Optimal Transport Destination for Ischemic Stroke Patients With Unknown Vessel Status

Use of Prehospital Triage Scores

Eckhard Schlemm, MBBS, PhD; Martin Ebinger, MD; Christian H. Nolte, MD; Matthias Endres, MD; Ludwig Schlemm, MD

Background and Purpose—Patients with acute ischemic stroke (AIS) and large vessel occlusion may benefit from direct transportation to an endovascular capable comprehensive stroke center (mothership approach) as opposed to direct transportation to the nearest stroke unit without endovascular therapy (drip and ship approach). The optimal transport strategy for patients with AIS and unknown vessel status is uncertain. The rapid arterial occlusion evaluation scale (RACE, scores ranging from 0 to 9, with higher scores indicating higher stroke severity) correlates with the National Institutes of Health Stroke Scale and was developed to identify patients with large vessel occlusion in a prehospital setting. We evaluate how the RACE scale can help to inform prehospital triage decisions for AIS patients.

Methods—In a model-based approach, we estimate probabilities of good outcome (modified Rankin Scale score of ≤2 at 3 months) as a function of severity of stroke symptoms and transport times for the mothership approach and the drip and ship approach. We use these probabilities to obtain optimal RACE cutoff scores for different transfer time settings and combinations of treatment options (time-based eligibility for secondary transfer under the drip and ship approach, time-based eligibility for thrombolysis at the comprehensive stroke center under the mothership approach).

Results—In our model, patients with AIS are more likely to benefit from direct transportation to the comprehensive stroke center if they have more severe strokes. Values of the optimal RACE cutoff scores range from 0 (mothership for all patients) to >9 (drip and ship for all patients). Shorter transfer times and longer door-to-needle and needle-to-transfer (door out) times are associated with lower optimal RACE cutoff scores.

Conclusions—Use of RACE cutoff scores that take into account transport times to triage AIS patients to the nearest appropriate hospital may lead to improved outcomes. Further studies should examine the feasibility of translation into clinical practice. (Stroke. 2017;48:2184-2191. DOI: 10.1161/STROKEAHA.117.017281.)

Key Words: emergency medical services • probability • stroke • thrombectomy • triage

Patients with acute ischemic stroke (AIS) and large vessel occlusion (LVO) benefit from endovascular therapy (EVT) in addition to thrombolysis. However, if transport time to the nearest non-EVT-capable stroke center (primary stroke center [PSC]) is shorter than to the nearest EVT-capable stroke center (comprehensive stroke center [CSC]), the optimal prehospital transport strategy for AIS patients with unknown vessel status is uncertain. Under these circumstances, initial transportation to the PSC would be associated with shorter delays to thrombolysis for eligible patients. However, if this stroke unit is not capable of endovascular treatment, longer delays to EVT for patients with LVO have to be expected. This delay is because of the need for secondary transfer (drip and ship approach). Direct transportation to the nearest CSC (mothership approach), on the other hand, would lead to quicker access to EVT for patients with LVO but possibly longer onset-to-thrombolysis times. Because the treatment effects of both thrombolysis and EVT diminish over time, early determination of the optimal transport destination is important. To identify patients with LVO, a large number of prehospital stroke severity scales (PSSS), mostly based on the National Institutes of Health Stroke Scale items, have been proposed. However, the sensitivity and specificity of these scales are limited, and there is currently no consensus.
as to whether they should be used to inform prehospital triage decisions. Recently, Holodinsky et al.\(^\text{10}\) described a model based on conditional probabilities to assess the problem of acute stroke triage for patients with AIS caused by LVO. They demonstrated that superiority of either the drip and ship or the mothership approach depends on the transport times to the nearest PSC and CSC. In their study, the authors assumed that vessel status is known. In the field, however, emergency medical services personnel—if not staffing a mobile stroke unit with computed tomography angiography\(^\text{11,12}\)—are ignorant of the vessel status of their patient. The decision about the initial transport destination for AIS patients, and indeed for all patients with suspected AIS (Discussion), must therefore be based on probabilities of LVO derived from clinical information, for example, the severity of symptoms, as well as the transportation times to the respective stroke centers.

We developed a probabilistic model that applies to AIS patients with unknown vessel status. For these patients, we aimed to answer the following questions: (1) How do probabilities of good outcome differ between the mothership and the drip and ship approaches? (2) What is the optimal PSSS cutoff score to inform triage decisions?

### Methods

We implemented a conditional probabilistic model to calculate probabilities of good outcome for AIS patients with unknown vessel status under the mothership and the drip and ship approaches. Good outcome is defined as modified Rankin Scale score of ≤2 after 3 months. The schematic structure of the underlying transportation time framework is depicted in Figure 1. We considered a geographic environment containing a single PSC and a single CSC. Similar to Holodinsky et al.\(^\text{10}\), we worked with relative positions of the 2 stroke centers on a 2-dimensional map, called the temporospatial plane. Each point on this plane represents a geographic location with specific transport times to the nearest PSC and the nearest CSC. Transport times represent the quickest mode of transport and take into account specific transport conditions (e.g., weather, rush hour, availability of air transport). We assume that the PSC is able to perform rapid assessment of patients with suspected ischemic stroke, administer thrombolysis if indicated, and perform emergency vessel imaging. Numeric values of time parameters used in our simulation are shown in the Table. The mathematical structure of our model, the composition of time variables used as input (including intrahospital delays), and the derivation of outcome probabilities from recently published meta-analyses\(^\text{13,14}\) are described in the online Data Supplement (Formula I in the online-only Data Supplement, Tables I and II in the online-only Data Supplement; Figures I through V in the online-only Data Supplement). Briefly, the expected probabilities of good outcome for the mothership and the drip and ship approaches are modeled as a function of 3 transport time variables (scene to PSC, scene to CSC, transfer time between hospitals) and the score of an established PSSS. The PSSS used to obtain probabilities of the presence of LVO is based on the rapid arterial occlusion evaluation scale (RACE),\(^\text{15}\) which ranged from 0 to 9 (higher score indicating more severe strokes; Figure I in the online-only Data Supplement). We used a physiological perspective which focused on the achievement of reperfusion (Figure 1). To examine only situations in which use of a clinical triage score is warranted, we assumed that patients did not have contraindications to either thrombolysis or EVT. In addition, we only considered combinations of input variables for which true equipoise between the mothership and the ship and drip transport option existed (ie, the equipoise region, Figure 2A; see Table III in the online-only Data Supplement for a formal definition).

At all points of the equipoise region, patients fulfill the time-based eligibility criteria for both thrombolysis at the PSC under the drip and ship approach and for EVT at the CSC under the mothership approach. At some points of the equipoise region, however, patients would not be able to receive EVT if they were first transported to the PSC (drip and ship approach) because they would arrive at the CSC too late after secondary transfer. Similarly, at some points of the equipoise region, patients would not be eligible to receive thrombolysis at the CSC if they were transported to the CSC directly under the mothership approach (but would still be eligible for EVT if they were found to have an LVO).

Thus, the equipoise region can be partitioned into ≤4 nonoverlapping treatment scenarios according to the time-based eligibility for 2 treatment options—namely thrombolysis at the CSC under the mothership approach and the possibility of secondary transfer from the PSC to the CSC under the drip and ship approach:

1. both thrombolysis at the CSC under the mothership approach and secondary transfer for EVT under the drip and ship approach possible;
2. thrombolysis at the CSC under the mothership approach not possible, secondary transfer for EVT under the drip and ship approach possible;
3. thrombolysis at the CSC under the mothership approach possible, secondary transfer for EVT under the drip and ship approach not possible; and
4. neither thrombolysis at the CSC under the mothership approach nor secondary transfer for EVT under the drip and ship approach possible.

Treatment scenarios are visualized in Figure 2B; formal definitions are provided in Table IV in the online-only Data Supplement.

For any given transfer time setting, we calculated 3-dimensional arrays (equipoise region × RACE score) of probabilities of good outcome for the mothership and the drip and ship approaches. Assuming that strokes at all points in the temporospatial plane occur with equal frequency, we obtained a distribution of probabilities of good outcome for each approach according to transfer time and RACE score. These distributions were used to calculate optimal treatment scenario-specific RACE cutoff scores for the 4 treatment scenarios and different transfer time settings. The optimal treatment scenario-specific RACE cutoff score is defined as the lowest RACE score \(s\) for which all RACE scores \(≥s\) would be associated with a higher average probability of good outcome under the mothership approach when compared with the drip and ship approach. The averages are calculated over each of the 4 treatment scenarios. Because there might be heterogeneity with regards to the optimal RACE cutoff score even within treatment scenarios, we also calculated optimal variable RACE cutoff scores that take into account the exact location of the patient who suffered a stroke within each treatment scenario. We then used these RACE cutoff scores to obtain probabilities of good outcome according to eligibility for treatment options, transfer time, and RACE score for the following triage strategy: direct transportation to the CSC for patients with a RACE score greater than or equal to the optimal RACE cutoff score (mothership approach), transportation to the PSC first (drip and ship) otherwise. The influence of the parameters door-to-needle time, door-out time at the PSC, and onset-to-alarm time was examined in sensitivity analyses. Simulations were performed in MATLAB.\(^\text{17}\) Distributions are visualized in R\(^\text{18}\) using beanplots.\(^\text{19}\)

### Results

First, we calculated absolute probabilities of good outcome for AIS patients according to RACE score and transfer time for the mothership and the drip and ship approaches (Figure 6 in the online-only Data Supplement). The distributions of the point-wise differences of the probabilities of good outcome between the mothership and the drip and ship approaches for different transfer time settings are shown in Figure 3. There is a treatment scenario-specific nonlinear relationship between the RACE score and the calculated differences. For shorter transfer times and for treatment scenario I, the absolute differences between the 2 approaches are small. In treatment
scenarios III and IV, on the other hand, differences between the mothership and the drip and ship approaches are substantial (maximum difference 30%). For different RACE scores, treatment scenario-specific mean differences for scenarios I, III, and IV lie above or below the zero line, indicating that neither a pure mothership approach nor a pure ship and drip approach can achieve optimal triage decisions for all patients. Strokes occurring in treatment scenario II benefit universally from the ship and drip approach. The RACE score at which the mothership approach begins to outperform the ship and drip approach, that is, the optimal treatment scenario-specific RACE cutoff score, is different for the 4 treatment scenarios and varies according to transfer time. With shorter transfer times, optimal treatment scenario-specific RACE cutoff scores are lower, that is, a higher percentage of patients, including less severely affected patients, would be triaged for direct transportation to the CSC (Figure 4). With longer door-to-needle and door-out times at the PSC, optimal treatment

Figure 1. Schematic structure of the model. The flowchart depicts the transportation time framework for the mothership (left) and the drip and ship approaches (right). Circled numbers correspond to terms in Formula I in the online-only Data Supplement for the total probability of good outcome. CSC indicates comprehensive EVT-capable stroke center; EMS, emergency medical services; EVT, endovascular therapy; LVO, large vessel occlusion; and PSC, primary non-EVT-capable stroke center.
probabilities of good outcome is small and varies between 0%

1, RACE score 7, transfer time 120 minutes). This signi-

Closer inspection of Figure 3 demonstrates that distribu-
tions belonging to different treatment scenarios for specific
RACE scores and specific transfer times may contain val-
ues above and below the zero line (eg, treatment scenario
I and II are lower; cutoff scores for treatment scenarios
III and IV do not change (Figure VII in the online-only Data
Supplement). Onset-to-alarm time only marginally influences
optimal treatment scenario–specific RACE cutoff scores
(Figure VIII in the online-only Data Supplement).

Finally, we examine the difference of the probability of good
outcome between a triage strategy based on optimal treatment
scenario–specific RACE cutoff scores and a strategy based on
optimal variable RACE cutoff scores. The absolute additional
benefit of using optimal variable RACE cutoff scores seems
modest (<6%) and most pronounced for longer transfer times
(Figure 5). In addition, the relative size of the subset of the
equipoise region in which the 2 triage strategies yield different
probabilities of good outcome is small and varies between 0% and 35%

Discussion

We modeled the effects of RACE score–based triage strategies
on the probability of good outcome for patients with AIS and
unknown vessel status. The main results of our study are (1)
the relative performances of the mothership approach and the
drip and ship approach depend on the transfer time between
hospitals, the severity of stroke symptoms, and the eligibility
for treatment options as determined by treatment time win-
dontheroporesphericspatialeonie,xact
transporttimes to the PSC and the CSC). In Figure 2C, the
distribution of the optimal variable RACE cutoff scores on the
temporospatial plane is visualized. For example, in a
setting with transfer time 60 minutes, the optimal treatment
scenario–specific RACE cutoff score for treatment scenario
I is equal to 7 and translates into optimal variable RACE
cutoff scores of 0 to undefined (all patients being triaged to
the PSC). For treatment scenario III, the optimal treatment
scenario–specific RACE cutoff score equals 2 and expands
into the range 0 to 4. Less heterogeneity is observed within
treatment scenarios II and IV.

Table. Time Variables Used in the Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (Range), min</th>
<th>Comments/References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to alarm</td>
<td>30 (1, 60)</td>
<td>Zock et al11</td>
</tr>
<tr>
<td>Alarm to scene</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>On scene</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Transfer (PSC to CSC)</td>
<td>15, 60, and 120</td>
<td></td>
</tr>
<tr>
<td>Door to needle</td>
<td>CSC: 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PSC: 30 (60, 90)</td>
<td></td>
</tr>
<tr>
<td>Door out*</td>
<td>30 (15, 60, 90)</td>
<td></td>
</tr>
<tr>
<td>Door to groin</td>
<td>Mothership approach: 90</td>
<td>Holodinsky et al10 with additional linear adjustment of the door-to-groin time under the drip and ship approach for short transfer times</td>
</tr>
<tr>
<td>Groin to reperfusion</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Treatment time windows</td>
<td>Thrombolysis: 270</td>
<td>American Heart Association1–11</td>
</tr>
<tr>
<td></td>
<td>EVT (onset to groin): 360</td>
<td></td>
</tr>
</tbody>
</table>

CSC indicates Thrombolysis: 270 comprehensive EVT-capable stroke center; EVT, endovascular therapy; and PSC, primary non-EVT-capable stroke unit.

*Drip and ship approach for short transfer times associated with reduced delays to EVT for eligible patients with acute stroke.21,22 A study that takes into account the inevitable risk of misclassification of non-LVO patients23 and the possibility of early recanalization after thrombolysis24 is ongoing (RACECAT, NCT0279596225) and will be completed in 2020. With our probabilistic model, we are able to consider these factors and to show that RACE cutoff scores used to inform triage decisions may improve outcome. In settings with a shorter transfer time between hospitals and poorer performance at the PSC in terms of timely thrombolysis (door-to-needle time) and onward transfer (door-out time), the optimal treatment scenario–specific RACE cutoff score is lower. The benefit associated with the use of a clinical triage strategy depends on the specific setting. For example, in a suburban area with a transfer time of 60 minutes, a severely affected patient who,
based on treatment time windows, would be a candidate for thrombolysis at the CSC under the mothership approach but not for a secondary transfer (treatment scenario III), would have a ≈20% higher probability of good outcome with a RACE cutoff score triage strategy when compared with the default scenario (drip and ship for all patients). On the other hand, for strokes occurring in treatment scenario I of an urban environment with short transfer times, the mothership and the drip and ship approaches yield almost identical probabilities of good outcome and may be equally valid across the whole range of RACE scores.

The clinical PSSS used in our model is based on the RACE score because the latter has been prospectively validated and the proportions of stroke mimics and patients with hemorrhagic stroke among patients without LVO are known. Other triage scores that have been proposed, for example, the Los Angeles Motor Scale, the Cincinnati Prehospital Stroke Severity Scale, the Field Assessment Stroke Triage for Emergency Destination score, or the G-FAST score (gaze–face–arm–speech–time), have been found to have similar sensitivities and specificities.

Our model was built with the objective to be applicable to AIS patients with unknown vessel status. We thereby expanded the model proposed by Holodinsky et al whose results apply to patients with AIS and proven LVO. Our model does not, however, include patients with hemorrhagic stroke and stroke mimics who are initially suspected to have a diagnosis of AIS. Because of heterogeneity of the group of stroke mimics and the current lack of specific time-dependent therapeutic interventions for most patients with hemorrhagic stroke, it is...
currently not clear if such patients should be transported to the nearest PSC or directly to the nearest CSC. Assuming similar probabilities of good outcome under both transport strategies for these patients, our main results concerning the relative performances of the mothership and the drip and ship approaches and the estimated RACE cutoff scores are also valid for the group of patients with suspected AIS.

In agreement with current guidelines,1 patients in our model were considered eligible for EVT if groin puncture could be achieved within 6 hours of symptom onset. However, recent evidence suggests that carefully selected patients with AIS caused by LVO who have clinical-imaging mismatch assessed by either diffusion-weighted magnetic resonance imaging or computed tomography perfusion may benefit from EVT ≤24 hours after symptom onset (DAWN study [Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo], NCT02142283).30,31 With regards to our model, implementation of these findings in clinical practice would translate into a larger equipoise region and a higher percentage of patients falling under treatment scenarios I and II as opposed to scenarios III and IV.

Population-based epidemiological studies have repeatedly shown that patients with more severe strokes have shorter onset-to-alarm times when compared with patients with milder strokes.32,33 In our model, determination of the optimal RACE cutoff score for an individual patient at a given location of the equipoise region and a given onset-to-alarm time is independent of the relationship between onset-to-alarm time and stroke severity. However, this relationship would need to be considered when modeling the population-wide effects on outcome of introducing a prehospital triage score strategy.

Some limitations have to be considered when interpreting the results of our study. First, to restrict complexity of the model, we assumed a uniform distribution of strokes in the temporospatial plane when calculating average probabilities of good outcome for different prehospital triage strategies. This is likely to be a simplification in comparison to reality where population density and transport time to the nearest stroke center might be inversely correlated and where strokes occur more often in regions with clusters of elderly populations. However, this simplification would affect all triage strategies to a similar degree and would have little effect on their relative performances. Second, we did not consider age as an input variable into our model because joint distributions of good outcome according to age and treatment time were not available. In addition, although absolute probabilities of good outcome are affected by age,2,34,35 the treatment effect of EVT and thrombolysis has been found to be similar across age groups.2,6 Third, this study focuses on the expected probability of good outcome and thereby analyzes the effect of different triage strategies from the patients’ point of view. Future studies should also examine how stroke centers are affected with regards to workload, patient mix, and resource utilization. Implementation of any prehospital triage strategy should be preceded by consideration of secondary effects, for example, diversion of local emergency medical services, treatment of patients at a greater distance from their homes, and the possible diminution of experience in treating acute stroke
patients at PSCs. Last, we used outcome data from recent randomized controlled trials. Outside of the controlled environment of such studies, the probabilities of good outcome may be lower. Because our model parameters are derived from average effect sizes observed in these studies, our parameters represent unbiased effect estimators but do not include confidence intervals. Confirmation of our findings in prospective studies is therefore needed.

Conclusions

In conclusion, our results suggest that the use of PSSS cutoff scores for prehospital triage of patients with suspected AIS and unknown vessel status may be associated with improved outcomes. The optimal PSSS cutoff score depends mainly on (1) the transfer time from the PSC to the CSC, (2) the combination of possible treatment options as determined by treatment time windows, and (3) the PSCs performance on timely thrombolysis and transfer if indicated. An easy to use mobile geolocation application that calculates these parameters live on scene could simplify triage decisions for emergency medical services personnel that are called to a patient with suspected ischemic stroke.

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Disclosures

None.

References


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Ludwig Schlemm
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1. Supplemental Methods
1.1 Details of the model

\[
P(\text{good outcome}|s, \{t\}) = P(\neg \text{LVO}|s) \times
\]
\[
P_\text{thrombolysis}(\text{good outcome}|\neg \text{LVO}, \text{NIHSS-S}(s), t_1)
\]
\[
+ P(\text{LVO}|s) \times
\]
\[
\left\{ P_\text{thrombolysis}(R|t_2) P_\text{EVT}(\text{good outcome}|R, \text{NIHSS-S}(s), t_3) \right. 
\]
\[
+ P_\text{thrombolysis}(\neg R|t_2) \times
\]
\[
\left. \left[ P_\text{EVT}(\neg R) P(\text{good outcome}|\text{LVO}, \neg R, \text{NIHSS-S}(s)) \right. 
\]
\[
+ P_\text{EVT}(R) P_\text{EVT}(\text{good outcome}|R, \text{NIHSS-S}(s), t_4) \right. 
\]
\]

Formula I Probabilistic conditional model used for the mothership and the drip and ship approach

Compound time variables \( t \) are specified in Table I. Constituents of the model are explained in detail in Table II. Circled numbers correspond to numbers in Figure 1 of the main text. Good outcome stands for modified Rankin scale score \( \leq 2 \) at three months, \( s \) for prehospital stroke severity scale score, LVO for large vessel occlusion, \( R \) for reperfusion, and NIHSS-S for National Institutes of Health Stroke Scale Score. \( \neg \) denotes the negation symbol.
Table I Composition of the variable “t” in Formula I

<table>
<thead>
<tr>
<th>Mothership approach</th>
</tr>
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<tbody>
<tr>
<td>$t_1$</td>
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<tr>
<td>$t_2$</td>
</tr>
<tr>
<td>$t_3$</td>
</tr>
<tr>
<td>$t_4$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drip and ship approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_1$</td>
</tr>
<tr>
<td>$t_2$</td>
</tr>
<tr>
<td>$t_3$</td>
</tr>
<tr>
<td>$t_4$</td>
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</tbody>
</table>

For the derivation of $t_2$, see Table II. EVT stands for endovascular therapy, CSC for comprehensive EVT-capable stroke center, PSC for primary non-EVT-capable stroke center.
Table II Constituents of the model presented in Formula I

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Description</th>
<th>Data</th>
<th>Explanations/ References/ Data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(good outcome</td>
<td>Probability of good outcome, given the score of a</td>
<td>Good outcome was defined as a modified Rankin scale score &lt;= 2 at three months.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PSSS and a set of time variables (scene-to-PSC, scene-to-CSC, transfer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS-S(t)</td>
<td>NIHSS score, given the score of the employed PSSS</td>
<td>Figure I</td>
<td>The PSSS of our model was based on the RACE score. Median NIHSS scores for each RACE score category were obtained from Perez de la Ossa (Personal Communication) and smoothed using a linear regression curve.</td>
</tr>
<tr>
<td>P(LVO</td>
<td>Probability of presence or absence of LVO, given the score of the employed PSSS</td>
<td>Figure II</td>
<td>Relative frequencies of ischemic stroke with LVO and ischemic stroke without LVO as a function of the RACE score were extracted from Perez de la Ossa et al. These were used to calculate the probability of ischemic stroke with LVO among ischemic stroke patients. Data were smoothed using a weighted logistic regression curve.</td>
</tr>
<tr>
<td>t)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P¬LVO</td>
<td>Probability of absence of LVO, given the score of the employed PSSS</td>
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<td></td>
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<tr>
<td>t)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>P(EVT</td>
<td>Probability to achieve or not achieve reperfusion using endovascular techniques</td>
<td>0.71</td>
<td>Values obtained from Saver et al. In first approximation, time was not considered as an independent variable. If time from symptom onset-to-groin was larger than 360 minutes, patients were assumed ineligible for EVT, and P(EVT(R) was set to zero.</td>
</tr>
<tr>
<td>(good outcome</td>
<td>Probability of good outcome after EVT for ischemic stroke with LVO if reperfusion can be achieved, given stroke severity (NIHSS score) and time t from symptom onset to reperfusion</td>
<td>Figure III</td>
<td>Probabilities for good outcome for specific NIHSS scores (13, 18, 25) were obtained for different reperfusion times from Saver et al., (Suppl.) Assuming a 100% probability of good outcome for patients with NIHSS score = 0 independent of reperfusion time, exponential decay curves of the form exp(B x NIHSS score) were fitted for different reperfusion times. The parameters B were then estimated as a function of reperfusion time by a linear regression model.</td>
</tr>
<tr>
<td>, NIHSS-S(t), t)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(good outcome</td>
<td>Probability of good outcome for ischemic stroke patients with LVO in whom reperfusion is not achieved by either thrombolysis or EVT, given stroke severity (NIHSS score) and time t from symptom onset to thrombolysis</td>
<td>Figure IV</td>
<td>For patients with a median NIHSS score of 16, this probability is 0.3 (Holodinsky et al., extracted the ESCAPE-trial data [Goyal et al.]). For patients with an NIHSS score &gt;= 20, we assumed a probability of 0.05 (Fink et al.). Assuming a probability of good outcome of 1 for patients with an NIHSS score of 0, we obtained a piecewise linear probability function to which we applied linear regression analysis in the NIHSS score interval [0 20].</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>LVO, ¬R, NIHSS-S(t), t)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(thermolysis</td>
<td>Probability of good outcome for ischemic stroke patients without LVO treated with thrombolysis, given stroke severity (NIHSS score) and time t from symptom onset to thrombolysis</td>
<td>Figure V</td>
<td>First, the probability of good outcome for untreated ischemic stroke patients with and without LVO according to the NIHSS score was extracted from the literature (Fink et al.), fitted by a quadratic curve, and extended to values of 0.05 for NIHSS scores &gt; 30. We assumed that this curve approximates the outcome probabilities for patients without LVO. Probabilities were transformed into odds and multiplied with the time-dependent odds ratio for good outcome associated with thrombolysis (there is no interaction between the treatment effect of thrombolysis and stroke severity [Emerson et al.]) and transformed back into probabilities. We did not find data in the literature from which to build this time-dependent odds ratio of thrombolysis for ischemic stroke patients without LVO. However, there is not consistent evidence that the odds ratio for good outcome associated with thrombolysis is different for patients with LVO as compared to patients with unselected vessel status. (Lahoti et al. have suggested a higher average treatment effect in patients without LVO as compared to patients with LVO [odds ratio for good outcome in patients without LVO: 3.42]), while results by Medlin et al. suggest a lower average odds ratio in patients without LVO [odds ratio 0.76]). We therefore assumed that the true curve would be approximated by the one obtained in Emerson et al. (good outcome defined as mRS score 0-1).</td>
</tr>
<tr>
<td>(good outcome</td>
<td>Probability of early reperfusion after thrombolysis</td>
<td>0.18 x min(70, t)/70 Using the arguments laid out by Holodinsky et al., we assumed a probability of early reperfusion of 0.18, linearly adjusted if the time from administration of thrombolysis to groin-puncture was shorter than 70 min. In cases with time based contraindications to thrombolysis, the probability was zero. Time t represents needle-to-groin time.</td>
<td></td>
</tr>
<tr>
<td>¬LVO, NIHSS-S(t), t)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(thermolysis</td>
<td>Probability of persistent LVO after thrombolysis</td>
<td>1 – P(thermolysis(R)</td>
<td></td>
</tr>
<tr>
<td>(R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(EVT</td>
<td>Probability of early reperfusion after thrombolysis</td>
<td>0.18 x min(70, t)/70 Using the arguments laid out by Holodinsky et al., we assumed a probability of early reperfusion of 0.18, linearly adjusted if the time from administration of thrombolysis to groin-puncture was shorter than 70 min. In cases with time based contraindications to thrombolysis, the probability was zero. Time t represents needle-to-groin time.</td>
<td></td>
</tr>
<tr>
<td>(R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(EVT</td>
<td>Probability of persistent LVO after thrombolysis</td>
<td>1 – P(thermolysis(R)</td>
<td></td>
</tr>
<tr>
<td>¬R, NIHSS-S(t), t)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Description, assumptions, explanations, data, and references for constituents of the model presented in Table I. Good outcome stands for modified Rankin scale score <= 2 at three months, EVT for endovascular therapy, CSC for comprehensive EVT-capable stroke center, PSC for primary non-EVT-capable stroke center, LVO for large vessel occlusion, NIHSS-S for National Institutes of Health Stroke Scale score, PSSS for prehospital stroke severity scale, s for prehospital stroke severity scale score, RACE for rapid arterial occlusion evaluation scale, R for reperfusion. ¬ denotes the negation symbol.
Table III Parameter conditions of time variables defining the equipoise region

<table>
<thead>
<tr>
<th>Condition</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scene-to-PSC + door-to-needle&lt;sub&gt;PSC&lt;/sub&gt; &lt; scene-to-CSC + door-to-needle&lt;sub&gt;CSC&lt;/sub&gt;</td>
<td>Thrombolysis at the PSC faster than thrombolysis at the CSC</td>
</tr>
<tr>
<td>Onset-to-alarm + alarm-to-scene + on-scene + scene-to-PSC + door-to-needle&lt;sub&gt;PSC&lt;/sub&gt; ≤ time-window&lt;sub&gt;thrombolysis&lt;/sub&gt;</td>
<td>Thrombolysis possible at PSC</td>
</tr>
<tr>
<td>Onset-to-alarm + alarm-to-scene + on-scene + scene-to-PSC + door-to-groin&lt;sub&gt;Mothership&lt;/sub&gt; ≤ time-window&lt;sub&gt;EVT&lt;/sub&gt;</td>
<td>EVT possible at CSC under the mothership approach</td>
</tr>
</tbody>
</table>

EVT stands for endovascular therapy, CSC for comprehensive EVT-capable stroke center, PSC for primary non-EVT-capable stroke center.
### Table IV  Formal definition of treatment scenarios

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Parameter condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary transfer for EVT possible under the drip and ship approach</td>
<td>Onset-to-alarm + alarm-to-scene + on-scene + scene-to-PSC + door-to-needle&lt;sub&gt;PSC&lt;/sub&gt; + door-out + transfer + door-to-groin&lt;sub&gt;drip and ship&lt;/sub&gt; ( \leq ) time-window&lt;sub&gt;EVT&lt;/sub&gt;</td>
</tr>
<tr>
<td>Thrombolysis at the CSC possible under the mothership approach</td>
<td>Onset-to-alarm + alarm-to-scene + on-scene + scene-to-CSC + door-to-needle&lt;sub&gt;CSC&lt;/sub&gt; ( \leq ) time-window&lt;sub&gt;thrombolysis&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

### B Assignment of treatment options to treatment scenarios

<table>
<thead>
<tr>
<th>Secondary transfer for EVT possible under the drip and ship approach</th>
<th>Thrombolysis at the CSC possible under the mothership approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>I</td>
</tr>
<tr>
<td>No</td>
<td>III</td>
</tr>
</tbody>
</table>

EVT stands for endovascular therapy, CSC for comprehensive EVT-capable stroke center, PSC for primary non-EVT-capable stroke center.
Figure I: Median NIHSS scores according to RACE score with linear regression curve

RACE stands for rapid arterial occlusion evaluation scale (RACE), NIHSS for National Institutes of Health Stroke Scale.
Figure II Probability of presence of LVO among acute ischemic stroke patients according to RACE score with weighted logistic regression curve

Patients with hemorrhagic stroke and stroke mimics were ignored in the calculation of these probabilities, as these patients need to be considered separately. LVO stands for large vessel occlusion, RACE for rapid arterial occlusion evaluation scale (RACE).\textsuperscript{1}
Figure III Probability of good outcome after EVT for ischemic stroke patients with LVO after successful recanalization, given stroke severity (NIHSS) and time from symptom onset to reperfusion

Panel A: Exponential regression of probabilities of good outcome against NIHSS scores for different onset-to-reperfusion times (60, 285, 360, and 480 minutes). Panel B: Linear regression of the exponential coefficients $B$ against onset-to-reperfusion times. EVT stands for endovascular therapy, LVO for large vessel occlusion, NIHSS for National Institutes of Health Stroke Scale, mRS for modified Rankin scale.
Figure IV Probability of good outcome for ischemic stroke patients with LVO in whom reperfusion is not achieved by either thrombolysis or EVT as a function of the NIHSS score

For patients with an initial NIHSS score $\geq 20$, the probability was assumed to be 0.05. EVT stands for endovascular therapy, LVO for large vessel occlusion, NIHSS for National Institutes of Health Stroke Scale, mRS for modified Rankin scale.
Figure V Probability of good outcome for ischemic stroke patients without LVO treated with thrombolysis, given stroke severity (NIHSS score) and time from symptom onset to thrombolysis

For a detailed explanation see Table II. Panel A: Probability of good outcome without treatment. Panel B: Time-dependent odds ratios of thrombolysis. LVO stands for large vessel occlusion, NIHSS for National Institutes of Health Stroke Scale, mRS for modified Rankin scale.
2. Supplemental Results

2.1 Absolute probabilities of good outcome

Figure VI Absolute probabilities of good outcome for the mothership and the drip and ship approach

Displayed are distributions of probabilities of good outcome (modified Rankin scale score ≤2 at three months) for the drip and ship approach (left side of the asymmetrical bean) and the mothership approach (right side of the asymmetrical bean) for different RACE scores and three different transfer time settings (15 min, 60 min, and 120 min) according to treatment scenario (I – IV, see main text). RACE stands for rapid arterial occlusion evaluation scale.
2.2 Relative size of the subset of the equipoise region with different probabilities of good outcome

Table V Relative size of the subset of the equipoise region with different probabilities of good outcome according to RACE score and transfer time

<table>
<thead>
<tr>
<th>Transfer time</th>
<th>RACE score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>0.0233</td>
<td>0.0588</td>
<td>0.1409</td>
<td>0.2002</td>
<td>0.3455</td>
<td>0.3444</td>
<td>0.2091</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>0.0192</td>
<td>0.0631</td>
<td>0.0670</td>
<td>0.0637</td>
<td>0.1183</td>
<td>0.1887</td>
<td>0.2237</td>
<td>0.3093</td>
<td>0.2141</td>
<td>0.2823</td>
<td></td>
</tr>
<tr>
<td>120 min</td>
<td>0.0116</td>
<td>0.0782</td>
<td>0.2064</td>
<td>0.1043</td>
<td>0.0275</td>
<td>0.0514</td>
<td>0.1608</td>
<td>0.0862</td>
<td>0.1282</td>
<td>0.1028</td>
<td></td>
</tr>
</tbody>
</table>

RACE stands for rapid arterial occlusion evaluation scale.
2.3 Bivariate sensitivity analysis: Door-to-needle time $\times$ door-out time

Door-to-needle time at PSC (min)

Door-out time (min)

15

30

60

90
Figure VII Optimal treatment scenario-specific RACE cut-off scores (previous page)

Optimal treatment scenario-specific RACE cut-off scores according to treatment scenario and transfer time setting for three different door-to-needle times (Column 1-3: 30, 60, and 90 min) and four different door-out times (Row 1-4: 15, 30, 60, 90 min). No line is drawn where a treatment scenario does not exist. ‘n/a’ signifies transportation of all patients to the primary non-endovascular therapy-capable stroke center. RACE stands for rapid arterial occlusion evaluation scale.
2.4 Univariate sensitivity analysis: Onset-to-alarm time
Figure VIII Optimal treatment scenario-specific RACE cut-off scores (previous page)

Optimal RACE cut-off scores according to treatment scenario and transfer time setting for three different onset-to-alarm times (Row 1-3: 1, 30, 60 min). No line is drawn where a treatment scenario does not exist. ‘n/a’ signifies transportation of all patients to the primary non-endovascular therapy-capable stroke center. RACE stands for rapid arterial occlusion evaluation scale.
3. Supplemental References


2. Perez de la Ossa N. Median National Institutes of Health Stroke Scale score according to Rapid Arterial Occlusion Scale score. E-Mail communication. 03/22/2017


