ρ >0.25), collateral status was not included in the analyses. The final models and related graphs only report main effects from variables that were statistically significant.

We used ordinal logistic regression to model the association between predictor variables (post treatment infarct volume [mL], 24hour NIHSS, delta NIHSS [baseline NIHSS–24 hour NIHSS], and side of stroke [left versus right]) and clinical outcome measured on the mRS at 90 days from stroke onset. Models satisfying the assumptions of parallel regression (tested using Brant's test) were compared using likelihood function tests (Akaike and Bayesian Information Criterion) to determine the model that provided the best fit to the data. This model was used to provide predicted outcomes, and these are displayed using graphs and contour plots to show the relationship between the adjusted probability of clinical outcome (mRS) at 90 days, NIHSS score change, and infarct volume. All statistical analyses were performed in Stata/MP version 14.0 (StataCorp LP). Statistical significance was assessed at α <0.05 in all analyses.

Results

Post-treatment infarct volume measured using MRI in 254 subjects and using NCCT in 60 subjects was not statistically different (P=0.19). Median post-treatment infarct volume in all subjects was 21 mL (interquartile range [IQR] 7-72 mL). Median post-treatment infarct volume in the intervention arm (15.5 mL, IQR 5-46.5 mL) was significantly lower than that in control arm (33.5 mL, IQR 11-95 mL; P<0.01). Early recanalization (Treatment in Cerebral Ischemia 2b/3 in the intervention arm, modified arterial occlusive lesion 2-3 in the control arm) occurred in 72% of subjects in the intervention arm and 31% of subjects in the control arm. Median posttreatment infarct volume in those who achieved recanalization in both arms (14.5 mL, IQR 4-46 mL) was significantly lower than those who did not (35 mL, IQR 12-104 mL; P<0.01). Median post-treatment infarct volume in the intervention arm in recanalizers was 13 mL (IQR 4-45 mL) versus 20 mL (IQR 9.5-67.5 mL) in the nonrecanalizers (P=0.05). Median posttreatment infarct volume in the control arm in recanalizers was 17.5 mL (IQR 4.5-48.5 mL) versus 47 mL (IQR 16-122 mL) in the nonrecanalizers (P=0.002). Distribution of posttreatment infarct volume by quartiles stratified by treatment type (intervention versus control) and recanalization achieved (yes versus no) is shown in Figure 1.

Baseline NIHSS (P<0.01), site of occlusion (P<0.01), baseline NCCT ASPECTS (P<0.01), and recanalization status (P<0.01) were independently associated with post-treatment infarct volume (cube root transformed) while age, sex, treatment type, intravenous alteplase, and time from onset to randomization were not (P>0.05). Treatment type was collinear with recanalization status. Relationship between baseline NIHSS, baseline NCCT ASPECTS, and post-treatment infarct volume (from final adjusted model) stratified by



Figure 1. Post-treatment infarct volumes by quartiles (data stratified by treatment type and early recanalization status).

early recanalization status are shown in Figure 2A and 2B. Distribution of post-treatment infarct volume by site of occlusion (from final adjusted model) stratified by early recanalization status is shown in Figure 2C.

Finally, when assessing the relationship between posttreatment infarct volume, 24-hour NIHSS, delta NIHSS (baseline NIHSS-24 hour NIHSS), side of stroke (left versus right), and mRS at 90 days, the model that best fit the data (Akaike Information Criterion 1031 and Bayesian Information Criterion 1061) included post-treatment infarct volume (P < 0.01) and delta NIHSS (P < 0.01) as independently associated with 90-day mRS. A model with delta NIHSS (Akaike Information Criterion 1054 and Bayesian Information Criterion 1080) was a better fit than a model with final infarct volume (Akaike Information Criterion 1123 and Bayesian Information Criterion 1149) in association with mRS at 90 days. No interaction was noted between post-treatment infarct volume and delta NIHSS (P>0.05) in predicting 90-day mRS. Side of occlusion (left versus right) was not a significant predictor of 90-day mRS. Models with the addition of age did not increase model fit substantially. Figure 3A shows the relationship between post-treatment infarct volume and estimated probability of excellent (mRS 0-1) outcome, independent (mRS 0-2) outcome, and death (mRS 6) at 90 days adjusted for laterality (quadratic best fit). Figure 3B and 3C are contour plots showing the relationship between post-treatment infarct volume, delta NIHSS, and estimated probability of achieving independent outcome (mRS 0-2) and death (mRS 6) at 90 days.

Discussion

Analysis from the ESCAPE trial shows that endovascular treatment in subjects with acute ischemic stroke and proximal anterior circulation occlusions was associated with significantly smaller infarct volumes. This effect of endovascular treatment on post-treatment infarct volumes was only seen when recanalization was achieved. Small infarct volumes were similarly noted in the control arm of the trial when early recanalization was achieved (Figure 1). These results provide supportive evidence for the physiological hypothesis that early recanalization saves brain.

Easily measured clinical and imaging variables at baseline (stroke severity, NCCT ASPECTS, and site of occlusion) are significant independent predictors of post-treatment infarct volume together with early recanalization status. Importantly, age itself is not a predictor of post-treatment infarct volume in this analysis, and it is probable that the influence of age on brain physiology is captured by baseline stroke severity and NCCT ASPECTS. Time to randomization was not a significant predictor of post-treatment infarct volume in our analysis, but we hypothesize that this is because of study design; imaging selection used in the ESCAPE trial (subjects selected using favorable imaging criteria independent of time from onset to randomization) may have contributed to these results. Stroke onset time is also imprecisely measured with many subjects either waking up after stroke onset or only last seen normal at a certain time.

Previous studies have examined the association between post-treatment infarct volume (measured at 24-48 hours) and functional ability at 90 days as measured by the mRS.^{8,9} Our results show that post-treatment infarct volume is a strong independent predictor of 90-day mRS. The mRS at 90 days is best predicted when information on acute treatment response (change in NIHSS from baseline to 24 hours) is available along with post-treatment infarct volumes. These results are not surprising; subjects with large brain infarcts after treatment could have better outcomes on the mRS if treatment succeeded in saving small but eloquent brain (significant reduction in NIHSS from baseline to 24 hours). Patients with small brain infarcts after treatment could have worse outcomes on the mRS if treatment did not succeed in saving small but eloquent brain (minimal change in NIHSS from baseline to 24 hours). Interestingly, no relationship was found between side of stroke and mRS at 90 days in our study. This lack of effect could be because the effect of side of stroke (and consequent eloquence of affected brain) on 90-day mRS may have been captured by delta NIHSS.

Our study has limitations. It is a post hoc exploratory analysis. Infarct volume was measured on NCCT in $\approx 20\%$ of subjects. This modality may be less precise than diffusion-weighted imaging. Although we used diffusionweighted imaging to measure infarct volume versus fluid attenuation inversion recovery,¹⁰⁻¹² there is debate in the stroke literature on the optimal MRI sequence and timing of imaging for the assessment of post-treatment infarct. We measured post-treatment infarct volume at 24 to 48 hours, but there remains a possibility of infarct growth after 24 to 48 hours.⁸⁻¹² Neither CT nor MRI has been compared with brain histology as methods measuring brain infarct in



Figure 2. Model estimated post-treatment infarct volume in mL (24–48 hours) by baseline National Institutes of Health Stroke Scale (NIHSS; **A**), baseline Alberta Stroke Program Early CT score (ASPECTS) (**B**), and site of occlusion at baseline (**C**); stratified by recanalization status (dash line=no recanalizers, dash and dot=recanalizers, grey boundaries indicate 95% confidence intervals, scatter plot in the background shows data distribution). MCA indicates middle cerebral artery; and NCCT, noncontrast computed tomographic scan.

humans, and it is therefore not well known how meaningful are the inherent differences between brain CT and MRI for measuring discrete infarct volumes.

In summary, our results support the primary results of the ESCAPE trial and show that the biological underpinning of



Figure 3. A, Laterality (left vs right) adjusted probability of achieving modified Rankin Scale score (mRS) 0 to 1, mRS score 0 to 2, and death at 90 days estimated using post-treatment infarct volume. Estimated probability of achieving mRS score 0 to 2 at 90 days estimated using post-treatment infarct volume (measured at 24–48 hours) and delta National Institutes of Health Stroke Scale (NIHSS; from baseline to 24 hours) (**B**) and achieving death at 90 days (**C**).

the success of arterial recanalization and brain tissue reperfusion therapies is reduction in infarct volume.

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Drs Menon and Hill had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors fulfill ICMJE criteria for authorship.

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