Drip 'n Ship Versus Mothership for Endovascular Treatment
Modeling the Best Transportation Options for Optimal Outcomes

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Background and Purpose—There is uncertainty regarding the best way for patients outside of endovascular-capable or Comprehensive Stroke Centers (CSC) to access endovascular treatment for acute ischemic stroke. The role of the nonendovascular-capable Primary Stroke Centers (PSC) that can offer thrombolysis with alteplase but not endovascular treatment is unclear. A key question is whether average benefit is greater with early thrombolysis at the closest PSC before transportation to the CSC (Drip 'n Ship) or with PSC bypass and direct transport to the CSC (Mothership). Ideal transportation options were mapped based on the location of their endovascular-capable CSCs and nonendovascular-capable PSCs.

Methods—Probability models for endovascular treatment were developed from the ESCAPE trial's (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) decay curves and for alteplase treatment were extracted from the Get With The Guidelines decay curve. The time on-scene, needle-to-door-out time at the PSC, door-to-needle time at the CSC, and door-to-reperfusion time were assumed constant at 25, 20, 30, and 115 minutes, respectively. Emergency medical services transportation times were calculated using Google's Distance Matrix Application Programming Interface interfaced with MATLAB's Mapping Toolbox to create map visualizations.

Results—Maps were generated for multiple onset-to-first medical response times and door-to-needle times at the PSCs of 30, 60, and 90. These figures demonstrate the transportation option that yields the better modeled outcome in specific regions. The probability of good outcome is shown.

Conclusions—Drip 'n Ship demonstrates that a PSC that is in close proximity to a CSC remains significant only when the PSC is able to achieve a door-to-needle time of ≤30 minutes when the CSC is also efficient.
(*Stroke*. 2017;48:791-794. DOI: 10.1161/STROKEAHA.116.015321.)

Key Words: endovascular therapy ■ probability ■ stroke ■ tissue-type plasminogen activator ■ uncertainty

Endovascular treatment (EVT) for acute ischemic stroke substantially improves outcomes compared with usual standard of care for acute ischemic stroke.[1–4] Currently, EVT is only offered at endovascular-capable or Comprehensive Stroke Centers (CSC), which creates uncertainty regarding the best transportation option for patients outside of the catchment area of CSCs to access EVT. As treatment for acute ischemic stroke is changing, the role of the nonendovascular-capable Primary Stroke Centers (PSC) that can offer medical thrombolysis with alteplase but not EVT is unclear. A key question is whether there is a greater benefit in receiving alteplase early at a PSC before being transported to a CSC for EVT (Drip 'n Ship approach).[5] Alternatively, the PSC can be bypassed, and the suspected stroke patient could be transported directly to the CSC (Mothership approach).[6,7] This uncertainly is because of the time dependence of good outcomes with both early intravenous alteplase and EVT[8,9] and the reduced efficacy of alteplase compared with EVT with large vessel occlusive stroke.[10,11]

One of the key factors in determining the best transportation option is the geographic location of the PSCs and CSCs in relation to the patient origin, as well as regional infrastructure. As part of the DESTINE (Decision Support Tool in Endovascular transport) project, we created mathematical models based on the decay curves for EVT and thrombolysis and generated map visualizations that modeled the best transportation option and the probability of good outcomes.

Received September 2, 2016; final revision received November 20, 2016; accepted November 30, 2016.

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Guest Editor for this article was Seemant Chaturvedi, MD.

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***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.116.015321**

Methods

A mathematical model was created using the stroke onset-to-reperfusion and onset-to-treatment decay curves for EVT and thrombolysis, respectively. Data from the ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) was used to generate a decay curve for patients treated with both EVT and alteplase.[1,8] The decay curve for EVT provided the average probability of good outcomes (P_{EVT}) as defined as modified Rankin Scale score 0 to 2 at 90 days as a function of time from onset to reperfusion. To determine the benefit of alteplase alone, a probability model (P_{tPA}) was developed using the US Get With The Guidelines–Stroke registry.[11] The average probability is defined as modified Rankin Scale score 0 to 1 at discharge based on time from onset to alteplase administration.

The total probability of good outcomes was calculated using the formula: $P=P_{tPA}+(1-P_{tPA})\times P_{EVT}$. This is a sum of the probability of good outcomes from alteplase (P_{tPA}) and the probability of good outcome with EVT (P_{EVT}) for those patients who do not have a good outcome with alteplase ($1-P_{tPA}$). The time used for P_{tPA} in the Drip 'n Ship scenario is a sum of the following time variables: onset-to-first medical response; on-scene; scene-to-PSC; and door-to-needle time (DNT) at PSC. The time variable for P_{tPA} in the Mothership scenario is the sum of the following variables: onset-to-first medical response; on-scene; scene-to-CSC; and DNT at CSC. The time variable for P_{EVT} in the Drip 'n Ship scenario is the sum of the following variables: onset-to-first medical response; on-scene; scene-to-PSC; DNT at PSC; needle-to-door-out time at PSC; PSC to CSC; and arrival-to-reperfusion at CSC. The time variable for the P_{EVT} in the Mothership scenario is the sum of the following variables: onset-to-first medical response; on-scene; scene-to-CSC; and arrival at CSC to reperfusion. This model assumes that all patients receive both alteplase and EVT.

PSC and CSC designations were compiled from the Canadian Stroke Audit and the Joint Commission list of accredited stroke centers in the United States. We incorporated Google's (Mountain View, CA) Distance Matrix Application Programming Interface into MATLAB (Mathworks, Natick, MA). Travel times for emergency medical services were calculated by finding the closest PSC and CSC for each region and calling Google's Distance Matrix Application Programming Interface to determine the drive times using both realistic road speeds and user generated data. Maps were created using MATLAB's Mapping Toolbox, custom color functions, and a generated time database of standard driving times. These maps model the best transportation option for each region that would result in the greatest probability of good outcomes. Maps were generated for all scenarios. All time assumptions are shown in Table.

Results

Maps were generated for California, United States; Alberta, Canada; and Ontario, Canada (Figure). These maps show the modeled probability of good outcome based on the previously discussed probability model. Green regions represent a greater probability of good outcome via Mothership, whereas red indicates that Drip 'n Ship is best. Orange indicates that either option yields a similar outcome (±2.5%) and neither is necessarily superior. The color tint increases (becomes more white) as the probability of good outcome decreases. Gray indicates areas with sparse infrastructure or little population. Maps are shown for varying DNTs at the PSCs and varying onset-to-first medical response times.

These maps show that the Drip 'n Ship scenario is predicted to result in better or similar outcomes compared with Mothership only when the PSCs are able to administer alteplase within 30 minutes of hospital arrival. When the DNT at the PSC is longer, the Drip 'n Ship scenario is predicted to be beneficial only for those PSCs that are further away from the CSC. When the onset-to-first medical response is longer, the Drip 'n Ship scenario predicts a better probability of good outcomes than the Mothership scenario. The predicted probability of good outcomes declines as the distance to the CSCs increases.

These results are only valid if the CSC has highly efficient workflow. If the DNT at the CSC is 60 minutes and the door-to-reperfusion time is 200 minutes, Drip 'n Ship is favored with distances of ≥45 minutes between the CSC and PSC (DNT at PSC is 30 minutes). Many CSCs may be able to consistently achieve shorter door-to-reperfusion times in the Drip 'n Ship. Our model favors Drip 'n Ship when the door-to-reperfusion time is ≥70 minutes.

Discussion

These maps demonstrate that any remote PSC retains its significance through the Drip n' Ship scenario, regardless of its DNT, but only if it is a significant distance from any CSC. For those PSCs that are in close proximity to a CSC, their significance is only retained though the Drip 'n Ship approach if they are able to administer alteplase within 30 minutes.[12] The Drip 'n Ship approach becomes more favorable when the onset-to-first medical response time increases. However, the CSC must be efficient in both administering alteplase and also in achieving reperfusion through EVT to retain benefit of the Mothership scenario.

This work provides an initial model incorporating geolocation mapping for the transportation of ischemic stroke patients for EVT; therefore, there are limitations to this work. We used the best available decay curves, but the patient groups for the 2 curves are different. The ESCAPE curves are from an ideal research trial for all patients who received EVT, and the Get With The Guidelines–Stroke curves are from a patient registry for all patients treated with alteplase, including those who would not be eligible for EVT, such as milder strokes with distal occlusions who tend to do better with alteplase. The probability of good outcomes for these 2 groups is different with a more rigid definition with the Get With The Guidelines–Stroke group (modified Rankin Scale score 0–1 at 90 days), which may provide some compensation for the inclusion of milder stroke patients in the alteplase decay curve. These data only show travel times through the fastest ground transport, and

Table. List of Time Assumptions Made in the Model

	Drip 'n Ship, min	Mothership, min
Onset-to-first medical response	30, 60, 90	30, 60, 90
Time on-scene	25	25
Scene to door	Geographic model	Geographic model
Door-to-needle	30, 60, 90	30*
Needle-to-door-out	20	NA
PSC to CSC	Geographic model	NA
Door-to-reperfusion	115*	115*

CSC indicates Comprehensive Stroke Centers; DNT, door-to-needle time; NA, not available; and PSC, Primary Stroke Centers.

*Sensitivity analysis is performed on these constants. For Mothership, DNT at CSC of 60 min and door-to-reperfusion of 200 min is also included. Additionally, the tipping point of door to reperfusion in the Drip 'n Ship option is also modeled.

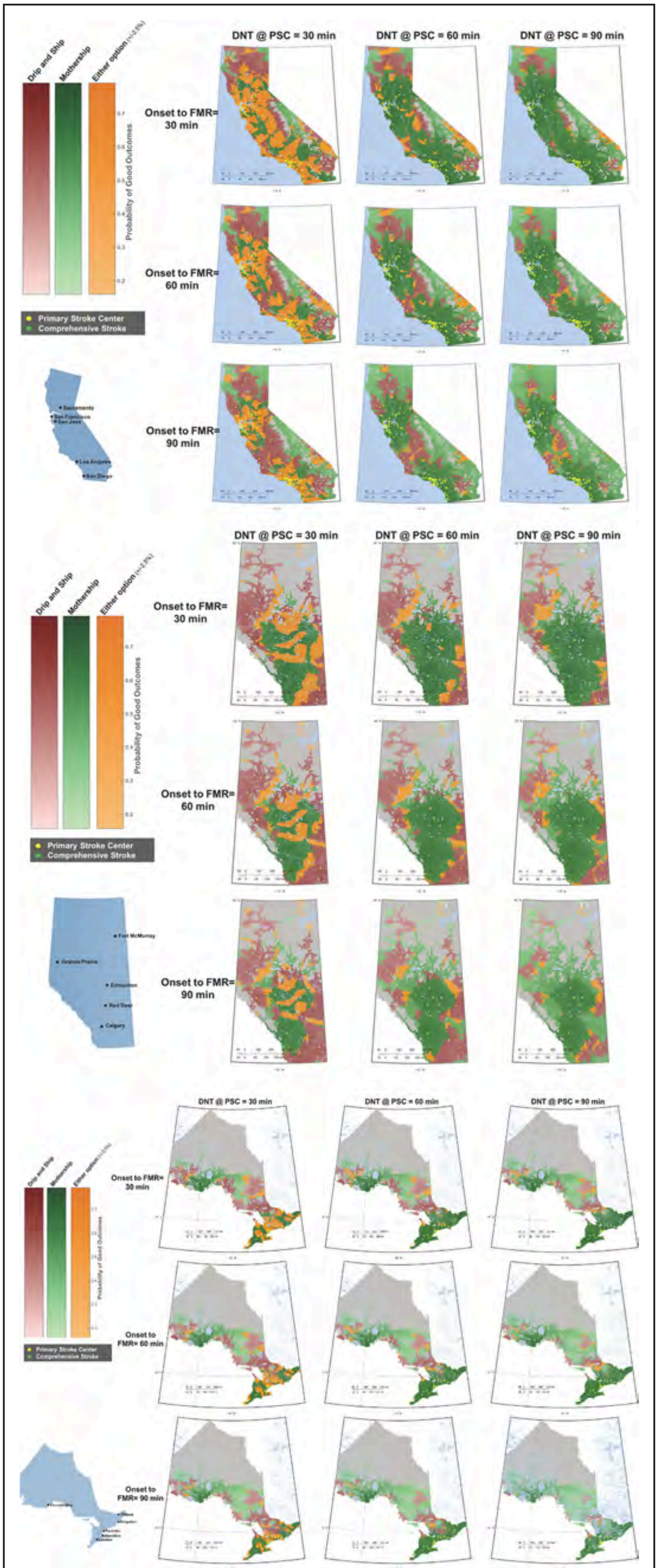

Figure. Modeled endovascular transport option map for California (**top**), Alberta, Canada (**middle**), and Ontario, Canada (**bottom**). DNT indicates door-to-needle time; FMR, first medical response; and PSC, Primary Stroke Center.

transport times may be shorter through both rotary and fixed-wing air transport. As more data become available, alteplase decay curves for large vessel occlusion and actual EVT data from registries can be used to improve this model.

Sources of Funding

This study was supported by Alberta Innovates Health Solutions, Heart & Stroke Foundation.

Disclosures

Drs Hill and Goyal have received grants from Medtronic to the University of Calgary for clinical research. Dr Hill has received a grant from Alberta Innovates Health Solutions, research support from Boehringer Ingleheim Canada, and has stock ownership interest in Calgary Scientific Inc. The other authors report no conflicts.

References

1. Goyal M, Demchuk AM, 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/NEJMoa1414905.
2. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587.
3. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792.
4. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061.
5. Smith EE, Schwamm LH. Endovascular clot retrieval therapy: implications for the organization of stroke systems of care in North America. *Stroke*. 2015;46:1462–1467. doi: 10.1161/STROKEAHA.115.008385.
6. Southerland AM, Johnston KC, Molina CA, Selim MH, Kamal N, Goyal M. Suspected large vessel occlusion: should emergency medical services transport to the nearest Primary Stroke Center or bypass to a Comprehensive Stroke Center with endovascular capabilities? *Stroke*. 2016;47:1965–1967. doi: 10.1161/STROKEAHA.115.011149.
7. Fisher M, Saver JL. Future directions of acute ischaemic stroke therapy. *Lancet Neurol*. 2015;14:758–767. doi: 10.1016/S1474-4422(15)00054-X.
8. Menon B, Sajobi TT, Zhang Y, Rempel JL, Shuaib A, Thornton J, et al. Analysis of workflow and time on thrombectomy outcome in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) randomized controlled trial. *Circulation*. 2016;133:2279–2286. doi: 10.1161/CIRCULATIONAHA.115.019983.
9. Khatri P, Yeatts SD, Mazighi M, Broderick JP, Liebeskind DS, Demchuk AM, et al; IMS III Trialists. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. *Lancet Neurol*. 2014;13:567–574. doi: 10.1016/S1474-4422(14)70066-3.
10. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effect of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomized trials. *Lancet*. 2014;384:1929–1935. doi: 10.1016/S0140-6736(14)60584-5.
11. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Navalkele D, Grotta JC, et al. Abstract 50: Shape of the tPA time – benefit curve: insights from the national US Get With The Guidelines – stroke population. *Stroke*. 2015;46:15.
12. Kamal N, Benavente O, Boyle K, Buck B, Butcher K, Casaubon LK, et al. Good is not good enough: the benchmark stroke door-to-needle time should be 30 minutes. *Can J Neurol Sci*. 2014;41:694–696. doi: 10.1017/cjn.2014.41.

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Stroke. 2017;48:791-794; originally published online January 18, 2017;
doi: 10.1161/STROKEAHA.116.015321
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628