ORIGINAL RESEARCH

Comparative Evaluation of 10 Prehospital Triage Strategy Paradigms for Patients With Suspected Acute Ischemic Stroke

Ludwig Schlemm, MD; Matthias Endres, MD; Jan F. Scheitz, MD; Marielle Ernst, MD; Christian H. Nolte, MD; Eckhard Schlemm, MBBS, PhD

***Background*—**The best strategy to identify patients with suspected acute ischemic stroke and unknown vessel status (large vessel occlusion) for direct transport to a comprehensive stroke center instead of a nearer primary stroke center is unknown.

***Methods and Results*—**We used mathematical modeling to estimate the impact of 10 increasingly complex prehospital triage strategy paradigms on the reduction of population-wide stroke-related disability. The model was applied to suspected acute ischemic stroke patients in (1) abstract geographies, and (2) 3 real-world urban and rural geographies in Germany. Transport times were estimated based on stroke center location and road infrastructure; spatial distribution of emergency medical services calls was derived from census data with high spatial granularity. Parameter uncertainty was quantified in sensitivity analyses. The mothership strategy was associated with a statistically significant population-wide gain of 8 to 18 disability-adjusted life years in the 3 real-world geographies and in most simulated abstract geographies (net gain −4 to 66 disability-adjusted life years). Of the more complex paradigms, transportation of patients with clinically suspected large vessel occlusion based on a dichotomous large vessel occlusion detection scale to the nearest comprehensive stroke center yielded an additional clinical benefit of up to 12 disability-adjusted life years in some rural but not in urban geographies. Triage strategy paradigms based on probabilistic conditional modeling added an additional benefit of 0 to 4 disability-adjusted life years over less complex strategies if based on variable cutoff scores.

***Conclusions*—**Variable stroke severity cutoff scores were associated with the highest reduction in stroke-related disability. The mothership strategy yielded better clinical outcome than the drip-'n'-ship strategy in most geographies. **(*J Am Heart Assoc*. 2019;8:e012665. DOI: 10.1161/JAHA.119.012665.)**

Key Words: decision analysis • endovascular treatment • ischemic stroke • mathematical modeling • prehospital triage • thrombectomy • thrombolysis

In patients with acute ischemic stroke (AIS) and cerebral proximal large vessel occlusion (LVO), treatment with mechanical thrombectomy (MT) leads to improved functional outcomes as compared with treatment with intravenous thrombolysis (IVT) alone.[1,2] In the prehospital setting, the presence of LVO cannot be determined reliably given currently available routine diagnostic tools.[3,4] The beneficial effects of both MT and IVT diminish over time[5,6] and not all acute hospitals that offer IVT can also perform MT. Furthermore, a secondary transfer of AIS patients with LVO from a non-MT-capable primary stroke center (PSC) to a MT-capable comprehensive stroke center (CSC) is associated with significant time delays.[7,8] Therefore, the clinical problem of determining the best primary transport destination for patients with suspected AIS and unknown vessel status to achieve optimal outcomes has gained increasing attention over the past 2 years.[9–11] Suggested strategies for prehospital triage have included algorithms based on the additional transport time to reach the nearest CSC[12]; the severity of stroke symptoms as surrogate marker for the probability of

From the Klinik und Hochschulambulanz für Neurologie (L.S., M. Endres, J.F.S., C.H.N.) and Center for Stroke Research Berlin (CSB) (L.S., M. Endres, J.F.S., C.H.N.), Charité—Universitätsmedizin Berlin, Germany; Berlin Institute of Health (BIH), Berlin, Germany (L.S., M. Endres, J.F.S., C.H.N.); DZHK (German Center for Cardiovascular Research), Berlin, Germany (M. Endres, J.F.S., C.H.N.); DZNE (German Center for Neurodegenerative Diseases), Berlin, Germany (M. Endres, C.H.N.); Medizinische Fakultät, Universität Hamburg, Germany (M. Ernst, E.S.); Abteilung für diagnostische und interventionelle Neuroradiologie (M. Ernst), and Klinik und Poliklinik für Neurologie, Kopf- und Neurozentrum (E.S.), Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

Accompanying Data S1, Tables S1 through S8 and Figures S1 through S9 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012665

Correspondence to: Ludwig Schlemm, Klinik und Hochschulambulanz für Neurologie, Charité—Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. E-mail: ludwig.schlemm@charite.de

Received March 28, 2019; accepted May 7, 2019.

Clinical Perspective

What Is New?

- At least 10 different strategy paradigms exist for the prehospital triage of patients with suspected acute stroke.
- In most geographic settings, the direct-to-comprehensive stroke center triage strategy paradigm (mothership approach) leads to a greater reduction in population-wide stroke-related disability and mortality (=gain in disability-adjusted life years) than transport to the nearest primary stroke center (drip-'n'-ship approach).
- With regard to the remaining prehospital triage strategy paradigms, additional gains of disability-adjusted life years can be achieved with more complex strategies; the greatest benefit is associated with the use of optimal variable (=location-dependent) ordinal stroke symptom severity scale cutoff scores.

What Are the Clinical Implications?

- The optimal prehospital triage strategy paradigm for a given region depends on region-specific parameters, such as geographic location of primary and comprehensive stroke centers and treatment time performance metrics (door-to-needle, door-to-groin, door-in-door-out).
- The optimal prehospital triage strategy paradigm for a given region can be determined before implementation through the approach presented in this article.
- Implementation of the regionally optimal prehospital triage strategy for acute stroke patients shortens prehospital delays to thrombectomy for patients with large vessel occlusions while also considering time-to-thrombolysis for patients without large vessel occlusions and is expected to improve outcomes.

the patient harboring an LVO[13,14]; and the estimated functional outcome derived from probabilistic conditional models associated with each available transport option.[15–21] Which of these increasingly complex strategy paradigms should be implemented in a given geographic scenario to achieve optimal results and whether the higher potential costs of the more complex strategy paradigms are offset by a correspondingly larger reduction of stroke-related disability is not clear.

In the current study, we use mathematical modeling to estimate and compare the impact of 10 increasingly complex prehospital triage paradigms on the reduction of stroke-related disability and mortality on the population level in specific real-world and abstract geographic scenarios.

Methods

Data and Research Materials Transparency

The authors declare that all supporting data are available within the article and the Online Data Supplement.

Model

We used an improved version of a previously published model[18,20] to estimate the impact of 10 different triage strategy paradigms on long-term disability and mortality for patients with suspected acute stroke and unknown vessel status for whom there is uncertainty about the optimal transport destination as a function of age, sex, stroke severity, time to thrombolysis, and time to groin puncture (Figure 1). Changes in long-term disability and mortality were expressed as disability-adjusted life years (DALYs) or disability-adjusted life days gained or lost. The model applies to unselected patients without prior disability for whom a Code Stroke is activated by emergency medical services (EMS) because of clinical suspicion of acute stroke within 8 hours of symptoms or unknown time of symptom onset. Parameters used in the model are presented in Tables S1 and S2 and Figures S1 through S4. The model assumes that patients with clinical symptoms suggestive of acute stroke that are managed by EMS personnel in the prehospital setting can either have a diagnosis of AIS with LVO, AIS without LVO, hemorrhagic stroke (HS), or stroke mimic. The probability of each diagnosis can be estimated as a function of the rapid arterial occlusion evaluation (RACE) scale, a clinical scale based on the items of the National Institutes of Health Stroke Scale (NIHSS) that quantifies the severity of stroke symptoms on a scale from 0 to 9, with higher scores indicating more severe stroke symptoms and a higher probability of IS with LVO and HS.[22] The RACE scale was chosen because it has been validated prospectively in a prehospital cohort of patients with suspected stroke seen by EMS and quantifies the probability of 1 of the 4 final diagnoses (AIS with LVO, AIS without LVO, HS, and stroke mimic) on 10 levels. When used as a dichotomous score (cutoff ≥5), its accuracy is comparable to that of other LVO detection scales.[11,23] For patients with AIS caused by LVO, the model adopts a physiological perspective with a focus on the achievement of recanalization: This can occur either after the administration of IVT,[24] or after MT with a procedure success rate of 80%.[16] Based on these probabilities, the time delay to IVT at the nearest PSC, the time delay to IVT at the nearest CSC, the transfer time between PSC and CSC, the previously published age- and sex-specific treatment effects of IVT and MT per minute faster treatment,[25,26] and the set of treatment time performance metrics at the stroke centers (door-to-needle, door-out, door-to-groin, needle-to-groin, groin puncture-to-recanalization), we estimated the gain or loss of disability-adjusted life days associated with direct transport to the nearest CSC as compared with the current standard of care of transporting all patients to the nearest IVT-ready stroke center. For patients with HS and stroke mimic, the gain/loss of disability-adjusted life days associated with different transport destinations was

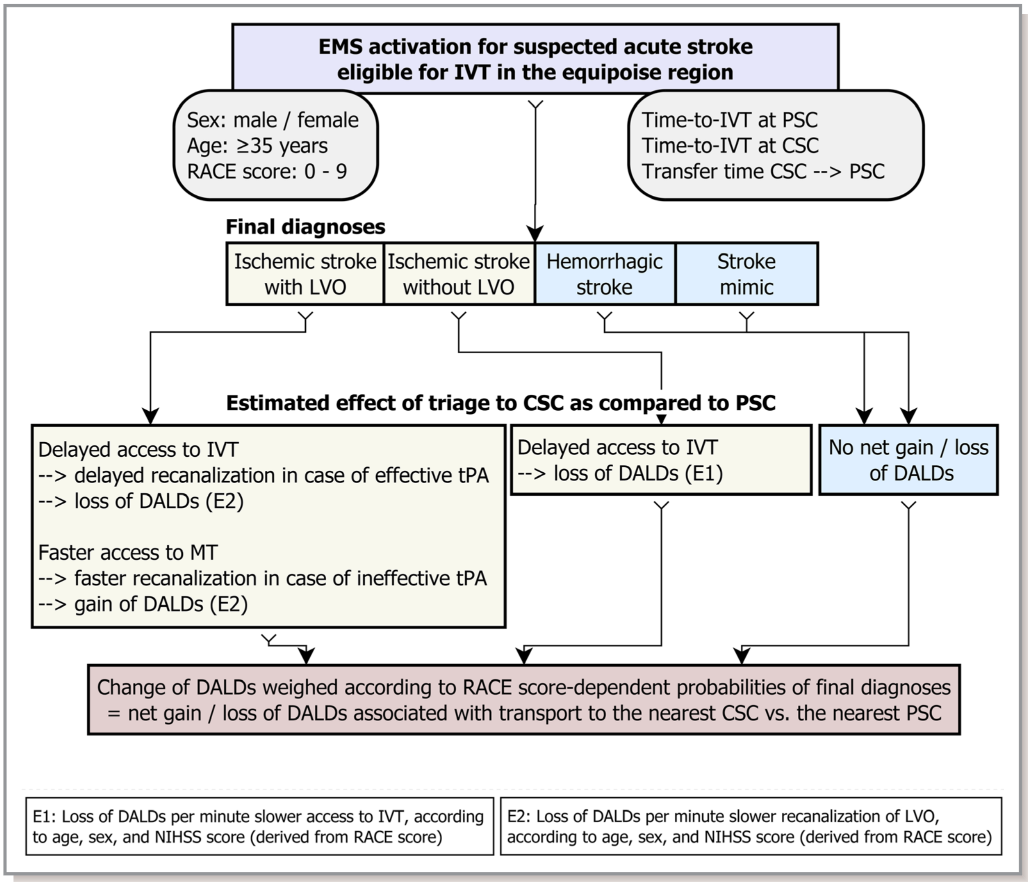

Figure 1. Model structure. CSC indicates comprehensive stroke center; DALD, disability-adjusted life day; EMS, emergency medical services; IVT, intravenous thrombolysis; LVO large vessel occlusion; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; PSC, primary stroke center; RACE, rapid arterial occlusion evaluation scale.

assumed to be zero because of lack of evidence of superiority of either transport strategy. Similarly, patients with contraindications to IVT (time from symptom onset >4.5 hours, oral anticoagulation, etc.) or need for advanced imaging (magnetic resonance imaging–based IVT in wake-up strokes) were assumed to be transported to the nearest CSC and to not derive any benefit from prehospital triage (no equipoise because of lack of treatment options at the PSC). A detailed description of the model in mathematical terms is available in Data S1 with Table S3.

Triage Strategy Paradigms

The set of triage strategy paradigms included in our comparison was based on clinical practice, review of the literature, and theoretical considerations. Figure 2 contains a description of the 10 identified paradigms. Paradigm I corresponds to the current standard of care of transporting all patients to the nearest PSC (drip-‘n’-ship). For strategy paradigm III that considered solely additional transport time, we used a time cutoff of 20 minutes[12] in the base case analysis and performed additional univariate analyses to explore the impact of different time limits. Paradigms VII, VIII, and X are of more theoretical interest because of lack of the necessary technology at the moment. Paradigm IX is currently evaluated in the form of mobile stroke units. Paradigms IX and X involve administration of IVT to eligible patients on scene and are therefore not triage strategy paradigms in the narrow sense, but are included in our analysis for comparison.

Geographic Scenarios

The effects of implementing 1 of the 10 triage paradigms were estimated in 3 specific real-world and 5000 abstract geographic scenarios (Table S4). The specific real-word scenarios included 2 urban geographic scenarios based on the city of Berlin, Germany (1 with centralized and 1 with decentralized MT services) and 1 rural geographic scenario based on the federal state of Schleswig-Holstein in Northern

No.	Designation	Description	Consideration of vessel status	Consideration of estimated transport times	Practicability / Complexity	Availability
I	All-to-PSC, drip-'n'-ship, current standard of care	All patients in the equipoise region are first transported to the nearest PSC.	No	No	No tools needed	Yes
II	All-to-CSC, mothership	All patients in the equipoise region are transported directly to the nearest CSC (equivalent to RACE cutoff score of 0).	No	No	No tools needed	Yes
III	Additional transport time threshold	Patients in the equipoise region are transported to the nearest CSC, if the additional transport time is below a certain threshold (15–30 min).	No	Yes	Real-time transport time estimation	Yes
IV	Fixed cutoff score	All patients in the equipoise region with suspected LVO (RACE score ≥ 5) are transported directly to the nearest CSC.	Yes, probabilistically on a dichotomous scale	No	Dichotomous stroke symptom severity scale	Yes
V	Fixed cutoff score with probabilistic outcome determination	For all patients in the equipoise region with suspected LVO (RACE score ≥ 5), optimal destination (nearest PSC or nearest CSC) is determined through comparison of the expected outcome in a probabilistic model; patients with a RACE score < 5 are transported to the nearest PSC.	Yes, probabilistically on a dichotomous scale	Yes	Dichotomous stroke symptom severity scale + Real-time transport time estimation	Yes
VI	Optimal variable cutoff scores	For all patients in the equipoise region (RACE score 0 – 9), optimal destination (nearest PSC or nearest CSC) is determined through comparison of the expected outcome in a probabilistic model using an ordinal stroke symptom severity scale.	Yes, probabilistically on an ordinal scale	Yes	Ordinal stroke symptom severity scale + Real-time transport time estimation	Yes
VII	Optimal LVO detection device	All patients in the equipoise region with LVO are transported to the nearest to CSC.	Yes, known	No	Optimal LVO detection device	Not currently available
VIII	Optimal LVO detection device with probabilistic outcome determination	For all patients in the equipoise region, optimal destination (nearest PSC or nearest CSC) is determined through comparison of the expected outcome in a probabilistic model assuming known vessel status.	Yes, known	Yes	Optimal LVO detection device + Real-time transport time estimation	Not currently available
IX†	Mobile IVT unit	IVT is administered on scene to all eligible patients, all patients in the equipoise region with LVO are transported to the nearest CSC.	Yes, known	*n.a.*	Ambulance vehicle equipped with computed tomography and point-of-care laboratory	Limited availability
X†	Mobile MT unit	IVT and MT are administered on scene to all eligible patients, all patients in the equipoise region with LVO are transported to the nearest CSC.	Yes, known	*n.a.*	Ambulance vehicle equipped with computed tomography, point-of-care laboratory, and angiography suite	Not currently available

Figure 2. Triage strategy paradigms. †Triage strategy paradigm in the wider sense, included for comparison. CSC indicates comprehensive stroke center; IVT, intravenous thrombolysis; LVO, large vessel occlusion; MT, mechanical thrombectomy; n.a. not applicable; PSC, primary stroke center; RACE, rapid arterial occlusion evaluation scale (score).

Germany. The age- and sex-specific population distributions according to 447 statistical geographic units in Berlin and 1112 communities in Schleswig-Holstein were used to model the spatial distribution of stroke incidences and demographic characteristics of stroke patients at specific locations. For the second urban geographic scenario, we defined that MT was only offered at the 3 university hospitals in order to examine the effect of a stroke care infrastructure with centralized MT services (while in reality, MT is offered at up to 11 of all 14 stroke centers, depending on the time of day [de-centralized MT services]). Transport times were calculated using freely available routing software (OSRM,[27] Table S5).

To avoid making interpretations based on only 3 specific geographic scenarios, we analyzed random realizations of urban and rural geographic scenarios with varying numbers of PSCs and CSCs. For these abstract geographic scenarios, between 1 and 5 PSCs and CSCs (maximum total number of stroke centers: 10) were located randomly on a disc of radius 15 km (abstract urban) and 70 km (abstract rural). In the abstract scenarios, we assumed a spatially homogeneous population density and age distribution derived from those of the real-world scenarios based on Berlin and Schleswig-Holstein. Transport times between 2 points in the abstract scenarios were first calculated using a Euclidean metric and then transformed to road-based transport times according to 2 nonlinear relationships estimated from the specific real-world geographic scenarios (Data S1, Figure S5).

Analysis

For analysis, a total of 10 000 positions were sampled from each geographic scenario (Data S1). The equipoise region was defined as the set of points for which the onset-to-thrombolysis time at the nearest PSC (including transport time and door-to-needle time) was smaller than the onset-to-thrombolysis time at the nearest CSC. For each sampled location in the equipoise region, and each of the 10 triage strategy paradigms, the preferred transport destination (nearest PSC or nearest CSC) was calculated for each of the [age×sex×RACE score] input combinations as shown in Figure 2. These triage strategy paradigm-specific transport destination decision rules were applied to simulated EMS calls in the examined regions and the results were weighed according to the population-specific incidence of EMS calls at the given location, stroke symptom severity distribution, and RACE-score-dependent probability of the diagnosis of IS with LVO, IS without LVO, HS, and stroke mimic. The incidence of EMS calls was assumed to be proportional to the estimated age- and sex-specific stroke incidence. EMS calls for patients aged 35 years or older with suspected acute stroke were considered in the analysis, because no reliable data for the amount of disability-adjusted life days saved per minute faster treatment were available for younger patients, and most stroke patients (in our model: 99.6%) are at least 35 years old. Besides the primary outcome of the population-wide annual gain/loss of DALYs associated with each triage strategy paradigm, we also extracted information on the average time to IVT and MT; the proportion of AIS patients being triaged to the "correct" destination (ie, patients without LVO to the nearest PSC, patients with LVO to the destination associated with better clinical outcome); the total volume of patients being triaged primarily to a PSC and CSC; and the total number of secondary transfers. Uncertainty was quantified in probabilistic sensitivity analyses. For this, each analysis in the 3 specific real-world geographic scenarios was repeated 1000 times with parameters drawn randomly and independently from their respective distributions and results presented as intervals that contained 95% of the obtained values (equal-tailed credible intervals [CI]). The effect of changes in the door-out time at PSCs was examined in separate univariate sensitivity analyses.

All simulations and analyses were performed in MATLAB[28] except for the calculation of transport times in real-world scenarios, which was done in R.[29] No ethical approval or informed patient consent were required for this study.

Results

Transport Destination Decision Rules

First, we calculated transport destination decision rules for each of the 10 prehospital triage strategy paradigms according to geographic location, age, sex, and stroke symptom severity (RACE score). For an exemplary 70-year-old male patient, Figure 3 shows the RACE cutoff scores at or above which a patient should be transported to the nearest CSC for stroke triage paradigms based solely on additional transport time (III) and optimal variable cutoff scores (VI). For the remaining currently available paradigms, drip-'n'-ship (I), mothership (II), and fixed cutoff score (IV), the transport destination rules are independent of the estimated transport times to the nearest stroke enters. For paradigm V (fixed cutoff score with probabilistic outcome determination), the RACE cutoff score was equal to 5 at all positions of the examined specific scenarios. The relative size of the equipoise region in the specific real-world geographic scenarios (ie, the region where a triage decision is necessary because the time-to-IVT at the nearest PSC is shorter than the time-to-IVT at the nearest CSC, calculated with regard to the estimated annual number of EMS calls for suspected acute stroke) was 30% in the urban scenario based on the city of Berlin with decentralized MT services, 81% in the urban scenario based on the city of Berlin with centralized MT services, and 61% in the rural scenario based on the state of Schleswig-Holstein. Transport destination decision rule maps for abstract geographic scenarios are presented in Figure S6.

Specific Real-World Geographic Scenarios

We next applied the 10 transport destination decision rule maps to simulated EMS calls for suspected acute stroke in specific urban and rural real-world geographic scenarios (Berlin I ["as is," decentralized MT services], Berlin II ["theoretical," centralized MT services], and Schleswig-Holstein, Figure 4). In all 3 examined specific scenarios, transporting all patients to the nearest PSC irrespective of transport times and stroke symptom severity (drip-'n'-ship, paradigm I) was associated with a slightly shorter onset-to-thrombolysis time for patients with AIS and a significantly longer onset-to-groin puncture time for AIS patients with LVO compared with all other currently available paradigms (II to VI). In comparison to the drip-'n'-ship approach (paradigm I), the remaining currently available triage strategy paradigms II to VI were associated with an estimated population-wide annual gain of DALYs of between 8 and 18 DALYs.

When considering whether a triage strategy paradigm should be implemented, the complexity of each paradigm needs to be taken into account. We therefore also analyzed the additional gain of DALYs associated with each triage strategy paradigm over and above the best performing less complex paradigm. Here we found that the mothership approach (paradigm II) was associated with a statistically significant gain of DALYs over the drip-'n'-ship approach (strategy I) in all examined specific geographic scenarios. In the specific real-world urban geographic scenario with decentralized MT

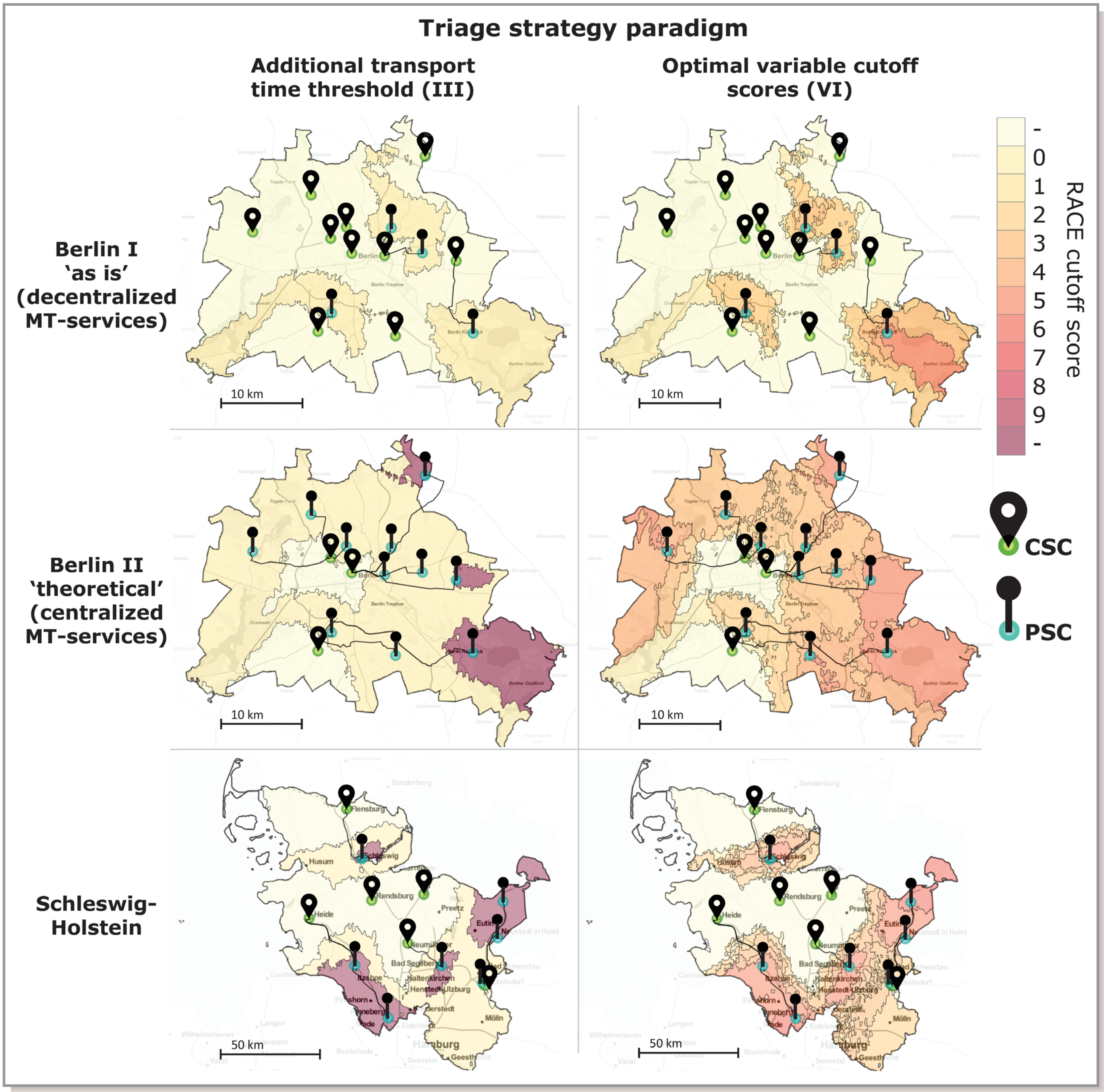

Figure 3. Prehospital triage strategy paradigm-associated transport destination decision rules in specific real-world urban and rural geographic scenarios. Color-coded are the RACE cutoff scores at or above which a 70-year-old male patient seen by emergency medical services personnel for suspected acute stroke should be transported to the nearest CSC instead of the nearest PSC for a triage strategy based solely on a maximum additional transport time of 20 minutes (paradigm III, left) and optimal variable stroke symptom severity cutoff scores (paradigm VI, right). A dash "-" signifies transport of all patients to the nearest CSC because of lack of equipoise because of a shorter transport time (light color) or to the nearest PSC (dark color). CSC indicates comprehensive stroke center; MT, mechanical thrombectomy; PSC, primary stroke center; RACE, rapid arterial occlusion evaluation scale.

services (Berlin I, "as is"), none of the remaining, currently available more complex triage strategy paradigms (III–VI) provided an additional clinical benefit. In the specific real-world urban geographic scenario with centralized MT services (Berlin II, "theoretical") and in the specific real-world rural scenario, a triage strategy based on optimal variable stroke severity cutoff scores (VI) offered a statistically significant additional benefit of 1.6 DALY per year (95% CI: 0.0–2.4 DALYs) and 1.1 DALY per year (95% CI: 0.2–2.0 DALYs), respectively. In addition, in the specific real-world rural scenario, a triage strategy based on a

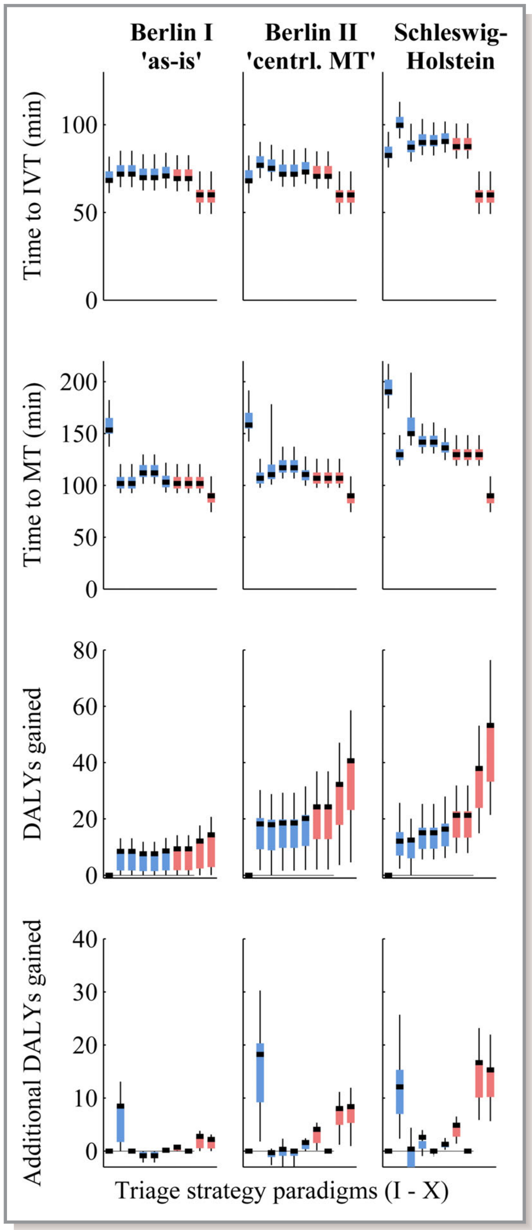

Figure 4. Impact of prehospital triage strategy paradigms on patient-centered outcome parameters in specific real-world geographic scenarios. Boxplots show data for prehospital triage strategy paradigms I to X from probabilistic sensitivity analyses; vertical extent of the boxes represents the interquartile range, the horizontal line represents the base case result, and the whiskers extend to include 95% of all values. Currently available triage strategy paradigms (I–VI) are shown in blue, the remaining paradigms (VII–X) in shades of red. Gain of DALYs is calculated with reference to triage strategy paradigm I (drip-'n'-ship approach). The last row depicts the additional gain in DALYs associated with each triage strategy paradigm over and above all less complex triage strategy paradigms. For a description of triage strategy paradigms, see Figure 2. DALY indicates disability-adjusted life year; IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

fixed stroke severity cutoff without consideration of transport times (IV) was associated with a not statistically significant additional benefit in comparison to less complex strategies (2.12 DALYs [−0.5 to 3.2 DALYs]).

In addition, we investigated how prehospital triage using any of the 10 paradigms would affect the proportion of patients triaged primarily to a CSC and a PSC, as well as the number of secondary transfers. Results are displayed in Figure 5. Of note, the proportions of AIS patients transported to the "correct" destination were significantly higher with strategy paradigms based on clinical stroke severity scales (IV, V; 75%% [95% CI: 73–77%]) than with the mothership strategy (II; 29% [95% CI: 27–31%]).

For comparison, we also analyzed the potential gain of DALYs associated with triage strategy paradigms based on technology that is currently not available (optimal LVO detection device [paradigms VII and VIII], mobile MT unit [X]), or has limited availability (mobile IVT unit [IX]). As shown in Figures 4 and 5 (red bars), such novel technologies have the potential to achieve clinically significant reductions of stroke-related disability in addition to what can be attained with currently available triage strategy paradigms. Numerical results of all examined outcome measures are presented in Tables S6 through S8.

Abstract Geographic Scenarios

The impact of prehospital triage of patients with suspected AIS depends not only on the absolute number of PSCs and CSCs (ie, the overall spatial density of stroke centers) but also on the CSC-to-PSC ratio and the relative location of the stroke centers to each other, all of which directly influence the size of the equipoise region. We therefore chose to examine the effect of prehospital triage strategy paradigms in abstract urban and rural scenarios according to the size of the equipoise region (Figure 6). Similar to the results obtained in the specific real-world geographic scenarios, we found that the mothership approach (paradigm II) offered significant additional clinical benefit over the drip-'n'-ship approach (I) in nearly all random abstract scenarios, with the difference in disability ranging from zero of 66 DALYs per year in the urban and from −4 to 31 DALYs per year in the rural scenarios. A strategy based on optimal variable cutoff scores (VI) was associated with a small additional benefit of up to ≈0 to 4 DALYs per year over all other paradigms. In rural, but not in urban scenarios, fixed cutoff scores (paradigm IV) offered some additional benefit (up to 12 DAYLs). Strategies only considering additional transport time (III) and strategies based on a fixed cutoff score with probabilistic outcome determination (V) did not offer additional benefit over less complex paradigms, except for a few rural scenarios with a large equipoise region. In summary, results in abstract scenarios confirmed the findings from the three specific real-world geographic scenarios.

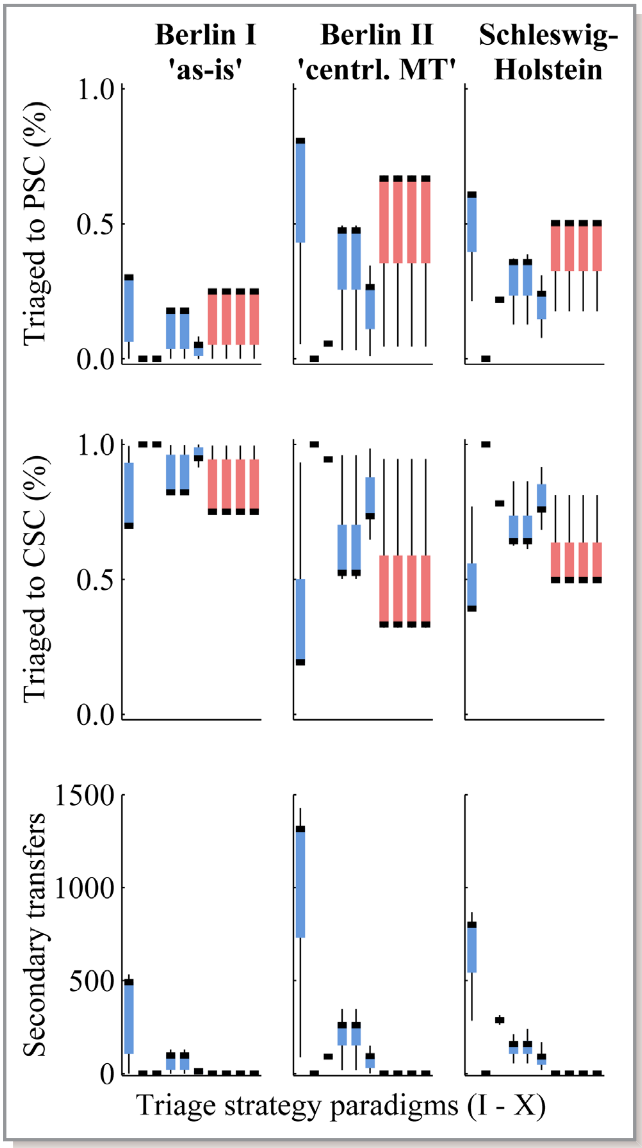

Figure 5. Impact of prehospital triage strategy paradigms on health system–related outcome parameters in specific real-world geographic scenarios. Boxplots show data for prehospital triage strategy paradigms I to X from probabilistic sensitivity analyses; vertical extent of the boxes represents the interquartile range, the horizontal line represents the base case result, and the whiskers extend to include 95% of all values. Currently available triage strategy paradigms (I–VI) are shown in shades of blue, the remaining paradigms (VII–X) in shades of red. For a description of triage strategy paradigms, see Figure 2. CSC indicates comprehensive stroke center; MT, mechanical thrombectomy; PSC, primary stroke center.

Univariate Sensitivity Analysis

In univariate sensitivity analyses assuming a shorter door-out time of 15 minutes, we found an overall diminished magnitude of the effect of the mothership strategy (II) on the gain of DALYs. In addition, the mothership approach was no longer superior to the drip-‘n’-ship approach (I) in a relevant proportion of abstract rural geographic scenarios with a large equipoise region. Instead, in abstract rural geographic scenarios, triage strategy paradigms based solely on transport times (III) and a fixed cutoff score with probabilistic outcome determination (V) were associated with a modest additional clinical benefit as compared with less complex strategy paradigms (additional DALYs gained up to 6 and 4, respectively). The additional benefit of optimal variable cutoff scores (triage paradigm VI) was similar to the base case results in urban, and decreased by ≈50% in rural scenarios (Figures S7 through S9, Tables S6 through S8).

In a second univariate sensitivity analysis, we assessed the impact of different time limits for strategies considering only additional transport time (paradigm III). Regarding the impact on the reduction of stroke-related disability and mortality, we found that in urban scenarios, most DALYs were gained with a time limit of 20 minutes; higher time limits provided similar benefit (identical to mothership approach for time limit ≥30 minutes). In rural scenarios, the optimal transport time limit was 30 to 40 minutes; when higher time limits were used, the benefit of triage started to decrease. In absolute terms, the differences between triage strategies using different time limits were modest (up to 5 DALYs in all 3 real-world geographic scenarios).

Discussion

Main Findings

We estimated the effect of 10 increasingly complex prehospital triage strategy paradigms for patients with suspected acute stroke in a probabilistic conditional model. In our model, for patients with suspected acute stroke and unknown vessel status for whom a Code Stroke is activated by EMS, direct transportation to the nearest CSC (mothership approach) instead of the nearest PSC (drip-‘n’-ship) was associated with a net gain of DALYs. The total amount of DALYs gained ranged from 8 to 18 in the specific real-world geographic scenarios and from −4 to 66 in the abstract geographic scenarios. Adjusting prehospital triage algorithms to include stroke symptom severity irrespective of expected transport times was associated with an additional gain of DALYs in rural scenarios, particularly in those with a relatively large equipoise region (ie, fewer stroke centers with centralized MT services). Of the triage strategy paradigms based on probabilistic conditional modeling, use of optimal variable cutoff scores, (ie, consideration of vessel status on an ordinal scale) yielded an additional gain of DALYs over and above less complex triage strategy paradigms in all scenarios. On the other hand, triage strategy paradigms based on a fixed cutoff score (ie, consideration of vessel status on a dichotomous scale) were associated with additional benefit only in rural

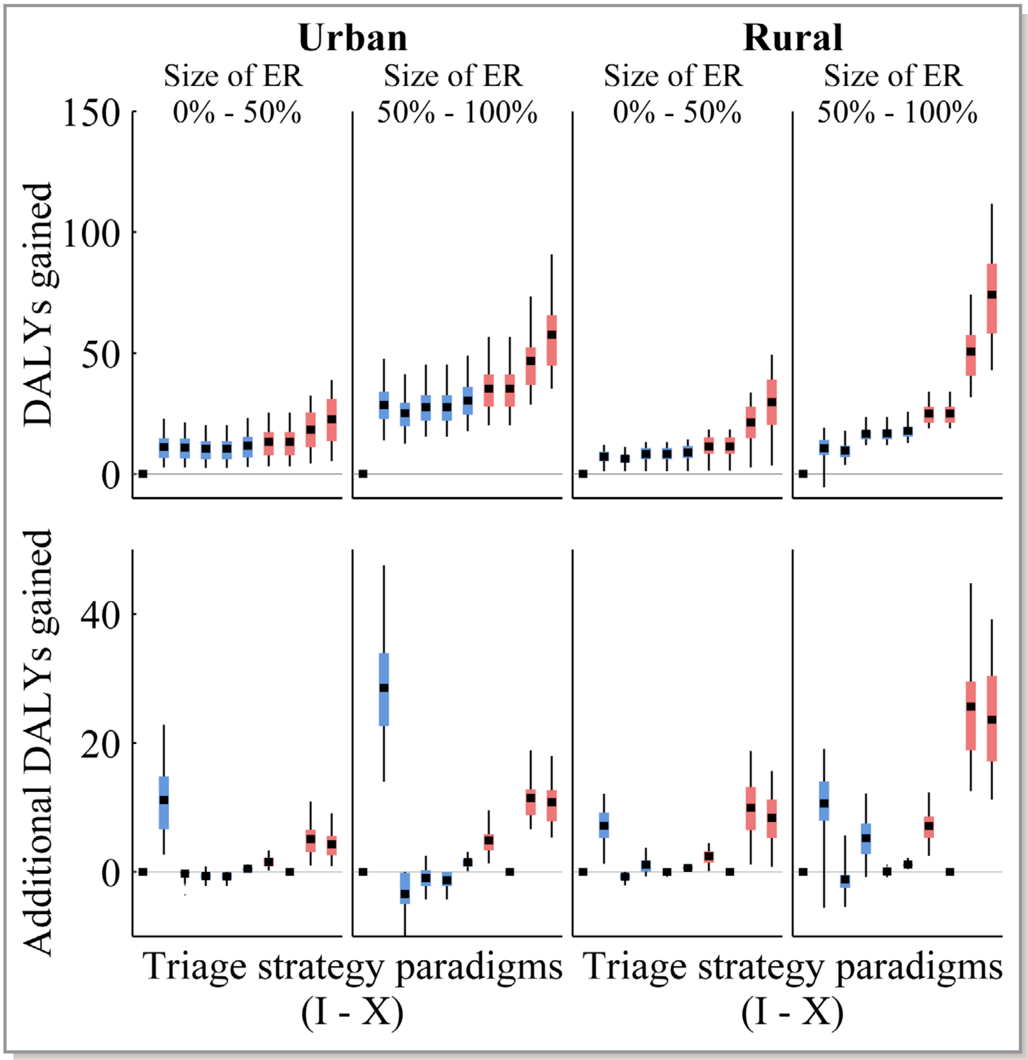

Figure 6. Impact of prehospital triage strategy paradigms on the reduction of stroke-related disability in abstract geographic scenarios. Boxplots show results for prehospital triage strategy paradigms I to X from repeated random generation of abstract rural and urban geographic scenarios with between 1 and 5 primary stroke centers and 1 and 5 comprehensive stroke centers according to the relative size of the equipoise region (ER). Vertical extent of the boxes represents the interquartile range, the horizontal line the mean, and the whiskers extend to include 95% of all values. Currently available triage strategy paradigms (I–VI) are shown in shades of blue, the remaining paradigms (VII–X) in shades of red. In the first row, gain of DALYs is calculated with reference to triage strategy paradigm I (drip-'n'-ship approach). The second row depicts the additional gain in DALYs associated with each triage strategy paradigm over and above all less complex triage strategy paradigms. For a description of triage strategy paradigms, see Figure 2. DALY indicates disability-adjusted life year.

scenarios under the assumption of a short door-out time of 15 minutes.

Previous Studies

Our study is the first to systematically collect a list of conceivable prehospital triage strategy paradigms for patients with suspected AIS and to compare the consequences of their implementation in specific real-world geographic scenarios in a single model. Hereby, our aim was not to compare the accuracy of different individual prehospital stroke symptom severity scales, but to evaluate a set of conceptually different triage strategy paradigms. Our study is also the first to estimate population-wide effects, which are ultimately the driving force for decisions for or against the implementation of a given triage strategy. For this, we aggregated the estimated outcomes of individual patients while taking into account the spatial distribution of stroke incidence, spatially heterogeneous demographics, and the distribution of stroke severity. Previously published reports using mathematical modeling for the evaluation of prehospital triage decision algorithms have been performed in simplified abstract geographic scenarios with only 2 stroke centers without considering spatially heterogeneously distributed population characteristics and true transport times, or have only analyzed the impact of 1 single triage strategy (see Holodinsky et al[21] for a recent review). Apart from mathematical modeling, robust evidence from real-world studies is still scarce for most of the examined triage strategy paradigms. In line with results of our study, there is some evidence from clinical studies that the mothership strategy (ie, direct transportation of all patients with suspected stroke to the nearest CSC irrespective of stroke symptom severity and transport times) might be beneficial if the additional transport time is below 30 to 45 minutes.[9] Regarding the benefit of prehospital triage strategy paradigm IV (ie, transportation of all patients with suspected LVO as determined by a higher score on a clinical prehospital stroke symptom severity scale to a CSC irrespective of transport times), a randomized controlled trial is currently ongoing (NCT02795962)[13] with results expected for 2020.

Clinical Implications

When planning the implementation of a prehospital triage strategy for patients with suspected AIS in order to reduce the time delay to the most adequate and effective reperfusion treatment, decision makers need to consider the impact of the intervention on clinical outcome, but also the cost of the intervention. In contrast to previous studies,[15,16,18] we chose to quantify the clinical impact of prehospital triage not as the probability of good functional outcome at 90 days but as the long-term reduction of disability and mortality, a more generic measure that permits a direct comparison with the effectiveness of other healthcare interventions.[30] When selecting one of the many available triage strategies, the additional benefit over less complex strategies needs to be weighed against the increasing cost of setting up and maintaining the triage strategy. For example, implementation of a strategy based on optimal variable cutoff scores would require dedicating resources to train EMS personnel to reliably use an ordinal stroke symptom severity scale such as the RACE scale and to maintain an updated online service to allow the real-time prediction of the expected outcome based on the stroke severity scale score and the expected transport times for each individual patient. On the other hand, the unconditional mothership approach would be easier to implement and maintain, but at the same time would be associated with greater shifts of patient volumes between hospitals and slightly smaller reductions of stroke-related disability and mortality. A formal cost-effectiveness analysis addressing these questions, which is beyond the scope of this article, is currently planned.

As shown previously for selected prehospital triage strategy paradigms, the impact of prehospital triage is strongly influenced by performance time metrics (door-to-needle time, door-out-time) at PSCs.[15,18] In our study, assuming a shorter door-out-time was associated with a lower proportion of abstract rural geographical regions in which patients would benefit from unconditional transportation to the nearest CSC (mothership). The decision for or against implementation of a specific prehospital triage strategy paradigm should therefore be preceded by an estimation of the expected impact considering regional performance time metrics at participating PSCs. In particular, our results indicate that better performance time metrics at PSCs should translate directly into higher patient volumes at PSCs, and vice versa.

In addition to its potential in improving patient-related outcomes, prehospital triage of patients with suspected acute stroke also affects health system–related parameters. Our current study confirms the findings of previous studies of increased numbers of patients managed in emergency departments of CSCs, lower patient volume in PSCs, and a lower number of secondary transfers.[19,31] These shifts would require providers to adapt their services over time to cope with the higher or lower volume. Although in our opinion, the most relevant parameter for decision making is the improvement of functional outcome and the reduction of disability of stroke patients, secondary and higher-order ramifications of shifts in patient volume should not be ignored. At the level of PSCs, such consequences may include efforts to offer MT in order to attract more patients with uncertain consequences for the quality of MT services offered, but also the establishment of policies and protocols to ensure rapid IVT-to-door-out times. Similarly, higher patient volumes at CSCs could lead to further streamlined processes with shorter pretreatment delays or, when no adequate resources can be made available, to a decrease in quality because of overcrowding. In comparison to the mothership strategy, use of clinical stroke symptom severity scales to inform triage decisions would be associated with a similar (sometimes even larger) reduction of stroke-related disability while at the same time causing a smaller shift of patients away from PSCs to CSCs.

Strengths and Limitations

Theoretical models offer the opportunity to answer questions that are difficult to examine in clinical trials, such as a direct comparison of 10 different triage strategy paradigms, and to vary input parameters over a wide range, in our case to examine several geographic scenarios and stroke care infrastructure settings simultaneously. However, we are aware that models to analyze complex decision problems represent simplified abstractions from reality whose results are influenced by the assumptions made when building the model. In the current study, we addressed some of the weaknesses of previous studies. In particular, we constructed our model to represent the real clinical scenario of patients with stroke symptoms, but unknown final diagnosis. In addition, we applied our model to specific real-world geographic scenarios for which demographic data were available at a high spatial granularity and derived the key parameters for the model from a large prospective prehospital cohort of patients with suspected acute stroke managed by EMS that is representative of the target population of our model.[22] Data on the time-dependent effectiveness of IVT and MT stratified by age, sex, and stroke symptom severity were estimated using the pooled effects of large randomized controlled trials.[25,26] In addition, we quantified the uncertainty of our results in probabilistic sensitivity analyses and present 95% CI for all outcome measures. On the other hand, we had to make certain assumptions in our model because of lack of availability of data that likely represent an oversimplification compared with reality. First, we were unable to model the correlation between demographic factors, especially age, stroke symptom severity, and the eligibility for IVT; and the correlation between the probability and timing of early recanalization of LVO after IVT, location of vessel occlusion, and stroke symptom severity. Second, data on the uncertainty of input parameters for probabilistic sensitivity analyses were not available from the literature for all parameters. Third, the spatial distribution of EMS calls was modeled using census data, which assume that strokes occur mostly close to home. Fourth, the possibility of MT in an extended time-window up to 24 hours for selected patients[32,33] was not considered because for most of such patients, there would not be equipoise between transport to the nearest PSC or nearest CSC in the first place because of ineligibility for IVT (maximum time from symptom onset 4.5 hours). For the small number of patients who could be treated at a PSC within 4.5 hours but who could not be transferred to arrive at a CSC within 6 hours, advanced imaging protocols could help to select patients who are likely to derive benefit from MT beyond 6 hours and for whom transfer should be considered. Since the time-decay of the treatment efficacy of MT in imaging-selected patients is not yet well characterized and the impact on the overall results of our study is expected to be small because of the small number of patients, we did not include this scenario in our model. Concerning the eligibility for IVT, we assumed that lack of eligibility (eg, wake-up stroke, anticoagulation, and recent major surgery) could be ascertained in the prehospital setting and excluded these patients from further analyses. The alternative assumption that eligibility for IVT can only be determined after transport to a stroke center would lead to more patients being affected by prehospital triage and larger effect sizes. Last, our model was based on a dichotomy of stroke center characteristics in terms of capability to perform MT; differences in procedural quality affecting outcome (eg, as a function of patient volume, or nonbinary quantification of the availability of MT) could not be considered because of lack of data.

Conclusions

In summary, we have applied a mathematical model based on conditional probabilities to highly granular real-world geographic and demographic data to compare the impact of 10 prehospital triage strategy paradigms for patients with suspected AIS and unknown vessel status. In general, unconditional transport to the nearest CSC (mothership approach) yielded better outcome than did transport to the nearest PSC (drip-'n'-ship) in urban and most rural scenarios. However, our results suggest that a stroke symptom severity-based triage using variable cutoff scores that depend on estimated transport times is associated with the highest reduction in stroke-related disability and mortality. Improvement of key performance measures at the PSC level has an important impact on the effect of the optimal triage strategy. Technologies that allow treating patients with IVT or MT on scene would be associated with significant additional reductions in stroke-related disability. Last, prehospital triage strategies can have a significant impact on the distribution of patient volume between CSCs and PSCs that needs to be considered before making a decision to implement one of the available triage strategy paradigms.

Author Contributions

L. Schlemm and E. Schlemm conceived the study. L. Schlemm reviewed the literature, developed the model, performed the simulation, analyzed the data, created the figures, and wrote the first draft of the manuscript. E. Schlemm reviewed the model, performed geostatistical analyses for the application of the model to real-world geographic data, and visualized spatial maps. Ernst contributed data about the stroke centers in Schleswig-Holstein. All authors contributed to interpreting the data, revised the manuscript for intellectual content, and approved the final version of the manuscript.

Sources of Funding

L. Schlemm is a participant in the Berlin Institute of Health—Charité Clinical Scientist Program funded by the Charité—Universitätsmedizin Berlin and the Berlin Institute of Health.

Disclosures

Endres reports grants from Bayer and fees paid to the Charité from Bayer, Boehringer Ingelheim, BMS/Pfizer, Daiichi Sankyo, Amgen, GSK, Sanofi, Covidien, and Novartis, all outside the submitted work. Scheitz reports fees for lectures from Stryker GmbH & Co. KG and Bristol-Myers Squibb, and grant support by the Corona Stiftung, all outside the submitted work. Nolte reports consulting and lecture fess from Boehringer Ingelheim, W.L. Gore and Associates, Bristol-Myers Squibb, Pfizer, and Sanofi, all outside the submitted work. The remaining authors have no disclosures to report.

References

1. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110.
2. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millan M, Davis SM, Roy D, Thornton J, Roman LS, Ribo M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731.
3. Heldner MR, Hsieh K, Broeg-Morvay A, Mordasini P, Buhlmann M, Jung S, Arnold M, Mattle HP, Gralla J, Fischer U. Clinical prediction of large vessel occlusion in anterior circulation stroke: mission impossible? *J Neurol*. 2016;263:1633–1640.
4. Turc G, Maier B, Naggara O, Seners P, Isabel C, Tisserand M, Raynouard I, Edjlali M, Calvet D, Baron JC, Mas JL, Oppenheim C. Clinical scales do not reliably identify acute ischemic stroke patients with large-artery occlusion. *Stroke*. 2016;47:1466–1472.
5. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, del Zoppo GJ, Baigent C, Sandercock P, Hacke W; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929–1935.
6. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, Cardona P, Devlin TG, Frei DF, du Mesnil de Rochemont R, Berkhemer OA, Jovin TG, Siddiqui AH, van Zwam WH, Davis SM, Castano C, Sapkota BL, Fransen PS, Molina C, van Oostenbrugge RJ, Chamorro A, Lingsma H, Silver FL, Donnan GA, Shuaib A, Brown S, Stouch B, Mitchell PJ, Davalos A, Roos YB, Hill MD; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288.
7. Goyal M, Jadhav AP, Bonafe A, Diener H, Mendes Pereira V, Levy E, Baxter B, Jovin T, Jahan R, Menon BK, Saver JL; SWIFT PRIME investigators. Analysis of workflow and time to treatment and the effects on outcome in endovascular treatment of acute ischemic stroke: results from the swift prime randomized controlled trial. *Radiology*. 2016;279:888–897.
8. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP, Haussen DC, Hellinger FR Jr, Yavagal DR, Yao TL, Liebeskind DS, Jadhav AP, Gupta R, Hassan AE, Martin CO, Bozorgchami H, Kaushal R, Nogueira RG, Gandhi RH, Peterson EC, Dashti SR, Given CA II, Mehta BP, Deshmukh V, Starkman S, Linfante I, McPherson SH, Kvamme P, Grobelny TJ, Hussain MS, Thacker I, Vora N, Chen PR, Monteith SJ, Ecker RD, Schirmer CM, Sauvageau E, Abou-Chebl A, Derdeyn CP, Maidan L, Badruddin A, Siddiqui AH, Dumont TM, Alhajeri A, Taqi MA, Asi K, Carpenter J, Boulos A, Jindal G, Puri AS, Chitale R, Deshaies EM, Robinson DH, Kallmes DF, Baxter BW, Jumaa MA, Sunenshine P, Majjhoo A, English JD, Suzuki S, Fessler RD, Delgado Almandoz JE, Martin JC, Mueller-Kronast NH, STRATIS Investigators. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the stratis registry (systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke). *Circulation*. 2017;136:2311–2321.
9. Chartrain AG, Shoirah H, Jauch EC, Mocco J. A review of acute ischemic stroke triage protocol evidence: a context for discussion. *J Neurointerv Surg*. 2018;10:1047–1052.
10. Schwamm LH. Optimizing prehospital triage for patients with stroke involving large vessel occlusion: the road less traveled. *JAMA Neurol*. 2018;75:1467–1469.
11. Scheitz JF, Abdul-Rahim AH, MacIsaac RL, Cooray C, Sucharew H, Kleindorfer D, Khatri P, Broderick JP, Audebert HJ, Ahmed N, Wahlgren N, Endres M, Nolte CH, Lees KR; Committee SS. Clinical selection strategies to identify ischemic stroke patients with large anterior vessel occlusion: results from SITS-ISTR (safe implementation of thrombolysis in stroke international stroke thrombolysis registry). *Stroke*. 2017;48:290–297.
12. Pride GL, Fraser JF, Gupta R, Alberts MJ, Rutledge JN, Fowler R, Ansari SA, Abruzzo T, Albani B, Arthur A, Baxter B, Bulsara KR, Chen M, Delgado Almandoz JE, Gandhi CD, Heck D, Hetts SW, Hirsch JA, Hussain MS, Klucznik R, Lee SK, Mack WJ, Leslie-Mazwi T, McTaggart RA, Meyers PM, Mocco J, Prestigiacomo C, Patsalides A, Rasmussen P, Starke RM, Sunenshine P, Frei D, Jayaraman MV; Standards and Guidelines Committee of the Society of NeuroInterventional Surgery (SNIS). Prehospital care delivery and triage of stroke with emergent large vessel occlusion (ELVO): report of the standards and guidelines committee of the society of neurointerventional surgery. *J Neurointerv Surg*. 2017;9:802–812.
13. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000. Identifier NCT02795962, Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion (RACECAT); 2016 [cited 2019 Jun 05]. Available at: https://clinicaltrials.gov/ct2/show/NCT02795962.
14. Zaidi SF, Shawver J, Espinosa Morales A, Salahuddin H, Tietjen G, Lindstrom D, Parquette B, Adams A, Korsnack A, Jumaa MA. Stroke care: initial data from a county-based bypass protocol for patients with acute stroke. *J Neurointerv Surg*. 2017;9:631–635.
15. 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 Neurol*. 2018;75:1477–1486.
16. 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;48:233–238.
17. Milne MS, Holodinsky JK, Hill MD, Nygren A, Qiu C, Goyal M, Kamal N. Drip 'n ship versus mothership for endovascular treatment: modeling the best transportation options for optimal outcomes. *Stroke*. 2017;48:791–794.
18. Schlemm E, Ebinger M, Nolte CH, Endres M, Schlemm L. Optimal transport destination for ischemic stroke patients with unknown vessel status: use of prehospital triage scores. *Stroke*. 2017;48:2184–2191.
19. Schlemm L, Ebinger M, Nolte CH, Endres M. Impact of prehospital triage scales to detect large vessel occlusion on resource utilization and time to treatment. *Stroke*. 2018;49:439–446.
20. Schlemm L, Schlemm E. Clinical benefit of improved prehospital stroke scales to detect stroke patients with large vessel occlusions: results from a conditional probabilistic model. *BMC Neurol*. 2018;18:16.
21. Holodinsky JK, Almekhlafi MA, Goyal M, Kamal N. Mathematical modeling for decision-making in the field for acute stroke patients with suspected large vessel occlusion. *Stroke*. 2018;50:212–217.
22. Carrera D, Gorchs M, Querol M, Abilleira S, Ribo M, Millan M, Ramos A, Cardona P, Urra X, Rodriguez-Campello A, Prats-Sanchez L, Purroy F, Serena J, Canovas D, Zaragoza-Brunet J, Krupinski JA, Ustrell X, Saura J, Garcia S, Mora MA, Jimenez X, Davalos A, Perez de la Ossa N; Catalan Stroke Code and Reperfusion Consortium (Cat-SCR). Revalidation of the RACE scale after its regional implementation in Catalonia: a triage tool for large vessel occlusion. *J Neurointerv Surg*. 2018. Available at: https://jnis.bmj.com/content/early/2019/03/29/neurintsurg-2018-014519. Accessed June 10, 2019.
23. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, Towfighi A, Whiteley WN, Zahuranec DB; American Heart Association Stroke C. Accuracy of prediction instruments for diagnosing large vessel occlusion in individuals with suspected stroke: a systematic review for the 2018 guidelines for the early management of patients with acute ischemic stroke. *Stroke*. 2018;49:e111–e122.
24. Seners P, Turc G, Maier B, Mas JL, Oppenheim C, Baron JC. Incidence and predictors of early recanalization after intravenous thrombolysis: a systematic review and meta-analysis. *Stroke*. 2016;47:2409–2412.
25. Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, Davis SM, Donnan GA, Churilov L. Stroke thrombolysis: save a minute, save a day. *Stroke*. 2014;45:1053–1058.
26. Meretoja A, Keshtkaran M, Tatlisumak T, Donnan GA, Churilov L. Endovascular therapy for ischemic stroke: save a minute-save a week. *Neurology*. 2017;88:2123–2127.
27. Luxen D, Vetter C. Real-time routing with openstreetmap data. Proceedings of the 19th ACM SIGSPATIAL international conference on advances in geographic information systems. 2011:513–516.
28. *MATLAB and Statistics Toolbox Release*. Natick, MA: TM, Inc.; 2013a.
29. R Core Team. R: a language and environment for statistical computing. 2015.
30. Murray CJ. Quantifying the burden of disease: the technical basis for disability-adjusted life years. *Bull World Health Organ*. 1994;72:429–445.

31. Zhao H, Coote S, Pesavento L, Churilov L, Dewey HM, Davis SM, Campbell BC. Large vessel occlusion scales increase delivery to endovascular centers without excessive harm from misclassifications. *Stroke*. 2017;48:568–573.

32. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, Sarraj A, Kasner SE, Ansari SA, Yeatts SD, Hamilton S, Mlynash M, Heit JJ, Zaharchuk G, Kim S, Carrozzella J, Palesch YY, Demchuk AM, Bammer R, Lavori PW, Broderick JP, Lansberg MG; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718.

33. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, Sila CA, Hassan AE, Millan M, Levy EI, Mitchell P, Chen M, English JD, Shah QA, Silver FL, Pereira VM, Mehta BP, Baxter BW, Abraham MG, Cardona P, Veznedaroglu E, Hellinger FR, Feng L, Kirmani JF, Lopes DK, Jankowitz BT, Frankel MR, Costalat V, Vora NA, Yoo AJ, Malik AM, Furlan AJ, Rubiera M, Aghaebrahim A, Olivot JM, Tekle WG, Shields R, Graves T, Lewis RJ, Smith WS, Liebeskind DS, Saver JL, Jovin TG; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11–21.

SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods and Results

Mathematical description of the model

An outline of the probabilistic model used in our study is presented in **Figure 1** and the Methods section in the main text. Here, we describe the model in detail using mathematical terms. **Table S3** contains a list definitions used in the following formulae.

First, we defined a function to estimate the change of disability-adjusted life days (DALDs) associated with transport to the nearest comprehensive stroke center (CSC) as compared to the nearest primary stoke center (PSC) as a function of demographic, clinical, and geographic input parameters:

$$\Delta \qquad = f\ \big(\qquad , \qquad , \qquad , t \qquad , t \qquad , t \qquad \big).$$

The total change of DALDs is calculated as the weighted mean of the change of DALDs associated with transport to the nearest CSC for patients in each of the four final diagnostic categories:

$$\Delta DALD = \sum_{d \in \mathfrak{D}} \left(\Delta DALD_d \times \mathcal{P}_d^{RACE} \right).$$

For patients with hemorrhagic stroke (HS) and stroke mimic (SM), we assumed no change of DALDs associated with transport to the nearest CSC as compared to transport to the nearest PSC:

$$\Delta DALD_{HS,SM} = 0.$$

For patients with acute ischemic stroke (AIS) without large vessel occlusion (LVO), the loss of DALDs associated with transport to the nearest CSC is calculated as:

$$\Delta DALD_{AIS\ without\ LVO} = \left(min\left(t_{IVT}^{CSC}, t_{IVT}^{max}\right) - min\left(t_{IVT}^{PSC}, t_{IVT}^{max}\right) \right) \times \mathfrak{E}_{AIS\ without\ LVO}^{NIHSS,age,sex}.$$

For patients with AIS with LVO, recanalization can occur after i.v. thrombolysis (IVT), after mechanical thrombectomy (MT), or not at all. Thus, we calculate the expected time of recanalization, depending on the transport destination, as:

$$t_R^{PSC} := \begin{cases} \mathcal{P}_R^{IVT} \times (1 - \mathcal{P}_R^{MT}) \times \left(OTEMS + t_{IVT}^{PSC} + t_R^{IVT}/2 \right) + \ldots. \\ (1 - \mathcal{P}_R^{IVT}) \times \mathcal{P}_R^{MT} \times \left(OTEMS + t_{IVT}^{PSC} + DO + t_{transfer} + DTG + GTR \right) + \ldots.. \\ (1 - \mathcal{P}_{ER}^{IVT}) \times (1 - \mathcal{P}_R^{MT}) \times (t_{GP}^{max} + GTR) \end{cases}$$

$$t_R^{CSC} := \begin{cases} \mathcal{P}_{ER}^{IVT} \times (1 - \mathcal{P}_R^{MT}) \times \left(OTEMS + t_{IVT}^{CSC} + t_R^{IVT}/2 \right) + \ldots. \\ (1 - \mathcal{P}_R^{IVT}) \times \mathcal{P}_R^{MT} \times \left(OTEMS + t_{IVT}^{CSC} + NTG + GTR \right) + \ldots.. \\ (1 - \mathcal{P}_R^{IVT}) \times (1 - \mathcal{P}_R^{MT}) \times (t_{GP}^{max} + GTR) \end{cases}$$

In addition, the time window for IVT to take effect (t_R^{IVT}) and the probability of early recanalization after IVT ($\mathcal{P}_R^{IVT}$) is adjusted if recanalization from MT would be expected to be achieved shortly after administration of IVT. If the expected time-to-IVT or time-to-groin puncture are greater than t_{IVT}^{max} and t_{MT}^{max}, respectively, then the corresponding probabilities to achieve recanalization with IVT or MT are set to zero.

Accordingly, the gain of DALDs for patients with AIS and LVO is estimated as:

$$\Delta DALD_{AIS\ with\ LVO} = \left(min(t_R^{PSC}, t_{GP}^{max} + GTR) - min(t_R^{CSC}, t_{GP}^{max} + GTR)\right) \times \mathfrak{E}_{AIS\ with\ LVO}^{NIHSS,age,sex}.$$

Second, we calculated two-dimensional prehospital triage strategy paradigm-specific transport destination decision rule maps for each geography according to **Figure 2** in the main text. These maps determine if a given patient at one of the sampled locations should be transported to the nearest PSC or CSC, taking into account demographic (age, sex,), clinical (stroke symptom severity), geographic parameters (transport times, transfer time) and treatment time performance metrics. For triage strategy paradigms V and VI, estimated outcome as outlined above was used to determine transport destination. For the following, let $\mathcal{T}_{s,age,sex}^{Z}$ denote the transport decision for a given patient at the sampled point *s* under triage strategy paradigm *Z*.

Third, we estimated the population-wide impact of different prehospital triage strategies. Let $\mathfrak{S}$ be the set of sampled points in a given geography, $\mathfrak{U}$ the set of the statistical geographical units for which data on the sex-specific age distribution was available (one single unit in abstract scenarios), and $n_{sex,age}^{u\in\mathfrak{U}}$ the total number of individuals of a given age and sex living in a given statistical geographical unit. In addition, let $m_{u\in\mathfrak{U}}$ be the total number of sampled points belonging to a given statistical geographical unit.

The following function was used to estimate the annual incidence of acute stroke as a function of age and sex (*m*: male, *f*: female) in a given statistical geographical unit: [1, 2]

$$I_{Stroke}^{age,sex,u} = \left((sex = m) \times 0.0671 \times \text{age}^{5.946} \times n_{m,age}^{u} + (sex = f) \times 6.95 \times \text{age}^{4.844} \times n_{f,age}^{u}\right) \times 10^{-12}.$$

The annual incidence of acute stroke in each statistical geographical unit and in the whole region was then calculated as:

$$I_{Stroke}^{u\in\mathfrak{U}} = \sum_{age=35}^{100}\left(I_{Stroke}^{age,m,u} + I_{Stroke}^{age,f,u}\right),$$

$$I_{Stroke} = \sum_{u\in\mathfrak{U}} I_{Stroke}^{u}.$$

The annual incidence of EMS-calls for suspected acute stroke was derived from the annual incidence of acute stroke using a proportionality factor $PF \coloneqq 15{,}473\ /\ 3{,}900\ =\ 3.7$ (see main text).

The population-wide impact of a given prehospital triage strategy Z, expressed as change of disability-adjusted life years (DALYs) in a geographic scenario compared to prehospital triage strategy I (transport of all patients to the nearest PSC) was then estimated using the following formula:

$$\Delta DALYs =$$

$$I_{Stroke}/PF \times \mathcal{P}_{IVT} \times \sum_{s\in\mathfrak{S}} \sum_{\substack{age=35 \\ sex\in(m,f)}}^{100} \sum_{RACE=0}^{9} (\mathcal{T}_{s,age,sex}^{Z} = \text{CSC}) \times \Delta DALD \times \frac{I_{Stroke}^{age,sex,u}}{I_{Stroke} \times m_{u(s)}} \times \mathcal{P}_{R=RACE.}$$

Sampling of data points and calculation of transport times

Using the R package osrm-r,[3, 4] for each real-world geographic scenario the boundary of the region of interest was defined as a spatial polygon. 10,000 points were then sampled from a regular spatial grid restricted to this polygon. For each point the Euclidean distance to the nearest location accessible by car was computed and points were discarded if that distance exceeded the spatial granularity of the sampling grid. The remaining points thus avoided uninhabited and unreachable areas such as parks and lakes as well as islands without road connection and were used as simulated stroke incident locations. OSRM with a custom transport profile representing the driving speeds and accessibility restrictions of an emergency vehicle (**Table S5**) was used to compute travel times between stroke locations and stroke centers as well as transport times between PSCs and CSCs.

In addition to osrm-r, the following R packages were used in the analysis: leaflet, rgdal, OpenStreetMap, raster, gdata, sf, geosphere, cleangeo, mapview, ggsci, RColorBrewer, webshot, and scales.

1.3 Calculation of transport times in abstract geographic scenarios

For the estimation of transport times in abstract geographic scenarios, we randomly sampled points in the specific urban and specific rural geographic scenario and calculated both Euclidean distances in km and transport times in minutes to all available stroke centers. Data were fitted using a one-term power series model. Results of the fit were used to convert Euclidean distances to transport times in the abstract geographic scenarios (**Figure S5**).

1.4 Model parameters

See **Tables S1** and **S2** and **Figures S1 – S4**.

1.5 Geographic scenarios

See **Table S4**.

1.6 Prehospital stroke triage strategy paradigm-associated transport destination decision rules in abstract geographic scenarios

See **Figure S6**.

1.7 Univariate sensitivity analyses: door-out time

See **Figures S7 – S9**.

1.8 Numerical results

See **Tables S6 – S8**.

Table S1. Model parameters – 1

Parameter	Base case value, 95% CI	Distr. in PSA	Distribution parameters	Comment
Probability of patients seen by EMS for suspected acute stroke having final diagnosis of 'AIS with LVO', per RACE score category	RACE 0: 0.03 RACE 1: 0.01 RACE 2: 0.04 RACE 3: 0.08 RACE 4: 0.13 RACE 5: 0.24 RACE 6: 0.28 RACE 7: 0.40 RACE 8: 0.43 RACE 9: 0.50	Beta	A: 2; B: 63 A: 2; B: 158 A: 10; B: 223 A: 13; B: 146 A: 21; B: 146 A: 36; B: 114 A: 63; B: 162 A: 62; B: 93 A: 58; B: 77 A: 42; B: 42	See **Figure S1**.
Probability of patients seen by EMS for suspected acute stroke having final diagnosis of 'AIS without LVO', per RACE score category	RACE 0: 0.57 RACE 1: 0.61 RACE 2: 0.53 RACE 3: 0.46 RACE 4: 0.46 RACE 5: 0.37 RACE 6: 0.26 RACE 7: 0.27 RACE 8: 0.27 RACE 9: 0.15	Beta	A: 37; B: 28 A: 98; B: 62 A: 123; B: 110 A: 73; B: 86 A: 77; B: 90 A: 56; B: 94 A: 59; B: 166 A: 42; B: 113 A: 36; B: 99 A: 13; B: 71	See **Figure S1**.
Probability of patients seen by EMS for suspected acute stroke having final diagnosis of 'hemorrhagic stroke', per RACE score category	RACE 0: 0.05 RACE 1: 0.09 RACE 2: 0.08 RACE 3: 0.18 RACE 4: 0.20 RACE 5: 0.25 RACE 6: 0.36 RACE 7: 0.26 RACE 8: 0.27 RACE 9: 0.27	Beta	A: 3; B: 62 A: 15; B: 145 A: 19; B: 214 A: 29; B: 130 A: 34; B: 133 A: 38; B: 112 A: 81; B: 144 A: 40; B: 115 A: 37; B: 98 A: 23; B: 61	See **Figure S1**.

Table S1. Model parameters – 1 (continued)				
Parameter	**Base case value, 95% CI**	**Distr. in PSA**	**Distribution parameters**	**Comment**
Probability of patients seen by EMS for suspected acute stroke having final diagnosis of 'stroke mimic', per RACE score category	RACE 0: 0.35 RACE 1: 0.28 RACE 2: 0.35 RACE 3: 0.28 RACE 4: 0.21 RACE 5: 0.13 RACE 6: 0.10 RACE 7: 0.07 RACE 8: 0.03 RACE 9: 0.07	Beta	A: 23; B: 42 A: 45; B: 115 A: 81; B: 152 A: 44; B: 115 A: 35; B: 132 A: 20; B: 130 A: 33; B: 203 A: 11; B: 144 A: 4; B: 131 A: 6; B: 78	See **Figure S1**.
Probability of RACE score 0 – 9 per EMS call for suspected stroke	RACE 0: 0.06 RACE 1: 0.13 RACE 2: 0.18 RACE 3: 0.11 RACE 4: 0.11 RACE 5: 0.09 RACE 6: 0.13 RACE 7: 0.08 RACE 8: 0.07 RACE 9: 0.04	Beta	A: 85; B: 1448 A: 198; B: 1335 A: 273; B: 1260 A: 175; B: 1358 A: 172; B: 1361 A: 144; B: 1389 A: 200; B: 1333 A: 127; B: 1406 A: 101; B: 1432 A: 57; B: 1476	See **Figure S2** for details on adjustment for selective recruitment of more severely affected patients.
National Institutes of Health Stroke Scale score per RACE score category	RACE 0: 3.40 RACE 1: 3.65 RACE 2: 5.11 RACE 3: 7.83 RACE 4: 10.05 RACE 5: 12.35 RACE 6: 17.37 RACE 7: 18.13 RACE 8: 19.26 RACE 9: 19.71	Gamma	k: 1.14; θ: 2.97 k: 2.36; θ: 1.55 k: 1.44; θ: 3.55 k: 1.91; θ: 4.09 k: 2.30; θ: 4.39 k: 2.19; θ: 5.64 k: 4.52; θ: 3.84 k: 11.21; θ: 1.62 k: 18.26; θ: 1.06 k: 19.96; θ: 1.16	See **Figure S3**.

Data from Carrera et al.[5] CI stands for confidence interval; PSA, probabilistic sensitivity analysis; EMS, emergency medical services; AIS, acute ischemic stroke; LVO, large vessel occlusion; RACE, rapid arterial occlusion evaluation scale (score).

Table S2. Parameters of the model – 2

Parameter	Base case value, 95% CI	Distribution type	Distribution parameters	Reference	Comment
Probability of eligibility for i.v. thrombolysis	25%			Carrera et al.[5]	Eligibility assumed to be ascertainable prehospitally.
Probability of early recanalization of LVO within 70 minutes after i.v. thrombolysis	20% (15 – 26%)	Beta	A: 60.63; B: 237.70	Seners et al.[6], Holodinsky et al.[7]	Linear adjustment for shorter time periods, i.e. expected recanalization through MT achieved less than 70 minutes after start of i.v. thrombolysis
Probability of successful recanalization of LVO following MT	80% (70 – 90%)	Beta	A: 53.34; B: 13.56	Holodinsky et al.[7]	Width of confidence interval estimate based on professional experience due to lack of data.
Door-to-needle time at primary stroke centers	30 min (20 – 60 min)	Gamma	k: 26.85; θ: 1.13		Additional constraint in PSA that door-to-needle time at primary stroke centers is at least as long as door-to-needle time at comprehensive stroke centers.
Door-to-needle time at comprehensive stroke centers	30 min (20 – 60 min)	Gamma	k: 26.85; θ: 1.13		
Needle-to-groin puncture time at comprehensive stroke centers	30 min (20 – 60 min)	Gamma	k: 26.85; θ: 1.13		
Door-to-groin puncture time at comprehensive stroke centers after secondary transfer from a primary stroke centers	30 min (20 – 60 min)	Gamma	k: 26.85; θ: 1.13		
Groin puncture-to-recanalization time (if MT is technically successful)	30 min (20 – 60 min)		k: 26.85; θ: 1.13	Holodinsky et al.[7]	

Table S2. Parameters of the model – 2 (continued)					
Parameter	**Base case value, 95% CI**	**Distribution type**	**Distribution parameters**	**Reference**	**Comment**
Door-out time at primary stroke centers before secondary transfer (time between recognition of LVO through imaging / administration of i.v. thrombolysis and departure of the patient to the comprehensive stroke center)	I: 45 min (30 – 60 min) II: 15 min (5 – 20 min)	Gamma	k: 37.55; θ: 1.21 k: 15.00; θ: 1.00	Carrera et al.[5]	The impact of shorter door-out times (II) was explored in univariate sensitivity analyses.
Maximum time from symptom onset-to-i.v. thrombolysis	270 min			Powers et al.[8]	
Maximum time from symptom onset-to-groin puncture	360 min			Powers et al.[8]	

CI stands for confidence interval; PSA, probabilistic sensitivity analysis; EMS, emergency medical services; AIS, acute ischemic stroke; LVO, large vessel occlusion; RACE, rapid arterial occlusion evaluation scale (score); MT, mechanical thrombectomy

Table S3. Definitions

Def.	**Parameter**	**Def.**	**Parameter**
DTN	door-to-needle time	$\mathfrak{D}$	Set of possible final diagnoses: AIS with LVO, AIS without LVO, hemorrhagic stroke, stroke mimic
DO	door-out time	$\mathcal{P}_{d\in\mathfrak{D}}^{RACE}$	Relative frequency of one of the four final diagnoses in each RACE score category 0 – 9.
DTG	door-to-groin puncture time	$\mathcal{P}_{R=X}$	Relative frequency of patients with a RACE score of X among patients seen by EMS personnel for suspected acute stroke.
NTG	needle-to-groin puncture time	$\mathfrak{E}_{AIS\ with\ LVO}^{NIHSS,age,sex}$	Gain of DALDs per minute faster recanalization of LVO.
GTR	groin puncture-to-reperfusion time	$\mathfrak{E}_{AIS\ without\ LVO}^{NIHSS,age,sex}$	Gain of DALDs per minute faster access to IVT.
OTEMS	onset-to-EMS time	$\mathcal{P}_{R}^{IVT}$	Probability of achieving recanalization of LVO with IVT
t_{IVT}^{max}	Maximum time from symptom onset-to-IVT	t_{R}^{IVT}	Time window within which recanalization of LVO after IVT can occur.
t_{GP}^{max}	Maximum time from symptom onset-to-groin puncture	$\mathcal{P}_{R}^{MT}$	Probability of achieving recanalization of LVO with MT
RACE	Rapid arterial occlusion evaluation scale (score)	$\mathcal{P}_{IVT}$	Relative frequency of eligibility for IVT
t_{IVT}^{PSC}	Time-to-thrombolysis at the nearest PSC (transport time + *DTN*)		
t_{IVT}^{CSC}	Time-to-thrombolysis at the nearest CSC (transport time + *DTN*)		
$t_{transfer}$	Transport time from nearest PSC to CSC		

See **Tables 1, S1,** and **S2** and **Figures S1 – S4** for values. IVT stands for i.v. thrombolysis; AIS, acute ischemic stroke; LVO, large vessel occlusion; EMS, emergency medical services; DALDs, disability-adjusted life days; NIHSS, National Institutes of Health Stroke Scale (score).

Table S4. Population and geographic parameters of the five geographic scenarios

Parameter	Specific real-world urban scenario: Berlin I ('as is')*	Specific real-world urban scenario: Berlin II (theoretical, centralized MT-services)*	Abstract urban scenario	Specific real-world rural scenario: Schleswig-Holstein†	Abstract rural Scenario†
Surface area – km^2	852 km^2	852 km^2	$(15\ km)^2 \times \pi = 706\ km^2$	15,763 km^2	$(70\ km)^2 \times \pi = 15{,}394\ km^2$
Total population – n	3.6 Mio	3.6 Mio	3.6 Mio	2.9 Mio	2.9 Mio
Mean population density – km^{-2}	4,052	4,052	5,099	182	188
Estimated annual incidence of acute stroke‡	9,328	9,328	9,328	7,586	7,586
Estimated annual incidence of Code Stroke activation by EMS§	2,292	2,292	2,292	1,864	1,864
Spatial granularity of population data	447 statistical units (*Lebensweltlich orientierte Räume*)	447 statistical units (*Lebensweltlich orientierte Räume*)	1, spatially homogenous population	1,112 communities (*Gemeinden*)	1, spatially homogenous population
Total number of PSC / CSCs	4 / 10	11 / 3	1 – 5 / 1 - 5	7 / 6	1 – 5 / 1 - 5

*Geographic and demographic data for Berlin from ([9]) and ([10]). The distribution of MT-capable stroke centers in the scenario 'Berlin I' corresponds to the current situation, in 'Berlin II' to a theoretical setting with centralized MT-services. †Geographic and demographic data for Schleswig-Holstein from ([11]) and ([12]) ‡Annual incidence of acute stroke per 1,000,000 estimated as $0.00000006708 \times age^{5.946}$ for men and $0.00000695 \times age^{4.844}$ for women.[1, 2] §Estimated under the assumption that the annual incidence of Code Stroke activation by EMS is proportional to the annual incidence of acute stroke, and that an estimated annual incidence of acute stroke of 15,473 corresponds to 3,900 Code Stroke activations by EMS (data from the region of Catalonia, Spain[5, 13]). EMS stands for emergency medical services; PSC, primary stroke center; CSC, comprehensive stroke center.

Table S5. Custom transport profile used with OSRM

Road type	**Driving speed (km h^{-2})**
Motorway	140
Motorway link	80
Trunk	120
Trunk link	60
Primary	100
Primary link	50
Secondary	80
Secondary link	40
Tertiary	60
Tertiary link	30
Unclassified	40
Residential	40
Living street	30
Service	25

Table S6. Patient-related outcome measures outcome measures in specific real-world geographic scenarios, including univariate and probabilistic sensitivity analyses.

		Univariate sensitivity analysis: I			Univariate sensitivity analysis: II		
		Berlin I	Berlin II	Schleswig-Holstein	Berlin I	Berlin II	Schleswig-Holstein
Mean gain of DALDs per Code Stroke activation by EMS for IVT-eligible patients with AIS							
Scenario I	Drip-‘n’-ship (reference)	-	-	-	-	-	-
Scenario II	Mothership	17.90 (8.74-33.06)	14.38 (6.33-30.49)	12.69 (3.33-31.84)	6.16 (2.93-12.35)	2.62 (-1.81-13.01)	2.34 (-3.24-12.15)
Scenario III	Additional transport time threshold	17.90 (8.74-33.06)	14.15 (3.58-27.38)	13.07 (1.35-21.21)	6.16 (2.93-12.35)	3.17 (-0.74-11.30)	4.35 (0.49-9.67)
Scenario IV	Fixed cutoff score	16.06 (8.22-28.56)	14.64 (7.03-27.75)	15.80 (7.17-31.06)	6.19 (3.87-10.90)	4.76 (1.95-11.87)	5.44 (1.99-12.53)
Scenario V	Fixed cutoff score with probabilistic outcome determination	16.06 (8.22-28.56)	14.64 (7.03-27.75)	15.80 (7.20-31.06)	6.19 (3.92-10.90)	4.80 (2.37-11.87)	5.73 (3.08-12.53)
Scenario VI	Optimal variable cutoff scores	18.24 (9.35-33.24)	15.91 (7.85-30.94)	17.15 (8.24-34.06)	6.81 (4.22-12.57)	5.10 (2.66-13.64)	6.14 (3.42-14.20)
Scenario VII	Optimal LVO detection device	19.80 (10.77-34.84)	19.14 (10.52-33.87)	22.27 (11.82-38.81)	8.06 (5.34-14.23)	7.39 (4.76-15.65)	8.83 (5.75-17.14)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	19.80 (10.77-34.84)	19.14 (10.52-33.87)	22.27 (11.82-38.81)	8.06 (5.34-14.23)	7.39 (4.76-15.65)	8.83 (5.76-17.14)
Scenario IX	Mobile IVT unit	25.64 (15.58-41.17)	25.47 (15.52-45.10)	39.73 (23.82-57.83)	13.91 (10.57-26.02)	13.72 (10.38-29.16)	22.31 (17.88-36.68)
Scenario X	Mobile MT unit	30.29 (18.49-50.69)	32.09 (19.22-57.53)	55.76 (34.22-83.37)	18.56 (14.13-37.22)	20.33 (15.41-42.39)	34.16 (26.78-56.64)
Population-wide total gain of DALYs							
Scenario I	Drip-‘n’-ship (reference)	-	-	-	-	-	-
Scenario II	Mothership	8.48 (0.14-13.15)	18.22 (2.48-30.24)	9.85 (2.51-20.83)	2.92 (0.22-4.68)	3.33 (-2.30-9.06)	1.55 (-2.15-5.20)
Scenario III	Additional transport time threshold	8.48 (0.14-13.15)	17.93 (0.38-28.81)	10.15 (0.40-16.31)	2.92 (0.22-4.68)	4.01 (-0.94-9.17)	2.89 (0.32-5.58)
Scenario IV	Fixed cutoff score	7.60 (0.12-11.92)	18.55 (2.34-29.27)	12.26 (4.75-20.55)	2.93 (0.21-4.30)	6.03 (2.46-9.75)	3.61 (1.32-6.00)
Scenario V	Fixed cutoff score with probabilistic outcome determination	7.60 (0.12-11.92)	18.55 (2.34-29.27)	12.26 (4.75-20.55)	2.93 (0.21-4.30)	6.08 (3.00-9.75)	3.80 (2.05-6.07)
Scenario VI	Optimal variable cutoff scores	8.64 (0.14-13.30)	20.16 (2.55-31.54)	13.31 (5.18-22.70)	3.23 (0.24-4.81)	6.46 (3.38-10.54)	4.07 (2.27-6.60)
Scenario VII	Optimal LVO detection device	9.37 (0.15-14.26)	24.26 (2.76-36.85)	17.29 (6.44-25.91)	3.82 (0.27-5.30)	9.36 (5.11-13.26)	5.86 (3.82-8.27)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	9.37 (0.15-14.26)	24.26 (2.76-36.85)	17.29 (6.44-25.91)	3.82 (0.27-5.30)	9.36 (5.11-13.26)	5.86 (3.82-8.27)
Scenario IX	Mobile IVT unit	12.14 (0.26-17.74)	32.28 (3.99-47.02)	30.85 (12.83-43.19)	6.59 (0.54-7.46)	17.38 (10.45-21.79)	14.80 (9.11-18.15)
Scenario X	Mobile MT unit	14.35 (0.32-20.77)	40.66 (5.21-58.53)	43.28 (17.78-62.08)	8.79 (0.72-10.27)	25.77 (14.33-33.23)	22.67 (13.14-29.20)

Table S6. Patient-related outcome measures outcome measures in specific real-world geographic scenarios (continued)

		Univariate sensitivity analysis: I			Univariate sensitivity analysis: II		
		Berlin I	Berlin II	Schleswig-Holstein	Berlin I	Berlin II	Schleswig-Holstein
Additional population-wide total gain of DALYs in addition to less complex triage strategies							
Scenario I	Drip-‘n’-ship (reference)	-	-	-	-	-	-
Scenario II	Mothership	8.48 (0.14-13.15)	18.22 (2.48-30.24)	9.85 (2.51-20.83)	2.92 (0.22-4.68)	3.33 (-2.30-9.06)	1.55 (-2.15-5.20)
Scenario III	Additional transport time threshold	0.00 (0.00-0.00)	-0.29 (-2.11-0.47)	0.30 (-6.54-3.57)	0.00 (0.00-0.00)	0.69 (-0.94-0.80)	1.34 (-0.66-1.34)
Scenario IV	Fixed cutoff score	-0.87 (-1.91-0.00)	0.33 (-2.88-2.32)	2.12 (-0.53-3.21)	0.02 (-0.37-0.44)	2.02 (-0.44-2.46)	0.72 (0.10-1.00)
Scenario V	Fixed cutoff score with probabilistic outcome determination	-0.87 (-1.91-0.00)	0.00 (-2.88-0.00)	0.00 (-0.53-0.37)	0.00 (-0.37-0.03)	0.04 (-0.44-0.54)	0.19 (0.00-0.72)
Scenario VI	Optimal variable cutoff scores	0.16 (0.00-0.37)	1.61 (0.04-2.41)	1.05 (0.24-2.00)	0.29 (0.00-0.29)	0.39 (0.18-0.78)	0.28 (0.14-0.52)
Scenario VII	Optimal LVO detection device	0.74 (0.00-0.98)	4.10 (0.19-5.36)	3.98 (1.17-5.29)	0.59 (0.03-0.74)	2.90 (0.71-3.39)	1.78 (0.77-2.06)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Scenario IX	Mobile IVT unit	2.77 (0.07-3.81)	8.02 (1.59-11.16)	13.56 (4.98-18.85)	2.77 (0.26-3.59)	8.02 (5.25-9.85)	8.94 (5.00-11.35)
Scenario X	Mobile MT unit	2.20 (0.06-3.13)	8.38 (1.08-11.94)	12.44 (4.70-17.84)	2.20 (0.19-2.81)	8.38 (3.88-11.45)	7.87 (4.03-11.05)
Time to IVT per AIS patient in the equipoise region							
Scenario I	Drip-‘n’-ship	68 (61-82)	68 (61-82)	83 (76-96)	68 (63-82)	68 (63-81)	78 (71-91)
Scenario II	Mothership	72 (65-85)	77 (70-90)	100 (92-113)	72 (68-85)	77 (70-90)	89 (82-103)
Scenario III	Additional transport time threshold	72 (65-85)	75 (68-88)	87 (79-100)	72 (68-85)	75 (68-89)	84 (75-97)
Scenario IV	Fixed cutoff score	70 (63-83)	72 (65-86)	90 (83-103)	70 (65-83)	72 (66-85)	83 (76-96)
Scenario V	Fixed cutoff score with probabilistic outcome determination	70 (63-83)	72 (65-86)	90 (83-101)	70 (65-83)	71 (66-85)	81 (76-94)
Scenario VI	Optimal variable cutoff scores	71 (64-84)	73 (67-87)	90 (85-102)	70 (66-84)	72 (67-84)	82 (76-94)
Scenario VII	Optimal LVO detection device	69 (62-83)	71 (64-85)	88 (81-101)	69 (65-83)	71 (65-84)	81 (74-94)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	69 (62-83)	71 (64-85)	88 (81-101)	69 (65-83)	71 (65-84)	81 (74-94)
Scenario IX	Mobile IVT unit	60 (49-73)	60 (49-73)	60 (49-73)	60 (49-73)	60 (49-73)	60 (49-73)
Scenario X	Mobile MT unit	60 (49-73)	60 (49-73)	60 (49-73)	60 (49-73)	60 (49-73)	60 (49-73)

Table S6. Patient-related outcome measures outcome measures in specific real-world geographic scenarios (continued)							
		Univariate sensitivity analysis: I			Univariate sensitivity analysis: II		
		Berlin I	Berlin II	Schleswig-Holstein	Berlin I	Berlin II	Schleswig-Holstein
Time to MT per AIS patient with LVO in the equipoise region							
Scenario I	Drip-‘n’-ship	153 (137-182)	158 (143-192)	190 (174-217)	123 (114-142)	128 (119-146)	145 (135-163)
Scenario II	Mothership	102 (93-121)	107 (98-126)	130 (120-148)	102 (95-117)	107 (98-122)	119 (110-135)
Scenario III	Additional transport time threshold	102 (93-121)	110 (102-178)	150 (139-209)	102 (95-117)	108 (101-124)	124 (116-140)
Scenario IV	Fixed cutoff score	112 (102-130)	117 (107-137)	142 (132-160)	106 (98-122)	111 (103-127)	124 (115-141)
Scenario V	Fixed cutoff score with probabilistic outcome determination	112 (102-130)	117 (107-137)	142 (132-161)	106 (98-122)	111 (103-128)	126 (116-143)
Scenario VI	Optimal variable cutoff scores	103 (93-122)	110 (100-128)	136 (125-155)	103 (96-119)	110 (99-127)	124 (113-141)
Scenario VII	Optimal LVO detection device	102 (93-121)	107 (98-126)	130 (120-148)	102 (95-117)	107 (98-122)	119 (110-135)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	102 (93-121)	107 (98-126)	130 (120-148)	102 (95-117)	107 (98-122)	119 (110-135)
Scenario IX	Mobile IVT unit	102 (93-121)	107 (98-126)	130 (120-148)	102 (95-117)	107 (98-122)	119 (110-135)
Scenario X	Mobile MT unit	90 (74-109)	90 (74-109)	90 (74-109)	90 (74-105)	90 (74-105)	90 (74-105)

For a description of triage strategy paradigms, see **Figure 2** in the main text. DALD stands for disability-adjusted life day; EMS, emergency medical services; IVT, i.v. thrombolysis; DALY, disability-adjusted life year; LVO, large vessel occlusion; AIS, acute ischemic stroke.

Table S7. Health system-related outcome measures in specific real-world geographic scenarios, including univariate and probabilistic sensitivity analyses.

		Univariate sensitivity analysis: I			Univariate sensitivity analysis: II		
		Berlin I	Berlin II	Schleswig-Holstein	Berlin I	Berlin II	Schleswig-Holstein
Proportion of patients triaged to a primary stroke center							
Scenario I	Drip-‘n’-ship	0.30 (0.01-0.30)	0.81 (0.07-0.81)	0.61 (0.23-0.61)	0.30 (0.01-0.30)	0.81 (0.24-0.81)	0.52 (0.20-0.52)
Scenario II	Mothership	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Scenario III	Additional transport time threshold	0.00 (0.00-0.00)	0.06 (0.06-0.06)	0.22 (0.22-0.22)	0.00 (0.00-0.00)	0.06 (0.06-0.06)	0.09 (0.09-0.09)
Scenario IV	Fixed cutoff score	0.18 (0.00-0.18)	0.48 (0.04-0.49)	0.36 (0.14-0.37)	0.18 (0.01-0.18)	0.48 (0.14-0.49)	0.31 (0.12-0.31)
Scenario V	Fixed cutoff score with probabilistic outcome determination	0.18 (0.00-0.18)	0.48 (0.04-0.49)	0.36 (0.14-0.39)	0.18 (0.01-0.18)	0.48 (0.14-0.54)	0.32 (0.12-0.36)
Scenario VI	Optimal variable cutoff scores	0.05 (0.00-0.08)	0.27 (0.02-0.35)	0.24 (0.08-0.31)	0.09 (0.00-0.12)	0.39 (0.05-0.50)	0.27 (0.06-0.33)
Scenario VII	Optimal LVO detection device	0.25 (0.00-0.25)	0.67 (0.05-0.68)	0.50 (0.19-0.51)	0.25 (0.01-0.25)	0.67 (0.20-0.67)	0.43 (0.17-0.43)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	0.25 (0.00-0.25)	0.67 (0.05-0.68)	0.50 (0.19-0.51)	0.25 (0.01-0.25)	0.67 (0.20-0.67)	0.43 (0.17-0.43)
Scenario IX	Mobile IVT unit	0.25 (0.00-0.25)	0.67 (0.05-0.68)	0.50 (0.19-0.51)	0.25 (0.01-0.25)	0.67 (0.20-0.67)	0.43 (0.17-0.43)
Scenario X	Mobile MT unit	0.25 (0.00-0.25)	0.67 (0.05-0.68)	0.50 (0.19-0.51)	0.25 (0.01-0.25)	0.67 (0.20-0.67)	0.43 (0.17-0.43)
Proportion of patients triaged to a comprehensive stroke center (without secondary transfers)							
Scenario I	Drip-‘n’-ship	0.70 (0.70-0.99)	0.19 (0.19-0.93)	0.39 (0.39-0.77)	0.70 (0.70-0.99)	0.19 (0.19-0.76)	0.48 (0.48-0.80)
Scenario II	Mothership	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Scenario III	Additional transport time threshold	1.00 (1.00-1.00)	0.94 (0.94-0.94)	0.78 (0.78-0.78)	1.00 (1.00-1.00)	0.94 (0.94-0.94)	0.91 (0.91-0.91)
Scenario IV	Fixed cutoff score	0.82 (0.82-1.00)	0.52 (0.51-0.96)	0.64 (0.63-0.86)	0.82 (0.82-0.99)	0.52 (0.51-0.86)	0.69 (0.69-0.88)
Scenario V	Fixed cutoff score with probabilistic outcome determination	0.82 (0.82-1.00)	0.52 (0.51-0.96)	0.64 (0.61-0.86)	0.82 (0.82-0.99)	0.52 (0.46-0.86)	0.68 (0.64-0.88)
Scenario VI	Optimal variable cutoff scores	0.95 (0.92-1.00)	0.73 (0.65-0.98)	0.76 (0.69-0.92)	0.91 (0.88-1.00)	0.61 (0.50-0.95)	0.73 (0.67-0.94)
Scenario VII	Optimal LVO detection device	0.75 (0.75-1.00)	0.33 (0.32-0.95)	0.50 (0.49-0.81)	0.75 (0.75-0.99)	0.33 (0.33-0.80)	0.57 (0.57-0.83)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	0.75 (0.75-1.00)	0.33 (0.32-0.95)	0.50 (0.49-0.81)	0.75 (0.75-0.99)	0.33 (0.33-0.80)	0.57 (0.57-0.83)
Scenario IX	Mobile IVT unit	0.75 (0.75-1.00)	0.33 (0.32-0.95)	0.50 (0.49-0.81)	0.75 (0.75-0.99)	0.33 (0.33-0.80)	0.57 (0.57-0.83)
Scenario X	Mobile MT unit	0.75 (0.75-1.00)	0.33 (0.32-0.95)	0.50 (0.49-0.81)	0.75 (0.75-0.99)	0.33 (0.33-0.80)	0.57 (0.57-0.83)

Table S7. Health system-related outcome measures in specific real-world geographic scenarios, including univariate and probabilistic sensitivity analyses (continued).

		Univariate sensitivity analysis: I			Univariate sensitivity analysis: II		
		Berlin I	Berlin II	Schleswig-Holstein	Berlin I	Berlin II	Schleswig-Holstein
Total number of secondary transfers (patients with acute ischemic stroke and large vessel occlusion triaged to a primary stroke center)							
Scenario I	Drip-‘n’-ship	492 (9-533)	1316 (114-1427)	801 (298-869)	492 (22-537)	1316 (385-1437)	685 (262-748)
Scenario II	Mothership	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Scenario III	Additional transport time threshold	0 (0-0)	91 (83-99)	288 (263-314)	0 (0-0)	91 (83-99)	124 (113-135)
Scenario IV	Fixed cutoff score	97 (2-130)	261 (21-347)	159 (57-211)	97 (5-132)	261 (83-353)	136 (57-184)
Scenario V	Fixed cutoff score with probabilistic outcome determination	97 (2-130)	261 (21-347)	159 (57-240)	97 (5-132)	284 (83-474)	183 (57-288)
Scenario VI	Optimal variable cutoff scores	13 (0-22)	94 (2-150)	91 (21-169)	32 (1-65)	216 (19-433)	143 (25-250)
Scenario VII	Optimal LVO detection device	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-11)
Scenario IX	Mobile IVT unit	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Scenario X	Mobile MT unit	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Proportion of patients with LVO in the equipoise region triaged correctly							
Scenario I	Drip-‘n’-ship	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.02)
Scenario II	Mothership	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.98-1.00)
Scenario III	Additional transport time threshold	1.00 (1.00-1.00)	0.93 (0.16-0.93)	0.64 (0.05-0.64)	1.00 (1.00-1.00)	0.93 (0.77-0.93)	0.82 (0.54-0.84)
Scenario IV	Fixed cutoff score	0.80 (0.75-0.85)	0.80 (0.75-0.85)	0.80 (0.75-0.85)	0.80 (0.75-0.81)	0.80 (0.75-0.81)	0.80 (0.75-0.81)
Scenario V	Fixed cutoff score with probabilistic outcome determination	0.80 (0.75-0.85)	0.80 (0.75-0.85)	0.80 (0.70-0.85)	0.80 (0.75-0.81)	0.78 (0.64-0.81)	0.73 (0.58-0.80)
Scenario VI	Optimal variable cutoff scores	0.97 (0.95-1.00)	0.93 (0.88-0.98)	0.89 (0.80-0.95)	0.94 (0.87-0.97)	0.84 (0.67-0.95)	0.79 (0.63-0.91)
Scenario VII	Optimal LVO detection device	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.98-1.00)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Scenario IX	Mobile IVT unit	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Scenario X	Mobile MT unit	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)

Table S7. Health system-related outcome measures in specific real-world geographic scenarios, including univariate and probabilistic sensitivity analyses (continued).							
		Univariate sensitivity analysis: I			Univariate sensitivity analysis: II		
		Berlin I	Berlin II	Schleswig-Holstein	Berlin I	Berlin II	Schleswig-Holstein
Proportion of patients without LVO in the equipoise region triaged correctly							
Scenario I	Drip-‘n’-ship	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Scenario II	Mothership	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Scenario III	Additional transport time threshold	0.00 (0.00-0.00)	0.07 (0.07-0.84)	0.36 (0.36-0.95)	0.00 (0.00-0.00)	0.07 (0.07-0.23)	0.18 (0.18-0.46)
Scenario IV	Fixed cutoff score	0.73 (0.69-0.76)	0.73 (0.69-0.76)	0.73 (0.69-0.76)	0.73 (0.71-0.76)	0.73 (0.71-0.76)	0.73 (0.71-0.76)
Scenario V	Fixed cutoff score with probabilistic outcome determination	0.73 (0.69-0.76)	0.73 (0.69-0.76)	0.73 (0.69-0.77)	0.73 (0.71-0.76)	0.73 (0.72-0.78)	0.75 (0.73-0.80)
Scenario VI	Optimal variable cutoff scores	0.23 (0.04-0.39)	0.43 (0.16-0.55)	0.51 (0.32-0.62)	0.40 (0.23-0.51)	0.60 (0.25-0.72)	0.63 (0.35-0.74)
Scenario VII	Optimal LVO detection device	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Scenario IX	Mobile IVT unit	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Scenario X	Mobile MT unit	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Proportion of AIS patients in the equipoise region triaged correctly							
Scenario I	Drip-‘n’-ship	0.71 (0.69-0.73)	0.71 (0.69-0.73)	0.71 (0.69-0.73)	0.71 (0.69-0.73)	0.71 (0.69-0.73)	0.71 (0.69-0.73)
Scenario II	Mothership	0.29 (0.27-0.31)	0.29 (0.27-0.31)	0.29 (0.27-0.31)	0.29 (0.27-0.31)	0.29 (0.27-0.31)	0.29 (0.27-0.31)
Scenario III	Additional transport time threshold	0.29 (0.27-0.31)	0.32 (0.30-0.63)	0.44 (0.44-0.69)	0.29 (0.27-0.31)	0.32 (0.31-0.40)	0.37 (0.36-0.48)
Scenario IV	Fixed cutoff score	0.75 (0.73-0.77)	0.75 (0.73-0.77)	0.75 (0.73-0.77)	0.75 (0.73-0.77)	0.75 (0.73-0.77)	0.75 (0.73-0.77)
Scenario V	Fixed cutoff score with probabilistic outcome determination	0.75 (0.73-0.77)	0.75 (0.73-0.77)	0.75 (0.73-0.77)	0.75 (0.73-0.77)	0.75 (0.73-0.77)	0.75 (0.73-0.77)
Scenario VI	Optimal variable cutoff scores	0.45 (0.31-0.55)	0.58 (0.39-0.66)	0.62 (0.50-0.68)	0.55 (0.43-0.62)	0.67 (0.45-0.71)	0.67 (0.50-0.71)
Scenario VII	Optimal LVO detection device	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Scenario IIX	Optimal LVO detection device with probabilistic outcome determination	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Scenario IX	Mobile IVT unit	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Scenario X	Mobile MT unit	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)

For a description of triage strategy paradigms, see **Figure 2** in the main text.

Table S8. Theoretical outcome measures in specific real-world geographic scenarios, including univariate and probabilistic sensitivity analyses.						
	Univariate sensitivity analysis: I			Univariate sensitivity analysis: II		
	Berlin I	Berlin II	Schleswig-Holstein	Berlin I	Berlin II	Schleswig-Holstein
Relative size of the equipoise region, calculated according to estimated number of Code Stroke activations by EMS						
Relative size of the equipoise region	0.3 (0.01-0.3)	0.81 (0.2-0.81)	0.61 (0.28-0.61)	identical to analysis I		
Spatial frequency of optimal variable cutoff score (% of the equipoise region, triage strategy paradigm VI)						
Optimal variable cutoff score < 5	0.92 (0.78-1.00)	0.83 (0.54-1.00)	0.70 (0.53-1.00)	0.85 (0.60-1.00)	0.40 (0.21-0.92)	0.49 (0.30-0.85)
Optimal variable cutoff score = 5	0.00 (0.00-0.01)	0.00 (0.00-0.11)	0.07 (0.00-0.26)	0.09 (0.00-0.15)	0.21 (0.00-0.62)	0.22 (0.10-0.50)
Optimal variable cutoff score > 5	0.08 (0.00-0.22)	0.17 (0.00-0.43)	0.23 (0.00-0.35)	0.06 (0.00-0.33)	0.39 (0.06-0.47)	0.29 (0.04-0.40)
Spatial frequency of fixed cutoff score = 5 (% of the equipoise region, triage strategy paradigm V)						
Fixed cutoff score = 5	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.93-1.00)	1.00 (0.91-1.00)	0.95 (0.79-1.00)	0.93 (0.78-1.00)

For a description of triage strategy paradigms, see **Figure 2** in the main text. EMS stands for emergency medical services

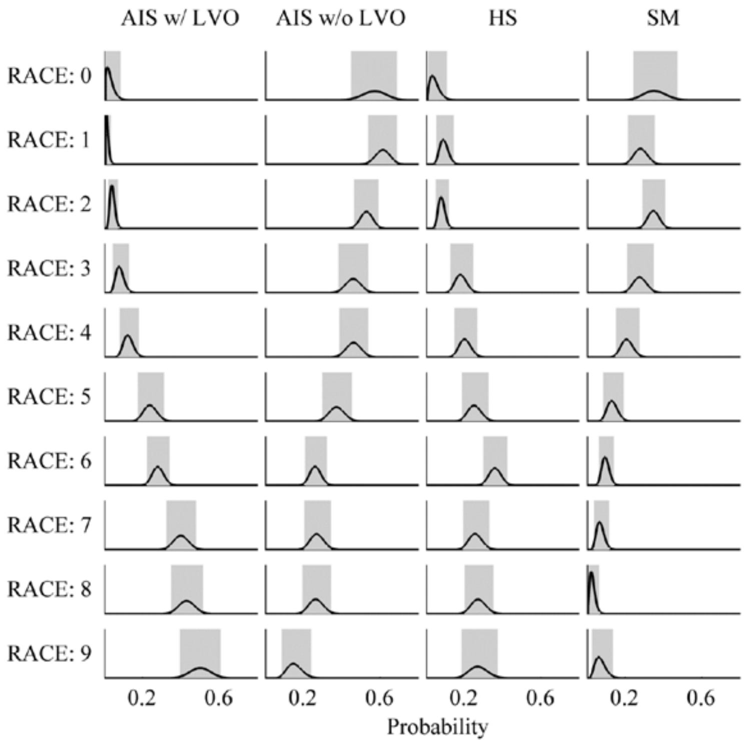

Figure S1. Probability density functions of probabilities for final diagnoses according to RACE score.

Gray boxes represent 95% probability mass intervals. AIS stands for acute ischemic stroke; LVO, large vessel occlusion; HS, hemorrhagic stroke; SM, stroke mimic; RACE, rapid arterial occlusion evaluation scale. Based on data from Carrera et al.[5]

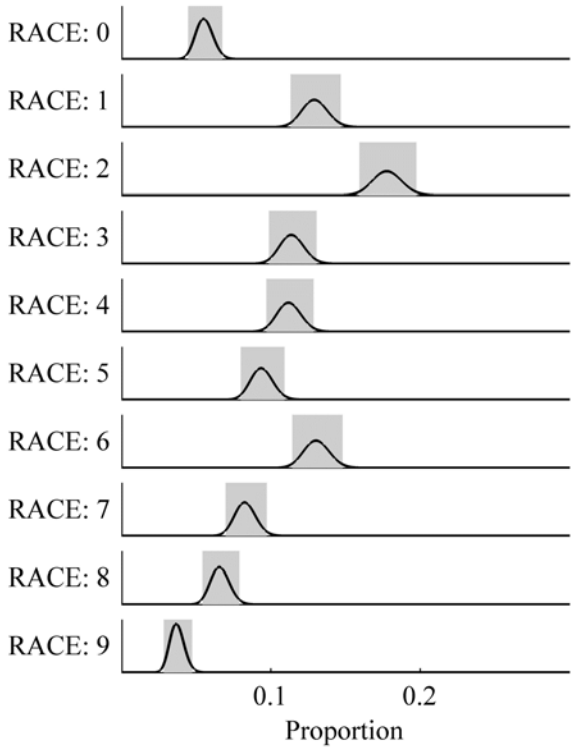

Figure S2. Probability density functions of the relative frequencies of each RACE score category encountered by emergency medical services (EMS) personnel in the prehospital setting.

Based on data from Carrera et al.[5] In this study, patients with more severe stroke symptoms (higher RACE/NIHSS scores) were more likely to receive a RACE score evaluation and be included in the study. To compensate for this effect, we applied a linear correction factor to the reported frequencies of patient in each RACE score category:

$$f = -0.068 \times RACE + 0.728.$$

The correction factor was chosen such that the overall mean stroke symptom severity would match that of the entire population of patients with Stroke Code Activation by EMS, including patients that did not receive a RACE score evaluation in the study. Gray boxes represent 95% probability mass intervals. RACE stands for rapid arterial occlusion evaluation scale; NIHSS, National Institutes of Health Stroke Scale.

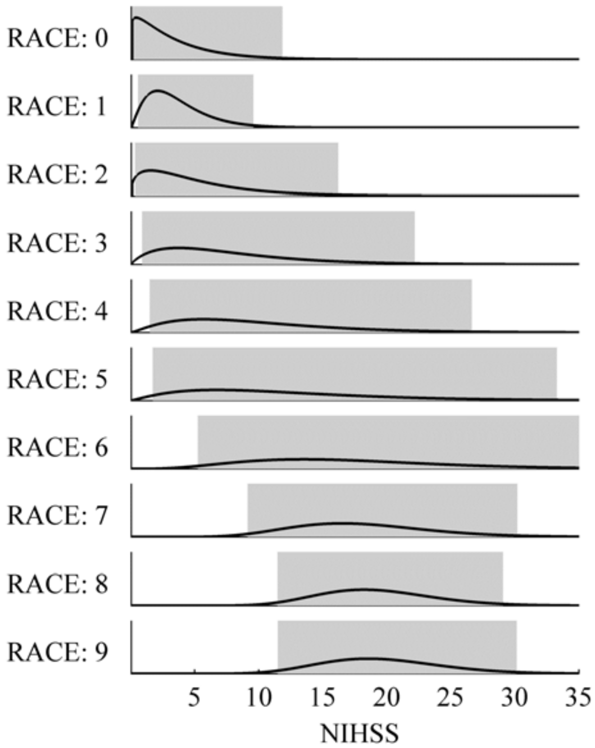

Figure S3. Probability density functions of National Institutes of Health Stroke Scale (NIHSS) scores according to RACE score.

Gray boxes represent 95% probability mass intervals. RACE stands for rapid arterial occlusion evaluation scale. Based on data from Carrera et al.[5]

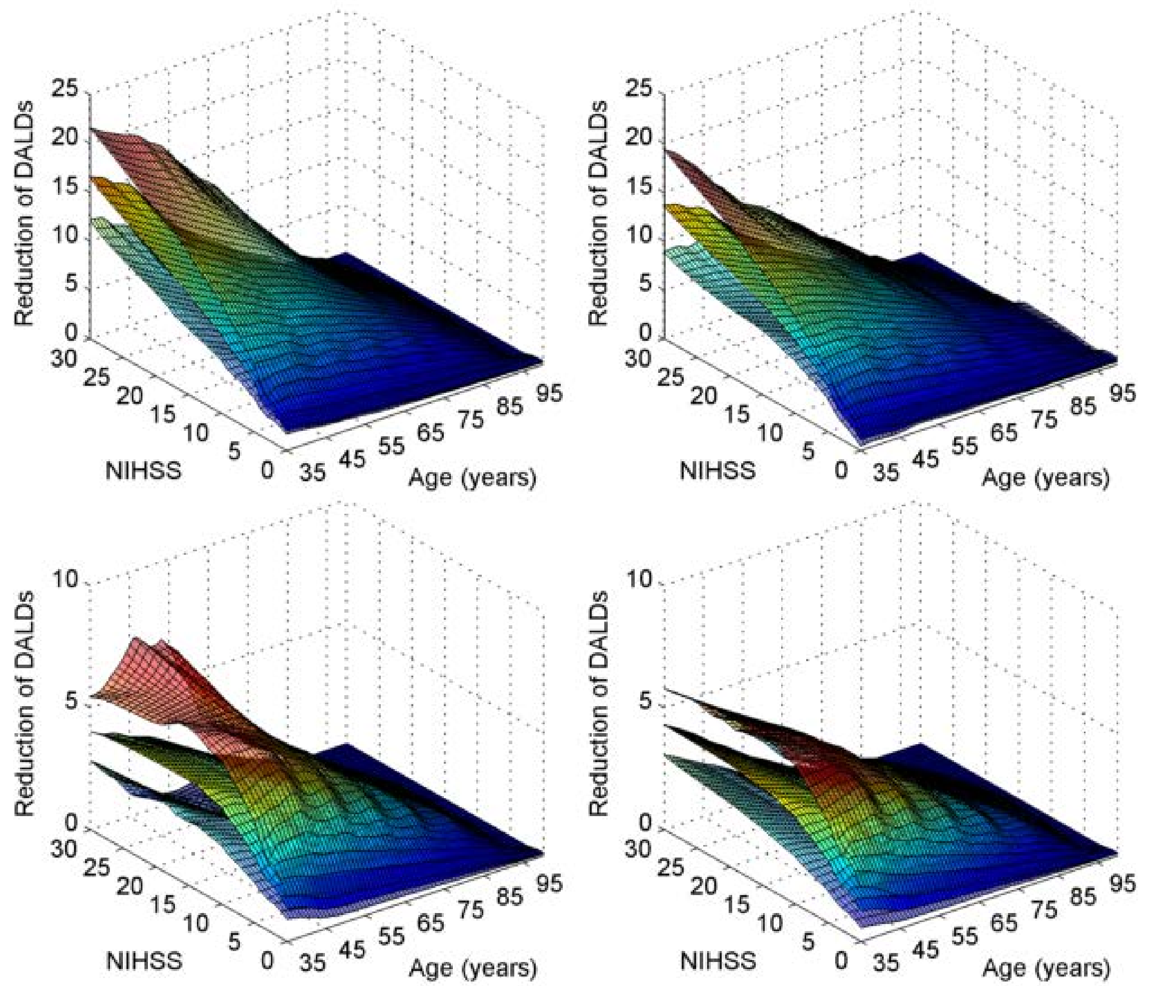

Figure S4. Reduction of DALDs per minute faster treatment for acute ischemic stroke patients.

Upper left: Reduction of disability-adjusted life days (DALDs) per minute faster access to successful recanalization for female acute ischemic stroke (AIS) patients with large vessel occlusion (LVO). **Upper right:** Reduction of DALDs per minute faster access to successful recanalization for male AIS patients with LVO. **Lower left:** Reduction of DALDs per minute faster access to i.v. thrombolysis for female AIS patients without LVO. **Lower right:** Reduction of DALDs per minute faster access to i.v. thrombolysis for male AIS patients without LVO. The upper and lower surface in each panel represent boundaries of the 95% probability mass intervals, the middle surface the mean.

Based on data from Meretoja et al.[14, 15] (Point estimates fitted using a locally weighted smoothing linear regression [span 0.2]). NIHHS stands for National Institutes of Health Stroke Scale.

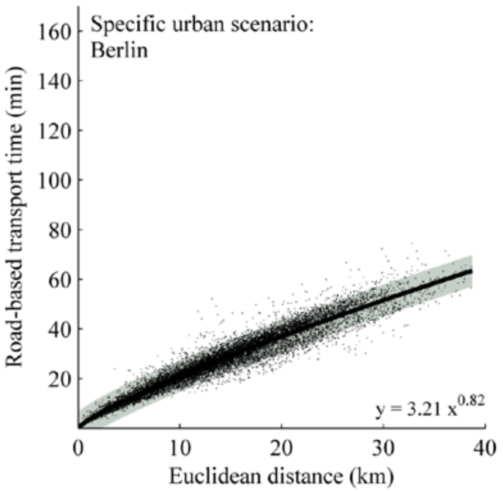

Figure S5. Fit of transport times vs. Euclidean distances in specific real-world geographic scenarios.

The grey areas represent the 95% non-simultaneous prediction intervals for a given observation.

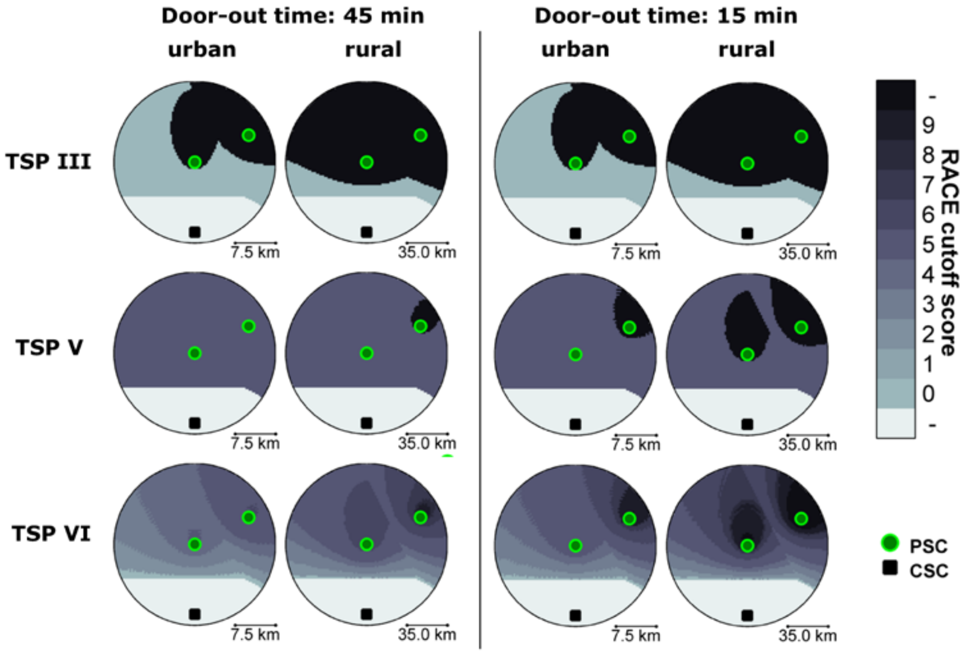

Figure S6. Prehospital stroke triage strategy paradigm-associated transport destination decision rule maps in abstract urban and rural geographic scenarios.

Shown are result for an exemplary 70-year-old male patient with suspected acute stroke in abstract urban (half radius 7.5 km) and rural (half radius 35 km) geographic scenarios. Patients with a RACE score greater than or equal to the color-coded RACE cutoff score would be transported to the nearest CSC instead of the nearest PSC. A dash '-' signifies transport of all patients to the nearest CSC due to lack of equipoise because of a shorter transport time (light color) or PSC ('RACE cutoff score ≥ 10', dark color). For a detailed description of the three shown triage strategy paradigms (TSP III, V, and VI), see **Figure 2** in main text.

RACE stands for rapid arterial occlusion evaluation scale; TSP, triage strategy paradigm; CSC, comprehensive stroke center; PSC, primary stroke center.

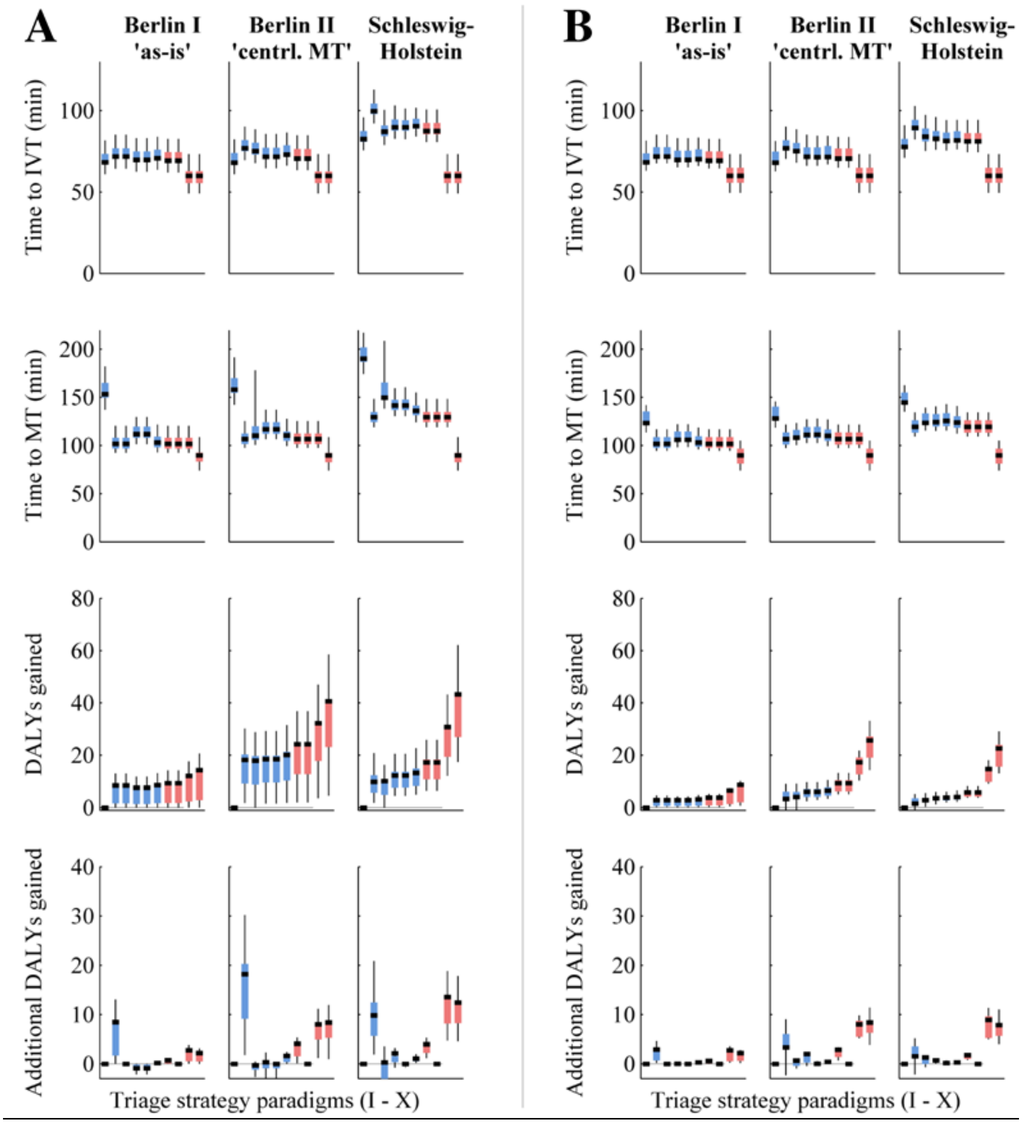

Figure S7. Impact of prehospital triage strategy paradigms on patient-centered outcome parameters in specific real-world geographic scenarios

Boxplots show data for prehospital triage strategy paradigms I – X from probabilistic sensitivity analyses; vertical extent of the boxes represent the interquartile range, the horizontal line the base case result, the whiskers extend to include 95% of all values. Currently available triage strategy paradigms (I – VI) are shown in shades of blue, the remaining paradigms (VII – X) in shades of red. Gain of DALYs is calculated with reference to triage strategy paradigm I (drip-'n'-ship approach). The last row depicts the additional gain in DALYs associated with each triage strategy paradigm over and above all less complex triage strategy paradigms. For a description of triage strategy paradigms, see **Figure 2** in the main text.

Panel A represents the base case scenario with a door-out time of 45 minutes**, Panel B** a door-out time of 15 minutes.

DALY stands for disability-adjusted life year; IVT, i.v. thrombolysis; MT, mechanical thrombectomy.

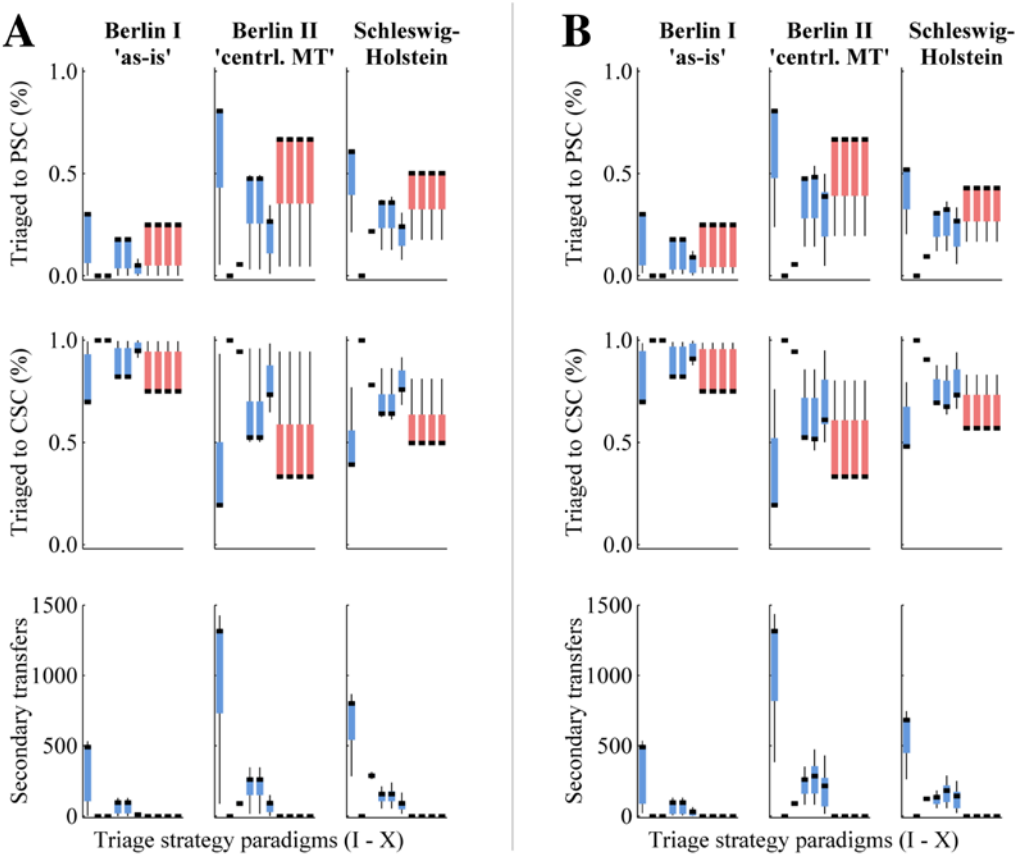

Figure S8. Impact of prehospital triage strategy paradigms on health system-related outcome parameters in specific real-world geographic scenarios

Boxplots show data for prehospital triage strategy paradigms I – X from probabilistic sensitivity analyses; vertical extent of the boxes represent the interquartile range, the horizontal line the base case result, the whiskers extend to include 95% of all values. Currently available triage strategy paradigms (I – VI) are shown in shades of blue, the remaining paradigms (VII – X) in shades of red. Gain of DALYs is calculated with reference to triage strategy paradigm I (drip-'n'-ship approach). The last row depicts the additional gain in DALYs associated with each triage strategy paradigm over and above all less complex triage strategy paradigms. For a description of triage strategy paradigms, see **Figure 2** in the main text.

Panel A represents the base case scenario with a door-out time of 45 minutes**, Panel B** a door-out time of 15 minutes.

DALY stands for disability-adjusted life year; IVT, i.v. thrombolysis; MT, mechanical thrombectomy.

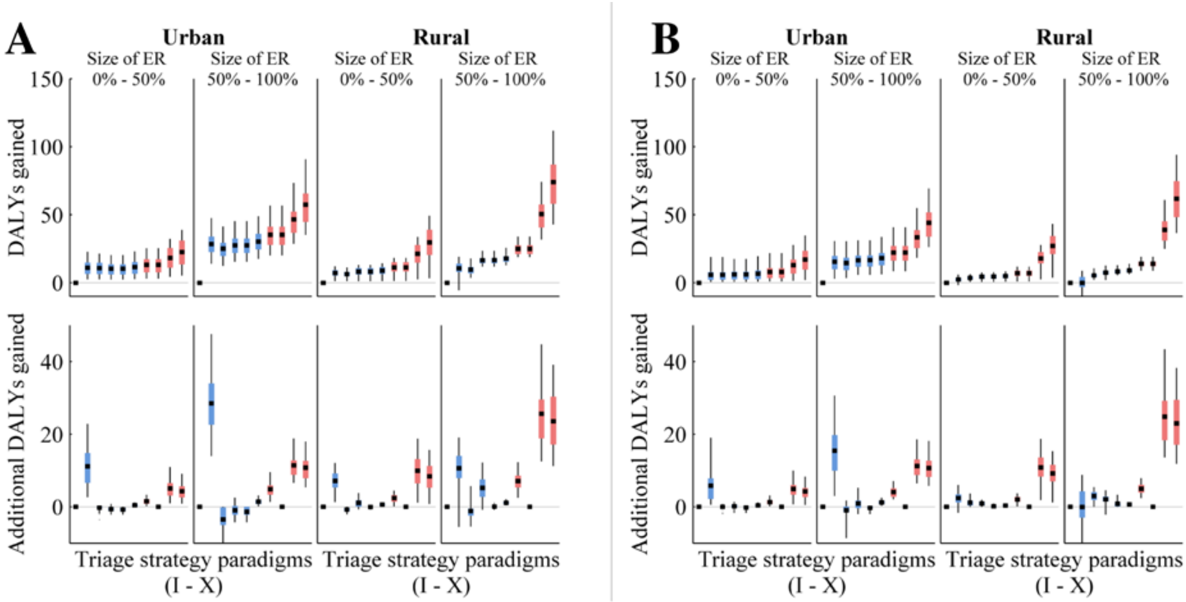

Figure S9. Impact of prehospital triage strategy paradigms on the reduction of stroke-related disability in abstract geographic scenarios

Boxplots show results for prehospital triage strategy paradigms I – X from repeated random generation of abstract rural and urban geographic scenarios with between 1 – 5 primary stroke centers and 1 – 5 comprehensive stroke centers according to the relative size of the equipoise region (ER). Vertical extent of the boxes represent the interquartile range, the horizontal line the mean, the whiskers extend to include 95% of all values. Currently available triage strategy paradigms (I – VI) are shown in shades of blue, the remaining paradigms (VII – X) in shades of red. In the first row, gain of DALYs is calculated with reference to triage strategy paradigm I (drip-’n’-ship approach). The second row depicts the additional gain in DALYs associated with each triage strategy paradigm over and above all less complex triage strategy paradigms. For a description of triage strategy paradigms, see **Figure 2** in the main text.

Panel A represents the base case scenario with a door-out time of 45 minutes, **Panel B** a door-out time of 15 minutes.

PSC stands for primary stroke center; CSC, comprehensive stroke center.

Supplemental References:

1. Kolominsky-Rabas PL, Sarti C, Heuschmann PU, Graf C, Siemonsen S, Neundoerfer B, Katalinic A, Lang E, Gassmann KG, von Stockert TR. A prospective community-based study of stroke in germany--the erlangen stroke project (espro): Incidence and case fatality at 1, 3, and 12 months. *Stroke*. 1998;29:2501-2506.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB, American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics-2016 update: A report from the american heart association. *Circulation*. 2016;133:e38-360.
3. Luxen D, Vetter C. Real-time routing with openstreetmap data. *Proceedings of the 19th ACM SIGSPATIAL international conference on advances in geographic information systems*. 2011:513-516.
4. R Core Team. R: A language and environment for statistical computing. 2015.
5. Carrera D, Gorchs M, Querol M, Abilleira S, Ribo M, Millan M, Ramos A, Cardona P, Urra X, Rodriguez-Campello A, Prats-Sanchez L, Purroy F, Serena J, Canovas D, Zaragoza-Brunet J, Krupinski JA, Ustrell X, Saura J, Garcia S, Mora MA, Jimenez X, Davalos A, Perez de la Ossa N, Catalan Stroke C, Reperfusion C. Revalidation of the race scale after its regional implementation in catalonia: A triage tool for large vessel occlusion. *J Neurointerv Surg*. 2018 Dec 22. [Epub ahead of print].
6. Seners P, Turc G, Maier B, Mas JL, Oppenheim C, Baron JC. Incidence and predictors of early recanalization after intravenous thrombolysis: A systematic review and meta-analysis. *Stroke*. 2016;47:2409-2412.
7. 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;48:233-238.
8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL, American Heart Association Stroke C. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2018;49:e46-e110.
9. Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, Davis SM, Donnan GA, Churilov L. Stroke thrombolysis: Save a minute, save a day. *Stroke*. 2014;45:1053-1058.
10. Meretoja A, Keshtkaran M, Tatlisumak T, Donnan GA, Churilov L. Endovascular therapy for ischemic stroke: Save a minute-save a week. *Neurology*. 2017;88:2123-2127.