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Published in:
Stroke

DOI:
10.1161/STROKEAHA.120.030392

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Pathway Design for Acute Stroke Care in the Era of Endovascular Thrombectomy
A Critical Overview of Optimization Efforts

Willemijn J. Maas, MSc; Maarten M.H. Lahr, PhD; Erik Buskens, MD, PhD; Durk-Jouke van der Zee, PhD*; Maarten Uyttenboogaart, MD, PhD*; on behalf of the CONTRAST Investigators

ABSTRACT: The efficacy of intravenous thrombolysis and endovascular thrombectomy (EVT) for acute ischemic stroke is highly time dependent. Optimal organization of acute stroke care is therefore important to reduce treatment delays but has become more complex after the introduction of EVT as regular treatment for large vessel occlusions. There is no singular optimal organizational model that can be generalized to different geographic regions worldwide. Current dominant organizational models for EVT include the drip-and-ship- and mothership model. Guidelines recommend routing of suspected patients with stroke to the nearest intravenous thrombolysis capable facility; however, the choice of routing to a certain model should depend on regional stroke service organization and individual patient characteristics. In general, design approaches for organizing stroke care are required, in which 2 key strategies could be considered. The first entails the identification of interventions within existing organizational models for optimizing timely delivery of intravenous thrombolysis and/or EVT. This includes adaptive patient routing toward a comprehensive stroke center, which focuses particularly on prehospital triage tools; bringing intravenous thrombolysis or EVT to the location of the patient; and expediting services and processes along the stroke pathway. The second strategy is to develop analytical or simulation model-based approaches enabling the design and evaluation of organizational models before their implementation. Organizational models for acute stroke care need to take regional and patient characteristics into account and can most efficiently be assessed and optimized through the application of model-based approaches.

Key Words: models, organizational • stroke, acute • thrombectomy • triage

During an acute ischemic stroke, around 2 million neurons are irrevocably lost every minute. The efficacy of intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) are strongly time dependent, and any delay in treatment initiation negatively impacts patients' functional outcomes. Although the effectiveness of EVT may be undisputed, optimal implementation and up scaling of this treatment does not automatically follow. Successful treatment delivery depends on the existing local infrastructure, comprising ambulance services and hospitals offering IVT and EVT. The drip-and-ship model entails initial routing of patients to the nearest primary stroke center (PSC) for diagnostic work-up and IVT. The drip-and-ship model entails initial routing of patients to the nearest primary stroke center (PSC) for diagnostic work-up and IVT. The drip-and-ship model entails initial routing of patients to the nearest primary stroke center (PSC) for diagnostic work-up and IVT. The drip-and-ship model entails initial routing of patients to the nearest primary stroke center (PSC) for diagnostic work-up and IVT. The drip-and-ship model entails initial routing of patients to the nearest primary stroke center (PSC) for diagnostic work-up and IVT. The drip-and-ship model entails initial routing of patients to the nearest primary stroke center (PSC) for diagnostic work-up and IVT. The drip-and-ship model entails initial routing of patients to the nearest primary stroke center (PSC) for diagnostic work-up and IVT.
The drip-and-ship model is more prevalent. Differences in reimbursement regulations between countries may also contribute to the design of acute stroke care organization. For example, in Scandinavian countries, reimbursement is regulated by national health care systems that facilitates central coordination and allocation of PSCs and CSCs. Presently, it remains unclear whether they included mothership patients, whose care providers had intentionally bypassed a PSC, or whether other referral strategies oriented to EVT treatment had been implemented.

Several observational studies have reported that the mothership model for routing patients with large vessel occlusion (LVO) is associated with a shorter onset-to-EVT interval, shorter onset-to-EVT interval, and better functional outcome. These previous observational studies did not explicitly account for differences in travel distances to the nearest PSC and CSC. Furthermore, only 2 studies explicitly mentioned their referral strategy: go to the nearest stroke center. For the majority of studies, it remained unclear whether a dominant organizational model would yield benefit for patients without knowing the regional and patients’ characteristics.

Adaptive Patient Routing

Since the introduction of IVT and EVT, attempts to improve the mothership and drip-and-ship models have been proposed. Examples of areas of improvement of specific regional infrastructural characteristics include workflow efficiency, distances to hospitals, treatment volumes, and interhospital transport delays, all of which have been shown to differ between drip-and-ship and mothership models. Another adaptive recommendation of the European Stroke Organization is to route patients according to the drip-and-ship model when the estimated travel time to the nearest CSC is 30 to 45 minutes longer than the time required to the nearest PSC. If a CSC can be reached within 30 minutes, patients with stroke should be routed according to the mothership model.

Shortest Time to Treatment

Hospitals demonstrate significant differences in workflow efficiency. This finding challenges the strategy to route patients to the nearest EVT center. For patients with LVO, a change of hospital for IVT administration may either increase or decrease the time to EVT treatment, depending on the hospital location and its level of stroke care (PSC or CSC). For example, a hypothetical analysis...
of case studies entailing avoidance of interhospital trans-
fer for patients located 20 miles from a CSC revealed
that despite a delay of 7 minutes in IVT administration,
EVT was initiated 94 minutes faster.29 These means that
distance as such is not the sole critical element relating
to timely reperfusion treatment.

According to the stroke guidelines, patients with LVO
are being treated with IVT and EVT.35 Although IVT is less
effective in recanalizing L VOs, rapid IVT administration for
patients with L VO is associated with increased recanaliza-
tion rate and less disability after 3 months. 36 Conversely,
patients with L VO also benefit from early EVT initiation.4 In

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Model</th>
<th>N</th>
<th>Study design</th>
<th>Transfer modality</th>
<th>mRS score ≤2 (%)</th>
<th>Onset-to-IVT, min</th>
<th>Onset-to-EVT, min</th>
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<tbody>
<tr>
<td>Asaithambi et al18</td>
<td>United States</td>
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<td>86</td>
<td>Observational</td>
<td>Unknown</td>
<td>43.4</td>
<td>117 (88–163)*</td>
<td>294.5 (244–379)*</td>
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<td>Unknown</td>
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<td>Observational</td>
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<td>35.1</td>
<td>NA</td>
<td>222 (181–296)*</td>
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<td>Froehler et al30</td>
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<td>Drip-and-ship</td>
<td>445</td>
<td>Observational</td>
<td>Ambulance</td>
<td>52.2*</td>
<td>NA</td>
<td>NA</td>
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<td>Gerschenfeld et al19</td>
<td>Paris, France</td>
<td>Drip-and-ship</td>
<td>100</td>
<td>Observational</td>
<td>Unknown</td>
<td>61.0</td>
<td>150 (120–190)*</td>
<td>248 (220–291)*</td>
</tr>
<tr>
<td>Park et al31</td>
<td>Gwangju, Korea</td>
<td>Drip-and-ship</td>
<td>28</td>
<td>Observational</td>
<td>Mostly ambulance</td>
<td>46.4</td>
<td>NA</td>
<td>300±63.3*</td>
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<tr>
<td>Park et al31</td>
<td>Korea</td>
<td>Drip-and-ship</td>
<td>71</td>
<td>Observational</td>
<td>Ambulance</td>
<td>NA</td>
<td>120 (82–150)</td>
<td>305 (260–345)*</td>
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<td>Perez de la Ossa et al32</td>
<td>Catalonia, Spain</td>
<td>Drip-and-ship</td>
<td>191</td>
<td>Observational</td>
<td>Both†</td>
<td>67.4</td>
<td>109 (80–165)**</td>
<td>312 (245–435)*</td>
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<td>Pfaff et al33</td>
<td>Heidelberg, Germany</td>
<td>Drip-and-ship</td>
<td>20</td>
<td>Observational</td>
<td>Both†</td>
<td>40.0</td>
<td>NA</td>
<td>274 (238–349)*</td>
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<tr>
<td>Prothmann et al34</td>
<td>Germany</td>
<td>Drip-and-ship</td>
<td>53</td>
<td>Observational</td>
<td>Unknown</td>
<td>58.0*</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Rinaldo et al35</td>
<td>Minnesota, United States</td>
<td>Drip-and-ship</td>
<td>78</td>
<td>Observational</td>
<td>Unknown</td>
<td>33.8</td>
<td>NA</td>
<td>316.4±110.5*</td>
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<tr>
<td>Sun et al36</td>
<td>Atlanta, United States</td>
<td>Drip-and-ship</td>
<td>132</td>
<td>Observational</td>
<td>Ambulance</td>
<td>29.0*</td>
<td>NA</td>
<td>301 (252–362)*</td>
</tr>
<tr>
<td>Weber et al37</td>
<td>Germany</td>
<td>Drip-and-ship</td>
<td>343</td>
<td>Observational</td>
<td>Unknown</td>
<td>35.7</td>
<td>115±116*</td>
<td>233*</td>
</tr>
</tbody>
</table>

All patients received EVT. Transfer modalities considered are ambulances and helicopters. Time variables are median (IQR) or mean±SD. mRS score ≤2 is from 3-mo follow-up when available, otherwise at discharge. N is the total study population, skip time, also in a study the mRS is calculated over less patients. EVT indicates endovascular thrombectomy; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; and NA, not applicable/available.

*Significant differences between groups in the same study (alpha 0.01 or 0.05).
†Indicated both ambulances and helicopters.
‡Significant difference between longer distance referral and the other 2 groups.

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Table 1. Model Performance and Patient Outcomes for the Drip-and-Ship and Mothership Organizational Models
light of the adage “time is brain,” the question of whether the benefits of direct EVT outweigh those of initial IVT becomes relevant. This question is particularly relevant for patients with LVO without a nearby CSC. A recent model-based study quantifying time to treatments and associated outcomes indicated potentially greater benefit of early EVT compared with initial IVT. Another model-based study suggested a 30-minute limit on IVT administration for PSCs that are located in close proximity of a CSC. Whether or not IVT can be skipped is currently being addressed in clinical trials, namely the MR CLEAN NO-IV (Intravenous Treatment Followed by Intra-Arterial Versus Direct Intra-Arterial Treatment for Acute Ischemic Stroke Caused by Proximal Intracranial Occlusion; URL: http://www.isrctn.com/; Unique identifier: ISRCTN806190839) and the SWIFT DIRECT (Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus Direct Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03192332) trials. These trials will influence future patient routing andprehospital triage. Recently, the DIRECT MT trial (Direct Intra-Arterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: A Multicenter Randomized Clinical Trial) has been published and demonstrated that direct EVT was noninferior compared with patients who received IVT before EVT (combined therapy group). As such, it remains appropriate to first treat eligible patients with IVT before thrombectomy.

**Tools for Prehospital Triage**

Various prehospital triage tools have been proposed to distinguish patients with LVO from non-LVO patients to enable patient routing for patients with and without LVO. Four prehospital triage tools to detect or predict LVO can be distinguished: prehospital triage scales, telemedicine supported triage, on site computed tomography (CT)-angiography, and some experimental noninvasive tools.

Several triage scales have been developed for identifying patients with LVO. Some scales are currently being used by ambulance paramedics. The Rapid Arterial Occlusion Evaluation scale has been prospectively validated by ambulance paramedics and has a sensitivity of 85% and a specificity of 68% for LVO detection. The National Institutes of Health Stroke Scale cutoff score ≥12 has been used by helicopter paramedics to predict LVO with a sensitivity of 52% and a specificity of 87%. The Los Angeles motor scale (cutoff score ≥4) and Cincinnati prehospital stroke screen (cutoff score ≥2) demonstrated a pooled sensitivity ranging from 47% to 62% and specificity between 70% and 90%. Within the Stockholm region (Sweden), a combination of symptom severity and teleconsultation demonstrated an overall accuracy of predicting LVO stroke of 87% (positive predictive value, 41%; negative predictive value, 93%). The European Stroke Organization states that there are currently no prehospital triage scales available with acceptable sensitivity and specificity.

Recent technological advances have enabled the inclusion of CT and CT-angiography in mobile stroke units (MSUs). Thus, on-scene CT-angiography can be performed, to distinguish patients with LVO from non-LVO. The usefulness of MSUs in improving clinical outcomes and shortening the time to treatment both for IVT and EVT has been proven. Economic evaluation of this innovation suggest that it can be cost-effective, at least on the short term, but substantial variation in MSU implementation and regional differences limits its generalizability.

Until conclusive evidence that direct EVT is more beneficial than initial IVT followed by EVT, the merits of prehospital triage tools in situations where the PSC is the nearest IVT center will remain unclear.

**Mobile Treatment Solutions**

Another strategy that might reduce time delays is to bring treatment to the patient. Two types of mobile treatment models have emerged: the MSU and a drive the doctor model, in which the neurointerventional or interventional stroke team is transported to a PSC.

The MSU approach does not require the patient to be transported to an IVT capable center, as it is equipped with a CT, a point-of care laboratory, and a telemedicine connection on board, enabling on-site IVT to be administered.

In the drive the doctor model, the neurointerventionalist or mobile interventional stroke team performs EVT at the PSC. This strategy avoids interhospital transfer time. The feasibility of this solution depends on the 24/7 availability of personnel and equipment to provide EVT treatment at every PSC. The cost-effectiveness of the above approaches is yet to be assessed.

Apart from such logistical challenges, preliminary findings on the use of the MSU and drive the doctor approaches indicate that the stroke onset-to-EVT time may be shorter than that associated with the drip-and-ship model (Table 2).

**Expediting Services**

Effective workflow management policies have been shown to reduce time delays associated with the provision of discrete services. Examples include prehospital workflow management, in-hospital patient transfer management, anesthetic management, teamwork, and providing feedback on time intervals.

There are 2 dominant modes of expedited transport: ambulances and helicopters. The use of air transport for interhospital transfers has been found to be beneficial.
Emergence of Modeling Methods

A new promising development is the use of remote robotic EVT. This development might have impact on prehospital care organization, as patient transfer from PSC to CSC may not be necessary. Another new development is the extension of inclusion criteria for EVT to more distal intracranial occlusions. As the total number of EVT procedures will then increase, the capacity of current CSCs should also increase or new CSCs should be installed. The impact and benefits of these new developments can be estimated by using simulation modeling.

Emergence of Modeling Methods

To date, we summarized distinct stroke organization models being applied in daily practice. In recent years, various modeling methods have emerged to study organization of acute stroke care before or substituting randomized clinical trials (RCTs). Clearly, RCTs can put specific interventions to the test in a real-life care system. The RACECAT trial (Transfer to the Local Stroke Center Versus Direct Transfer to Endovascular Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory) is one such RCT comparing the drip-and-ship and mothership models in Catalonia, Spain. Another RCT is the TRIAGE-STROKE trial (Treatment Strategy in Acute Large Vessel Occlusion: Prioritize IV or Endovascular Treatment – A Randomized Trial) in Denmark that addresses the same question. These RCTs will answer which model is best for a specific region, but it is uncertain whether these results may be generalized to other regions. Computer modeling methods typically capture the essential components of the care system and allow flexible testing of alternative organizational models. Compared with classic RCTs, simulation models have the advantage that they are less time consuming in obtaining data, are less expensive and allow comprehensive and detailed analyses.

Simulation enables realistic in silico modeling of stroke care, closely mimicking the set-up of RCTs. Essential strengths of simulation are the ability to reflect the entire care pathway and the flexibility to adapt the model. This enables the simulation to capture the complexity of regional organizational models in detail. The performance of organizational models relating to patient lead-times and their outcomes can be estimated. Examples of interventions that have been studied include the establishment of regional health-related infrastructure (the number of PSCs and CSCs), the use of alternative triage and ambulance protocols, and hospital staff availability. Up to now, simulation modeling has only been performed for

Table 2. Findings of Proposed Organizational Models

<table>
<thead>
<tr>
<th>Proposed interventions</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSU vs drip-and-ship and mothership</td>
<td>16</td>
<td>MSU door-to-IAT decreased compared with PSC door-to-EVT (drip-and-ship) and CSC door-to-EVT (mothership): 93 (75–116.6), 200 (185–223), and 140.5 (70–163.75), respectively (min [IQR]).</td>
</tr>
<tr>
<td>Drip-and-ship vs drip-and-drive</td>
<td>64</td>
<td>Onset-to-angiographic run decreased from 349 (319–384) to 201 (176–242), (min [IQR]).*</td>
</tr>
<tr>
<td>Drip-and-ship vs trip-and-treat</td>
<td>86</td>
<td>Initial (PSC) door-to-EVT decreased from 222 (55) min to 143 (41), (min [SD]).*</td>
</tr>
<tr>
<td>No expediting of care services by using a certain protocol vs the use of rapid diagnosis and transfer to a CSC protocol</td>
<td>70</td>
<td>Onset-to-IVT decreased from 113 (92–165) to 90 (60–112), (min [IQR]).* Onset-to-EVT decreased from 218.5 (176–326) to 185 (137–209), (min [IQR]).* mRS score ≤2 increased from 25% to 50%.*</td>
</tr>
<tr>
<td>Patients transferred by ambulance vs helicopter for interhospital transfers above 80 km</td>
<td>965</td>
<td>Onset-to-EVT decreased from 367 (316–425) to 320 (270–375), (min [IQR]).*</td>
</tr>
<tr>
<td>Helicopter transfer vs ground ambulance</td>
<td>8929</td>
<td>Helicopter transfer was associated with significantly shorter 911 call to hospital arrival intervals for all distances &gt;10 miles from the hospital.</td>
</tr>
<tr>
<td>Air mobile stroke unit for patients living in remote or rural areas</td>
<td>NA</td>
<td>The air mobile stroke unit may represent a novel innovation to reduce treatment disparities; however, further implementation research is necessary.</td>
</tr>
<tr>
<td>Helicopter transfer of a neurointerventionalist to the PSC</td>
<td>1</td>
<td>This proof-of-concept case may be another option in the spoke-and-hub design of stroke care systems.</td>
</tr>
</tbody>
</table>

Time variables are median (IQR) or mean±SD. mRS score ≤2 is from 3-mo follow-up when available, otherwise at discharge. CSC indicates comprehensive stroke center; EMS, emergency medical services; EVT, endovascular thrombectomy; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; MSU, mobile stroke unit; NA, not applicable; and PSC, primary stroke center. *Significant difference.
IVT. With the introduction of EVT, extended simulation modeling to optimize its application seems useful.

In addition to simulation, approximate models may be applied in studies of stroke organizational models. **Approximate models are based on crude estimations using previously published or collected aggregated data, as opposed to simulation which builds on experimental results and patient-level data. Two examples of analytic studies have been published. For example, a study performed in the United States in 4 states demonstrated that increasing the number of EVT centers resulted in an absolute gain in access to EVT center within 15 minutes between 2.8% and 28.1%, thereby assuming patient transport delays to be equal to ambulance driving time from the population geocentroid to the respective hospital. A similar model applied in studies of stroke organizational models, was that investigated the result of bypassing non-EVT centers to be equal to ambulance driving time from the population geocentroid to the respective hospital. A similar model applied in studies of stroke organizational models.**

**CONCLUSIONS**

Organizational models for acute stroke care need to take regional characteristics into account and can most efficiently be assessed and optimized through the application of model-based approaches.

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