Prehospital Stroke Triage

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Neurology® 2021;97:S25-S33. doi:10.1212/WNL.0000000000012792

Abstract

Purpose of the Review
This article reviews prehospital organization in the treatment of acute stroke. Rapid access to an endovascular therapy (EVT) capable center and prehospital assessment of large vessel occlusion (LVO) are 2 important challenges in acute stroke therapy. This article emphasizes the use of transfer protocols to assure the prompt access of patients with an LVO to a comprehensive stroke center where EVT can be offered. Available prehospital clinical tools and novel technologies to identify LVO are also discussed. Moreover, different routing paradigms like first attention at a local stroke center (“drip and ship”), direct transfer of the patient to an endovascular center (“mothership”), transfer of the neurointerventional team to a local primary center (“drip and drive”), mobile stroke units, and prehospital management communication tools all aimed to improve connection and coordination between care levels are reviewed.

Recent Findings
Local observational data and mathematical models suggest that implementing triage tools and bypass protocols may be an efficient solution. Ongoing randomized clinical trials comparing drip and ship vs mothership will elucidate which is the more effective routing protocol.

Summary
Prehospital organization is critical in realizing maximum benefit from available therapies in acute stroke. The optimal transfer protocols directed to accelerate EVT are under study, and more accurate prehospital triage tools are needed. To improve care in the prehospital setting, efficient tools based on patient factors, local geography, and hospital capability are needed. These tools would optimally lead to individualized real-time decision-making.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
Reperfusion is the most effective treatment in ischemic acute stroke. IV thrombolysis (IVT) with alteplase is widely available in local or primary stroke centers (PSCs). However, endovascular thrombectomy (EVT) has been shown to improve the chances of stroke recovery and thus has become the treatment of choice for large vessel occlusion (LVO) stroke. Each 15-minute reduction in symptom onset to groin puncture time is associated with a 1.14% absolute increase in the likelihood of achieving functional autonomy at discharge and a 0.77% absolute decrease in in-hospital mortality.1 In light of this evidence, prehospital protocols must be adapted to assure prompt access of patients with LVO to a comprehensive stroke center (CSC) or thrombectomy-capable stroke center where EVT can be offered.

This article focuses specifically on the identification of patients with LVO for EVT. Because other stroke sequelae might benefit from earlier management at a specialized center, prehospital triage and transfer decisions may extend further. The benefit for IVT in patients with unknown time from onset or wake-up stroke has been supported by recent trials (WAKE-UP, EXTEND, ECASS-4) but patient selection depends on MRI or CT perfusion neuroimaging, which is only accessible in select centers.2-4 In addition, patients with an acute hemorrhage may benefit from early reversal of anticoagulant drugs or neurosurgical therapies only available at CSCs and some PSCs. Furthermore, patients with fluctuating symptoms, symptomatic carotid stenosis, or high risk of developing malignant infarct may also benefit from a higher level of care.

**Prehospital Selection of Patients With LVO**

The first step in organizing prehospital care is developing and implementing scales that identify and further discriminate patients with stroke with severe symptoms benefitting from care in highly specialized centers. Less severe strokes that require routine care can be triaged to a local stroke center or PSC. The ideal LVO identification tool should have high sensitivity and specificity, thus leaving no LVO behind while at the same time including as few false-positives as possible. In order to achieve its wide implementation, this tool must be simple and inexpensive. Tools based on clinical data are relatively simple to implement but their accuracy is not optimal. Several prehospital stroke scales have been proposed to identify LVO strokes in the prehospital setting (Table 1). Most LVO scales have been designed and validated in retrospective cohorts of selected patients, for example, patients with ischemic stroke who underwent neuroimaging. Very few scales have been prospectively validated in the real world.5-8

The rapid arterial occlusion evaluation (RACE) scale is the most widely validated. It was first tested in a local pilot study and later validated utilizing 3 large cohorts involving different geographical territories.9-12 Data comparing different scales in retrospective cohorts demonstrate comparable performance on their accuracy to identify LVO.13-17 More recently, the PRESTO trial prospectively validated different LVO scales in 1,039 patients transported by ambulance, showing the highest accuracy for the RACE scale (area under the curve 0.83).18 In general, all scales typically demonstrate poor specificity for the desired sensitivity, so that LVO scales are able to detect more than 80% of patients with LVO but approximately 50% of patients usually have other diagnoses, thus resulting in over triage. Other trials such as the Stroke Cincinnati Prehospital Stroke Severity Scale Evaluation in Prehospital in France (SCENE trial; NCT03181412) and the Implementation of Finnish Prehospital Stroke Scale to Emergency Medical Services trial (NCT03520335) are being developed to prospectively validate different LVO scales.

In addition to the trials mentioned above, real-world experiences are needed to better assess the feasibility and accuracy of prehospital tools when performed by emergency medical services (EMS) technicians or paramedics. Efforts should focus on training EMS professionals integrating these scales in the stroke code protocol, thus allowing quick initiation of these algorithms based on triage tools. Online training material available in different languages, such as the official RACE scale training course, facilitates the training of end users. Moreover, free apps allow the calculation of different scales in real time (Table 1).

The main differences between scales are the domains assessed and their complexity. The inclusion of cortical symptoms associated with LVO such as gaze deviation (odds ratio [OR] for LVO 9.6), aphasia/agnosia (OR 7.3), and arm motor impairment (OR 7.6) provide improved accuracy when compared to other symptoms like facial (OR 5.5) or leg motor impairment (5.7).19 Details regarding the cortical signs included in these different scales are shown in Table 1. Some scales include level of consciousness (Cincinnati Prehospital Stroke Severity Scale, 3-Item Stroke Scale, Prehospital Acute Stroke Severity scale), which is not revealing of LVO. These confounding factors lead to the inclusion of a higher number of false-positive hemorrhagic cases.

Although binary scoring scales may be advantageous because of their simplicity for general use, the strength of a gradable
score scale like RACE is its adaptability. Gradable scales can provide a lower cutoff point in urban areas, thus improving sensitivity and capturing more patients with LVO. At the same time, a higher cutoff point in a more remote/rural area improves specificity and avoids false-positive transfers. Data from the revalidation study of the RACE scale in Catalonia showed that when a cutoff point of RACE $\geq 5$ is considered, 42% of patients harbored LVO (considering proximal and distal occlusion), 29% hemorrhagic stroke, 21% ischemic with no LVO, and 8% mimic stroke.10 Similar results have been obtained in other validation studies in different geographical areas such as Texas and Ohio.12,20 These results showed a sensitivity of 77% and specificity of 75% for detection of patients with LVO eligible for EVT and an overall accuracy of 75.3% (95% confidence interval [CI] 73.1%–77.4%).

New and Future Technology to Identify LVO

Prehospital stroke care faces 2 critical challenges ahead: refining triage of patients with LVO beyond the limitations of prehospital stroke scales and improving communication and coordination between EMS and hospitals to help with decision-making and route assistance. Hence, there is significant potential for new and future technology to boost prehospital stroke management.21 The ideal components of a prehospital LVO detection technology are simplicity, low cost, quickness, accuracy, reproducibility, reliability, and generalizability. A few devices are being developed to improve LVO triage. These devices are in a preliminary stage of development and their use has not been widely validated. The main concern with these devices is their cost and complexity, which may limit their adoption to specific geographic regions.

Transcranial doppler (TCD) is a strong candidate for triage evaluation of LVO as it is portable, inexpensive, and has been validated. At least 2 TCD devices are under development. One of these devices is the Lucid Robotic System (Lucid M1 Transcranial Doppler Ultrasound System, Neural Analytics Inc.), which is a robotically assisted ultrasound system with similar accuracy to detect LVO as an expert technician with a traditional ultrasound platform.22 The device is cleared by the Food and Drug Administration and CE marked since May 2018. SONAS (BURL Concepts Inc.) is a portable battery-powered device that utilizes ultrasound microbubbles as acoustic traces to detect

### Table 1 Prehospital Large Vessel Occlusion Scales

<table>
<thead>
<tr>
<th>Items, n</th>
<th>Cortical signs</th>
<th>Prospective validation in the field</th>
<th>Online training material</th>
<th>App available</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPSSS 3</td>
<td>Yes: gaze</td>
<td>Yes (n = 112), (n = 138)</td>
<td>Yes: YouTube</td>
<td>Yes: MDCalc, Stroke Scales, Join Triage</td>
</tr>
<tr>
<td>LAMS 3</td>
<td>No</td>
<td>Yes (n = 94)</td>
<td>Yes: YouTube</td>
<td>Yes: Stroke Scales, Join Triage</td>
</tr>
<tr>
<td>RACE 5</td>
<td>Yes: gaze, aphasia/agnosia</td>
<td>Yes (n = 357), (n = 1822), (n = 440)</td>
<td>Yes: Coursera, racescale.org</td>
<td>Yes: MDCalc, Stroke Scales, Join Triage</td>
</tr>
<tr>
<td>FAST-PLUS 3 + 2</td>
<td>No: aphasia (or dysarthria)</td>
<td>Yes (n = 435)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>FAST-ED 5</td>
<td>Yes: gaze, aphasia/agnosia</td>
<td>Yes (n = 402)</td>
<td>Yes: neurovascularexchange.com</td>
<td>Yes: Stroke Scales, Join Triage</td>
</tr>
<tr>
<td>VAN 4</td>
<td>Yes: gaze, aphasia/agnostic, visual field</td>
<td>No</td>
<td>Yes: YouTube</td>
<td>Yes: Stroke Scales, Join Triage</td>
</tr>
<tr>
<td>ACT-FAST 2 (+ EVT eligibility)</td>
<td>Yes: aphasia, neglect</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>G-FAST 4</td>
<td>Yes: aphasia (or dysarthria), gaze</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pomona 3</td>
<td>Yes: gaze, aphasia, neglect</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>s-NIHSS 6</td>
<td>Yes: aphasia</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NIHSS-8 8</td>
<td>Yes: gaze, aphasia, neglect</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3I-SS 3</td>
<td>Yes: gaze</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PASS 3</td>
<td>Yes: gaze</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>FPSS 5</td>
<td>Yes: gaze, aphasia, visual</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: 3I-SS = 3-Item Stroke Scale; ACT-FAST = Ambulance Clinical Triage for Acute Stroke Treatment; CPSSS = Cincinnati Prehospital Stroke Severity Scale; EVT = endovascular thrombectomy; FAST-ED = Field Assessment Stroke Triage for Emergency Destination; FAST-PLUS = face–arm–speech–time plus severe arm or leg motor deficit test; FPSS = Finnish Prehospital Stroke Scale; G-FAST = gaze–face–arm–speech–time; LAMS = Los Angeles Motor Scale; NIHSS-8 = National Institutes of Health Stroke Scale–8; PASS = Prehospital Acute Stroke Severity scale; RACE = rapid arterial occlusion evaluation; sNIHSS = shortened version of the National Institutes of Health Stroke Scale; VAN = vision, aphasia, neglect.
LVO. Results from this device are unpublished. Another promising device is volumetric impedance phase shift spectroscopy (VIPS; Cerebrotech Medical Systems). This is a helmet technology that predicts large strokes in approximately 30 seconds through electromagnetic waves of different frequencies evaluating for hemispheric bioimpedance asymmetry. Asymmetry of >10% demonstrated 93% sensitivity and 87% specificity for detecting severe stroke (LVO or intracerebral hemorrhage [ICH] >60 mL) from other pathology. A major limitation of this device is the inability to rule out hemorrhagic stroke. These pilot validation studies conducted for the different tools are based on hemispheric stroke and do not include posterior territory stroke with basilar artery occlusion.

Other technologies for LVO detection are emerging but in the experimental or proof-of-concept phase. One of these technologies is the Brain Pulse monitor. This technology is based on accelerometers that detect, amplify, and capture the skull motion caused by pulsatile cerebral blood flow (Non-Blinded Data Collection Pilot Study of Acute Stroke Using the Brainpulse; NCT03235271). StrokeFinder MD100 is another device that uses low-energy microwave technology to differentiate ICH and ischemic strokes. EEG-based detection to assess asymmetry to differentiate stroke from stroke mimics and artificial intelligence to interpret video images for automated clinical examination are also being developed.

New technologies for prehospital care are focused not only on clinical assessment but also on medical communication. This will improve the connection and coordination between care levels. Despite improvements in EMS equipment, communications between EMS and hospitals continues to rely on outdated radio technology. Radio technology has inherent flaws that lead to difficulties in structure and in transmission of relevant information in an effective way to all stroke system components involved. Recently, the Join App smartphone system has demonstrated the ability to facilitate treatment decisions at in-hospital level. The application allows for rapid sharing of clinical and imaging data in a safe environment and with a remote connection. Likewise, data from Stop Stroke Pulsara application, which also integrates communication, stroke scales, time tracking, and imaging transmission, demonstrates a 20–40 minutes decrease in door to needle times when using the application. Telemedicine has also shown feasibility in the prehospital triage setting. Implementation of such technology at a prehospital level would help accelerate decision-making about prehospital care and routing protocols in stroke. These communication applications ideally should include routing assistance with information about traffic conditions, location of the nearest PSC and CSC, and on-route localization of the ambulance.

Transfer Protocols for Patients With Suspiration of LVO

Drip and Ship vs Direct to Mothership
It is estimated that the optimal population rate of EVT centers is 10–15/100,000 inhabitants, but few geographic areas reach this goal. Access to an EVT-capable center in time is a main obstacle. Stroke networks are often organized according to a decentralized model based on the drip and ship paradigm. In this model, patients are initially treated in PSC or local stroke centers capable of administering IVT. Then, in cases of LVO, they are later transferred to a CSC. Hence, access to EVT is up to 3 times less and is initiated up to 2 hours later for patients located distant from a CSC when compared to patients who have a CSC as their referral center. Although in-hospital workflow can be reduced, data from several cohorts such as the STRATIS registry and the MR CLEAN trial show that the door-in/door-out time (from arrival at the local center to initiation of the interhospital transfer) is extended to 90–120 minutes. With the aim to solve this delay and accelerate the initiation of EVT, the mothership model proposes the direct transfer of selected patients with stroke to a CSC bypassing the local center (Figure).

If definitive identification of EVT-eligible patients in the field could be possible, direct triage to a CSC would likely be beneficial. Several meta-analyses show that patients treated with EVT have better outcome when they are transferred directly to a CSC compared to those who are shipped from other centers (adjusted risk ratio for modified Rankin Scale [mRS] score 0–2 0.87, 95% CI 0.77 to 0.98). However, there are several areas of uncertainty regarding the transport of patients with suspicion of LVO. First, available data do not directly compare both transport options in remote areas. Second, the benefit of direct care at a CSC has been demonstrated in patients who underwent EVT, but it is unknown whether these findings are valid for all patients with suspicion of LVO, including those who do not undergo EVT.

Consequences of bypassing paradigms are especially relevant in patients with ischemic stroke. Direct transfer may result in a delay in the start of IVT in favor of accelerating the EVT. On the one hand, this could benefit patients with LVO, in which IVT may have a limited benefit. A recent review and a meta-analysis from randomized clinical trials and observational studies have shown a modest effect (11%) in tissue plasminogen activator (tPA)–related recanalization rate in LVO candidates for EVT. On the other hand, IVT recanalization effect is not negligible in certain patients. Stroke severity measured with the National Institutes of Health Stroke Scale (NIHSS), site of occlusion, and time from onset to treatment are factors related to the IVT recanalization effect. Reperfusion rates increase to 56% in patients with NIHSS <15 treated in <90 minutes, but this effect is insignificant in patients with NIHSS >15 treated in 180 minutes and in patients with NIHSS >19 regardless of time until treatment (data presented at the 2018 European Stroke Organization Conference by Pérez de la Ossa et al.: “Factors associated with successful recanalization after IV–tPA initiated at local centers in acute stroke patients with LVO transferred to endovascular centers”). Data based on meta-analyses of observational studies and a recent clinical trial demonstrated comparable safety and efficacy results of EVT alone in comparison to treatment with
IVT prior to EVT.\textsuperscript{35,36} Direct transfer protocols may be harmful to triaged patients with ischemic stroke without LVO who may have either had a delay or missed the opportunity to receive thrombolysis due to bypass of PSC.

International recommendations have been published on bypass protocols. Mothership transfer is recommended for non-tPA candidates and for tPA candidates depending on the additional time involved in the transfer to a CSC compared to the local center, ranging from 15 to 45 minutes depending on the source.\textsuperscript{37-39} There are no data from randomized controlled trials on which to base these recommendations. Results from clinical trials (cited later in the article) may emerge in the coming months and should clarify which transport protocols are most beneficial for select patients in the prehospital setting.

**Real-world Experiences With Bypass Protocols**

Direct transfer to the mothership is feasible and could be highly beneficial. Real-world published experiences show feasibility of bypass protocols with no noticeable harm and significant reduction in time to EVT.

Zaidi et al.\textsuperscript{20} published a bypass protocol derived from their experience in Lucas County, Ohio. Their stroke network consisted of 2 CSCs and 3 local stroke centers located within 30 minutes from a CSC. Patients with a RACE score \(\geq 5\) and unknown or last 24 hours onset were classified as RACE-Alerts and directed to the closest CSC. Compared to the preimplementation period, the rate of mechanical thrombectomy increased (20.1\% vs 7.7\%; \(p = 0.03\)) and treatment times improved (median arrival to recanalization times 101 vs 205 minutes; \(p = 0.001\)). In a subsequent 1-year follow-up study, Jumaa et al.\textsuperscript{13} demonstrated the feasibility of a countywide EMS-based triage protocol. Among RACE-Alert patients, 1 in 3 patients had acute ischemic stroke secondary to LVO and 1 in 4 patients received EVT. A high proportion of stroke mimics (28\%) and 13\% of ICH were observed. A RACE cutoff point \(\geq 5\) was able to identify 77\% of patients eligible for EVT. The RACE-Alert protocol is being expanded to rural areas in northwest Ohio, including 8 local hospitals. It will also be monitored in the Triage of Acute Strokes Using a RACE Protocol in Urban and Rural Communities (TRACER) Registry.

Mohamad et al.\textsuperscript{40} described a bypass protocol in central Denmark where part of the population is covered by a non-endovascular center located 120 km apart from the CSC. Patients were selected with an EMS questionnaire. Patients from the entire region receiving reperfusion therapy (IVT, EVT, or both) during the pre–post implementation period were compared. Time from onset to EVT was reduced (234 vs 185 minutes) with no significant delay in IVT initiation. Patients treated with EVT after the postimplementation period showed better outcome compared to the preimplementation period (mRS 0–2, 62\% vs 42\%, OR 3.08, CI 1.08–8.78).

Another similar experience in an urban area in Rhode Island and southeastern Massachusetts with 16 local stroke centers and 1 CSC was published by Jayaraman et al.\textsuperscript{41} Part of the region implemented a stroke severity scale–based bypass protocol for patients scoring LAMS \(\geq 4\) within 24 hours from last known well and located within 30 minutes from a CSC. Metrics and outcomes of patients from areas that followed a drip and ship or a mothership routing protocol were compared. The mothership paradigm was associated with 7 additional minutes of transport time (from scene to first hospital arrival) but the scene to IVT time was shorter. This was mainly due to more efficient workflow at the CSC. EVT time was reduced (93 vs 152 minutes; \(p < 0.001\)) and clinical outcome at 3 months was better (OR for less disability 1.47, 95\% CI 1.13 to 1.93, \(p = 0.003\)) in patients fulfilling the mothership transfer protocol.
The implementation of new protocols and the consequent training of professionals may have an effect on streamlining efficiencies at the level of both pre- and in-hospital workflows. Thus, these results should be considered with caution. It is necessary to have data from randomized trials with a comparable and concurrent control group. Moreover, mothership protocols are being implemented in areas relatively close to a CSC. Additional research is warranted to determine the feasibility and benefit of triage protocols in more remote areas.

**Ongoing Randomized Clinical Trials**

Several randomized clinical trials are ongoing with the aim of evaluating feasibility of the drip and ship vs mothership paradigm and the benefit of bypass protocols in different geographies and scenarios (Table 2).

The RACECAT trial (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion; NCT02795962) is being performed in Catalonia. The study involves 19 local stroke centers and 6 CSCs covering a total population of 3.85 million inhabitants with distances to an EVT stroke center ranging from 20 to 150 minutes and average transfer times between centers of 45 minutes. Patients located in areas covered by a non-EVT center with a RACE of ≥5 and expected time from onset to EVT <8 hours are evaluated by an on-call neurologist and assigned to one of the routing protocols in a temporal cluster design. Primary outcome is a shift analysis of the mRS at 90 days in patients with ischemic stroke. Preliminary results of the RACECAT trial were presented at the European Stroke Organization Conference in November 2020. The main results showed no differences in clinical outcome between the 2 groups. The rate of endovascular treatment was very high, in up to 40% of patients with ischemic stroke, and times from onset to treatment were extremely short in both groups, even in the drip and ship group, with only 60 minutes difference from onset to endovascular treatment compared to the mothership group. Publication of the final results and subanalysis will help to elucidate which clinical, geographic, and logistical situations on transfer paradigm may be most beneficial.

The TRIAGE trial (Treatment Strategy in Acute Ischemic Large Vessel Stroke: Prioritize Thrombolysis or Endovascular Treatment; NCT03542188) is being performed in Denmark. In this trial, both transfer paradigms are being compared in patients eligible for IVT within the 4.5-hour time window for IVT. Patients are selected by EMS using a Prehospital Acute Stroke Severity scale score ≥2. Primary outcome is a shift analysis of the mRS at 90 days in patients ending with diagnosis of ischemic stroke and secondary outcomes will also include hemorrhagic and stroke mimics.

The PRESTO-F trial (Prehospital Routage of Acute Stroke Patients With Suspected Large Vessel Occlusion: Mothership vs Drip and Ship; NCT04121013) will compare both routing protocols in a region of France. Patients within the 4.5-hour time window will be selected for IVT based on a RACE ≥5. RACE will be performed by a physician from the EMS coordination center. Primary outcome is the incremental cost–utility ratio at 12 months and secondary outcomes include mRS at 90 days and generic health status measured by the EuroQoL-5D scale at 90 days.

The applicability of results derived from these clinical trials will depend on geographical characteristics and local resources, which vary greatly between territories. However, these studies will help clarify whether these triage systems can identify patients who benefit from a mothership model. They should also elucidate the proximity/distance from a CSC required for patients to incur benefit from a mothership protocol.

**Other Routing Paradigms**

The drip and drive model involves the transfer of a neurointerventionalist to a PSC equipped with a fully staffed angiography. Recent experiences demonstrate drip and drive is feasible and more efficient when compared to the drip and ship approach (Figure). Wei et al., in New York, showed a significant reduction in the time from arrival to recanalization (79 minutes faster). Similarly, Brekenfeld et al., in Germany, showed a 2-hour reduction in the time from CT scanner to groin puncture. Secondary effects of the drip and drive approach is to avoid overloading of the CSC and EMS resources. Even more promising is the use of remote control thrombectomy with teleoperated robotic technology, which would mitigate the transfer of the interventionalist. This technology

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### Table 2 Randomized Clinical Trials Comparing Drip and Ship vs Mothership Routing Paradigms

<table>
<thead>
<tr>
<th>Trial</th>
<th>Region</th>
<th>Triage method</th>
<th>Inclusion criteria (regarding time from onset)</th>
<th>Primary outcome</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>RACECAT</td>
<td>Catalonia</td>
<td>RACE ≥5: contact with a neurologist on call</td>
<td>Estimated arrival at the CSC &lt;8 hours</td>
<td>mRS at 90 days in patients with ischemic stroke</td>
<td>1,774 (2 interim analyses at 700 and 1,224)</td>
</tr>
<tr>
<td>PRESTO-F</td>
<td>France</td>
<td>RACE ≥5: evaluated by EMS central coordinator physician</td>
<td>Eligible for IV tPA within the 4.5-hour time window</td>
<td>Cost-utility ratio at 12 months</td>
<td>800</td>
</tr>
<tr>
<td>TRIAGE</td>
<td>Denmark</td>
<td>PASS ≥2</td>
<td>Eligible for IV tPA within the 4.5-hour time window</td>
<td>mRS at 90 days in patients with ischemic stroke</td>
<td>600</td>
</tr>
</tbody>
</table>

Abbreviations: CSC = comprehensive stroke center; EMS = emergency medical services; mRS = modified Rankin Scale; PASS = Prehospital Acute Stroke Severity scale; RACE = rapid arterial occlusion evaluation; tPA = tissue plasminogen activator.
is under development and has already matured in other conditions such as percutaneous coronary angioplasty.46,47

Mobile stroke units (MSU) are ambulances equipped with a neuroimaging system, point-of-care laboratory, and telemedicine connection. MSU allow specific on-board staff to evaluate a patient, obtain appropriate imaging, and treat with IVT on site. Randomized trials concluded that using MSU significantly decreases time to IVT without increasing adverse events.48 New generation MSU incorporate the possibility of performing an angio-CT. This allows for highly accurate selection of patients who are candidates for EVT. Recently, Helwig et al.49 published a randomized clinical trial comparing triage of patients who require attention at a CSC using a preclinical stroke severity scale (LAMS ≥4) vs MSU. The study was stopped prior to the intended number of patients being enrolled based on reaching a prespecified superiority threshold in favor of MSU (accurate triage decision in 69.8% in the clinical scoring group vs 100% in the MSU group; difference 30.2%; 95% CI, 17.8%–42.5%; p < 0.001).

Although the time savings in decision and treatment is clear, more research is necessary to assess the MSU effect on clinical outcomes and the balance between cost and benefit. MSU are being deployed in several territories around the world, but their widespread use is limited by their complexity and price. Moreover, it is important to note that the catchment area for the MSU is usually a 15-minute drive time radius or 10-mile radius at most. This option might be favorable for specific areas with a high population density but unlikely to be a global solution for prehospital selection. Implementing more resource-consuming and complex strategies might be possible in densely populated regions. However, this may not be pragmatic for all environments. Simpler options such as organizing a direct to mothership strategy for selected patients would likely offer greater clinical benefit to patients with stroke at less cost. These options could be widely applicable.

Mathematical Models
Another approach to evaluate the benefit of different routing paradigms for patients with acute stroke is the use of mathematical models. These theoretical models can be used to simulate the complex prehospital decision-making environment and predict patient outcomes in various scenarios.

Modeling includes several inputs: time from onset to EMS attention, stroke severity, distance from the scene to a PSC or to a CSC, and in-hospital workflow. Based on the inputs, the algorithm uses conditional probability modeling and calculates the probability of achieving good outcome for each of the transfer paradigms (usually comparing drip and ship vs mothership). Finally, the model gives a recommendation about the best routing protocol for a particular scenario. The results of these models can be displayed using map visualizations that show the areas best suited a specific routing protocol.50 Destine Health software is a web-based interactive tool that allows customizing the map of a specific area considering its geographical characteristics and workflows.

Overall, the data suggest that the transport strategy depends on the patient’s distance to the centers and in-hospital workflow. Mainly, the mothership model offers greater benefits than the drip and ship model except in very remote areas. However, in-hospital times have a great effect on the results. Efficient in-hospital workflow at the PSC can potentially increase the drip and ship catchment area. As an example, Holodinsky et al.51 concluded that if treatment times are slow at the thrombolysis center, bypass should be considered when PSC is 60 minutes or less from the CSC. Another important factor favoring the mothership approach is stroke severity. The higher the score on the prehospital RACE scale, the smaller the area that benefits from a drip and ship model, limited to areas in close proximity to the PSC.52

Recommendations made by mathematical models cannot be interpreted similarly to data obtained from clinical trials. An important caveat when interpreting the results of mathematical models is the utilization of assumptions based on previous clinical trials or cohorts. For example, the outcome of hemorrhagic stroke is considered to be similar irrespective of the transfer paradigm. However, this assumption may not be correct. Thus, it is necessary to validate and populate the models with data based on real experiences. In addition, models make the best strategy recommendations based on the probability of achieving a favorable outcome, but they do not provide data on the magnitude of the benefit. If the difference in outcome between 2 different routing paradigms is 1%, the model may recommend it, but the number of bypassed patients needed to achieve the benefit in 1 case would be 100 cases. This has important logistical implications.

Nonetheless, models offer several advantages. Models are flexible and dynamic and can be adapted to different scenarios. Inputs such as in-hospital metrics, the location of PSC and CSC, the addition or removal of centers, the implementation of MSU or drip and drive strategy,53 or the use of more effective thrombolytic agents such as tenecteplase can be included and modified. This allows for the evaluation of new variables. In fact, models are a good mechanism to offer a rapid and low-cost outcome prediction of stroke organization in scenarios where clinical trials are difficult to perform.

Pragmatic Consequences of Routing Protocols
Establishment of a prehospital routing protocol for EVT candidates is a complex task that involves the coordination of various stakeholders, including hospitals and EMS systems. One of the main barriers to a direct to CSC bypass protocol is the overcrowding of these centers with patients who might not need EVT. Schleier et al.54 offer data based on mathematical models that allow estimating this effect. They concluded that implementation of a prehospital triage strategy based on a RACE score ≥5 was associated with 11.7% more patients with suspected acute stroke at CSC and 18.4% less patients at PSC. Regarding EMS resource consumption, the mothership model was associated with a reduction in the
number of secondary transfers by 60.9% with no differences in time of ambulance use.

Mothership protocols not only mean rapid access to EVT but also admission far from the patients’ residence. This can result in isolation and lack of critical family support. Secondary decentralization might ensure urgent access to EVT when needed and prevention of overcrowding of CSCs by returning patients to local hospitals or PSC when stable. Thus, it is also necessary to establish interfacility return agreements in order to preserve appropriate resource allocation and optimize patient comfort. The real-world effect of routing paradigms on logistics and resources must be explored in clinical trials.

The training of EMS professionals is a critical step in the successful implementation of a triage paradigm. The formal education of EMS first responders varies between regions. It also varies from paramedics to EMS technicians to emergency physicians to firefighters. However, irrespective of the first responder background, the implementation of stroke triage protocols requires continuous training and quality evaluation. Experiences based on different territories are encouraging. An example of this is the region of Catalonia. In this region, EMS technicians received a 4-hour online training course on prehospital triage before starting the RACECAT trial. A central and unique coordination of all EMS companies in the territory alongside periodic feedback was decisive in achieving successful implementation of the triage paradigm. The accuracy of stroke severity–based triage may not be generalizable to EMS agencies that rely on volunteers or that lack rigorous training and feedback processes. Nonetheless, there are several online resources that can simplify the task.

Summary

Prehospital organization is crucial to achieving the maximum benefit from available therapies in patients with acute stroke. In the coming years, we will have more evidence on which transfer protocols are most effective in certain patients and distances. New and more accurate prehospital triage tools will become available to identify EVT candidate patients. As more data emerge, it is expected that prehospital predictive algorithms will be developed to assist in transfer decision-making. This will allow individualized real-time decisions that account for transfer-specific factors (i.e., the patient, the geography, and the hospital).

Meanwhile, access to endovascular treatment remains the main constraint to its widespread use, Health systems must make efforts to improve this situation. It is necessary for EMS, hospitals, and policymakers to work together locally to ensure an effective stroke network. While waiting for the results of clinical trials, data coming from local experiences and mathematical models suggest that implementing triage tools and bypass protocols may be an efficient solution.

Establishing prehospital protocols, collecting prehospital data, and training and providing feedback to medical professionals are essential elements of successful prehospital care in acute stroke. The entire team must work on the premise that the sooner the better and be flexible in adapting new treatment options, changing geographical resources, and incorporating novel technology. All the efforts made in this area will translate to earlier care and better outcomes for patients with acute stroke.

Study Funding

The authors report no targeted funding.

Disclosure

A. Ramos and W.R. Guerrero report no disclosures. N. Pérez de la Ossa is principal investigator of RACECAT’ trial, funded by Medtronic. Go to Neurology.org/N for full disclosures.

Publication History

Received by Neurology June 28, 2020. Accepted in final form October 7, 2020.

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