Stroke systems of care in high-income countries: What is optimal?

Peter Langhorne PhD, Professor, University of Glasgow, Institute of Cardiovascular and Medical Sciences, New Lister Building, Royal Infirmary, 10-16 Alexandra Parade, Glasgow G31 2ER, UK.

Heinrich J Audebert MD, Professor, Charité-Universitätsmedizin Berlin, Department of Neurology and Center for Stroke Research Berlin (CSB), Hindenburgdamm 30, 12203 Berlin, Germany.

Dominique A Cadilhac PhD, Professor, Monash University, Department of Medicine, School of Clinical Sciences at Monash Health, Clayton VIC 3168, Australia.

Joosup Kim PhD, Monash University, Department of Medicine, School of Clinical Sciences at Monash Health, Clayton VIC 3168, Australia.

Patrice Lindsay PhD, Heart and Stroke Foundation of Canada, Toronto, Ontario M4P 1E4, Canada.

Corresponding author: Peter Langhorne PhD, University of Glasgow, Institute of Cardiovascular and Medical Sciences, New Lister Building, Royal Infirmary, 10-16 Alexandra Parade, Glasgow G31 2ER, UK. Email: Peter.Langhorne@glasgow.ac.uk, Telephone +44 (0)141 201 8510.

Summary

Stroke is a complex, time-sensitive, medical emergency that requires well-functioning systems of care to optimise treatment and improve patient outcomes. Education and training campaigns are needed to improve both the recognition of stroke among the general public and the response of emergency medical services. Specialised stroke ambulances (mobile stroke units) have been piloted in many cities to speed up the diagnosis, triage and emergency treatment of people with acute stroke symptoms. Hospital-based interdisciplinary stroke units remain the central feature of a modern stroke service. Many have now developed a role in the very early phase (hyperacute units) plus outreach for patients who return home (early supported discharge services). Different levels (comprehensive and primary) of stroke centre and telemedicine networks have been developed to coordinate the various service components with specialist investigations and interventions including rehabilitation. Major challenges include balancing the resources for stroke across the whole patient journey including the rapid, accurate triage of those patients who require highly specialised treatment in comprehensive stroke centres and developing technology to improve communication across different parts of a service. (178 words)

Introduction

Stroke is recognised as a global health problem[1] and in many high income countries, stroke accounts for over 5% of health expenditure.[2] The organisation of services has gained particular prominence over the last two decades with the recognition that the timely delivery of best-practice stroke care can improve patient outcomes.[2]

We review the organisation of services for people who have had a stroke in a high-income country, with particular reference to Western Europe, North America, and Australia. While we try to focus on evidence of effectiveness and efficiency of stroke services, other factors may influence the organisation of services including; a) the local health care culture and economy (particularly whether a private or publicly-funded service), b) the needs and expectations of different patient groups and the degree to which they are prioritised, and c) the resources available to support optimal provision of stroke care services including rehabilitation.

An ideal stroke service should deliver the care required by patients and their families in the most effective, efficient, equitable, and humane manner possible. It would cover the needs of people with suspected acute stroke and be integrated to provide a seamless interdisciplinary (medical, nursing, allied health), specialised service from time of presentation until discharge from the stroke service. While many components will be stroke specific, some may overlap with other services (e.g. ambulance, emergency department, neurology, rehabilitation, care of the elderly, palliative care). Although the focus tends to be on ischaemic stroke the same principles apply to intracerebral haemorrhage. We have not included primary stroke prevention or long-term care, as these are beyond the scope of this review.

Several evidence-based acute stroke treatments can reduce disability but are very time-sensitive, in particular reperfusion treatments for ischaemic stroke such as intravenous thrombolysis[3] and endovascular thrombectomy[4]. A major barrier to such treatments is that patients do not arrive to hospital within the recommended time windows for treatment.[5] While recent advances in the use of imaging technology has meant that time windows for reperfusion therapies may be extended in selected cases,[6] equity of access to hospitals with advanced imaging modalities remains a challenge. Other barriers include lack of specialist services and equipment to support diagnosis and treatment decisions.

Figure 1 provides an idealised summary of an patient journey commencing with the prompt recognition and response to symptoms, rapid diagnosis and reperfusion (if appropriate), and early measures to prevent complications (including recurrent stroke) and promote recovery, rehabilitation and return to normal living.[7,8] For simplicity we focus on the typical patient pathway. Some services aimed at specific subgroups (for example vascular prevention services for patients not admitted to hospital) are beyond the scope of this review. The various interventions currently available to address these challenges within high-income health systems are also summarised in Figure 1. These interventions will be further discussed in this article.

Ideally, all our decisions about stroke services should be based on robust evidence from randomised trials or similar quality evidence. However, such trials are complex and challenging to carry out and it is frequently difficult to develop, describe, and measure the intervention satisfactorily.[9] We have used information from randomised trials, high quality cohort studies and recent clinical practice guidelines. Planners should be aware that lack of evidence of benefit is not the same as evidence of lack of benefit.

Search strategy and selection criteria

This is a pragmatic review where key word searches were undertaken to identify relevant literature using Medline and other databases. We also searched the Cochrane Library from first publication to 12 May 2020 with the search terms “stroke” and various topic specific terms (such as “telemedicine”, “telestroke”, “telerehabilitation”). We also searched the Cochrane Stroke Group section of the Cochrane Library containing 197 reviews and protocols of which 17 reviews and protocols were relevant to this review. We also reviewed the most up-to-date clinical practice guidelines, which provided a more consensual analysis of the evidence. We specifically sought guidelines published in the last three years from Europe, North America, and Australia. Finally, we crosschecked the references identified for appropriate information.

Components of stroke services

Education and training campaigns

A major focus of public health initiatives has been to improve the time to treatment for patients with ischaemic stroke. There are several inter-related reasons that contribute to patients with stroke experiencing delays with the provision of reperfusion therapies. In a recent systematic review,[8] four categories of factors associated with delays were identified: 1) patient-related factors, plus health system factors related to 2) training, 3) resources, and 4) lack of coordination. In another similar systematic review,[10] the authors reported that patients' attitudes, knowledge, and education were associated with time to presentation to hospital after stroke. Visiting the primary care physician after stroke was associated with delayed presentation.

Various strategies directed at the public and emergency medical services appear to improve stroke recognition and time to presentation and treatment for people with stroke. A systematic review of 39 studies of stroke knowledge conducted in the UK, North America, Asia and Australia[11] provided an illustration of the wide variability between studies in terms of the ability of the public to name stroke risk factors, to name signs and symptoms of stroke, and the decision to call emergency medical services. In other studies it was also found that the general public would opt to contact or attend their primary care physician first, rather than emergency medical services following onset of their symptoms.[11]

Public awareness campaigns are designed to improve time to diagnosis and treatment metrics. However, of the studies of educational campaigns and stroke awareness conducted in Europe, Asia, North America, and Australia, few have been found to be effective for improving response times after stroke onset.[12] There has been limited research on how knowledge and attitudes of paramedic staff, emergency medical staff and primary care physicians can reduce delays within stroke care. In one study, primary care physicians stated that stroke and TIA were medical emergencies, but would admit patients to hospital as a medical emergency only in approximately two-thirds of case vignettes with clear stroke symptoms.[13] However, educational interventions for emergency medical services can improve access to thrombolysis and several validated pre-hospital stroke screening tools used by paramedics can improve the accuracy of paramedic diagnosis.[14,15] Similar tools have been adapted for use by emergency medical services to identify and rapidly transfer patients with suspected stroke to hospitals able to provide thrombolysis[16] or for endovascular thrombectomy.[17] Such protocols are particularly relevant to provide pre-hospital triage, in areas underserved with specialist stroke services.

Until awareness among the general public is greater, educational interventions to improve the recognition of stroke in general practices and by emergency medical services are essential.

Mobile Stroke Unit ambulances

A relatively novel solution to minimise delays to diagnosis and treatment is to bring the stroke team and necessary diagnostic tools to the patient, prior to hospital arrival. Within some highly developed health systems, there are specialised stroke ambulances, often called mobile stroke units (MSUs), that expedite diagnosis, triage, and treatment by bringing CT scanning capability and a point-of-care laboratory to a patient with suspected stroke. Currently, MSUs are operational in over 20 cities, mainly in North America and Europe.[18,19] While models of operation vary, MSUs are generally staffed with specialised stroke clinicians (advanced practice nurses, stroke specialists with or without telemedicine support) so that patients can be diagnosed with stroke and provided thrombolysis if eligible prior to arrival at hospital.[20,21] The choice of hospital (thrombectomy capable or not) can also then be prioritised.

When the provision of thrombolysis provided by several MSU services was compared to registry data, a larger proportion of MSU patients was treated faster after stroke[18] with a trend towards better functional outcome.[22] In studies utilising a week-by-week randomisation procedure in Germany, patients treated by the MSU had a shorter alarm to treatment time compared to patients treated with standard care; median difference of 44 minutes in Homburg,[21] and 25 minutes in Berlin.[23]

MSUs also raise the possibility of providing other pre-hospital treatments, including the early reversal of warfarin, dabigatran or other anticoagulant after ICH or prior to thrombolysis.[24] Having a pre-hospital diagnosis may also enable efficiencies with appropriate transfer to hospitals for treatment of stroke mimics,[25] or the provision of endovascular thrombectomy,[26] or neurosurgery for ICH.[27]

The limited information available has provided mixed views on whether MSUs represent good value for investment. One evaluation of MSUs concluded they were likely to be cost effective, with health benefits attributable to improvements in the provision of reperfusion therapies.[28,29] However, other authors have been more cautious, citing the limited evidence to support reliable analyses.[30]

Stroke Centres (Comprehensive Stroke Centres and Primary Stroke Centres)

Initiatives to improve stroke care through the provision of stroke centres (Comprehensive and Primary Stroke Centres) started in the North America[31] but have also been developed in Australia and Europe.[32] The objective was to improve the delivery of evidence-based stroke care by establishing two levels of specialist stroke centres (see summary in Table 2).

Primary Stroke Centre (PSC) – typically this is a more local service provided by a hospital with the necessary staffing, infrastructure, and programmes to manage the majority of patients with acute stroke.[31] In practice, these tend to be closely aligned with the stroke unit concept outlined below.

Comprehensive Stroke Centre (CSC) – typically this is a centralised, regional service based in a hospital that can provide care to patients with the most complex stroke needs including specialist investigations and interventions.[31] These initiatives gained further impetus with the publication of trials demonstrating the benefit of mechanical thrombectomy for large vessel occlusion stroke,[33] an intervention that requires centralisation in a neuroscience centre. CSCs are also considered to provide neurosurgical or neuroradiological interventions for cerebral aneurysms, arteriovenous malformations, and decompressive neurosurgery. It was anticipated that CSCs could provide a higher quality of care but would not have the capacity to manage the patient numbers for a whole region.

Empirical studies comparing the impact of CSCs and PSCs in Europe[34] and United States[35,36] indicate that both approaches have achieved improvements in the quality and outcome of care compared with non-specialist care in general hospitals. When CSCs and PSCs were directly compared, both achieved similar quality measures for acute ischaemic stroke patients. Although the process of care tended to be more efficient in the larger CSCs (in particular the speed and delivery of acute reperfusion therapies), important patient outcomes such as in-hospital mortality, recovery of mobility, and discharge home were found to be comparable after adjusting for casemix variables. In the North American study[36] the risk adjusted mortality was actually higher in CSCs than PSCs but this could possibly be due to residual confounding.

These observational studies indicate that both CSC and PSC approaches appear to improve the quality of care and patient outcomes. While CSCs are required for the most complex stroke interventions (such as mechanical thrombectomy or neurosurgical interventions), the

needs of many acute stroke patients can normally be met within PSCs. This then raises the challenge of how to achieve the rapid, accurate triage of appropriate patients in the prehospital setting from their local stroke service to a regional CSC (see below).

Some geographical situations, such as in very low population density areas, will not allow the implementation of specialized stroke services such as PSCs. In such environments, acute stroke patients should be referred to appropriate specialized facilities. To avoid critical delays, time sensitive thrombolysis should be enabled before transportation. Telemedicine can help to make smaller hospitals "tPA-ready" (see TeleStroke section below). Even hospitals which provide thrombectomy may lack Neurosurgery or Neuro-intensive care services. In such cases, transfer to full-service facilities should be timely and ideally through an interdisciplinary consensus (e.g. within telemedicine-enabled case consultations). Whether ground ambulances or helicopters are used for emergency interhospital transport will depend on distance, traffic and availability, and should be monitored as part of quality assessment.

Stroke unit care

Stroke unit care is now established as the central feature of a modern stroke service in most higher income countries.[37] Compared with care in a general medical or neurology ward, admission to a stroke unit can result in more patients surviving, returning home, and regaining independence; number needed to treat (NNT) of around 20 for one extra independent survivor.[38] Clinical trial evidence indicates that stroke unit care can benefit a broad range of patients irrespective of age, sex, stroke severity, or stroke type although the survival benefit is greater with more severe stroke. The core features of stroke unit care include; a) a discrete ward area, b) specialist medical, nursing, and therapy staff with an expertise in stroke, c) multidisciplinary team working through regular meetings, and d) standard protocols to address common challenges and reduce the risk of complications.

While the evidence strongly supports the concept of providing care in a specialist stroke unit, in practice, people have tried to deliver this type of care in a variety of different ways (Table 1). In recent years many stroke services have promoted a model of care ('hyper-acute' stroke units) equipped to support reperfusion therapies or other acute interventions. These newer service models have been evaluated in non-randomised studies[39,40] but not formally tested in randomised controlled trials. Clinicians and planners should ensure that every stroke patient receives the core service characteristics described in the randomised trials of stroke unit care[38] and that the patient experiences a continuous process of stroke unit care from initial assessment to discharge from hospital.[41] This is particularly important as stroke unit care appears to benefit the majority of patients who are not eligible for reperfusion therapies.[38] The ideal size and configuration of services within a particular hospital site will depend on other factors such as rurality and other services and resources available.[42,43] Most randomised trial research has been carried out on comprehensive stroke units, which combine acute care and rehabilitation, and rehabilitation stroke units. Mixed rehabilitation units may have a role in small hospitals or very specialised services such as those for young adult rehabilitation. Some countries have a tradition of admitting patients with stroke to intensive care units. While this approach has an intuitive appeal, it lacks evaluation in rigorous clinical trials.

Transfer from hospital to community

A major area of concern for patients and caregivers is the period of transition from hospital back home. Patient surveys often highlight a sense of abandonment and concern at this stage in the patient journey.[44,45] One approach to addressing these concerns is through careful preparation including; a) provision of adequate information and training, b) home assessments prior to discharge, and c) training and education with carers and family.[46]

However, such measures often fail to meet all reported needs and more recently early supported discharge (ESD) services have been developed to improve this period of transition.[47]

The ESD concept is to accelerate the discharge home from hospital but also provide more rehabilitation in the home setting. This package of care is typically provided by a multidisciplinary team of nurses and therapists with some medical input. A typical care pathway[48] is outlined in Figure 2.

To date, many small randomised trials have tested this approach and provide evidence that patients who receive input from an ESD team can return home earlier and have a greater chance of remaining at home and regaining independence in daily activities. The NNT is approximately 20 to obtain one extra independent individual. These impressive results appear to require a well-resourced, co-ordinated, multidisciplinary ESD team with a focus on patients with mild to moderate disability. The full range and role of such services is not well understood. Other forms of post-hospital support may include specialised nurse-led outpatient clinics and day hospitals.

Continuing rehabilitation and reintegration to regular living

This aspect of the patient journey appears to have the greatest diversity of service delivery and most diverse research models, possibly reflecting the unique challenges that individual patients may face after stroke. Recommendations tend to focus on processes of care with less clear advice on what interventions should be delivered. For example the Action Plan for Europe[37] recommends; a) providing a documented plan for community rehabilitation and self-management support for all patients with stroke with residual difficulties on discharge from hospital, b) ensuring that all survivors and caregivers have a review of the rehabilitation and other needs at three to six months after stroke and annually thereafter, and c) offering physical fitness programmes for those living independently in the community. One potential advantage of ESD teams is to provide a structure to link hospital care to community-based services to coordinate ongoing rehabilitation. However much more research is needed into how best to improve this phase of the journey.

Telemedicine networks (acute telemedicine and telerehabilitation)

Many patients can miss out on effective treatments after stroke because of geographical isolation and/or a lack of access to specialist medical or allied health services. Since the era of stroke thrombolysis in the late 1990s, many regions have sought to reduce inequities in accessing treatment for ischaemic stroke through telecommunications.[49] The establishment of telemedicine programs for acute stroke treatment is based on three important factors.[50] Firstly, diagnosis is possible with access to cerebral imaging scans that are now easy to transmit electronically and stroke symptoms can be assessed via audio-visual examination.[51] Therefore, remote controlled videoconferencing combined with teleradiology offers an appropriate tool for stroke assessment. Second, acute stroke workup requires expertise from stroke specialists who are not always available onsite in many smaller, particularly rural areas. Third, because the effects of recanalisation therapies are highly time dependent and favour immediate decision-making in the local hospital in order to start thrombolysis or when indicated, to transfer appropriate patients to an endovascular thrombectomy capable hospital.

While acute telestroke has been evaluated in multiple domains[52–54] and has now become a widespread application in many regions,[55-56] telerehabilitation approaches are less well developed[57,58] and further development and investigation is urgently needed.

Appropriate telestroke assessment and decision making requires meeting technological and organisational quality standards including remote control and broadband streaming for

videoconferencing, rigorous data protection, standard operating procedures, together with accreditation for service providers, and clinical quality management and reviews.[52] Telestroke is used in different forms ranging from exclusive remote consultation e.g. for indicating thrombolytic treatment[59] to comprehensive networks enabling smaller hospitals to run local (tele-) stroke units.[60]

Evidence for telestroke

Investigations across multiple scenarios have shown equivalent reliability and validity of remote neurological assessment[51,61] and imaging reading[62,63] compared to onsite examinations. This prompted the use of telemedicine to support delivery of intravenous thrombolysis in hospitals without full-time stroke specialists available.[60] Randomized studies showed there was better accuracy of diagnosis and decision-making when based on video examination compared to telephone consultation only[64,65] while other controlled studies found equivalent safety and functional outcomes after telemedicine-based administration of thrombolysis in smaller hospitals compared to its application in larger experienced stroke centers.[66–68] Such systems can achieve similar levels of quality (as measured with door-to-needle times)[69,70] as well as reductions in complications after thrombolysis such as symptomatic intracerebral bleeding.[68] In a large controlled study with a matched-hospitals design, telemedicine embedded in such a comprehensive telestroke network concept resulted in significantly better quality measures and patient outcomes up to 30-months follow-up.[71,72]

Telestroke networks are cost-effective from a societal,[73] health insurers,[74] and a hospital[75] perspective. Importantly, this model of care can improve the triage of patients located outside metropolitan areas in determining those eligible for endovascular thrombectomy.[76] Telestroke may also facilitate more hospitals being included in stroke clinical trials by enabling the identification of patients who might qualify for trials of new or improved therapies.

Mobile telemedicine

The higher bandwidth available in mobile telecommunication has facilitated the use of telemedicine in the prehospital field over more recent years.[77,78] While videoconferencing based on third generation (3G) telecommunication standards failed to provide sufficient streaming stability[77,79] several groups have reported reliable video-examination using 4G standard.[80–82] In MSUs, telemedicine is also successfully used for transfer and interpretation of computer tomography (CT) scans.[83,84]

Telerehabilitation

The provision of physical rehabilitation,[85] speech and language therapy,[86] and occupational therapy[87] can improve mobility, communication skills, and activities of daily living in survivors of stroke. As most rehabilitation treatments are provided in inpatient facilities, the duration of such treatment is restricted to a few weeks and resources are limited in long-term outpatient rehabilitation. Telerehabilitation comprising a remote administration or supervision of rehabilitation therapies could enhance the intensity of post-stroke rehabilitation, increase the duration of service provision, and at the same time be more convenient and less expensive than conventional rehabilitation.

The evidence supporting telerehabilitation is variable. An initial systematic review found insufficient evidence to reach conclusions about the effectiveness of telerehabilitation,[57] while one including with studies up to 2017[88] reported evidence that telerehabilitation interventions were better or equivalent to conventional face-to-face therapy for motor, higher cortical, and mood disorders. In the most recent systematic review,[58] positive effects of telerehabilitation on several outcomes were observed, but conclusive recommendations could not be made due to methodological and practical concerns. At present, we lack robust

evidence to support the widespread implementation of telerehabilitation, but it is likely to be useful particularly in areas with low population density or remote access to rehabilitation facilities.

Coordination and monitoring of services for stroke

Importance of prehospital triage

Modern stroke incidence studies in high income countries[89] indicate that approximately half of patients with ischaemic stroke will present with relatively mild but potentially important symptoms (NIHSS <5) that are outside the licence for thrombolysis or thrombectomy. Recent estimates[90] indicate that approximately 25% of all ischaemic strokes could be eligible for medical thrombolysis and 10–12% eligible for endovascular treatment. The remaining patients will still require high quality stroke care. A major challenge for modern stroke services is to balance the delivery of high quality, local services with those that must be centralised in regional centres. This challenge has been addressed in a range of ways and the key elements are summarised in Figure 3. The crucial step is to be able to rapidly and accurately select those patients who need to be moved urgently to the centralised service for consideration of specialist investigations and treatment. The approaches to achieving this have included; a) rapid selection tools such as clinical scoring systems,[14,92] b) MSUs,[18] c) telemedicine links,[52] or d) combinations of the above. The ideal balance between primary ('ship') and secondary transfer ('drip-and-ship') approaches for patients is a subject of ongoing research and likely to vary between regions.[92]

A basic agreement with emergency medical services should be in place to ensure that patients with symptoms suspicious of acute stroke are delivered to stroke-ready hospitals. Multiple prehospital scales for identification of patients with large vessel occlusion in the field have been published in recent years. Authors of systematic reviews have concluded that no scale predicts large vessel occlusion with both high sensitivity and high specificity.[93] Prospective controlled studies evaluating their clinical benefits are missing. So long as vessel imaging is not available in standard ambulances, such scales may be useful to route patients to the ideal facility. However, local information on distances from scene to different hospitals, total transfer times and times of in-hospital procedures both in PSCs and CSCs need to be included in probabilistic models[94] – ideally supported by online tools to aid decision-making.

Monitoring service quality

With the growth of clinical guidelines and concerns about variations in practice between hospitals and equity of access to best-practice management for acute stroke, monitoring the quality of care has become very important. The essence of the available evidence is that as many patients as possible should receive evidence-based treatments with minimal time delays. Regular stroke quality monitoring must therefore include the proportions of patients receiving (and delays to receiving); Stroke Unit care, intravenous thrombolysis and mechanical thrombectomy. The continuum of care should also be evaluated starting with prehospital emergency care and triage to the optimal facility, multiprofessional in-hospital management and stroke aftercare tailored to individual patient needs. However, this is more difficult because of the multiple sectors involved.

While local registries can provide valuable information to the participating sites, simple comparisons between hospitals are unreliable for reporting trends in demographics, access to interventions, and outcomes. Standardised data collection via national audits or state-wide registries are to be encouraged (Table 3). In a recent review of national stroke registries only 26 countries had a national registry for acute stroke care monitoring.[95] In countries that have a national clinical quality registry of stroke care to enable standardised collection of data to

monitor acute stroke care in hospitals, the reporting of the data (and responding to the findings) has led to improvements in the quality of care, patient outcomes, and health policy.[96,97] Large scale observational studies[35,36,98] have shown impressive improvements in patient outcomes.

Conclusions

While the hospital stroke unit remains the central component of a modern stroke service major developments have taken place to streamline the systems of care and improve the speed of recognition, response, triage, and delivery of acute treatments to people with stroke symptoms. The development of new hyper-acute investigations and treatments has driven the development of centralised (comprehensive) stroke centres but there remains the challenge of how to optimise the triage of appropriate patients to these services while maintaining high quality local services for the majority who will not require this level of care. Future initiatives are likely to see ongoing development of telemedicine networks and possibly mobile stroke units to improve rapid decision making. In the future, technology may be further exploited to facilitate communication between service providers, to facilitate the transition to home, and provide ongoing support for rehabilitation including programs such as early supported discharge services and telerehabilitation.

Declaration of Interests

Dr. Langhorne reports grants from Chief Scientist's Office, Chest Heart and Stroke Scotland, and National Institute of Health Research, outside the submitted work. Dr. Cadilhac reports grants from National Health and Medical Research Council, Boehringer Ingelheim, Shire, Medtronic, Heart Foundation (Australia), Stroke Foundation (Australia), Melbourne Health, outside the submitted work. Dr. Cadilhac is the Data Custodian for the Australian Stroke Clinical Registry and a member of the Pre-hospital Stroke Treatment Organization. Dr. Audebert reports grants from German Federal Ministry of Education and Research, Pfizer, German Stroke Foundation; personal fees from Bayer Vital, Boehringer Ingelheim, Bristol-Myers-Squibb, Novo-Nordisk, Pfizer, and Takeda, outside the submitted work. No specific funding was used for this review.

Author's contributions

Peter Langhorne drafted the review structure, wrote sections of the text, revised the manuscript and acts as guarantor. Heinrich Audebert, Dominique Cadilhac, Joosup Kim and Patrice Lindsay wrote sections of the text and revised the manuscript. All authors approved the final version. (4406 words)

References

1. Feigin VL, Roth GA, Naghavi M, 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**:913–24.
2. Hankey GJ (Editor), Macleod M (Editor), Gorelick PB (Editor), Chen C (Editor), Caprio FZ (Editor), Mattle H (Editor). Warlow's Stroke: Practical Management, 4th Edition. 2019. Wiley Blackwell. ISBN: 978–1–118–49222–2.
3. Emberson J, Lees KR, Lyden P, 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* (London, England) 2014; **384**(9958): 1929–35.

4. Goyal M, Menon BK, van Zwam WH, et al.; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; **387**:1723–1731.
5. Meretoja A, Keshtkaran M, Tatlisumak T, Donnan GA, Churilov L. Endovascular therapy for ischemic stroke: Save a minute-save a week. *Neurology* 2017; **88**(22): 2123–7.
6. Coutts SB, Menon BK. Late thrombolysis for stroke works, but how do we do it? *Lancet* 2019; **394**:97–98.
7. McDermott M, Skolarus LE, Burke JF. A systematic review and meta-analysis of interventions to increase stroke thrombolysis. *BMC Neurol* 2019; **19**(1):86.
8. Lachkhem Y, Rican S, Minvielle É. Understanding delays in acute stroke care: a systematic review of reviews. *Eur J Public Health* 2018; **28**(3):426–33.
9. Cadilhac DA, Fisher R, Bernhardt J. How to do health services research in stroke: A focus on performance measurement and quality improvement. *Int J stroke* 2018; **13**(2):166–174.
10. Pulvers JN, Watson JDG. If Time Is Brain Where Is the Improvement in Prehospital Time after Stroke? *Front Neurol* 2017; **8**:617–13.
11. Jones SP, Jenkinson AJ, Leathley MJ, Watkins CL. Stroke knowledge and awareness: an integrative review of the evidence. *Age and Ageing* 2009; **39**(1):11–22.
12. Vondráčková L, Mikulík R. Public stroke education: Current status worldwide and projects to increase awareness in the Czech Republic. Cor et Vasa 2017; **59**(6): e546–e52.
13. Roebers S, Wagner M, Ritter Martin A, Dornbach F, Wahle K, Heuschmann Peter U. Attitudes and Current Practice of Primary Care Physicians in Acute Stroke Management. *Stroke* 2007; **38**(4):1298–303.
14. Zhelev Z, Walker G, Henschke N, Fridhandler J, Yip S. Prehospital stroke scales as screening tools for early identification of stroke and transient ischemic attack. Cochrane Database of Systematic Reviews 2019, Issue 4. Art. No.: CD011427. DOI: 10.1002/14651858.
15. Oostema JA, Chassee T, Baer W, Edberg A, Reeves Mathew J. Brief Educational Intervention Improves Emergency Medical Services Stroke Recognition. *Stroke* 2019; **50**(5):1193–200.
16. Quain DA, Parsons MW, Loudfoot AR, et al. Improving access to acute stroke therapies: a controlled trial of organised pre-hospital and emergency care. *Med J Aust* 2008; **189**(8):429–33.
17. Zhao H, Pesavento L, Coote S, et al. Ambulance Clinical Triage for Acute Stroke Treatment. *Stroke* 2018; **49**(4):945–51.
18. Fassbender K, Grotta JC, Walter S, Grunwald IQ, Ragoschke-Schumm A, Saver JL. Mobile stroke units for prehospital thrombolysis, triage, and beyond: benefits and challenges. *Lancet Neurol* 2017; **16**(3):227–37.
19. Calderon VJ, Kasturiarachi BM, Lin E, Bansal V, Zaidat OO. Review of the Mobile Stroke Unit Experience Worldwide. *Interv Neurol* 2018; **7**(6):347–58.
20. Audebert H, Fassbender K, Hussain MS, et al. The PRE-hospital Stroke Treatment Organization. *Int J stroke:*official journal of the International Stroke Society 2017; **12**(9):932–40.
21. Walter S, Kostopoulos P, Haass A, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. *Lancet Neurol* 2012; **11**(5):397–404.

22. Kunz A, Ebinger M, Geisler F, et al. Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. *Lancet Neurol* 2016; **15**:1035–43.
23. Ebinger M, Winter B, Wendt M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: a randomized clinical trial. *JAMA* 2014; **311**(16):1622–31.
24. Zhao H, Coote S, Pesavento L, et al. Prehospital idarucizumab prior to intravenous thrombolysis in a mobile stroke unit. *Int J stroke* 2018; **14**(3):265–9.
25. Shuaib A, Amlani S, Kalashyan H, et al. Mobile stroke unit triage of patients with a suspected stroke: a novel solution to reducing suspected stroke admissions in busy emergency departments. *BMJ Innovations* 2018; **4**(2):54.
26. Helwig SA, Ragoschke-Schumm A, Schwindling L, et al. Prehospital Stroke Management Optimized by Use of Clinical Scoring vs Mobile Stroke Unit for Triage of Patients With Stroke: A Randomized Clinical Trial. *JAMA Neurol*. 2019 Sep 3: e192829. Published online 2019 Sep 3. doi: 10.1001/jamaneurol.2019.2829)
27. Wendt M, Ebinger M, Kunz A, et al, for the STEMO Consortium. Improved Prehospital Triage of Patients With Stroke in a Specialized Stroke Ambulance. *Stroke*. 2015; **46**:740–745
28. Dietrich M, Walter S, Ragoschke-Schumm A, et al. Is prehospital treatment of acute stroke too expensive? An economic evaluation based on the first trial. *Cerebrovasc Dis* (Basel, Switzerland) 2014; **38**(6):457–63.
29. Gyrd-Hansen D, Olsen KR, Bollweg K, Kronborg C, Ebinger M, Audebert HJ. Cost-effectiveness estimate of prehospital thrombolysis: results of the PHANTOM-S study. *Neurology* 2015; **84**(11):1090–7.
30. Kobayashi A, Czlonkowska A, Ford GA, et al. European Academy of Neurology and European Stroke Organization consensus statement and practical guidance for pre-hospital management of stroke. *Eur J Neurol* 2018; **25**:425–33. doi: 10.1111/ene.13539.
31. Alberts MJ, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. *JAMA* 2000; **283**:3102–3109.
32. Ringelstein EB, Chamorro A, Kaste M, et al ESO Stroke Unit Certification Committee. European Stroke Organisation recommendations to establish a stroke unit and stroke center. *Stroke* 2013; **44**:828–840.
33. Goyal M, Kurz KD, Fisher M. Organization of Endovascular Thrombectomy: The Need for a 2-Tier System. Stroke 2019; 50(6):1325-1326.
34. Mereoja A, Roine RO, Kaste M, et al. Effectiveness of primary and comprehensive stroke centers. PERFECT Stroke: a nationwide observational study from Finland. *Stroke* 2010; **41**:1102–1107.
35. Man S, Cox M, Patel P, Smith EE, et al. Differences in Acute Ischemic Stroke Quality of Care and Outcomes by Primary Stroke Center Certification Organization. *Stroke* 2017; **48**:412–419.
36. Man S, Zhao X, Uchino K, 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 Jun; **11**(6):e004512. doi: 10.1161/CIRCOUTCOMES.117.004512.
37. Norrving B, Barrick J, Davalos A, et al; on behalf of the Action Plan for Stroke in Europe Working Group. Action Plan for Stroke in Europe 2018–2030. *ESJ* 2018; Vol. **3**(4) 309–336.

38. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2013; **9**: CD000197.
39. Cadilhac D, Andrew N, Lannin N, et al. Quality of acute care and long-term quality of life and survival: the Australian Stroke Clinical Registry. *Stroke* 2017; **48**(4):1026–1032.
40. Morris S, Ramsay AIG, Boaden RJ, et al. Impact and sustainability of centralising acute stroke services in English metropolitan areas: retrospective analysis of hospital episode statistics and stroke national audit data. *BMJ* 2019; **364**: l1.
41. Busingye D, Kilkenny MF, Purvis T, et al. Is length of time in a stroke unit associated with better outcomes for patients with stroke in Australia? An observational study. *BMJ Open* 2018; **8**:e022536. doi: 10.1136/bmjopen–2018–022536
42. Cadilhac, DA, Kilkenny, MF, Andrew, NE et al. Hospitals admitting at least 100 patients with stroke a year should have a stroke unit: a case study from Australia. *BMC Health Serv Res* 2017; **17**:212. https://doi.org/10.1186/s12913–017–2150–2
43. Royal College of Physicians. Sentinel Stroke National Audit Programme (SSNAP) Clinical Audit, Public Report. London: Royal College of Physicians, 2016.
44. Hafsteinsdottir TB, Vergunst M, Lindeman E, Schuurmans M. Educational needs of patients with a stroke and their caregivers: a systematic review of the literature. *Patient Educ Couns* 2011; **85**(1):14–25.
45. McKevitt C, Fudge N, Redfern J, et al. Self-reported long-term needs after stroke. *Stroke* 2011; **42**(5):1398–403.
46. Forster A, Dickerson J, Young J, et al. A structured training programme for caregivers of inpatients after stroke (TRACS): a cluster randomised controlled trial and cost-effectiveness analysis. *Lancet* 2013; **382**(9910):2069–76.
47. Langhorne P and Baylan S. Early Supported Discharge Trialists. Early supported discharge services for people with acute stroke. *Cochrane Database Syst Rev* 2017; **7**: CD000443.
48. Langhorne P, Widen-Holmqvist L. Early supported discharge after stroke. *J Rehabil Med* 2007; **39**(2):103–108.
49. Bladin CF, Cadilhac DA. Effect of telestroke on emergent stroke care and stroke outcomes. *Stroke* 2014; **45**(6):1876–80.
50. Levine SR, Gorman M. "Telestroke" : the application of telemedicine for stroke. *Stroke* 1999; **30**(2):464–9.
51. Schwamm LH, Holloway RG, Amarenco P, et al. A review of the evidence for the use of telemedicine within stroke systems of care: a scientific statement from the American Heart Association/American Stroke Association. *Stroke* 2009; **40**(7):2616–34.
52. Wechsler LR, Demaerschalk BM, Schwamm LH, 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**(1):E3–E25.
53. Bagot K, Moloczij N, Arthurson L, et al. Nurses' Role in Implementing and Sustaining Acute Telemedicine: A Mixed-Methods, Pre-Post Design Using an Extended Technology Acceptance Model. *J Nurs Scholarsh. 202052(1):34-46.*
54. Bagot KL, Cadilhac DA, Kim J, et al. Transitioning from a single-site pilot project to a state-wide regional telehealth service: The experience from the Victorian Stroke Telemedicine programme. *J Telemed Telecare* 2017; **23**(10):850–5.

562 55. Schwamm LH, Audebert HJ, Amarenco P, et al. Recommendations for the
563 implementation of telemedicine within stroke systems of care: a policy statement
564 from the American Heart Association. *Stroke* 2009; **40**(7):2635–60.
565 56. Muller-Barna P, Schwamm LH, Haberl RL. Telestroke increases use of acute stroke
566 therapy. *Curr Opin Neurol* 2012; **25**(1):5–10.
567 57. Laver KE, Schoene D, Crotty M, George S, Lannin NA, Sherrington C.
568 Telerehabilitation services for stroke. *Cochrane Database Syst Rev* 2013; **12**:
569 CD010255.
570 58. Appleby E, Gill ST, Hayes LK, Walker TL, Walsh M, Kumar S. Effectiveness of
571 telerehabilitation in the management of adults with stroke: A systematic review. *PLoS*
572 *One* 2019; **14**(11): e0225150.
573 59. Schwamm LH, Rosenthal ES, Hirshberg A, et al. Virtual TeleStroke support for the
574 emergency department evaluation of acute stroke. *Acad Emerg Med:* official journal
575 of the Society for Academic Emergency Medicine 2004; **11**(11):1193–7.
576 60. Audebert HJ, Kukla C, Clarmann von Claranau S, et al. Telemedicine for safe and
577 extended use of thrombolysis in stroke: the Telemedic Pilot Project for Integrative
578 Stroke Care (TEMPiS) in Bavaria. *Stroke* 2005; **36**(2):287–91.
579 61. Handschu R, Littmann R, Reulbach U, et al. Telemedicine in emergency evaluation of
580 acute stroke: interrater agreement in remote video examination with a novel
581 multimedia system. *Stroke* 2003; **34**(12):2842–6.
582 62. Demaerschalk BM, Bobrow BJ, Raman R, et al. CT interpretation in a telestroke
583 network: agreement among a spoke radiologist, hub vascular neurologist, and hub
584 neuroradiologist. *Stroke* 2012; **43**(11):3095–7.
585 63. Puetz V, Bodechtel U, Gerber JC, et al. Reliability of brain CT evaluation by stroke
586 neurologists in telemedicine. *Neurology* 2013; **80**(4):332–8.
587 64. Meyer BC, Raman R, Hemmen T, et al. Efficacy of site-independent telemedicine in
588 the STRokE DOC trial: a randomised, blinded, prospective study. *Lancet Neurol*
589 2008; **7**(9):787–95.
590 65. Demaerschalk BM, Raman R, Ernstrom K, Meyer BC. Efficacy of telemedicine for
591 stroke: pooled analysis of the Stroke Team Remote Evaluation Using a Digital
592 Observation Camera (STRokE DOC) and STRokE DOC Arizona telestroke trials.
593 *Telemed J E-Health:* the official journal of the American Telemedicine Association
594 2012; **18**(3):230–7.
595 66. Audebert HJ, Kukla C, Vatankhah B, et al. Comparison of tissue plasminogen
596 activator administration management between Telestroke Network hospitals and
597 academic stroke centers: the Telemedical Pilot Project for Integrative Stroke Care in
598 Bavaria/Germany. *Stroke* 2006; **37**(7):1822–7.
599 67. Schwab S, Vatankhah B, Kukla C, et al. Long-term outcome after thrombolysis in
600 telemedical stroke care. *Neurology* 2007; **69**(9):898–903.
601 68. Bladin CF, Kim J, Bagot K, et al. Improving acute stroke care in regional hospitals:
602 early impact of the Victorian Stroke Telemedicine program. *Med J Aust* 2020;
603 Provisional acceptance November 26th.
604 69. Hubert GJ, Meretoja A, Audebert H, et al. Comparison of stroke thrombolysis rates
605 and delays in a centralized (Helsinki, Finland) and decentralized (Tempis Telestroke
606 Unit Network, Germany) setting. *Int J stroke* 2014; **9**:41–331.
607 70. Nguyen-Huynh MN, Klingman JG, Avins AL, et al. Novel Telestroke Program
608 Improves Thrombolysis for Acute Stroke Across 21 Hospitals of an Integrated
609 Healthcare System. *Stroke* 2018; **49**(1):133–9.
610 71. Audebert HJ, Schenkel J, Heuschmann PU, Bogdahn U, Haberl RL. Effects of the
611 implementation of a telemedical stroke network: the Telemedic Pilot Project for

612 Integrative Stroke Care (TEMPiS) in Bavaria, Germany. *Lancet Neurol* 2006;
613 **5**(9):742–8.
614 72. Audebert HJ, Schultes K, Tietz V, et al. Long-term effects of specialized stroke care
615 with telemedicine support in community hospitals on behalf of the Telemedical
616 Project for Integrative Stroke Care (TEMPiS). *Stroke* 2009; **40**(3):902–8.
617 73. Nelson RE, Saltzman GM, Skalabrin EJ, Demaerschalk BM, Majersik JJ. The cost-
618 effectiveness of telestroke in the treatment of acute ischemic stroke. *Neurology* 2011;
619 **77**(17):1590–8.
620 74. Schenkel J1, Reitmeir P, Von Reden S, Holle R, Boy S, Haberl R, Audebert H. Cost
621 Analysis of Telemedical Treatment of Stroke. Gesundheitswesen. 2013;75(7):405-12.
622 75. Switzer JA, Demaerschalk BM, Xie J, Fan L, Villa KF, Wu EQ. Cost-effectiveness of
623 hub-and-spoke telestroke networks for the management of acute ischemic stroke from
624 the hospitals' perspectives. *Circ Cardiovasc Qual Outcomes* 2013; **6**(1):18–26.
625 76. Kepplinger J, Dzialowski I, Barlinn K, et al. Emergency transfer of acute stroke
626 patients within the East Saxony telemedicine stroke network: a descriptive analysis.
627 *Int J stroke*: official journal of the International Stroke Society 2014; **9**(2):160–5.
628 77. Bergrath S, Reich A, Rossaint R, et al. Feasibility of prehospital teleconsultation in
629 acute stroke - a pilot study in clinical routine. *PLoS One* 2012; **7**(5): e36796.
630 78. Geisler F, Kunz A, Winter B, et al. Telemedicine in Prehospital Acute Stroke Care. *J*
631 *Am Heart Assoc* 2019; **8**(6): e011729.
632 79. Liman TG, Winter B, Waldschmidt C, et al. Telestroke Ambulances in Prehospital
633 Stroke Management. *Stroke* 2012; **43**:2086–2090.
634 80. Itrat A, Taqui A, Cerejo R, et al. Telemedicine in Prehospital Stroke Evaluation and
635 Thrombolysis: Taking Stroke Treatment to the Doorstep. *JAMA neurology* 2016;
636 **73**(2):162–8.
637 81. Wu TC, Parker SA, Jagolino A, et al. Telemedicine can replace the Neurologist on a
638 Mobile Stroke Unit. *Stroke* 2017; **48**(2):493–6.
639 82. Winter B, Wendt M, Waldschmidt C, et al. 4G versus 3G-enabled telemedicine in
640 prehospital acute stroke care. *Int J stroke*: official journal of the International Stroke
641 Society 2019; **14**(6):620–9.
642 83. Grunwald IQ, Ragoschke-Schumm A, Kettner M, et al. First Automated Stroke
643 Imaging Evaluation via Electronic Alberta Stroke Program Early CT Score in a
644 Mobile Stroke Unit. *Cerebrovasc Dis* (Basel, Switzerland) 2016; **42**(5–6):332–8.
645 84. Weber JE, Ebinger M, Rozanski M, et al. Prehospital thrombolysis in acute stroke:
646 results of the PHANTOM-S pilot study. *Neurology* 2013; **80**(2):163–8.
647 85. Pollock A, Campbell P, Baer G, et al. Challenges in integrating international evidence
648 relating to stroke rehabilitation: experiences from a Cochrane systematic review. *Int J*
649 *stroke*: official journal of the International Stroke Society 2014; **9**(8):965–7.
650 86. Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy
651 for aphasia following stroke. *Cochrane Database Syst Rev* 2016; **6**: CD000425.
652 87. Legg LA, Lewis SR, Schofield-Robinson OJ, Drummond A, Langhorne P.
653 Occupational therapy for adults with problems in activities of daily living after stroke.
654 *Cochrane Database Syst Rev* 2017; **7**: CD003585.
655 88. Sarfo FS, Ulasavets U, Opare-Sem OK, Ovbiagele B. Tele-Rehabilitation after
656 Stroke: An Updated Systematic Review of the Literature. *J Stroke Cerebrovasc Dis*
657 2018; **27**(9):2306–18.
658 89. Béjot Y, Mehta Z, Giroud M, Rothwell PM. Impact of Completeness of
659 Ascertainment of Minor Stroke on Stroke Incidence Implications for Ideal Study
660 Methods. *Stroke* 2013; **44**:1796–1802.

90. Zerna C, Thomalla G, Campbell BCV, Rha J, Hill MD. Current practice and future directions in the diagnosis and acute treatment of ischaemic stroke. *Lancet* 2018; **392**:1247–56.
91. Mokin M, Snyder KV, Siddiqui AH, Levy EI, Hopkins LN. Recent Endovascular Stroke Trials and Their Impact on Stroke Systems of Care. *J Am Coll Cardiol* 2016; **67**(22):2645–55.
92. Holodinsky JK, Williamson TS, Kamal N, Mayank D, Hill MD, Goyal M. Drip and Ship Versus Direct to Comprehensive Stroke Center: Conditional Probability Modeling. Stroke 2017;48:233–238
93. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, Towfighi A, Whiteley WN, Zahuranec DB, on behalf of the 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.
94. Schlemm L, Endres M, Scheitz JF, Ernst M, Nolte CH, Schlemm E. Comparative Evaluation of 10 Prehospital Triage Strategy Paradigms for Patients With Suspected Acute Ischemic Stroke. Journal of the American Heart Association. 2019;8:e012665.
95. Cadilhac DA, Kim J, Lannin NA, et al. National stroke registries for monitoring and improving the quality of hospital care: A systematic review. *Int J stroke*: official journal of the International Stroke Society 2016; **11**(1):28–40.
96. Asplund K, Hulter Asberg K, Appelros P, et al. The Riks-Stroke story: building a sustainable national register for quality assessment of stroke care. *Int J stroke*: official journal of the International Stroke Society 2011; **6**(2):99–108.
97. Silver FL, Kapral MK, Lindsay MP, Tu JV, Richards JA. International experience in stroke registries: lessons learned in establishing the Registry of the Canadian Stroke Network. *Am J Prev Med* 2006; **31**(6 Suppl 2):S235–7.
98. Ganesh A, Lindsay P, Fang J, Kapral MK, Côté R, Joiner I, Hakim AM, Hill MD. Integrated systems of stroke care and reduction in 30-day mortality. Neurology Mar 2016, 86 (10) 898-904.