

University of Groningen

## Pathway Design for Acute Stroke Care in the Era of Endovascular Thrombectomy

CONTRAST Investigators; Maas, Willemijn J; Lahr, Maarten M H; Buskens, Erik; van der Zee, Durk-Jouke; Uyttenboogaart, Maarten

*Published in:*  
Stroke

*DOI:*  
[10.1161/STROKEAHA.120.030392](https://doi.org/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):*

CONTRAST Investigators, Maas, W. J., Lahr, M. M. H., Buskens, E., van der Zee, D.-J., & Uyttenboogaart, M. (2020). Pathway Design for Acute Stroke Care in the Era of Endovascular Thrombectomy: A Critical Overview of Optimization Efforts. *Stroke*, 51(11), 3452-3460. [STROKEAHA120030392]. <https://doi.org/10.1161/STROKEAHA.120.030392>

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy



If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

## TOPICAL REVIEW

# 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

**D**uring an acute ischemic stroke, around 2 million neurons are irrevocably lost every minute.<sup>1</sup> 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.<sup>2-5</sup>

### See related article, p 3190

Although the effectiveness of EVT may be undisputed, optimal implementation and up scaling of this treatment does not automatically follow.<sup>6</sup> 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. Subsequently, patients may be transported to the nearest comprehensive stroke center (CSC) to undergo EVT. Conversely, in the mothership model, patients are routed directly to a CSC for IVT administration and, if appropriate, EVT treatment. Typically, these patients are already in proximity of a CSC.

Worldwide, there is a huge variation in the ratio of PSCs/CSCs, as well as the number of PSCs/CSCs per

Correspondence to: Willemijn J. Maas, MSc, Department of Epidemiology, University Medical Center Groningen, PO Box 30001, 9700 RB Groningen, the Netherlands. Email w.j.maas@umcg.nl

\*Drs van der Zee and Uyttenboogaart contributed equally.

For Sources of Funding and Disclosures, see page 3457.

© 2020 American Heart Association, Inc.

Stroke is available at [www.ahajournals.org/journal/str](http://www.ahajournals.org/journal/str)

## Nonstandard Abbreviations and Acronyms

<b>CSC</b>	comprehensive stroke center
<b>CT</b>	computed tomography
<b>EVT</b>	endovascular thrombectomy
<b>IVT</b>	intravenous thrombolysis
<b>LVO</b>	large vessel occlusion
<b>MSU</b>	mobile stroke unit
<b>PSC</b>	primary stroke center
<b>RCT</b>	randomized controlled trial

inhabitant.<sup>7</sup> For example, Denmark has 3 CSCs<sup>8</sup> compared with 20 CSCs in the Netherlands, while population size is only 3-fold higher in the Netherlands. In urban areas, more CSCs are available, leading to a predominant mothership model, whereas in rural areas a drip-and-ship model is more prevalent.<sup>9,10</sup> 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.<sup>11</sup>

Previous reviews and meta-analyses have summarized and compared patient outcomes in relation to different types of organizational models that are currently used in daily clinical practice.<sup>12–15</sup> Generally, these previous studies tend to ignore regional health-related infrastructure and patients' characteristics.<sup>12</sup> These characteristics are critical and must be considered in the design of organizational models. A systematic design approach identifying modifiable elements within an existing regional stroke care infrastructure with subsequent testing of several interventions is currently lacking. Given the complexity of the organizational aspects of acute stroke care, such a systematic design approach should be formulated for developing optimized EVT treatment models.

This review presents a summary of current stroke care models from an analytical perspective, while recognizing modifiable elements in the stroke care pathway. We draw attention to key elements that determine the timely delivery of IVT and/or EVT (eg, transport modalities, prehospital triage, and improved workflow). Next, we assess their potential contribution to the provision of improved care in terms of faster onset-to-treatment times and better patient outcomes, with a focus on timely EVT. These interventions include developing adaptive patient routing strategies and prehospital triage systems, establishing alternative care networks, expediting intrahospital transfers and transport, and designing mobile solutions that may reduce time intervals and distances from facilities offering EVT.

## Dominant Organizational Models

The American Heart Association/American Stroke Association guidelines recommend the transfer of patients with acute stroke to the nearest IVT capable facility.<sup>16</sup> Depending on the geographic location of stroke onset, the drip-and-ship model or the mothership model, is applied in practice. The European Stroke Organization recommends an organizational model that takes the regional stroke service organization and patients' characteristics into account.<sup>17</sup>

Several observational studies have reported that the mothership model for routing patients with large vessel occlusion (LVO) is associated with a shorter onset-to-IVT interval,<sup>18–20</sup> shorter onset-to-EVT interval,<sup>18,19,21–28</sup> and better functional outcome<sup>27,29,30</sup> (Table 1).

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.<sup>19,21</sup> For the majority of studies, it remained 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.

Presently, it remains 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,<sup>31</sup> distances to hospitals, treatment volumes,<sup>32</sup> and interhospital transport delays,<sup>33</sup> 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.<sup>17</sup>

## Shortest Time to Treatment

Hospitals demonstrate significant differences in workflow efficiency.<sup>34</sup> This finding challenges the strategy to route patients to the nearest IVT 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

**Table 1. Model Performance and Patient Outcomes for the Drip-and-Ship and Mothership Organizational Models**

Reference	Location	Model	N	Study design	Transfer modality	mRS score ≤2 (%)	Onset-to-IVT, min	Onset-to-EVT, min
Asaithambi et al <sup>18</sup>	United States	Drip-and-ship	86	Observational	Unknown	43.4	117 (88–163)*	294.5 (244–379)*
		Mothership	88			40	91 (70–147)*	160 (123–303)*
Barlinn et al <sup>22</sup>	Dresden, Germany	Drip-and-ship	48	Observational	Unknown	18.8	108 (90–160)	319 (270–384)*
		Mothership	103			13.7	115 (90–150)	225 (175–293)*
Bücker et al <sup>23</sup>	Stuttgart, Germany	Drip-and-ship, inner-city transfer	239	Observational	Unknown	35.1	NA	222 (181–296)*
		Drip-and-ship, long-distance referral	578			37.0	NA	239.5 (202–309)*
		Mothership	124			39.5	NA	169 (127–210)*
Froehler et al <sup>29</sup>	United States	Drip-and-ship	445	Observational	Ambulance	52.2*	NA	NA
		Mothership	539			60.0*	NA	NA
Gerschenfeld et al <sup>19</sup>	Paris, France	Drip-and-ship	100	Observational	Unknown	61.0	150 (120–190)*	248 (220–291)*
		Mothership	59			50.8	135 (114–155)*	189 (163–212)*
Park et al <sup>24</sup>	Gwangju, Korea	Drip-and-ship	28	Observational	Mostly ambulance	46.4	NA	300±63.3*
		Mothership	77			50.6	NA	219.2±55.9*
Park et al <sup>25</sup>	Korea	Drip-and-ship	71	Observational	Ambulance	NA	120 (82–150)	305 (260–345)*
		Mothership	438			NA	113 (80–161)	200 (155–245)*
Perez de la Ossa et al <sup>21</sup>	Catalonia, Spain	Drip-and-ship <1 h transfer	191	Observational	Both†	67.4	109 (80–165)*‡	312 (245–435)*
		Drip-and-ship >1 h transfer	112			67.9	135 (116–189)*‡	350 (284–408)*
		Mothership	662			59.8	110 (80–156)*‡	230 (160–407)*
Pfaff et al <sup>26</sup>	Heidelberg, Germany	Drip-and-ship <42.2 km	20	Observational	Both†	40.0	NA	274 (238–349)*
		Drip-and-ship >42.2 km	18			50.0	NA	293 (256–329)*
		Mothership	74			35.1	NA	178 (150–210)*
Prothmann et al <sup>30</sup>	Germany	Drip-and-ship	53	Observational	Unknown	58.0*	NA	NA
		Mothership	38			78.4*	NA	NA
Rinaldo et al <sup>28</sup>	Minnesota, United States	Drip-and-ship	78	Observational	Unknown	33.8	NA	316.4±110.5*
		Mothership	62			38.3	NA	217.6±76.8*
Sun et al <sup>27</sup>	Atlanta, United States	Drip-and-ship	132	Observational	Ambulance	29.0*	NA	301 (252–362)*
		Mothership	61			51.0*	NA	177 (145–268)*
Weber et al <sup>20</sup>	Germany	Drip-and-ship	343	Observational	Unknown	35.7	115±116*	233*
		Mothership	300			44.0	92±114*	150*

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.

of case studies entailing avoidance of interhospital transfer 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.<sup>29</sup> 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.<sup>35</sup> Although IVT is less effective in recanalizing LVOs, rapid IVT administration for patients with LVO is associated with increased recanalization rate and less disability after 3 months.<sup>36</sup> Conversely, patients with LVO also benefit from early EVT initiation.<sup>4</sup> In

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.<sup>37</sup> Another model-based study suggested a 30-minute limit on IVT administration for PSCs that are located in close proximity of a CSC.<sup>38</sup> 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 Treatment Versus Direct Intra-Arterial Treatment for Acute Ischemic Stroke Caused by Proximal Intracranial Occlusion; URL: <http://www.isrctn.com/>; Unique identifier: ISRCTN8061908839) 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)<sup>40</sup> trials. These trials will influence future patient routing and prehospital 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).<sup>41,42</sup> 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,<sup>43</sup> on site computed tomography (CT)-angiography, and some experimental noninvasive tools.<sup>44,45</sup>

Several triage scales have been developed for identifying patients with LVO. Some scales are currently being used by ambulance paramedics.<sup>46,47</sup> 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.<sup>48</sup> The National Institutes of Health Stroke Scale cutoff score  $\geq 12$  has been used by helicopter paramedics to predict LVO with a sensitivity of 52% and a specificity of 87%.<sup>49</sup> The Los Angeles motor scale (cutoff score  $\geq 4$ ) and Cincinnati prehospital stroke screen (cutoff score  $\geq 2$ ) demonstrated a pooled sensitivity ranging from 47% to 62% and specificity between 70% and 90%.<sup>46</sup> 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%).<sup>50</sup> The European Stroke Organization states that there are currently no prehospital triage scales available with acceptable sensitivity and specificity.<sup>51</sup>

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.<sup>52</sup> The usefulness of MSUs in improving clinical outcomes and shortening the time to treatment both for IVT and EVT has been proven.<sup>53,54</sup> Economic evaluation of this innovation suggest that it can be cost-effective, at least on the short term,<sup>55</sup> 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 neurointerventionalist 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.<sup>56</sup>

In the drive the doctor model, the neurointerventionalist<sup>57,58</sup> or mobile interventional stroke team<sup>59</sup> 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).<sup>57,60,61</sup>

### Expediting Services

Effective workflow management policies have been shown to reduce time delays associated with the provision of discrete services.<sup>62,63</sup> Examples include prehospital workflow management, in-hospital patient transfer management, anesthetic management, teamwork, and providing feedback on time intervals.<sup>62</sup>

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

**Table 2. Findings of Proposed Organizational Models**

Proposed interventions	N	Findings
MSU vs drip-and-ship and mothership <sup>61</sup>	16	MSU door-to-IAT decreased compared with PSC door-to-EVT (drip-and-ship) and CSC door-to-EVT (mothership): 93 (75–116.5), 200 (185–223), and 140.5 (70–163.75), respectively (min [IQR]).
Drip-and-ship vs drip-and-drive <sup>57</sup>	64	Onset-to-angiographic run decreased from 349 (319–384) to 201 (176–242), (min [IQR]).*
Drip-and-ship vs trip-and-treat <sup>60</sup>	86	Initial (PSC) door-to-EVT decreased from 222 (55) min to 143 (41), (min [SD]).*
No expediting of care services by using a certain protocol vs the use of rapid diagnosis and transfer to a CSC protocol <sup>63</sup>	70	Onset-to-IVT decreased from 113 (92–165) to 92 (60–112), (min [IQR]).* Onset-to-EVT decreased from 218.5 (176–326) to 185 (137–209), (min [IQR]).* mRS score $\leq 2$ increased from 25% to 50%.*
Patients transferred by ambulance vs helicopter for interhospital transfers above 80 km <sup>21</sup>	965	Onset-to-EVT decreased from 367 (318–425) to 320 (270–375), (min [IQR]).*
Helicopter transfer vs ground ambulance <sup>64</sup>	8929	Helicopter transfer was associated with significantly shorter 911 call to hospital arrival intervals for all distances >10 miles from the hospital.
Air mobile stroke unit for patients living in remote or rural areas <sup>65</sup>	NA	The air mobile stroke unit may represent a novel innovation to reduce treatment disparities; however, further implementation research is necessary.
Helicopter transfer of a neurointerventionalist to the PSC <sup>66</sup>	1	This proof-of-concept case may be another option in the spoke-and-hub design of stroke care systems.

Time variables are median (IQR) or mean $\pm$ SD. mRS score  $\leq 2$  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.

for distances >80 km (Table 2).<sup>21</sup> Similar trade-offs may occur for prehospital transport.<sup>64</sup>

Two studies have presented proposals for combining prehospital triage and expediting services within a single organizational model. The first is the air-MSU,<sup>65</sup> in which an airplane or helicopter is appropriately staffed and equipped with a CT scanner, point-of-care laboratory, and a telemedicine connection, thereby enabling on-scene IVT administration. The second fly the doctor intervention entails transporting the doctor to the PSC by air.<sup>66</sup>

Because all these studies had an observational design and had region-specific characteristics, no conclusions can be drawn about the superiority of transport modalities in general.

## New Developments

A new promising development is the use of remote robotic EVT.<sup>67</sup> This development might have impact on stroke 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).<sup>68,69</sup> 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.<sup>70</sup> 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.<sup>71</sup> 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.<sup>72,73</sup> 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),<sup>74</sup> the use of alternative triage and ambulance protocols,<sup>73</sup> and hospital staff availability.<sup>75</sup> Up to now, simulation modeling has only been performed for

IVT.<sup>73–75</sup> 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.<sup>37,38</sup> 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%,<sup>9</sup> thereby assuming patient transport delays to be equal to ambulance driving time from the population geocentroid to the respective hospital. A similar model that investigated the result of bypassing non-EVT centers (PSCs) resulted in a gain between 0.6% and 43.1%. Holodinsky et al,<sup>37</sup> who examined the added value of prehospital triage scales, assumed that deterministic (nonrandom) patient delays were incurred along the care pathway. The advantages of approximate models include a fast development, lower data requirements, and less detail in terms of distributions of delays and outcomes and their mutual dependencies. Clearly, the development and computational requirements for these models are less.

Ideally, approximate and simulation models should be integrated. Promising interventions can be quickly identified using approximate models, allowing for a focused simulation study. Moreover, these simulation studies can be used to estimate cost-effectiveness of various intervention studies in regional stroke organizations, not only for IVT,<sup>76</sup> but also extended for use in new RCTs comparing primary EVT to IVT and EVT.<sup>39</sup>

## Toward a Design Approach

Efforts to improve the mothership and drip-and-ship models has elucidated 3 main strategies. Rapid EVT may be achieved through adaptive routing, mobile treatment, and expediting services. Clearly, not every solution may be feasible or available in a given setting and at a specific point in time, implying that a uniform model is not feasible.

Instead of relying exclusively on RCTs, in silico model-based approaches potentially offer possibilities for quick identification of promising interventions, whereas extensive simulation enables realistic experimental computerized replications of proposed organizational models and comprehensive assessments of these interventions. In a rapidly evolving environment such as stroke the availability of model-based approaches may enhance responsiveness in tailoring regional stroke organization for best care.

Evidently, optimal stroke care strategies are based on the existing regional infrastructure, which generally reflects historical arrangements. The resulting infrastructure warrants scrutiny. For example, in the case of EVT,

some poorly covered regions may be identified along with nearby regions with CSCs in undesirable competition.<sup>77</sup> Both of these issues would need to be resolved for the sake of patients, and to ensure the efficient allocation of scarce resources.

## 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.

## ARTICLE INFORMATION

### Affiliations

Department of Neurology (W.J.M., M.U.), Department of Epidemiology, Health Technology Assessment unit (W.J.M., M.M.H.L., E.B.), and Department of Radiology, Medical Imaging Center (M.U.), University of Groningen, University Medical Center Groningen, the Netherlands. Department of Operations, Faculty of Economics and Business, University of Groningen, the Netherlands (E.B., D.-J.v.d.Z.).

### Acknowledgments

We acknowledge the support of the Netherlands Cardiovascular Research Initiative which is supported by the Dutch Heart Foundation (CVON2015-01: Collaboration for new treatment of acute stroke), the support of the Brain Foundation Netherlands (HA2015.01.06), and the support of Health~Holland, Top Sector Life Sciences and Health (LSHM17016) and of Medtronic.

### Sources of Funding

The Collaboration for New Treatment of Acute Stroke (CONTRAST) consortium is supported by Netherlands Cardiovascular Research Initiative, an initiative of the Dutch Heart Foundation, by the Brain Foundation Netherlands and powered by Health~Holland, Top Sector Life Sciences and receives unrestricted funding from Medtronic.

### Disclosures

None.

## REFERENCES

- Desai SM, Rocha M, Jovin TG, Jadhav AP. High variability in neuronal loss. *Stroke*. 2019;50:34–37. doi: 10.1161/STROKEAHA.118.023499
- Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, et al; 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. doi: 10.1016/S0140-6736(14)60584-5
- Campbell BCV, Ma H, Ringleb PA, Parsons MW, Churilov L, Bendzus M, Levi CR, Hsu C, Kleinig TJ, Fatar M, et al; EXTEND, ECASS-4, and EPI-THET Investigators. Extending thrombolysis to 4.5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet*. 2019;394:139–147. doi: 10.1016/S0140-6736(19)31053-0
- Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288. doi: 10.1001/jama.2016.13647
- Desai SM, Rocha M, Molyneaux BJ, Starr M, Kenmuir CL, Gross BA, Jankowitz BT, Jovin TG, Jadhav AP. Thrombectomy 6–24 hours after stroke in trial ineligible patients. *J Neurointerv Surg*. 2018;10:1033–1037. doi: 10.1136/neurintsurg-2018-013915
- Eissa A, Krass I, Bajorek BV. Barriers to the utilization of thrombolysis for acute ischaemic stroke. *J Clin Pharm Ther*. 2012;37:399–409. doi: 10.1111/j.1365-2710.2011.01329.x

7. Aguiar de Sousa D, von Martial R, Abilleira S, Gattringer T, Kobayashi A, Gallofre M, Fazekas F, Szikora I, Feigin V, Caso V, et al. Access to and delivery of acute ischaemic stroke treatments: a survey of national scientific societies and stroke experts in 44 European countries. *Eur Stroke J*. 2019;4:13–28.
8. Truelsen T, Hansen K, Andersen G, Sørensen L, Madsen C, Diaz A, Stavngaard T, Hundborg HH, Højgaard J, Hjort N, et al. Acute endovascular reperfusion treatment in patients with ischaemic stroke and large-vessel occlusion (Denmark 2011–2017). *Eur J Neurol*. 2019;26:1044–1050. doi: 10.1111/ene.13931
9. Sarraj A, Savitz S, Pujara D, Kamal H, Carroll K, Shaker F, Reddy S, Parsha K, Fournier LE, Jones EM, et al. Endovascular thrombectomy for acute ischemic strokes: current US access paradigms and optimization methodology. *Stroke*. 2020;51:1207–1217. doi: 10.1161/STROKEAHA.120.028850
10. Man S, Zhao X, Uchino K, Hussain MS, Smith EE, Bhatt DL, Xian Y, Schwamm LH, Shah S, Khan Y, et al. Comparison of acute ischemic stroke care and outcomes between comprehensive stroke centers and primary stroke centers in the United States. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004512. doi: 10.1161/CIRCOUTCOMES.117.004512
11. Douw K, Nielsen CP, Pedersen CR. Centralising acute stroke care and moving care to the community in a Danish health region: challenges in implementing a stroke care reform. *Health Policy*. 2015;119:1005–1010. doi: 10.1016/j.healthpol.2015.05.007
12. Ciccone A, Berge E, Fischer U. Systematic review of organizational models for intra-arterial treatment of acute ischemic stroke. *Int J Stroke*. 2019;14:12–22. doi: 10.1177/1747493018806157
13. Ismail M, Armoiry X, Tau N, Zhu F, Sadeh-Gonik U, Piotin M, Blanc R, Mazighi M, Bracard S, Anxionnat R, et al. Mothership versus drip and ship for thrombectomy in patients who had an acute stroke: a systematic review and meta-analysis. *J Neurointerv Surg*. 2019;11:14–19. doi: 10.1136/neurintsurg-2018-014249
14. Détraz L, Ernst M, Bourcier R. Stroke transfer and its organizational paradigm: review of organizational paradigms and the impact on outcome. *Clin Neuroradiol*. 2018;28:473–480. doi: 10.1007/s00062-018-0715-z
15. Mistry EA, Mistry AM, Nakawah MO, Chitale RV, James RF, Volpi JJ, Fusco MR. Mechanical thrombectomy outcomes with and without intravenous thrombolysis in stroke patients: a meta-analysis. *Stroke*. 2017;48:2450–2456. doi: 10.1161/STROKEAHA.117.017320
16. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demerschalk BM, Hoh B, et al; 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. doi: 10.1161/STR.0000000000000158
17. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, Schellinger PD, Toni D, de Vries J, White P, et al. European Stroke Organisation (ESO)-European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischemic stroke. *J Neurointerv Surg*. 2019;11:535–538. doi: 10.1136/neurintsurg-2018-014568
18. Asaithambi G, Castle AL, Stein LJ, Marino EH, Ho BM, Wallace-Jackson AC, Hanson SK, Lassig JP. Real-world treatment of large vessel occlusions: combined outcomes of directly presenting and transferred-in patients to a stroke center. *Neurol Res*. 2018;40:637–643. doi: 10.1080/01616412.2018.1460700
19. Gerschenfeld G, Muresan IP, Blanc R, Obadia M, Abrivard M, Piotin M, Alamowitch S. Two paradigms for endovascular thrombectomy after intravenous thrombolysis for acute ischemic stroke. *JAMA Neurol*. 2017;74:549–556. doi: 10.1001/jamaneurol.2016.5823
20. Weber R, Reimann G, Weimar C, Winkler A, Berger K, Nordmeyer H, Hadisurya J, Brassel F, Kitzrow M, Krogias C, et al; Neurovascular Net Ruhr. Outcome and periprocedural time management in referred versus directly admitted stroke patients treated with thrombectomy. *Ther Adv Neurol Disord*. 2016;9:79–84. doi: 10.1177/1756285615617081
21. Perez de la Ossa N, Abilleira S, Dorado L, Urrea X, Ribo M, Cardona P, Giral E, Martí-Fabregas J, Purroy F, Serena J, et al. Access to endovascular treatment in remote areas: analysis of the reperfusion treatment registry of catalonia. *Stroke*. 2016;47:1381–1384.
22. Barlann J, Gerber J, Barlann K, Pallesen LP, Siepmann T, Zerna C, Wojciechowski C, Puetz V, von Kummer R, Reichmann H, et al. Acute endovascular treatment delivery to ischemic stroke patients transferred within a telestroke network: a retrospective observational study. *Int J Stroke*. 2017;12:502–509. doi: 10.1177/1747493016681018
23. Bücke P, Pérez MA, Schmid E, Nolte CH, Bätzner H, Henkes H. Endovascular thrombectomy in acute ischemic stroke: outcome in referred versus directly admitted patients. *Clin Neuroradiol*. 2018;28:235–244. doi: 10.1007/s00062-017-0558-z
24. Park MS, Lee JS, Park TH, Cho YJ, Hong KS, Park JM, Kang K, Lee KB, Kim JG, Lee SJ, et al. Characteristics of the drip-and-ship paradigm for patients with acute ischemic stroke in South Korea. *J Stroke Cerebrovasc Dis*. 2016;25:2678–2687. doi: 10.1016/j.jstrokecerebrovasdis.2016.07.015
25. Park MS, Yoon W, Kim JT, Choi KH, Kang SH, Kim BC, Lee SH, Choi SM, Kim MK, Lee JS, et al. Drip, ship, and on-demand endovascular therapy for acute ischemic stroke. *PLoS One*. 2016;11:e0150668. doi: 10.1371/journal.pone.0150668
26. Pfaff J, Pham M, Herweh C, Wolf M, Ringleb PA, Schönenberger S, Bendszus M, Möhlenbruch M. Clinical outcome after mechanical thrombectomy in non-elderly patients with acute ischemic stroke in the anterior circulation: primary admission versus patients referred from remote hospitals. *Clin Neuroradiol*. 2017;27:185–192. doi: 10.1007/s00062-015-0463-2
27. Sun CH, Nogueira RG, Glenn BA, Connelly K, Zimmermann S, Anda K, Camp D, Frankel MR, Belagaje SR, Anderson AM, et al. "Picture to puncture": a novel time metric to enhance outcomes in patients transferred for endovascular reperfusion in acute ischemic stroke. *Circulation*. 2013;127:1139–1148. doi: 10.1161/CIRCULATIONAHA.112.000506
28. Rinaldo L, Brinjikji W, McCutcheon BA, Bydon M, Cloft H, Kallmes DF, Rabinstein AA. Hospital transfer associated with increased mortality after endovascular revascularization for acute ischemic stroke. *J Neurointerv Surg*. 2017;9:1166–1172. doi: 10.1136/neurintsurg-2016-012824
29. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP, Haussen DC, Hellinger FR Jr, Yavagal DR, Yao TL, et al; 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. doi: 10.1161/CIRCULATIONAHA.117.028920
30. Prothmann S, Schwaiger BJ, Gersing AS, Reith W, Niederstadt T, Felber A, Kurre W. Acute Recanalization of Thrombo-Embolic Ischemic Stroke with pREset (ARTESp): the impact of occlusion time on clinical outcome of directly admitted and transferred patients. *J Neurointerv Surg*. 2017;9:817–822. doi: 10.1136/neurintsurg-2016-012556
31. Strbian D, Ahmed N, Wahlgren N, Lees KR, Toni D, Roffe C, Surakka IL, Tattisumak T; SITS Investigators. Trends in door-to-thrombolysis time in the safe implementation of stroke thrombolysis registry: effect of center volume and duration of registry membership. *Stroke*. 2015;46:1275–1280. doi: 10.1161/STROKEAHA.114.007170
32. Gupta R, Horev A, Nguyen T, Gandhi D, Wisco D, Glenn BA, Tayal AH, Ludwig B, Terry JB, Gershon RY, et al. Higher volume endovascular stroke centers have faster times to treatment, higher reperfusion rates and higher rates of good clinical outcomes. *J Neurointerv Surg*. 2013;5:294–297. doi: 10.1136/neurintsurg-2011-010245
33. Shah S, Xian Y, Sheng S, Zachrisson KS, Saver JL, Sheth KN, Fonarow GC, Schwamm LH, Smith EE. Use, temporal trends, and outcomes of endovascular therapy after interhospital transfer in the United States. *Circulation*. 2019;139:1568–1577. doi: 10.1161/CIRCULATIONAHA.118.036509
34. Bray BD, Campbell J, Cloud GC, Hoffman A, Tyrrell FJ, Wolfe CD, Rudd AG; Intercollegiate Stroke Working Party Group. Bigger, faster? Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. *Stroke*. 2013;44:3129–3135. doi: 10.1161/STROKEAHA.113.001981
35. Chalos V, LeCouffe NE, Uyttenboogaart M, Lingsma HF, Mulder MJHL, Venema E, Treurniet KM, Eshghi O, van der Worp HB, van der Lugt A, et al; MR CLEAN Registry Investigators. Endovascular treatment with or without prior intravenous alteplase for acute ischemic stroke. *J Am Heart Assoc*. 2019;8:e011592. doi: 10.1161/JAHA.118.011592
36. Goyal M, Almekhlafi M, Dippel DW, Campbell BCV, Muir K, Demchuk AM, Bracard S, Davalos A, Guillemin F, Jovin TG, et al; HERMES Collaborators. Rapid alteplase administration improves functional outcomes in patients with stroke due to large vessel occlusions. *Stroke*. 2019;50:645–651. doi: 10.1161/STROKEAHA.118.021840
37. 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. doi: 10.1001/jamaneurol.2018.2424
38. 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. doi: 10.1161/STROKEAHA.116.015321



39. MR CLEAN-NOIV. <https://mrclean-noiv.nl/>. Accessed June 16, 2020.
40. SWIFT DIRECT. SolitaireTM With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT SolitaireTM Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke. <https://www.swift-direct.ch/>. Accessed June 16, 2020.
41. HOME - DIRECT-MT. <http://www.direct-mt.com/>. Accessed June 16, 2020.
42. Yang P, Zhang Y, Zhang L, Zhang Y, Treurniet KM, Chen W, Peng Y, Han H, Wang J, Wang S, et al; DIRECT-MT Investigators. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med*. 2020;382:1981–1993. doi: 10.1056/NEJMoa2001123
43. Demaerschalk BM, Berg J, Chong BW, Gross H, Nystrom K, Adeyoye O, Schwamm L, Wechsler L, Whitchurch S. American telemedicine association: telestroke guidelines. *Telemed J E Health*. 2017;23:376–389. doi: 10.1089/tmj.2017.0006
44. Thorpe SG, Thibeault CM, Canac N, Wilk SJ, Devlin T, Hamilton RB. Decision criteria for large vessel occlusion using transcranial doppler waveform morphology. *Front Neurol*. 2018;9:847. doi: 10.3389/fneur.2018.00847
45. Kellner CP, Sauvageau E, Snyder KV, Fargen KM, Arthur AS, Turner RD, Alexandrov AV. The VITAL study and overall pooled analysis with the VIPS non-invasive stroke detection device. *J Neurointerv Surg*. 2018;10:1079–1084. doi: 10.1136/neurintsurg-2017-013690
46. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, Towfighi A, Whiteley WN, Zahuranc DB; American Heart Association Stroke Council. 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. doi: 10.1161/STR.000000000000160
47. Krebs W, Sharkey-Toppen TP, Cheek F, Cortez E, Larrimore A, Keseg D, Panchal AR. Prehospital stroke assessment for large vessel occlusions: a systematic review. *Prehosp Emerg Care*. 2018;22:180–188. doi: 10.1080/10903127.2017.1371263
48. Perez de la Ossa N, Carrera D, Gorchs M, Querol M, Millan M, Gomis M, Dorado L, Lopez-Cancio E, Hernandez-Perez M, Chicharro V, et al. Design and validation of a prehospital stroke scale to predict large arterial occlusion: the rapid arterial occlusion evaluation scale. *Stroke*. 2014;45:87–91.
49. Kesinger MR, Sequeira DJ, Buffalini S, Guyette FX. Comparing National Institutes of Health Stroke Scale among a stroke team and helicopter emergency medical service providers. *Stroke*. 2015;46:575–578. doi: 10.1161/STROKEAHA.114.007850
50. Mazya MV, Berglund A, Ahmed N, von Euler M, Holmin S, Laska AC, Mathé JM, Sjöstrand C, Eriksson EE. Implementation of a prehospital stroke triage system using symptom severity and teleconsultation in the Stockholm Stroke Triage Study. *JAMA Neurol*. 2020;77:691–699. doi: 10.1001/jamaneurol.2020.0319
51. Ahmed N, Audebert H, Turc G, Cordonnier C, Christensen H, Sacco S, Sandset EC, Ntaios G, Charidimou A, Toni D, et al. Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11–13 November 2018. *Eur Stroke J*. 2019;4:307–317. doi: 10.1177/2396987319863606
52. John S, Stock S, Masaryk T, Bauer A, Cerejo R, Uchino K, Winners S, Rasmussen P, Hussain MS. Performance of CT angiography on a mobile stroke treatment unit: implications for triage. *J Neuroimaging*. 2016;26:391–394. doi: 10.1111/jon.12346
53. Czap AL, Singh N, Bowry R, Jagolino-Cole A, Parker SA, Phan K, Wang M, Sheth SA, Rajan SS, Yamal JM, et al. Mobile stroke unit computed tomography angiography substantially shortens door-to-puncture time. *Stroke*. 2020;51:1613–1615. doi: 10.1161/STROKEAHA.119.028626
54. Fatima N, Saqqur M, Hussain MS, Shuaib A. Mobile stroke unit versus standard medical care in the management of patients with acute stroke: a systematic review and meta-analysis. *Int J Stroke*. 2020;15:595–608. doi: 10.1177/1747493020929964
55. Kim J, Easton D, Zhao H, Coote S, Sookram G, Smith K, Stephenson M, Bernard S, Parsons M, Yan B, et al. Economic evaluation of the Melbourne Mobile Stroke Unit. *Int J Stroke*. 2020;15. doi: 10.1177/1747493020929944
56. Walter S, Kostopoulou P, Haass A, Helwig S, Keller I, Licina T, Schleichriemen T, Roth C, Papanagiotou P, Zimmer A, et al. Bringing the hospital to the patient: first treatment of stroke patients at the emergency site. *PLoS One*. 2010;5:e13758. doi: 10.1371/journal.pone.0013758
57. Brekenfeld C, Goebell E, Schmidt H, Henningsen H, Kraemer C, Tebben J, Flottmann F, Thomalla G, Fiehler J. 'Drip-and-drive': shipping the neurointerventionalist to provide mechanical thrombectomy in primary stroke centers. *J Neurointerv Surg*. 2018;10:932–936. doi: 10.1136/neurintsurg-2017-013634
58. Seker F, Möhlenbruch MA, Nagel S, Ulfert C, Schönenberger S, Pfaff J, Ringleb PA, Steiner T, Bendszus M, Herweh C. Clinical results of a new concept of neurothrombectomy coverage at a remote hospital—"drive the doctor". *Int J Stroke*. 2018;13:696–699. doi: 10.1177/1747493018765267
59. Uchiyama N, Misaki K, Mohri M, Kamide T, Hirota Y, Higashi R, Minamide H, Kohda Y, Asahi T, Shoin K, et al. Treatment result in the initial stage of Kanazawa mobile embolectomy team for acute ischemic stroke. *Neurol Med Chir (Tokyo)*. 2016;56:737–744. doi: 10.2176/nmc.oa.2016-0101
60. Wei D, Oxley TJ, Nistal DA, Mascitelli JR, Wilson N, Stein L, Liang J, Turkheimer LM, Morey JR, Schwegel C, et al. Mobile interventional stroke teams lead to faster treatment times for thrombectomy in large vessel occlusion. *Stroke*. 2017;48:3295–3300. doi: 10.1161/STROKEAHA.117.018149
61. Cerejo R, John S, Buletko AB, Taqui A, Itrat A, Organek N, Cho SM, Sheikh L, Uchino K, Briggs F, et al. A mobile stroke treatment unit for field triage of patients for intraarterial revascularization therapy. *J Neuroimaging*. 2015;25:940–945. doi: 10.1111/jon.12276
62. Janssen PM, Venema E, Dippel DWJ. Effect of workflow improvements in endovascular stroke treatment. *Stroke*. 2019;50:665–674. doi: 10.1161/STROKEAHA.118.021633
63. McTaggart RA, Yaghi S, Cutting SM, Hemendinger M, Baird GL, Haas RA, Furie KL, Jayaraman MV. Association of a primary stroke center protocol for suspected stroke by large-vessel occlusion with efficiency of care and patient outcomes. *JAMA Neurol*. 2017;74:793–800. doi: 10.1001/jamaneurol.2017.0477
64. Diaz MA, Hendey GW, Bivins HG. When is the helicopter faster? A comparison of helicopter and ground ambulance transport times. *J Trauma*. 2005;58:148–153. doi: 10.1097/O1.ta.0000124264.43941.41
65. Walter S, Zhao H, Easton D, Bil C, Sauer J, Liu Y, Lesmeister M, Grunwald IQ, Donnan GA, Davis SM, et al. Air-mobile stroke unit for access to stroke treatment in rural regions. *Int J Stroke*. 2018;13:568–575. doi: 10.1177/1747493018784450
66. Hui FK, El Mekabaty A, Schultz J, Hong K, Horton K, Urrutia V, Naqvi I, Brast S, Lynch JK, Nadareishvili Z. Helistroke: neurointerventionalist helicopter transport for interventional stroke treatment: proof of concept and rationale. *J Neurointerv Surg*. 2018;10:225–228. doi: 10.1136/neurintsurg-2017-013050
67. Panesar SS, Volpi JJ, Lumsden A, Desai V, Kleiman NS, Sample TL, Elkins E, Britz GW. Telerobotic stroke intervention: a novel solution to the care dissemination dilemma. *J Neurosurg*. 2019;1:1–8. doi: 10.3171/2019.8.JNS191739
68. 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. doi: 10.1161/STROKEAHA.118.021381
69. Vidale S, Agostoni EC. Organizing healthcare for optimal acute ischemic stroke treatment. *J Clin Neurol*. 2020;16:183–190. doi: 10.3988/jcn.2020.16.2.183
70. Abilleira S, Pérez de la Ossa N, Jiménez X, Cardona P, Cocho D, Purroy F, Serena J, Román LS, Urrea X, Vilaró M, et al. 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 (RACECAT): study protocol of a cluster randomized within a cohort trial. *Int J Stroke*. 2019;14:734–744. doi: 10.1177/1747493019852176
71. Behrntz A, Johnsen SP, Valentin JB, Gude MF, Blauenfeldt RA, Andersen G, Majolie CB, Fisher M, Simonsen CZ. TRIAGE-STROKE: Treatment strategy in Acute large vessel occlusion: prioritize IV or endovascular treatment—a randomized trial. *Int J Stroke*. 2020;15:103–108. doi: 10.1177/1747493019869830
72. Monks T, Pitt M, Stein K, James M. Maximizing the population benefit from thrombolysis in acute ischemic stroke: a modeling study of in-hospital delays. *Stroke*. 2012;43:2706–2711. doi: 10.1161/STROKEAHA.112.663187
73. Lahr MM, van der Zee DJ, Luijckx GJ, Vroomen PC, Buskens E. A simulation-based approach for improving utilization of thrombolysis in acute brain infarction. *Med Care*. 2013;51:1101–1105. doi: 10.1097/MLR.0b013e3182a3e505
74. Lahr MM, van der Zee DJ, Luijckx GJ, Vroomen PC, Buskens E. Centralising and optimising decentralised stroke care systems: a simulation study on short-term costs and effects. *BMC Med Res Methodol*. 2017;17:5. doi: 10.1186/s12874-016-0275-3
75. Churilov L, Fridriksdottir A, Keshikaran M, Mosley I, Flitman A, Dewey HM. Decision support in pre-hospital stroke care operations: a case of using simulation to improve eligibility of acute stroke patients for thrombolysis treatment. *Comput Oper Res*. 2013;40:2208–2218.

76. Freriks RD, Mierau JO, Buskens E, Pizzo E, Luijckx GJ, van der Zee DJ, Lahr MMH. Centralising acute stroke care within clinical practice in the Netherlands: lower bounds of the causal impact. *BMC Health Serv Res*. 2020;20:103. doi: 10.1186/s12913-020-4959-3

77. Adeoye O, Albright KC, Carr BG, Wolff C, Mullen MT, Abruzzo T, Ringer A, Khatri P, Branas C, Kleindorfer D. Geographic access to acute stroke care in the United States. *Stroke*. 2014;45:3019–3024. doi: 10.1161/STROKEAHA.114.006293



# Stroke