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Drip and Ship versus Mothership: Transportation and Treatment Strategies for Acute Ischemic Stroke Patients

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Drip and Ship versus Mothership: Transportation and Treatment Strategies for Acute Ischemic Stroke Patients

by

Jessalyn Kathryn Holodinsky

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
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Abstract

Ischemic stroke with large vessel occlusion can be treated with alteplase and/or endovascular therapy. While endovascular therapy has been proven more effective than alteplase the administration of both treatments is highly time sensitive. There are geographic disparities in access to endovascular therapy. For patients outside the immediate vicinity of a hospital equipped to perform endovascular therapy it is unknown whether transport directly to an endovascular center for alteplase and endovascular therapy (mothership) or transport to the closest centre for immediate alteplase treatment followed by transfer to the endovascular center (drip-and-ship) will result in best patient outcomes.

In this thesis, this is explored using theoretical conditional probability. Models were generated using existing data from clinical trials of stroke treatment, the accuracy of prehospital large vessel occlusion screening tools, and time from onset to stroke treatment (a function of both geography and hospital efficiency). The models were used to determine which strategy predicts the greatest probability of excellent outcome for stroke patients in several different scenarios.

The optimal transport strategy is influenced by three different factors, the impact of which is summarized as follows from the perspective of the drip and ship approach. First, the most probable diagnosis of the patient. As the positive predictive value of the large vessel occlusion screening tool decreases the importance of the drip and ship model is appreciated. Second, the speed of treatment at the receiving hospitals. Fast treatment at thrombolysis centres is key for the drip and ship model to remain viable. Finally, the
patient’s travel time to and between the different hospitals. As the distance between the thrombolysis and endovascular centre increases again the importance of the drip and ship model is realized.

This thesis presents a novel way of conceptualizing the pre-hospital transport of suspected stroke patients. Decision making for pre-hospital transport can be modelled using existing clinical trial data; these models can be dynamically adapted to changing realities. As the radius of superiority of the different transport strategy is context specific regional customization transport protocols for stroke patients is essential.
Preface


Acknowledgements

I would like to thank those who granted me their support throughout this learning process. First and foremost, I would like to give my thanks to my supervisory committee: Drs. Michael Hill, Tyler Williamson, Andrew Demchuk, and Alka Patel. Michael, you saw research and leadership potential in me that I did not know I had, your guidance over the last four years has been crucial to my progression as a researcher and an epidemiologist. I am forever grateful that you always pushed me to try new things and gave me the freedom to explore several different areas of academia throughout my degree. My degree had both great depth and breadth because of this. But most of all, thank you for pushing me to pursue this degree when I came to your office looking for a job 5 years ago – it has changed my life. Tyler, your influence on my development as an academic goes far beyond the scope of this thesis. While my sessions writing formulae on your office windows were paramount to the completion of this work, it is the time you spent fostering my development as an instructor that I am most grateful for. The freedom and encouragement you gave to me as an instructor has changed my career aspirations for the better and I believe I will be a better academic because of this. I never knew teaching could be such an enjoyable and fulfilling endeavour until I got to do it alongside you – thank you. Andrew, thank you making sure this project would be relevant to clinicians worldwide and for pushing me to expand the scope of my modelling so I could have the most impactful and relevant project possible. Alka, there is a richness to my findings that would not be present without your geospatial expertise; you have brought a new perspective to my thinking and data visualization capabilities that has greatly increased the impact of this project. Thank you all.
I would also like to express my gratitude to the following University of Calgary students (current and former), staff, and faculty who have provided support and encouragement throughout my program: Dr. Amy Yu, Dr. Charlotte Zerna, Dr. Noreen Kamal, Levi Frehlich, Dr. Isabelle Barrette-Ng, Dr. Tolulope Sajobi, Andrew Stewart, Iffat Naeem, James King, Dr. Kiara Mikita, and Dr. Mayank Goyal. I thank you all! In addition, I would like to thank the entire Calgary Stroke Program and Hotchkiss Brain Institute for their support throughout my studies.

My research benefitted greatly from international exposure throughout my program. I would like to sincerely thank Dr. David Williams, the stroke teams at Beaumont Hospital and the Mater Misericordiae University Hospital, and Royal College of Surgeons in Ireland for giving me “a thousand welcomes” to Ireland and for providing a new international perspective to my work. This would not have been possible without the support of the Ireland Canada University Foundation. I would also like to thank Drs. Bruce Campbell, Henry Zhao, and Stephen Davis, for hosting me at the Melbourne Brain Centre to gain yet another international perspective on stroke care. This would not have been possible without the support of the Hotchkiss Brain Institute and the Florey Institute of Neuroscience and Mental Health.

I would also like to acknowledge Alberta Innovates, QuICR – Alberta Stroke Program, and the Department of Community Health Sciences for funding this project.
I wish to thank my family for their consistent support throughout this journey. None of my academic ventures would be possible without the emotional and financial support of my parents Kathryn and David Holodinsky. You both instilled the importance of education in me at a young age – I know this was probably more than you bargained for but thanks for never batting an eye when I said I was going back for just one last degree! Mom, I am fearless in the pursuit of my dreams because I grew up watching you fearlessly pursue yours – I will never be able to thank you enough for that gift. Dad, thank you for always keeping me level and grounded and knowing exactly the advice I need to hear – your ability to handle tough situations with dignity and tact inspires me and I only hope I can take all I’ve learned from you forward in my career. I would also like to thank my brother Matthew Holodinsky, sister-in-law Caitlin Newton, and sister-at-heart Stephanie Fox for their unconditional love and support through this chapter in my life – I would not be where I am today without each of your influence, thank you. Finally, Eric Jack, thank you for being my number one supporter in everything that I do. I followed my dreams around the world, literally, because I knew I always had your support and encouragement. Thank you for pushing me to achieve all my goals, being there to celebrate all victories large and small, and reminding me why I started this journey through the setbacks. I cannot thank you enough – I love you.
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<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVT</td>
<td>Endovascular therapy (also Endovascular thrombectomy)</td>
</tr>
<tr>
<td>LVO</td>
<td>Large vessel occlusion</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>tPA</td>
<td>Tissue plasminogen activator (Alteplase)</td>
</tr>
<tr>
<td>PSC</td>
<td>Primary stroke centre</td>
</tr>
<tr>
<td>CSC</td>
<td>Comprehensive stroke centre</td>
</tr>
<tr>
<td>nECC</td>
<td>Non-endovascular capable centre</td>
</tr>
<tr>
<td>ECC</td>
<td>Endovascular capable centre</td>
</tr>
<tr>
<td>ESUS</td>
<td>Embolic stroke of undetermined source</td>
</tr>
<tr>
<td>mRS</td>
<td>modified Rankin Scale</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>IA</td>
<td>Intra arterial</td>
</tr>
<tr>
<td>TICI</td>
<td>Thrombolysis in cerebral infarction</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed tomography angiography</td>
</tr>
<tr>
<td>aOR</td>
<td>Adjusted odds ratio</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>EMS</td>
<td>Emergency medical services</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
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<td>STEMI</td>
<td>ST-elevated myocardial infarction</td>
</tr>
<tr>
<td>ECG</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td>MSU</td>
<td>Mobile stroke unit</td>
</tr>
<tr>
<td>LAPSS</td>
<td>Los Angeles Prehospital Stroke Scale</td>
</tr>
<tr>
<td>LAMS</td>
<td>Los Angeles Motor Scale</td>
</tr>
<tr>
<td>RACE</td>
<td>Rapid Arterial oCclusion Evaluation</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>QuICR</td>
<td>Quality Improvement and Clinical Research</td>
</tr>
<tr>
<td>ICA</td>
<td>Internal carotid artery</td>
</tr>
<tr>
<td>M1</td>
<td>M1 segment of the middle cerebral artery</td>
</tr>
<tr>
<td>M2</td>
<td>M2 segment of the middle cerebral artery</td>
</tr>
<tr>
<td>DTN</td>
<td>Door to needle time</td>
</tr>
<tr>
<td>DTP</td>
<td>Door to puncture time</td>
</tr>
<tr>
<td>GPS</td>
<td>Global positioning system</td>
</tr>
<tr>
<td>DIDO</td>
<td>Door in door out time</td>
</tr>
<tr>
<td>C-STAT</td>
<td>Cincinnati Prehospital Stroke Severity Scale</td>
</tr>
<tr>
<td>MCA</td>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td>ICH</td>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>SM</td>
<td>Stroke mimic</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National institute of health stroke scale</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>OTT</td>
<td>Onset to treatment time</td>
</tr>
<tr>
<td>FMC</td>
<td>First medical contact</td>
</tr>
<tr>
<td>MS</td>
<td>Mothership</td>
</tr>
<tr>
<td>DnS</td>
<td>Drip and ship</td>
</tr>
<tr>
<td>GPS</td>
<td>Global Positioning System</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability Adjusted Life Year</td>
</tr>
</tbody>
</table>
“Densely packed, intricately patterned, substrate of mind and awareness, the human brain is a wonder of nature. In an acute ischemic stroke, vast numbers of neurons, synapses, and nerve fibers are irretrievably lost every moment in which treatment does not occur. The figures stagger and motivate. Ischemic stroke is a highly treatable neuroemergency. For patients experiencing acute ischemic stroke, and for the physicians and allied health personnel treating them, every second counts.”

- J.L. Saver, 2006
Chapter 1: Statement of Author Contributions

Below is a statement of contribution for each author for the multi-authored manuscripts included in this thesis.


JKH created the outline for and wrote the first draft of this review manuscript. AYXY, ASA, and ZAA assisted in literature review, manuscript editing and revising. BKM, AMD, MG, and MD revised the manuscript for important clinical and intellectual content. JKH assumes responsibility for the integrity of the manuscript. Portions of this manuscript are adapted with permission and included in Chapter 2.


JKH, NK, MDH, and MG designed the study. TSW provided statistical and methodological expertise. JKH performed all analyses and drafted the manuscript. All authors revised the manuscript for important intellectual content. JKH assumes responsibility for the integrity of the manuscript. This manuscript in its entirety is included in Chapter 4.
Chapter 1: Statement of Author Contributions


JKH, MDH, and DW designed the study. JM and PM obtained and analyzed treatment time data. JKH performed all other analyses. ABP and LRJ provided geographic methodological expertise. JT, NK, PJK, SM, RC, TW, SC, SP, PB, AO, DJHM, BM, SL, GW, JH provided important intellectual content and centre specific insights. JKH, MDH, and DW drafted the initial manuscript. JKH assumes responsibility for the integrity of the manuscript. This manuscript in its entirety is included in Chapter 5.


JKH, AMD, MG, MDH, and NK conceived and designed the study. TSW provided statistical and methodological expertise. JKH, LZ, and MJF performed all analyses. HZ provided critical data. All authors revised the manuscript for important intellectual content. JKH assumes responsibility for the integrity of the manuscript. This manuscript in its entirety is included in Chapter 6.
2.1 Background

Stroke is a leading cause of disability and death in Canada and worldwide. It was estimated in 2013 that 405,000 Canadians experienced the effects of stroke (population prevalence of approximately 1%).\(^1\) As a result of both population growth and aging it is expected that by 2038 these estimates will rise to between 654,000 and 726,000 Canadians. Specifically, the prairie provinces are predicted to have the largest projected increase in stroke rates over this 25-year period.\(^1\) In 2016 in Alberta there were 3,385 stroke cases, with 2,814 of these being ischemic strokes.\(^2\) Left untreated, ischemic stroke can cause severe disability or death. The severity of outcome post ischemic stroke depends on the timeliness of treatment. Where stroke treatment is concerned “time is brain” – in a typical large vessel, supratentorial ischemic stroke 1.9 million neurons, 14 billion synapses, and 12 km of myelinated fibers are lost every minute.\(^3\) Early, fast, and appropriate treatment is essential in order to ensure the best outcomes for patients.

For the past two decades the standard of care for acute ischemic stroke treatment has been the administration of intravenous thrombolytic drugs; however recently the evidence from several large randomized trials has shifted the treatment paradigm to include endovascular therapy (EVT) as a superior treatment option for patients with large vessel occlusions (LVO).\(^4\)\(^-\)\(^8\) Current Canadian best practice guidelines recommend that all eligible patients without contraindication should receive intravenous alteplase (IV-tPA) as soon as possible after hospital arrival. Regardless of IV alteplase eligibility, these
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guidelines recommend that eligible patients without contraindication also receive EVT. Patients who are eligible for IV alteplase should have this therapy initiated while simultaneously preparing for EVT.

However, due to the specialized facilities needed for endovascular therapy in combination with Alberta’s geography and low population density, rapid access to endovascular treatment is not available to all Albertans. In Alberta, thrombolysis is offered at 15 primary stroke centres (PSC) or thrombolysis centres across the province, however EVT is only offered at 2 comprehensive stroke centres (CSC) or endovascular therapy centres,¹ one in Calgary and one in Edmonton. This means that for the rural stroke patient the most efficacious treatment option may not be immediately accessible.

In transporting rural stroke patients there are two options 1) directly transport the patient to the nearest CSC for thrombolytic therapy and immediate EVT, potentially bypassing a nearer PSC (mothership model), or 2) transporting the patient to a PSC for thrombolysis and then immediate transfer to the nearest CSC for EVT (drip and ship model). It is currently unknown which transport option provides the best probability of disability free survival for the patient.

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¹ While in Alberta, Canada these centres are referred to as primary stroke centres and comprehensive stroke centres this is not the case across the rest of the world. As such in the chapters to follow, which are published manuscripts, different terminologies are used per editorial requirements. In this thesis, the terms primary stroke centre (PSC), thrombolysis centre, and non-endovascular capable centre (nECC) are synonymous and the terms comprehensive stroke centre (CSC), endovascular therapy centre (EVT centre), and endovascular capable centre (ECC) are synonymous.
2.2 Acute Ischemic Stroke: Definitions, History, and Treatments

Portions of this section are adapted with permission from Holodinsky et al. History, Evolution, and Importance of Emergency Endovascular Treatment of Acute Ischemic Stroke. Current Neurological and Neuroscience Reports. 2016;16(5):42.10

2.2.1 What is Stroke?

Stroke can be broadly classified into two categories: ischemic and hemorrhagic. Ischemic stroke is defined as the disruption of blood flow to a portion of the brain caused by an arterial blockage. Hemorrhagic stroke is the release of blood into the brain and/or intracranial extravascular spaces. The degree of damage caused depends on the volume of bleeding, how rapidly the bleeding occurs, the pressure buildup resulting from the bleed, and the location of the bleed.11 This work will focus primarily on ischemic stroke.

There are three main causes of ischemic stroke. About 50% of large vessel ischemic stroke is caused by cardiac or arterial emboli.12 Most cardiac emboli are caused by the embolization of mural thrombi harbored in the atrial appendage associated with atrial fibrillation; arterial emboli are commonly generated from atherosclerosis of the aortic arch or extracranial cervical (carotid and vertebral) arteries.13,14 Another mechanism of atherosclerosis-related stroke is atherosclerotic narrowing or complete occlusion of an artery resulting in downstream hypoperfusion.11 Roughly 25% of ischemic strokes are lacunar infarcts, which are small infarcts in the deeper parts of the brain due to occlusion of smaller penetrating vessels.12,14 In roughly 25% of patients a
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definite cause of ischemic stroke cannot be identified (termed cryptogenic stroke).\(^{15}\) These strokes often have an imaging appearance similar to embolic stroke, and the term – embolic stroke of undetermined source (ESUS) – has been recently used to describe this sub-type of cryptogenic stroke.\(^{16}\) Additionally, intracranial atherosclerosis, which is uncommon in Caucasian populations (accounting for <10\% of ischemic stroke), is a more common cause of stroke among Hispanic, Asian, and African American populations (accounting for twice as many (20\%) but up to 54\% of ischemic stroke depending on population).\(^{14,17}\) An ischemic stroke can happen in any portion of the brain, and most ischemic stroke is minor with positive long term prognosis for most patients. However this proposed work primarily addresses large vessel (internal carotid artery and middle cerebral artery) occlusions where prognosis ranges from complete functional and cognitive recovery to severe disability and death.\(^{14,18}\)

2.2.2 Ischemic Stroke Treatment: Thrombolysis

The use of thrombolytic agents to treat ischemic stroke began with intravenous treatment under diagnostic angiogram control in 1958. Sussman and Fitch documented the use of intravenous plasmin in three patients, one of which showed complete recanalization and another partial recanalization.\(^{19}\) Trials of various intravenous thrombolytic drugs for the treatment of ischemic stroke began in the late 1980s. The first trials of thrombolytic agents for ischemic stroke (MAST-I, ASK, and MAST-E) compared streptokinase (with aspirin in MAST-I) to placebo and found no difference in 6 month outcome, however there was greater early mortality in the streptokinase group.\(^{20-22}\)
During this same period, the use of tissue plasminogen activator (tPA) to treat ischemic stroke was studied in animal models and was found to improve neurologic function when administered up to 45 minutes after stroke. In 1992 the first dose-finding and safety studies of alteplase in humans were published which found 0.9 mg/kg as the safest tolerable dose of alteplase (single chain tPA). In 1995 the National Institute of Neurologic Disorders (NINDS) group published a randomized trial of alteplase versus placebo for acute ischemic stroke treatment which showed patients treated with alteplase were 30% more likely to have minimal or no disability at 90-day follow-up. Compared to prior trials, the patients in NINDS were treated much faster (all patients <180 minutes and half of the patients <90 minutes from onset), blood pressure parameters were established, and there was no concurrent antiplatelet or anticoagulation treatment.

Currently intravenous alteplase has been the accepted treatment for acute ischemic stroke for nearly two decades, however the drug’s recanalization rates are relatively low which in turn leads to low rates of good outcome. Broken down by occlusion location alteplase shows very low recanalization in proximal occlusions (8% recanalization in the internal carotid artery), recanalization rates increase with more distal occlusion locations (26% in M1 occlusions, 35% in M2 occlusions, and 40% in M3 occlusions) but remain far from perfect. These occlusions in the proximal anterior circulation, for which alteplase is relatively ineffective, account for approximately one third of cases of acute ischemic stroke. When considering long term outcomes, a recent meta-analysis demonstrated that only 46% of patients treated with intravenous alteplase achieved an independent outcome [modified Rankin Scale (mRS) 0 –2] at 90 days.
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The effectiveness of intravenous alteplase is highly time dependent. A meta-analysis of nine randomized trials of alteplase versus placebo found on odds ratio (OR) of good outcome over placebo of 1.75 [95% confidence interval (CI) 1.35 –2.27] for those treated within 3 hours of stroke onset; this OR decreased to 1.26 (95%CI 1.05 –1.51) for those treated between 3 and 4.5 hours after onset, and a treatment delay of more than 4.5 hours resulted in no difference between treatments (OR 1.15; 95%CI 0.95 –1.40). The 2013 Canadian Best Practice Guidelines for Stroke care, the American Stroke Association and the European Stroke Organization acute ischemic stroke care guidelines all recommend administering intravenous alteplase for ischemic stroke patients without contraindications who can be treated within 4.5 hours of stroke onset. However, it has been estimated that only approximately 25% of ischemic stroke patients present to hospital early enough to even consider intravenous alteplase administration within 4.5 hours of symptom onset.

2.2.3 Stroke Treatment: Endovascular Therapy

Given the lack of efficacy of intravenous alteplase alone for patients with major ischemic stroke new techniques for treating ischemic stroke needed to be developed. The evolution of endovascular stroke treatment began with administering thrombolytic agents directly into the affected artery rather than intravenously. This therapy, which was previously successful in the treatment of coronary artery occlusions, was first used in the early 1980’s by Zeumer and colleagues to treat basilar artery and internal carotid artery occlusions. The first trials of intra-arterial (IA) thrombolytic agents were PROACT
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and PROACT-II.\textsuperscript{39,40} PROACT randomized patients to receive intra-arterial recombinant prourokinase or placebo, PROACT-II used a similar design but with the addition of heparin to both trial arms.\textsuperscript{39,40} Both of these trials showed higher rates of recanalization in the intra-arterial therapy arm (57\% - 66\%) than the control arm (14\% - 18\%).\textsuperscript{39,40} PROACT-II also found higher rates of 90-day functional independence in the intra-arterial treatment arm compared to the control arm (40\% versus 25\%).\textsuperscript{40} The MELT trial also studied the use of intra-arterial urokinase in middle cerebral artery infarction; this trial found a significant difference in excellent outcome (mRS 0 – 1) between the urokinase and control groups (OR 2.46, 95\%CI 1.09 – 5.54). However there was no significant difference in good outcome (mRS 0 – 2) between the groups (OR 1.54, 95\%CI 0.73 – 3.23).\textsuperscript{41}

The combination of intra-arterial and intravenous alteplase was studied in the EMS bridging trial, which found better recanalization in the IV/IA group than the placebo/IA group (54\% vs. 10\%) however, there was no difference in 90-day patient outcomes between the groups.\textsuperscript{42} These results lead to the development of the IMS-I trial which compared IV/IA alteplase treatment to historical control patients from the NINDS study (IV alteplase treatment).\textsuperscript{27,43} This trial, which used a lower dose of alteplase than the NINDS trial (max dose of 82mg vs. 90mg), found better outcomes (mRS 0 – 1) in the IV/IA alteplase group (OR 2.26, 95\%CI 1.15 – 4.47) warranting a future randomized trial comparing these two therapies.\textsuperscript{43}

During this time, endovascular catheters suitable for treating ischemic stroke were developed. The EKOS device added low intensity ultrasound to an infusion catheter to
augment IA alteplase treatment.\textsuperscript{44} The efficacy of the EKOS device was evaluated in the IMS-II trial where it was shown to be associated with a 60% recanalization rate.\textsuperscript{45} In 2005 the MERCI coil retriever became the first device to be approved for mechanical thrombectomy.\textsuperscript{46,47} This system consists of a corkscrew shaped coil, which passes distal to the thrombus, snares the thrombus and then physically removes it. The MERCI retriever showed a recanalization rate of 43% after thrombectomy alone and 64% with the addition of intra-arterial thrombolysis, with half of these revascularized patients making a significant recovery at 90 days.\textsuperscript{48} The Penumbra system was the second device approved for thrombectomy, this device was more versatile than the MERCI retriever and offered two options for thrombectomy: clot debulking followed by aspiration, or thrombus removal.\textsuperscript{49} This system had a high recanalization rate of 81% with 31% of patients having a good clinical outcome (mRS 0 – 2) at 90 days.\textsuperscript{49}

In 2013 the first three trials of endovascular therapy versus standard medical therapy were published\textsuperscript{50-52} All three of these trials failed to show any significant difference between endovascular therapy and standard medical treatment on disability-free survival (mRS 0 – 2) at 90 days. These early trials were far from perfect, they had long treatment delays and did not require confirmation of the presence of a vascular occlusion prior to randomization. Nevertheless, important conclusions can be drawn from these trials. First, the safety profile of endovascular therapy suggests that concurrent treatment with intravenous alteplase does not significantly increase hemorrhagic transformation. Second, the efficacy of intravenous alteplase is dependent on site of occlusion and thrombus burden with the most proximal occlusions having the lowest
recanalization rates.\textsuperscript{53,54} Third, clinical outcomes were highly correlated with time to angiographic reperfusion.\textsuperscript{55} Finally, rates of achieving good reperfusion, (thrombolysis in cerebral infarction) TICI score of 2b or 3,\textsuperscript{56} with endovascular intervention was relatively low (ranging from 23\% to 48.9\% depending on study and occlusion location).\textsuperscript{50-52}

Additionally, IMS-III assessed recanalization using 24-hour computed tomography angiography (CTA), which may have resulted in the inclusion of late recanalizing patients (>6 hours), this late recanalization (which is also known as futile recanalization) generally does not improve patient outcomes.\textsuperscript{57} This is partially related to the use of first generation devices.\textsuperscript{50-52}

While the MERCI retriever seemed promising it did have a major downfall in that it only engages with the thrombus at one point, and that the retriever could not consistently capture the entire thrombus. The next advancement in endovascular technology was the development of stent retrievers (Trevo and Solitaire devices). These stent retrievers were superior to the MERCI retriever as they engage the thrombus at multiple points leading to more successful extraction and also allowing for immediate reperfusion as the thrombus becomes entrapped between the expanded stent and the vessel wall.\textsuperscript{58-60} These stentriever were shown to be superior to the MERCI retriever in the SWIFT and TREVO-2 trials.\textsuperscript{59,60} In TREVO-2 both reperfusion (86\% vs. 60\%) and 90-day functional independence rates (40\% vs. 22\%) were greater in the TREVO group compared to the MERCI group.\textsuperscript{60} The SWIFT trial, which compared the Solitaire stentriever to the MERCI device, also found higher rates of recanalization (89\% vs. 67\%) and 90-day functional independence (36\% vs. 29\%) in the Solitaire group.\textsuperscript{59} Additionally
these studies showed that the MERCI retriever was associated with higher perforation and intracerebral hemorrhage rates than the stent retrievers.\textsuperscript{59,60}

The newly available stent retrievers were used in a new wave of positive trials using these devices in conjunction with more rigorous patient inclusion criteria.\textsuperscript{4-8,61,62} The Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), whose positive results led to the early stopping of several other trials after interim analysis confirmed efficacy of endovascular therapy.\textsuperscript{5} An individual patient data meta-analysis of these trials has shown a significant mRS score reduction [adjusted odds ratio (aOR) 2.49; 95%CI 1.76 – 3.53].\textsuperscript{63} Endovascular therapy was also associated with significantly higher rates of 90-day functional independence (mRS of 0 – 2) (aOR 2.71; 95%CI 2.07 – 3.55).\textsuperscript{63} Four of these trials showed no mortality difference between the two groups\textsuperscript{5-8}, however the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial showed lower mortality in the treatment arm (OR 0.49, 95%CI 0.26 – 0.94) as compared to the control arm\textsuperscript{4}.

This newly available and highly efficacious treatment has created a dilemma in healthcare access for acute ischemic stroke patients with large vessel occlusion as the geographic organization of healthcare systems is such that EVT may not be immediately accessible to a high proportion of patients.
2.3 Access to Healthcare

Access to health care is a complex topic and the meaning of access can change depending on the lens it is viewed through. In its most simple terms access has been described as “whether those who need care get into the system or not”\textsuperscript{64} this has later been expanded to “the measure of potential and actual entry of a given population group into the healthcare system.”\textsuperscript{65} This expanded definition highlights that available services may not be utilized (potential access) and that users are a part of the access equation. Given the complexity of the term access it has been suggested by Gulliford and colleagues that it can be broken into four dimensions: service availability, utilization of services, relevance and effectiveness, and equity.\textsuperscript{66} Khan and colleagues break down access a different way into characteristics of the healthcare system, characteristics of the users, and facilitators and barriers to access; each of these are further broken down into spatial (geographic) and aspatial (social) components as well.\textsuperscript{65} In Table 1 below a conceptual overview of healthcare access is provided. Access is broken down broadly into two categories, having access, having services available, and gaining access, the process of actually utilizing the service. These categories are further broken down into user factors and system factors as well as spatial and aspatial factors.
Table 1. Conceptual Framework for Access

<table>
<thead>
<tr>
<th></th>
<th>Having Access</th>
<th>Gaining Access</th>
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</thead>
<tbody>
<tr>
<td><strong>User Level Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Having services available</td>
<td>— Predisposing factors: sex, age, race, religion, education, values concerning health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— Distribution and location of users</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— Recognition of need for healthcare</td>
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<tr>
<td></td>
<td></td>
<td>— Perception of illness and need for healthcare</td>
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<tr>
<td></td>
<td></td>
<td>— Finance/insurance (ability to cover cost of services)</td>
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<tr>
<td></td>
<td></td>
<td>— Travel associated costs including lost wages</td>
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<tr>
<td></td>
<td></td>
<td>— Patient outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— Consumer satisfaction</td>
</tr>
<tr>
<td><strong>System Level Factors</strong></td>
<td>— Number of services</td>
<td>— Wait times</td>
</tr>
<tr>
<td></td>
<td>— Size of services</td>
<td>— Inefficiencies/organization</td>
</tr>
<tr>
<td></td>
<td>— Location of services</td>
<td>— Variations in referral practices</td>
</tr>
<tr>
<td></td>
<td>— Appropriate personnel</td>
<td>— Preferences/prejudices of system personnel</td>
</tr>
<tr>
<td></td>
<td>— Equipment and materials</td>
<td>— Quality of care provided (may differ based on location)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— Cost of services provided</td>
</tr>
</tbody>
</table>

*Spatial factors show in italics

2.3.1 Having Access

Having access is a system level factor which deals with service availability. Before utilization of a service can be considered there must be an adequate supply of services available. These are all characteristics of the healthcare system including the number, size, and location of services. There are no user level factors in the having access domain. Other resources including appropriate health care personnel, equipment, and materials would be included in this category as well. These characteristics can be
summarized using measures such as number of hospital beds/doctors/specialists per capita in the specified region.66

2.3.2 Gaining Access

Just because a service is available does not mean it will be utilized, much of the healthcare access issue lies in the utilization of existing services. There may be barriers, both user and system level, that influence an individual’s ability to gain access.66 On a user level there are several predisposing factors that will influence their access to healthcare including age, sex, race, religion, and values concerning health.64 First and foremost, the individual (or somebody around them) must recognize their need for healthcare and make the decision to seek it out. This is not just as simple as an individual recognizing they are sick, they must also perceive that their illness requires medical attention. Additionally, the perception of being ill and requiring medical attention in engrained in the individuals preconceived notions about health and the healthcare system. It is also important to remember that individual perceptions about healthcare and its importance may not always align with healthcare provider’s perceptions, especially in the case of preventative medicine.66 Another significant personal barrier is finance. This may seem to be an obvious barrier in private healthcare systems but it is important to keep in mind the indirect financial costs users bear in a publically funded system as well including travel costs, lost wages, and prescription medications.66

System level factors can also influence access. These include long wait times, inefficiencies, and variations in referral practices.66 The systems organization and
preferences/prejudices of system personnel can also influence an individual’s ability to gain access. How the system organizes its resources is also important. System organization can be broken down into two components, entry and structure. Entry organization refers to the individual getting into the healthcare system and includes issues such as wait times/lists. Whereas structural organization refers to what happens to the patient once they are in the system including which healthcare providers are seen, referral practices, and tests and treatments performed.

Yet, simply gaining access in not enough. The access achieved should be both relevant and effective. This implies that outcomes should be considered when evaluating access, as without this, conclusions may be invalid. For example, both organizational barriers and ineffective or inappropriate care can lead to poor outcomes, this may cause increased utilization of services given the perception of increased access. On the other hand, effective services may lead to favourable outcomes which may decrease service utilization and therefore give the perception of low access. Subjective outcomes including consumer satisfaction should also be considered when evaluating access as consumer satisfaction may influence future attempts at gaining access positively or negatively.

2.3.3 Reasons to Study Geography in Relation to Access to Healthcare

Geography can be an important and interesting barrier to accessing healthcare. Where you live affects the treatment you get, health and geographies are inextricably linked. Geographic access to healthcare has also been referred to at the “friction of space.” Some issues surrounding access to healthcare are directly related to geography.
(spatial factors), these factors deal directly with space or distance as a barrier/facilitator to access. These spatial factors take many forms, one being that health risks arising from environmental conditions, air quality, water quality, and other contaminants vary over space. However, it is also important to note that some aspatial factors (economics, social, or cultural factors) have geographic manifestations. Due to all of these factors the need for healthcare often varies over space, something that is often neglected in individual level studies.

There are several aspects to consider when evaluating geographic access to healthcare. One such aspect is user mobility. Services which can be reached by car or public transport have higher accessibility than those that cannot. This is twofold as it depends both on the service being in an accessible place and the user having access to mobility (car, public transport, etc.). However, eventually accessibility will decrease as variations in the use of health services have been shown to be associated with road distance and estimated travel times to services. Another important dimension of geographic analyses is that the nearest service is not necessarily the one that is actually used so travel times may be underestimated, thus simplistic analyses drawing conclusions off of the existence of a service in a specific location may be missing the mark. Geography also allows us to put a different lens on some of the economic inequities in healthcare access by looking at aspatial factors that present geographically. For example, it has been proposed that service availability can be measured from a health economic perspective by evaluating the cost to individuals (travel, lost wages, etc.) for obtaining care.
Another reason to take geographic factors into consideration is that inferences based on aggregate data at the regional level may not tell the entire story. Hidden inside these regions may be a mix of both poorly and well-resourced districts which are lost in data aggregation, but may be teased out using a geographic analysis. Measures such as hospital beds/doctors/specialists per capita do not tell the entire story. There may be a very favourable ratio of doctors to potential patients in a region however, if the doctors are all located in one specific area not all potential patients would have access to these providers. Studying geography in relation to healthcare allows us to look at equity in healthcare access with a different lens – space.

Providing equal access to healthcare is not always possible where geography is concerned. In countries where health care resources are scarce to begin with it is easy to postulate how geography and distance may play into healthcare access but even in countries with developed healthcare systems, if populations are sparsely distributed (such as in Western Canada) equal access may not be attainable due to geography. There are two main components of geographic access to healthcare: location of services, and mobility of users.

In healthcare systems, there is often a tradeoff between equity and efficiency. Efficient services often provide the greatest level of access to healthcare on a whole, however, this access may not be distributed fairly among all groups of individuals. Efforts to increase equity may actually decrease efficiency by decentralizing services which may lead to their underutilization. Conversely efforts to create more efficient healthcare systems has led to the centralization of services. This means combining
practices or services into a single centralized location. While this may have many efficiency and cost benefits it often increases the geographic burden of accessing healthcare as services are no longer widely distributed.69

2.4 Access to Endovascular Therapy

The centralization of care, a necessary trade-off between equity and efficiency, has created geographic disparities in the access to EVT in most health systems. The amount of specialized equipment, high level of expertise, and need for a high procedure volume to keep up skills has necessarily caused EVT services to be centralized in large urban hospitals. This creates a two-fold access problem for the health system: first, due to the centralized location of services there are some individuals who do not have immediate access to EVT; second, to remedy this an organizational process must be put in place to ensure these individuals can gain access to EVT.

For example, in Alberta, there are 15 PSCs where thrombolysis is available; however, there are only 2 CSCs (where EVT is available). These CSCs are in Calgary and Edmonton meaning that sub-urban and rural stroke patients do not have immediate access to the most efficacious treatment option. In transporting patients with suspected acute ischemic stroke due to LVO there are two options to gain access to EVT: 1) transporting the patient directly to the nearest CSC for thrombolytic therapy and immediate EVT, potentially bypassing a nearer PSC (mothership model); or 2) transporting the patient to a PSC for thrombolysis and then immediate transfer to the nearest CSC for EVT (drip and ship model). Given that early reperfusion is key for
disability free survival and “time is brain”, it is currently unknown if it is beneficial for patients to forgo early thrombolysis and endure a longer transport to obtain EVT treatment.

A similar dilemma was faced in ST-elevated myocardial infarction (STEMI) care over a decade ago when percutaneous coronary intervention (PCI) was shown to be favourable to fibrinolytic therapy. In pre-hospital STEMI care guidelines the American Heart Association recommends a standardized reperfusion care pathway that designates PCI is the preferred reperfusion strategy if initiated within 90 minutes of medical contact, and if this is not achievable fibrinolytic therapy should be initiated. This means that EMS should bypass non-PCI hospitals and take patients directly to a PCI performing centre if the transport is short enough to achieve PCI within 90 minutes.

There currently is no such guideline is available for ischemic stroke patients. In early 2017 the American Heart Association proposed the Severity-Based Stroke Triage Algorithm for Emergency Medical Services (EMS) which suggests that patients with suspected LVO (based on a LVO screening tool) should be transported directly to an EVT center if direct transport only results in an additional transport of 15 minutes or less otherwise the patient should be taken to the thrombolysis center first. However, this time threshold was developed using current guidelines at the time and observational studies and is not the product of a modelling study evaluating transport methods. Since then there is much debate in the scientific community over whether this is an appropriate recommendation. In the original publication of the 2018 American Heart
Association/American Stroke Association Guidelines for the Early Management of Patients with Acute Ischemic Stroke EMS Systems recommendation 4 stated:

“When several IV alteplase-capable hospital options exist within a defined geographic region, the benefit of bypassing the closest to bring the patient to one that offers a higher level of stroke care, including mechanical thrombectomy, is uncertain. Further research is needed.”

This was classified as Class of Recommendation IIb (Weak, Benefit ≥ Risk) and Quality of Evidence B-NR (moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies). This was qualified with the associated knowledge byte:

“At least 6 stroke severity scales targeted at recognition of large vessel occlusion (LVO) in the prehospital setting to facilitate transfer to endovascular centers have been published. The performance of all available scales based on published literature was recently compared. All the scales were initially derived from data sets of confirmed stroke cases or selected prehospital cases, and there has been only limited study of their performance in the prehospital setting. For prehospital patients with suspected LVO by a stroke severity scale, the Mission: Lifeline Severity–based Stroke Triage Algorithm for EMS recommends direct transport to a comprehensive stroke center if the travel time to the comprehensive stroke center is <15 additional minutes compared with the travel time to the closest primary stroke center or acute stroke-ready hospital. However, at this time, there is insufficient evidence to recommend 1 scale over the other or a specific threshold of additional travel time for which bypass of a primary stroke center or acute stroke-ready hospital is justifiable. Given the known impact of delays to IV alteplase on outcomes, the known impact of delays to mechanical thrombectomy on outcome, and the anticipated delays in transport for mechanical thrombectomy in eligible patients originally triaged to a non-endovascular center, the Mission: Lifeline algorithm may be a reasonable guideline in some circumstances. Customization of the guideline to optimize patient outcomes will be needed to account for local and regional factors, including the availability of endovascular centers, door-in-door out times for non-endovascular stroke centers, interhospital transport times, and DTN and door-to-puncture times. Rapid, protected, collaborative, regional quality review, including EMS agencies and hospitals, is recommended for operationalized bypass algorithms.”

However, six-months post publication this section (among several others) was removed from the guidelines based on feedback received from the clinical stroke
community while work to clarify, modify, and/or update this section takes place. With
this retraction, again there is no clear guideline for the stroke community to follow in the
creation of a bypass protocol for accessing EVT.

The current Canadian Stoke Best Practice Guidelines recommend that in the pre-
hospital phase a dispatch protocol such that probable signs of stroke, the need for a
priority response, and rapid transport be developed and implemented. Once on scene
EMS should screen for signs of stroke using the FAST (face, arm, speech, and time) tool
and any patients who demonstrate FAST signs should undergo secondary screening to
assess stroke severity (i.e. to screen for potential large vessel occlusion). These guidelines
also recommend that a direct transport protocol be put in place to facilitate the transfer of
suspected acute stroke patients who are potentially eligible for alteplase and/or EVT. The
items considered in generating a transport protocol are outlined in Table 2.

**Table 2. Items to be considered in stroke transport protocol generation from the
Canadian Stroke Best Practice Guidelines**

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>— Categorize suspected acute stroke patients as high priority for evaluation, response, and transport</td>
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<tr>
<td>— Medical stability of the patient</td>
</tr>
<tr>
<td>— Presenting signs and symptoms of stroke</td>
</tr>
<tr>
<td>— Probability the patient is treatable with alteplase and/or EVT</td>
</tr>
<tr>
<td>— Patients are eligible for alteplase within 4.5 hours of stroke onset</td>
</tr>
<tr>
<td>— Transport time and receiving hospital treatment time must be considered</td>
</tr>
<tr>
<td>— Some patients are eligible for EVT when selected using neurovascular imaging up to 24 hours from onset</td>
</tr>
<tr>
<td>— Transport time and receiving hospital treatment time must be considered</td>
</tr>
<tr>
<td>— Emergency departments ability to provide alteplase within the target median door to needle time of 30 minutes (90\textsuperscript{th} percentile of 60 minutes)</td>
</tr>
<tr>
<td>— Other acute needs of the patient</td>
</tr>
</tbody>
</table>
Chapter 2: Introduction

These criteria do not prescribe a time threshold in which bypassing a primary stroke centre is appropriate and leave the door open for individual jurisdictions to custom generate these protocols. In a country as geographically spread and sparsely populated as Canada these protocols will very likely be unique region to region. Canada (~10M km$^2$ and population of ~37.3M) currently has 133 PSCs and 23 CSCs. Across the country, the density of these stroke centres is highly variable. The province of Ontario has the largest number of stroke centers with 10 CSCs and 28 PSCs. However, there are large areas of Canada without access to stroke care; the three territories do not house any stroke centres, and the provinces of Newfoundland and Prince Edward Island are without CSCs entirely (although this will likely change in the future). This means that transport decision making will likely be radically different in different areas of the country.

Further complicating this matter is that unlike STEMI acute ischemic stroke cannot be definitively identified in the field. STEMI can be easily and accurately diagnosed using a 12-lead echocardiogram (ECG) which can be administered and interpreted by a pre-hospital health care provider. This is not the case for ischemic stroke. While ischemic stroke has many common symptoms including limb weakness/paralysis, facial droop, and sensory deficits there are no symptoms that are 100% sensitive or specific to ischemic stroke. There also are no biomarkers which are 100% indicative of ischemic stroke. To complicate matters there are many other neurologic conditions which can present with similar symptom profiles as ischemic stroke including hemorrhagic stroke, seizures, migraines, and various other stroke mimicking conditions. The only way to definitively diagnose an ischemic stroke is with
imaging (non-contrast CT at minimum). While there are a handful of mobile stroke units (MSU; ambulances equipped with CT scanners), around the world this technology is not widely available in the pre-hospital environment.\textsuperscript{76-78}

This makes the ischemic stroke diagnosis in the field a probabilistic one. There have been several screening tools developed which attempt to identify stroke in the field, two of the most commonly used being the Los Angeles Prehospital Stroke Scale (LAPSS) and the Cincinnati Prehospital Stroke Scale.\textsuperscript{79,80} A positive screen on either of these scales can identify a stroke patient with 66-91\% sensitivity and 87-97\% specificity.\textsuperscript{79,80} However, in determining patients that could be candidates for direct transport to EVT centers a tool is needed which can identify ischemic stroke due to LVO in the field. There have been several LVO screening tools developed in recent years. The most common of which include the Los Angeles Motor Score (LAMS, an abbreviated version of the LAPSS)\textsuperscript{81} and the Rapid Arterial occlusion Evaluation Scale (RACE).\textsuperscript{82} While these tools have been shown to have high sensitivity and specificity in identifying ischemic stroke with LVO their positive predictive values (PPV) in prospective paramedic use are only moderate (RACE $\geq5$: 41\%, LAMS $\geq4$: 43\%).\textsuperscript{83} This is likely due to a combination of LVO stroke and other neurologic conditions having similar clinical presentation and the low prevalence of ischemic stroke with LVO. For this reason, a probabilistic approach must be taken when creating transportation algorithms given there is uncertainty in these patients’ true diagnoses, which leads to uncertainty in the most appropriate treatment course of action.
2.5 Rationale and Objectives

While EVT has changed acute ischemic stroke care, it does not impact all patients equally; those living close to urban areas will have immediate access to EVT and thus will benefit disproportionally as compared to those in rural areas without immediate access. It is, therefore, prudent to study different models of access to EVT to make the most appropriate plan for its access for all patients suspected of having a LVO.

The objective of this research is to model two different methods for accessing EVT: drip and ship and mothership, with the aim of creating a model which will calculate the method predicted to result in best patient outcomes at the population level. The results of this project will impact the care of all persons who experience a major ischemic stroke. It will lead to faster and more appropriate stroke care, which will ensure the best outcome possible for every ischemic stroke patient.

2.6 Thesis Structure

This thesis is structured as a manuscript based dissertation. To fulfil the objectives described above a program of research was developed and three manuscripts were produced and published. Chapter 3, not in manuscript format, provides a detailed overview of the methodology used across the entire program of research. Chapter 4 is a commentary published in Stroke which describes a way of thinking about the transport of patients with acute ischemic stroke due to known LVO (conditional probability modelling) and the results of such a model in several generalized scenarios. Chapter 5 is
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an original research article published in *European Stroke Journal* which describes a case study applying the results of the conditional probability model for patients with acute ischemic stroke due to known LVO to the Republic of Ireland. Chapter 6 is an original research article published in *JAMA Neurology* which describes a conditional probability model for patients suspected to have an acute ischemic stroke due LVO. Chapter 7, not in manuscript format, provides further discussion of the work presented in Chapters 4 – 6 and conclusions. Each chapter contains individually numbered reference lists. A complete bibliography of all cited works appears at the end of the thesis.
2.7 References:


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64. Aday LA, Andersen R. A framework for the study of access to medical care.


Chapter 3: Methods

This chapter contains all methodologies used in this thesis. Due to manuscript space limits the method sections in manuscript based chapters 4 through 6 are quite brief. Below is an expansion on this methodology. Section 3.1 pertains directly to the methods used in Chapter 4, section 3.2 pertain directly to the methods used in Chapter 5, and section 3.3 pertain directly to the methods used in Chapter 6.

3.1 Development of a Conditional Probability Framework

A visualization of the drip and ship and mothership transport models is shown in Figure 1. In the drip and ship method the patient is first transported to their nearest primary stroke centre where they will receive alteplase treatment, if eligible, and then be transferred to the nearest comprehensive stroke centre to receive EVT. In contrast the mothership method involves direct transport to the comprehensive stroke centre for both alteplase and EVT treatment, if eligible, this may involve bypassing a closer primary stroke centre.
Figure 1. Drip ‘n Ship vs. Mothership Framework.

The dashed line represents the mothership model; the solid lines represent the drip and ship model. Time X is the transportation time from the patient to the PSC. Time Y is the transportation time from the PSC to the CSC. Time Z is the transportation time from the patient to the CSC. Time A is the time from the patient’s arrival at the PSC to the administration of alteplase and time B is the time from alteplase administration to leaving the PSC. Time A' is the time from the patient’s arrival at the CSC to administration of alteplase. Time C is the time from the patient’s arrival at the CSC to the beginning of the endovascular procedure.

To gain an understanding of where stroke outcomes differ by transportation method theoretical conditional probabilities models were created using existing stroke trial data. These models included available aggregate data regarding efficacy of stroke
treatment and outcomes for patients with ischemic stroke due to large vessel occlusion. The purpose of these models is not to generate a definite answer to the drip and ship versus mothership question but rather to generate a framework for thinking about these two transport scenarios and the modeling process when time to event is a predictor rather than an outcome (as it classically is) and to understand what process level factors have a large effect on modeling.

The initial model generation was approached from a physiologic basis and is based on time from stroke onset to reperfusion, as achieving reperfusion is what ensures better outcomes in stroke patients. The conditional probabilities which were considered included the probabilities of achieving reperfusion for each given treatment (IV alteplase and EVT), the probabilities of achieving a good outcome (defined as mRS 0 – 2 at 90 days) given a specific time from first medical contact to reperfusion, as well as the probability of achieving a good outcome given reperfusion is not achieved. Linear models were used in the absence of evidence of the relationship between time to reperfusion and good outcome being non-linear. In this first iteration of this model generation process several simplifying assumptions were made which are summarized in Table 1.
Table 1. Simplifying assumptions made in model generation including rationale and implications of the assumptions.

<table>
<thead>
<tr>
<th>Model Assumption</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is true uncertainty regarding which transport and treatment decision to make</td>
<td>This model would not be needed in cases where the most favourable treatment option was certain.</td>
</tr>
<tr>
<td>The primary stroke centre is the closest treatment centre to the patient</td>
<td>If the comprehensive stroke centre was the closest treatment centre the patient should be transported directly to the comprehensive centre as all treatment options are available here.</td>
</tr>
<tr>
<td>There is only one decision making point (at the scene) and this decision is never reneged upon</td>
<td>While we acknowledge bad weather, traffic, road closures, and hospital capacity may cause an ambulance to divert to another centre on route this cannot be accounted for in these models at this time.</td>
</tr>
<tr>
<td>This model does not apply to “found down” or stroke-on-awakening patients</td>
<td>It is impossible to account for the time between stroke onset and first medical contact if the stroke is not witnessed</td>
</tr>
<tr>
<td>Relationship between probability of successful reperfusion and time</td>
<td></td>
</tr>
<tr>
<td>a. The probability of successful reperfusion with alteplase therapy varies linearly with time, but is capped at a maximum rate</td>
<td>a. In both in vitro and in vivo studies clot dissolution rates with alteplase have been shown to progress linearly in the initial treatment phase (^1,2)</td>
</tr>
<tr>
<td>b. The probability of successful reperfusion with endovascular therapy is time invariant</td>
<td>b. While, we know that this is not strictly true, the variation with time is probably relatively small (^3) and without robust data on the change in effectiveness over time we cannot account for this variation.</td>
</tr>
<tr>
<td>All patients with occlusions are eligible for alteplase and all patients with large vessel occlusions are eligible for endovascular therapy</td>
<td>This is an extension of Assumption 1, for there to be true uncertainty patients must be eligible for either treatment option.</td>
</tr>
<tr>
<td>For patients with large vessel occlusions reperfusion is only achieved through treatment (i.e. no spontaneous reperfusion)</td>
<td>This is known to be true in 95% of cases in the first 1-2 hours after stroke onset (^4,5)</td>
</tr>
</tbody>
</table>
3.1.1 Time Considerations in the Model

There are also several time components including door to needle time, door to puncture time, and door in door out time which are incorporated into the models. For these components, aggressive treatment time targets were used to show what transport would look like in an optimal system given all treatment targets are met (Table 2). This will also serve to further support ongoing efforts to optimize treatment times for stroke across the globe.\(^6\)\(^\text{-}^{11}\)

Table 2. Treatment Times Used in the Model

<table>
<thead>
<tr>
<th>Model Component</th>
<th>Base Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to Needle Time</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Door in Door Out Time</td>
<td>Door to needle time + 15 minutes</td>
</tr>
<tr>
<td>Door to Arterial Access</td>
<td>45 minutes (mothership)</td>
</tr>
<tr>
<td></td>
<td>30 minutes (drip and ship)</td>
</tr>
<tr>
<td>First reperfusion after endovascular therapy</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Early reperfusion after alteplase administration</td>
<td>30 minutes</td>
</tr>
<tr>
<td>a. Time from alteplase administration to comprehensive stroke centre arrival (\geq 70) minutes</td>
<td>a. 70 mins</td>
</tr>
<tr>
<td>b. Time from alteplase administration to comprehensive stroke centre arrival &lt; 70 minutes</td>
<td>b. Time from alteplase administration to comprehensive stroke centre arrival</td>
</tr>
<tr>
<td>Time from first medical contact to ambulance arrival and ambulance scene time</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

\(^2\) Door to puncture time indicates the time from the patient’s arrival at the comprehensive stroke centre to the start of the endovascular procedure (arterial access, most commonly achieved by groin puncture). In the following chapters, which are published manuscripts, due to editorial requirements this is sometimes referred to as “door to groin puncture time” additionally as sometimes arterial access is achieved via a different artery (ex. radial artery) this is sometimes referred to as “door to arterial access time”. All terms are synonymous.
Chapter 3: Methods

As an aggressive treatment target a median door to needle time of 30 minutes was chosen as this should be the standard for stroke treatment and door to needle times of close to or below 30 minutes have been reported in several centres around the world. In sensitivity analyses 60 minutes was chosen as it reflective of the median door to needle time found in the Target Stroke initiative (median = 67 minutes, 41% DTN less than 60 mins) as well as the upper quartiles in the other studies. Assuming a door-to-needle time of 30 minutes, a door-in-door-out time of 45 minutes is estimated to be an appropriate target. This is the target time for the QuICR quality improvement project in Alberta, and this a target time for STEMI care. For simplicity, this parameter was not varied in analyses. For door to puncture times the aggressive target was chosen to be 45 minutes in the mothership scenario and 30 minutes in the drip and ship scenario. The shorter workflow in the drip and ship scenario is reflective of workflow findings in the SWIFT PRIME trial where drip and ship patients had shorter workflow at the comprehensive stroke centre compared to mothership patients.

Thirty minutes was chosen as the time of first reperfusion after endovascular procedure start based on the median time from groin puncture to first reperfusion in both the ESCAPE and SWIFT PRIME trials. For simplicities sake, this was not varied. For alteplase the time of reperfusion is harder to define. We defined early reperfusion as 70 minutes post treatment initiation as angiography studies have shown that 1.6% of internal carotid artery (ICA), 23.9% of M1 segment of the middle cerebral artery (M1), and 38.9% of M2 segment of the middle cerebral artery (M2) occlusions were recanalized at first angiography post alteplase administration (median 70 minutes). Also, this is a relevant time point when considering inter-facility transportation.
3.1.2 Estimating the Conditional Probabilities with Existing Data

All probabilities were estimated using existing clinical trial data from the ESCAPE trial\textsuperscript{4} wherever possible. All probabilities are listed in Table 3. Utilizing ESCAPE trial data, the probability of good outcome given reperfusion with endovascular therapy was found to be time dependent and decreased by 0.0006 for every minute delay in onset to reperfusion.\textsuperscript{17} As the time of reperfusion for patients receiving alteplase is unknown, the rate of decay in probability of good outcome related to this is also unknown, we have assumed that the same rate of decay for endovascular therapy applies to alteplase.

The probability of achieving reperfusion given endovascular therapy was estimated from the ESCAPE trial at 0.74.\textsuperscript{4} In sensitivity analyses this was increased to 0.90 to show the potential effect of better devices and more advanced training in the future. The probability of early reperfusion given alteplase therapy varies by occlusion location. The prevalence of large vessel occlusion with a LAMS score \( \geq 4 \) is 62\% and occlusion locations are estimated at: 28\% ICA, 65\% M1, and 5\% M2.\textsuperscript{18} In combination with the above data on early reperfusion estimates by occlusion location proportions we estimate that overall 18\% of patients with a proven large vessel occlusion will achieve early reperfusion with intravenous alteplase. In the cases where a full 70 minutes was not available for early reperfusion to be achieved (time from alteplase administration to comprehensive stroke centre arrival < 70 minutes) the time of early reperfusion was adjusted to reflect the available reperfusion time (time from alteplase administration to
comprehensive stroke centre arrival). Given this, the probability of early reperfusion also needed to be adjusted. In pre-clinical studies it has been shown that clot dissolution rates progress linearly in the early treatment phase therefore these probabilities were adjusted linearly.\textsuperscript{1,2} The probability of achieving early reperfusion with thrombolytic agents is also increased to 0.40 (with the same early reperfusion time of 70 minutes and the same linear decay applied when early reperfusion time was less than 70 minutes) to display the effects of better thrombolytic medications that may be available in the future. The probability of good outcome given no reperfusion was estimated from the ESCAPE trial to be 0.30.\textsuperscript{4}
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Sensitivity Analyses</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in ( P(\text{good outcome</td>
<td>successful reperfusion}) ) over time</td>
<td>0.0006 per minute</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alteplase: Same rate is assumed due to lack of data.</td>
</tr>
<tr>
<td>( P(\text{reperfusion</td>
<td>EVT}) )</td>
<td>0.74</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.90 was used in sensitivity analyses to reflect future improvements in devices or techniques.</td>
</tr>
<tr>
<td>( P(\text{early reperfusion</td>
<td>alteplase}) )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Alteplase start to CSC arrival ( \geq 70 ) minutes</td>
<td>a. 0.18</td>
<td>a. 0.40</td>
<td>b. Clot dissolving rates with alteplase progress linearly over time.(^{12}) These probabilities were adjusted in a linear fashion for shorter reperfusion times.</td>
</tr>
<tr>
<td></td>
<td>b. 0.18[(\text{Alteplase start to CSC arrival}/70)]</td>
<td>b. 0.40[(\text{Alteplase start to CSC arrival}/70)]</td>
<td>0.40 was chosen for sensitivity analyses to reflect the greater efficacy of tenecteplase.(^{19})</td>
</tr>
<tr>
<td>2. Alteplase start to CSC arrival ( &lt; 70 ) minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P(\text{good outcome</td>
<td>no reperfusion}) )</td>
<td>0.30</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Models were created for varying times between the primary and comprehensive stroke centres (10, 20, 30, 45, 90, 120, and 180 minutes) using a combination of the different estimates and sensitivity values (Table 4). Time rather than distance is used so...
that all transport options (ground, helicopter, and fixed wing ambulance) could be considered in the application of these results to real world systems. The model’s results are visualized using a novel visualization, the two dimensional temporospatial diagram.

Table 4. Parameters Used in Different Modelling Scenarios

<table>
<thead>
<tr>
<th>Model</th>
<th>Mothership</th>
<th>Drip and Ship</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: baseline</td>
<td>$P(\text{good outcome}) = 0.74 \times [0.75 - 0.0006(30+Z+90+30)] + 0.26\cdot0.30$</td>
<td>$P(\text{good outcome}) = 0.18 \times [0.75 - 0.0006(30+X+60+15+70)] + 0.82 \times [0.74 \times [0.75 - 0.0006(30+X+60+15+Y+50+30)] + 0.26\cdot0.30]$</td>
</tr>
<tr>
<td>B</td>
<td>$P(\text{good outcome}) = 0.74 \times [0.75 - 0.0006(30+Z+75+30)] + 0.26\cdot0.30$</td>
<td>$P(\text{good outcome}) = 0.18 \times [0.75 - 0.0006(30+X+30+15+70)] + 0.82 \times [0.74 \times [0.75 - 0.0006(30+X+30+15+Y+45+30)] + 0.26\cdot0.30]$</td>
</tr>
<tr>
<td>C</td>
<td>$P(\text{good outcome}) = 0.90 \times [0.75 - 0.0006(30+Z+90+30)] + 0.10\cdot0.30$</td>
<td>$P(\text{good outcome}) = 0.82 \times [0.74 \times [0.75 - 0.0006(30+X+60+15+Y+50+30)] + 0.26\cdot0.30]$</td>
</tr>
<tr>
<td>D</td>
<td>Unchanged from Model A</td>
<td>$P(\text{good outcome}) = 0.40 \times [0.75 - 0.0006(30+X+60+15+70)] + 0.60 \times [0.74 \times [0.75 - 0.0006(30+X+60+15+Y+50+30)] + 0.26\cdot0.30]$</td>
</tr>
</tbody>
</table>

*Changes from Model A shown in bold face

X: travel time from patient to primary stroke centre; Y: travel time from primary stroke centre to comprehensive stroke centre; Z: travel time from patient to comprehensive stroke centre

3.1.3 Methods for Generation of Two Dimensional Temporospatial Diagrams

The two dimensional temporospatial diagrams are a novel abstract non-geography specific way of visualizing the best transport option for patients based upon their travel time to the primary and comprehensive stroke centres and the travel time between these two centres (also in conjunction with the different treatment times at the centres). As mentioned, travel time is used rather than distance as travel time can be equated to a variety of different distances based on 1) mode of transportation being ground, helicopter, or fixed wing air ambulance and 2) traffic and weather conditions.
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These diagrams are generated using a multistep process. First, the travel time between the primary and comprehensive stroke centre is plotted as a straight vertical line using an established scale where a certain number of pixels is equated to an increment of travel time (ex. 10 pixels = 1 minute). Second, concentric circles representing 5 minute increments of travel time are drawn around the primary stroke centre. Of note: typically, the diagrams are generated such that the largest increment of travel time to the primary stroke centre is equal to the travel time between the primary and comprehensive stroke centres although any portions of the concentric circles which cross the half way point between the primary and comprehensive stroke centres are not displayed (see Figure 2).

![Diagram](image)

**Figure 2. The basic set up of a two-dimensional temporospatial diagram.** Both the primary and comprehensive stroke centres are plotted on the temporospatial plane with 5 minute increments of travel time to the primary stroke centre plotted as concentric circles surrounding the primary stroke centre.

Utilizing a specified set of treatment time parameters (door to needle, door in door out, and door to puncture) and pre-hospital time parameters (onset to first medical
contact, ambulance response time, time spent on scene with patient) the probability of good outcome in the mothership scenario is calculated and graphed against the travel time to the comprehensive stroke centre. This is restricted to plausible travel time values in consideration of the relative location of the primary stroke centre to the comprehensive stroke centre. For example, given the assumption that the primary stroke centre is always the closest centre to the patient, if the travel time from the primary stroke centre to the comprehensive stroke centre is 120-minutes the travel times from the patient to the comprehensive stroke centre must be greater than 60-minutes (otherwise the closest centre could the comprehensive stroke centre). Then the probability of good outcome in the drip and ship scenario is calculated using the same treatment time parameters for a specified travel time from the patient to the primary stroke centre (ex. 45 minutes) (Figure 3 – Panel A). Note that the domain of this function must be restricted to plausible travel times in relation to the travel time between the primary and comprehensive stroke centres. In this example, the domain of this function (the travel time to the comprehensive stroke centre) is restricted to values between 75 and 165 minutes as in relation to a comprehensive stroke centre which is 120 minutes from the primary stroke centre if the patient is 45 minutes from the primary stroke centre the closest they could be to the comprehensive stroke centre is 75 minutes away and the furthest they could be is 165 minutes.

Here we can see that if the patient is 45 minutes away from the primary stroke centre both drip and ship and mothership predict equivalent probabilities of good outcome if the patient’s travel time to the comprehensive stroke centre is ~139.4 minutes. If the patient’s travel time to the comprehensive stroke centre is further than this
threshold drip and ship predicts best outcomes but if it is less than this threshold mothership predicts best outcomes. In two-dimensional space, there are two different places that a patient could be simultaneously 45 minutes from the primary stroke centre and 139.4 minutes from the comprehensive stroke centre and this is marked on the diagram (Figure 3 – Panel B).
Figure 3. Generation of 2-Dimensional Temporospatial Diagrams – 2.
Panel A displays the probability of good outcome for drip and ship (orange) and mothership (blue) scenarios in a system where the primary and comprehensive stroke
centres are 120-minutes travel time apart. The x-axis is the travel time from the patient to the comprehensive stroke centre. The domain for the mothership function is restricted to values greater than 60 minutes as in this example if the patient was less than 60 minutes travel time from the comprehensive stroke centre this would be the closest centre to them and a transport decision would not need to be made. In this specific example, the patient is 45 minutes travel time from the primary stroke centre. As such the domain of the drip and ship function is restricted to between 75 and 165 minutes as these are the minimum and maximum travel times the patient could be from the comprehensive stroke centre while simultaneously being 45 minutes from the primary stroke centre. The point of equivalence between drip and ship and mothership is found at ~139.4 minutes from the comprehensive stroke centre. Panel B displays the two places in the temporospatial plane where the patient could simultaneously be 45 minutes from the primary stroke centre and 139.4 minutes from the comprehensive stroke centre.

This process is repeated for all plausible distances that the patient could be from the primary stroke centre and all points of equivalence are marked and then joined. Commonly this forms a parabolic or oval shape (Figure 4 – Panel A). Areas within the parabola or oval are areas where drip and ship predicts best outcomes and are coloured red and areas outside of the parabola or oval are areas where mothership predicts best outcomes and are coloured green (Figure 4 – Panel B).

**Figure 4. Generation of 2-Dimensional Temporospatial Diagrams – 3.**
Panel A displays the parabolic shaped line of equivalence between drip and ship and mothership which is drawn from connecting all possible points of equivalence for all possible combinations of travel times the patient could be from the primary and comprehensive stroke centres. Panel B shows the final two dimensional temporospatial
diagram which is colour coded such that areas inside the line of equivalence are colour coded red signifying that the probability of good outcome is higher using the drip and ship method in these areas and areas outside the line of equivalence are coloured green signifying that the probability of good outcome is highest with mothership transport in these areas.

3.2 The Application of the Conditional Probability Model to a Real Geography

3.2.1 Setting

The conditional probability model describe in section 3.1 was then applied to a real geographic space: the Republic of Ireland. In Ireland (population 4.5M, ~70,000km²), there are approximately 4,500 ischemic strokes every year. Ireland has 25 hospitals that provide 24/7 thrombolysis services. Among these 23 provide only this service. There is one hospital which also provides 24/7 endovascular therapy services (Beaumont Hospital, Dublin – herein referred to as EVT Centre 1). There is a second endovascular centre in development (Cork University Hospital, Cork – herein referred to as EVT Centre 2). The location of these centres is shown in Figure 5.
Figure 5. The Republic of Ireland broken down into 139 regions by postal code with hospital locations shown.
Hospitals shown in white are thrombolysis centres. Hospitals shown in blue are endovascular therapy centres. The endovascular therapy centre in the Northeast is Beaumont Hospital and the endovascular therapy centre in the Southwest is Cork University Hospital. The geographic centre of each postal code region is shown with a black dot.

3.2.2 Patient Data

Data for this analysis was obtained from the Irish National Stroke Register. The National Stroke Register contains clinical data including stroke onset time, hospital arrival time, and time of alteplase administration for ischemic stroke patients. Among the 8,969 ischemic strokes in 2014 and 2015 in Ireland, 6,026 were captured in the register (67%). Only hospitals submitting complete data for >80% of stroke patients are included.
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in the register. Between January 1, 2014 and December 31, 2015 there were 699 ischemic stroke patients (from 22 hospitals) in the National Stroke Register which were treated with thrombolysis. Data from 312 ischemic stroke patients who received EVT at EVT Centre 1 over the same time-period were obtained from a local registry. Among these patients 53% received thrombolysis beforehand. Patients did not receive thrombolysis for a variety of reasons including: unknown time of onset, outside of treatment time window, elevated INR, elevated blood pressure, or recent trauma/surgery.

3.2.3 Analyses

Using the conditional probability modelling method described above the probability of good outcome (mRS 0 – 2 at 90 days) for patients with LVO was modelled for both the drip and ship and mothership transport scenarios. As described above, there were several simplifying assumptions in this model including the following: 1) stroke onset is witnessed, 2) the probability of good outcome given reperfusion for both EVT and alteplase decays with time, the probability of achieving reperfusion with EVT is time invariant and the probability of reperfusion with alteplase decays linearly, 3) all LVOs are treatment eligible, and 4) reperfusion is only achieved through treatment.

The treatment time intervals used for modelling were obtained from two data sources. The median door to needle times for each centre were obtained from the Irish National Stroke Register. For hospitals not included in the registry, the DTN was imputed as the national median. Door to puncture times were obtained from an EVT registry at EVT Centre 1. Patients were stratified into two groups: those who presented directly to
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EVT Centre 1 (mothership) and those who were referred from a thrombolysis centre (drip-and-ship). Median DTP for each group was calculated; it was assumed these times would be similar at EVT Centre 2 once it is fully operational. Treatment time parameters used in the models are shown in Table 5. Treatment times were varied to show the effects of more efficient treatment on transportation options.

Table 5. Treatment Time Parameters Used in Models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Sensitivity Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to Needle Time</td>
<td>Actual median door to needle time. (Ranged from 52 to 137 minutes depending on hospital)</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Door in Door Out Time</td>
<td>Door to Needle Time + 60 minutes.</td>
<td>Door to Needle Time + 30 minutes.</td>
</tr>
<tr>
<td>Door to Arterial Access</td>
<td>100 minutes (mothership)</td>
<td>60 minutes (mothership)</td>
</tr>
<tr>
<td>Access Time</td>
<td>10 minutes (drip and ship)</td>
<td>10 minutes (drip and ship)</td>
</tr>
</tbody>
</table>

3.2.4 Map Generation

Ireland was divided into 139 regions using postal codes. The postal code shape files were imported into ArcGIS 10.3 (Esri, Redlands, CA). Using the Feature-To-Point tool, the geographic centre of each region was identified, mapped, and its global positioning system (GPS) coordinates identified (Figure 6). This GPS point was used to represent its corresponding postal code region. Each thrombolysis and EVT centre was also mapped using GPS coordinates (Figure 5). Using Google’s Distance Matrix Application Programming Interface (Mountain View, CA), the ground transportation time from each region’s central GPS coordinate to the nearest thrombolysis and EVT centres was estimated, as well as the time between each thrombolysis and EVT centre.
Figure 6. A zoom in view of one of the 139 postal code regions in Ireland.
Utilizing the Feature-To-Point tool in ArcGIS the geographic centre of this shape was found and plotted (black dot). The GPS coordinates of this dot were then determined. This process was repeated for all postal code regions.

Once the travel times were calculated the closest hospital (by estimated transport time) to each postal code region was determined. If the closest hospital to the postal code region was an EVT centre the mothership model became the default transport option for this area and drip and ship was not considered. For the rest of the postal code areas, the closest thrombolysis centre (by transport time) was determined and this centre is the one which was always used in drip and ship transport – transport to a further thrombolysis centre was never considered. In scenarios where only EVT centre 1 was operational it was always considered as the hospital EVT would be performed at. In scenarios where EVT centre 2 was also operational the thrombolysis centres closest to this centre (by
transport time) would refer patients to this centre over EVT centre 1 in drip and ship transport and patients in the catchment area of these thrombolysis centres would be transported to EVT centre 2 in mothership transport.

These treatment time variables as well as predicted transport times were entered into the drip-and-ship and mothership models and the model with the greatest probability of good outcome for each region was determined. If these probabilities were within 0.02 of one another, the two transport methods were classified as equivalent. Using the model results a map was generated in ArcGIS 10.3 where each postal code region was color coded to illustrate whether the drip and ship model or mothership model of stroke patient transportation predicted superior, inferior, or similar final stroke outcome. The maps were colour coded using two different colour palettes: green and blue. Areas in green indicated that the EVT centre the patient would be routed to (either as first or second destination) was EVT Centre 1 and areas in blue indicated that the EVT centre the patient would be routed to (either as first or second destination) was EVT Centre 2. The darkest shade of either colour indicated that mothership predicted best outcomes, the lightest shade of either colour indicated that drip and ship predicted best outcomes, and the middle shade indicated equivalence between the two methods. As EVT Centre 2 does not yet perform EVT on a 24/7 basis, scenarios were created both with and without this EVT centre. A total of 16 different scenarios were mapped (Table 6).
Table 6. Modelling Scenarios Generated in the Republic of Ireland

<table>
<thead>
<tr>
<th>Model</th>
<th>Thrombectomy Centre(s)</th>
<th>Door to Needle Time</th>
<th>Door In Door Out Time</th>
<th>Door To Groin Puncture Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(base)</td>
<td>EVT Centre 1</td>
<td>Actual centre median</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>2</td>
<td>EVT Centre 1</td>
<td>30 minutes</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>3</td>
<td>EVT Centre 1</td>
<td>Actual centre median</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>4</td>
<td>EVT Centre 1</td>
<td>Actual centre median</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>5</td>
<td>EVT Centre 1</td>
<td>30 minutes</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>6</td>
<td>EVT Centre 1</td>
<td>Actual centre median</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>7</td>
<td>EVT Centre 1</td>
<td>30 minutes</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>8</td>
<td>EVT Centre 1</td>
<td>30 minutes</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>9</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>Actual centre median</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>10</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>30 minutes</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>11</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>Actual centre median</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>12</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>Actual centre median</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>13</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>30 minutes</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>14</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>Actual centre median</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>15</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>30 minutes</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>16</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>30 minutes</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
</tbody>
</table>

*bold indicates change from base model*
3.3 The Expansion of the Modelling Framework to Include All Patients with Suspected Large Vessel Occlusion

3.3.1 Simplifying Assumptions Made

This is an extension of the modelling framework proposed in Section 3.1. While important assumptions made in the original framework are addressed below there are still several simplifying assumptions which were made in this framework. It is assumed that stroke onset time is known and transport decisions are made after EMS evaluation using a LVO screening tool and that the decision does not change en-route. It is assumed that patients with occlusions within the guideline treatment time window and without medical contraindications to thrombolysis are eligible for alteplase and that patients with LVOs are eligible for EVT. Lastly, because the rate of spontaneous early recovery among patients with LVO is low, it is assumed that patients predicted to have an LVO only achieve reperfusion with treatment. As in the prior iterations from Section 3.1 this model was built by combining conditional probabilities of excellent outcome constructed from clinical trials of stroke treatment and therefore reflects population averages and applies at the population level. In this model, excellent outcome is defined as mRS 0 – 1 at 90 days and we calculate the probability of achieving excellent outcome with a given time from stroke onset to treatment.

3.3.2 Conditional Probabilities Used

Due to the imperfect nature of pre-hospital screening, in addition to patients with LVO being identified, patients without LVO will also be identified (false positives). This includes patients with ischemic stroke without LVO, patients with intracerebral...
hemorrhage, and stroke mimics. Patients with sub-arachnoid hemorrhage or cerebral venous sinus thrombosis are not considered in this study.

In this model, patients with LVO (extra/intra-cranial ICA, M1-MCA, or proximal M2-MCA occlusion) will receive both alteplase and EVT either at the EVT center or in a drip and ship approach. For EVT, the time dependent probability of excellent outcome was derived from the HERMES collaboration time to treatment analysis. For alteplase, the time dependent probability of excellent outcome was derived from an individual patient data meta-analysis (Table 7).

Patients with ICH may eventually require a higher level care however there is currently indeterminate evidence on the efficacy of emergency medical or surgical treatment. By combining the excellent outcome rates from several trials of emergency ICH treatment, the probability of excellent outcome for ICH is estimated to be 0.24 and is assumed to be time invariant (Table 7). As most stroke mimics are not immediately life threatening and do not have time dependent treatment options, the probability of excellent outcome for these patients is considered time invariant (Table 7).
### Table 7. Conditional Probability Values and Data Sources Used in Model

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
<th>Rationale/Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large Vessel Occlusion Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P(\text{mRS 0} - 1</td>
<td>\text{EVT} &amp; \text{OTT} = x) )</td>
<td>0.3394+ (0.00000004x^2 - 0.0002x; ) minimum = 0.129</td>
</tr>
<tr>
<td>( P(\text{mRS 0} - 1</td>
<td>\text{alteplase} &amp; \text{OTT} = x) )</td>
<td>0.2359+ (0.00000002x^2 - 0.0004x; ) minimum = 0.1328</td>
</tr>
<tr>
<td><strong>Non-Large Vessel Occlusion Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P(\text{mRS 0} - 1</td>
<td>\text{alteplase} &amp; \text{OTT} = x) )</td>
<td>0.6343- (0.00000005x^2 - 0.0005x; ) minimum = 0.4622</td>
</tr>
<tr>
<td>Probability</td>
<td>Value</td>
<td>Rationale/Data Source</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Intracerebral Hemorrhage</strong></td>
<td></td>
<td>This was generated by combining the overall excellent outcome rate in several trials of intracerebral hemorrhage treatment. The STICH-II trial in patients with spontaneous ICH of 10-100ml showed early surgery had no benefit over conservative treatment. The FAST trial showed no difference between recombinant factor VII (at two different doses) and placebo. Of importance to this analysis there was also no significant interaction found between treatment effect and time from onset to treatment. The INTERACT2 trial showed no difference between early intensive blood pressure lowering (SBP &lt; 140 mmHg within one hour) and guideline recommended therapy (SBP &lt;180 mmHg) in the primary outcome (death and disability at 90 days), however a favorable shift in the overall distribution of mRS scores at 90 days was found. The greatest benefit was found in patients who were able to achieve the greatest SBP reductions within one hour of randomization, however randomization occurred a median of 3.7 hours after ICH onset thus it remains unknown if this time benefit would persist in the hyperacute window after onset. The INCH trial found no difference between fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) in 90 day clinical outcomes in patients with vitamin K antagonist related hemorrhages. As none of these trials showed emergency treatment to be superior to standard of care this probability is considered time invariant.</td>
</tr>
<tr>
<td>P(mRS 0 – 1)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke Mimics</strong></td>
<td></td>
<td>As most stroke mimics do not have time dependent treatment options, the probability of excellent outcome for these patients was considered to be time invariant and set at 0.90 based on the outcomes of stroke mimic patients in prior studies.</td>
</tr>
<tr>
<td>P(mRS 0 – 1)</td>
<td>0.90</td>
<td></td>
</tr>
</tbody>
</table>
3.3.3 Proportion of Different Patient Diagnoses Used

Three pre-hospital LVO screening tools were modelled in this study. LAMS, a 5-point scale in which higher scores indicate ischemic stroke with LVO; RACE, a 9-point scale in which higher scores indicate ischemic stroke with LVO; and C-STAT, a 3-item scale, originally developed to detect thrombolysis candidates, where scores $\geq 2$ are indicative of LVO. In this study a positive screen for LVO using the LAMS score was a score $\geq 4$, using the RACE scale was a score $\geq 5$, and using the C-STAT scale was a score $\geq 2$. Data for the diagnostic breakdown of patients who screened positive for LVO on these scales were taken from a recent study of 565 consecutive paramedic initiated ‘code strokes’ in Melbourne, Australia. Table 8 shows the diagnostic breakdown for patients who screened positive for LVO using these screening tools.

<table>
<thead>
<tr>
<th>Screening Tool and Score</th>
<th>Proportion LVO</th>
<th>Proportion nLVO</th>
<th>Proportion ICH</th>
<th>Proportion Mimic</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMS $\geq 4$</td>
<td>0.4538</td>
<td>0.1092</td>
<td>0.3445</td>
<td>0.0924</td>
</tr>
<tr>
<td>RACE $\geq 5$</td>
<td>0.5294</td>
<td>0.1176</td>
<td>0.3137</td>
<td>0.0392</td>
</tr>
<tr>
<td>C-STAT $\geq 2$</td>
<td>0.4000</td>
<td>0.1826</td>
<td>0.2957</td>
<td>0.1217</td>
</tr>
</tbody>
</table>

*Unpublished data courtesy of Henry Zhao, MBBS. The prevalence of proximal anterior circulation LVO in this study was 14.5%.36*
3.3.4 Time Parameters Used in Models

For mothership transport, time from onset to treatment is the sum of time from onset to medical contact, ambulance response and time spent on scene, travel to the EVT center, and door-to-needle time (alteplase treatment) or door to groin puncture time (EVT treatment) at the EVT center. For drip-and-ship transport, time from onset to treatment is the sum of time from onset to medical contact, ambulance response and time spent on scene, travel to the thrombolysis center, and door-to-needle time at the thrombolysis center (alteplase treatment), time from thrombolysis administration to departure for the EVT center, travel from the thrombolysis center to the EVT center, and door to groin puncture time at the EVT center (EVT treatment). Three different time scenarios were generated: Scenario A describes an optimized system, Scenario B assumes slow treatment at the thrombolysis center, and Scenario C assumes slow treatment at both centers (Table 9).
Table 9. Time Parameters Used in Analyses

<table>
<thead>
<tr>
<th>Time Parameter</th>
<th>Scenario A</th>
<th>Scenario B</th>
<th>Scenario C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to first medical contact</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Time from first medical contact to ambulance</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>arrival and ambulance scene time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Door to Needle Time (thrombolysis center)</td>
<td>30 minutes</td>
<td>60 minutes</td>
<td>60 minutes</td>
</tr>
<tr>
<td>Door In Door Out Time</td>
<td>Door to Needle + 20 minutes</td>
<td>Door to Needle + 60 minutes</td>
<td>Door to Needle + 60 minutes</td>
</tr>
<tr>
<td>Door to Needle Time (endovascular therapy center)</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>60 minutes</td>
</tr>
<tr>
<td>Door to Groin Puncture Time</td>
<td>60 minutes</td>
<td>60 minutes</td>
<td>90 minutes</td>
</tr>
<tr>
<td>(mothership)</td>
<td>(mothership)</td>
<td>(mothership)</td>
<td>(mothership)</td>
</tr>
<tr>
<td>(drip-and-ship)</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>60 minutes</td>
</tr>
<tr>
<td>(drip-and-ship)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Changes from Scenario A shown in boldface

3.3.5 Visualizations

Using a combination of the three screening tools, three sets of time parameters, and five different travel times between the thrombolysis and EVT centres (10, 30, 60, 90, and 120 minutes) 45 different scenarios were modelled and visualized using two-dimensional temporal-spatial diagrams. These diagrams were created using MATLAB v9.1 in accordance to the procedure described in section 3.1.3. In addition to the procedure described in section 3.1.3 these figures have the addition of an equivalence zone which is any area where |P(mRS 0 – 1|mothership) – P(mRS 0 – 1|drip and ship)| < 0.01. In these areas, the underlying red or green coloring is covered with white stippling. A blue line was also added to the figures, in areas beyond this line if using the mothership transport method patients would arrive at the EVT centre >4.5 hours from stroke onset.
and as such would be ineligible for alteplase treatment. Additionally, rather than just solid colour hues as used in section 3.1.3 in these figures color intensity increases as the probability of achieving excellent outcome increases.

To show the results in a specific geographic context nine models (using all combinations of the three screening tools and three sets of time parameters) were generated and visualized in the state of California, USA. For the purposes of this illustration, data from The Joint Commission Quality Check Stroke Certification program was used as a surrogate for EVT capability. We considered acute stroke ready and advanced primary stroke centers to be thrombolysis centers and advanced comprehensive stroke centers to be EVT centers. Maps were generated using a desktop application developed specifically for this research. Esri’s ArcGIS Software Development Kit was used to access a map of California, USA. A 3 by 3-kilometer grid was overlaid on the state and the GPS coordinates of the center of each grid section were determined. The ground travel times between each of these GPS points and each hospital under optimal driving conditions was determined using Googles Distance Matrix API (Google, Mountain View, USA). These travel times were fed into the conditional probability models and the probability of excellent outcome for each strategy in each grid section was calculated. The grid sections were colour coded in the same manner as the two-dimensional temporal-spatial diagrams including the addition of the stippling to show areas of equivalence and the colour gradation to show the value of the probability of excellent outcome. However, for simplicity the blue line which indicated alteplase eligibility time cut off for the mothership method was not included in the maps. Special
call-out sections for the greater Los Angeles and San Francisco areas were generated to show best modelling options in these dense urban areas.

3.4 Comparison of Models Proposed in Sections 3.1 and 3.3

Several common assumptions were maintained within both of these models including: 1) there is uncertainty regarding which transport and treatment decision to make, 2) there is only one decision making point (at the scene) and this decision is never reneged upon, 3) the model does not apply to found down or stroke on awakening patients, and 4) for patients with LVOs reperfusion is only achieved through treatment (i.e. no spontaneous reperfusion). The two primary differences in the assumptions made between the models proposed in sections 3.1 and 3.3 are listed in Table 10.

Table 10. Differences in Assumptions Made Between Models Proposed in Sections 3.1 and 3.3

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Model from Section 3.1</th>
<th>Model from Section 3.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is known to have a LVO</td>
<td>✓ — This could also be thought of as having a LVO screening tool with a PPV of 1</td>
<td>✗ — Patients were assumed to have a suspected LVO based on a LVO screening tool (ex. Los Angeles Motor Scale, PPV: 0.4536). The PPV of the screening tool was used and the treatment options for other possible diagnoses (nLVO, hemorrhagic stroke, and stroke mimics) were also included in the model.</td>
</tr>
<tr>
<td>All patients with occlusions are eligible for alteplase and all patients with LVOs are eligible for EVT</td>
<td>✓ — The caveat of no obvious contraindications to alteplase being present (Coumadin, recent surgery, and most importantly late time window) was added</td>
<td>✗ —</td>
</tr>
</tbody>
</table>
The reason for addressing assumption one inherent in the model proposed in section 3.1 (that the patient was known to have a LVO) was to generate a model which was more practical for use in real decision making scenarios as LVO cannot be diagnosed without brain imaging which in the vast majority of cases does not occur in the field (unless a mobile stroke unit is in the picture). In keeping with practicality, and going along with the assumption that there is true uncertainty in decision making, we have also added the eligibility caveat that obvious contraindications to alteplase are not present.

As a direct result of these two assumption changes nearly all model components needed to be updated. The change in focus to building a model which would produce usable results in the field also required a shift in focus from modelling based on time from onset to reperfusion to modelling based on time from onset to treatment as future reperfusion status will never be known in the field. Based on data availability the definition of good outcome also needed to be updated from mRS 0 – 2 at 90 days to mRS 0 – 1 at 90 days. A comparison in model components including the reason for the change in model component is provided in Table 11.
### Table 11. Differences in Model Components Between Models Proposed in Sections 3.1 and 3.3

<table>
<thead>
<tr>
<th>Component</th>
<th>Models from Section 3.1</th>
<th>Model from Section 3.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of Good Outcome</td>
<td>mRS 0 – 2 at 90 days</td>
<td>mRS 0 – 1 at 90 days</td>
</tr>
<tr>
<td>Probability of achieving reperfusion</td>
<td>EVT: 0.74 (0.90 used in sensitivity analyses), assumed time invariant</td>
<td>✗ — This model was built from a more practical standpoint and is based on onset to treatment times and no assumptions about achieving reperfusion were made</td>
</tr>
<tr>
<td></td>
<td>Alteplase: 0.18 (early reperfusion within 70 minutes, varied linearly if a full 70 minutes was not available; 0.40 used in sensitivity analyses, also varied linearly)</td>
<td>✗ — This model was built from a more practical standpoint and is based on onset to treatment times and no assumptions about achieving reperfusion were made</td>
</tr>
<tr>
<td>Time of early reperfusion after alteplase administration</td>
<td>70 minutes (varied linearly when travel time did not allow for a full 70 minutes to pass)</td>
<td>✗ — This model was based on onset to treatment times from the HERMES collaboration meta-analysis(^\text{22}) which includes patients who eventually reperfused and patients who did not achieve reperfusion, so separate estimates for patients not achieving reperfusion were not needed.</td>
</tr>
<tr>
<td>Probability of good outcome given no reperfusion</td>
<td>0.30</td>
<td>Decay curves in this model are based on the time from onset to treatment (not reperfusion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EVT: 0.3394+0.00000004x(^2)-0.0002x; minimum value = 0.129</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alteplase in LVO: 0.2359+0.0000002x(^2)-0.0004x; minimum value = 0.1328</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alteplase in non-LVO: 0.6343-0.00000005x(^2)-0.0005x; minimum value = 0.4622</td>
</tr>
<tr>
<td>Decrease in probability of good outcome given successful reperfusion in relation to time</td>
<td>0.75 – 0.0006/minute for EVT and alteplase (where good outcome was defined as mRS 0 – 2 at 90 days)</td>
<td>(where good outcome was defined at mRS 0 – 1 at 90 days)</td>
</tr>
</tbody>
</table>
Finally, due to the shift in focus from modelling based on time from onset to reperfusion to modelling based on time from onset to treatment the first reperfusion after endovascular therapy time component was dropped from the model proposed in section 3.3.
3.5 References


Chapter 3: Methods


Chapter 4: Drip ‘N Ship vs. Direct to Comprehensive Stroke Centre: Conditional Probability Modeling

This chapter is comprised of a commentary originally published in Stroke: Holodinsky JK, Williamson TS, Kamal N, Mayank D, Hill MD, Goyal M. Drip and Ship Versus Direct to Comprehensive Stroke Center: Conditional Probability Modeling. Stroke. 2017;48(1):233-238. This chapter outlines a framework for thinking about pre-hospital stroke transportation, conditional probability modelling. Due to manuscript brevity an expansion of the methods used in this chapter can be found in Chapter 3 Section 3.1.

4.1 Introduction

The outcome of ischemic stroke is related to the volume of brain that is infarcted, and the volume of infarction is directly related to the time to reperfusion. In an anterior circulation, large vessel ischemic stroke 1.9 million neurons are lost every minute. Treatment efficacy is dependent on time to treatment initiation. Acute ischemic stroke is treated medically with the administration of intravenous alteplase. Recent results of several randomized trials established the efficacy of endovascular treatment in ischemic stroke.

The facilities and expertise needed for endovascular procedures are only available at endovascular capable centres (ECC), which are typically tertiary care hospitals. Medical treatment with alteplase is more widely available. This creates two options for pre-hospital destination decision-making for suspected stroke: 1) transport the patient directly to the nearest ECC to receive alteplase and if appropriate, immediate
endovascular therapy even though this might mean bypassing a closer non-ECC, (mothership model); or 2) transport the patient to the nearest nECC to receive alteplase and then transfer the patient to the nearest ECC for endovascular therapy (drip and ship model). There are advantages and disadvantages to each of these options and it is currently unknown which of these options will lead to the highest probability of good outcome for the patient. The RACECAT trial in Barcelona, Spain is planned to directly address this question (NCT02795962). Herein, we propose a methodology for addressing this problem using statistical probability modelling and suggest a candidate model for evaluation.

4.2 Building the Model

4.2.1 Assumptions

We make several assumptions in the development of the prediction models (Table I in online only data supplement). First, these models apply when there is uncertainty regarding which transport and treatment decision to choose. Second, the nECC is the closest treatment centre to the location of stroke occurrence. If an ECC is the closest treatment centre, we assume that the patient should be transported directly to the ECC because all treatment options are available at the ECC. Third, this discussion assumes there is only one decision-making point (at the scene) and that decision is always followed. Fourth, this does not apply to “found down” or stroke-on-awakening patients, as it is not possible to account for the time between stroke onset and first medical contact. Fifth, we assume that the probability of successful reperfusion with alteplase therapy
Chapter 4: Conditional Probability Modelling

varies linearly with time but has an upper limit.\textsuperscript{9,10} We assume that the probability of successful reperfusion with endovascular therapy is time invariant. While, we know that this is untrue, the variation with time is probably small.\textsuperscript{11} Sixth, we assume that all patients with occlusions are eligible for alteplase, and all patients with large vessel occlusion (LVO) are eligible for endovascular therapy. And lastly, we assume that for patients with large vessel occlusions reperfusion is only achieved through treatment, something which is known to be approximately 95\% true in the first 1-2 hours after stroke onset.\textsuperscript{7,12}

4.2.2 Conditional Probabilities

A variety of conditional probabilities are considered (Table II in online only data supplement). We have approached the problem physiologically, considering the probability of achieving reperfusion with each given treatment strategy in combination with the probability of good outcome as a function of time to reperfusion, and including the possibility of good outcome without reperfusion. The components of this model are shown in Table 1.

4.2.3 Time Considerations

The time from stroke onset to treatment initiation is vital.\textsuperscript{2} Figure 1 displays the parameterization of the times involved in transportation and treatment. We assume time A (door-to-needle time) equals 60 minutes and time B (alteplase bolus to departure for ECC time) equals 15 minutes. Time C (door-to-arterial access time) is assumed to be 90
minutes in the mothership scenario and 50 minutes in the drip and ship scenario as treatment times have been shown to be faster at the ECC due to pre-notification in the drip and ship case.\textsuperscript{13}

We assume first reperfusion is achieved 30 minutes into the endovascular procedure. For alteplase the time of reperfusion is harder to define. We define early reperfusion as 70 minutes post treatment initiation as angiography studies have shown that 1.6\% of ICA, 23.9\% of M1, and 38.9\% of M2 occlusions were recanalized at first angiography post alteplase administration (median 70 minutes).\textsuperscript{14} Also, this is a relevant time point when considering inter-facility transportation. When the nECC and ECC are close together (i.e. closer than the duration of the alteplase infusion) we adjust the rate of reperfusion to vary linearly with time (Table III in online only data supplement). A constant 30 minutes has been added to represent the average time from first medical contact to ambulance arrival and ambulance scene time.

\subsection*{4.2.4 Estimating the Conditional Probabilities with Existing Data}

We utilized data from the ESCAPE trial\textsuperscript{7} to estimate the time dependent probability of good outcome given reperfusion. The probability of good outcome given successful reperfusion decreases by 0.0006 for every minute delay.\textsuperscript{1} As the time of reperfusion for patients receiving alteplase is unknown, we assume the same rate of decay applies.

The probability of achieving reperfusion given endovascular therapy was estimated from the ESCAPE trial at 0.74.\textsuperscript{7} The probability of early reperfusion given
alteplase therapy varies by occlusion location. The prevalence of large vessel occlusion with a positive LAMS screen (score of 4-5) is 62% and occlusion locations are estimated at: 28% ICA, 65% M1, and 5% M2. These data are combined with the above early reperfusion proportions to estimate that overall 18% of patients with a proven large vessel occlusion will achieve early reperfusion with intravenous alteplase. In the cases where the time of early reperfusion needed to be adjusted to less than 70 minutes this probability was also adjusted. In pre-clinical studies it has been shown that clot dissolution rates progress linearly in the early treatment phase therefore these probabilities were adjusted linearly (Table III in online only data supplement). The probability of good outcome given no reperfusion was estimated from the ESCAPE trial to be 0.30. The models with these calculated probabilities are shown in Table 1.

4.3 Example Scenarios

Utilizing the above model (base model: Model A), we have created example scenarios where the patient is closer to the nECC than the ECC at stroke onset, with varying times between the nECC and ECC (time Y; 10 (Figure SI), 20 (Figure 2), 30 (Figure 3), 45 (Figure SII), 90 (Figure 4), 120 (Figure 5), and 180 mins (Figure SIII)). Distances are represented as travel times as the crow flies. For real world use the nECC/ECC can be plotted on a map and road network analyses used to create “catchment areas” for the drip and ship and mothership models. As these models are displayed in terms of travel times (and not physical distance) both ground and air transport modalities can be considered.
Model A (base model) shows that the mothership model is superior when the time between the nECC and ECC is between 10 and 30 minutes. The drip and ship model becomes a superior option when the patient is very close to the nECC (or would have to travel past the nECC) and the time between the nECC and ECC is 45 minutes or longer (Panel A in Figures 2-5 and Figures I-III in online only data supplement). These models can be used to show how altering parameters could change decision making (Table IV in online only data supplement). Model B shows the effect of faster treatment times; door to needle times are decreased to 30 minutes and door to arterial access times are decreased to 75 minutes for patients (mothership) and 45 minutes (drip and ship). Model B shows faster systems of care make the drip and ship model a more favourable option when the patient is very close to the nECC or would have to travel past the nECC (Panel B in Figures 2-5 and Figures I-III in online only data supplement).

Models C and D show the effect of more efficacious treatments. In Model C the probability of reperfusion given endovascular therapy is increased to 0.90 (from 0.74). New techniques in endovascular therapy and new catheters may improve technical efficacy. Here the mothership option is always superior unless the distance between the nECC and ECC is 120 minutes or greater (and the patient is very close to the nECC or would have to be transported past the nECC) (Panel C in Figures 2-5 and Figures I-III in online only data supplement). Model D simulates more efficacious medical thrombolytic therapies; initial data suggest that tenecteplase may be more effective than alteplase and alternate approaches are being developed. In this model the probability of early reperfusion given thrombolytic therapy is increased to 0.40 (from 0.18), using the same methodology described above this is adjusted for the shorter times between nECC and
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ECC (Table III in online only data supplement). This model shows the drip and ship method is favourable in nearly all scenarios (Panel D in Figures 2-5 and Figures I-III in online only data supplement). Both Model C and D demonstrate that pre-hospital destination decision-making is highly dependent upon the efficacy of reperfusion treatments. This implies that as treatments incrementally improve the best destination hospital triage systems may have to adapt to new treatment realities.\(^\text{17}\)

4.4 Considering All Patient Diagnoses

This model applies to patients with large vessel ischemic strokes, however pre-hospital health care providers do not have access to imaging making a definitive diagnosis impossible in the field. The Los Angeles Motor Scale (LAMS), a three item tool (scores range from 0 – 5 with higher scores indicating more severe symptoms), is a fast and effective way to identify patients with a probable large vessel ischemic stroke.\(^\text{15}\)

The probability that a patient has a large artery occlusion given they have an ischemic stroke diagnosis and a LAMS score of 4 or 5 is 0.62.\(^\text{15}\) In the FAST-MAG trial, which enrolled suspected stroke patients in the field, among patients with a LAMS score of 4 or 5, 70% had an acute ischemic stroke, 28% had an intracranial hemorrhage (ICH), and 2% were stroke mimics (Jeffrey Saver, personal communication, December 2015). Combining these two estimates if the patient has a LAMS score of 4 or 5 in the field the joint probability of having an acute ischemic stroke, which is a large vessel occlusion is 0.43, and the joint probability for non-large vessel occlusion ischemic stroke is 0.27. The
use of technology such as video conferencing could improve the detection of large vessel ischemic stroke in the field and impact these probabilities.

The drip and ship versus mothership decision may not apply to patients who are not candidates for endovascular therapy (non-large vessel ischemic stroke, ICH, or stroke). Non-large vessel occlusions and stroke mimics make up roughly half of these patients. These patients can be adequately treated at either a nECC or an ECC, so they should be transported to the nearest stroke centre, which under the above assumptions is a nECC. This makes the drip and ship model the most appropriate for stroke mimics and stroke due to small vessel occlusions. Intracranial hemorrhage makes up the other half of these patients and while these patients may require intensive care treatment at a comprehensive stroke centre, there is currently no evidence that emergency treatment within minutes is beneficial.\textsuperscript{18-20} Thus, it remains uncertain if they should be transported directly to an ECC or if they are best initially treated and stabilized at a nECC. If it is assumed that all hemorrhage patients should be transported directly to an ECC the outcome of above models are not affected. However, if it is assumed that hemorrhage patients would benefit from stabilization at a nECC the area where the drip and ship model is more favourable will increase when considering all patients with LAMS 4 – 5.

\subsection*{4.5 Discussion}

These models represent an explicit way of conceptualizing the problem of pre-hospital stroke triage. For real world application there are many other factors to consider. Age, stroke severity, comorbidities, premorbid functional status, and the patient’s wishes
will impact decision-making. Practical considerations such as capacity at the ECC, weather conditions, and redundancy in ambulance systems when an ambulance has to travel outside of its jurisdiction are additionally relevant.

These models assumed an average door to needle time of 60 minutes for all hospitals. This is based on the Get With The Guidelines: Target Stroke Initiative data which reports a the median door to needle time of 67 minutes. However, on the basis of this modeling, it is abundantly clear that the door-to-needle time at the nECC must be reduced to an average of 30 minutes for the drip and ship model to be viable. We have assumed the door to needle time to be the same at the nECC and the ECC, however door to needle times are related to the both volume of ischemic stroke admissions and alteplase utilization. It is highly likely that ECCs will have lower door to needle times than nECCs. In addition, nECCs may be more vulnerable to slow workflow during non-business hours or weekends due to limited staffing. Slower treatment times at the nECC only tilt the scales in favour of the mothership model. Similarly, if the ECC were to have slower treatment times the area where the drip and ship model is more favourable would increase.

In most urban and suburban areas where hospitals are geographically close together, the mothership model is always superior to the drip and ship model when transport times between the nECC and ECC are short. The American Heart Association policy on interactions within stroke systems recommend that EMS not bypass a closer nECC in favour of an ECC if such a diversion would add more than 15-20 minutes of transport time. The results of these models show that these recommendations may be
too conservative. Hence, it is imperative that these data be systematically collected in each jurisdiction and applied locally so that data-driven policy change may occur.

There are many factors that contribute to transportation time besides distance. Other factors such as ambulance response time, ambulance scene time, traffic, weather, and ambulance availability among other things will contribute to transport time. When considering all of these factors the relationship between time and distance may not be linear and as such the concentric time circles shown in Figures 2 – 5 and Figures I – III in online only data supplement may not correspond to concentric distance circles. These models only consider patient outcomes in decision-making. Given the expenses associated with both alteplase and endovascular therapy as well as long transports by ground or helicopter these models should be supplemented with both real-world data and an economic analysis.

Notable limitations include: all probabilities presented were generated from randomized controlled trials, representing a highly selected patient population. Enrolled patients had known vessel occlusions and were deemed good candidates for endovascular therapy using imaging selection. These probabilities do not represent all patients seen in the field by first responders and the probabilities of good outcome, with or without reperfusion, are likely an overestimate. We assumed that all patients with large vessel occlusions are eligible for both alteplase and endovascular therapy. However, patients who have longer transport times may be outside the 4.5-hour alteplase treatment time window by the time they reach an ECC (in the mothership model), this should be considered when transport times are long. Yet, a proportion of patients will be technically ineligible for endovascular therapy due to anatomy or unfavourable imaging profiles.
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Further data on the proportion of patients who become ineligible for endovascular therapy during the onset-to-imaging epoch\textsuperscript{24} are needed. The border zones between the drip and ship and mothership models in Figures 2 – 5 and Figures I – III in online only data supplement are represented as sharp edges, as this is simply a threshold effect where one probability becomes superior to the other. The differences in probabilities very close to this border are small, thus in real world application these boundaries would be gray areas and likely would be highly sensitive to changes in model components.

4.6 Conclusions and Future Directions

These conditional probability models provide a framework for evaluation. Real-world data including interval times, reperfusion rates and patient outcomes are needed to assess model application in a given geographic locale. The models assess the problem of acute stroke triage from a population-based perspective and should be thought of as candidate models for evaluation using real world ischemic stroke patient data. New technology, such as the mobile stroke unit (MSU), consisting of an ambulance equipped with a CT scanner, point of care laboratory, and specialized pre-hospital stroke team, could additionally change these models.\textsuperscript{25-27} This early imaging capability is critical to improving upon screening tests such as the LAMS score which have only moderately good accuracy in identifying large vessel ischemic strokes (81% sensitivity and 89% specificity).\textsuperscript{15} Alteplase can be administered in the MSU while on route to hospital giving patients much faster access to medical treatment. While this is a new, and resource
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intensive, treatment option it does have the potential to greatly streamline the drip and ship treatment option by eliminating the need to stop at a nECC to receive alteplase.
### 4.7 Tables

#### Table 1. Mothership and Drip and Ship Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Conditional Probabilities</th>
<th>Time Considerations</th>
<th>Conditional Probability Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothership</td>
<td>[ P(\text{good outcome}</td>
<td>\text{mothership model}) = P(\text{reperfusion}</td>
<td>\text{EVT}) \cdot P(\text{good outcome}</td>
</tr>
<tr>
<td>Drip and Ship</td>
<td>[ P(\text{good outcome}</td>
<td>\text{drip and ship model}) = P(\text{early reperfusion}</td>
<td>\text{alteplase}) \cdot P(\text{good outcome}</td>
</tr>
</tbody>
</table>

EVT: endovascular therapy
4.8 Figures

**Figure 1. Transportation Time Framework.**
The dashed line represents the mothership model, the solid lines represent the drip and ship model. Time X is the transportation time from the patient to the non-endovascular capable hospital (nECC). Time Y is the transportation time from the nECC to the endovascular capable hospital (ECC). Time Z is the transportation time from the patient to the ECC. Time A is the time from the patient’s arrival at the nECC to the administration of alteplase and time B is the time from alteplase administration to leaving the nECC. Time C is the time from the patient’s arrival at the ECC to the beginning of the endovascular procedure.
### Figure 2. The optimization of the use of the drip and ship vs. mothership models when the endovascular capable centre (ECC) and non-endovascular capable centre (nECC) are 20 minutes apart.

Red indicates regions where the drip and ship approach is more favourable; green indicates regions where the mothership approach is more favourable. Model A assumes a door-to-needle time of 60 minutes, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, $P(\text{reperfusion}|\text{endovascular therapy}) = 0.74$ and $P(\text{early reperfusion}|\text{alteplase}) = 0.18$ (adjusted for short travel times) and shows that the mothership option is most effective. In Model B door-to-needle time is 30 minutes and door to arterial access is 75 minutes (mothership) and 45 minutes (drip and ship). Here the drip and ship model is the most effective strategy if the patient is very close to the nECC or would have to drive past the nECC. Model C assumes $P(\text{reperfusion}|\text{endovascular therapy}) = 0.90$ and shows that the mothership approach is the superior option. Model D assumes a novel intravenous thrombolytic agent where $P(\text{early reperfusion}|\text{thrombolysis}) = 0.40$ (adjusted for shorter travel times) and shows that the drip and ship option is superior.
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Figure 3. The optimization of the use of the drip and ship vs. mothership models when the endovascular capable centre (ECC) and non-endovascular capable centre (nECC) are 30 minutes apart.

Red indicates regions where the drip and ship approach is more favourable; green indicates regions where the mothership approach is more favourable. Model A assumes a door-to-needle time of 60 minutes, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, P(reperfusion|endovascular therapy) = 0.74, and P(early reperfusion|alteplase) = 0.18 (adjusted for short travel times). Model A shows that the mothership model is the most effective strategy. In Model B door-to-needle time is 30 minutes and door to arterial access is 75 minutes (mothership) and 45 minutes (drip and ship). Here the drip and ship model now becomes an effective when the patient is very close to the nECC or would have to drive past the nECC. Model C assumes P(reperfusion|endovascular therapy) = 0.90 and shows that the mothership approach is always the superior option. Model D assumes a novel intravenous thrombolytic agent with P(early reperfusion|thrombolysis) = 0.40 (adjusted for shorter travel times) and shows that the drip and ship approach is superior in almost all scenarios.
Figure 4. The optimization of the use of the drip and ship vs. mothership models when the endovascular capable centre (ECC) and non-endovascular capable centre (nECC) are 90 minutes apart.

Red indicates regions where the drip and ship approach is more favourable; green indicates regions where the mothership approach results is more favourable. Model A assumes a door-to-needle time of 60 minutes, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, $P(\text{reperfusion}|\text{endovascular therapy}) = 0.74$, and $P(\text{early reperfusion}|\text{alteplase}) = 0.18$. Model A shows that the drip and ship model is the most effective option if the patient is very close to the nECC or would have to drive past the nECC. In Model B door-to-needle time is 30 minutes and door to arterial access is 75 minutes (mothership) and 45 minutes (drip and ship). Here the area where the drip and ship model is the most effective option has increased. Model C assumes $P(\text{reperfusion}|\text{endovascular therapy})$ and shows that the mothership approach is always the superior option. Model D assumes a novel intravenous thrombolytic agent with $P(\text{early reperfusion}|\text{thrombolysis}) = 0.40$ and shows that the drip and ship approach is superior in almost all scenarios.
Figure 5. The optimization of the use of the drip and ship vs. mothership models when the endovascular capable centre (ECC) and non-endovascular capable centre (nECC) are 120 minutes apart.

Red indicates regions where the drip and ship approach is more favourable; green indicates regions where the mothership approach is more favourable. Model A assumes a door-to-needle time of 60 minutes, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, $P(\text{reperfusion|endovascular therapy}) = 0.74$, and $P(\text{early reperfusion|alteplase}) = 0.18$. Model A shows that the drip and ship model is the most effective option when the patient is close to the nECC or would have to travel past the nECC. In Model B door-to-needle time is 30 minutes and door to arterial access is 75 minutes (mothership) and 45 minutes (drip and ship). Here the area where the drip and ship model is the most effective option has increased. Model C assumes $P(\text{reperfusion|endovascular therapy}) = 0.90$ and shows that the mothership model is always the superior option. Model D assumes a novel intravenous thrombolytic agent with $P(\text{early reperfusion|thrombolysis}) = 0.40$ and shows that the drip and ship approach is superior in almost all scenarios.
4.9 References


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### 4.10 Supplemental Tables

#### Table I. Model Assumptions

<table>
<thead>
<tr>
<th>Model Assumption</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. There is true uncertainty regarding which transport and treatment decision to make</td>
<td>This model would not be needed in cases where the most favourable treatment option was certain.</td>
</tr>
<tr>
<td>2. The nECC is the closest treatment centre to the patient</td>
<td>If the ECC was the closest treatment centre the patient should be transported directly to the ECC as all treatment options are available here.</td>
</tr>
<tr>
<td>3. There is only one decision making point (at the scene) and this decision is never reneged upon</td>
<td>While we acknowledge bad weather, traffic, road closures, and hospital capacity may cause an ambulance to divert to another centre on route this cannot be accounted for in these models at this time.</td>
</tr>
<tr>
<td>4. This model does not apply to “found down” or stroke-on-awakening patients</td>
<td>It is impossible to account for the time between stroke onset and first medical contact if the stroke is not witnessed.</td>
</tr>
<tr>
<td>5. Relationship between probability of successful reperfusion and time</td>
<td>c. In both in vitro and in vivo studies clot dissolution rates with alteplase have been shown to progress linearly in the initial treatment phase(^1,2)</td>
</tr>
<tr>
<td>a. The probability of successful reperfusion with alteplase therapy varies linearly with time, but is capped at a maximum rate</td>
<td>d. While, we know that this is not strictly true, the variation with time is probably relatively small(^3) and without robust data on the change in effectiveness over time we cannot account for this variation.</td>
</tr>
<tr>
<td>b. The probability of successful reperfusion with endovascular therapy is time invariant</td>
<td></td>
</tr>
<tr>
<td>6. All patients with occlusions are eligible for alteplase and all patients with large vessel occlusions are eligible for endovascular therapy</td>
<td>This is an extension of Assumption 1, in order for there to be true uncertainty patients must be eligible for either treatment option.</td>
</tr>
<tr>
<td>7. For patients with large vessel occlusions reperfusion is only achieved through treatment (i.e. no spontaneous reperfusion)</td>
<td>This is known to be true in 95% of cases in the first 1-2 hours after stroke onset.(^4,5)</td>
</tr>
</tbody>
</table>

nECC: non-endovascular capable centre (primary stroke centre); ECC: endovascular capable centre (comprehensive stroke centre)
Table II. Model Baseline and Sensitivity Analysis Values

<table>
<thead>
<tr>
<th>Model Component</th>
<th>Base Values</th>
<th>Values Used in Sensitivity Analyses</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| 3. Door to Needle Time | 60 minutes        | 30 minutes                          | 60 minutes was chosen as the base case for door to needle time as it reflective of the median door to needle time found in the Target Stroke initiative (median = 67 minutes, 41% DTN less than 60 mins)\(^6\) as well as the upper quartiles in the other studies.\(^7\)\(^-\)\(^9\)
|                        |                   |                                     | However, as we move forward with ischemic stroke treatment door to needle times of 30 minutes should be the standard.\(^10\) Median door to needle times of close to or below 30 minutes have been reported in several centres around the world.\(^7\)\(^-\)\(^9\) |
| 4. Door in Door Out    | 75 minutes (60 min DTN) | 45 minutes (30 min DTN)            | Assuming a door-to-needle time of 60 minutes, a door-in-door-out time of 75 minutes is estimated to be an appropriate target. This is the target time for the QuICR project in Alberta, and this the target time for STEMI care. |
| 5. Door to Arterial Access | 90 mins (mothership) | 75 mins (mothership)               | Among a group of patients who had a median door to needle time of 60 minutes who presented at the ECC in ESCAPE the median door to arterial access time was approximately 90 minutes.\(^4\) This was adjusted to be 45% faster in the drip and ship model as it has been shown that treatment times are faster at the ECC when the patient was first seen at the nECC.\(^4\)  
|                        | 50 mins (drip and ship) | 45 mins (drip and ship)           | In sensitivity analyses when door to needle times are decreased to 30 minutes, door to arterial access times are also adjusted. Among a group of patients who had a median door to needle time of 30 minutes who presented at the ECC in ESCAPE the median door to arterial access time was approximately 75 minutes.\(^4\) Similarly, this was adjusted to be faster in the drip and ship model. |
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#### Model Component

<table>
<thead>
<tr>
<th>Model Component</th>
<th>Base Values</th>
<th>Values Used in Sensitivity Analyses</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. First reperfusion after endovascular therapy</td>
<td>30 minutes</td>
<td>N/A</td>
<td>This is representative of the median time from groin puncture to first reperfusion in both ESCAPE and SWIFT PRIME.(^{4,11})</td>
</tr>
<tr>
<td><strong>7. Early reperfusion after alteplase administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Time B + Y ≥ 70 minutes</td>
<td>c. 70 mins</td>
<td>a. N/A</td>
<td>For the purposes of this model we define early reperfusion as 70 minutes post treatment initiation for two reasons. First, it has been shown in angiography studies that 1.6% of ICA, 23.9% of M1, and 38.9% of M2 occlusions were recanalized at first angiography post alteplase administration (median 70 minutes).(^{12}) Second, this is a relevant time point when considering inter-facility transportation times.</td>
</tr>
<tr>
<td>b. Time B + Y &lt; 70 minutes</td>
<td>d. Time B+Y</td>
<td>b. N/A</td>
<td></td>
</tr>
<tr>
<td>8. Time from first medical contact to ambulance arrival and ambulance scene time</td>
<td>30 minutes</td>
<td>N/A</td>
<td>There are representative times from Canadian cities.</td>
</tr>
<tr>
<td>Model Component</td>
<td>Base Values</td>
<td>Values Used in Sensitivity Analyses</td>
<td>Rationale</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------</td>
<td>-------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>9. Decrease in probability of successful reperfusion in relation to time to reperfusion</td>
<td>0.0006</td>
<td>N/A</td>
<td>Endovascular therapy: Estimate from the ESCAPE trial and HERMES data collaboration.(^{13,14}) Alteplase: As the exact time of reperfusion for patients receiving alteplase is not known, we assume the same rate of decay for alteplase-treated patients.</td>
</tr>
<tr>
<td>10. (P(\text{reperfusion</td>
<td>endovascular therapy}))</td>
<td>0.74</td>
<td>0.90</td>
</tr>
<tr>
<td>11. (P(\text{early reperfusion</td>
<td>alteplase}))</td>
<td>c. 0.18&lt;br&gt;d. 0.18[(B+Y)/70]</td>
<td>c. 0.40&lt;br&gt;d. 0.40[(B+Y)/70]</td>
</tr>
<tr>
<td>12. (P(\text{good outcome</td>
<td>no reperfusion}))</td>
<td>0.30</td>
<td>N/A</td>
</tr>
</tbody>
</table>
nECC: non-endovascular capable centre; ECC: endovascular capable centre; DTN: door to needle time; ICA = internal carotid artery; M1 = M1 segment of the middle cerebral artery; M2 = M2 segment of the middle cerebral artery; STEMI = ST-elevation myocardial infarction; LAMS = Los Angeles Motor Scale; time B: time from alteplase bolus to leaving the nECC; time Y: travel time from nECC to ECC
Table III. Alternate Values for Early Reperfusion Given Alteplase in Models A and D

| Time Y | Time of Early Reperfusion | Model A: P(early reperfusion|alteplase) | Model D: P(early reperfusion|thrombolysis) |
|--------|---------------------------|------------------------------------------|-------------------------------------------|
| 10     | 25 minutes                | 0.06                                     | 0.14                                      |
| 20     | 35 minutes                | 0.09                                     | 0.20                                      |
| 30     | 45 minutes                | 0.11                                     | 0.26                                      |
| 45     | 60 minutes                | 0.15                                     | 0.34                                      |
| ≥90    | 70 minutes                | 0.18                                     | 0.40                                      |

Table IV. Mothership and Drip and Ship Models with Baseline and Sensitivity Analysis Values

<table>
<thead>
<tr>
<th>Model</th>
<th>Mothership</th>
<th>Drip and Ship</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (base model)</td>
<td>( P(\text{good outcome}</td>
<td>\text{mothership model}) = 0.74 \cdot [0.75-0.0006(30+Z+90+30)] + 0.26 \cdot 0.30 )</td>
</tr>
<tr>
<td>B</td>
<td>( P(\text{good outcome}</td>
<td>\text{mothership model}) = 0.74 \cdot [0.75-0.0006(30+Z+75+30)] + 0.26 \cdot 0.30 )</td>
</tr>
<tr>
<td>C</td>
<td>( P(\text{good outcome}</td>
<td>\text{mothership model}) = 0.90 \cdot [0.75-0.0006(30+Z+90+30)] + 0.10 \cdot 0.30 )</td>
</tr>
<tr>
<td>D</td>
<td>Unchanged from Model A</td>
<td>( P(\text{good outcome}</td>
</tr>
</tbody>
</table>

Changes from Model A shown in bold face
4.11 Supplemental Figures

<table>
<thead>
<tr>
<th>Model A</th>
<th>Model B</th>
<th>Model C</th>
<th>Model D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Model with 60 minute door to needle time and 90 minute (mothership) or 50 minute (drip and ship) door to arterial access time</td>
<td>Model B Base Model adjusted to decrease door to needle time to 30 minutes and door to arterial access time to 75 minutes (mothership) and 45 minutes (drip and ship)</td>
<td>Model C Base Model adjusted to show the effect of more efficacious (90% vs. 74% reperfusion) endovascular therapy</td>
<td>Model D Base Model adjusted to show the effect of more efficacious (40% vs. 18% early reperfusion) thrombolytics</td>
</tr>
</tbody>
</table>

**Figure I. Hospitals are 10 minutes apart**

The effect of door to needle times and increasing reperfusion rates on the optimization of the use of the drip and ship vs. mothership models of stroke triage and treatment when the endovascular capable centre and non-endovascular capable centre are 10 minutes apart is shown. Red indicates regions where the drip and ship approach is predicted to result in the highest probability of good outcome; green indicates regions where the direct to mothership approach results in the highest probability of good outcome. Model A assumes a door-to-needle time of 60, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, P(reperfusion|endovascular therapy) = 0.74 and P(early reperfusion (within 70 minutes of bolus)|alteplase) = 0.18, this is adjusted linearly for shorter travel times where there is not 70 minutes of time for alteplase to take effect and shows that the mothership option is the most effective strategy. In Model B the door-to-needle time is reduced to 30 minutes and door to arterial access times are reduced to 75 minutes and 45 minutes for mothership and drip and ship, respectively. This model shows the drip and ship model is the most effective strategy if the patient is very close to the nECC or would have to drive past the nECC. Model C assumes an increased probability of complete reperfusion with endovascular therapy of 90% (compared to 74%) and shows that the mothership approach is the superior option. Model D assumes a novel intravenous thrombolytic agent with 40% recanalization within 70 minutes (compared to the observed 18% for M1-MCA and ICA occlusions), in similar fashion this is adjusted linearly for shorter travel times, and shows that the drip and ship option is the most relevant approach in almost all scenarios.
Figure II. Hospitals are 45 minutes apart

The effect of door to needle times and increasing reperfusion rates on the optimization of the use of the drip and ship vs. mothership models of stroke triage and treatment when the endovascular capable centre and non-endovascular capable centre are 45 minutes apart is shown. Red indicates regions where the drip and ship approach is predicted to result in the highest probability of good outcome; green indicates regions where the direct to mothership approach results in the highest probability of good outcome. Model A assumes a door-to-needle time of 60, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, P(reperfusion|endovascular therapy) = 0.74 and P(early reperfusion (within 70 minutes of bolus)alteplase) = 0.18, this is adjusted linearly for shorter travel times where there is not 70 minutes of time for alteplase to take effect and shows that the drip and ship option is the most effective strategy if the patient is very close to the nECC or would have to travel past the nECC to get to the ECC. In Model B the door-to-needle time is reduced to 30 minutes and door to arterial access times are reduced to 75 minutes and 45 minutes for mothership and drip and ship, respectively. This model shows the area where drip and ship model is the most effective strategy has increased. Model C assumes an increased probability of complete reperfusion with endovascular therapy of 90% (compared to 74%) and shows that the mothership approach is the superior option. Model D assumes a novel intravenous thrombolytic agent with 40% recanalization within 70 minutes (compared to the observed 18% for M1-MCA and ICA occlusions), in similar fashion this is adjusted linearly for shorter travel times, and shows that the drip and ship option is the most relevant approach in almost all scenarios.
Figure III. Hospitals are 180 minutes apart

The effect of door to needle times and increasing reperfusion rates on the optimization of the use of the drip and ship vs. mothership models of stroke triage and treatment when the endovascular capable centre and non-endovascular capable centre are 180 minutes apart is shown. Red indicates regions where the drip and ship approach is predicted to result in the highest probability of good outcome; green indicates regions where the direct to mothership approach results in the highest probability of good outcome. Model A assumes a door-to-needle time of 60, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, $P(\text{reperfusion}|\text{endovascular therapy}) = 0.74$ and $P(\text{early reperfusion (within 70 minutes of bolus)|alteplase}) = 0.18$, this is adjusted linearly for shorter travel times where there is not 70 minutes of time for alteplase to take effect and shows that the drip and ship option is the most effective strategy when the patient is very close to the nECC or would have to travel past the nECC to get to the ECC. In Model B the door-to-needle time is reduced to 30 minutes and door to arterial access times are reduced to 75 minutes and 45 minutes for mothership and drip and ship, respectively. In this model the area where the drip and ship model is the most effective strategy has increased. Model C assumes an increased probability of complete reperfusion with endovascular therapy of 90% (compared to 74%) and shows that the mothership approach is the superior option in more areas than in Model A or B. Model D assumes a novel intravenous thrombolytic agent with 40% recanalization within 70 minutes (compared to the observed 18% for M1-MCA and ICA occlusions), in similar fashion this is adjusted linearly for shorter travel times, and shows that the drip and ship option is the most relevant approach in almost all scenarios.
4.12 Supplemental References:


Chapter 4: Conditional Probability Modelling


Chapter 5  Drip ‘N Ship Versus Direct to Endovascular Thrombectomy: The Impact of Treatment Times on Transport Decision Making

This chapter is comprised of an original research article originally published in European Stroke Journal: Holodinsky JK, Patel AB, Thornton J, Kamal N, Jewett LR, Kelly PJ, Murphy S, Collins R, Walsh T, Cronin S, Power S, Brennan P, O’Hare A, McCabe DJH, Moynihan B, Looby S, Wyse G, McCormack J, Marsden P, Harbison J, Hill MD, Williams D. Drip ‘N Ship Versus Direct to Endovascular Thrombectomy: The Impact of Treatment Times on Transport Decision Making. European Stroke Journal. 2018; 3(2):126-135. doi:10.1177/2396987318759362. In the previous chapter a conditional probability model which determines the transport method (drip and ship or mothership) which predicts the best outcomes for patients with ischemic stroke due to LVO was outlined. In this manuscript, this methodology is applied to the stroke system in the Republic of Ireland using actual treatment times representative of the workflow in the Irish stroke system. Due to manuscript brevity an expansion of the methods outlined here can be found in Chapter 3 Section 3.2.

5.1 Abstract

Introduction: In ischemic stroke, fast reperfusion is essential for disability free survival. It is unknown if bypassing thrombolysis centres in favor of endovascular thrombectomy (mothership) outweighs transport to the nearest thrombolysis centre for alteplase and then transfer for endovascular thrombectomy (drip-and-ship). We use conditional probability
modelling to determine the impact of treatment times on transport decision-making for acute ischemic stroke.

**Materials and Methods:** Probability of good outcome was modelled using a previously published framework, data from the Irish National Stroke Register, and an endovascular thrombectomy registry at a tertiary referral centre in Ireland. Ireland was divided into 139 regions, transport times between each region and hospital were estimated using Google’s Distance Matrix API. Results were mapped using ArcGIS 10.3.

**Results:** Using current treatment times, drip-and-ship rarely predicts best outcomes. However, if door to needle times are reduced to 30 minutes drip-and-ship becomes more favorable; even more so if turnaround time (time from thrombolysis to departure for the endovascular thrombectomy centre) is also reduced. Reducing door to groin puncture times predicts better outcomes with the mothership model.

**Discussion:** This is the first case study modelling pre-hospital transport for ischemic stroke utilizing real treatment times in a defined geographic area. A moderate improvement in treatment times results in significant predicted changes to the optimization of a national acute stroke patient transport strategy.

**Conclusions:** Modelling patient transport for system level planning is sensitive to treatment times at both thrombolysis and thrombectomy centres and has important implications for the future planning of thrombectomy services.
5.2 Introduction

In ischemic stroke care, fast reperfusion is essential to improve disability free survival.¹⁻⁵ Endovascular thrombectomy (EVT) is an extremely effective therapy with early reperfusion rates of ~75% and a number needed to treat of only 7 to prevent one poor outcome (mRS 2 – 6 at 90 days).⁶ However, this therapy is only applicable to ischemic stroke patients with large vessel occlusions. Medical thrombolysis with alteplase is more widely available but is less effective in patients with large vessel occlusions; only achieving early reperfusion rates of 8-35%.⁷⁻⁹

For both treatments, time is critical. The probability of achieving good outcome with EVT decreases with time. For every 9-minute delay in onset to reperfusion, 1 out of every 100 patients will have greater functional disability at 90 days.¹⁰ The equipment and expertise needed restricts this procedure to large tertiary hospitals, typically situated in urban areas. For patients outside the catchment area of EVT centres it is unknown if delayed, but more effective, reperfusion with EVT outweighs the benefits of early thrombolysis. In the prehospital scenario, this manifests as an option between bypassing a thrombolysis centre in favor of EVT at an EVT centre (mothership) or direct transport to the thrombolysis centre for thrombolysis followed by transfer for EVT (drip-and-ship).

The natural extension of more widely available thrombolysis usage and the introduction of EVT has led to a re-evaluation of the drip-and-ship model.¹¹⁻¹³ Adding complexity, only a small proportion of suspected stroke patients have large vessel occlusions (LVO) and are eligible for EVT. Thus, adopting a mothership method for all stroke patients may result in unnecessary and long transports for patients that will never
Chapter 5: Case Study In Ireland

undergo EVT. However, for the patients with LVO, only 8-35% achieve recanalization with thrombolysis meaning that transport to a thrombolysis centre may be futile. A retrospective analysis of drip-and-ship versus mothership in Korea found no difference in recanalization or 90-day outcome between the two transportation strategies. However, this was performed prior to publication of positive trials of EVT, the number of patients was small (N=105, of whom 88 received EVT), and the difference in onset to arterial access between the groups was relatively short (219 vs 300 minutes) suggesting that the thrombolysis and EVT centres were likely close in proximity. Bypassing thrombolysis centres (mothership) for patients with suspected LVO led to improved outcomes in a recent Danish study.

Recently, using conditional probability modelling techniques the drip-and-ship and mothership transport options (Figure 1) have been explored to help plan future EVT services. In this analysis we apply one of these frameworks in conjunction with both real and optimized transport and treatment times to the Irish Healthcare system to explore patient transport in a geographically defined area and assess how changes in treatment times impact transport decisions.

5.3 Methods

5.3.1 Setting

In Ireland (population 4.5M, ~70,000km²), there are approximately 4,500 ischemic strokes per annum. There are 25 hospitals that provide 24/7 thrombolysis services; one of which (Beaumont Hospital, herein referred to as EVT Centre 1) is a
tertiary neurosurgical centre in Dublin equipped to provide EVT, a second EVT centre is currently in development (Cork University Hospital, herein referred to as EVT Centre 2).

### 5.3.2 Patients

Data from 699 ischemic stroke patients (from 22 hospitals) treated with thrombolysis between January 1, 2014 and December 31, 2015 were obtained from the Irish National Stroke Register. The National Stroke Register contains clinical data including stroke onset time, hospital arrival time, and time of alteplase administration. Among the 8969 ischemic strokes in 2014 and 2015, 6026 were captured in the register (67%). Only hospitals submitting complete data for >80% of stroke patients are included in the register. Data from 312 ischemic stroke patients who had EVT at EVT Centre 1 over the same time-period were obtained from a local registry. Among these patients 53% received thrombolysis beforehand – the primary reasons for not receiving thrombolysis were unknown time of onset, outside of treatment time window, elevated INR, elevated blood pressure, or recent trauma/surgery.

### 5.3.3 Analyses

Probability of good outcome for patients with LVO was modelled for each transport scenario using a pre-defined strategy. These models approach this problem physiologically and are based on the probability of achieving reperfusion, the time from onset to reperfusion, and the probability of achieving a good outcome (mRS 0 – 2 at 90 days) given reperfusion at a certain time from symptom onset. See Supplemental Data
File for complete modelling methods. There are several simplifying assumptions in this model including the following: 1) stroke onset is witnessed, 2) the probability of good outcome given reperfusion for both EVT and alteplase decays with time, the probability of achieving reperfusion with EVT is time invariant and the probability of reperfusion with alteplase decays linearly, 3) all LVOs are treatment eligible, and 4) reperfusion is only achieved through treatment.\textsuperscript{17}

Time intervals used for modelling were obtained from two data sources. The median door to needle (DTN) times for each centre were obtained from the Irish National Stroke Register. For hospitals not included in the registry, the DTN was imputed as the national median. Door to puncture (DTP) times were obtained from an EVT registry at EVT Centre 1. Patients were stratified into two groups: those who presented directly to EVT Centre 1 (mothership) and those who were referred from a thrombolysis centre (drip-and-ship). Median DTP for each group was calculated; it was assumed these times would be similar at EVT Centre 2 once it is fully operational. A detailed list of model variables, definitions, values, and data sources is listed in Table I in the Supplemental Data File.

Ireland was divided into 139 regions using postal codes. The postal code shape files were imported into ArcGIS 10.3 (Esri, Redlands, CA). Using the Feature To Point tool, the geographic centre of each region was identified and mapped. Each thrombolysis and EVT centre was mapped using GPS coordinates. Using Google’s Distance Matrix Application Programming Interface (Mountain View, CA), the ground transportation time from each region’s centre to the nearest thrombolysis and EVT centres was estimated, as well as the time between each thrombolysis and EVT centre.
These variables were entered into the drip-and-ship and mothership models and the model with the greatest probability of good outcome for each region was determined. If these probabilities were within 0.02 of one another, the two transport methods were classified as equivalent. As EVT Centre 2 does not yet perform EVT on a 24/7 basis, scenarios were created both with and without this EVT centre. The impact of faster treatment times was also explored.

The output of the models is shown graphically using color coded maps to illustrate whether the drip ‘n ship model or mothership model of stroke patient transportation predicted superior, inferior or similar final stroke outcome.

5.4 Results

5.4.1 Data Summary

Over the two-year study period there were 699 patients treated with alteplase and 312 treated with EVT (258 using the drip-and-ship method), with a median DTN time of 75 minutes and a median DTP time of 100 minutes (mothership) and 10 minutes (drip-and-ship). Sixteen different scenarios were generated using combinations of EVT availability and treatment times (Table II in the Supplemental Data File.)

5.4.2 Model Application

Utilizing current treatment times and one EVT centre, for most regions, the two strategies are approximately equivalent. There are only a few regions where the drip-
and-ship strategy is the best choice (Figure 2 Panel A). In areas where the patient’s closest thrombolysis centre is in the opposite direction of the EVT centre, mothership is the best option, because the drip-and-ship model involves driving the same road twice and extra drive time is therefore avoided.

Figure 2 Panel B shows the same model with the addition of EVT Centre 2 in the southwest corner of the country. The 6 thrombolysis centres closest to this centre have been designated as its referral sites which serve approximately 27% of Ireland’s population. In this region, with current treatment times over a relatively short distance, the drip-and-ship approach never provides the best probability of good outcome and for the majority of regions the mothership approach is the preferred transport strategy.

### 5.4.3 Impact of Reducing DTN

Holding other treatment times at baseline values, if DTN time is reduced to a median of 30 minutes at all hospitals, the drip-and-ship model almost always provides the greatest probability of good outcome (Figure 3 Panel A). The mothership model is predicted to be better only in regions close to an EVT centre. In a few regions, further away from the EVT centre in which travel to the closest thrombolysis centre would require moving away from the EVT centre, both transport approaches result in equivalent outcomes.

With the addition of EVT Centre 2 the mothership model results in better predicted outcomes in regions close to this centre and in two regions where the closest
thrombolysis centre requires travel away from EVT Centre 2 (Figure 3 Panel B). For the majority of regions, the drip-and-ship approach predicts the best patient outcomes.

5.4.4 Impact of Reducing Door-In-Door-Out Time

Door-in-door-out (DIDO) time is comprised of both DTN time and the time from thrombolysis administration to departure for the EVT centre (turnaround time). Reducing DIDO time by reducing the turnaround time to 30 minutes, while holding other times at baseline values, has a significant impact on transport decisions. The area where the drip-and-ship model provides the best probability of good outcome for the patient increases (Figure 4 Panel A). This impact is also seen when both EVT centres are operational (Figure 4 Panel B).

Figure I in the Supplemental Data File shows the impact of reducing DIDO time to 60 minutes overall (while holding DTP times at baseline values) by both reducing DTN to 30 minutes and reducing the turnaround time to 30 minutes. This has a profound impact on transport decision making and the drip-and-ship model predicts the best outcome for the patient in almost all regions of the country.

5.4.5 Impact of Reducing Door to Groin Puncture Time

Holding all other treatment times at baseline values, transport decision making is highly sensitive to changes in DTP time at the EVT centre. Door to groin puncture times at EVT Centre 1 in the drip-and-ship scenario are very fast (median = 10 minutes). This can be attributed to the ability to pre-alert the neuroradiology team while the patient is
being transported, the decision to forgo re-imaging on arrival (the size and population
distribution of Ireland makes most transfers times very short thus baseline imaging at the
referring hospital is still medically appropriate), and the patient being brought directly to
the neuro-angiography suite by EMS on arrival. However, for patients who present
directly to EVT Centre 1, DTP time was substantially longer (median = 100 minutes).
Figure 5 illustrates the impact of decreasing DTP time to 60 minutes in the mothership
scenario (DTP time in drip-and-ship remains unchanged) holding other times at baseline
values. Here the drip-and-ship scenario never provides the best probability of good
outcome for the patient, even when there is only one fully operational EVT centre serving
the entire country.

Figure II in the Supplemental Data File shows the impact of simultaneously
reducing DTN and DTP times, while holding the turnaround time at baseline value. In
contrast to the model showing only reduced DTN time, here the drip-and-ship model is
rarely favorable when there is only one EVT referral centre and is never favorable in the
catchment area of EVT Centre 2. A similar result is seen when simultaneously reducing
DTP time and turnaround time, while holding DTN time at baseline values. Again, the
drip-and-ship model is rarely favorable (Figure III in the Supplemental Data File).

5.4.6 Impact of Having Optimal Treatment Times

If all treatment times are optimized; 60 minute DIDO time (comprised of 30
minute DTN time and 30 minute turnaround time) and 60 minute DTP time in the
mothership scenario the drip-and-ship model remains relevant in the majority of the
country (Figure 6). The mothership model prevails in areas very close to EVT centres and in a few further regions where the drip-and-ship method would require initial transport away from the EVT centre.

5.5 Discussion

We have presented the first case study of modelling pre-hospital transport for ischemic stroke patients with LVO utilizing real treatment times in a defined geographic area. While, prior analyses have shown modelling results using optimized treatment times\textsuperscript{17,18} few jurisdictions are currently achieving such optimized times\textsuperscript{21,22} and therefore modelling utilizing current treatment times is of benefit to system planners. Modelling patient transport for system level planning is highly sensitive to treatment times at thrombolysis and EVT centres. A moderate improvement in treatment times results in significant predicted changes to the optimization of a national acute stroke patient transport strategy.

The two single changes that had the largest impact on transport decisions were reducing DTN time and DTP time. Reducing DTN time highlights the benefits of early thrombolysis treatment if direct access to EVT is not efficient. Alternatively, if the time to EVT can be reduced the predicted benefit of early thrombolysis is negated in all scenarios. The impact of minimizing the time between thrombolysis and EVT is also important. Even when DTN and DTP times are optimized, if DIDO time remains long (due to delay in departing for the EVT centre) the predicted benefit of early thrombolysis rarely supersedes direct transport to EVT services (mothership). For system level
planning it is crucial that all stroke centres are operating as efficiently as possible and variability in treatment times is kept to a minimum as changes in treatment times at any point have large predicted impacts on the transport decision.

The effect these changes have on workload at the EVT centre must also be considered. If DTP is reduced in isolation there will be substantial increase in volume at the EVT centres as the mothership model predicts the best outcome for all potential strokes. While our model is based on patients with known LVO, a proportion of these patients may not be EVT candidates and this unnecessary increase in volume may adversely affect workflow for EVT candidates. Conversely, in an optimized system the drip-and-ship scenario predicts the best outcome for most regions. This scenario also has the benefit of early imaging and specialist consults (either in house or via telehealth) ensuring that only appropriate EVT candidates are transferred to the EVT centre, thereby reducing unnecessary workload at the EVT centre.

The potential impact of having a second fully operational EVT centre is also illustrated. With current treatment times, there are several regions in the immediate vicinity of EVT Centre 2 which would still benefit most from direct transport to EVT Centre 1 in Dublin, a ~300km drive, even when there is the potential to have EVT services in their own region. Apart from improved patient outcomes, having two fully operational EVT centres will allow patients to remain closer to home and reduce the caseload at the current single EVT centre. Additionally, this will lessen the burden on ambulance services. Taking a patient from the southwest of Ireland to EVT Centre 1 is not only costly but it also removes an ambulance from this region for an entire day, which is potentially detrimental to the remaining population in these areas. This scenario
is entirely preventable by having EVT services available 24/7 in southwest Ireland. A recent health technology assessment of providing EVT services on a national basis in Ireland, which included two fully operational EVT centres found providing this service to be cost-effective under typical willingness-to-pay thresholds.23

These models have limitations. Our model includes a simplifying assumptions that LVO can be identified in the field and currently that is only partly true. Screening tools have incomplete sensitivity and specificity for identifying LVO. There are several clinical screening tools which can be used by paramedics to identify ischemic stroke with reasonable but imperfect accuracy. For example, the Los Angeles Motor Scale (LAMS) score has been shown to identify LVOs with high sensitivity and specificity, especially in patients with severe middle cerebral artery syndrome at presentation.24,25 Patients who present as false positives on a LAMS screen include minor ischemic stroke, hemorrhagic stroke, and stroke mimics. Those with minor ischemic stroke could have better outcomes if first transported to their nearest stroke centre for thrombolysis, rather than incurring a delay to treatment with transport to a more distant comprehensive centre. Including minor stroke patients in the transport model may bias the model towards the drip-and-ship strategy. This analysis considers ground transport only as it is the primary mode of prehospital transport in Ireland. Ground transport times can be variable due to traffic, weather, and ambulance availability. The addition of air transport in the model may impact transport decisions. Future research should also include the impact that mobile stroke units may have on transport decisions in metropolitan areas.

The data source is not without limitation. The Irish National Stroke Register does not capture all ischemic stroke patients (67% captured in 2014 – 2015) as it covers all
major stroke centres but not all hospitals in Ireland where stroke patients are treated. However, the majority of LVO patients, which this study applies to, would have been treated at major stroke centres and are therefore be captured in the register. This analysis was performed in a small country (~70,000km²) similar in size to the state of West Virginia USA, making the results relevant to other small countries, various states, health care regions, or even large metropolitan areas.

We have used this modelling and mapping technique as a case study to show how real treatment data entered into a pre-specified conditional probability model can be used to visualize and inform policy around acute stroke transport and treatment. Using this methodology, the impact of system wide changes such as the addition of a new EVT centre and the reduction of treatment times can be determined. This case study can be expanded to other health jurisdictions using local treatment times for similar purposes.

In conclusion, modelling patient transport for system level planning is sensitive to treatment times at both thrombolysis and EVT centres. Optimizing all aspects of major acute ischemic stroke care, including decreasing DTN and DIDO at thrombolysis centres and DTP at EVT centres will result in more favorable patient outcomes for patients with stroke due to large vessel occlusion, and will favor a continued drip-and-ship strategy for patients requiring EVT.
5.6 Acknowledgements

The authors would like to acknowledge Carmel Brennan and Emer Shelley (National Stroke Register); Siobhan Jennings (earlier work); Sinead Duff (EVT); Professor Anne Hickey (providing critical feedback); Alan Moore, Alan Martin, Linda Brewer, and Ciaran Donegan (consult geriatricians); Paul O’Brien (thrombectomy services); and Patricia Daly (data collection).
5.7 Figures

Figure 1. Drip-and-ship and Mothership Transport Components.

The dashed line represents the mothership model; the solid lines represent the drip-and-ship model. Times X, Y and Z are transportation times. Times A, B and C are treatment times. Adapted from Holodinsky et al. (2017) Drip-and-ship versus Direct to Comprehensive Stroke Centre: Conditional Probability Modelling.\textsuperscript{17}
Figure 2. Current State of Ireland.
Map shows Ireland broken into 139 regions with geographic centres plotted. Actual median door to needle time for each centre is used, time from alteplase administration to departure for the endovascular thrombectomy (EVT) centre is 60 minutes, door to groin puncture time is 100 minutes in the mothership scenario and 10 minutes in the drip-and-ship scenario. Panel A displays one EVT centre; panel B shows two EVT centres. Regions are color coded to show the method predicting the best probability of good outcome.
Figure 3. Impact of Reducing Door to Needle Time.

Map shows Ireland broken into 139 regions with geographic centres plotted. Door to needle time is reduced to 30 minutes, time from alteplase administration to departure for the endovascular thrombectomy (EVT) centre is 60 minutes, door to groin puncture time is 100 minutes in the mothership scenario and 10 minutes in the drip-and-ship scenario. Panel A displays one EVT centre; panel B shows two EVT centres. Regions are color coded to show the method predicting the best probability of good outcome.
Figure 4. Impact of Reducing Door In Door Out Time.

Map shows Ireland broken into 139 regions with geographic centres plotted. Actual median door to needle time for each centre is used, door in door out time is reduced by reducing time from alteplase administration to departure for the endovascular thrombectomy (EVT) centre to 30 minutes, door to groin puncture time is 100 minutes in the mothership scenario and 10 minutes in the drip-and-ship scenario. Panel A displays one EVT centre; panel B shows two EVT centres. Regions are color coded to show the method predicting the best probability of good outcome.
Figure 5. Impact of Reducing Door to Groin Puncture Time.

Map shows Ireland broken into 139 regions with geographic centres plotted. Actual median door to needle time for each centre is used, time from alteplase administration to departure for the endovascular thrombectomy (EVT) centre is 60 minutes, door to groin puncture time is reduced to 60 minutes in the mothership scenario and remains at 10 minutes in the drip-and-ship scenario. Panel A displays one EVT centre; panel B shows two EVT centres. Regions are color coded to show the method predicting the best probability of good outcome.
Figure 6. Impact of an Optimized System.

Map shows Ireland broken into 139 regions with geographic centres plotted. Door to needle time is reduced to 30 minutes, time from alteplase administration to departure for the endovascular thrombectomy (EVT) centre is reduced to 30 minutes, door to groin puncture time is reduced to 60 minutes in the mothership scenario and remains at 10 minutes in the drip-and-ship scenario. Panel A displays one EVT centre; panel B shows two EVT centres. Regions are color coded to show the method predicting the best probability of good outcome.
5.8 References:


5.9 Supplemental Methods

For full methodology see Holodinsky et al. Drip and Ship Versus Direct to Comprehensive Stroke Center: Conditional Probability Modeling. Stroke. 2017;48(1):233-238. doi:10.1161/STROKEAHA.116.014306. The models were generated using a physiological approach, considering the probability of achieving reperfusion with each given treatment strategy in combination with the probability of good outcome as a function of time to reperfusion, and including the possibility of good outcome without reperfusion. The probability of achieving reperfusion given endovascular therapy was estimated from the ESCAPE trial at 0.74. The probability of good outcome given successful reperfusion decreases by 0.0006 for every minute delay.

As the time of reperfusion for patients receiving alteplase is unknown, we assume the same rate of decay applies. The probability of early reperfusion given alteplase therapy was estimated at 0.18. The probability of good outcome given no reperfusion was estimated from the ESCAPE trial to be 0.30. The door to needle time (A), alteplase bolus to departure for EVT centre time (B), door to groin puncture time (C), travel time from the patient to the thrombolysis centre (X), travel time from the thrombolysis centre to the EVT centre (Y), and travel time from the patient to the EVT centre (Z) are incorporated (see Figure 1 for a flow diagram showing these time parameters). It is assumed first reperfusion is achieved 30 minutes into the endovascular procedure. A constant 30 minutes has been added to represent the average time from first medical contact to ambulance arrival and ambulance scene time. Table I displays the model variables, definitions, and data sources. Table II displays the time parameters used in the models,
and Table III shows how these elements combine to form the conditional probability
models.
Table I. Model Variables, Definitions, Values, and Data Sources

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<th>Model Variable</th>
<th>Definition</th>
<th>Value</th>
<th>Data Source</th>
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<td>Time X</td>
<td>Travel time from patient to thrombolysis centre</td>
<td>Variable</td>
<td>Using Google’s Distance Matrix API drive time from the geographic centre of each Eircode routing key region to the nearest thrombolysis centre was estimated.</td>
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<tr>
<td>Time Y</td>
<td>Travel time from thrombolysis centre to thrombectomy centre</td>
<td>Variable</td>
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<tr>
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<td>Variable</td>
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<td>Time from arrival at thrombolysis centre to alteplase administration</td>
<td>Actual thrombolysis centre median door to needle time.</td>
<td>Irish National Stroke Register, years 2014 – 2015.</td>
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<tr>
<td>Door in Door Out Time (Time A + B)</td>
<td>Time from arrival at thrombolysis centre to departure for thrombectomy centre</td>
<td>Actual thrombolysis median door to needle time + 60 minutes.</td>
<td>Irish National Stroke Register, years 2014 – 2015 (door to needle time). Beaumont Hospital (EVT Centre 1) thrombectomy registry. The difference in time from arrival at the thrombectomy centre and alteplase administration was taken for all patients, this was then stratified by thrombolysis centre and the travel time from the appropriate thrombolysis centre to the thrombectomy centre was subtracted to obtain the time from alteplase administration to departure for the</td>
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<td>Door to Arterial Access Time (Time C)</td>
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<td>100 minutes (mothership) 10 minutes (drip and ship)</td>
<td>Beaumont Hospital (EVT Centre 1) thrombectomy registry, years 2014 - 2015</td>
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<td>Time from first medical contact to ambulance arrival and ambulance scene time</td>
<td>Time from 999 call to ambulance leaving scene with patient</td>
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<td>Representative of response and scene times in major Canadian cities.</td>
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<td>thrombectomy)</td>
<td>The probability that endovascular thrombectomy results in reperfusion (TICI 2b/3 flow)</td>
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</tr>
<tr>
<td>First reperfusion after endovascular thrombectomy</td>
<td>Time from groin puncture to first reperfusion (TICI 2b/3 flow)</td>
<td>30 minutes</td>
<td>The ESCAPE trial.²</td>
</tr>
<tr>
<td>P(early reperfusion</td>
<td>alteplase)</td>
<td>The probability that alteplase therapy results in the patient achieving reperfusion before they reach the thrombectomy centre.</td>
<td>0.18 0.18[(B+Y)/70]</td>
</tr>
</tbody>
</table>
## Chapter 5: Case Study In Ireland

<table>
<thead>
<tr>
<th>Model Variable</th>
<th>Definition</th>
<th>Value</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early reperfusion after alteplase administration</td>
<td>Time of early reperfusion, should patient achieve reperfusion with alteplase before reaching the thrombectomy centre</td>
<td>a. 70 minutes</td>
<td>a. We have defined early reperfusion as 70 minutes post alteplase administration as angiography studies have shown that 1.6% of ICA, 23.9% of M1, and 38.9% of M2 occlusions recanalized a median of 70 minutes after alteplase administration. Additionally, this is a relevant time point when considering inter-facility transport times. b. If time B+Y &lt; 70 minutes, then there is not 70 minutes available for early reperfusion to occur before the patient reaches the thrombectomy centre. In these cases, the time of early reperfusion has been adjusted to be equal to B+Y.</td>
</tr>
<tr>
<td>P(good outcome</td>
<td>reperfusion at time ø)</td>
<td>The rate per minute at which probability of good outcome (mRS 0 – 2 at 90 days) given successful reperfusion decreases</td>
<td>0.75 – 0.0006 ø</td>
</tr>
<tr>
<td>P(good outcome</td>
<td>no reperfusion)</td>
<td>The probability the patient achieves a mRS 0 – 2 at 90 days given they did not achieve reperfusion.</td>
<td>0.30</td>
</tr>
</tbody>
</table>

alteplase clot dissolving rates progress linearly with time in the initial treatment phase.⁶,⁷
Table II. Model Parameters

<table>
<thead>
<tr>
<th>Model</th>
<th>Thrombectomy Centre(s)</th>
<th>Median Door to Needle Time</th>
<th>Median Door In Door Out Time</th>
<th>Median Door To Groin Puncture Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(base)</td>
<td>EVT Centre 1</td>
<td>Actual centre median</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>2</td>
<td>EVT Centre 1</td>
<td>30 minutes</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>3</td>
<td>EVT Centre 1</td>
<td>Actual centre median</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>4</td>
<td>EVT Centre 1</td>
<td>Actual centre median</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>5</td>
<td>EVT Centre 1</td>
<td>30 minutes</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>6</td>
<td>EVT Centre 1</td>
<td>Actual centre median</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>7</td>
<td>EVT Centre 1</td>
<td>30 minutes</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>8</td>
<td>EVT Centre 1</td>
<td>30 minutes</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>9</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>Actual centre median</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>10</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>30 minutes</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>11</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>Actual centre median</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 100 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>12</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>Actual centre median</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 60 minutes Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>13</td>
<td>EVT Centre 1 and EVT</td>
<td>30 minutes</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 100 minutes</td>
</tr>
<tr>
<td>Model</td>
<td>Thrombectomy Centre(s)</td>
<td>Median Door to Needle Time</td>
<td>Median Door In Door Out Time</td>
<td>Median Door To Groin Puncture Time</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------</td>
<td>---------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td>Centre 2</td>
<td></td>
<td></td>
<td>Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>14</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>Actual centre median</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 60 minutes&lt;br&gt;Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>15</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>30 minutes</td>
<td>DTN + 60 minutes</td>
<td>Mothership: 60 minutes&lt;br&gt;Drip and Ship: 10 minutes</td>
</tr>
<tr>
<td>16</td>
<td>EVT Centre 1 and EVT Centre 2</td>
<td>30 minutes</td>
<td>DTN + 30 minutes</td>
<td>Mothership: 60 minutes&lt;br&gt;Drip and Ship: 10 minutes</td>
</tr>
</tbody>
</table>

*bold indicates change from base model*
## Table III. Mothership and Drip and Ship Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Conditional Probabilities</th>
<th>Time Considerations</th>
<th>Conditional Probability Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothership</td>
<td>[ P(\text{good outcome}</td>
<td>\text{mothership model}) = P(\text{reperfusion}</td>
<td>\text{EVT}) \cdot P(\text{good outcome}</td>
</tr>
<tr>
<td>Drip and Ship</td>
<td>[ P(\text{good outcome}</td>
<td>\text{drip and ship model}) = P(\text{early reperfusion}</td>
<td>\text{alteplase}) \cdot P(\text{good outcome}</td>
</tr>
</tbody>
</table>
5.11 Supplemental Figures

Figure I. Impact of Reduction in Door To Needle and Door In Door Out Times.

This map shows the country broken into 139 geographic regions with the geographic centre plotted. In this model, door to needle time is reduced to 30 minutes, time from alteplase administration to departure for the endovascular thrombectomy (EVT) centre is reduced to 30 minutes, door to groin puncture time is 100 minutes in the mothership scenario and is 10 minutes in the drip and ship scenario. Panel A displays one EVT centre; panel B shows the addition of a second EVT centre. Each geographic region is color coded to show the transport method that provides patients with the greatest probability of good outcome.
Figure II. Impact of Reduction in Door To Needle and Door To Groin Puncture Times.

This map shows the country broken into 139 geographic regions with the geographic centre plotted. In this model, door to needle time is reduced to 30 minutes, time from alteplase administration to departure for the endovascular thrombectomy (EVT) centre is 60 minutes, door to groin puncture time is reduced to 60 minutes in the mothership scenario and remains at 10 minutes in the drip and ship scenario. Panel A displays one EVT centre; panel B shows the addition of a second EVT centre. Each geographic region is color coded to show the transport method that provides patients with the greatest probability of good outcome.
Figure III. Impact of Reduction in Door In Door Out and Door To Groin Puncture Times.

This map shows the country broken into 139 geographic regions with the geographic centre plotted. In this model, actual median door to needle time from each centre is used, time from alteplase administration to departure for the endovascular thrombectomy (EVT) centre is reduced to 30 minutes, door to groin puncture time is reduced to 60 minutes in the mothership scenario and remains at 10 minutes in the drip and ship scenario. Panel A displays one EVT centre; panel B shows the addition of a second EVT centre. Each geographic region is color coded to show the transport method that provides patients with the greatest probability of good outcome.
5.12 Supplemental References:


Chapter 6: Modeling Stroke Patient Transport for All Patients With Suspected Large-Vessel Occlusion

This chapter is comprised of an original research article originally published in JAMA Neurology: Holodinsky JK, Williamson TS, Demchuk AM, Zhao H, Zhu L, Francis MJ, Goyal M, Hill MD, Kamal N. Modeling Stroke Patient Transport for All Patients With Suspected Large-Vessel Occlusion. JAMA Neurology. 2018; 75(12): 1477-1486. doi:10.1001/jamaneurol.2018.2424. In Chapter 4 a conditional probability was proposed which determined the best transport option (drip and ship or mothership) for patients with ischemic stroke due to LVO. In this manuscript, the primary limiting assumption of this model – that the patient must have a large vessel occlusion, as well as others inherent in the work in Chapter 4, are addressed. The model proposed here is applicable to all patients who are suspected of having an ischemic stroke with LVO based on a pre-hospital paramedic screening tool as such it is more immediately applicable to designing stroke systems. Due to manuscript brevity an expansion of the methods used in this chapter can be found in Chapter 3 Section 3.3.

6.1 Key Points:

Question: In suspected acute ischemic stroke with large vessel occlusion, should thrombolysis-capable stroke centers be bypassed in favor of direct transfer to endovascular-capable stroke centers?

Findings: The dominant transport strategy depends on the patient’s distance to both centers and treatment speed. If treatment times are slow at the thrombolysis center,
bypass should be considered when the centers are \( \leq 60 \) minutes apart. At greater transport times between centers bypass is not always favorable.

**Meaning:** Regional centralization of stroke triage to endovascular therapy centers will increase excellent outcomes after ischemic stroke treatment. The drip-and-ship approach requires fast treatment and is most relevant for longer transport times.

### 6.2 Abstract

**Importance:** Ischemic stroke with large vessel occlusion can be treated with alteplase and/or endovascular therapy, however the administration of both treatments is time sensitive.

**Objective:** To identify the optimal triage and transport strategy, direct to the endovascular center (mothership) or immediate alteplase treatment followed by transfer to the endovascular center (drip-and-ship), for all suspected large vessel occlusion stroke patients.

**Design Setting & Participants:** This is a theoretical conditional probability modelling study. Existing data from clinical trials of stroke treatment were used for model generation.

**Main Outcome:** The time-dependent efficacy of alteplase and endovascular therapy and the accuracy of large vessel occlusion screening tools were modelled to predict the probability of excellent outcome (mRS 0 – 1 at 90 days) for both the drip-and-ship and
mothership transport strategies. Based from onset to treatment the strategy which predicts the greatest probability of excellent outcome is determined in several different scenarios.

**Results:** The patient’s travel time from both thrombolysis and endovascular therapy centers, speed of treatment, and positive predictive value of the screening tool, impact whether drip-and-ship or mothership predicts best outcomes. With optimal treatment times both options predict similar outcomes when the centers are ≤60 minutes apart. However, with increasing travel time between the two centers, drip-and-ship is favored if the patient would have to travel past the thrombolysis center to reach the endovascular therapy center or if the patient would arrive outside the alteplase treatment time window in the mothership scenario. If treatment times are slow at the thrombolysis center, the area where mothership predicts best outcomes expands, especially when the two centers are close together. The area where mothership predicts best outcome also expands as the positive predictive value of the screening tool increases.

**Conclusions and Relevance:** Decision making for pre-hospital transport can be modelled using existing clinical trial data; these models can be dynamically adapted to changing realities. Based on current average treatment times to realize the full benefit of endovascular therapy on a population level its delivery should be regionally centralized. Transport decision making is context specific and the radius of superiority of the transport strategy changes based on treatment times at both centers, transport times, and the triaging tool used.
6.3 Introduction

Fast treatment of acute ischemic stroke is essential for disability free survival.\textsuperscript{1,2} The evolution of time-dependent therapeutics for ischemic stroke refocuses the need to consider how to triage suspected stroke in the field. Endovascular therapy (EVT), a minimally-invasive endovascular procedure, is a more effective reperfusion method than intravenous alteplase for ischemic stroke with large vessel occlusion (LVO).\textsuperscript{3} The facilities and expertise needed for EVT are typically limited to urban tertiary hospitals. Conversely, intravenous alteplase is widely available and relevant for ischemic stroke patients with and without LVO. Both treatments are time-sensitive and may be given alone or in combination.\textsuperscript{4,5}

EVT has resulted in the new problem of identifying patients with probable LVO such that they could be preferentially moved to an EVT center.\textsuperscript{6-10} EVT patients with long inter-hospital transfer delays experienced worse outcomes than those without inter-hospital transfer.\textsuperscript{11} Neurovascular imaging is the gold standard to determine EVT eligibility but high quality imaging in the field (e.g. a mobile stroke unit capable of CT angiography\textsuperscript{12}) is not available for most patients. Several clinical scores, for use by paramedics, modelled after the National Institute of Health Stroke Scale have been developed.\textsuperscript{13} Three commonly used scales are the Cincinnati Prehospital Stroke Severity Scale (C-STAT), the Rapid Arterial Occlusion Evaluation (RACE), and the Los Angeles Motor Scale (LAMS) each with varying predictive value.\textsuperscript{14-16}
Chapter 6: Modelling for Patients with Suspected Large Vessel Occlusion

We sought to model the best transport strategies for acute stroke, balancing the benefit of early alteplase, the greater efficacy of EVT, and declining benefit of both treatments over time.

6.4 Methods

6.4.1 Terminology and Simplifying Assumptions

Hospitals are classified as either thrombolysis or EVT centers. A thrombolysis center can administer intravenous alteplase (with onsite stroke expertise or telemedicine services) but does not provide EVT. An EVT center provides both EVT and intravenous alteplase. We assume treatments are available around the clock, every day of the year. Mothership means patients are transported directly to an EVT center (potentially bypassing closer thrombolysis centers) and drip-and-ship means patients are first treated with intravenous alteplase at a thrombolysis center and then transferred to an EVT center.

This is an extension of previously published modelling frameworks (Table I). We assume stroke onset time is known and transport decisions are made after EMS evaluation using a LVO screening tool and that the decision does not change en-route. We assume patients with occlusions within the guideline treatment time window and without medical contraindications to thrombolysis are eligible for alteplase and that patients with LVOs are eligible for EVT. Lastly, because the rate of spontaneous early recovery among patients with LVO is low, we assume that patients predicted to have an LVO only achieve reperfusion with treatment. As this is a modelling study using
6.4.2 Model Components

This model is built by combining conditional probabilities of excellent outcome constructed from clinical trials of stroke treatment and therefore reflects population averages and applies at the population level. We have approached the problem practically using the probability of achieving excellent outcome (mRS 0 – 1 at 90 days) within a given time from stroke onset to treatment.

Patients with LVO (extra/intra-cranial ICA, M1-MCA, or proximal M2-MCA occlusion) will receive both alteplase and EVT either at the EVT center or in a drip-and-ship approach. For EVT the time dependent probability of excellent outcome was derived from the HERMES collaboration time to treatment analysis. For alteplase the time dependent probability of excellent outcome was derived from an individual patient data meta-analysis (Table 1). For mothership transport, time from onset to treatment is the sum of time from onset to medical contact, ambulance response and time spent on scene, travel to the EVT center, and door-to-needle time or door to groin puncture time at the EVT center (alteplase treatment). For drip-and-ship transport time from onset to treatment is the sum of time from onset to medical contact, ambulance response and time spent on scene, travel to the thrombolysis center, and door-to-needle time at the thrombolysis center (alteplase treatment), time from thrombolysis administration to
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departure for the EVT center, travel from the thrombolysis center to the EVT center, and
door to groin puncture time at the EVT center (EVT treatment) (Figure I). Three different
time scenarios were used: Scenario A describes an optimized system, Scenario B assumes
slow treatment at the thrombolysis center, and Scenario C assumes slow treatment at both
centers (Table II).

Because clinical screening is imperfect, patients without LVO (false positives)
will also be identified including (1) ischemic stroke without LVO; (2) intracerebral
hemorrhage (ICH); and (3) stroke mimics. Patients with sub-arachnoid hemorrhage or
cerebral venous sinus thrombosis are not considered in this study. Patients with ischemic
stroke without LVO within guideline treatment window will treated with alteplase. For
this the time dependent probability of excellent outcome was derived from an individual
patient data meta-analysis (Table 1).  

Patients with ICH may eventually require a higher level care however there is
currently indeterminate evidence on the efficacy of emergency medical or surgical
treatment.  
By combining the excellent outcome rates from several trials of emergency
ICH treatment, the probability of excellent outcome for ICH is estimated to be 0.24 and is
assumed to be time invariant (Table 1). As most stroke mimics are not immediately
life threatening and do not have time dependent treatment options, the probability of
excellent outcome for these patients is considered time invariant (Table 1).
6.4.3 *Patient Diagnoses*

Three pre-hospital LVO screening tools were modelled. LAMS, a 5-point scale in which higher scores indicate ischemic stroke with LVO\(^{16}\), RACE, a 9-point scale in which higher scores indicate ischemic stroke with LVO\(^{15}\), and C-STAT, a 3-item scale, originally developed to detect thrombolysis candidates, where scores $\geq 2$ are indicative of LVO\(^{14}\). In a recent study of 565 consecutive paramedic initiated ‘code strokes’ in Melbourne, Australia, these scales were evaluated\(^{29}\). It was found that LAMS $\geq 4$, RACE $\geq 5$, and C-STAT $\geq 2$ had positive predictive values (PPV) for identifying LVO of 0.4538, 0.5294, and 0.4000 respectively. (Henry Zhao MBBS, e-mail personal correspondence, April 21, 2017) The prevalence of proximal anterior circulation LVO among these patients was 14.5%.\(^{29}\) See Supplemental Equations for detailed explanation of model components.

6.4.4 *Visualizations*

Results are visualized using two-dimensional temporal-spatial diagrams. These diagrams depict a single thrombolysis center in the middle of the figure and a single EVT center at varying transport times below it. Concentric circles representing 5-minute increments of travel time radiate from the thrombolysis center. Color coding is used to represent the transport option with the greatest predicted probability of excellent outcome. Red and green indicate that drip-and-ship and mothership respectively predict the best probability of excellent outcome. Areas where the two options predict near equivalent outcomes (probabilities within 0.01 of each other) are indicated using white
stippling. Color intensity increases as the probability of achieving excellent outcome increases.

To show geographic context results are also visualized in the state of California, USA. For the purposes of this illustration we have used data from The Joint Commission Quality Check Stroke Certification program as a surrogate for EVT capability. We considered acute stroke ready and advanced primary stroke centers to be thrombolysis centers and advanced comprehensive stroke centers to be EVT centers. Maps were generated using a desktop application developed for this research (DESTINE, Calgary, CAN). Esri’s ArcGIS Software Development Kit was used to access a map of California, USA. A 3 by 3-kilometer (1.86 miles) grid was overlaid on the state and the geographic coordinates of the center of each grid section was passed through Google’s Distance Matrix API (Google, Mountain View, USA) to estimate the ground transport time to each hospital under optimal driving conditions. These travel times were fed into the conditional probability models and the probability of excellent outcome for each strategy in each grid section was calculated. The grid sections were color coded in the same manner as the two-dimensional temporal-spatial diagrams.

6.5 Results

We modelled the probability of excellent outcome for both the drip-and-ship and mothership transport, with varying transport times to and between centers (Supplemental Equations and Figure I). This model differs from prior published models.\textsuperscript{17,18} Prior
models assumed patients were known to have an acute ischemic stroke with LVO. In this model, patients are suspected to have an LVO based on an LVO screening tool. The treatment options for other possible diagnoses (non-LVO, ICH, and stroke mimics) were also included. See Table I for a comparison of this and prior models.

Several scenarios were created illustrating the effect of varying transport times, treatment times, and screening tool PPV on decision making (Table III), each scenario was visualized using two-dimensional temporal-spatial diagrams. There scenarios (Table II) were also visualized in the state of California, USA.

When the patient is closest to the EVT center, mothership always predicts the greatest probability of excellent outcome. Patients with known contraindications to thrombolysis, including those beyond 4.5 hours from onset, should also be transported directly to an EVT center. When the patient is closest to the thrombolysis center, outcomes vary by transport time and treatment efficiency. With optimal treatment times (Scenario A) when the thrombolysis and EVT centers are less than 60 minutes travel time apart, both strategies predicts near equivalent probabilities of excellent outcome (Figure 1). As the transport time between centers lengthens, a region where drip-and-ship clearly outweighs mothership appears, this includes locations close to the thrombolysis center and the narrow corridor where patients would have to travel past the thrombolysis center en-route to the EVT center. This drip-and-ship area expands as the centers are moved further apart and is especially pronounced when the centers are 120 minutes apart. In this instance, there is an area in the temporal-spatial plane where if transported by mothership
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route, the patient foregoes the opportunity for treatment with alteplase under current guidelines as onset to needle time would exceed 4.5 hours.

In Scenario B, the effect of slow treatment at thrombolysis centers is shown; drip-and-ship is no longer associated with the greatest probability of excellent outcome when the travel time between centers is 60 minutes or less (Figure 2). Even as the travel time between centers increases drip-and-ship only clearly outweighs mothership when travel time would preclude patients from receiving alteplase in the mothership model.

In Scenario C, we consider slow treatment times at both centers. Here drip-and-ship only outweighs mothership when travel time would preclude alteplase administration in the mothership scenario or if the centers are 120 minutes apart and the patient is in the immediate vicinity of the thrombolysis center (Figure 3).

The results for all three time scenarios, using the LAMS screening tool, in the state of California are shown in Figure 4 (enlarged maps of Los Angeles and San Francisco in Figures II and III). Consistent with the two-dimensional temporal-spatial diagrams in an optimal scenario, drip-and-ship only outweighs mothership when the thrombolysis center is far away from EVT centers. In Figure 4 – Panel A, both strategies predict equivalent outcomes in the greater Los Angeles area. However, drip-and-ship is the best option for patients in Bakersfield which is a ~2-hour drive from Los Angeles. In Panel B, where treatment at the thrombolysis center is slow, the areas where drip-and-ship clearly outweighs mothership have shrunk and is now only the best option for patients near Fresno, San Luis Obispo/Santa Maria, Redding, and a portion of Mendocino County. When treatment times are slow at both thrombolysis and EVT centers (Figure 4
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– Panel C), areas where drip-and-ship clearly outweighs mothership have decreased in size as compared to Panel A, but remain larger than those in Panel B.

When using RACE \( \geq 5 \) (higher PPV than LAMS \( \geq 4 \)) to identify patients with probable LVO a similar pattern of results are obtained. However, the area where mothership predicts best outcomes enlarges slightly (Figures IV – VI). Overall, the probability of excellent outcome decreases because a greater proportion of patients with LVO, who have inherently poorer outcomes, are identified. When using C-STAT \( \geq 2 \) (lower PPV than LAMS \( \geq 4 \)) to identify probable LVO the drip-and-ship area expands (Figures VII – IX), and the overall probability of excellent outcome increases as fewer patients with LVO are identified. Overall, the choice of pre-hospital scale does not substantively change the transport decision as these scales have similar positive predictive values and the prevalence of LVO is low. The scenarios outlined deal with the complex interaction of several parameters. The effect of varying a single parameter on the models is detailed in Table IV.

6.6 Discussion

We have modelled and visualized a pre-hospital transport system for acute ischemic stroke patients with suspected LVO using clinical trial data. The transport time threshold for bypass varies depending upon treatment speed at the thrombolysis and EVT center. This is especially pronounced in Scenario B where door-to-needle time at thrombolysis centers is 60 minutes (door-in-door-out time = 120 minutes). This is the
current reality in many stroke systems. Among hospitals in the Get With The Guidelines Target Stroke program the post-intervention median door-to-needle time was 67 minutes (IQR 51 – 87 minutes). Our results imply, based on current treatment times, that to realize the full benefit of EVT on a population basis, its delivery should be regionally centralized.

Transport decision making is highly context specific; the radius of superiority for mothership changes based on the relative location of centers to each other and the treatment times at these centers thus model inputs need to be customized regionally. This has potential implications for current accreditation standards and time metrics for quality stroke care. One way to drive change is to accredit centers that cannot meet efficiency targets and are within a short travel time to centers which can at a lower level than those meeting targets and use such accreditation to guide bypass decisions for EMS. Importantly, the same considerations on efficient treatment times apply equally to thrombolysis and EVT centers. Population density and distribution, not modelled here, is also important when establishing regional transport and triage policy. Areas where both transport options produce near equivalent outcomes may be treated differently jurisdiction to jurisdiction due to economics, staffing, and/or redundancy in resources.

An ongoing randomized controlled trial is addressing the question of transport strategy in Barcelona (The RACECAT trial; NCT02795962). Due to context specific factors having such a large effect on decision making, the results of RACECAT may not be generalizable to other jurisdictions with different geographic constraints. However,
empiric data from RACECAT may be combined with this modelling approach to predict the ideal strategy in regions where a randomized comparison is not feasible.

The effect of pre-hospital screening tools on transport decision making appears to be modest. Given the need to keep things simple in the pre-hospital environment the most easily taught of these scales is likely to gain the most traction with EMS. The merits of each tool should be considered when choosing one for implementation. Any intervention that would speed up triage and transport in the pre-hospital environment may change the transport strategy predicted to be most favorable. However, this would benefit all patients as time from onset to treatment would be shortened.

In taking a population perspective, we have ignored the political and economic realities that sometimes govern system design. Stroke due to suspected LVO only accounts for a minority of the total stroke population. In the Melbourne triaging study, LVO prevalence was only 14.5%, depending on the screening tool used anywhere from 18.4% - 21.4% of patients would have screened positive for LVO and therefore guided by this model.29 The remaining ~80% of patients would not be considered potential bypass candidates and thus would require treatment at thrombolysis centers. Strategies need to be in place for urgent drip-and-ship transport for patients identified to have a LVO at the thrombolysis center but missed by the pre-hospital screen. Another consideration is the level of ambulance redundancy in each jurisdiction as mothership transport could leave ambulances out of their home region for longer than typical. Although beyond the scope of this analysis, the potential volume increase at EVT centers, especially regarding false positive patients, should be considered when implementing a transport protocol.
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There are limitations to the model due to assumptions and available data. We have assumed ICH treatment outcomes are time invariant however, ICH patients may require the higher level of care available at EVT centers (e.g. neurosurgical teams and neuro-intensive care units) and that care may not be time invariant. Conversely, although unproven to date, it remains plausible that hyperacute medical treatment (e.g. procoagulant drug < 120 minutes from onset) could improve outcomes and as such patients might benefit from transport to the nearest stroke center. We have assumed all patients with LVO will be eligible for EVT. However, this may not be the case and as further data become available on the relationship between time and EVT eligibility the models can be updated. The treatment of EVT patients will evolve and changes in technology, treatment paradigms, or the use of mobile stroke units may impact the organization of stroke care. As further data become available these models can be updated. The temporal spatial diagrams are transport modality agnostic as they are based upon transport time, not distance. However, the map of California was generated using ground transport times, including air transport could change the results. Ground transport times are dependent on time of day and weather patterns. Thus, for jurisdictional planning health systems may wish to evaluate several scenarios including some in non-optimal driving conditions before deciding on a transport strategy. We used average times for time from onset to first-medical contact and time on-scene, changing these will influence the model results. Lastly, we have defined excellent outcome as mRS 0 – 1 at 90 days; using another definition may impact model results.
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6.7 Conclusions

Decision making for pre-hospital transport can be effectively modelled using existing clinical trial data. These models are dynamic and can be adapted to different geographies or changing treatment realities. For ischemic stroke with suspected LVO, regional centralization of care is predicted to result in the best outcomes given current average treatment times.
### 6.8 Tables

**Table 1. Conditional Probability Values and Data Sources**

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
<th>Rationale/Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large Vessel Occlusion Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P(\text{mRS (0 - 1)</td>
<td>EVT &amp; OTT = x}) )</td>
<td>0.3394+0.00000004x^2-0.0002x; minimum value = 0.129</td>
</tr>
<tr>
<td>( P(\text{mRS (0 - 1)</td>
<td>alteplase &amp; OTT = x}) )</td>
<td>0.2359+0.0000002x^2-0.0004x; minimum value = 0.1328</td>
</tr>
<tr>
<td><strong>Non-Large Vessel Occlusion Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P(\text{mRS (0 - 1)</td>
<td>alteplase &amp; OTT = x}) )</td>
<td>0.6343-0.0000005x^2-0.0005x; minimum value = 0.4622</td>
</tr>
</tbody>
</table>
## Probability, Value, Rationale/Data Source

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
<th>Rationale/Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>with nLVO. Using ( P(\text{mRS } 0 \rightarrow 1</td>
<td>\text{NIHSS } 0-10 &amp; \text{control}) ) as the baseline value this was transformed into a 2(^{nd}) order polynomial function depicting ( P(\text{mRS } 0 \rightarrow 1</td>
<td>\text{alteplase} &amp; \text{nLVO}) ) over time. At 4.5 hours from onset the function is set to a minimum value of 0.4622 which is the ( P(\text{mRS } 0 \rightarrow 1) ) given no treatment in the patients with NIHSS 0-10 in this meta-analysis.(^4)</td>
</tr>
<tr>
<td>Intracerebral Hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P(\text{mRS } 0 \rightarrow 1) )</td>
<td>0.24</td>
<td>This was generated by combining the overall excellent outcome rate in several trials of intracerebral hemorrhage treatment.(^{19-23}) The STICH-II trial in patients with spontaneous ICH of 10-100ml showed early surgery had no benefit over conservative treatment.(^{19}) The FAST trial showed no difference between recombinant factor VII (at two different doses) and placebo. Of importance to this analysis there was also no significant interaction found between treatment effect and time from onset to treatment.(^{20}) The INTERACT2 trial showed no difference between early intensive blood pressure lowering (SBP &lt; 140 mmHg within one hour) and guideline recommended therapy (SBP &lt;180 mmHg) in the primary outcome (death and disability at 90 days), however a favorable shift in the overall distribution of mRS scores at 90 days was found.(^{21}) The greatest benefit was found in patients who were able to achieve the greatest SBP reductions within one hour of randomization,(^{22}) however randomization occurred a median of 3.7 hours after ICH onset thus it remains unknown if this time benefit would persist in the hyperacute window after onset. The INCH trial found no difference between fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) in 90 day clinical outcomes in patients with vitamin K antagonist related hemorrhages.(^{23}) As none of these trials showed emergency treatment to be superior to standard of care this probability is considered time invariant.</td>
</tr>
<tr>
<td>Stroke Mimics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Probability

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
<th>Rationale/Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(mRS 0 – 1)</td>
<td>0.90</td>
<td>As most stroke mimics do not have time dependent treatment options, the probability of excellent outcome for these patients is considered to be time invariant and is set at 0.90 based on the outcomes of stroke mimic patients in prior studies. [^{24\text{-}28}]</td>
</tr>
</tbody>
</table>

EVT: endovascular therapy, OTT: onset to treatment time, LVO: large vessel occlusion
Figure 1. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, defined as Los Angeles Motor Scale Score $\geq 4$, in an optimally performing system.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at varying travel times (10, 30, 60, 90, and 120 minutes) below it. There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip-and-ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is always best in this scenario.

The degree of color saturation reflects the value of the probability of excellent outcome. The blue line represents the point where the onset to needle time in the mothership scenario is $> 270$ minutes.
Figure 2. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, defined as Los Angeles Motor Scale Score $\geq 4$, in a system with slow treatment times at the thrombolysis center.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at varying travel times (10, 30, 60, 90, and 120 minutes) below it. There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip-and-ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is always best in this scenario. The degree of color saturation reflects the value of the probability of excellent outcome. The blue line represents the point where the onset to needle time in the mothership scenario is $> 270$ minutes.
Figure 3. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, defined as Los Angeles Motor Scale Score \( \geq 4 \), in a system with slow treatment times at the thrombolysis center and endovascular therapy center.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at varying travel times (10, 30, 60, 90, and 120 minutes) below it. There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip-and-ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is always best in this scenario. The degree of color saturation reflects the value of the probability of excellent outcome. The blue line represents the point where the onset to needle time in the mothership scenario is > 270 minutes.
Figure 4. Maps depicting the probability of excellent outcome and best predicted transport strategy for patients with suspected ischemic stroke with large vessel occlusion, defined as Los Angeles Motor Scale Score $\geq 4$, in the state of California, USA.

In the maps thrombolysis centers are depicted by black dots and endovascular therapy centers are depicted by blue diamonds. Panel A displays a system with optimized treatment times. Panel B displays a system with fast treatment at endovascular therapy centers but slow treatment at thrombolysis centers. Panel C displays a system with slow treatment at both thrombolysis and endovascular therapy centers. Red indicates areas where drip-and-ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. The degree of color saturation reflects the value of the probability of excellent outcome. Grey areas indicate a lack of road infrastructure data thus transport times and therefore optimal transport method could not be determined.
Chapter 6: Modelling for Patients with Suspected Large Vessel Occlusion

6.10 References


9. Caplan LR. Primary Stroke Centers vs Comprehensive Stroke Centers With Interventional Capabilities: Which Is Better for a Patient With Suspected Stroke?
Chapter 6: Modelling for Patients with Suspected Large Vessel Occlusion


Chapter 6: Modelling for Patients with Suspected Large Vessel Occlusion


Chapter 6: Modelling for Patients with Suspected Large Vessel Occlusion


6.11 Supplemental Equations: Breakdown of Model Components

A. Total patient group

\[ 1.0 = \alpha + \beta + \chi + \gamma \]

\[ \alpha = P(LVO|\text{positive screen}) \]
Proportion of LVO patients that have a positive screen

\[ \beta = P(nLVO|\text{positive screen}) \]
Proportion of small vessel occlusion patients that have a positive screen

\[ \chi = P(\text{intracerebral hemorrhage}|\text{positive screen}) \]
Proportion of intracerebral hemorrhage patients that have a positive screen

\[ \gamma = P(\text{stroke mimic}|\text{positive screen}) \]
Proportion of stroke mimics that have a positive screen

Where:

\[ P(LVO|\text{positive screen}) \]
Varies depending on LVO screen used.
Using LAMS $\geq 4$: 0.4538
Using RACE $\geq 5$: 0.5294
Using C-STAT $\geq 2$: 0.4000
(Henry Zhao MBBS, e-mail, April 21, 2017)

\[ P(nLVO|\text{positive screen}) \]
Varies depending on LVO screen used.
Using LAMS $\geq 4$: 0.1092
Using RACE $\geq 5$: 0.1176
Using C-STAT $\geq 2$: 0.1826
(Henry Zhao MBBS, e-mail, April 21, 2017)

\[ P(\text{intracerebral hemorrhage}|\text{positive screen}) \]
Varies depending on LVO screen used.
Using LAMS $\geq 4$: 0.3445
Using RACE $\geq 5$: 0.3137
Using C-STAT $\geq 2$: 0.2957
(Henry Zhao MBBS, e-mail, April 21, 2017)

\[ P(\text{stroke mimic}|\text{positive screen}) \]
Varies depending on LVO screen used.
Using LAMS $\geq 4$: 0.0924
Using RACE $\geq 5$: 0.0392
Using C-STAT $\geq 2$: 0.1217
(Henry Zhao MBBS, e-mail, April 21, 2017)
Chapter 6: Modelling for Patients with Suspected Large Vessel Occlusion

B. Overall Probability of Good Outcome:

\[ P_{mRS0-1|\text{positive LVO screen}} = \alpha(P_{mRS0-1|LVO}) + \beta(P_{mRS0-1|nLVO}) + \chi(P_{mRS0-1|ICH}) + \gamma(P_{mRS0-1|SM}) \]

Where:
- \( P_{mRS0-1|LVO} \) is the overall probability of good outcome given a large vessel occlusion (Section C)
- \( P_{mRS0-1|nLVO} \) is the overall probability of good outcome given a non-large vessel occlusion (Section D)
- \( P_{mRS0-1|ICH} \) is the overall probability of good outcome given intracerebral hemorrhage (Section E)
- \( P_{mRS0-1|SM} \) is the overall probability of good outcome given a stroke mimic (Section F)

See Figure I for diagrammatic representation of these equations

C. Overall Probability of good outcome given a large vessel occlusion

\[ P_{mRS0-1|LVO} = P_{mRS0-1|LVO \& alteplase \& EVT} + P_{mRS0-1|LVO \& alteplase \& no EVT} + P_{mRS0-1|LVO \& no alteplase \& EVT} + P_{mRS0-1|LVO \& no alteplase \& no EVT} \]

This simplifies to the equation below using the following assumptions: (1) all eligible patients must be treated in order to obtain an excellent outcome; (2) all patients with occlusions without obvious medical contraindications are eligible for alteplase treatment. Time, including late presentations >4.5 hours from onset, is accounted for in the \( P_{mRS0-1|LVO \& alteplase} \) decay curve given below; (3) all patients with large vessel occlusion are eligible for treatment with endovascular therapy; and (4) we have not assumed any modification of the \( P_{mRS0-1|LVO \& EVT} \) decay curve by alteplase treatment status.

\[ P_{mRS0-1|LVO} = P_{mRS0-1|LVO \& alteplase} + \left[ \left( 1 - P_{mRS0-1|LVO \& alteplase} \right) \cdot P_{mRS0-1|LVO \& EVT} \right] \]

\[ P_{mRS0-1|LVO \& alteplase} = 0.2359 + 0.0000002(t_{\text{onset to needle}})^2 - 0.0004(t_{\text{onset to needle}}); \text{ at 4.5 hrs from onset set to minimum value of 0.1328} \]

(P_{mRS0-1|control and NIHSS 11+})
Chapter 6: Modelling for Patients with Suspected Large Vessel Occlusion

To generate the above equation the exponential decay presented in the Emberson et al effect of treatment delay meta-analysis was used.\textsuperscript{1} This decay was extrapolated to onset to treatment times of less than 60 minutes. As this study includes data from patients with both small and large occlusions we have adjusted this decay using NIHSS as a surrogate for occlusion location to estimate the effect of alteplase treatment over time in patients with LVO. Using $P(mRS 0 - 1|\text{NIHSS 11+ & control})$ as the baseline value this was transformed into a 2\textsuperscript{nd} order polynomial function depicting $P(mRS 0 - 1|\text{alteplase & LVO})$ over time. At 4.5 hours from onset the function is set to a minimum value of 0.1328 which is the $P(mRS 0 - 1)$ given no treatment in the patients with NIHSS 11+ in this meta-analysis.\textsuperscript{1}

$$P_{mRS0-1|LVO \& EVT} = 0.3394 + 0.00000004(t_{\text{onset to puncture}})^2 - 0.0002(t_{\text{onset to puncture}}), \text{minimum value} = 0.129$$

To generate the above equation the exponential common odds ratio decay presented in the HERMES collaboration time to treatment analysis was used.\textsuperscript{2} This decay was extrapolated to symptom onset to treatment times less than 120 minutes. Using $P(mRS 0 - 1|\text{control})$ as the baseline this was transformed into a 2\textsuperscript{nd} order polynomial function depicting $P(mRS 0 - 1|\text{EVT})$ over time. This decay is capped at a minimum probability of excellent outcome of 0.129, which is the $P(mRS 0 - 1)$ given no treatment in the patients with NIHSS 11+ in this HERMES data.

Where in Mothership:
$$t_{\text{onset to needle|MS}} = t_{\text{onset-FMC}} + t_{\text{response}} + t_{\text{on-scene}} + t_{\text{scene-EVT centre}} + t_{\text{DTN EVT centre}}$$
$$t_{\text{onset to puncture|MS}} = t_{\text{onset-FMC}} + t_{\text{response}} + t_{\text{on-scene}} + t_{\text{scene-EVT centre}} + t_{\text{DTP|MS}}$$

Where in Drip-and-ship:
$$t_{\text{onset to needle|DnS}} = t_{\text{onset-FMC}} + t_{\text{response}} + t_{\text{on-scene}} + t_{\text{scene-thrombolysis centre}} + t_{\text{DTN thrombolysis centre}}$$
$$t_{\text{onset to puncture|MS}} = t_{\text{onset-FMC}} + t_{\text{response}} + t_{\text{on-scene}} + t_{\text{scene-thrombolysis centre}} + t_{\text{DTN thrombolysis centre}} + t_{\text{needle-door out}} + t_{\text{thrombolysis centre-EVT centre}} + t_{\text{DTP|DnS}}$$
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D. Overall Probability of good outcome with a non-large vessel occlusion

\[
P_{\text{mRS}0-1|\text{nLVO \& alteplase}} = 0.6343 - 0.00000005(t_{\text{onset to needle}})^2 - 0.0005(t_{\text{onset to needle}}), \text{ at 4.5 hrs from onset set to 0.4622 (P}_{\text{mRS 0-1|control and NIHSS 0-10}})
\]

To generate the above equation the exponential decay presented in the Emberson et al effect of treatment delay meta-analysis was used.\(^1\) This decay was extrapolated to onset to treatment times of less than 60 minutes. As this study includes data from patients with both small and large occlusions we have adjusted this decay using NIHSS as a surrogate for occlusion location to estimate the effect of alteplase treatment over time in patients with nLVO. Using \(P(\text{mRS 0–1|NIHSS 0-10 \& control})\) as the baseline value this was transformed into a 2\(^{nd}\) order polynomial function depicting \(P(\text{mRS 0–1|alteplase \& nLVO})\) over time. At 4.5 hours from onset the function is set to a minimum value of 0.4622 which is the \(P(\text{mRS 0–1})\) given no treatment in the patients with NIHSS 0-10 in this meta-analysis.\(^1\)

Where \(t\) is as defined above in Section C

E. Overall Probability of good outcome with intracerebral hemorrhage

\[
P_{\text{mRS}0-1|\text{ICH}} = 0.24
\]

This was generated by combining the overall excellent outcome rate in several trials of intracerebral hemorrhage treatment.\(^3\)\(^-\)\(^7\) The STICH-II trial in patients with spontaneous ICH of 10-100ml showed early surgery had no benefit over conservative treatment.\(^3\) The FAST trial showed no difference between recombinant factor VII (at two different doses) and placebo. Of importance to this analysis there was also no significant interaction found between treatment effect and time from onset to treatment.\(^4\) The INTERACT2 trial showed no difference between early intensive blood pressure lowering (SBP < 140 mmHg within one hour) and guideline recommended therapy (SBP <180 mmHg) in the primary outcome (death and disability at 90 days), however a favourable shift in the overall distribution of mRS scores at 90 days was found.\(^5\) The greatest benefit was found in patients who were able to achieve the greatest SBP reductions within one hour of randomization,\(^6\) however randomization occurred a median of 3.7 hours after ICH onset thus it remains unknown if this time benefit would persist in the hyperacute window after onset. The INCH trial found no difference between fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) in 90 day clinical outcomes in patients with vitamin K antagonist related hemorrhages.\(^7\) As
none of these trials showed emergency treatment to be superior to standard of care
this probability is considered time invariant.

F. Overall Probability of good outcome for stroke mimics

\[ P_{m|RS0-1|SM} = 0.90 \]

As most stroke mimics do not have time dependent treatment options, the probability of excellent outcome for these patients is considered to be time invariant and is set at 0.90 based on the outcomes of stroke mimic patients in prior studies.\textsuperscript{8-12}
### Supplemental Tables

**Table I. Comparison of Prior and Current Models**

<table>
<thead>
<tr>
<th>Component</th>
<th>Prior Models(^{13,14})</th>
<th>Current Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assumptions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient is known to have a LVO</td>
<td>✓</td>
<td>× — Patients were assumed to have a suspected LVO based on a LVO screening tool (ex. Los Angeles Motor Scale, PPV: 0.45(^{15})). The PPV of the screening tool was used and the treatment options for other possible diagnoses (non-LVO, hemorrhagic stroke, and stroke mimics) were also included.</td>
</tr>
<tr>
<td>There is uncertainty regarding which transport and treatment decision to make</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>There is only one decision making point (at the scene) and this decision is never reneged upon</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>The model does not apply to found down or stroke on awakening patients</td>
<td>✓ — Time from onset to first medical contact was varied from 30 to 90 minutes</td>
<td>✓ — Time from onset to first medical contact was assumed to be 30 minutes</td>
</tr>
<tr>
<td>All patients with occlusions are eligible for alteplase and all patients with LVOs are eligible for EVT</td>
<td>✓</td>
<td>✓ — The caveat of no obvious contraindications to alteplase being present (Coumadin, recent surgery, late time window) was added</td>
</tr>
<tr>
<td>For patients with LVOs reperfusion is only achieved through treatment (i.e. no spontaneous reperfusion)</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Chapter 6: Modelling for Patients with Suspected Large Vessel Occlusion

<table>
<thead>
<tr>
<th>Component</th>
<th>Prior Models(^{13,14})</th>
<th>Current Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model Components</strong></td>
<td>Probability of mRS 0 – 2 at 90 days(^{14}) Probability of good outcome at 90 days where good outcome was defined at mRS 0 – 2 at 90 days for endovascular therapy and mRS 0 – 1 at 90 days for alteplase treatment.(^{14})</td>
<td>Probability of mRS 0 – 1 at 90 days</td>
</tr>
<tr>
<td><strong>Model Outcome</strong></td>
<td>EVT: 0.74 (0.90 used in sensitivity analyses)(^{13}) time invariant Alteplase: 0.18 (early reperfusion within 70 minutes, or varies linearly if full 70 minutes is not available; 0.40 used in sensitivity analyses)(^{13})</td>
<td>× — This model was built practically and is based on onset to treatment times and no assumptions about achieving reperfusion were made</td>
</tr>
<tr>
<td><strong>Probability of achieving reperfusion</strong></td>
<td>70 minutes (or varies linearly if travel time does not allow for a full 70 minutes to pass)(^{13})</td>
<td>× — This model was based on onset to treatment times from the HERMES collaboration meta-analysis(^{2}) which includes patients who eventually reperfused and patients who did not achieve reperfusion, so separate estimates for patients not achieving reperfusion were not needed.</td>
</tr>
<tr>
<td><strong>Time of early reperfusion after alteplase administration</strong></td>
<td>0.30(^{13})</td>
<td></td>
</tr>
<tr>
<td><strong>Probability of good outcome given no reperfusion</strong></td>
<td>0.75 – 0.0006/minute for EVT and alteplase(^{13}) (e^{-0.0019x/0.7239}/1+e^{-0.0019x+0.7239}) for EVT(^{14}) ((0.0703x + 41.02)/(x + 113.7)) for alteplase(^{14})</td>
<td>Good Outcome: mRS 0 – 1 at 90 days As stated above decay curves in this model are based on the time from onset to treatment (not reperfusion) EVT: 0.3394+0.00000004x(^2)-0.0002x; minimum value = 0.129 Alteplase in LVO: 0.2359+0.0000002x(^2)-0.0004x; minimum value = 0.1328</td>
</tr>
</tbody>
</table>
### Component

<table>
<thead>
<tr>
<th>Time Parameters Analyzed</th>
<th>Prior Models&lt;sup&gt;13,14&lt;/sup&gt;</th>
<th>Current Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from Onset to First Medical Contact</td>
<td>Varied from 30 to 90 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Ambulance response and scene time</td>
<td>25&lt;sup&gt;14&lt;/sup&gt; and 30&lt;sup&gt;13&lt;/sup&gt; minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Door to Needle Time</td>
<td>30, 60, and 90 minutes</td>
<td>30 and 60 minutes</td>
</tr>
</tbody>
</table>
| Door In Door Out Time | Door to Needle Time + 15 minutes<sup>13</sup>  
Door to Needle Time + 20 minutes<sup>14</sup> | Door to Needle Time + 20 minutes |
| Door to Groin Puncture + Reperfusion Time | Drip-and-ship: 45 and 50 minutes (door to groin puncture) + 30 minutes for reperfusion, 13 and 115 minutes total<sup>14</sup>  
Mothership: 75 and 90 minutes (door to groin puncture) + 30 minutes for reperfusion, 13 and 115 minutes total<sup>14</sup> | Drip-and-ship: 30 and 60 minutes (door to groin puncture time; model is built using onset to treatment times, as stated above no assumptions about reperfusion are made)  
Mothership: 60 and 90 minutes (door to groin puncture time; model is built using onset to treatment times, as stated above no assumptions about reperfusion are made) |

LVO: large vessel occlusion; PPV: positive predictive value; EVT: endovascular therapy
### Table II. Time Parameters Used in Analyses

<table>
<thead>
<tr>
<th>Time</th>
<th>Scenario A</th>
<th>Scenario B</th>
<th>Scenario C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to first medical contact</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Time from first medical contact to ambulance arrival and ambulance</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>scene time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Door to Needle Time (thrombolysis center)</td>
<td>30 minutes</td>
<td>60 minutes</td>
<td>60 minutes</td>
</tr>
<tr>
<td>Door In Door Out Time</td>
<td>Door to Needle + 20 minutes</td>
<td>Door to Needle + 60 minutes</td>
<td>Door to Needle + 60 minutes</td>
</tr>
<tr>
<td>Door to Needle Time (endovascular therapy center)</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>60 minutes</td>
</tr>
<tr>
<td>Door to Groin Puncture Time</td>
<td>60 minutes (mothership)</td>
<td>60 minutes (mothership)</td>
<td>90 minutes (mothership)</td>
</tr>
<tr>
<td></td>
<td>30 minutes (drip-and-ship)</td>
<td>30 minutes (drip-and-ship)</td>
<td>60 minutes (drip-and-ship)</td>
</tr>
</tbody>
</table>

Changes from Scenario A shown in boldface
### Table III. Modelling Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Screening Tool (PPV)</th>
<th>Onset to FMC</th>
<th>Response Time</th>
<th>On-Scene Time</th>
<th>DTN EVT Centre</th>
<th>DTN Thrombolysis Centre</th>
<th>Needle to door out Thrombolysis Centre</th>
<th>Time from Thrombolysis Centre to EVT Centre</th>
<th>DTP Mothership</th>
<th>DTP Drip-and-ship</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LAMS ≥ 4 (0.4538)</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>30</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>LAMS ≥ 4 (0.4538)</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>30</td>
<td>30</td>
<td>20</td>
<td>30</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>LAMS ≥ 4 (0.4538)</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>30</td>
<td>30</td>
<td>20</td>
<td>60</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
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### Table IV. Impact of Varying Each Model Parameter on Model Results

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<th>Parameter Variation</th>
<th>Effect on Drip-and-Ship Model (relative to results prior to parameter variation holding all other variables constant)</th>
<th>Effect on Mothership Model (relative to results prior to parameter variation holding all other variables constant)</th>
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<tr>
<td></td>
<td>Effect on LVO patients</td>
<td>Effect on LVO patients</td>
</tr>
<tr>
<td></td>
<td>• Increases time from onset to alteplase administration</td>
<td>• Increases time from onset to alteplase administration</td>
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<td></td>
<td>• Increases time from onset to groin puncture</td>
<td>• Increases time from onset to groin puncture</td>
</tr>
<tr>
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<td>• Decreases P(mRS 0-1) for drip-and-ship model</td>
<td>• Decreases P(mRS 0-1) for mothership model</td>
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<td>Increasing time in the pre-hospital environment (time from onset to first medical contact and/or time spent on scene)</td>
<td>Effect on nLVO patients</td>
<td>Effect on nLVO patients</td>
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<td>• Increases time from onset to alteplase administration</td>
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<td>• Decreases P(mRS 0-1) for drip-and-ship model</td>
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<td>Effect on stroke mimic patients</td>
<td>Effect on stroke mimic patients</td>
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<td>Increasing DTN at Thrombolysis Center</td>
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<td>Effect on stroke mimic patients</td>
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<th>Effect on Mothership Model (relative to results prior to parameter variation holding all other variables constant)</th>
</tr>
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</table>
| Increasing DIDO at Thrombolysis Center (while holding DTN constant)                  | **Effect on LVO patients**  
  - Increases time from onset to groin puncture  
  - Decreases P(mRS 0-1) for drip-and-ship model  
  **Effect on nLVO patients**  
  - None  
  **Effect on ICH patients**  
  - None  
  **Effect on stroke mimic patients**  
  - None | **No Effect**                                                                                                                                                                |
| Increasing DTN at Endovascular Therapy Center                                       | **No Effect**                                                                                                                                                                 | **Effect on LVO patients**  
  - Increases time from onset to alteplase administration  
  - Decreases P(mRS 0-1) for mothership model  
  **Effect on nLVO patients**  
  - Increases time from onset to alteplase administration  
  - Decreases P(mRS 0-1) for mothership model  
  **Effect on ICH patients**  
  - None  
  **Effect on stroke mimic patients**  
  - None | **Effect on LVO Patients**  
  - Increases time from onset to groin puncture  
  - Decreases P(mRS 0-1) in drip-and-ship model  
  **Effect on nLVO patients**  
  - None | **Effect on nLVO patients**  
  - None |
<table>
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<th>Effect on Mothership Model (relative to results prior to parameter variation holding all other variables constant)</th>
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</table>
| increasing positive predictive value of LVO screening tool | • Increased proportion of LVO patients in the model  
  • These patients benefit most from early endovascular therapy  
  o P(mRS 0-1) for drip and ship model decreases relative to mothership  
  • These patients also have inherently poorer outcomes than nLVO patients  
  o P(mRS 0-1) for drip-and-ship model decreases | • Increased proportion of LVO patients in the model  
  • These patients benefit most from early endovascular therapy  
  o P(mRS 0-1) for mothership increases relative to drip-and-ship  
  • These patients also have inherently poorer outcomes than nLVO patients  
  o P(mRS 0-1) for mothership model decreases |
| increasing the travel time from the thrombolysis to the endovascular therapy center | Effect on LVO Patients  
  • Increases time from onset to groin puncture  
  • Decreases P(mRS 0-1) in drip-and-ship model  
 Effect on nLVO patients  
  • None  
 Effect on ICH patients  
  • None  
 Effect on stroke mimic patients  
  • None | No Effect |
6.13 Supplemental Figures

Figure I. Diagram Showing Model Components.
Panel A shows the different probabilities and time factors come together to form the overall probability of good outcome for the patient. The times from onset to treatment will vary depending on which transport option is used. Panel B displays the two transport options, including transport and treatment times. The solid line represents the drip-and-ship transport method while the dashed line represents the mothership transport method. Time from onset to leaving the scene is not shown however this does not vary with transport strategy.
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Figure II. Maps depicting the probability of excellent outcome and best predicted transport strategy for patients with suspected ischemic stroke with large vessel occlusion, defined as Los Angeles Motor Scale Score $\geq 4$, in the Greater Los Angeles Area, California, USA.

In the maps thrombolysis centers are depicted by black dots and endovascular therapy centers are depicted by blue diamonds. Panel A displays a system with optimized treatment times. Panel B displays a system with fast treatment at endovascular therapy centers but slow treatment at thrombolysis centers. Panel C displays a system with slow treatment at both thrombolysis and endovascular therapy centers. Red indicates areas where drip-and-ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. The degree of color saturation reflects the value of the probability of excellent outcome. Grey areas indicate a lack of road infrastructure data thus transport times and therefore optimal transport method could not be determined.
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Figure III. Maps depicting the probability of excellent outcome and best predicted transport strategy for patients with suspected ischemic stroke with large vessel occlusion, defined as Los Angeles Motor Scale Score $\geq 4$, in the Greater San Francisco Area, California, USA.

In the maps thrombolysis centers are depicted by black dots and endovascular therapy centers are depicted by blue diamonds. Panel A displays a system with optimized treatment times. Panel B displays a system with fast treatment at endovascular therapy centers but slow treatment at thrombolysis centers. Panel C displays a system with slow treatment at both thrombolysis and endovascular therapy centers. Red indicates areas where drip-and-ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. The degree of color saturation reflects the value of the probability of excellent outcome. Grey areas indicate a lack of road infrastructure data thus transport times and therefore optimal transport method could not be determined.
Figure IV. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, defined as Rapid Arterial oCclusion Evaluation Scale Score $\geq 5$, in an optimally performing system.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at varying travel times (10, 30, 60, 90, and 120 minutes) below it. There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip and ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is always best in this scenario. The degree of color saturation reflects the value of the probability of excellent outcome. The blue line represents the point where the onset to needle time in the mothership scenario is $> 270$ minutes.
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Figure V. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, defined as Rapid Arterial Occlusion Evaluation Scale Score >= 5, in a system with slow treatment at thrombolysis centers.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at varying travel times (10, 30, 60, 90, and 120 minutes) below it. There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip and ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is always best in this scenario. The degree of color saturation reflects the value of the probability of excellent outcome. The blue line represents the point where the onset to needle time in the mothership scenario is > 270 minutes.
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Figure VI. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, defined as Rapid Arterial Occlusion Evaluation Scale Score >= 5, in a system with slow treatment at thrombolysis and endovascular therapy centers.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at varying travel times (10, 30, 60, 90, and 120 minutes) below it.

There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip and ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is always best in this scenario. The degree of color saturation reflects the value of the probability of excellent outcome. The blue line represents the point where the onset to needle time in the mothership scenario is > 270 minutes.
Figure VII. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, defined as Cincinnati Stroke Triage Assessment Tool $\geq 2$, in an optimally performing system.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at varying travel times (10, 30, 60, 90, and 120 minutes) below it. There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip and ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is always best in this scenario. The degree of color saturation reflects the value of the probability of excellent outcome. The blue line represents the point where the onset to needle time in the mothership scenario is $> 270$ minutes.
Figure VIII. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, defined as Cincinnati Stroke Triage Assessment Tool >= 2, in a system with slow treatment at thrombolysis centers.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at varying travel times (10, 30, 60, 90, and 120 minutes) below it. There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip and ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is always best in this scenario. The degree of color saturation reflects the value of the probability of excellent outcome. The blue line represents the point where the onset to needle time in the mothership scenario is > 270 minutes.
Figure IX. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, defined as Cincinnati Stroke Triage Assessment Tool $\geq 2$, in a system with slow treatment at thrombolysis and endovascular therapy centers.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at varying travel times (10, 30, 60, 90, and 120 minutes) below it. There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip and ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is always best in this scenario. The degree
of color saturation reflects the value of the probability of excellent outcome. The blue line represents the point where the onset to needle time in the mothership scenario is > 270 minutes.
6.14 Supplemental References:


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Chapter 7: Discussion and Conclusions

7.1 Summary of Key Findings

This thesis presents a novel way of conceptualizing the pre-hospital transport of suspected stroke patients in the era of endovascular therapy. Using clinical trial data, a conditional probability model which predicts the probability of good outcomes for stroke patients based upon their suspected diagnosis, treatments provided, and the time from stroke onset to treatment was generated. This model was iterated from a simplistic version pertaining only to patients with known LVO to a more complex version inclusive of all patients who would be suspected of having a LVO stroke in the field based on a LVO screening tool administered by paramedics.

The results of the different modelling scenarios generated in Chapters 4 to 6 displayed the importance of three different factors in the stroke transport decision making process: 1) the most probable diagnosis of the patient, 2) the treatment times at the thrombolysis and EVT centres, and 3) the relative distance between the thrombolysis and EVT centres.

7.1.1 Influence of the Diagnostic Distribution of Patients

In moving from a model considering only patients with known LVO to one where between 40% and 53% of patients have a LVO the importance of the drip and ship transport method is illuminated. When modelling transport for only patients with LVO the mothership model is heavily favoured, especially when the distances between the thrombolysis centre and EVT centre are short. Thinking physiologically this is expected
because patients with LVO require effective reperfusion for good outcome to be achieved and the efficacy of alteplase is low in these patients. As such, immediate access to EVT is paramount and mothership transport would ensure this. However, the drip and ship method cannot be totally discounted. While the efficacy of alteplase for patients with LVO is low it is not negligible and the benefits of early alteplase in these patients can be seen in the scenarios outlined in Chapter 4 where door to needle times and door in door out times at the thrombolysis centre are short. In these scenarios, there are areas in the temporospatial plane – especially in places where patients would have to travel past the thrombolysis centre to get to the EVT centre – where drip and ship is the best option for the patient. However, there is a limitation in these results in that the diagrams were only produced using a two-colour scale so it is unknown which areas equivalence between the two transport methods may lie in.

When considering the best transport option for the spectrum of possible patient diagnoses for all patients who screen positive for LVO based on an EMS screening tool the best transport option changes in many scenarios (Chapter 6). In these scenarios, the drip and ship transport method becomes more prominent. This result is also logical considering that a portion of the patients who screen positive for LVO on an EMS screening tool may have an ischemic stroke without LVO. As such, the only treatment option for these patients is alteplase and the earliest access to alteplase for these patients would be achieved by drip and ship transport. Additionally, while not as effective as EVT the time dependency of alteplase in treating LVO cannot be ignored.

However, the effect of the PPV of the different pre-hospital LVO screening tools on transport decision making appears to be modest (Chapter 6). Using RACE ≥5, LAMS
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≥ 4, and C-STAT ≥2 as examples these tools have been shown to have PPVs of 0.5294, 0.4538, and 0.4000 respectively when used in the field by paramedics (unpublished data from a study of paramedic initiated code strokes,\(^1\) courtesy of Henry Zhao, MBBS). In looking at the change in decision making when using a different tool taking LAMS ≥4 as baseline tool the increase in PPV by 0.0756 points using RACE ≥5 does not predict a substantial change in transport decision making; however, the decrease in PPV by 0.0538 using C-STAT ≥2 does change transport decision making slightly (Figure 1).

Figure 1. Two dimensional temporal spatial diagrams depicting transport decision making for patients with suspected ischemic stroke with large vessel occlusion, using three different screening tools: Los Angeles Motor Scale Score >= 4, Rapid Arterial oCclusion Evaluation Score >=5, and Cincinnati Stroke Triage Tool >=2 in an optimally performing system.

The diagrams depict a single thrombolysis center in the middle of the figure, depicted with a circle, and an endovascular therapy center, depicted by a diamond, at 60 minutes travel time below it. There are 5 minute concentric travel time circles radiating from the thrombolysis center. Red indicates areas where drip and ship predicts the greatest probability of excellent outcome and green indicates areas where mothership predicts the greatest probability of excellent outcome. White stippling indicates areas where the optimal transport method supersedes the other by 1% or less. Area where the patient is closest to the endovascular therapy center is not shown as the mothership option is
always best in this scenario. The degree of color saturation reflects the value of the probability of excellent outcome.

This can be explained not by the PPV of the tools but the ratio of LVO to nLVO patients picked up by the tool. When examining the ratio of LVO to nLVO patients among those screening positive for LVO using RACE \( \geq 5 \), LAMS \( \geq 4 \), and C-STAT \( \geq 2 \) the ratios are 4.5:1, 4.2:1, and 2.2:1 respectively. Put differently although the absolute difference in PPV is larger between RACE \( \geq 5 \) and LAMS \( \geq 4 \) than it is for LAMS \( \geq 4 \) and C-STAT \( \geq 2 \) in both cases just under 20% of patients with time sensitive treatment options will only see benefit from quick alteplase whereas for patients with C-STAT \( \geq 2 \) 31% will benefit. As such when considering whether a different pre-hospital screening tool will substantively change transport protocols more than just the PPV should be considered. Additionally, increasing prehospital screening tool complexity to achieve a mild increase in PPV which is unaccompanied by changes in the LVO to nLVO ratio may not be worth the effort of re-training EMS personnel or the risk of inappropriate use or interpretation of a more complex tool.

An additional consideration to be made is that the PPV of any tool used is a function of the prevalence of the disease at hand. As disease prevalence falls the PPV of the tool used will also fall while the NPV rises simply because there are fewer disease positive individuals in the pool the test is applied to. In the study in which the PPV of the different LVO screening tools was examined the prevalence of LVO stroke was 14%. This is an important data point to take stock of as if these scales are applied to a patient population with a much lower prevalence of LVO stroke the PPV of these scales will fall (and conversely if they are applied to a population with a higher prevalence of LVO
stroke the PPV will rise). Due to the low prevalence of LVO stroke selecting a screening tool with high discriminatory power (high positive likelihood ratio) is important as a positive test result from a tool with a poor likelihood ratio used on a population with low disease prevalence will not provide a meaningful increase in the post test probability of disease.

7.1.2 Impact of Treatment Times at the Thrombolysis and EVT Centres

One of the primary learnings from these models is that transport decisions are context specific in terms of treatment times at the thrombolysis and EVT centres. The model results are primarily driven by the time from stroke onset to treatment and door to needle, door in door out, and door to groin puncture times are an integral part of this. These treatment times were shown to be especially important at thrombolysis centres in order for the drip and ship option to remain a viable treatment option for patients.

As door to needle times increased at thrombolysis centres mothership was predicted to be the best option for patients. Long door to needle times are currently the reality in many hospital systems. Among hospitals in the Get With The Guidelines Target Stroke program the post-intervention median door-to-needle time was 67 minutes (IQR 51 – 87 minutes). These model results show that based on these current treatment times the delivery of EVT should be regionally centralized.

In many of the examples shown in Chapters 4 – 6 the treatment times were assumed to be the same across hospital types (i.e. all thrombolysis centres having the same door to needle time or all EVT centres having the same door to groin puncture
time). However, in using these models for decision making purposes across a health region treatment times should be individualized for each hospital to reflect local practices. Additionally, several different scenarios per hospital may need to be considered to reflect differential treatment times based on different staffing patterns which may exist during day, evening, night, and weekend operations. Finally, regional protocols which may affect hospital workflow times should be taken into consideration for regional decision making. For example, door in door out time at thrombolysis centres may be adversely affected by policies requiring a registered nurse or physician to accompany a patient being transported while IV thrombolysis is being administered.

Workflow at the EVT centres is also an important consideration in modelling patient transport. While it is often the assumption that EVT centres have equivalent or faster workflow than thrombolysis centre (as illustrated in all scenarios presented in Chapters 4 – 6) this is not always the case as pointed out by Maas and colleagues in a letter to the editor in response to the published version of Chapter 6 of this thesis. Appendix A contains the reply to this letter including additional figures which illustrate the importance of the drip and ship model in these scenarios where thrombolysis centres exhibit more efficient workflow than EVT centres – especially when the two centres are close together.

7.1.3 Relative Distance Between the Thrombolysis and EVT Centres

The relative distance between the thrombolysis and EVT centres also impacts the choice of most optimal transport method. In a model in which the patient is known to
have a LVO (Chapter 4) the mothership model is always superior to the drip and ship model when transport times between the thrombolysis and EVT centres are short, as is the case in most urban and sub-urban areas. However, when considering a wider range of possible diagnoses (ex. patients with LAMS $\geq 4$) this is not always the case. Even when the centres are 10 minutes apart from one another the mother ship model does not show clear superiority over the drip and ship model (Chapter 6). As the centres move further apart more area where drip and ship predicts marginally better outcomes than mothership appears, however in an optimally performing system it is not until the centres are 90 minutes apart that space where drip and ship is clearly superior to mothership occurs. As the transport time between the centres increases beyond this the area where drip and ship is superior also increases. There is also a relationship between the distance between the two centres and the treatment times at the centres such that this area only shrinks as the thrombolysis centre becomes less efficient.

The American Heart Association policy on interactions within stroke systems recommend that EMS not bypass a closer thrombolysis centre in favour of an EVT centre if this diversion would add more than 15-20 minutes of transport time for the patient.\textsuperscript{4} However, the results of these models illustrate that these recommendations are likely only appropriate in a few very specific scenarios. Hence, it is imperative that when generating transport protocols they are generated with each regions preferred LVO screening tool, treatment efficiency, and hospital locations taken into account so that any policy change is data-driven.
7.1.4 Other Factors for Consideration when Designing Transport Protocols

It is important to note that the transport models generated are based on differing travel times, not physical distances, and that there are many factors that contribute to transportation time besides distance. Notably, transport modality (fixed wing, rotary wing, or ground ambulance), weather conditions, and traffic conditions (for ground ambulance transport) will affect how travel time related to physical distance. For this reason, transport policies for differing weather and traffic patterns may need to be generated. Other logistical issues such as ambulance response time, ambulance scene time, and ambulance availability (especially in rural areas) may also contribute to time from onset to treatment.

These models were built from a suspected stroke patient outcome standpoint only and from a health system level there are several other factors that should be considered when implementing transport protocols. Given the expenses associated with both alteplase and EVT treatment, and long transports by ground, helicopter, or fixed wing air ambulance these models should be supplemented with an economic analysis. Additionally, other patient groups outside of suspected stroke patients should be considered – especially in rural areas where taking an ambulance out of its home range for an extended transport may be especially detrimental to the community. Population density and distribution of stroke patients were also not included in these models but would also be important when establishing regional transport and triage policy. If a large area of mothership transport also coincides with an area of high stroke density it is possible that the EVT centre may be overloaded with additional patients, especially with
false positive patients. Taking these factors into account areas where both transport options produce near equivalent outcomes may be treated differently jurisdiction to jurisdiction due to economics, staffing, and/or redundancy in resources.

The redirection of patients away from thrombolysis centres may also have the unintended consequence of slowing workflow at these centres due to decreased volume and familiarity with stroke patients. However, stroke due to suspected LVO only accounts for a minority of the total stroke population. In a study of pre-hospital stroke triage among suspected strokes LVO prevalence was only 14.5%. Depending on the screening tool used anywhere from 18.4% - 21.4% of patients would have screened positive for LVO and therefore guided by these models. The remaining ~80% of patients would not be considered potential bypass candidates and thus would require treatment at thrombolysis centers so while some patients will be directed away from these centres the vast majority of suspected strokes will still be directed to these centres for potential thrombolytic treatment. There would need to be strategies in place for urgent drip-and-ship transport for patients identified to have a LVO at the thrombolysis center but missed by the pre-hospital screening tools.

There is an ongoing randomized controlled trial addressing the question of drip and ship versus mothership in Barcelona, Spain (The RACECAT trial; NCT02795962). Due to the context-specific factors illustrated above having such a large effect on decision making, the results of RACECAT may not be generalizable to other jurisdictions with different geographic constraints. However, the empiric data derived from RACECAT may be used to strengthen these models.
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7.2 Limitations

For real world application, there are many other factors to consider when implementing a stroke transport protocol. On an individual patient level age, stroke severity, comorbidities, premorbid functional status, and the patient’s wishes will impact decision-making. Additionally, practical considerations such as capacity at both the primary and comprehensive stroke centre, traffic and weather conditions, and redundancy in ambulance systems when an ambulance needs to travel outside of its jurisdiction are also relevant when looking at this problem through a system level lens.

An important consideration for the real-world application of this work is that these models represent theoretical modelling from one point of decision making which may not reflect the practical implementation of care. Specifically, this leads to the mathematical possibility of “double counting” good outcome rate for a select group of patients. This was first discussed via private correspondence from Professor Michael Allen of the University of Exeter. This correspondence and detailed response with examples has been included in Appendix B and is summarized here. Our perspective is from the pre-hospital area where final treatment, or probability of final treatment, of the patient would not be known. There are no strong data to estimate the probability of final treatment for these patients, leading to the assumption that all eligible patients will be treated. Following from this, for modelling at a population level, the implicit assumption is made that it is known which patients will have a good outcome after alteplase treatment at a specified time from onset to treatment. This means that the model proposed depicts a situation where there are a group of patients who will have a good outcome with
alteplase treatment and as such theoretically do not need to receive EVT. However, from a practical standpoint it is not known which patients would have had a good outcome with alteplase only so these patients do receive EVT – meaning that in *practical implementation* all patients are treated although in *theory (as represented in this model)* they didn’t need to be. A potential change to the model proposed in Chapter 6 to accommodate this as well as the magnitude of difference in estimated good outcome rate associated with this change is illustrated in Appendix B.

In terms of the model generation there are other limitations to be considered. First, all probabilities used in these models were generated from randomized controlled trials, which represent a highly-selected patient population. Patients enrolled in these clinical trials had known large vessel occlusions and were deemed good candidates for endovascular therapy using imaging selection. As such these decay curves likely do not generalize to all patients seen in the field by EMS and the probabilities of good outcome, with or without reperfusion, are likely an overestimate. Recently the MR CLEAN registry has reported an EVT good outcome decay curve for all treated patients between 2014 – 2016 which showed a steeper decay in good outcome rate as compared to the HERMES trial results.\(^5\) The inclusion of these more real world data into a model will change decision making.

We have assumed that all patients with large vessel occlusions are eligible for both alteplase and endovascular therapy; provided that they arrive within current guideline treatment time windows for alteplase treatment. However, given the recent positive trials of late time window treatment for EVT we have not put a time restriction on EVT treatment. The assumption that all patients with large vessel occlusions will be
eligible for EVT is problematic. Studies have shown that anywhere between 14 – 32% of patients with LVO may be eligible for EVT.\textsuperscript{6,7} Assuming only these eligible patients receive treatment and adding this flat proportion into modelling as in Figure 2 will decrease the overall probability of good outcome in the model; additionally, this will serve to slightly decrease the radius of superiority for mothership in areas where there is a primary stroke centre nearby (holding the proportion of alteplase treated patients constant). However, if there is a relationship between onset to imaging time and eligibility for EVT then decision making would be further influenced by the addition of these data to a model. Although while it is believed that there likely is a relationship between time and eligibility for EVT further data on the proportion of patients who become ineligible for endovascular therapy during the onset-to-imaging epoch\textsuperscript{8} are needed to quantify this. Similarly, if not all alteplase eligible patients are treated this will increase the radius of superiority for mothership (holding the proportion of EVT treated patients constant). As with EVT if there is a relationship between time and treatment eligibility this will further influence decision making.
Figure 2. Flow chart of the different probabilities and time factors come together to form the overall probability of good outcome for patients including branches representing the probability of receiving each treatment.

* this is a failed alteplase scenario with no EVT therefore is akin to no treatment at all
Another limitation which is related to a lack of available data is that we have assumed ICH treatment outcomes are time invariant. However, this may not be the case and if a relationship between time, ICH treatment, and ICH outcomes does exist this will impact transport decision making. As an example, ICH patients may require the high level of care (e.g. neurosurgical teams and neuro-intensive care units) which is available at EVT centers and that care may not be time invariant. In this case, the mothership option may be most favourable for ICH patients which may overall lead to more mothership utilization. The magnitude of the effect would be dependent on the strength of the time relationship compared to that of reperfusion therapy for ischemic stroke patients. Conversely, although unproven to date, it remains plausible that hyperacute medical treatment (e.g. hemostatic drug < 120 minutes from onset) could improve outcomes for ICH patients. This therapy could be administered at primary stroke centres and as such ICH patients might benefit from transport to the nearest stroke center (drip and ship). This may lead to more drip and ship utilization and again the magnitude of the effect would be dependent on the strength of the time relationship compared to that of reperfusion therapy for ischemic stroke patients.

7.3 Future Research Directions

The limitations mentioned in this work lend themselves well to future research in this area. One of the primary advantages of using a modelling technique such as this is that as the treatment of stroke care evolves and there are advances in treatment options or techniques, as an example the use of tenecteplase over alteplase, any of the model’s data
sources can be updated to reflect this. As mentioned in the limitations the data used to build these models was primarily obtained from clinical trials which enrol a highly-selected group of patients. As more data from population-based registries of stroke care become available these models can be updated to reflect the broader population of patients with suspected LVO. Additionally, as patterns of stroke treatment evolve these models can be updated to reflect this. One specific example of this would be the increasing popularity of the mobile stroke unit, an ambulance equipped with a CT scanner and specially trained personnel for stroke treatment such that the patient can be scanned and alteplase administered in the ambulance if appropriate.9-11 As these units become implemented in jurisdictions worldwide the stroke transport decision become more complex: drip and ship, vs. mothership, vs. mobile stroke unit. The methodology proposed here can be easily adapted to the mobile stroke unit scenario. The mobile stroke unit acts much like a roving primary stroke centre so in modelling the drip and ship approach could be easily updated such that rather than looking at the travel time from the patient to the primary stroke centre one would need to use the travel time from the mobile stroke unit base to the patient and treatment times at the primary stroke centre would be replaced with treatment times in the mobile stroke unit.12-14 Another change in treatment paradigm which could be modelled using this methodology is the drip and drive or drip and fly approach. This approach, which is currently being used in regions of Germany and New York15,16 where there are hospitals with the appropriate infrastructure to perform EVT but lack in house neurointerventionalists, involves the patient being taken to the closest primary stroke centre and the interventionalist coming to the patient either by helicopter, private car, or sometimes by subway. Again, this scenario could be
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modelled using a modified drip and ship approach however now rather than a door in door out time at the primary stroke centre information would be needed on the time to “activation” of the mobile interventional team and the estimated travel time from the home base of this team to the receiving hospital. This scenario as well as the use of a mobile stroke unit are resource heavy and as such their use should be accompanied by an economic analysis.

In terms of the practical application of these models as they were designed using population level data sources and thus predict the best transport method for the average patient in a specific geographic area. Meaning implementation of this work should occur at the population level in terms of protocol generation but may not necessarily be appropriate for individual patient decision making – especially if the patient has known contraindications to treatment. In the future, additional work could be done to produce estimates stratified by age, sex, or other pertinent patient level factors such that more individualized predictions could be made. Following from this, the choice of outcome metric in this model being dichotomous with a good outcome being defined as mRS 0 – 1 at 90 days may not be the most appropriate choice when looking from an individual patient lens. If the data sources were updated to include age and sex specific estimates the choice of outcome could also be updated to reflect this. One option would be to move to the full spectrum of mRS scores and quantify outcomes in terms of disability adjusted life years (DALY) saved vs. lost between the drip and ship and mothership transport methods. This outcome choice would reflect the life expectancies of men and women of different ages in the decision-making process. It is probable that as the age of stroke onset increases there will be less of a relative difference in positive outcomes between the drip
and ship and mothership transport methods. Taking this in consideration with other factors such as economics, staffing, and ambulance redundancy the decision-making process may change for these patients. Another outcome option which would capture a more holistic view of patient outcomes would be to use the utility weighted mRS score. This score incorporates the desirability of a given health outcome to patients and has the advantage of being convertible to Quality Adjusted Life Years and as such may be useful for economic analyses or policy level planning. In the future, with additional data, the full mRS spectrum or utility weighted mRS could be used in modelling.

Importantly, economics, which often governs health system design has not been analyzed here. While the use of EVT has been shown to be economically viable an economic analysis of drip and ship versus mothership should accompany this before system level change is made especially in the sprawling jurisdictions where mothership transports may be very lengthy by ground ambulance or may require air ambulance transport. An economic analysis may be especially relevant if age and sex specific modelling using DALYs is performed in the future. If, as expected, the relative difference in DALYs lost/saved between the two transport methods decreases as patients age the economics of these transport and treatment methods may play a larger role in decision making.

Finally, there may be a natural extension of this modelling approach to other time sensitive disease processes with different levels of care available to patients. Of particular interest may be: thrombolysis versus percutaneous coronary intervention for myocardial infarction, bypass to higher level of care for trauma patients, and bypass to specialist centres for pediatric emergencies.
7.4 Putting These Findings into the Alberta Context

The province of Alberta (population: ~4.3M; 661,848km$^2$) has 15 primary stroke centres and two comprehensive stroke centres (Figure 3). Due to province’s large geography and rural population many Albertans do not have immediate access to EVT making this modelling work of importance in Alberta.

Using the model proposed in Chapter 6 a map of Alberta has been generated showing two different transport scenarios. The first showing very efficient treatment parameters with door to needle time being 30 minutes, door in door out time being 50 minutes, and door to groin puncture times of 60 minutes (mothership) or 30 minutes (drip and ship) (Figure 4 – left panel). In the second scenario door to needle time at the primary stroke centre has been increased to 60 minutes with a door in door out time of 120
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minutes (Figure 4 – right panel). Due to the large distance and long ground transport time between many of Alberta’s primary stroke centres to a comprehensive stroke centre, drip and ship is a predominant treatment strategy in much of rural Alberta. Although it should be noted that even though increasing treatment times at the thrombolysis centre did not change the transport option with best predicted outcomes, overall patients will fare better with faster treatment. For the four primary stroke centres which are closest to one of Alberta’s comprehensive stroke centres (Red Deer Regional Hospital, St. Mary’s Hospital, Grey Nuns Hospital, and Westlock Healthcare Centre) increasing treatment time did have an effect on the transport option predicted to produce best outcomes. As seen in Figure 4 (left panel) there are large areas around Red Deer Regional Hospital, St. Mary’s Hospital, and Westlock Healthcare Centre and a small area southeast of Grey Nun’s Hospital where drip and ship predicts slightly better outcomes than mothership. However, when treatment times at the primary stroke centre are increased this is no longer the case.
Figure 4. Transport Decision Making in Two Different Scenarios in Alberta.

Maps depicting the best transport option in two different scenarios in Alberta. The left panel depicts a very efficient system with door to needle time being 30 minutes, door in door out time being 50 minutes, and door to groin puncture times of 60 minutes (mothership) or 30 minutes (drip and ship). In the right panel door to needle time at the primary stroke centre has been increased to 60 minutes with a door in door out time of 120 minutes. Primary stroke centres are depicted in yellow and comprehensive stroke centres are depicted in blue. Areas in red indicate drip and ship predicts best patient outcomes. Areas in green indicate mothership predicts best patient outcomes. Areas in white stippling indicate that the absolute difference in probability of good outcome between drip and ship and mothership is <0.01. Areas in grey indicate minimal or no road infrastructure is present.
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While these are only two possible scenarios for treatment times in Alberta it illustrates the context specificity of transport decision making as described above. First, the relative distance between the primary and comprehensive stroke centres matters. There are some primary stroke centres which are so far away from comprehensive stroke centres that drip and ship will always be the best transport option for patients regardless of treatment time (although faster treatment is always in the patient’s best interest). Second, the speed of treatment influences decision making. For primary centres in relatively close proximity to a comprehensive centre the speed of treatment did influence the best transport method and as such knowing current treatment efficiencies at all hospitals, but especially ones closest to comprehensive centres, is paramount in generating an effective transport protocol.

7.5 Conclusions and Original Contribution to the Research Area

The initial model presented in Chapter 4 of this thesis was the first published framework for stroke transport decision making and displayed that decision making for pre-hospital transport could be effectively modelled using existing clinical trial data. Between the publication of the work presented in Chapter 4\(^1\) and Chapter 6\(^2\) three other frameworks for drip and ship versus mothership have been proposed.\(^{21-23}\) One of which including a geographic extension of the work contained in Chapter 4,\(^{21}\) one evaluating the lowest RACE score for which all patients with higher scores should be transported via mothership (although patients with hemorrhagic stroke or stroke mimics were excluded),\(^{22}\) and a third using discrete event simulation to determine the amount of over
or under triage predicted using different bypass thresholds. Chapter 6 contains the advancement of the conditional probability model proposed in Chapter 4 and represents the first study to consider all patients who screen positive for LVO in decision making and as such represents the most usable model for policy making – with the caveats of the above-mentioned limitations.

These models are dynamic and can be adapted to different geographies or changing treatment realities and the results of this work demonstrate that they should be adapted to these parameters for each individual stroke system at hand. The results of this work show that there is no one size fits all solution for stroke transport decision making and the consideration of geography, transport times, and treatment times are key in determining the best transport protocol for a specific jurisdiction. However, some generalizations across jurisdictions can be made: fast treatment at all centres is key but especially at the primary stroke centre if drip and ship is to be a viable transport option, the impact of different LVO screening tools on transport decision making is minimal, and finally using current average treatment times in areas where transport time between centres is minimal regional centralization of care for LVO patients predicts best outcomes.
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APPENDIX A: LETTER TO EDITOR AND RESPONSE

Response to letter to the editor by Maas and colleagues commenting on the published version of Chapter 6 of this thesis. Reprinted with permission.


We thank Maas et al. for commenting on our recent article. We would like to emphasize that this modelling is intended to be a thoughtful framework for pre-hospital decision making, particularly for system-wide planning. Our approach follows from the pragmatic reality that transport decision making must be made with both system and geographic context and the realization that there can never be randomized controlled trials of drip and ship vs. mothership in all regions globally. The main advantage of a modelling approach is that these context specific factors can be considered, entered to a model, and varied appropriately to ensure the models results are reflective of the system at hand.

One of these system level considerations is the extrapolation of randomized clinical trial data to real life treatment practice. We acknowledge that data from explanatory trials may not always be generalizable to real-world practice. In this case, the data relating the average probability of good outcome to onset to treatment times allows for individual onset to treatment times within real life workflow to be simulated. Similarly, the trial data are from a highly-selected group of patients (small infarct core, good collateral circulation, functionally independent pre-stroke, etc.). However, again, the model is adaptable and flexible and as results of more pragmatic trials or registries of EVT
treatment (ex. MR-CLEAN registry\(^3\)) become available such data can be incorporated into the modelling. While this type of data may be reflective of this specific local practice regional customization is the key to modelling local circumstance in this kind of model.

The writers also identify a scenario not explored in the paper: that of the very efficient thrombolysis centre and the less efficient endovascular therapy centre. The model’s flexibility allows for scenarios as such to be examined; see Figure for an example comparing transport in a system with efficient thrombolysis centres and non-efficient endovascular therapy centres to transport in a totally efficient system. As expected in this scenario, the drip and ship method is predicted to result in better patient outcomes due to the early alteplase administration at the efficient thrombolysis centres.

**Figure. Comparison of Drip-and-Ship vs Mothership Transport in a completely efficient system (B and D) and one with less efficient endovascular therapy centers**
than thrombolysis centers (A and C) using a Los Angeles Motor Scale score of greater than or equal to 4 patient distribution.

Green indicates that the mothership model predicts the greatest probability (P) of a good outcome, defined as modified Rankin scale (mRS) score of 0 to 1 (P[mRS 0-1]). Red indicates that the drip-and-ship model predicts the greatest P (mRS, 0-1). Stippling indicates the following equation: |P(mRS 0-1 | mothership) − P(mRS 0-1 | drip-and-ship)| < .01. DIDO indicates door-in–door-out time; DTN, door-to-needle time; DTP, door-to-puncture time; EVT, endovascular therapy.

References:


APPENDIX B. CORRESPONDANCE WITH PROFESSOR MICHAEL ALLEN

This appendix contains an email correspondence with Professor Michael Allen of the University of Exeter regarding the mathematical possibility of double counting the good outcome rate for some patients in the model proposed in Chapter 6 of this thesis.

Initial correspondence

Hello,

I'm just double checking things in the model. May I ask you about the equation you use for predicting the effect of treatment on LVO (I copied just the equations in the attached document).

I'm looking at the equation on page 3.

If we set the response to alteplase at a minimum of 0.1328 we have 0.8672 not responding to thrombolysis and going on to receive thrombectomy. If we set their outcome to a minimum of 0.129 then our overall outcome is.....

\[0.1328 + (0.8672 \times 0.129) = 0.245\]

So our minimum response rate is 24.5% rather than the minimum response for either thrombolysis and thrombectomy.

I'm probably missing something, but it looks like the equation might be giving a patient two chances at the minimum outcome which are then added?

Mike

- 

Michael Allen

PenCHORD (Peninsula Collaboration for Health Operational Research & Development)

NIHR CLAHRC South West Peninsula (PenCLAHRC)

University of Exeter Medical School
Reply

We thank you for this great question. It sparked a lot of thinking on our end and has spurred some great discussion on the assumptions we made when developing the model. In summary, we believe that 1) there were certain simplifying assumptions which needed to be made to generate this model; 2) this model was built from a single point of decision making in the field and therefore differs from clinical practice where there are multiple decision making points; and 3) there is still room for growth in this model.

Below you will find a detailed discussion of these points. In reading this we hope that the common theme which emerges is while we move from a theoretical model to one which is more reflective of clinical practice: 1) transport predictions follow a similar pattern; and 2) fast treatment (with alteplase and/or EVT) is always key for patient outcomes, especially in a drip-and-ship scenario.

Simplifying Assumption: No modification of EVT efficacy by alteplase treatment status.

One of the assumptions we made in building this portion of the model (Equation 1):

\[
E_{\text{quation 1}}: \quad P_{mRS0-1\mid LVO} = P_{mRS0-1\mid LVO \& alteplase} + \left[ (1 - P_{mRS0-1\mid LVO \& alteplase}) \cdot \right] P_{mRS0-1\mid LVO \& EVT}
\]

...is that there is no modification of $P(mRS \ 0 - 1 \mid LVO\&EVT)$ by alteplase treatment status. This is how we could represent a truer to life equation (Equation 2 below) to Equation 1 above.
Appendix B

Equation 2: 
\[ P_{\text{MRS0-1}|LVO} = P_{\text{MRS0-1}|LVO \& alteplase \& EVT} + P_{\text{MRS0-1}|LVO \& alteplase \& no EVT} + P_{\text{MRS0-1}|LVO \& no alteplase \& EVT} + P_{\text{MRS0-1}|LVO \& no alteplase \& no EVT} \]

Additional assumptions of the model include: (1) all patients with LVO within guideline time windows could be treated with either treatment; (2) \( P(\text{treatment}) \) was time invariant; (3) outcome from one treatment did not affect the other treatment both in terms of eligibility for treatment and outcome from both treatments.

Thus, these simplifying assumptions led us to Equation 3.

Equation 3:
\[ P_{\text{MRS0-1}|LVO} = P_{\text{MRS0-1}|LVO \& alteplase} + \left[ 1 - P_{\text{MRS0-1}|LVO \& alteplase} \right] \cdot P_{\text{MRS0-1}|LVO \& EVT} \]

Nevertheless, the question of whether the assumptions are valid and result in “double-counting” of baseline good outcome rates is a good one. The following contains some additional considerations.

Theoretical modelling from point of decision making vs. the practical implementation of such a model.

Our perspective is from the pre-hospital arena when actual treatments are not known. Thus, if we could know which treatments might be used on a given patient, our model would develop into Equation 4:

Equation 4:
\[ P_{\text{MRS0-1}|LVO} = \left( P_{\text{alteplase \& EVT} \mid LVO} \cdot P_{\text{MRS0-1}|LVO \& alteplase \& EVT} \right) + \left( P_{\text{alteplase \& no EVT} \mid LVO} \cdot P_{\text{MRS0-1}|LVO \& alteplase \& no EVT} \right) + \left( P_{\text{no alteplase \& EVT} \mid LVO} \cdot P_{\text{MRS0-1}|LVO \& no alteplase \& EVT} \right) + \left( P_{\text{no alteplase \& no EVT} \mid LVO} \cdot P_{\text{MRS0-1}|LVO \& no alteplase \& no EVT} \right) \]
Appendix B

However, we have no strong data to draw from to determine the probability of treatment modality at the outset (which is clinically a time dependent function). Furthermore, we have only allowed for one point of decision making in our model (on scene) which leads to the following assumption: From the point of decision making we assume that it is known which patients will have a good outcome after alteplase treatment at time from onset to needle = x and therefore do not need to be accounted for in the EVT curve because they would not receive EVT. An example follows in Table 1 and the implications of this assumption are further exemplified in the below second example in Table 2.

Where these two scenarios differ is that at the time of decision making we have no information about which patients may do well given each treatment at a given onset to treatment time, or which patients may do well given no treatment at all. However, at time of decision making we do have information about which patients will not be eligible for alteplase treatment due to time window constraints (i.e. transport time is too long). Given this, a re-evaluation of scenario 2 is given in Table 3 below.
Table 1. Example 1: patient with time from onset to needle = 3 hours, time from onset to groin puncture = 3.5 hours utilizing the model as published in JAMA Neurology

<table>
<thead>
<tr>
<th>Example 1 Parameters</th>
<th>Time from onset to needle = 3 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time from onset to groin puncture = 3.5 hrs</td>
</tr>
</tbody>
</table>

P(mRS = 0–1|LVO) formula

\[ P_{mRS0-1|LVO} = P_{mRS0-1|LVO \& alteplase} + \left[ (1 - P_{mRS0-1|LVO \& alteplase}) \cdot P_{mRS0-1|LVO \& EVT} \right] \]

\[ P_{mRS0-1|LVO \& alteplase} = 0.2359 + 0.0000002(t_{onset to needle})^2 - 0.0004(t_{onset to needle}); \text{ at 4.5 hrs from onset set to minimum value of 0.1328} \]

\[ P_{mRS0-1|LVO \& EVT} = 0.3394 + 0.00000004(t_{onset to puncture})^2 - 0.0002(t_{onset to puncture}); \text{ minimum value = 0.129} \]

Worked out with numbers

\[ P_{mRS0-1|LVO \& alteplase} = 0.2359 + 0.0000002(180)^2 - 0.0004(180) = 0.1645 \]

\[ P_{mRS0-1|LVO \& EVT} = 0.3394 + 0.00000004(210)^2 - 0.0002(210) = 0.2992 \]

\[ P_{mRS0-1|LVO} = 0.1645 + [(1 - 0.1645) \cdot 0.2992] = 0.4145 \]

What are we implying

\[ P_{mRS0-1|LVO \& alteplase} = 0.2359 + 0.0000002(180)^2 - 0.0004(180) = 0.1645 \]

On average LVO patients receiving alteplase at 3 hrs from onset P(good outcome) = 0.1654. Stated differently ~16 out of 100 LVO patients treated with alteplase at 3 hrs from onset will have mRS 0–1 at 90 days.

\[ P_{mRS0-1|LVO \& EVT} = 0.3394 + 0.00000004(210)^2 - 0.0002(210) = 0.2992 \]

On average patients with an onset to groin puncture time of 3.5 hrs have a probability of good outcome = 0.2992. Stated differently approximately ~30 out of 100 LVO patients treated with EVT at 3.5 hrs from onset will have mRS 0–1 at 90 days.

Combining this…

\[ P_{mRS0-1|LVO} = 0.1645 + [(1 - 0.1645) \cdot 0.2992] = 0.4145 \]

This statement is implying that 16% of patients who receive alteplase at 3 hrs from onset will have a good outcome and
therefore do not proceed on to EVT. Among the other 84%, 30% will have a good outcome from EVT with a groin puncture at 3.5 hrs from onset. So overall 41% will have a good outcome. Only 84% of patients are subjected to the EVT curve because you wouldn’t subject the patients with good outcome to another treatment. Importantly, 16% is the rate of good outcome with alteplase only, and not the rate of alteplase without EVT treatment.

However, this implies that good outcome status is known immediately (i.e. you don’t even have an EVT procedure because recanalization has already happened), when in fact good outcome is measured at 90 days. So, this really is not true (some recanalize before EVT can start but others might have recanalized later on if left be). We do not know what these probabilities are in a time dependent fashion; in the ESCAPE trial ~5% of patients with LVO who received alteplase did not require an EVT procedure because they had recanalized.

So, from a theoretical standpoint, the model depicts a situation where there are a group of patients who will have a good outcome with alteplase only and thus theoretically do not need to receive EVT to obtain a good outcome. In real life or from a practical (or implementation) standpoint we do not know which patients would have had a good outcome with alteplase treatment alone so practically, we do treat everybody anyways (under the assumption we made that all LVO patients are eligible for EVT).

So PRACTICALLY you treat everybody even though THEORETICALLY you didn’t have to.
Table 2. Example 2: patient with time from onset to needle = 5 hours, time from onset to groin puncture = 5.5 hours utilizing the model as published in JAMA Neurology

| Example 2 Parameters | Time from onset to needle = 5 hrs  
| Time from onset to groin puncture = 5.5 hrs |  

\[
P_{m_{RS0-1|LVO}} = P_{m_{RS0-1|LVO \& alteplase}} + \left[(1 - P_{m_{RS0-1|LVO \& alteplase}}) \cdot P_{m_{RS0-1|LVO \& EVT}}\right]  
\]

\[
P_{mRS 0 - 1|LVO \& alteplase} = 0.2359 + 0.0000002(t_{onset to needle})^2 - 0.0004(t_{onset to needle}) 
\]

at 4.5 hrs from onset set to minimum value of 0.1328

\[
P_{m_{RS0-1|LVO \& EVT}} = 0.3394 + 0.00000004(t_{onset to puncture})^2 - 0.0002(t_{onset to puncture}) 
\]

minimum value = 0.129

| Worked out with numbers |  
|  

\[
P_{m_{RS 0 - 1|LVO \& alteplase}} = 0.1328  
\]

\[
P_{m_{RS0-1|LVO \& EVT}} = 0.3394 + 0.00000004(330)^2 - 0.0002(330) = 0.2778  
\]

| What are we implying |  
|  

\[
P_{m_{RS 0 - 1|LVO \& alteplase}} = 0.1328  
\]

Patients beyond 4.5 hrs from onset do not receive alteplase but still have a baseline \( P(\text{good outcome}) = 0.1328 \). Stated differently \(~13\) out of \(100\) LVO patients not treated with alteplase at all will have \(mRS \ 0\ – \ 1\) at 90 days.

\[
P_{m_{RS0-1|LVO \& EVT}} = 0.3394 + 0.00000004(330)^2 - 0.0002(330) = 0.2778  
\]

On average patients with an onset to groin puncture time of 5.5 hrs have a probability of good outcome = 0.2278. Stated differently approximately \(~28\) out of \(100\) LVO patients treated with EVT at 5.5 hrs from onset will have \(mRS \ 0\ – \ 1\) at 90 days.

Combining this...

\[
P_{m_{RS0-1|LVO}} = 0.1328 + [(1 - 0.1328) \cdot 0.2778] = 0.3737  
\]

Again, we are making the statement that 13% of untreated patients will have a good outcome at 90 days (which is true) and as such it is only the other 87% of patients that will not have a good outcome given no treatment who are subjected to the EVT \(P(\text{good outcome})\) curve. However, at time of treatment we do not know which patients belong to which group so practically we would treat all patients with EVT even though theoretically we did not have to.

---

Appendix B
Table 3. Example 2a: patient with time from onset to needle = 5 hours, time from onset to groin puncture = 5.5 hours incorporating a correction in the P(good outcome | alteplase) formula.

<table>
<thead>
<tr>
<th>Scenario 2a Parameters</th>
<th>Time from onset to needle = 5 hrs</th>
<th>Time from onset to groin puncture = 5.5 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(mRS 0 – 1</td>
<td>LVO) formula</td>
<td>$P_{mRS=0-1</td>
</tr>
<tr>
<td></td>
<td>$P_{mRS=0-1</td>
<td>LVO &amp; alteplase} = 0.2359 + 0.0000002(t_{onset to needle})^2 - 0.0004(t_{onset to needle});$ at 4.5 hrs from onset set to minimum value of 0</td>
</tr>
<tr>
<td></td>
<td>$P_{mRS=0-1</td>
<td>LVO &amp; EVT} = 0.3394 + 0.0000004(t_{onset to puncture})^2 - 0.0002(t_{onset to puncture}),$ minimum value = 0.129</td>
</tr>
<tr>
<td>Worked out with numbers</td>
<td>$P_{mRS=0-1</td>
<td>LVO &amp; alteplase} = 0$</td>
</tr>
<tr>
<td></td>
<td>$P_{mRS=0-1</td>
<td>LVO &amp; EVT} = 0.3394 + 0.00000004(330)^2 - 0.0002(330) = 0.2778$</td>
</tr>
<tr>
<td></td>
<td>$P_{mRS=0-1</td>
<td>LVO} = 0 + [(1 - 0) \cdot 0.2778] = 0.2778$</td>
</tr>
<tr>
<td>What are we implying</td>
<td>$P_{mRS=0-1</td>
<td>LVO &amp; alteplase} = 0$</td>
</tr>
<tr>
<td></td>
<td>Patients beyond 4.5 hrs from onset do not receive alteplase thus their P(good outcome) data lies solely in the P(good outcome</td>
<td>EVT) curve.</td>
</tr>
<tr>
<td></td>
<td>$P_{mRS=0-1</td>
<td>LVO &amp; EVT} = 0.3394 + 0.00000004(330)^2 - 0.0002(330) = 0.2778$</td>
</tr>
<tr>
<td></td>
<td>On average patients with an onset to groin puncture time of 5.5 hrs have a probability of good outcome = 0.2278. Stated differently approximately ~28 out of 100 LVO patients treated with EVT at 5.5 hrs from onset will have mRS 0 – 1 at 90 days.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combining this… $P_{mRS=0-1</td>
<td>LVO} = 0 + [(1 - 0) \cdot 0.2778] = 0.2778$</td>
</tr>
<tr>
<td></td>
<td>Given the patients only treatment option is EVT at this time all patients are treated with EVT (under our assumption that all patients with LVO are eligible for EVT treatment) and thus their P(good outcome) lies solely in the P(good outcome</td>
<td>EVT) curve.</td>
</tr>
</tbody>
</table>
Appendix B

As shown above, there is a difference in P(mRS 0 – 1 | LVO & onset to needle = 5hrs & onset to groin puncture = 5.5 hrs) using the two different methods of ~0.10. Figure 1 shows the difference in P(mRS 0 – 1 | LVO) for each of these two methods for patients with onset to needle time > 4.5 hrs and onset to groin puncture = onset to needle + 30 min.

Figure 1. P(mRS 0 – 1 | LVO) with onset to needle time > 4.5 hrs and onset to groin puncture time = onset to needle time + 30 mins.

The blue line shows P(mRS 0 – 1 | LVO) as written in the JAMA Neurology publication (Equation 6):

Equation 6:  
\[ P_{mRS0-1|LVO} = P_{mRS0-1|LVO \text{ & alteplase}} \times (1 - P_{mRS0-1|LVO \text{ & alteplase}}) \]  
\[ P_{mRS0-1|LVO \text{ & alteplase}} = 0.2359 + 0.0000002(t_{onset \text{ to needle}})^2 - 0.0004(t_{onset \text{ to needle}}); \text{ at 4.5 hrs from onset set to minimum value of 0.1328} \]  
\[ P_{mRS0-1|LVO \text{ & EVT}} = 0.3394 + 0.0000004(t_{onset \text{ to puncture}})^2 - 0.0002(t_{onset \text{ to puncture}}); \text{ minimum value = 0.129} \]

The orange line shows P(mRS 0 – 1 | LVO) as outlined below (Equation 7):

Equation 7:  
\[ P_{mRS0-1|LVO} = P_{mRS0-1|LVO \text{ & alteplase}} \times (1 - P_{mRS0-1|LVO \text{ & alteplase}}) \]  
\[ P_{mRS0-1|LVO \text{ & alteplase}} = 0.2359 + 0.0000002(t_{onset \text{ to needle}})^2 - 0.0004(t_{onset \text{ to needle}}); \text{ at 4.5 hrs from onset set to minimum value of 0} \]
The grey line shows the difference in $P(\text{mRS } 0 - 1 \mid \text{LVO})$ between the two methods (current model – corrected model).

Figure 2 shows the impact of this on the entire model shown below (Equation 8):

$$P_{\text{mRS}0-1|LVO \& EVT} = 0.3394 + 0.00000004(t_{\text{onset to puncture}})^2 - 0.0002(t_{\text{onset to puncture}}), \text{ minimum value } = 0.129$$

Where, $P(\text{LVO} \mid \text{LAMS } \geq 4) = 0.4538$, $P(\text{nLVO} \mid \text{LAMS } \geq 4) = 0.1092$, $P(\text{ICH} \mid \text{LAMS } \geq 4) = 0.3445$, $P(\text{mimic} \mid \text{LAMS } \geq 4) = 0.0924$. $P(\text{mRS } 0 - 1 \mid \text{nLVO})$ is given by the Equation 9 below:

$$P_{\text{mRS}0-1|\text{nLVO}} = 0.6343 - 0.00000005(t_{\text{onset to needle}})^2 - 0.0005(t_{\text{onset to needle}}), \text{ at 4.5 hrs from onset set to 0.4622}$$

And the ICH, and mimic pieces of the equation are constants shown in Equation 10:

$$P_{\text{ICH}|\text{LAMS} \geq 4}(P_{\text{mRS}0-1|\text{ICH}}) + (P_{\text{mimic}|\text{LAMS} \geq 4})(P_{\text{mRS}0-1|\text{SM}}) = (0.3445 \cdot 0.24) + (0.0924 \cdot 0.90) = 0.1658$$
Figure 2. P(mRS 0 – 1 | LAMS ≥4) vs. onset to groin puncture time with alteplase administration occurring 30 minutes prior to groin puncture.

The blue line shows P(mRS 0 – 1 | LAMS ≥4) as written in the JAMA Neurology publication (Equation 11):

Equation 11: \[
P_{\text{mRS}0-1|LAMS \geq 4} = \left( P_{\text{LVO}|LAMS \geq 4} \right) \left( P_{\text{mRS}0-1|LVO} \right) + \left( P_{\text{nLVO}|LAMS \geq 4} \right) \left( P_{\text{mRS}0-1|nLVO} \right) + \left( P_{\text{ICH}|LAMS \geq 4} \right) \left( P_{\text{mRS}0-1|ICH} \right) + \left( P_{\text{mimic}|LAMS \geq 4} \right) \left( P_{\text{mRS}0-1|SM} \right)
\]

\[P_{\text{mRS}0-1|LVO \ & \ alteplase} = 0.2359 + 0.0000002(t_{\text{onset to needle}})^2 - 0.0004(t_{\text{onset to needle}}); \text{ at 4.5 hrs from onset set to minimum value of 0.1328}
\]

\[P_{\text{mRS}0-1|LVO \ & \ EVT} = 0.3394 + 0.0000004(t_{\text{onset to puncture}})^2 - 0.0002(t_{\text{onset to puncture}}); \text{ minimum value = 0.129}
\]

\[P_{\text{LVO} | \text{LAMS} \geq 4} = 0.4538\]

\[P_{\text{mRS0-1|nLVO \ & \ alteplase}} = 0.6343 - 0.0000005(t_{\text{onset to needle}})^2 - 0.0005(t_{\text{onset to needle}}); \text{ at 4.5 hrs from onset set to 0.4622}
\]

\[P_{\text{LVO} | \text{LAMS} \geq 4} = 0.4538\]

\[P_{\text{mRS0-1|ICH \ & \ alteplase}} = (0.3445 \cdot 0.24) + (0.0924 \cdot 0.90) = 0.1658\]

The orange line shows P(mRS 0 – 1 | LAMS ≥4) as outlined below (Equation 12):

Equation 12: \[
P_{\text{mRS}0-1|LAMS \geq 4} = \left( P_{\text{LVO}|LAMS \geq 4} \right) \left( P_{\text{mRS}0-1|LVO} \right) + \left( P_{\text{nLVO}|LAMS \geq 4} \right) \left( P_{\text{mRS0-1|nLVO}} \right) + \left( P_{\text{ICH}|LAMS \geq 4} \right) \left( P_{\text{mRS0-1|ICH}} \right) + \left( P_{\text{mimic}|LAMS \geq 4} \right) \left( P_{\text{mRS0-1|SM}} \right)
\]

\[P_{\text{mRS0-1|LVO \ & \ alteplase}} = 0.2359 + 0.0000002(t_{\text{onset to needle}})^2 - 0.0004(t_{\text{onset to needle}}); \text{ at 4.5 hrs from onset set to minimum value of 0}
\]

\[P_{\text{mRS0-1|LVO \ & \ EVT}} = 0.3394 + 0.0000004(t_{\text{onset to puncture}})^2 - 0.0002(t_{\text{onset to puncture}}); \text{ minimum value = 0.129} \]
Appendix B

\[
P_{LVO \mid LAMS \geq 4} = 0.4538
\]

\[
P_{mRS0-1\mid LVO \& alteplase} = 0.6343 - 0.00000005(t_{onset to needle})^2 - 0.0005(t_{onset to needle}) \text{ at 4.5 hrs from onset set to 0.4622}
\]

\[
(P_{ICH \mid LAMS \geq 4})(P_{mRS0-1\mid ICH}) + (P_{mimic \mid LAMS \geq 4})(P_{mRS0-1\mid SM})
\]

\[
= (0.3445 \cdot 0.24) + (0.0924 \cdot 0.90) = 0.1658
\]

The grey line shows the difference in \(P(\text{mRS } 0 – 1 \mid \text{LAMS } \geq 4)\) between the two methods (current model – corrected model).

As exemplified above, for patients with time from onset to needle > 4.5 hours (with groin puncture occurring 30 minutes after alteplase administration in this example) with the given correction there are small differences observed in the LVO arm of the model which in turn effects the overall \(P(\text{good outcome})\) predicted by the model. However, what is interesting is that these differences are small so we believe that using this theoretical model to simulate a practical scenario to be reasonable.

Figure 3 below illustrates how this correction affects decision making in long transport scenarios where onset to needle time \(\geq 4.5\) hrs in some situations.
Figure 3. Two-dimensional temporospatial diagrams depicting 120 mins of travel time between the thrombolysis and EVT centre in three different efficiency scenarios.

Left: efficient treatment at all centres. Center: efficient treatment at EVT centre, slow treatment at thrombolysis centre. Right: slow treatment at all centres. Time from onset to first medical contact = 30 and ambulance response and scene time = 30 minutes in all scenarios. The top row was generated with the model as published in JAMA Neurology and the bottom row was generated using the correction discussed above.
As shown, due to the decreased probability of good outcome for patients beyond 4.5 hrs from onset there is an increased utilization of the drip-and-ship model in the region of the temporospatial plane where the patient would forgo the opportunity for alteplase treatment if taken via mothership route due to onset to treatment time exceeding 4.5 hours. The absolute probability of good outcome has also decreased in this area slightly although it is difficult to discern in this colour scale (which was made to be consistent with the JAMA Neurology publication figures). However, it should be noted that both models predict similar transport patterns. In both models, fast treatment at the thrombolysis centre is key if drip-and-ship is to be a viable option for the patient. As door to needle and door in door out time increase at the thrombolysis centre the area where drip-and-ship predicts best outcomes decreases. Further, in a completely inefficient system (right panel) the overall probability of good outcome for all patients decreases (compared to left panel).

*Future modelling directions: Hypothetical model for patients with LVO considering non-time dependent probability of treatment with each modality*

Using some additional data from the ESCAPE trial we present below a hypothetical update to the LVO arm of the model with the addition of non-time dependent probability of treatment with each modality (Equation 13).

Equation 13:  

\[
P_{\text{mRS } 0-1|LVO} = \left(P_{\text{alteplase } \& \text{ EVT } | \ LVO } \cdot P_{m\text{RS } 0-1|LVO \ & \text{alteplase } \& \text{ EVT}} \right) + \\
\left(P_{\text{alteplase } \& \text{ no EVT } | \ LVO } \cdot P_{m\text{RS } 0-1|LVO \ & \text{alteplase } \& \text{ no EVT}} \right) + \\
\left(P_{\text{no alteplase } \& \text{ EVT } | \ LVO } \cdot P_{m\text{RS } 0-1|LVO \ & \text{no alteplase } \& \text{ EVT}} \right) + \\
\left(P_{\text{no alteplase } \& \text{ no EVT } | \ LVO } \cdot P_{m\text{RS } 0-1|LVO \ & \text{no alteplase } \& \text{ no EVT}} \right)
\]
Appendix B

Where \( P(\text{alteplase} \& \text{no EVT} \mid \text{LVO}) = 0.05 \) when onset to needle time is < 4.5 hrs, estimated from the ESCAPE trial where 5% of alteplase treated patients recanalized prior to EVT procedure start. Therefore, \( P(\text{alteplase} \& \text{EVT} \mid \text{LVO}) = 0.95 \) when onset to needle time < 4.5 hrs. \( P(\text{no alteplase} \& \text{EVT} \mid \text{LVO}) = 0 \) when onset to needle time is < 4.5 hrs. When onset to needle time is \( \geq 4.5 \) hrs \( P(\text{no alteplase} \& \text{EVT}) = 1 \). \( P(\text{no alteplase} \& \text{no EVT} \mid \text{LVO}) = 0 \) given our assumption that all patients within time window will be eligible for treatment.

Given the assumption that there is no modification of \( P(\text{mRS 0–1} \mid \text{LVO}\&\text{EVT}) \) by alteplase treatment status \( P(\text{mRS 0–1} \mid \text{LVO} \& \text{no alteplase} \& \text{EVT}) = P(\text{mRS 0–1} \mid \text{LVO} \& \text{alteplase} \& \text{EVT}) \). Using this updated model, we re-visit the above examples in Tables 4 – 6.
Table 4. Example 1 revisited: patient with time from onset to needle = 3 hours, time from onset to groin puncture = 3.5 hours utilizing a model which incorporates P(treatment)

| Example 1 Parameters | Time from onset to needle = 3 hrs  
| Time from onset to groin puncture = 3.5 hrs |
| --- | --- |
| $P(mRS\ 0-1|LVO)$ formula | $P_{mRS\ 0-1|LVO} = (P_{alteplase\ &\ EVT\ |\ LVO\ \cdot\ P_{mRS\ 0-1|LVO\ \&\ alteplase\ &\ EVT})$  
$+ (P_{alteplase\ \&\ no\ EVT\ |\ LVO\ \cdot\ P_{mRS\ 0-1|LVO\ \&\ alteplase\ \&\ no\ EVT})$  
$+ (P_{no\ alteplase\ &\ EVT\ |\ LVO\ \cdot\ P_{mRS\ 0-1|LVO\ \&\ no\ alteplase\ \&\ EVT})$  
$+ (P_{no\ alteplase\ \&\ no\ EVT\ |\ LVO\ \cdot\ P_{mRS\ 0-1|LVO\ \&\ no\ alteplase\ \&\ no\ EVT})$ |
| $P_{mRS\ 0-1|LVO\ \&\ alteplase} = 0.2359 + 0.0000002(t_{onset\ to\ needle})^2 - 0.0004(t_{onset\ to\ needle})$: at 4.5 hrs from onset set to minimum value of 0.1328 |
| $P_{mRS0-1|LVO\ &\ EVT} = 0.3394 + 0.00000004(t_{onset\ to\ puncture})^2 - 0.0002(t_{onset\ to\ puncture})$, minimum value = 0.129 |
| Worked out with numbers | $P_{mRS\ 0-1|LVO} = (0.95 \cdot P_{mRS\ 0-1|LVO\ \&\ alteplase\ &\ EVT}) + (0.05 \cdot P_{mRS\ 0-1|LVO\ \&\ alteplase\ \&\ no\ EVT})$  
$+ (0 \cdot P_{mRS\ 0-1|LVO\ \&\ no\ alteplase\ \&\ EVT}) + (0 \cdot P_{mRS\ 0-1|LVO\ \&\ no\ alteplase\ \&\ no\ EVT})$ |
| $P_{mRS\ 0-1|LVO\ \&\ alteplase} = 0.2359 + 0.0000002(180)^2 - 0.0004(180) = 0.1645$ |
| $P_{mRS0-1|LVO\ &\ EVT} = 0.3394 + 0.00000004(210)^2 - 0.0002(210) = 0.2992$ |
| $P_{mRS0-1|LVO} = (0.95 \cdot 0.2992) + (0.05 \cdot 0.1645) = 0.2925$ |
| What are we implying | $P_{mRS\ 0-1|LVO\ \&\ alteplase} = 0.2359 + 0.0000002(180)^2 - 0.0004(180) = 0.1645$ |
| On average LVO patients receiving alteplase at 3 hrs from onset $P$(good outcome) = 0.1654. Stated differently ~16 out of 100 LVO patients treated with alteplase at 3 hrs from onset will have mRS 0 – 1 at 90 days. |
| $P_{mRS0-1|LVO\ &\ EVT} = 0.3394 + 0.00000004(210)^2 - 0.0002(210) = 0.2992$ |
| On average patients with an onset to groin puncture time of 3.5 hrs have a probability of good outcome = 0.2992. Stated differently approximately ~30 out of 100 LVO patients treated with EVT at 3.5 hrs from onset will have mRS 0 – 1 at 90 days. |
Combining this...

\[ P_{mR50-1|LVO} = (0.95 \cdot 0.2992) + (0.05 \cdot 0.1645) = 0.2925 \]

This statement is implying that while 16% of LVO patients treated with alteplase at 3 hrs from onset will have a good outcome at 90 days, this is only known prior to EVT start for 5% of patients (i.e. recanalization before EVT procedure start). Among the other 95%, 30% will have a good outcome from EVT with a groin puncture at 3.5 hrs from onset. So overall 29% will have a good outcome.
Table 5. Example 2 revisited: patient with time from onset to needle = 5 hours, time from onset to groin puncture = 5.5 hours utilizing a model which incorporates P(treatment)

<table>
<thead>
<tr>
<th>Example 2 Parameters</th>
<th>Time from onset to needle = 5 hrs</th>
<th>Time from onset to groin puncture = 5.5 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{\text{mRS 0 - 1}</td>
<td>\text{LVO}} ) formula</td>
<td>( P_{\text{mRS 0 - 1}</td>
</tr>
<tr>
<td></td>
<td>( P_{\text{mRS 0 - 1}</td>
<td>\text{LVO &amp; EVT}} = 0.3394 + 0.00000004(t_{\text{onset to puncture}})^2 - 0.0002(t_{\text{onset to puncture}}), ) minimum value = 0.129</td>
</tr>
<tr>
<td>Worked out with numbers</td>
<td>( P_{\text{mRS 0 - 1}</td>
<td>\text{LVO}} = \left( 0 \cdot P_{\text{mRS 0 - 1}</td>
</tr>
<tr>
<td></td>
<td>( P_{\text{mRS 0 - 1}</td>
<td>\text{LVO &amp; EVT}} = 0.3394 + 0.00000004(330)^2 - 0.0002(330) = 0.2778 )</td>
</tr>
<tr>
<td></td>
<td>( P_{\text{mRS 0 - 1}</td>
<td>\text{LVO}} = (0 \cdot 0.1328) + (1 \cdot 0.2778) = 0.2778 )</td>
</tr>
<tr>
<td>What are we implying</td>
<td>( P_{\text{mRS 0 - 1}</td>
<td>\text{LVO &amp; alteplase}} = 0.1328 )</td>
</tr>
</tbody>
</table>

Patients beyond 4.5 hrs from onset do not receive alteplase but still have a baseline \( P(\text{good outcome}) = 0.1328 \). Stated differently ~13 out of 100 LVO patients not treated with alteplase at all will have mRS 0 – 1 at 90 days.

\( P_{\text{mRS 0 - 1}|\text{LVO \& EVT}} = 0.3394 + 0.00000004(330)^2 - 0.0002(330) = 0.2778 \)

On average patients with an onset to groin puncture time of 5.5 hrs have a probability of good outcome = 0.2278. Stated differently approximately ~28 out of 100 LVO patients treated with EVT at 5.5 hrs from onset will have mRS 0 – 1 at 90 days.
Combining this…

\[ P_{m_{RS0-1|\text{LVO}}} = (0 \cdot 0.1328) + (1 \cdot 0.2778) = 0.2778 \]

Given the patients only treatment option is EVT at this time all patients are treated with EVT (under our assumption that all patients with LVO are eligible for EVT treatment) and thus their P(good outcome) lies solely in the P(good outcome | EVT) curve.
## Appendix B

Table 6: Example 2a revisited: patient with time from onset to needle = 5 hours, time from onset to groin puncture = 5.5 hours utilizing a model which incorporates P(treatment)

| Example 2a Parameters | Time from onset to needle = 5 hrs
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time from onset to groin puncture = 5.5 hrs</td>
</tr>
</tbody>
</table>

\[
P_{mRS \ 0-1|LVO} = (P_{alteplase \ & \ EVT \ | \ LVO} \cdot P_{mRS \ 0-1|LVO \ & \ alteplase \ & \ EVT})
+ (P_{alteplase \ & \ no EVT \ | \ LVO} \cdot P_{mRS \ 0-1|LVO \ & \ alteplase \ & \ no EVT})
+ (P_{no \ alteplase \ & \ EVT \ | \ LVO} \cdot P_{mRS \ 0-1|LVO \ & \ no \ alteplase \ & \ EVT})
+ (P_{no \ alteplase \ & \ no \ EVT \ | \ LVO} \cdot P_{mRS \ 0-1|LVO \ & \ no \ alteplase \ & \ no \ EVT})
\]

\[
P_{mRS \ 0-1|LVO \ & \ alteplase} = 0.2359 + 0.0000002(t_{onset \ to \ needle})^2 - 0.0004(t_{onset \ to \ needle}); \text{ at } 4.5 \text{ hrs from onset set to minimum value of 0}
\]

\[
P_{mRS0-1|LVO \ & \ EVT} = 0.3394 + 0.00000004(t_{onset \ to \ puncture})^2 - 0.0002(t_{onset \ to \ puncture}), \text{ minimum value = 0.129}
\]

| Worked out with numbers | \[
P_{mRS \ 0-1|LVO} = (0 \cdot P_{mRS \ 0-1|LVO \ & \ alteplase \ & \ EVT}) + (0 \cdot P_{mRS \ 0-1|LVO \ & \ alteplase \ & \ no \ EVT})
+ (1 \cdot P_{mRS \ 0-1|LVO \ & \ no \ alteplase \ & \ EVT}) + (0 \cdot P_{mRS \ 0-1|LVO \ & \ no \ alteplase \ & \ no \ EVT})
\]
|--------------------------|----------------------------------------------------------------------------------|
|                          | \[
P_{mRS \ 0-1|LVO \ & \ alteplase} = 0.1328
\]
|                          | \[
P_{mRS0-1|LVO \ & \ EVT} = 0.3394 + 0.00000004(330)^2 - 0.0002(330) = 0.2778
\]
|                          | \[
P_{mRS0-1|LVO} = (0 \cdot 0.1328) + (1 \cdot 0.2778) = 0.2778
\]

| What are we implying | \[
P_{mRS \ 0-1|LVO \ & \ alteplase} = 0
\]
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients beyond 4.5 hrs from onset do not receive alteplase thus their P(good outcome) data lies solely in the P(good outcome</td>
</tr>
</tbody>
</table>
|                       | \[
P_{mRS0-1|LVO \ & \ EVT} = 0.3394 + 0.00000004(330)^2 - 0.0002(330) = 0.2778
\]
|                       | On average patients with an onset to groin puncture time of 5.5 hrs have a probability of good outcome = 0.2278. Stated differently approximately ~28 out of 100 LVO patients treated with EVT at 5.5 hrs from onset will have mRS 0 – 1 at 90 days. |
Combining this…

\[ P_{mRS0-1|LVO} = (0 \cdot 0.1328) + (1 \cdot 0.2778) = 0.2778 \]

Given the patients only treatment option is EVT at this time all patients are treated with EVT (under our assumption that all patients with LVO are eligible for EVT treatment) and thus their \( P(\text{good outcome}) \) lies solely in the \( P(\text{good outcome} \mid \text{EVT}) \) curve.
Appendix B

Figure 4 below shows the impact of the above adjustment, which while not perfect, we believe begins to move closer to a true to life model.

Figure 4. P(mRS 0 – 1 | LAMS ≥4) vs. onset to groin puncture time with alteplase administration occurring 30 minutes prior to groin puncture.

The blue line shows P(mRS 0 – 1 | LAMS ≥4) as written in the JAMA Neurology publication (Equation 14):

\[
P_{mRS0-1|LAMS\geq4} = (P_{LVO|LAMS\geq4})(P_{mRS0-1|LVO}) + \\
(P_{nLVO|LAMS\geq4})(P_{mRS0-1|nLVO}) + (P_{ICH|LAMS\geq4})(P_{mRS0-1|ICH}) + \\
(P_{mimic|LAMS\geq4})(P_{mRS0-1|SM})
\]

\[
P_{mRS0-1|LVO \& alteplase} = 0.2359 + 0.0000002(t_{onset \ to \ needle})^2 - \\
0.0004(t_{onset \ to \ needle}): \ at \ 4.5 \ hrs \ from \ onset \ set \ to \ minimum \ value \ of \ 0.1328
\]

\[
P_{mRS0-1|LVO \& EVT} = 0.3394 + 0.0000004(t_{onset \ to \ puncture})^2 - \\
0.0002(t_{onset \ to \ puncture}), \ minimum \ value = 0.129
\]

\[
P_{LVO \ | \ LAMS \geq 4} = 0.4538
\]

\[
P_{mRS0-1|nLVO \ & \ alteplase} = 0.6343 - 0.00000005(t_{onset \ to \ needle})^2 - \\
0.0005(t_{onset \ to \ needle}): \ at \ 4.5 \ hrs \ from \ onset \ set \ to \ 0.4622
\]

\[
(P_{ICH|LAMS\geq4})(P_{mRS0-1|ICH}) + (P_{mimic|LAMS\geq4})(P_{mRS0-1|SM})
\]

\[
= (0.3445 \cdot 0.24) + (0.0924 \cdot 0.90) = 0.1658
\]

The orange line shows P(mRS 0 – 1 | LAMS ≥4) as outlined below (Equation 15):
Appendix B

Equation 15: 
\[ P_{mRS=0-1|LAMS \geq 4} = (P_{LVO|LAMS \geq 4})(P_{mRS=0-1|LVO}) + (P_{nLVO|LAMS \geq 4})(P_{mRS=0-1|nLVO}) + (P_{ICH|LAMS \geq 4})(P_{mRS=0-1|ICH}) + (P_{mimic|LAMS \geq 4})(P_{mRS=0-1|SM}) \]

\[ P_{mRS=0-1|LVO \& alteplase} = 0.2359 + 0.0000002(t_{onset to needle})^2 - 0.0004(t_{onset to needle}) \text{ at 4.5 hrs from onset set to minimum value of 0} \]

\[ P_{mRS=0-1|LVO \& EVT} = 0.3394 + 0.0000004(t_{onset to puncture})^2 - 0.0002(t_{onset to puncture}) \text{ at 4.5 hrs from onset set to 0.4622 minimum value} = 0.129 \]

\[ P_{LVO | LAMS \geq 4} = 0.4538 \]

\[ P_{mRS=0-1|LVO \& alteplase} = 0.6343 - 0.00000005(t_{onset to needle})^2 - 0.0005(t_{onset to needle}) \text{ at 4.5 hrs from onset set to 0.4622} \]

\[ (P_{ICH|LAMS \geq 4})(P_{mRS=0-1|ICH}) + (P_{mimic|LAMS \geq 4})(P_{mRS=0-1|SM}) \]

\[ = (0.3445 \cdot 0.24) + (0.0924 \cdot 0.90) = 0.1658 \]

The black dashed line shows \( P(mRS \ 0-1 \ LAMS \geq 4) \) incorporating the additional ESCAPE data as outlined in Equation 16 below:

Equation 16: 
\[ P_{mRS=0-1|LVO} = (P_{alteplase \ & \ EVT \ | \ LVO} \cdot P_{mRS=0-1|LVO \ & \ alteplase \ & \ EVT}) + (P_{alteplase \ & \ no \ EVT \ | \ LVO} \cdot P_{mRS=0-1|LVO \ & \ alteplase \ & \ no \ EVT}) + (P_{no \ alteplase \ & \ EVT \ | \ LVO} \cdot P_{mRS=0-1|LVO \ & \ no \ alteplase \ & \ EVT}) + (P_{no \ alteplase \ & \ no \ EVT \ | \ LVO} \cdot P_{mRS=0-1|LVO \ & \ no \ alteplase \ & \ no \ EVT}) \]

Where \( P(alteplase \ & \ no \ EVT \ | \ LVO) = 0.05 \) when onset to needle time is < 4.5 hrs, \( P(alteplase \ & \ EVT \ | \ LVO) = 0.95 \) when onset to needle time < 4.5 hrs. \( P(no \ alteplase \ & \ EVT \ | \ LVO) = 0 \) when onset to needle time is < 4.5 hrs. When onset to needle time is ≥ 4.5 hrs \( P(no \ alteplase \ & \ EVT) = 1 \). \( P(no \ alteplase \ & \ no \ EVT \ | \ LVO) = 0 \) given our assumption that all patients within time window will be eligible for treatment. Given the assumption that there is no modification of \( P(mRS \ 0-1 \ | \ LVO&EVT) \) by alteplase treatment status \( P(mRS \ 0-1 \ | \ LVO \ & \ alteplase \ & \ EVT) = P(mRS \ 0-1 \ | \ LVO \ & \ alteplase \) and EVT).

Incorporating the \( P(treatment \ modality) \) for LVO patients (still under the assumption that all patients within time windows are treated) begins to illustrate what we believe to be moving closer to a true to life model. It should be noted that these probabilities are entered into the model as non-time dependent and were based off the ESCAPE trial where there was a median of 75 minutes between alteplase administration and groin puncture and 5% of patients were shown to have full reperfusion at the time of selective cerebral angiography. However, this may not always be the case, as it is likely that as time from alteplase administration to groin puncture increases (i.e. long drip-and-
ship scenarios) the probability of recanalization prior to groin puncture increases and thus $P(\text{alteplase & no EVT | LVO})$ increases while $P(\text{alteplase & EVT | LVO})$ decreases. However, there is a lack of time dependent data on recanalization rates after alteplase administration in patients with LVO to draw from here. This hypothetical model still assumes all patients will receive EVT treatment which is not reflective of clinical practice. Due to these assumptions, while overall $P(\text{mRS 0–1 | LVO})$ has decreased compared to published model, we believe $P(\text{mRS 0–1 | LVO})$ is overestimated, especially in the mothership scenario where time from onset to groin puncture is shorter than that in the drip-and-ship scenario (Figure 5). In the future, $P(\text{alteplase | LVO})$, $P(\text{alteplase | nLVO})$, and $P(\text{EVT eligible | time from onset})$ will need to be incorporated into the model to fully illustrate the entire clinical scenario.
Figure 5. Two-dimensional temporospatial diagrams depicting 120 mins of travel time between the thrombolysis and EVT centre in three different efficiency scenarios.

Left: efficient treatment at all centres. Center: efficient treatment at EVT centre, slow treatment at thrombolysis centre. Right: slow treatment at all centres. Time from onset to first medical contact = 30 and ambulance response and scene time = 30 minutes in all scenarios. The top row was generated with the model as published in JAMA Neurology the middle row was generated using the correction discussed above, and the bottom row was generated using the model which includes P(treatment).
Appendix B

It should be noted again that the common thread running through all scenarios is fast treatment being key at the thrombolysis centre if drip-and-ship is to remain an option for patients and the overall decrease in P(good outcome) as time from onset to treatment lengthens.

Conclusion

Overall, your question is a good one. There is a small difference in effect in our published model compared to more refined models under some scenarios which changes the average probability of good outcome sometimes by a few percent up or down. The assumptions we made in the published model were necessary simplifications to deal with the available data and still result in helpful overall estimates of the direction of effect in making system-wide transport and triage rules. These do not change. One of the overall conclusions of the modelling work is to really emphasize the need for speed, both at the level of medical thrombolysis with intravenous alteplase and surgical treatment with EVT. The speed of treatment is a dominant factor under all assumptions.
CHAPTER 2

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Chapter 6

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