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

Fahad S. Al-Ajlan, MD; Mayank Goyal, MD; Andrew M. Demchuk, MD; Priyanka Minhas, MD; Farahna Sabiq, MD; Zarina Assis, MD; Robert Willinsky, MD; Walter J. Montanera, MD; Jeremy L. Rempel, MD; Ashfaq Shuaib, MD; John Thornton, MD; David Williams, MB, PhD; Daniel Roy, MD; Alexandre Y. Poppe, MD; Tudor G. Jovin, MD; Biggya L. Sapkota, MD; Blaise W. Baxter, MD; Timo Krings, MD; Frank L. Silver, MD; Donald F. Frei, MD; Christopher Fanale, MD; Donatella Tampieri, MD; Jeanne Teitelbaum, MD; Cheemun Lum, MD; Dar Dowlatshahi, MD; Jai J. Shankar, MD; Philip A. Barber, MD; Michael D. Hill, MD, MSc; Bijoy K. Menon, MD, MSc; for the ESCAPE Trial Investigators

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.

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. Post-treatment 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.

(Stroke. 2016;47:777-781. DOI: 10.1161/STROKEAHA.115.012424.)

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

Received December 13, 2015; final revision received January 8, 2016; accepted January 11, 2016.

From the Department of Clinical Neurosciences and Department of Radiology, Cumming School of Medicine, University of Calgary, Calgary (F.S.A.-A., M.G.; A.M.D., F.M., F.S., Z.A., P.A.B., M.D.H., B.K.M.); Department of Community Health Sciences and Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary (M.D.H., B.K.M.); Department of Medical Imaging, UHN, Toronto Western Hospital, Toronto (R.W., W.J.M.); Department of Surgery (Neurosurgery), University of Alberta, Edmonton (J.L.R.); Department of Medicine (Neurology), University of Alberta, Edmonton (A.S.); Department of Neuroradiology, Beaumont Hospital and the Royal College of Surgeons in Ireland (J. Thornton); Department of Geriatric and Stroke Medicine, Beaumont Hospital and the Royal College of Surgeons in Ireland (D.W.); Department of Radiology, CHUM, University of Montreal, Montreal (D.R.); Department of Neurosciences, CHUM, University of Montreal, Montreal (A.Y.P.); Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh (T.G.J.); Division of Neurology, University of Tennessee, Chattanooga (B.L.S.); Department of Radiology, UHN, Toronto Western Hospital, Toronto (T.K.); Division of Neurology, Department of Medicine, UHN, Toronto Western Hospital, Toronto (F.L.S., C.F.); Colorado Neurological Institute, Englewood (D.E.F., D.T.); Montreal Neurological Institute, McGill University, Montreal (J. Teitelbaum); Department of Radiology, The Ottawa Hospital, University of Ottawa, Ottawa (C.L.); Department of Neurology, The Ottawa Hospital Research Institute, University of Ottawa, Ottawa (D.D.); Department of Neuroradiology, Dalhousie University, Halifax (J.J.S.); and Hotchkiss Brain Institute, University of Calgary (M.G., A.M.D., P.A.B., M.D.H., B.K.M.).

Guest Editor for this article was Emmanuel Touzé, PhD.
Correspondence to Bijoy K. Menon, MD, MSc, Foothills Medical Centre, 1403-29th St NW, Calgary, AB T2N 2T9. E-mail docbijoymenon@gmail.com
© 2016 American Heart Association, Inc.
Everyday life is supported by the human brain. Our language, our arts and culture, the very things 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. 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 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). 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. All subjects enrolled in the trial had follow-up imaging (magnetic resonance imaging [MRI] or computed tomographic scan [CT]) at 24 to 48 hours from stroke symptom onset. Magnetic resonance diffusion-weighted imaging was the modality of choice for measurement of post-treatment 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) to delineate infarct and measure early recanalization was the modality of choice for measurement of post-treatment 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 (P<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], 24-hour 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 post-treatment 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 post-treatment 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 post-treatment 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 (cubed 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 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 post-treatment 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 (P<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.

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...
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 post-treatment 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 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.\textsuperscript{4,5} 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 =20% of subjects. This modality may be less precise than diffusion-weighted imaging. Although we used diffusion-weighted imaging to measure infarct volume versus fluid attenuation inversion recovery,\textsuperscript{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.\textsuperscript{8–12} Neither CT nor MRI has been compared with brain histology as methods measuring brain infarct in

**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.\textsuperscript{4,5} 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 =20% of subjects. This modality may be less precise than diffusion-weighted imaging. Although we used diffusion-weighted imaging to measure infarct volume versus fluid attenuation inversion recovery,\textsuperscript{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.\textsuperscript{8–12} Neither CT nor MRI has been compared with brain histology as methods measuring brain infarct in

---

**Figure 1.** Post-treatment infarct volumes by quartiles (data stratified by treatment type and early recanalization status).
In summary, our results support the primary results of the ESCAPE trial and show that the biological underpinning of the success of arterial recanalization and brain tissue reperfusion therapies is reduction in infarct volume.

Acknowledgments

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.
Sources of Funding

The study sponsor was the University of Calgary. Cvidien Inc provided major funding through an unrestricted grant to the University of Calgary. Additional active and in-kind support for the trial is from a consortium of funding public and charitable sources (Heart & Stroke Foundation Canada, Alberta Innovates Health Solutions, Alberta Health Services, CSPIN network through CIHR) and the University of Calgary (Hotchkiss Brain Institute, Department of Clinical Neurosciences, Department of Radiology, and Calgary Stroke Program). The sponsor of the trial was the Governors of the University of Calgary. The sponsor had no role in the design, data gathering, analysis, or reporting of the trial. The University of Calgary received unrestricted grants from Medtronic (Cvidien), Alberta Innovates Health Solutions, Heart & Stroke Foundation Canada, Canadian Institute for Health Research through the CSPIN Network, and Alberta Health Services. The University of Calgary provided internal funding from the Hotchkiss Brain Institute, the Department of Clinical Neurosciences, and Department of Radiology.

Disclosures

Dr Roy reports grants and personal fees from University of Calgary during the conduct of the study. Dr Williams reports personal fees from Boehringer Ingelheim, Bayer, Bristol Myers Squibb, and Daiichi Sankyo outside the submitted work. Dr Demchuk reports research support from Cvidien/Medtronic, unrestricted grant for ESCAPE trial, and no compensation. Speaker’s Bureau: Medtronic: Significant >$10K compensation. Dr Poppe reports personal fees from Cvidien and Pfizer-BMS outside the submitted work. Dr Frei reports personal fees from Stryker (modest), personal fees from Penumbra (modest), honoraria from the Neuro-critical Care Society (modest), stocks in Penumbra (modest), and consultant relationship with Penumbra. Dr Thornton reports personal fees from Neuravi, Galway, and Ireland outside the submitted work. Dr Baxter reports personal fees from Penumbra, Stryker Neurovascular, Cvidien (MedTronics), Rapid Medical, and Silk Road Medical outside the submitted work. Dr Jovin reports being a consultant for Neuravi, Codman Neurovascular, Blockade Medical, Silk Road, Stryker, and Cvidien/Medtronic. Michael Hill reports grants from Cvidien (Medtronic), Alberta Innovates Health Solutions, Heart & Stroke Foundation, Hotchkiss Brain Institute, CSPIN Network (ICRH-CIRR), Calgary Stroke Program, DCNS, University of Calgary, and nonfinancial support from Alberta Health Services, during the conduct of the study; personal fees from Merck, nonfinancial support from Hoffmann-La Roche Canada Ltd, outside the submitted work. In addition, Dr Hill has a patent Systems and Methods for intra-cerebral haemorrhage. Dr Demchuk AM, Goyal M, Menon BK, Eesa M, Rempel JL, Thornton J, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414005.

References

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


Stroke. 2016;47:777-781; originally published online February 18, 2016;
doi: 10.1161/STROKEAHA.115.012424

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/3/777

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/