Which Acute Ischemic Stroke Patients Are Fast Progressors?: Results From the ESCAPE Trial Control Arm

Johanna M. Ospel
Clinical Neurosciences (J.M.O., M.D.H., A.M.D., B.K.M., A.M., M.G.), University of Calgary, Canada.

Michael D. Hill
Clinical Neurosciences (J.M.O., M.D.H., A.M.D., B.K.M., A.M., M.G.), University of Calgary, Canada.

Manon Kappelhof
UMC Amsterdam, the Netherlands (M.K.).

Andrew M. Demchuk
Clinical Neurosciences (J.M.O., M.D.H., A.M.D., B.K.M., A.M., M.G.), University of Calgary, Canada.

Bijoy K. Menon
Clinical Neurosciences (J.M.O., M.D.H., A.M.D., B.K.M., A.M., M.G.), University of Calgary, Canada.

See next page for additional authors

Recommended Citation

Ospel, J. M., Hill, M. D., Kappelhof, M., Demchuk, A. M., Menon, B. K., Mayank, A., Dowlatshahi, D., Frei, D., Rempel, J. L., Baxter, B. W., & Goyal, M. (2021). Which Acute Ischemic Stroke Patients Are Fast Progressors?: Results From the ESCAPE Trial Control Arm. *LVHN Scholarly Works*. Retrieved from https://scholarlyworks.lvhn.org/research-historical-works/70
DOI: 10.1161/STROKEAHA.120.032950

Stroke

BRIEF REPORT

Which Acute Ischemic Stroke Patients Are Fast Progressors?

Results From the ESCAPE Trial Control Arm

Johanna M. Ospel, MD; Michael D. Hill, MD; Manon Kappelhof, MD; Andrew M. Demchuk, MD; Bijoy K. Menon, MD; Arnuv Mayank; Dar Dowlatshahi, MD; Don Frei, MD; Jeremy L. Rempel, MD; Blaise Baxter, MD; Mayank Goyal, MD, PhD

BACKGROUND AND PURPOSE: Fast infarct progression in acute ischemic stroke has a severe impact on patient prognosis and benefit of endovascular thrombectomy. In this post hoc analysis of the ESCAPE trial (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke), we identified acute ischemic stroke patients with rapid infarct growth and investigated their baseline clinical and imaging characteristics.

METHODS: Control arm patients were included if they had follow-up imaging at 2-8 hours without substantial recanalization, and if their baseline Alberta Stroke Program Early CT Score was ≥9. Fast infarct progression was defined as Alberta Stroke Program Early CT Score decay ≥3 points from baseline to 2- to 8-hour follow-up imaging. Clinical and imaging baseline characteristics were compared between fast progressors and other patients, and occlusion site and collateral flow patterns were assessed in detail.

RESULTS: Fast infarct progression occurred in 15 of 43 included patients (34.9%). Fast progressors had worse collaterals (poor in 3/15 [20%] versus 0/28 patients, P=0.021) and more carotid-T or -L occlusions (8/15 [53.4%] versus 3/28[10.7%], P=0.021). In 8 out of 15 (53.3%), occlusion site and circle of Willis configuration prevented collateral flow via the anterior or posterior cerebral artery.

CONCLUSIONS: Most patients with fast infarct progression had terminal carotid occlusions and impaired collateral flow via the anterior or posterior cerebral artery, indicating that occlusion location and intracranial vascular anatomy are relevant for infarct progression.

Key Words: circle of Willis ■ ischemic stroke ■ posterior cerebral artery ■ prognosis ■ thrombectomy

In acute ischemic stroke due to large vessel occlusion, the area of ischemic but not irreversibly damaged brain tissue—the penumbra—will progress to infarction if recanalization does not occur. The speed of infarct progression is highly variable among individuals.[1] Some patients show rapid infarct growth—so-called fast progressors.[2]

Identifying fast progressors would allow physicians to estimate treatment benefits depending on the estimated time to treatment. In ultrafast progressors, transfer to an endovascular thrombectomy-capable center may be futile. However, our understanding of the mechanisms determining infarct progression is limited, and as such, it is currently not possible to accurately estimate infarct growth rate at the time of presentation.

We used baseline and early follow-up imaging at 2 to 8 hours to identify large vessel occlusion patients with rapid infarct growth and compared clinical and imaging characteristics of patients with and without fast infarct progression.

Correspondence to: Mayank Goyal, MD, PhD, Department of Radiology, Foothills Medical Centre, 1403 29th St.NW, Calgary, AB T2N2T9, Canada. Email mgoyal@ucalgary.ca

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.032950.

For Sources of Funding and Disclosures, see page 1850.

Stroke is available at www.ahajournals.org/journal/str

BRIEF REPORT

Nonstandard Abbreviations and Acronyms

ACA	anterior cerebral artery
EVT	endovascular treatment

METHODS

Patients and Imaging

The ethics board at each site approved the trial. Raw data are available upon reasonable request. ESCAPE (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; https://www.clinicaltrials.gov; Unique identifier: NCT01778335) was a randomized controlled trial on endovascular thrombectomy for acute ischemic stroke due to large vessel occlusion,[3] enrolling 316 patients between February 2013 and October 2014. Noncontrast head computed tomography (NCCT) and CT angiography (CTA, mostly multiphase) were obtained at baseline. In control arm patients, follow-up CTA (±NCCT) was performed at 2 to 8 hours.

This study included control arm patients with (1) onset-presentation time ≤6 hours, (2) baseline Alberta Stroke Program Early CT Score [ASPECTS] 9–10, (3) no substantial recanalization on 2- to 8-hour follow-up CTA (modified arterial occlusive lesion score 0–1). The ASPECTS threshold of 9 was based on the median baseline ASPECTS in the trial population.[3]

An independent core lab reviewed all imaging. Detailed imaging assessment methodology was reported previously.[4] For this study, additionally, anterior cerebral artery (ACA) and posterior cerebral artery collateral flow through the circle of Willis were assessed on CTA (intact versus impaired collateral flow; Table I in the Data Supplement).

Outcomes

Our primary outcome was fast infarct progression, defined as ASPECTS decay ≥3 points from baseline to 2- to 8-hour imaging. Final infarct volume, 24-hour National Institutes of Health Stroke Scale score, and 90-day functional independence (modified Rankin Scale score of 0–2) were compared between fast progressors and other patients.

Statistical Analysis

Comparisons between fast progressors and the remaining patients were made with nonparametric tests. Vessel anatomy was described using descriptive statistics. We refrained from adjusted comparisons because of the small sample size. A sensitivity analysis was performed in which patients with baseline ASPECTS of 8 were included in the patient sample as well. All tests were 2-sided with conventional levels of significance (α=0.05). Data analysis was performed in Stata 15.1.

RESULTS

We included 49 out of 150 control arm patients (Figure I in the Data Supplement). ASPECTS at 2 to 8 hours was assessed on NCCT in 19 out of 43 (44.2%) and on CTA source images in 24 out of 43 (55.8%).

Fifteen of 43 patients (34.9%) were fast progressors. Their baseline National Institutes of Health Stroke Scale was higher and collateral status worse than in other patients (Table). Occlusion sites were more proximal and often involved the A1 and M1 segments (internal carotid artery T or internal carotid artery L occlusions in fast progressors 8/15 [53.4%] versus 3/28 [10.7%] in other patients). Fast progressors had higher final infarct volumes (median 146 mL [interquartile range (IQR), 58–258] versus 16 mL [IQR, 7–46.5]) and lower 24-hour ASPECTS (median 4 [IQR, 0–5] versus 8 [IQR, 7–9]). Their 24-hour National Institutes of Health Stroke Scale was higher (median 18 [IQR, 14–24] versus 10 [IQR, 6–15]) and functional independence rate lower (2/15 [13.3%] versus 9/28 [32.1%]), although the latter did not reach statistical significance.

Table II in the Data Supplement describes the 15 fast progressors in detail. Baseline collateral status was poor in 3 out of 15 fast progressors (20.0%), moderate in 1 (6.7%), and good in 11 (73.3%). Collateral flow via the ACA was impaired in 7 out of 15 (46.7%). In 4 fast progressors (26.7%), both ACA and posterior cerebral artery collateral flow were disturbed. The maximal ASPECTS decay was 7 (n=4). In all 4 of these ultrafast progressors, ACA collateral supply was impaired. Figures II and III in the Data Supplement show a fast progressor example case. Table III in the Data Supplement shows collateral status and occlusion location of nonfast progressors.

DISCUSSION

In this study, terminal internal carotid artery occlusions were significantly more common in fast progressors compared to other patients, and collateral flow via the ACA or posterior cerebral artery was impaired in most patients with fast infarct progression.

Infarct progression depends on tissue oxygen demand and collateral blood supply. Although our understanding of tissue oxygen demand and its determinants is limited,[2] leptomeningeal collaterals are known to be influenced by factors such as genetics, old age, hyperglycemia, hyperuricemia, and preexisting comorbidities.[5,6] In addition, incomplete Circle of Willis configurations may prevent collateral flow.[6,7] Our findings indicate that occlusion location and circle of Willis anatomy might be an important determinant of infarct progression rate. Infarct progression in this study occurred mostly in cortical ASPECTS regions, which, in contrary to the basal ganglia, depend heavily on leptomeningeal collateral supply. Interestingly, nearly 3 out of 4 fast progressors had however good collateral status, probably due to the stringent trial inclusion criteria which only allowed for enrollment of patients with good or intermediate collateral status. Thrombus extension/apposition and clot migration could be other possible explanations.

In this patient sample, endovascular thrombectomy was not performed, and only patients without early

Table. Baseline, Treatment, and Clinical Outcome Data

	All (n=43)	Fast progressors (n=15)	Other patients (n=28)	*P* value
Clinical baseline characteristics				
Age in years, median (IQR)	75.5 (62.9–84.0)	70.2 (64.7–84.0)	78.2 (61.8–84.1)	0.760
Female sex, n (%)	21 (48.8)	6 (40.0)	15 (53.6)	0.526
Medical history, n (%)				
Diabetes	14 (32.6)	5 (33.3)	9 (32.1)	1.000
Atrial fibrillation	19 (44.2)	6 (40.0)	13 (46.4)	0.755
Baseline NIHSS, median (IQR)	14 (11–19)	18 (14–20)	12 (9–17.5)	0.003
Imaging baseline characteristics				
Occlusion location on baseline CTA, n (%)				0.021
ICA-T*	9 (20.9)	7 (46.7)	2 (7.1)	
ICA-L†	2 (4.7)	1 (6.7)	1 (3.6)	
ICA-I ‡	2 (4.7)	0	2 (7.1)	
Proximal M1	7 (16.3)	3 (20.0)	4 (14.3)	
Mid M1	10 (23.3)	1 (6.7)	9 (32.1)	
Distal M1	13 (30.2)	3 (20.0)	10 (35.7)	
Ipsilateral cervical ICA occlusion, n (%)	3 (7.0)	1 (6.7)	2 (7.1)	1.000
Collateral Status, n (%)				0.021
Poor	3 (7.1)	3 (20.0)	0	
Intermediate	2 (4.8)	1 (6.7)	1 (3.7)	
Good	37 (88.1)	11 (73.3)	26 (96.3)	
Treatment and time				
Intravenous alteplase, n (%)	33 (76.7)	14 (93.3)	19 (67.9)	0.127
Onset-to-imaging time, min, median (IQR)	101 (66–156)	75 (59–115)	101.5 (74.5–190.5)	0.090
Imaging-to-repeat CTA time, min, median (IQR)	312 (239–360), n=41	312 (252–347)	297 (219–378), n=26	0.705
Clinical and imaging outcomes				
24-h NIHSS, median (IQR)	13.5 (9–18), n=42	18 (14–24)	10 (6–15), n=27	0.001
mRS score 0–2 at 90 d, n (%)	11 (25.6)	2 (13.3)	9 (32.1)	0.276
24-h ASPECTS, median (IQR)	8 (4–9)	4 (0–5)	8 (7–9)	<0.001
24-h infarct, mL, median (IQR)	33 (12–105)	146 (58–258)	16 (7–46.5)	<0.001
24-h parenchymal hemorrhage, n (%)	7 (16.3)	2 (13.3)	5 (17.9)	1.000

A1 indicates first segment of anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; CTA, CT angiography; ICA, internal carotid artery; IQR, interquartile range; M1, first segment of middle cerebral artery; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Terminal ICA+proximal M1+A1 occlusion.

†Terminal ICA+proximal M1, without A1 occlusion.

‡Terminal ICA without M1/A1 occlusion.

recanalization were included. Speed of infarct progression was hence not expected to be associated with worse clinical outcomes: infarcts would have been completed in all patients at 24 hours because recanalization did not occur. However, 24-hour infarct volume was much larger in fast progressors, and short-term neurological outcome was worse, likely related to more proximal occlusions in fast progressors.

Limitations

We excluded patients with baseline ASPECTS<9 because assessing infarct progression in the presence of large ischemic changes is challenging. A sensitivity analysis including ASPECTS 8 patients showed no substantially different findings. Second, our definition of fast infarct progression was based on ASPECTS rather than volumetric measurements. Third, 2- to 8-hour ASPECTS was assessed on NCCT or CTA, possibly introducing variability. Fifth, NCCT may be insensitive to early ischemic changes; infarction may have been present but invisible at the time of NCCT. Finally, our small sample size did not allow multivariable analyses.

Conclusions

Most patients with fast infarct progression in this study had terminal internal carotid artery occlusions and

impaired collateral flow via the ACA or posterior cerebral artery, indicating that occlusion location and intracranial vascular anatomy might be important in infarct progression in large vessel occlusion stroke.

ARTICLE INFORMATION

Received July 6, 2020; final revision received January 7, 2021; accepted February 26, 2021.

Affiliations

Clinical Neurosciences (J.M.O., M.D.H., A.M.D., B.K.M., A.M., M.G.) and Radiology (M.D.H., A.M.D., B.K.M., M.G.), University of Calgary, Canada. Radiology, University Hospital of Basel, Basel, Switzerland (J.M.O.). UMC Amsterdam, the Netherlands (M.K.). Neurology, University of Ottawa, Ottawa, Canada (D.D.). Swedish Medical Center, Colorado Neurological Institute, Denver (D.F.). Radiology, University of Alberta, Edmonton, Canada (J.L.R.). Lehigh Valley Health Network, Allentown, PA (B.B.).

Acknowledgments

Drs Ospel, Kappelhof, Goyal, and Hill contributed to conceptualization, drafting, critical revision. All other authors participated in critical revision.

Sources of Funding

Supported by Grants to the University of Calgary from Covidien, Alberta Innovates–Health Solutions, the Heart and Stroke Foundation of Canada, and Alberta Health Services.

Disclosures

Dr Hill reports the following: grants (Merck, Covidien [Medtronic LLC], University of Calgary [Hotchkiss Brain Institute, DCNS, Calgary Stroke Program], Alberta Innovates, CSPIN Network [CIHR], Heart & Stroke Foundation Alberta), nonfinancial support (Alberta Health Services during conduct of study), patent (US Patent office number 62/086,077 issued and licensed), director (for profit sector: Circle NVI, not for profit sector: Canadian Stroke Consortium, Canadian Neuroscience Federation). Dr Menon reports the following: patent (systems of triage in acute stroke), shareholder (Circle Neurovascular). Dr Goyal reports the following: consultant (Medtronic, Stryker, Microvention, GE Healthcare, Mentice). Dr Baxter reports the following: consultant (Penumbra, Artio Medical, Route 92, Medtronic, Stryker, Cerenovus, Vizai, Rapid Medical, 880 Medical), investments (Marblehead). Dr Demchuk reports the following: personal (Medtronic during conduct of study), others (Circle NVI outside submitted work), patent (Circle NVI issued). The other authors report no conflicts.

Supplemental Materials

Online Tables I–IV
Online Figures I–III

REFERENCES

1. Saver JL. Time is brain–quantified. *Stroke*. 2006;37:263–266. doi: 10.1161/01.STR.0000196957.55928.ab
2. Rocha M, Jovin TG. Fast versus slow progressors of infarct growth in large vessel occlusion stroke: clinical and research implications. *Stroke*. 2017;48:2621–2627. doi: 10.1161/STROKEAHA.117.017673
3. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, 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/NEJMoa1414905
4. Coutts SB, Lev MH, Eliasziw M, Roccatagliata L, Hill MD, Schwamm LH, Pexman JH, Koroshetz WJ, Hudon ME, Buchan AM, et al. ASPECTS on CTA source images versus unenhanced CT: added value in predicting final infarct extent and clinical outcome. *Stroke*. 2004;35:2472–2476. doi: 10.1161/01.STR.0000145330.14928.2a
5. Ribo M, Molina CA, Delgado P, Rubiera M, Delgado-Mederos R, Rovira A, Munuera J, Alvarez-Sabin J. Hyperglycemia during ischemia rapidly accelerates brain damage in stroke patients treated with tPA. *J Cereb Blood Flow Metab*. 2007;27:1616–1622. doi: 10.1038/sj.jcbfm.9600460
6. van Seeters T, Biessels GJ, Kappelle LJ, van der Graaf Y, Velthuis BK; Dutch Acute Stroke Study (DUST) Investigators. Determinants of leptomeningeal collateral flow in stroke patients with a middle cerebral artery occlusion. *Neuroradiology*. 2016;58:969–977. doi: 10.1007/s00234-016-1727-5
7. Hendrikse J, Hartkamp MJ, Hillen B, Mali WP, van der Grond J. Collateral ability of the circle of Willis in patients with unilateral internal carotid artery occlusion: border zone infarcts and clinical symptoms. *Stroke*. 2001;32:2768–2773. doi: 10.1161/hs1201.099892