Mobile stroke units for prehospital thrombolysis, triage, and beyond: benefits and challenges

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In acute stroke management, time is brain. Bringing swift treatment to the patient, instead of the conventional approach of awaiting the patient's arrival at the hospital for treatment, is a potential strategy to improve clinical outcomes after stroke. This strategy is based on the use of an ambulance (mobile stroke unit) equipped with an imaging system, a point-of-care laboratory, a telemedicine connection to the hospital, and appropriate medication. Studies of prehospital stroke treatment consistently report a reduction in delays before thrombolysis and cause-based triage in regard to the appropriate target hospital (eg, primary *vs* comprehensive stroke centre). Moreover, novel medical options for the treatment of stroke patients are also under investigation, such as prehospital differential blood pressure management, reversal of warfarin effects in haemorrhagic stroke, and management of cerebral emergencies other than stroke. However, crucial concerns regarding safety, clinical efficacy, best setting, and cost-effectiveness remain to be addressed in further studies. In the future, mobile stroke units might allow the investigation of novel diagnostic (eg, biomarkers and automated imaging evaluation) and therapeutic (eg, neuroprotective drugs and treatments for haemorrhagic stroke) options in the prehospital setting, thus functioning as a tool for research on prehospital stroke management.

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Introduction

Stroke is one of the most frequent causes of disability and death, and results in enormous societal costs associated with rehabilitation, long-term care, and loss of workforce.[1] Safe and effective treatments for acute ischaemic stroke are available, including coordinated physiological care in a stroke unit, aspirin, intravenous thrombolysis with recombinant tissue plasminogen activator (alteplase) within 4·5 h for many acute patients,[2] and intra-arterial treatment within the first 6 h for the subset of acute patients with cerebral ischaemia caused by large-vessel occlusion.[3]

However, the success of intravenous[4,5] or intra-arterial[3,6] treatment for ischaemic stroke is extremely time-dependent. Every minute of delay before recanalisation counts, with an estimated 2 million neurons lost every minute.[7] Based on the findings from large intravenous thrombolysis trials, the number needed to treat for one excellent outcome is approximately five in the first 90 min after symptoms onset, nine with treatment between 91 and 180 min, and more than 14 with treatment between 181 and 270 min.[8] Other estimates show that for every 30-min delay before reperfusion by intra-arterial treatment, the relative likelihood of a good clinical outcome decreases by approximately 15%.[6,9]

Despite two decades of substantial efforts to streamline systems of care, reported alteplase treatment rates extracted from hospital-derived databases range from 3·4 to 9·1% for patients with acute ischaemic stroke,[10–12] and the rates of delivery of intra-arterial treatment are far lower. The main reason for such undertreatment is that patients do not reach the hospital quickly enough to be assessed and treated within the narrow therapeutic window. Studies have found that only 15–60% of acute stroke patients arrive at the hospital within 3 h after onset of symptoms.[13,14] Disappointingly, data from the Get With The Guidelines-Stroke programme (NCT02693223) show that the proportion of patients with stroke arriving in time did not increase from 2003 to 2009, despite substantial efforts to improve the system.[15]

This Review aims to describe the mobile stroke unit (MSU) approach to improving the care of patients with acute stroke. We also discuss the risks and opportunities associated with this novel medical option.

Bringing the hospital to the patient: the mobile stroke unit

Existing recommendations for prehospital management of stroke, after early stabilisation and initial assessment, include rapid transfer to the nearest hospital for treatment.[16,17] However, effective treatments are available for patients with acute stroke that could, in principle, be administered immediately. Thus, by contrast to the approach of awaiting for the patient arrival at the hospital, the approach of administering treatment directly at the emergency site (termed the MSU concept) was developed in 2003 and investigated in clinical reality in 2008,[18] adhering to current stroke guidelines and emergency medical services legislations.

As a mobile emergency room,[19,20] the MSU contains imaging, a point-of-care laboratory, and a telemedicine connection with a hospital, in addition to appropriate medication and assessment tools. Its aim is the delivery of state-of-the-art prehospital diagnosis and treatment, as well as diagnosis-based triage of the patient to the most appropriate target hospital. Treatments include thrombolysis for acute cerebral ischaemia, anticoagulant reversal for acute intracranial haemorrhage, management of physiological variables for ischaemic or haemorrhagic stroke, and management of further emergencies. Thus, the MSU extends specialised stroke care specifically to the prehospital phase of stroke management and could act synergistically with hospital stroke units to close the existing treatment gap for patients with acute stroke.

In general, acute stroke management involves complex multistep testing and multidisciplinary cooperation. Different groups of health-care professionals in various locations are sequentially involved and repeatedly collect medical history, perform clinical examinations, and hand off patients and information to others before treatment can begin (figure 1). The multiple interfaces can contribute to errors and delays. The MSU concept,[18] apart from reducing prehospital and in-hospital transport times, saves crucial time by substantially reducing those interfaces. At one location, a single, specialised, interdisciplinary team, consisting of paramedics, physicians, nurses, and technicians, performs the complete diagnostic work-up and acute treatment in a parallel workflow (figure 1).

The mobile stroke unit ambulance

The MSU is an ambulance that contains all the tools necessary for guideline-adherent initial acute stroke treatment, and standard emergency care equipment.[18] Dimensions of existing ambulances vary according to the specific needs of various regions and health-care systems. In a second-generation MSU, the size of the equipment has been substantially reduced so that it can fit into a commercially available standard ambulance, which not only improves speed, accessibility to narrow roads, and acceptance by emergency care personnel, but also reduces cost.[21] However, in other settings, larger vehicle solutions might be advantageous—eg, an extra space allowing relatives to accompany the patient might be beneficial to collect a medical history and obtain informed consent for subsequent treatments.[22] A more robust vehicle might also be important to cope with bad roads or for transportation of large scanners.

Telecommunication between ambulance and hospital

Telecommunication approaches between standard ambulances and the stroke centre via systems that can provide real-time audiovisual conferencing and sharing of images have been studied for more than a decade. Pioneering work using early mobile broadband systems indicated potential benefits when hospital neurologists were able to assess neurological presentation en route by telemedicine, aiding in the best choice of target hospital and accelerating subsequent in-hospital care processes. However, the first studies faced problems with the reliability of telecommunication and were performed in simulated scenarios rather than in real clinical settings. In later studies, telemedicine transmission of videos of neurological examinations in ambulances, using actors mimicking stroke symptoms[23–26] or involving stroke patients,[27] was considerably better but still not completely reliable because of the suboptimal 3G public network available at the time. Further improvements have been reported with use of 4G mobile systems.[28] Similarly, studies have demonstrated the feasibility of en-route transmission of structured patient information to the target hospital via personal digital assistants.[29,30]

Telemedicine, including telestroke assessment (real-time bidirectional videoconferencing and high-speed transmission of videos) and teleradiology (transmission of high-quality images), is an integral component of the MSU concept.[18] Commercially available systems, routinely used for telemedicine between hospitals, allow MSUs to transmit digital imaging and communication data to the picture-archiving and communication system of the associated health-care facility,[18,31] acting within the same firewall. As a result of available 4G connectivity and the prioritisation of telecommunication in emergency medical services, a study[32] has reported that telemedicine

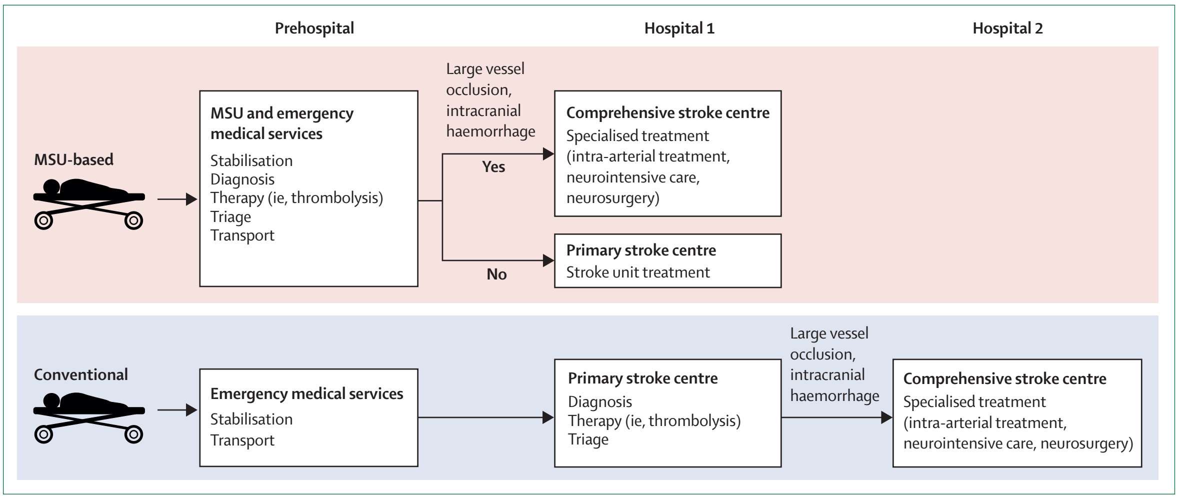

***Figure 1:* MSU-based stroke management compared with conventional stroke management**

In MSU-based stroke management, patients are diagnosed at the site of emergency, allowing case-specific treatment and triage to the most appropriate stroke centre, thus avoiding secondary transfers. In conventional stroke management, due to insufficient knowledge about the cause of the symptoms, patients are transported to the primary stroke centre and eventually, by secondary transfer, brought to a comprehensive stroke centre. MSU=mobile stroke unit.

encounters between MSUs and hospitals were successfully completed in the management of 99 (99%) of 100 patients. A study[33] of simultaneous independent assessment by a vascular neurologist on board an MSU and a remote telemedicine-based vascular neurologist showed 98% satisfactory connectivity and 88% agreement on the alteplase decision. This level of agreement was the same as that between two vascular neurologists evaluating the same patients face-to-face in the emergency department.[34]

Staffing: who needs to be on board?

Although most research projects have included a vascular neurologist on board the ambulance,[18,31,35–37] absolutely reliable telecommunication connectivity permits the sole reliance on paramedics, with or without nurses and radiographers, guided by neurologists and neuroradiologists at a remote hospital via telemedicine.[32–34] Research in Norway[38] is exploring whether a prehospital stroke diagnostic work-up, including neuroradiological assessment, can be performed by trained non-neurologist physicians.

Because of legal restrictions, most MSUs operate in addition to conventional emergency medical services. Moreover, in published studies, use of MSUs has been restricted to daytime and evening hours. For example, in the first randomised trial,[35] the MSU was in operation from 0800 h to 2200 h from Monday to Friday, and from 0800 h to 1800 h on weekends. With further evidence, and the resolution of legal and reimbursement issues, operational models might change.

Prehospital brain imaging

Imaging is key in the management of acute stroke. For acute cerebral ischaemia, CT or MRI must exclude haemorrhage before intravenous thrombolysis can be provided.[16,17] Signs of early infarction can predict a reduced response to alteplase and an increased rate of adverse effects. In addition, vascular imaging (CT angiography or MR angiography) is recommended for identification of large-vessel occlusion, in light of novel endovascular treatment options.[39] For acute intracerebral haemorrhage, imaging results such as the so-called spot sign can allow estimation of the risk of early haematoma growth.[40]

So far, multimodal imaging (non-contrast CT, CT angiography, and CT perfusion)[18,31,35] excluding MRI has been integrated into MSUs (figure 2).[41] Most scanners used in ambulances were originally designed for use in intensive care units. As such, they are portable, accumulator driven, and radiation shielded.[18,35] The images produced by the 8-slice CT scanners most frequently used in MSUs (eg, Ceretom, Neurologica/Samsung, Boston, MA, USA) are of sufficient quality for brain parenchymal imaging and for CT angiography of the intracranial circulation, including the circle of Willis, although these scanners do not allow assessment of the proximal neck vessels or the aortic arch. A different scanner (Somatom Scope, Siemens, Erlangen, Germany), which is being used in an MSU research project in Memphis (TN, USA), allows not only higher-resolution imaging than does the Ceretom but also assessment of the neck vessels and the aortic arch. However, these improvements come at the expense of bigger size, requiring more space, and on-board power generation.

Prehospital point-of-care laboratory

According to guidelines,[16,17] a limited number of laboratory tests (eg, platelet, leucocyte, and erythrocyte counts; haemoglobin and glucose levels; activated partial thromboplastin time and international normalised ratio; γ-glutamyltransferase and pancreatic amylase activity)

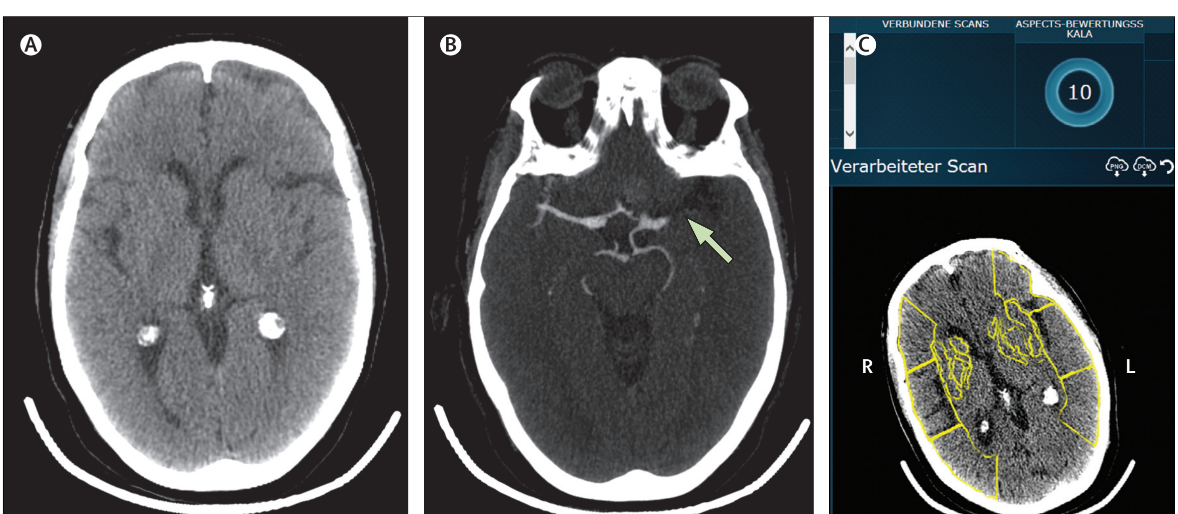

Figure 2: **Multimodal imaging in a mobile stroke unit**
Non-contrast CT (A), CT angiography (B), and ASPECTS (C) done in a mobile stroke unit of a 73-year-old woman with acute right hemiparesis. Although the parenchyma shows no signs of infarction (ASPECTS 10), CT angiography allowed prehospital diagnosis of an occlusion of the left middle cerebral artery (B, arrow). Reproduced from Grunwald et al,[41] by permission of *Cerebrovascular Diseases* (Karger). ASPECTS=Alberta Stroke Program Early CT Score.

are recommended, but should not delay the start of thrombolysis. The only laboratory test required in most patients before start of fibrinolytic therapy is glucose level. Platelet count and measures of coagulation function should be obtained before therapy in case of clinical suspicion of bleeding abnormality or thrombocytopenia, or if the patient could have received anticoagulant therapy. Knowledge of creatinine level is considered helpful for concerns regarding renal function.

Generally, evidence is poor regarding the relevance of these laboratory tests in decision making in acute stroke management and, to avoid delays, many centres do not await the laboratory work-up (except of glucose levels and international normalised ratio) in the absence of known coagulopathy before administering alteplase. Extended laboratory testing was shown to be more expeditiously conducted with a point-of-care laboratory system than in a hospital laboratory and can be used in MSUs.[18,31,35] Point-of-care testing devices must comply with legislative directives to assure patient safety (ie, CE marking, indicating conformity for products sold in the European Community). A preliminary in-hospital proof-of-principle study[42] has shown that use of a point-of-care laboratory decreased time from door to therapy decision (end of all diagnostic procedures) from 84 min (SD 26) to 40 min (SD 24; $p<0 \cdot 0001$) compared with use of a centralised hospital laboratory. Nonetheless, the relevance of point-of-care laboratory results on treatment decisions is unclear, and requires clarification in further studies.

Instruments for dispatch of the ambulance

For the most efficient use of MSUs, dispatchers need to identify patients with stroke with the highest possible sensitivity and specificity. Generally, identification of stroke through telephone calls is a serious challenge for dispatchers at emergency medical services.[43,44] This requirement might be facilitated by the use of stroke checklists during the initial screening.[44–46] So far, the Recognition of Stroke in the Emergency Room (ROSIER) scale[46] with a reported sensitivity of 93% and specifity of 83% and the Dispatcher Identification Algorithm of Stroke Emergency (DIASE), with a reported sensitivity of 53% and a specificity of 97% for stroke,[47] have been used as inventories for dispatch in MSU studies.[18,31,35,37,48] For the future development of a dispatch tool, a good balance between sensitivity and specificity is necessary so that strokes will not be missed, but the MSU will not be dispatched too often for conditions mimicking stroke.

Prehospital stroke management

After prehospital stroke thrombolysis was shown to be feasible,[18] a randomised, single-centre trial,[35] in which 361 patients were screened and 100 recruited, was done by Saarland University in Homburg, Germany. In this MSU trial,[35] prehospital stroke management achieved a median time from symptom onset to therapy decision of 56 min (IQR 43–103) and a median time from symptom onset to treatment of 72 min (53–108), without safety concerns (table). Such reductions in delays before treatment were confirmed in the PHANTOM–S (Pre–Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke) study,[37] in an observational study[50] in Houston (TX, USA), and in a case series[51] in Cleveland (OH, USA; table). The times from these studies are much faster than those observed in all earlier studies evaluating the effect of interventions on reduction of delays to treatment in the emergency department,[44] with reported time from symptom onset to treatment usually exceeding 120 min. These metrics also exceed those of stroke management observed in clinical practice, with reported median time from symptom onset to treatment of 140 min (110–165) in the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS–MOST),[54] which involved 6853 patients treated at 285 European centres between 2002 and 2006, or of 144 min (115–170) in the Get With The Guidelines-Stroke registry, which involved 58 353 patients treated in 1395 US hospitals between 2003 and 2012.[5] In addition to accelerating the initiation of therapy for patients who would have been treated with thrombolysis in hospital, MSU treatment will also enable more patients to be treated within the recommended therapeutic window of $4 \cdot 5$ h.[16,17] This capacity is also suggested by the improved treatment rates in the MSU trial[35] and the significant increase in treatment rates of prehospital stroke treatment in the PHANTOM-S trial[37] (table). The question of how many additional patients could be treated with thrombolysis if the MSU concept were widely used is intriguing, and should be answered in future studies done in specific health-care systems and settings.

Breaking the golden hour limit

The term golden hour has been attributed to the trauma surgeon R Adams Cowley, who recognised that the sooner trauma patients receive definitive care—particularly within the first hour after trauma—the better their chance of survival. To illustrate the pronounced time sensitivity of acute stroke management,[3–9,55] the term has also been applied to this clinical situation. However, only a very small proportion of patients with stroke receive treatment during the golden hour. In the National Institute of Neurological Disorders and Stroke (NINDS) study,[56] only two (<1%) of 302 patients were randomly assigned to a study group within 60 min (both were assigned to placebo). In the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Registry (SITS–ISTR) observational study,[57] only 166 ($1 \cdot 4$%) of 11 429 patients were treated within 60 min, and in the Get With The Guidelines-Stroke registry,[5,58] 750 ($1 \cdot 3$%) of 58 353 patients were treated within this time, despite substantial efforts to improve stroke management over the past decade. Even in studies with streamlined protocols leading to door-to-needle times as short as 20 min, no more than 10% of patients were

	Site	Study design	Condition	Number of patients with intervention vs standard care*	Time from alarm† to CT (min)	Time from alarm† to therapy decision or therapy (min)	Time from symptom onset to therapy decision or therapy (min)	Number (%) of treated patients with ischaemic stroke	Number (%) of patients with time to therapy decision‡ or therapy ≤60 min
Walter et al[18]	Homburg, Germany	Case report	Acute stroke	2	34, 33	To therapy decision: 35, 33	To therapy decision: 60, 50	··	··
Kostopoulos et al[31]	Homburg, Germany	Case series	Acute stroke	4	38, 41, 41, 27	To therapy decision: 38, 41, 41, 27	To therapy decision: 98, 78, 46, 35	··	··
Walter et al[35]	Homburg, Germany	Randomised	Acute stroke	53 vs 47	34 (30–38) vs 71 (62–87), p<0·0001	To therapy decision: 35 (31–39) vs 76 (63–94), p<0·0001; to alteplase: 38 (34–42) vs 73 (60–93), p<0·0001	To therapy decision: 56 (43–103) vs 104 (80–156), p<0·0001; to alteplase: 72 (53–108) vs 153 (136–198), p=0·0011	12 (41%) of 29 vs 8 (32%) of 25, p=0·48	To therapy decision: 30 (57%) of 53 vs 2 (4%) of 47, p<0·0001
Weber et al[48]	Berlin, Germany	Observational	Acute stroke	45 vs 50 historical controls	··	To alteplase: 58 (50–65) vs 92 (79–112)	To alteplase: 97 (69–156)	23 (51%) of 45	To alteplase: 4 (17%) of 23
Ebinger et al[37,49]	Berlin, Germany	Randomised	Acute stroke	1804 vs 2969	35 (30–42) vs 50 (43–59)	To alteplase: 48 (39–56) vs 72 (62–85), p<0·001	To alteplase: 81 (56–129) vs 105 (81–145), p<0·001	200 (33%) of 614 vs 220 (21%) of 1 041, p<0·001	To alteplase (subgroup analysis of treated patients): 62 (31%) of 200 vs 16 (5%) of 330, p<0·01
Bowry et al[50]	Houston, TX, USA	Case series	Acute stroke	24	··	··	To alteplase: 98 (47–265)‡; to intra-arterial therapy: 175 (140–224)‡	12 (50%) of 24	To alteplase: 4 (33%) of 12
Parker et al[36]	Houston, TX, USA	Case series	Acute stroke	24	··	On-scene time to alteplase: 24 (12–53)‡	··	··	4 (31%) of 13
Taqui et al[51]	Cleveland, OH, USA	Case series	Acute stroke	23 vs 34 historical controls	41 (33–47) vs 62 (50·5–97·5), p<0·0001	To alteplase: 64 (58·3–72·3) vs 105 (99–115), p=0·008	To alteplase: 115 (77·5–144) vs 125 (97·5–151·5), p=0·52	6 (26%) of 23 vs 5 (15%) of 34	··
Itrat et al[32]	Cleveland, OH, USA	Observational study	Acute stroke	100 vs 56 historical controls	From door: 13 (9–21) vs 18 (12–26), p=0·003	Door to alteplase: 32 (24–47) vs 58 (53–68), p<0·001	··	··	··
Cerejo et al[52]	Cleveland, OH, USA	Observational study	Acute stroke treated with intra-arterial therapy	5 vs 5 historical controls	From door: 12 (9–14) vs 32 (22–375)	CT to intra-arterial therapy: 82 (65–103) vs 165 (150–201)	··	··	··
Kunz et al[53]	Berlin, Germany	Observational registry study§	Acute stroke treated with alteplase	305 vs 353	··	To alteplase: 46 (39–53) vs 76 (64–93), p<0·0005	To alteplase: 73 (53–120) vs 112 (85–175), p<0·0005	··	··

Times are given as individual times or median (IQR) unless otherwise stated. Therapy decision defined as end of all stroke diagnostic examinations. *If applicable. †If starting point is not otherwise specified. ‡Data are mean (range). §Including patients from the PHANTOM-S Trial[35] and its pilot study.[45]

Table: **Studies of stroke management in prehospital mobile stroke units**

treated within 70 min after symptom onset[59]—a finding suggesting a possible ceiling effect with regard to the timing of conventional stroke management.

MSUs can break this golden hour limit, as shown in the first MSU trial,[35] by the increase in rates of patients with therapy decision within 60 min of symptom onset (table). Further studies support this conclusion, with increased rates of treatment within 60 min in the PHANTOM-S trial[49] and in the Houston MSU programme[36] (table). These unprecedentedly short times to treatment could translate into improved clinical outcomes, although the extent of this improvement is not fully known owing to the small number of patients treated within such time dimensions to date.[44,60,61] So far, stroke patients treated within such an early time frame have been reported to have significantly better clinical outcomes than those treated later.[5,58]

Prehospital treatment of haemorrhagic stroke

Because haemorrhage enlargement occurs very early in the course of intracerebral haemorrhage, the time is brain concept probably also applies to haemorrhagic stroke. Differential adjustment of blood pressure might be beneficial for patients with ischaemic or haemorrhagic stroke,[62] and recommendations for blood pressure management differ for stroke caused by ischaemia (elevated blood pressure as high as 185/110 mm Hg can be tolerated by patients receiving thrombolysis)[17] or by haemorrhage (reduction of systolic blood pressure to 140–160 mm Hg is safe and can be clinically effective).[63]

However, during the prehospital phase in conventional ambulances, the cause of stroke remains unknown, meaning that early differential blood pressure management is impossible. Diagnostic clarification using an MSU allows differential adjustment of physiological variables such as blood pressure before hospital arrival.[18] Warfarin-related intracranial haemorrhage composes 15–20% of intracerebral haemorrhages and is associated with a high mortality.[64] Guidelines recommend reversal of warfarin's effects by medication, such as prothrombin complex concentrates.[63] With prehospital diagnosis of haemorrhagic stroke, warfarin effects can be reversed directly at the emergency site.[65] In the future, such an approach might even be extended to reversal of the effects of novel oral anticoagulants by antidotes.

Triage to the target hospital

International guidelines[16,17] recommend prenotification of the target hospital about a patient en route as an evidence-based measure to accelerate in-hospital stroke management.[44] MSUs offer the unique option to provide the target hospital with detailed information about the cause of the disease and any information needed for subsequent specialised treatment.

Guidelines recommend that patients must be transported to the closest available hospital or to a stroke centre or, if no such facility is nearby, to the most appropriate institution that can provide stroke care.[16,17] This practice is under discussion in light of the emerging evidence for the safety and efficacy of intra-arterial treatment, and the possibility of performing this specialised treatment only at comprehensive stroke centres, but not at primary stroke centres. Indeed, patients with large-vessel occlusion often arrive at endovascular centres too late for effective treatment if they are first transferred to a hospital without endovascular treatment capabilities and later transferred to a comprehensive stroke centre (figure 1). Patients in the Interventional Management of Stroke III study[66] who were given alteplase at a primary stroke centre before transfer to a comprehensive stroke centre (ie, the drip and ship method) had significantly longer median times from alteplase to groin puncture (105 min, IQR 47) than did those directly admitted to and treated in the comprehensive stroke centre (ie, the mothership method; 83 min, IQR 31; $p<0\cdot0001$). Similar delays were observed in patients treated in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial,[67] in which time from symptom onset to door of the comprehensive stroke centre was 41% (32 min) longer if patients received alteplase at the referring hospital rather than at the comprehensive stroke centre. It has been estimated that every minute of delay in transfer reduces the probability that patients will receive intra-arterial treatment by 2·5%.[68]

Therefore, accurate triage with regard to the appropriate target hospital would avoid the transfer of patients with large-vessel occlusion to hospitals without endovascular treatment services and, at the same time, prevent the transfer of all patients to comprehensive stroke centres, which prevents efficient use of limited resources.

Options being discussed to improve the accuracy of triage under discussion include the use of clinical stroke scales aimed at differentiating patients with or without large-vessel occlusion.[69] A retrospective study[70] involving 119 patients showed that a score of 4 or higher on the Los Angeles Motor Scale predicts the presence of large-vessel occlusion with a sensitivity of 81% and a specificity of 89%. A prospective evaluation[71] involving 357 patients found that a score of 5 or higher on the Rapid Arterial Occlusion Evaluation scale predicts the presence of large-vessel occlusion with a sensitivity of 88% and a specificity of 68%. In a prospective study,[72] the Field Assessment Stroke Triage for Emergency Destination scale, based on items of the National Institutes of Health Stroke Scale with a cutoff value of 2 or higher, exhibited a sensitivity of 60% and a specificity of 89% for predicting large-vessel occlusion. A retrospective investigation[73] found that the Prehospital Acute Stroke Severity scale, with a cutoff of 2 or higher, exhibited a sensitivity of 66% and a specificity of 83% in predicting large-vessel occlusion. However, all studies have found that a sizable number of large-vessel occlusions are missed by clinical scores.[74,75] Furthermore, all of these scales have been developed in emergency departments by physicians, and none have been tested by personnel in the prehospital environment. Development of such a scale or validation of existing scales is another area ripe for investigation on the MSU.

By contrast, when vascular imaging such as CT angiography is implemented in the MSU,[35] correct triage of patients with stroke to the appropriate target hospital becomes possible owing to knowledge about the presence or absence of large-vessel occlusion directly at the emergency site (figure 2).[31] Use of a MSU even with non-contrast imaging has been associated with reduction of delay before intra-arterial treatment in patients with large-vessel occlusion.[52]

Analogously, prehospital imaging has been shown to allow the triage of patients with haemorrhagic stroke to hospitals with neurosurgery services, bypassing hospitals without such capabilities.[31] A subgroup analysis[76] of the PHANTOM-S study[37] found that the rate of patients with haemorrhage delivered to hospitals without neurosurgery services decreased from 65 (43%) of 151 patients in the conventional treatment group to seven (11%) of 62 patients in the intervention group.

Finally, although prehospital diagnosis and treatment of stroke are likely to remain the main indications for the use of MSUs, patients with several time-sensitive cerebral conditions other than stroke, such as traumatic brain injury or status epilepticus, could also benefit from the diagnosis-based triage enabled by MSUs.[77]

Conclusions and future directions

Worldwide, the number of prehospital stroke treatment programmes is rapidly increasing, with more than 20 sites studying their provision (figure 3). Most of these groups cooperate in the context of the Pre-hospital Stroke Treatment Organization (PRESTO), dedicated to improving data exchange and collaboration. However, whether prehospital stroke treatment will be increasingly implemented and sustainable over time remains to be seen; this outcome depends on the resolution of issues on safety, long-term clinical benefit, best setting (eg, rural *vs* urban, regional emergency medical services configuration), and cost-effectiveness. The MSU strategy cannot replace continuous efforts to improve the quality of the standard prehospital and in-hospital stroke care.[44] Because the time from stroke onset to emergency call is beyond the influence of the deployment of an MSU, public education projects are of relevance.[44] The MSU, as a sort of rolling billboard in the community, might in itself promote public awareness.

Diagnosis and treatment in an MSU can occur with a level of expertise and equipment comparable to those in a hospital;[18] thus, treatment in an MSU is expected to be as safe as treatment in a hospital. Technical failure rates are, at present, within the range of those associated with routine emergency ambulances, and the corresponding hospital equipment. One concern might be that earlier evaluation might result in alteplase treatment for an increased number of stroke mimics. This concern applies to every intervention that aims to decrease time to treatment, which inherently shortens the time to observe the natural disease course. Although previous studies[32,35–37,48] of the deployment of an MSU have found no significant differences with regard to indicators of safety, such as haemorrhagic complications or mortality, safety is still a relevant issue for future research.

According to the generally accepted concept that time is brain,[7–9] the clear reduction of delays before treatment argues for a clinical benefit. However, the first randomised trial[35] of prehospital stroke treatment found no differences in 7-day modified Rankin scores and National Institutes of Health Stroke Scale scores—a finding that can be explained by the insufficient power of the trial to detect differences in these endpoints. Also, although the PHANTOM-S trial[37] found that patients who received prehospital stroke treatment were more likely to be discharged home, the study did not find significant improvements in short-term outcomes. An evaluation[53] of a large registry of patients treated with alteplase between 2011 and 2015 did not find a significant increase in the primary outcome of a 90-day modified Rankin score of 0 or 1 (53% *vs* 47%; p=0·14), despite the fact that 112 (37%) of 305 patients treated in the MSU received thrombolysis within the golden hour. However, results significantly favoured the MSU cohort when the analysis was adjusted for baseline differences between the non-randomised groups, and the study also found positive dichotomised secondary outcomes, such as a modified Rankin score of

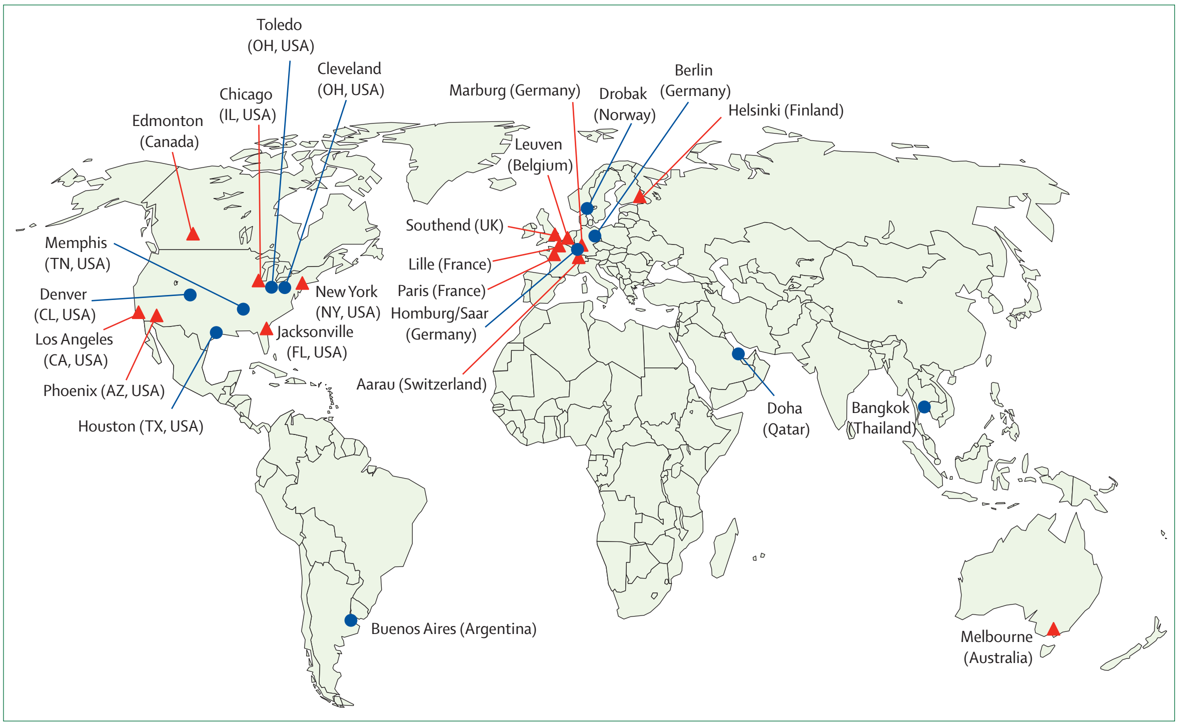

Figure 3: **Mobile stroke unit research projects**
Blue circles indicate sites with active mobile stroke units and red triangles indicate sites in which such projects are in the state of implementation.

2 or lower and mortality. Thus, direct evidence from controlled trials comparing similar patients managed by the MSU or by standard emergency medical care is still needed. Indeed, the Benefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST-MSU) trial[50]—a prospective, randomised multicentre trial coordinated in Houston (TX, USA)—was initiated in 2015. This study, which is planned to include 900 patients, is expected to provide information about clinical and cost-effectiveness of the MSU approach.

Importantly, the generalisability of the previous results on prehospital stroke treatment needs to be demonstrated in various health-care systems with differing configurations of emergency care, legislation requirements, market forces, and demography. The results of the more than 20 ongoing and planned projects worldwide (figure 3) might provide such much-needed information.

The configuration of emergency services is highly variable across different countries. For example, in some European countries the presence of a physician is mandatory, whereas in other countries emergency services are exclusively staffed by paramedics.[44] Regional differences in conventions and legislation clearly affect the configuration of MSUs and the degree of integration of the MSU concept into the setting of emergency services. Further research is also needed regarding optimised interaction between MSUs and primary or comprehensive stroke centres in different health-care environments. The benefit of this approach strongly depends on the regional medical standard. Thus, in countries with no thrombolytic options available, bottom-up implementation of such treatment options in the hospital takes priority. Moreover, more research is needed to determine the suitability of the MSU concept in urban, suburban, and rural regions. Because the number of dispatches increases with population density, the MSU appears, at first glance, to be especially advantageous in urban regions. However, because rural regions are often highly underserved with regard to stroke expertise,[79] the value of this strategy could also be substantial in rural areas.[78] MSUs could also meet the regular emergency medical services ambulance en route at a predefined meeting point. This approach is comparable to that of bringing CT scanners to rural hospitals without such imaging facilities.[80]

Despite the evidence indicating improvements in process management for one of the most expensive diseases,[1] important concerns remain with regard to the potentially unacceptable costs of the MSU, its staffing, and its deployment. However, two independent preliminary cost-effectiveness analyses of MSU systems based on modelling health-care costs and outcomes had encouraging results. Dietrich and colleagues[78] performed a 1-year cost–benefit analysis of MSUs across a number of scenarios, based on the first controlled MSU trial.[35] The economic benefits outweighed its costs: the benefit–cost ratio was 1·96, even in the baseline experimental setting and with two physicians on board. Benefit–cost ratios increased substantially with gradual reductions of staff (eg, use of telemedicine) and with higher population density. Maximum benefit–cost ratios between 2·16 and 6·85 were identified at optimum operating distances ranging from 26·73 to 40·32 miles, depending on the staff configuration. Although efficiency is positively related to population density, benefit–cost ratios can also be greater than 1 in rural settings.

A further estimate by Gyrd-Hansen and colleagues[81] also suggested the cost-effectiveness of prehospital stroke treatment. This estimate considered the results of the PHANTOM-S trial,[37] with an annual net cost of €963 954 because of more frequent and earlier administration of alteplase, and calculated an annual expected health gain, related to the avoidance of 18 cases of disability, equal to 29·7 quality-adjusted life-years. This calculation produced an incremental cost-effectiveness ratio of €32 456 per quality-adjusted life-year. This estimate meets the standard threshold to judge a system innovation as a cost-effective intervention. In the future, cost-effectiveness might be considerably improved by various measures—eg, substitution of physically present physicians for remote hospital experts linked via telemedicine,[32] use of standard ambulance solutions as the basis of the unit,[21] increased usage rates, or improved stroke-identification algorithms for dispatchers.[78]

Demonstrating the cost-effectiveness of MSU deployment as a precondition for its future reimbursement remains a key research issue. This research should include prospective data on the actual costs for establishing and maintaining MSUs, and for both acute and long-term care of patients managed both on MSUs and by standard emergency services, and should include analysis from the perspective of MSU providers, tax payers, and patients.

In conclusion, this Review of prehospital stroke treatment and the data emanating from MSU studies shows that diagnostic clarification in the ambulance allows not only prehospital thrombolysis, comprehensive prenotification, and correct triage to the most appropriate target hospital, but novel options that might also include cause-specific adjustment of physiological parameters, reversal of anticoagulant effects, and prehospital management of other cerebral emergencies. The MSU allows future research on diagnostic and therapeutic options such as blood markers of cerebral damage,[82] transcranial duplex ultrasonography[83] and automated imaging decision support tools,[41] improved

Search strategy and selection criteria

We searched PubMed between Jan 1, 2010, and Dec 31, 2016, for the terms “stroke” combined with “prehospital”, “pre-hospital”, “ambulance”, “emergency medical service”, or “mobile stroke unit” and found 717 publications. We reviewed articles focusing on originality, timeliness, and relevance to the broad scope of this Review.

clot-dissolving medications, sonothrombolysis,[84] neuroprotectants,[85] and haemostatic treatments to reduce haematoma growth.[86] MSUs can serve as an ideal tool for research on hyperacute stroke, profiting from the valuable contribution of paramedics.[85,87,88] Additional studies are needed to substantiate safety, clinical benefit, best setting, and cost-effectiveness as preconditions for a wide implementation of MSUs in clinical practice.

Contributors

All authors contributed to the literature search and to writing and reviewing the manuscript.

Declaration of interests

JCG is an employee of Memorial Hermann Hospital. Genentech supplies alteplase for his MSU research. JCG is a consultant to Stryker, which manufactures equipment used on MSUs and devices for stroke treatment, and to Frazer Ltd, which manufactures MSUs. IQG is co-founder and Medical Director of Brainomix Ltd, an Oxford University spin-out that is not in competition with this Review. She is involved in the running of medical conferences that have received industry support from Penumbra, Medtronic/Covidien, Micrus/Codman, Acandis, Stryker, Phenox, Gore, Siemens, Phillips, Toshiba, GE, Simbionix/3D Systems, Cook, Microvention, Balt, Abbott and Mentice, but does not receive payments for this. She has received consultancy fees or travel support from Micrus, Medtronic, Penumbra, 3D Systems, and Mentice. JLS has served as an unpaid site investigator in multicentre trials run by Medtronic and Stryker for which the University of California Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled. JLS receives funding for services as a scientific consultant regarding trial design and conduct from Medtronic/Covidien, Stryker, Neuravi, BrainsGate, Pfizer, Squibb, Boehringer Ingelheim (prevention only), ZZ Biotech, and St Jude Medical. JLS serves as an unpaid consultant to Genentech, advising on the design and conduct of the PRISMS trial; neither the University of California nor JLS have received any payments for this voluntary service. The University of California has patent rights in retrieval devices for stroke. All remaining authors declare that they have no competing interests.

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