Stroke is a major health-care problem that represents a leading cause of death and also the top cause of disability in adulthood. In recent years there has been a significant paradigm shift in treatments for acute ischemic stroke to favor earlier reperfusion therapy, mainly using the systemic infusion of recombinant tissue plasminogen activator. Subsequent trials found that combining this treatment with endovascular therapy was effective in selected patients. The increased complexity of acute stroke treatments has resulted in a substantial reorganization of stroke care. This review reports on the evolution of acute ischemic stroke treatment and describes the main organizational models based on the hub-and-spoke system. The lack of evidence for comparisons of the effectiveness of different paradigms means that some decision-analysis models predicting the best organizational pathways are also reported, with a particular emphasis on the workflow timing in the prehospital and in-hospital settings. Major benchmarks and performance measures are also reported, focusing on the timing of interventions and rates of process indicators. Finally, future directions are illustrated, including using telemedicine for stroke, mobile stroke units, and artificial intelligence and automated machines to produce software for detecting large-vessel occlusion.

**Key Words** stroke, fibrinolysis, thrombectomy, critical pathways.

**INTRODUCTION**

Stroke is a major health-care problem that represents a leading cause of death and the top cause of disability in adulthood. Acute cerebrovascular disease accounts up to an estimated 13 million events worldwide annually, which mostly comprise ischemic strokes, with more than 5 million fatalities. At the same time, about 18 million stroke survivors cannot perform their daily activities independently, and hence they present challenges to their families, societies, and health-care systems. In the US, 7 million people older than 20 years experience a stroke annually, and the overall prevalence of this disease is estimated to be 2.5%. In Europe, stroke is the second-most-common single cause of death, accounting up to 1.3 million events yearly. Projections show that the overall stroke burden will be 35% greater by 2050.

**EVOLUTION OF ACUTE STROKE TREATMENTS**

Over the last 20 years there has been a significant paradigm shift in treatments for acute ischemic stroke treatment to favor earlier reperfusion therapy. The "time is brain" rule was assumed in the workflow management of these patients, and all reperfusion treatments were performed under this fundamental criterion. The first randomized controlled trials (RCTs) compared the systemic infusion of recombinant tissue plasminogen activator with...
The publication of two RCTs. These studies increased the rule was changed to “each brain has each time” in 2018 by the bridging therapy with medical treatment alone found an OR of 1.82 (95% CI=1.53–2.16), as presented in Fig. 1. An overall pooled analysis of previously published meta-analyses comparing systemic thrombolysis with endovascular treatment (ET) found no differences between the two therapies in their efficacy in obtaining a good functional outcome,10-12 while other RCTs from 2015 and following years produced very different results.13-19 The key factors for the clinical success were represented by the presence of large-vessel occlusion (LVO) as an eligibility criterion and the use of latest-generation devices. Many meta-analyses have confirmed the pooled results of these trials, and many international guidelines have included the combination of systemic thrombolysis and mechanical thrombectomy as the gold-standard treatment for patients with LVO within 6 hours from symptom onset. In a patient-level meta-analysis using data from five RCTs, the best odds ratio (OR) obtained was 2.49 [95% confidence interval (CI)=1.76–3.53],20 with other study-level meta-analyses finding ORs between 1.56 and 1.71.21-23 An overall pooled analysis of previously published meta-analyses comparing the bridging therapy with medical treatment alone found an OR of 1.82 (95% CI=1.53–2.16), as presented in Fig. 1.

The previous paradigm expressed by the “time is brain” rule was changed to “each brain has each time” in 2018 by the publication of two RCTs.24,25 These studies increased the therapeutic window for ET in patients selected using neuroimaging at up to 24 hours from symptom onset. A recent meta-analysis confirmed positive intervention outcomes also beyond 6 hours from stroke onset.26 However, there are no significant results available for comparisons between bridging therapy and direct ET, even if combining the two treatments seems to be slightly superior than a single-therapy approach.27-29 In particular, these meta-analyses produced ORs between 1.18 and 1.21, and the overall pooled analysis of these studies resulted in an OR of 1.20 (95% CI=1.01–1.47) in favor of the bridging therapy. There are currently some ongoing RCTs attempting to clarify this issue.

**ORGANIZATIONAL MODELS FOR ACUTE STROKE TREATMENT**

When organizing systems for managing acute ischemic stroke, two main phases have to be considered: the prehospital and in-hospital settings. The first phase requires a prompt activation of emergency medical services to perform an initial clinical evaluation of the patient. A first assessment of suspected stroke is recommended by the main international guidelines. According to the evolution of acute stroke treatment and the indication for endovascular therapy, in recent years several prehospital stroke scales for detecting LVO have been investigated. However, a previous meta-analysis found wide variations in the accuracies of these scales. In light of these findings and based on the current guidelines, the use of a prehospital scale for LVO is not recommended when selecting the hospital destination for stroke patients. However, in the case of positive stroke scale (e.g., the Cincinnati prehospital scale), a prenotification to the transferring hospital is also useful for reducing in-hospital delays.

The evolution of ischemic stroke treatment and the associated increasing procedure complexity determined that the systems of stroke care have been organized to transport patients in the nearest hospital with a initial possibility to perform reperfusion therapy (i.e., a PSC). These centers are organized to manage stroke patients by diagnosing LVO and treating it with intravenous thrombolysis (IVT). For this reason PSCs require the availability of vascular neurologists, brain CT and CT angiography, neurosonology, early rehabilitation, and beds with continuous monitoring. Further evidence increased the possibility of treatment with ET, but

| Study or subgroup | IVT+ET | IVT | Odds ratio IVT+ET | Odds ratio IVT |
|-------------------|--------|-----|------------------|----------------|
| Total (95% CI)    | 7,457  | 6,571 | 1.82 [1.53–2.16] |                 |
| Total events      | 3,340  | 2,053 | 100.0            |                 |
| Heterogeneity:    |        |      |                  |                 |
| Tau2=0.05; Chi2=41.62, df=7 (p<0.00001); I²=83% |  |
| Test for overall effect: Z=6.80 (p<0.00001) |  |

**Fig. 1.** Forest plot of the pooled analysis considering the previous main published meta-analyses comparing bridging therapy with medical treatment alone. CI: confidence interval, ET: endovascular treatment, IVT: intravenous thrombolysis, M-H: Mantel-Haenszel method.
fewer hospitals are able to perform these procedures [called comprehensive stroke centers (CSCs)]. CSCs require facilities that guarantee the availability of more-complex procedures such as acute ET and neurosurgical interventions. For these reasons, neurosurgeons, neurointerventionalists, or interventional radiologists are needed in these centers. Different national laws and declarations as well as recommendations by scientific societies have defined specific hospital characteristics for classifying PSCs and CSCs by considering structural settings and the presence of certain departments and technological equipments (Table 1). In each stroke center the workflow has to be as fast as possible, including the use of multidisciplinary equipment (Fig. 2).

In light of the previous evidence concerning treatments for acute ischemic stroke, three main organizational models have been introduced: mothership (MS), drip and ship (DS), and drip and drive (DD; also called trip and treat). In the MS paradigm, a patient with suspected stroke is directly transported to the CSC where acute management ensures all diagnostic and therapeutic phases are applied, starting from initial neurological evaluation and ending with mechanical thrombectomy in an angiosuite. All procedures are performed in the same hospital. In the DS model, the patient with suspected stroke is transported to the nearest PSC (called a spoke center) to diagnose the disease and detect its etiology. IVT has to be administered if this is indicated, and if LVO is detected the patient is transported to the CSC of the territorial

Table 1. Requirements and standards of care for PSCs and CSCs

| Standards of care                                      | PSCs                                                                 | CSCs                                                                 |
|-------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|
| Multiprofessional competences in hospitals            | Neurosurgical on-call availability (also in other hospitals)         | The same as PSCs and 500 admissions/year at least                     |
| Dedicated neurologists and nurses                      | Neurosonology with Doppler ultrasonography and echocardiography      | 24/7 neuroradiology with CT (64 multislices) and CT angiography, MRI with DWI and PWI, and MR angiography |
| One bed with continuous monitoring (at least)         | 24/7 availability of CT and CT angiography (at least 16 multislices) and/or MRI (also with DWI) and MR angiography | Endovascular interventional unit                                    |
| Early rehabilitation                                   | Linking with CSCs and rehabilitation units                           | 24/7 neurosurgery                                                    |
| IVT                                                   |                                                                      | 24/7 vascular surgery                                                |
| Neurosurgeons on-call availability                     |                                                                      | Cerebral angiography                                                 |
| Neurosonology                                         |                                                                      | Intra-arterial thrombolysis (emergency), mechanical thrombectomy (emergency), and extracranial and intracranial stenting |
| Neurosurgeons on-call availability                     |                                                                      | Decompressive hemicraniectomy                                        |

CSC: comprehensive stroke center, DWI: diffusion-weighted imaging, IVT: intravenous thrombolysis, MR: magnetic resonance, PSC: primary stroke center, PWI: perfusion-weighted imaging.

Fig. 2. Examples of in-hospital workflows in PSCs (A) and CSCs (B). CSC: comprehensive stroke center, ER: emergency department, PSC: primary stroke center, Revasc: revascularization.
network (called the hub center) by primary transportation. In this organizational model, we hypothesized that if the place of the rescue and the PSC are separated by more than 60 minutes for transportation by ambulance, helicopter use is indicated and the transport should be centralized to the referring CSC of that territory. Finally, the DD paradigm consists of a mobile interventional stroke team comprising interventionalists and radiological technologists that travels from a central hospital (the CSC) to treat stroke patients presenting at peripheral hospitals with interventional capacity.

The DD paradigm is the least common worldwide, while the DS organizational model is the most common. The popularity of the DS paradigm is due to several factors including the rationalization of resources, the distribution of few CSCs and more PSCs, the reduced number of neurointerventionalists required, and the availability of an efficient emergency transportation system (Table 2). Although it remains unclear which type of organizational model is superior in achieving good functional outcomes, the American Heart Association (AHA)/American Stroke Association (ASA) has recommended the MS paradigm if bypassing a PSC for a CSC increases the travel time by less than 15 minutes. A recent meta-analysis of observational studies showed that the 90-day outcome is better in patients who are directly admitted to CSCs (adjusted relative risk=0.87, 95% CI=0.77–0.98). However, a multicenter registry found an association between the DS paradigm and poor functional outcomes. These contradictory results indicate that RCTs are needed to provide robust findings for determining the best organizational paradigm, also while applying different instruments for a prehospital triage, such as a stroke scale predicting LVO or a mobile stroke ambulance. Some trials with these aims are ongoing or in a start-up phase (i.e., direct transfer to an Endovascular Center compared to transfer to the closest Stroke Center in acute stroke patients with suspected large vessel occlusion in Catalonia – RACECAT trial, Spain, and mothership versus drip and ship for endovascular treatment in large-vessel occlusion strokes - MODEL trial, in Northern Italy). A critical point in choosing the best organizational paradigm is the financial cost. The optimal economic trade-off might be achieved by distributing the high-level centers according to the travelling distances between different CSCs and PSCs and to the population density in a defined territory or geographical area. The territorial organization and the economic investment for CSCs could start by determining the “isochrones” of the hub centers. PSCs should then be placed along these temporal lines that have a travelling cut-off time of 60 minutes. An example of this geographical distribution is presented in Fig. 3.

DECISION-ANALYSIS MODELS TO PREDICT THE BEST ORGANIZATIONAL PATHWAYS

The current uncertainty concerning the best paradigm for the organizational pathway stimulated the development of different decision-analysis models based on probability the-

| Model            | Advantages                                      | Disadvantages                      |
|------------------|-------------------------------------------------|-----------------------------------|
| Mothership       | All procedures performed in the same center     | Potentially longer onset-to-needle time |
|                  | No secondary transfers                           | Smaller number of CSCs            |
|                  | Shorter door-to-groin time in LVO                | Higher workload                   |
| Drip and ship    | Shorter onset-to-needle time                     | Longer door-to-groin time in LVO   |
|                  | Rationalization of the geographical distribution of the PSC and CSC | Cost of medical transfers         |
|                  | Rapid initial clinical assessment                |                                   |
| Drip and drive   | No secondary transfers for patients              | Long door-to-groin time            |
|                  | Shorter onset-to-needle time                     | Different angiosuite settings for neurointerventionists |

CSC: comprehensive stroke center, LVO: large-vessel occlusion, PSC: primary stroke center.

Fig. 3. Distribution of hub centers and spoke centers using “isochrones.” Black lines represent the distance from hub centers for a maximum traveling time of 80 minutes as calculated using a Google Maps application programming interface. □ Comprehensive stroke center, ○ primary stroke center.
ory. Different steps for acute stroke management were considered in each model, with the final endpoint represented by the best clinical outcome. Two main studies provided statistical models to identify the organizational paradigm with the highest probability of achieving good functional outcomes. In the study of Milne et al., the DS model showed effectiveness for any PSCs that are remote from CSCs, regardless of the door-to-needle time (DNT). In the case of the PSC and CSC being in close proximity, the DS paradigm remained effective only if the DNT for the PSC was shorter than 30 minutes. On the other hand, the MS scenario was more effective only if bridging therapy was effectively applied in the CSC. In the model of Holodinsky et al., the DS paradigm was effective if the patients were close to a PSC and this center was more than 45 minutes from a CSC, regardless of the DNT. The same model was effective also when the distance between the PSC and CSC was 10–45 minutes with a DNT of shorter than 30 minutes. Finally, if the DNT was longer than 60 minutes, the MS model was effective if the distance between the PSC and CSC was shorter than 30 minutes.

The results of a previous geographical modelling analysis to quantify the impact of PSC and CSC destination policies showed low time cost values—adding median durations of only 3.1 and 8.3 minutes—when bypassing the closest PSC and CSC, respectively. A recent decision-analysis model introduced LVO screening methods and key time metrics, and found that the DS paradigm was superior when LVO screening was not performed, while the MS paradigm was superior when LVO positivity was found in formal screening and the additional transport time to a CSC was shorter than 23 minutes. Transferring these results in the real-world setting with a PSC workflow slower than the ideal settings indicates that the MS model is superior to the DS model even when formal LVO screening is available.

In conclusion, different decision-analysis models have yielded results favouring the DS paradigm only if the workflow times in PSCs are optimized with a DNT of shorter than 30 minutes. Fig. 4 summarizes the effectiveness of the two main probabilistic models (MS and DS).

**MAJOR BENCHMARKS AND PERFORMANCE MEASURES FOR ACUTE STROKE TREATMENT**

A frequent situation involves a goal being identified by a panel of experts and set as a benchmark as an objective to strive for. The key aspect of benchmarking is that it forms part of a comprehensive and participative policy of continuous quality improvement. Benchmarking should be based on voluntary and active collaboration among several organizations to create a spirit of competition, to apply the best practices, and to achieve the goal of reaching the defined benchmark. According to this definition, the organizational model for acute stroke treatment is based on a network in which different hospitals that collaborate so as to create an uninterrupted pathway for managing these patients.

The following major time benchmarks for acute ischemic stroke treatment are all tracked by international standard of recommendations, and they were chosen by a group of experts at the National Institutes of Health; they have subsequently been adopted by the ASA:

- Door to medical doctor: 10 minutes.
- Door to neurologist/strokologist: 15 minutes.
- Door to imaging: 25 minutes.
- Door to image reading: 45 minutes.
- Door to needle: 60 minutes.
- Door to groin: 120 minutes.
- Groin to start of revascularization: 45 minutes.
- Clinical outcomes for ET of at least 30%, with a score on the modified Rankin Scale of 0–2 at 90 days.

The stroke Joint Commission provided some core stroke measures related to the overall care of stroke patients, such as venous thromboembolism prophylaxis, discharged on antithrombotic therapy, anticoagulation therapy for atrial fibrillation, and thrombolytic therapy. However, this commission also elucidated some performance measures for PSCs.
and CSCs that could have benchmarks:

1) Rate of patients for whom the score on the National Institutes of Health Stroke Scale (NIHSS) is recorded on arrival.
2) Rate of eligible patients treated with IVT within 60 minutes of arrival.
3) Rate of patients who arrive by 3.5 hours and are treated by 4.5 hours.
4) Rate of patients with any score on the modified Rankin Scale at 90 days.
5) Rate of patients with stroke severity measurement on arrival using the NIHSS.
6) Rate of patients with a symptomatic intracranial hemorrhage treated with both IVT and ET within 36 hours.
7) Median time to recanalization therapy for ET patients.
8) Rate of patients treated with ET exhibiting at least thrombolysis in cerebral infarction (TICI) 2b recanalization.

**FUTURE DIRECTIONS**

The increasing burden of ischemic stroke will increase the number of patients eligible for ET, and the health-care organizational model has to consider this changing epidemiology. Rapid technological developments will make it possible to also apply artificial intelligence (AI) and automated machines to produce software to promptly detect LVO and brain mismatch areas. Early in 2018 the FDA approved an AI algorithm for use in a clinical decision support system in a triage setting. This algorithm, called Viz. AI, is able to analyze CT and CT angiography scans, and can automatically identify suspected LVO strokes and promptly alert the on-call stroke team, including that in other hub centers. Another application is the development of software that automatically calculates mismatch areas, also when no radiologists or neuroradiologists expert in CT perfusion are present in PSCs. Finally, some software and apps provide platforms with text messaging and calling for facilitating communication between clinical teams in hub-and-spoke networks. However, the ability of these AI systems to provide useful information is crucially dependent on the correctness of input data and the method used to instruct the model.

In addition to these promising applications, the use of mobile stroke units and CT ambulances have shown positive results in previous studies, by shortening time metrics and increasing the number of patients eligible for acute ischemic stroke treatment and concomitant transportation to the most-appropriate center for receiving the acute treatment. The use of helicopters mitigates larger distances between PSCs and CSCs. The application of telemedicine for stroke provides the possibility of treating patients with IVT by a rapid strokeologist evaluation for intravenous tissue plasminogen activator eligibility in centers without expertise and all of the required facilities. This application could also facilitate the sharing of neuroimaging facilities that would improve the ability to detect LVO or the volume of the damaged ischemic area, using also apps derived from AI as described above. Previous AHA/ASA guidelines have recommended the use of telemedicine for stroke, identifying also the quality of application and measurable outcomes. The future use of telemedicine for stroke to cover extensive geographical areas will increase the application of IVT when vascular neurologists or strokologists are not present, as well as the use of software or apps based on AI. The use of these technologies will reduce temporal delays in acute stroke management, as well as the effective distance between centers with different facilities.

Regarding the organizational model, the MS and DS paradigms could also coexist in the same geographical area. A mixed organizational model considering urban and rural areas could be implemented based on which performs better (e.g., MS in urban areas and DS in rural areas), based on information about traffic levels that potentially slow the transportation of patients. However, the feasibility of such a mixed organizational network system needs to be validated in a future RCT.

**CONCLUSIONS**

Bridging therapy in acute ischemic stroke involving the administration of IVT followed by mechanical thrombectomy has become the current standard of care for patients with LVO. However, the best organizational paradigm for this acute treatment remains to be defined, and the current international guidelines do not recommend bypassing PSCs since this might result in lower-accuracy screening tools being used to detect LVO. In light of these observations, the DS model remains today the paradigm that shows the best ratio of clinical effectiveness to financial cost. Further studies are required to better understand the best health-care organizational model for ischemic stroke patients.

**Author Contributions**

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**Conflicts of Interest**

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol* 2016;15:913-924.

2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation* 2019;139:e56-e528.

3. Wilkins E, Wilson I, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, et al. European Cardiovascular Disease Statistics 2017. Brussels: European Heart Network, 2017.

4. Truelsen T, Pichowiak R, Bonita R, Mathers C, Bogousslavsky J, Boyesen G. Stroke incidence and prevalence in Europe: a review of available data. *Eur J Neurol* 2006;13:581-598.

5. United Nations, Department of Economic and Social Affairs, Population Division. World population aging 2017-highlights. New York, NY: United Nations, 2017.

6. Saver JL. Time is brain—quantified. *Stroke* 2006;37:263-266.

7. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-1587.

8. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA* 1995;274:1017-1025.

9. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-1329.

10. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013;368:893-909.

11. Ciccone A, Valvasorri L, Nichelatti M, Spogo A, Ponzio M, Sterzi R, et al. Endovascular treatment for acute ischemic stroke. *N Engl J Med* 2013;368:904-913.

12. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med* 2013;368:914-923.

13. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11-20.

14. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019-1030.

15. Jovin TJG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015;372:2296-2306.

16. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015;372:2285-2295.

17. Campbell BC, Mitchell PJ, KLEINIG TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;372:1009-1018.

18. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THROMBE): a randomised controlled trial. *Lancet Neurology* 2016;15:1138-1147.

19. Muir KW, Ford GA, Messow CA, Ford I, Murray A, Clifton A, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurosurg Psychiatry* 2017;88:38-44.

20. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723-1731.

21. Badihwalla JH, Nassiri F, Alhazzani W, Selim MH, Farrokhyar F, Spears J, et al. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. *JAMA* 2015;314:1832-1843.

22. Rodrigues FB, Neves JB, Caldeira D, Ferro JM, Ferreira JJ, Costa J. Endovascular treatment versus medical care alone for ischaemic stroke: systematic review and meta-analysis. *BMJ* 2016;353:i1754.

23. Vidale S, Agostoni E. Endovascular treatment of ischemic stroke: an updated meta-analysis of efficacy and safety. *Vasc Endovascular Surg* 2017;51:215-219.

24. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018;378:708-718.

25. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhava P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;378:11-21.

26. Vidale S, Longoni M, Valvassori L, Agostoni E. Mechanical thrombectomy in strokes with large-vessel occlusion beyond 6 hours: a pooled analysis of randomized trials. *J Clin Neurol* 2018;14:407-412.

27. Mistry EA, Mistry AM, Nakawah MG, Chitale RV, James RF, Volpi JJ, et al. Mechanical thrombectomy outcomes with and without intravenous thrombolysis in stroke patients: a meta-analysis. *Stroke* 2017;48:2450-2456.

28. Khan P, Dmytriw AA, Maingard J, Assadi H, Griessenauer CJ, Ng W, et al. Endovascular thrombectomy alone versus combined with intravenous thrombolysis. *World Neurosurg* 2017;108:850-858.e2.

29. Kaesmacher J, Mordasini P, Arnold M, López-Cancio E, Cerdà N, Boeckel-Behrens T, et al. Direct mechanical thrombectomy in TPA-eligible and -eligible patients versus the bridging approach: a meta-analysis. *J Neurinterv Surg* 2019;11:20-27.

30. Vidale S, Agostoni E. Prehospital stroke scales and large vessel occlusion: a systematic review. *Acta Neurol Scand* 2018;138:24-31.

31. Agostoni E, Carolei A, Micieli G, Provinciali L, Tonici D, Vidale S. The organisation of the acute ischemic stroke management: key notes of the Italian Neurological Society and of the Italian Stroke Organization. *Neurologia* 2018;39:415-422.

32. American Heart Association, Severity-based Stroke Triage Algorithm for EMS [Internet]. Dallas, TX: American Heart Association; 2010 [cited 2019 Dec 1]. Available from: https://www.heart.org/-/media/files/professional/quality-improvement/mission-lifeline/extent-based-stroke-triage-algorithm-for-ems-ucm_498615.pdf?la=en&hash=BF7B28286E1DEE20045BC00CCEB1442D09A20E768.

33. Ismail M, Armoiry X, Tau N, Zhu F, Sadeh-Gonik U, Piotin M, et al. Mothership versus drip and ship for thrombectomy in patients who had an acute stroke: a systematic review and meta-analysis. *J Neurinterv Surg* 2019;11:14-19.

34. Froehle MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Khcznik RP, et al. 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.

35. Milne MS, Holodinsky JK, Hill MD, Nygren A, Qiu C, Goyal M, et al. Drip ’n ship versus mothership for endovascular treatment: modeling the best transportation options for optimal outcomes. *Stroke* 2017;48:791-794.

36. Holodinsky JK, Williamson TS, Kamal N, Mayank D, Hill MD, Goyal M. Drip and ship versus direct to comprehensive stroke center. *Stroke* 2017;48:233-238.

37. Mullen MT, Pajerowski W, Messé SR, Mechem CC, Jia J, Abboud M, et al. Geographic modeling to quantify the impact of primary and comprehensive stroke center destination policy. *Stroke* 2018;49:1021-1023.

38. Xu Y, Parikh NS, Jiao B, Willey JZ, Boehme AK, Elkind MS. Decision analysis model for prehospital triage of patients with acute stroke. *Stroke* 2019;50:970-977.

39. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bamhakidis
NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.

40. The Joint Commission (US). Stroke [Internet]. Oakbrook Terrace, IL: The Joint Commission [cited 2019 Apr 30]. Available from: https://www.jointcommission.org/stroke.

41. Austein F, Riedel C, Kerby T, Meyne J, Binder A, Lindner T, et al. Comparison of perfusion CT software to predict the final infarct volume after thrombectomy. Stroke 2016;47:2311-2317.

42. Calderon VJ, Kasturiarachi BM, Lin E, Bansal V, Zaidat OO. Review of the Mobile Stroke Unit experience worldwide. Interv Neurol 2018;7:347-358.

43. Wechsler LR, Demaerschalk BM, Schwamm LH, Adeoye OM, Audebert HJ, Fanale CV, et al. Telemedicine Quality and outcomes in stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2017;48:e3-e25.

44. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 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.

45. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, 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: neurintsurg-2018-014569.

46. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, et al. 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.

47. Balami JS, Sutherland BA, Edmunds LD, Grunwald IQ, Neuhaus AA, Hadley G, et al. A systematic review and meta-analysis of randomized controlled trials of endovascular thrombectomy compared with best medical treatment for acute ischemic stroke. Int J Stroke 2015;10:1168-1178.

48. Campbell BC, Hill MD, Rubiera M, Monen BK, Demchuk A, Donnan GA, et al. Safety and efficacy of solitaire stent thrombectomy: individual patient data meta-analysis of randomized trials. Stroke 2016;47:798-806.

49. Elgendy IY, Kumbhani DJ, Mahmoud A, Bhatt DL, Bavry AA. Mechanical thrombectomy for acute ischemic stroke a meta-analysis of randomized trials. J Am Coll Cardiol 2015;66:2498-2505.

50. Singh B, Parsaik AK, Prokop LJ, Mittal MK. Endovascular therapy for acute ischemic stroke: a systematic review and meta-analysis. Mayo Clin Proc 2013;88:1056-1065.