Comments and Opinions

Drip and Ship Versus Direct to Comprehensive Stroke Center

Conditional Probability Modeling

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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.[1] In an anterior circulation, large-vessel ischemic stroke 1.9 million neurons are lost every minute.[2] 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.[3–8]

The facilities and expertise needed for endovascular procedures are only available at endovascular capable centers (ECCs), which are typically tertiary care hospitals. Medical treatment with alteplase is more widely available. This creates 2 options for prehospital 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 (nECC; 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 modeling and suggest a candidate model for evaluation.

Building the Model

Assumptions

We make several assumptions in the development of the prediction models (Table I in the online-only Data Supplement). First, these models apply when there is uncertainty on which transport and treatment decision to choose. Second, the nECC is the closest treatment center to the location of stroke occurrence. If an ECC is the closest treatment center, 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 that there is only 1 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 because 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 varies linearly with time but has an upper limit.[9,10] We assume that the probability of successful reperfusion with endovascular therapy is time invariant. Although we know that this is untrue, the variation with time is probably small.[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 last, we assume that for patients with LVOs, reperfusion is only achieved through treatment, something which is known to be ≈95% true in the first 1 to 2 hours after stroke onset.[7,12]

Conditional Probabilities

A variety of conditional probabilities are considered (Table II in the 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 the Table.

Time Considerations

The time from stroke onset to treatment initiation is vital.[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

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Table. Mothership and Drip and Ship Models

Model	Conditional Probabilities	Time Considerations	Conditional Probability Estimates
Mothership	*P*(good outcome|mothership model)=*P*(reperfusion|EVT)·*P*(good outcome|reperfusion at ϕ mins)+*P*(no reperfusion|EVT)·*P*(good outcome|no reperfusion)	*P*(good outcome|mothership model)=*P*(reperfusion |EVT)·*P*(good outcome|reperfusion at 30+Z+C+30 mins)+*P*(no reperfusion|EVT)·*P*(good outcome|no reperfusion)	*P*(good outcome|mothership model)=0.74·[0.75-0.0006(30+Z+C+30)]+0.26·0.30
Drip and Ship	*P*(good outcome|drip and ship model)=*P*(early reperfusion|alteplase)·*P*(good outcome|reperfusion at ϕ mins)+*P*(no early reperfusion|alteplase) ·[*P*(reperfusion|EVT)·*P* (good outcome|reperfusion at ϕ mins)+*P*(no reperfusion|EVT)·*P*(good outcome|no reperfusion)]	*P*(good outcome|drip and ship model)=*P*(early reperfusion|alteplase)·*P*(good outcome|reperfusion at 30+X+A+70 mins)+*P*(no early reperfusion|alteplase) ·[*P*(reperfusion|EVT)·*P*(good outcome|reperfusion at 30+X+A+B+Y+C+30 mins)+*P*(no reperfusion|EVT)·*P*(good outcome|no reperfusion)]	*P*(good outcome|drip and ship model)=0.18·[0.75-0.0006(30+X+A+B+70)]+0.82·[0.74·[0.75-0.0006(30+X+A+B+Y+C+30)]+0.26·0.30

EVT indicates endovascular therapy. A indicates the time from the patient's arrival at the nonendovascular capable centre (nECC) to the administration of alteplase. B is the time from alteplase administration to leaving for the endovascular capable centre (ECC). C is the time from the patients arrival at the ECC to the beginning of the endovascular procedure. X is the transportation time from the patient to the nECC. Y is the transportation time from the nECC to the ECC. Z is the transportation time from the patient to the ECC.

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 has been shown to be faster at the ECC because of prenotification in the drip and ship case.[13]

We assume that 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 because angiography studies have shown that 1.6% of internal carotid artery, 23.9% of M1 (M1 segment of the middle cerebral artery), and 38.9% of M2 (M2 segment of the middle cerebral artery) occlusions were recanalized at first angiography post alteplase administration (median 70 minutes).[14] Also, this is a relevant time point when considering interfacility transportation. When the nECC and ECC are close together (ie, closer than the duration of the alteplase infusion), we adjust the rate of reperfusion to vary linearly with time (Table III in the 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.

Estimating the Conditional Probabilities With Existing Data

We used data from the ESCAPE trial (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke)[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.[1]

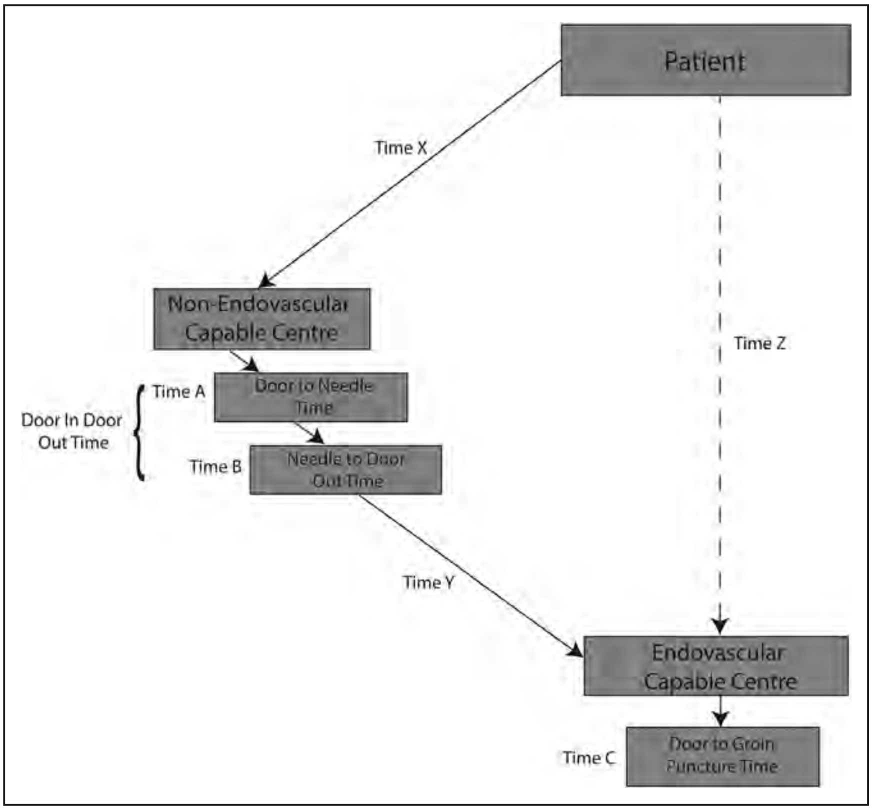

Figure 1. Transportation time framework. The dashed line represents the mothership model, the solid lines represent the drip and ship model. Time X is the transportation time from the patient to the nonendovascular capable center (nECC). Time Y is the transportation time from the nECC to the endovascular capable center (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.

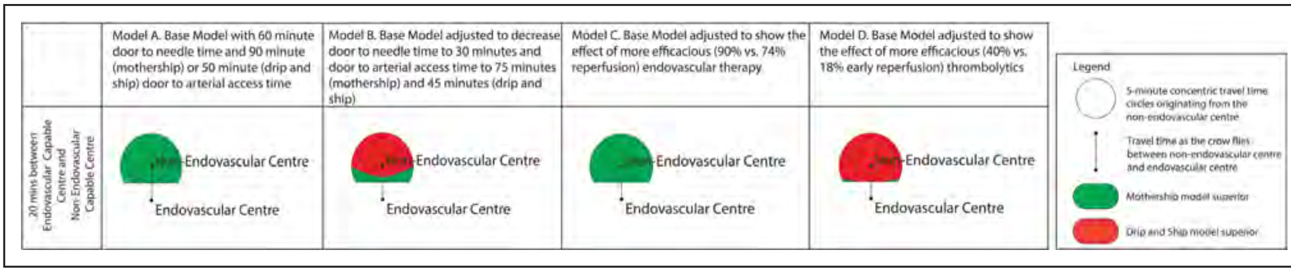

Figure 2. Optimization of the use of the drip and ship vs mothership models when the endovascular capable center (ECC) and non-ECC (nECC) are 20 min apart. Red indicates regions where the drip and ship approach is more favorable; green indicates regions where the mothership approach is more favorable. Model A assumes a door-to-needle time of 60 min, door-to-arterial access time of 90 min for mothership, and 50 min for drip and ship, *P*(reperfusion|endovascular therapy)=0.74 and *P*(early reperfusion|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 min, and door-to-arterial access is 75 min (mothership) and 45 min (drip and ship). Here, the drip and ship model is the most effective strategy if the patient is 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 the superior option. Model D assumes a novel intravenous thrombolytic agent where *P*(early reperfusion|thrombolysis)=0.40 (adjusted for shorter travel times) and shows that the drip and ship option is superior.

Because the time of reperfusion for patients receiving alteplase is unknown, we assume that the same rate of decay applies.

The probability of achieving reperfusion given endovascular therapy was estimated from the ESCAPE trial at 0.74.[7] The probability of early reperfusion given alteplase therapy varies by occlusion location. The prevalence of LVO with a positive Los Angeles Motor Scale (LAMS) screen (score of 4–5) is 62%, and occlusion locations are estimated at 28% internal carotid artery, 65% M1, and 5% M2.[15] These data are combined with the above early reperfusion proportions to estimate that overall 18% of patients with a proven LVO will achieve early reperfusion with intravenous alteplase. In the cases where the time of early reperfusion needed to be adjusted to <70 minutes, this probability was also adjusted. In preclinical 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 the online-only Data Supplement).[9,10] The probability of good outcome given no reperfusion was estimated from the ESCAPE trial to be 0.30.[7] The models with these calculated probabilities are shown in the Table.

Example Scenarios

Using 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 I in the online-only Data Supplement), 20 (Figure 2), 30 (Figure 3), 45 (Figure II in the online-only Data Supplement), 90 (Figure 4), 120 (Figure 5), and 180 minutes (Figure III in the online-only Data Supplement). 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 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 (model A in Figures 2 through 5; Figures I through III in the online-only Data Supplement). These models can be used to show how altering parameters could change decision-making (Table IV in the 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

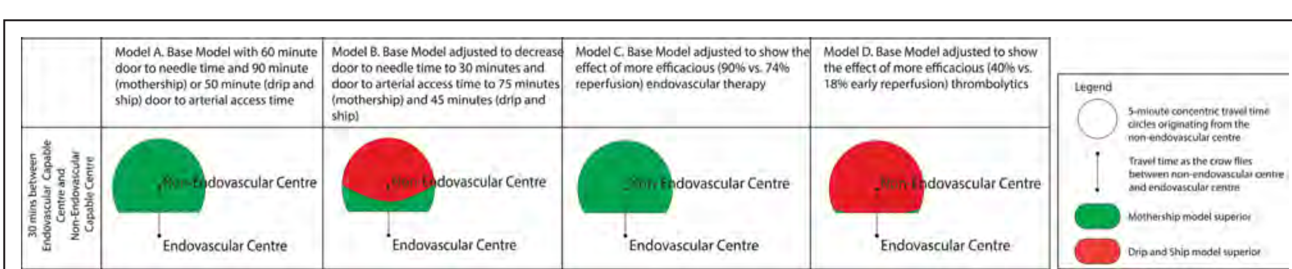

Figure 3. Optimization of the use of the drip and ship vs mothership models when the endovascular capable center (ECC) and non-ECC (nECC) are 30 min apart. Red indicates regions where the drip and ship approach is more favorable; green indicates regions where the mothership approach is more favorable. Model A assumes a door-to-needle time of 60 min, door-to-arterial access time of 90 min for mothership, and 50 min 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 min, and door-to-arterial access is 75 min (mothership) and 45 min (drip and ship). Here, the drip and ship model now becomes an effective option when the patient is 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.

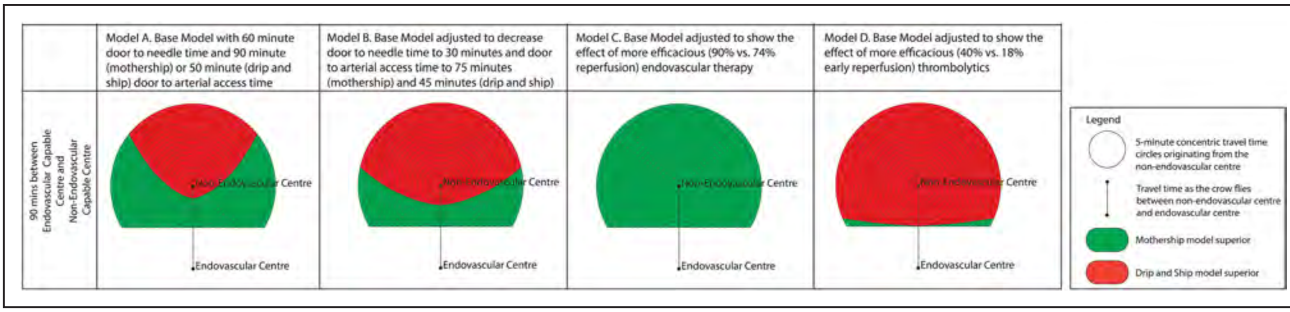

Figure 4. Optimization of the use of the drip and ship vs mothership models when the endovascular capable center (ECC) and non-ECC (nECC) are 90 min apart. Red indicates regions where the drip and ship approach is more favorable; green indicates regions where the mothership approach is more favorable. Model A assumes a door-to-needle time of 60 min, door-to-arterial access time of 90 min for mothership, and 50 min for drip and ship, *P*(reperfusion|endovascular therapy)=0.74, and *P*(early reperfusion|alteplase)=0.18. Model A shows that the drip and ship model is the most effective option if the patient is close to the nECC or would have to drive past the nECC. In model B, door-to-needle time is 30 min, and door-to-arterial access is 75 min (mothership) and 45 min (drip and ship). Here, the area where the drip and ship model is the most effective option has increased. Model C assumes *P*(reperfusion|endovascular therapy) 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 and shows that the drip and ship approach is superior in almost all scenarios.

to 75 minutes for patients (mothership) and 45 minutes (drip and ship). Model B shows that faster systems of care make the drip and ship model a more favorable option when the patient is close to the nECC or would have to travel past the nECC (model B in Figures 2 through 5; Figures I through III in the 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 (and the patient is close to the nECC or would have to be transported past the nECC; model C in Figures 2 through 5 and Figures I through III in the 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.[16] 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 ECC (Table III in the online-only Data Supplement). This model shows that the drip and ship method is favorable in nearly all scenarios (model D in Figures 2 through 5; Figures I through III in the online-only Data Supplement). Both models C and D demonstrate that prehospital destination decision-making is highly dependent on 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.[17]

Considering All Patient Diagnoses

This model applies to patients with large-vessel ischemic strokes; however, prehospital healthcare providers do not have access to imaging making a definitive diagnosis impossible in the field. The LAMS, a 3-item tool (scores range from 0–5 with higher scores indicating more severe symptoms), is a fast and an effective way to identify patients with a probable large-vessel ischemic stroke.[15] The probability that a patient has a large artery occlusion given that they have an ischemic stroke diagnosis and a LAMS score of 4 or 5 is 0.62.[15] In the FAST-MAG trial (Field Administration of Stroke Therapy-Magnesium), which enrolled suspected stroke patients in the field, among patients with an LAMS score of 4 or 5, 70% had an acute ischemic stroke, 28% had an intracranial hemorrhage, and 2% were stroke mimics

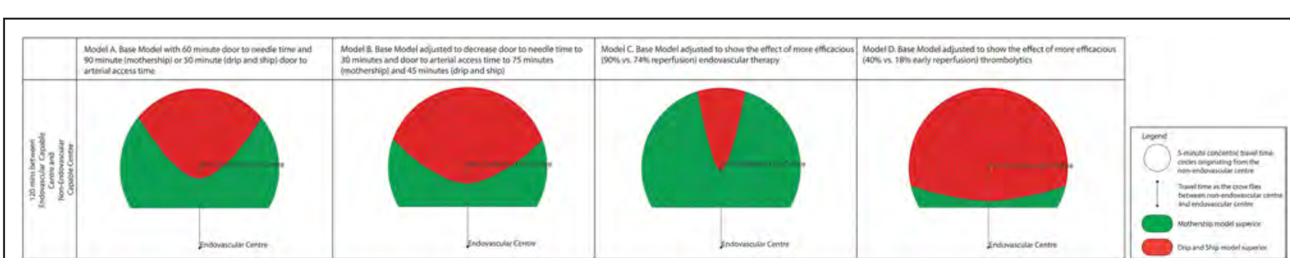

Figure 5. Optimization of the use of the drip and ship vs mothership models when the endovascular capable center (ECC) and non-ECC (nECC) are 120 min apart. Red indicates regions where the drip and ship approach is more favorable; green indicates regions where the mothership approach is more favorable. Model A assumes a door-to-needle time of 60 min, door-to-arterial access time of 90 min for mothership, and 50 min for drip and ship, *P*(reperfusion|endovascular therapy)=0.74, and *P*(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 min, and door-to-arterial access is 75 min (mothership) and 45 min (drip and ship). Here, the area where the drip and ship model is the most effective option has increased. Model C assumes *P*(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*(early reperfusion|thrombolysis)=0.40 and shows that the drip and ship approach is superior in almost all scenarios.

(J. Saver, personal communication, 2015). Combining these 2 estimates if the patient has an LAMS score of 4 or 5 in the field, the joint probability of having an acute ischemic stroke, which is a LVO, is 0.43, and the joint probability for non-LVO 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 (nonlarge-vessel ischemic stroke, intracranial hemorrhage, or stroke). Non-LVOs and stroke mimics make up roughly half of these patients. These patients can be adequately treated at either an nECC or an ECC, so they should be transported to the nearest stroke center, which under the above assumptions is an nECC. This makes the drip and ship model the most appropriate for stroke mimics and stroke because of small-vessel occlusions. Intracranial hemorrhage makes up the other half of these patients, and although these patients may require intensive care treatment at a comprehensive stroke center, there is currently no evidence that emergency treatment within minutes is beneficial.[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 an nECC. If it is assumed that all hemorrhage patients should be transported directly to an ECC, the outcome of above models is not affected. However, if it is assumed that hemorrhage patients would benefit from stabilization at an nECC, the area where the drip and ship model is more favorable will increase when considering all patients with LAMS score of 4 to 5.

Discussion

These models represent an explicit way of conceptualizing the problem of prehospital 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 that report a median door-to-needle time of 67 minutes.[21] 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.[22] 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 nonbusiness hours or weekends because of limited staffing. Slower treatment times at the nECC only tilt the scales in favor of the mothership model. Similarly, if the ECCs were to have slower treatment times, the area where the drip and ship model is more favorable 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 emergency medical services not bypass a closer nECC in favor of an ECC if such a diversion would add >15 to 20 minutes of transport time.[23] 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 through 5 and Figures I through III in the 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 and 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 LVOs 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 because of anatomy or unfavorable imaging profiles. Further data on the proportion of patients who become ineligible for endovascular therapy during the onset-to-imaging epoch[24] are needed. The border zones between the drip and ship and mothership models in Figures 2 through 5 and Figures I through III in the 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 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.

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, consisting of an ambulance equipped with a computed tomographic scanner, point-of-care laboratory, and specialized prehospital stroke team, could additionally change these models.[25–27] This early imaging capability is critical to improve on screening tests, such as the LAMS score, that have only moderately good accuracy in identifying large-vessel ischemic strokes (81% sensitivity and 89% specificity).[15] Alteplase can be administered in the mobile stroke unit while on route to hospital giving patients much faster access to medical treatment. While this is a new and resource intensive, treatment option, it does have the potential to greatly streamline the drip and ship treatment option by eliminating the need to stop at an nECC to receive alteplase.

Disclosures

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Key Words: brain ■ reperfusion ■ stroke ■ thrombectomy ■ thrombolytic therapy

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Drip and Ship Versus Direct to Comprehensive Stroke Center: Conditional Probability Modeling

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SUPPLEMENTAL MATERIAL

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Supplemental Tables:

Supplemental Figures:

Supplemental References

Table I. Model Assumptions

Model Assumption	Rationale
1. There is true uncertainty regarding which transport and treatment decision to make	This model would not be needed in cases where the most favourable treatment option was certain.
2. The nECC is the closest treatment centre to the patient	If the ECC was the closest treatment centre the patient should be transported directly to the ECC as all treatment options are available here.
3. There is only one decision making point (at the scene) and this decision is never reneged upon	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.
4. This model does not apply to "found down" or stroke-on-awakening patients	It is impossible to account for the time between stroke onset and first medical contact if the stroke is not witnessed
5. Relationship between probability of successful reperfusion and time a. The probability of successful reperfusion with alteplase therapy varies linearly with time, but is capped at a maximum rate b. The probability of successful reperfusion with endovascular therapy is time invariant	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] 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.
6. All patients with occlusions are eligible for alteplase and all patients with large vessel occlusions are eligible for endovascular therapy	This is an extension of Assumption 1, in order for there to be true uncertainty patients must be eligible for either treatment option.
7. For patients with large vessel occlusions reperfusion is only achieved through treatment (i.e. no spontaneous reperfusion)	This is known to be true in 95% of cases in the first 1-2 hours after stroke onset.[4,5]

nECC: non-endovascular capable centre (primary stroke centre); ECC: endovascular capable centre (comprehensive stroke centre)

Table II. Model Baseline and Sensitivity Analysis Values

Model Component	Base Values	Values Used in Sensitivity Analyses	Rationale
1. 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]
2. Door in Door Out Time	75 minutes (60 minute DTN)	45 minutes (30 minute 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.
3. Door to Arterial Access	90 mins (mothership) 50 mins (drip and ship)	75 mins (mothership) 45 mins (drip and ship)	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] 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.
4. First reperfusion after endovascular therapy	30 minutes	N/A	This is representative of the median time from groin puncture to first reperfusion in both ESCAPE and SWIFT PRIME.[4,11]
5. Early reperfusion after alteplase administration a. Time B + Y $\geq$ 70 minutes b. Time B + Y < 70 minutes	a. 70 mins b. Time B+Y	a. N/A b. N/A	a. 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 b. If time B+Y < 70 minutes, then there is not 70 minutes of time available for alteplase to have full effect between the bolus being given at the nECC and the patient arriving at the ECC. In these cases, the early reperfusion time has been adjusted to be equal to B+Y

Model Component	Base Values	Values Used in Sensitivity Analyses	Rationale
6. Time from first medical contact to ambulance arrival and ambulance scene time	30 minutes	N/A	There are representative times from Canadian cities.
7. Decrease in probability of successful reperfusion in relation to time to reperfusion	0.0006	N/A	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.
8. P(reperfusion| endovascular therapy)	0.74	0.90	Estimate from the ESCAPE trial.[4]
9. P(early reperfusion| alteplase) a. Time B + Y $\geq$ 70 minutes b. Time B + Y < 70 minutes	a. 0.18 b. 0.18[(B+Y)/70]	a. 0.40 b. 0.40[(B+Y)/70]	a. Angiography studies have shown that 1.6% of ICA, 23.9% of M1, and 38.9% of M2 occlusions recanalized after alteplase administration (median 70 minutes).[12] The prevalence of large vessel occlusion with a positive LAMS screen (score of 4 or 5) is 62% and occlusion locations are estimated at: 28% ICA, 65% M1, and 5% M2.[15] These data are combined estimate that 18% of patients with a proven large vessel occlusion will achieve early reperfusion with intravenous alteplase. 0.40 was used as a sensitivity analysis to reflect the efficacy of tenecteplase which has shown greater reperfusion rates than alteplase.[16] b. In pre-clinical studies it has been shown that clot dissolving rates with alteplase progress linearly in the initial treatment phase therefore these probabilities were adjusted in a linear fashion (ex. P(early reperfusion|alteplase) within 35 minutes of bolus = 0.09).[1,2]
10. P(good outcome| no reperfusion)	0.30	N/A	The probability of good outcome given no reperfusion was estimated from the cohort of patients in the ESCAPE trial who did not achieve reperfusion after treatment. In this group of patients 30% achieved a good outcome.[4]

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
$\geq$90	70 minutes	0.18	0.40

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

Model	Mothership	Drip and Ship
A (base model)	*P(good outcome|mothership model)=0.74·[0.75-0.0006(30+Z+90+30)]+0.26·0.30*	*P(good outcome|drip and ship model)=0.18·[0.75-0.0006(30+X+60+15+70)]+0.82·[0.74·[0.75-0.0006(30+X+60+15+Y+50+30)]+0.26·0.30]*
B	*P(good outcome|mothership model)=0.74·[0.75-0.0006(30+Z+**75**+30)]+0.26·0.30*	*P(good outcome|drip and ship model)=0.18·[0.75-0.0006(30+X+**30**+15+70)]+0.82·[0.74·[0.75-0.0006(30+X+**30**+15+Y+**45**+30)]+0.26·0.30]*
C	*P(good outcome|mothership model)=**0.90**·[0.75-0.0006(30+Z+90+30)]+**0.10**·0.30*	*P(good outcome|drip and ship model)=0.18·[0.75-0.0006(30+X+60+15+70)]+0.82·[**0.90**·[0.75-0.0006(30+X+60+15+Y+50+30)]+**0.10**·0.30]*
D	Unchanged from Model A	*P(good outcome|drip and ship model)=**0.40**·[0.75-0.0006(30+X+60+15+70)]+**0.60**·[0.74·[0.75-0.0006(30+X+60+15+Y+50+30)]+0.26·0.30]*

Changes from Model A shown in bold face

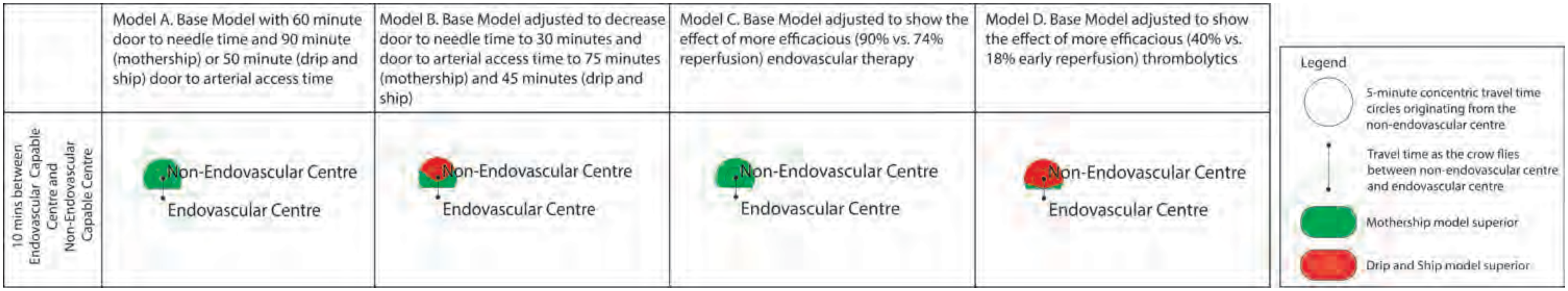

Figure I. Hospitals are 10 minutes apart: The effect of door to needle times and increasing reperfusion rates on the optimization of the use of the drip and ship vs. mothership models of stroke triage and treatment when the endovascular capable centre and non-endovascular capable centre are 10 minutes 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.

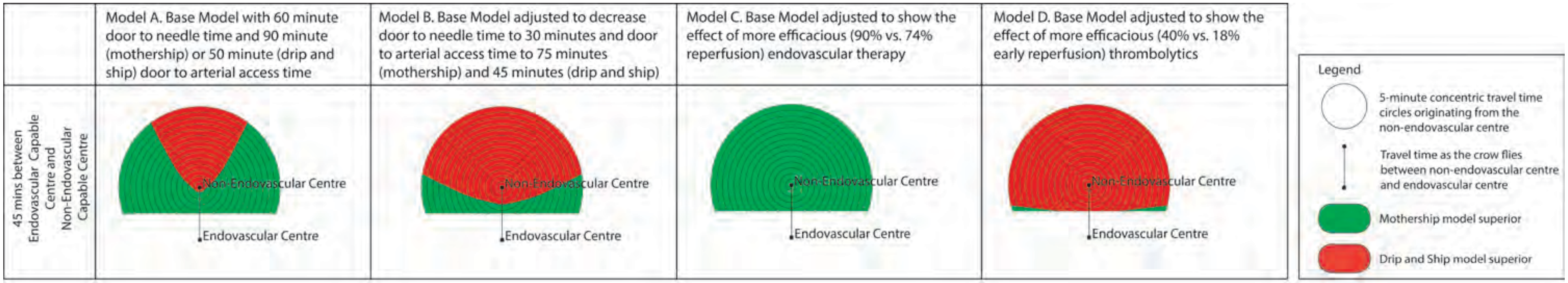

Figure II. Hospitals are 45 minutes apart: The effect of door to needle times and increasing reperfusion rates on the optimization of the use of the drip and ship vs. mothership models of stroke triage and treatment when the endovascular capable centre and non-endovascular capable centre are 45 minutes 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.

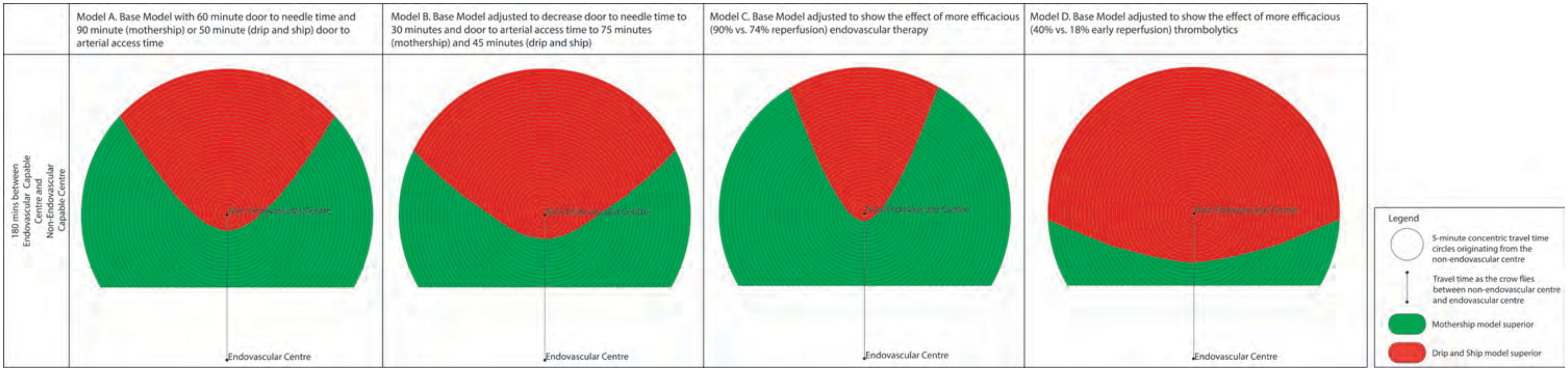

Figure III. Hospitals are 180 minutes apart: The effect of door to needle times and increasing reperfusion rates on the optimization of the use of the drip and ship vs. mothership models of stroke triage and treatment when the endovascular capable centre and non-endovascular capable centre are 180 minutes 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(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 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.

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