

Translation of the 'time is brain' concept into clinical practice: focus on prehospital stroke management

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Acute stroke is one of the main causes of death and chronic disability. Thrombolysis with recombinant tissue plasminogen activator within the first hours after onset of symptoms is an effective therapeutic option for ischemic stroke. However, fewer than 2% to 7% of patients receive this treatment, primarily because most patients reach the hospital too late for the initiation of successful therapy. Several measures can reduce detrimental delay until treatment. It is of importance to use continual public awareness campaigns to reduce delays in patients' alarm of emergency medical services. Further relevant measures are repetitive education of emergency medical services teams to ensure the systematic use of scales designed for recognition of stroke symptoms and the proper triage of patients to stroke centers. A most important time-saving measure is prenotification of the receiving hospital by the emergency medical services team. In the future, treatment already at the emergency site may allow more than a small minority of patients to benefit from available treatment.

Key words: emergency medical service, mobile stroke unit, prehospital phase, stroke management, thrombolysis

Background

Stroke is one of the leading causes of death and the most frequent reason for permanent disability (1). Thrombolysis with recombinant tissue plasminogen activator (rt-PA) is the only approved and causal therapy for acute ischemic stroke (2). The benefit of this therapy is, however, extremely time sensitive: The number needed to treat to achieve a good outcome is 4.5 if treatment starts within 1.5 h. This number doubles to 9 if treatment is initiated within 1.5 to 3.0 h and reaches 14.1 if treatment occurs within the temporal window of 3.0 to 4.5 h (3). The 'time is brain' concept that has been derived from such observations is also supported by earlier experimental animal research (4,5) and by calculations indicating that for each minute in which a stroke remains untreated, as many as 1.9 million neurons and 14 billion synapses may die (6).

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However, before rt-PA can be administered, a complex diagnostic workup, including neurological examination, imaging studies, and laboratory tests, is necessary to exclude hemorrhage or other contraindications to rt-PA therapy. For this reason, treatment within the narrow temporal window of a few hours is difficult to achieve in clinical reality, and, in the end, no more than 2% to 7% of all acute stroke patients currently receive treatment (7).

The blame for this problem of undertreatment with thrombolysis can be placed primarily on activities that occur before the patient reaches the doors of the hospital. In Germany, for example, the median prehospital time is 151 mins, and only 45% of patients reach the hospital within three-hours (8). Data from the American Get With the Guidelines Stroke Registry clearly show that, despite considerable attempts to improve stroke management (e.g., by public education programs), delays in the time to hospital admission did not improve in recent years (9) [for a detailed systematic literature review on prehospital delays, see Evenson *et al.* (10)].

Methods

This review examined reports published since 1980 and found by searching PubMed for articles containing the terms 'stroke management'; 'prehospital' and 'stroke'; 'stroke' and 'educational campaign(s)'; 'stroke' and 'public awareness'; and 'emergency medical service' and 'stroke'. Articles were selected on the basis of their originality and their relevance to the topic of prehospital stroke management.

Results and discussion

Role of patients and relatives

Problems in prehospital stroke management can be attributed to two groups: the patients and their families, and the emergency medical services (EMS) team. With regard to the role of the patients and their relatives, it is important to consider that 24% to 55% of acute stroke patients or their relatives do not notify the EMS within one-hour, but rather use a private vehicle to transport the patient to the hospital, visit their family doctor, wait too long, or do not notify anyone (11–13). Many reasons for this inadequate response to stroke symptoms have been described and may be demographic, social, medical, or psychological in nature [(11–19), Table 1].

Stroke educational campaigns could, therefore, be a solution for improving patients' and families' awareness of the correct response in case of stroke. Such campaigns have been shown to have a short-term impact on stroke symptom knowledge. However, consistent evidence confirms an existing gap between

Table 1 Determinants of care-seeking behavior in acute stroke

Factors	Early alarm	Late alarm	References
Demographic	Women	Men	11
	High level of education	Low level of education	12, 14, 15
	High income	Low income	
Social	Presence of bystanders	Ethnic minorities	16
	Family history of stroke	Being alone	12, 17, 18
Medical	Severe symptoms	No family history	13, 18
	Acute onset	Mild symptoms	
Psychological		Delayed onset	
		Fear of disease and hospital	11, 19

the knowledge and recognition of stroke symptoms and the appropriate urgent response to such symptoms (for detailed systematic literature reviews, see Teuschl & Brainin, Jones *et al.*, and Lecouturier *et al.* (20–22)).

A very recent study consisting of individual semi-structured interviews with stroke patients, stroke witnesses, and primary care clinicians examined the perceived impact of and views about the United Kingdom's mass media campaign Act FAST. Most participants were aware of the Act FAST campaign, and some patients and witnesses reported that the campaign affected their stroke recognition and response, but most reported no effect. Clinicians were positive about the campaign and believed that it had affected stroke awareness and recognition, but doubted its impact on response behavior (23).

Only a few of these existing studies, however, analyzed the effects on clinically relevant end-points of stroke management, such as time to hospital admission or thrombolysis rates [(24–31), Table 2]. These variables are examined primarily in interventional studies with a noncontrolled 'before and after intervention' design. Only two of the currently existing studies applied a controlled design, including control groups of patients from catchment areas without such interventions (Table 2). Most of these studies revealed the effects of public awareness campaigns on patients' behavior (Table 2); however, these effects probably last for no more than five-months. Because of studies showing that the nature of the effects of such campaigns is rather transient (26), constant repetition of their message is a central precondition for their success (26).

These findings suggest that public education efforts are worthwhile, and future efforts should focus more strongly on specific target groups, such as the elderly, minorities, neighbors of stroke survivors, medical students, and even children (who may be future relatives, patients, or physicians) (32–36). Importantly, educational campaigns should present in a very simple message the action that should be undertaken in case of emergency (e.g., 'call EMS immediately'). However, rather than relying on a fear appeal alone, which is more likely to cause people to stop a behavior rather than to perform an action, such a message should also be encouraging. Thus, a still-ongoing campaign, the National Stroke Association's Faces of Stroke multimedia public awareness campaign (37) presents the personal and emotional side of stroke, including stories of stroke survivors and caregivers, thereby aiming to generate empathic feelings and to transmit the positive message of the

existence of treatment. In general, the major problem of under-treatment of stroke and change of behavior is a highly interdisciplinary task, including, for example, the contribution of health behavior scientists in assessing concepts of behavior change.

Role of the EMS

Structures of EMS systems differ not only between countries but also within single countries. This is especially the case with regard to the variable disposition of an emergency physician when acute stroke is suspected. However, a large body of evidence already exists for some measures of acute stroke management, and, therefore, clear recommendations have been given by national and international stroke management guidelines (38,39). These guidelines include the recommendation of continued education of the EMS team regarding the use of instruments for the recognition of stroke symptoms, the emergency transport of patients to a hospital with stroke expertise, and, finally, the prenotification of the receiving hospital.

Use of instruments for symptom recognition

It has been shown that the accuracy with which EMS dispatchers identify stroke symptoms is highly variable, ranging from 30% to 83% (40,41); this finding highlights the need for continued further training. Most national and international stroke guidelines recommend, apart from medical training, the use of structured interviews by the dispatcher and the application of instruments designed for recognition of stroke symptoms by the EMS team in the field. For example, the Cincinnati Prehospital Stroke Scale (sensitivity of 90% and specificity of 66% for the presence of acute stroke) is based on the presence of facial paresis, one-sided paresis of an upper extremity, and speech disorder (by asking the patients to repeat specific sentences) (42). The Los Angeles Prehospital Stroke Screen includes, in addition to these items, four additional questions about history and the results of a glucose test (43). The sensitivity (91%) and specificity (97%) of this scale are very high (43); however, this scale is quite complex for routine daily use and is also time consuming. The Face Arm Speech Time (FAST) Stroke Assessment is based on the three elements of the Cincinnati Prehospital Stroke Scale, but it assesses possible speech disorders during normal conversation (44). This scale has a sensitivity of 79% and is so easy to perform that it can even be used by the general public.

Whereas in the United States either the Los Angeles Prehospital Stroke Screen or the Cincinnati Prehospital Stroke Scale is most

Table 2 Studies on the effect of public awareness campaigns on indicators of stroke management quality

References	Site (number of stroke centers)	Study design	Study duration	Number of stroke patients with and without intervention	Target group		Time until hospital admission with and without intervention	Thrombolysis rates with and without intervention
					General public	EMS		
Alberts <i>et al.</i> (24)	Durham, United States (1)	Before vs. after implementation	Three-years	189 vs. 290	+	+	Within 24 h: 86% vs. 37%, $P < 0.00001$	–
Wojner-Alexandrov <i>et al.</i> (25)	Houston, TX, United States (6)	Before vs. after implementation	Three-years	1072 vs. 446	+	+	Within two-hours: 62% vs. 58%, $P = 0.002$	Increase in 4/6 centers, decrease in 2/6
Hodgson <i>et al.</i> (26)	Ontario, Canada (11)	Longitudinal observation	31 months	12534	+	–	within 2.5 h: continuous increase between 2003 and 2005, $R^2 = 0.60$, $P < 0.001$	–
Morgenstern <i>et al.</i> (27)	Texas, United States (10)	Controlled observation	15 months	interventional region: 400 vs. 218; control region: 365 vs. 206	+	+	Within two-hours: 36.5% vs. 26.5%, $P < 0.05$ in the interventional region and 30.4% vs. 21.4%, $P = 0.07$ in the control region	5.8% vs. 1.4%, $P < 0.05$ in the interventional region vs. 0.6 vs. 0.5%, n. s. in the control region
Barsan <i>et al.</i> (28)	United States (12)	Before vs. after implementation	Three-years	487 vs. 487	+	+	1.5 h vs. 3.2 h (means, $P < 0.05$)	–
Müller-Nordhorn <i>et al.</i> (29)	Berlin, Germany (3)	Controlled observation	One-year	647 vs. 741	+	–	Within three-hours: 34% vs. 28% (significant only for women, acceleration factor 0.73; 95% CI: 0.58–0.94; $P < 0.05$)	–
Addo <i>et al.</i> (16)	London, UK (1)	Before vs. after implementation	Two-years	154 vs. 195	+	+	Within three-hours: 44.9% vs. 40.7%, n.s.	16.4% vs. 16.9%, n.s.
Behrens <i>et al.</i> (30)	Mannheim, Germany (1)	Before vs. after implementation	Three-months	113 vs. 83	+	+	3.28 h \pm 40 min vs. 5.22 h \pm 84 min (means \pm SD, $P < 0.05$)	10.5% vs. 2%, $P < 0.01$
Rau <i>et al.</i> (31)	Wesel, Germany (8)	Before vs. after implementation	Two-years	375 vs. 326	+	–	Within three-hours: 27.5% vs. 27.3%, n. s.	–

EMS, emergency medical services; n.s., not significant.

frequently used, in Europe the FAST Scale is most widely distributed; and in Australia the Melbourne Stroke Screen (45) is most often used. In general, however, the daily routine of the dispatcher and of the EMS team is still characterized by the mostly nonsystematic and undocumented use of such instruments; this finding underscores the importance of further training efforts.

Prioritized transport to hospitals with stroke expertise

Prioritized transport to hospitals with stroke expertise and with the option for thrombolytic treatment is crucial in optimized prehospital stroke management. Such measure has been shown to reduce time to treatment and to increase thrombolysis rates without negatively influencing the quality of treatment of other emergencies (46). An additional reason for this recommendation is the strong evidence of a general benefit for treatment in a specialized stroke unit. In specific settings, the use of helicopters for transport to more distant stroke centers can also save critical time to treatment (47). A recent prospective multicentric study showed that treatment rates increase from 14.1% to 21.9% (OR, 1.72; 95% CI, 1.22–2.43) if patients are transported to stroke centers rather than to nonspecialized institutions (48). This is even the case if the distance to a stroke center is considerably greater than that to a nonspecialized hospital.

Most advanced stroke management protocols, such as a city-wide protocol implemented in Toronto, Ontario, Canada (49), also include, apart from the use of standardized screening systems by the EMS team, the implementation of protocols for bypassing hospitals without stroke expertise. Such a protocol can be achieved by innovative regional cooperation, with contracts between hospitals regarding the later repatriation of the patients.

Key role of prenotification

Apart from the fact that the transmission of information regarding the onset of symptoms or thrombolysis contraindications is an integral component of the initial interaction between the EMS team and the hospital stroke team, stroke management guidelines (38,39) additionally recommend prenotification of the receiving hospital about the arriving patient. This prenotification allows the fastest possible activation of the stroke team and, especially, the reservation of computed tomography (CT) scanners. Previous interventional studies of the effects of prenotification of the hospital team alone or in combination with further restructuring of stroke management plans showed that crucial time to therapy can be saved and thrombolysis rates can significantly be increased [(50–57), Table 3]. The existing studies compared findings regarding the effects of a prenotification intervention either with findings from a historical control group or with findings from a parallel observation of patients for whom no such prenotification intervention was used (Table 3). So far, no data from randomized studies are available, and, in light of ethical aspects and because the existing studies already consistently show a considerable acceleration of in-hospital treatment, it is unlikely that such studies will ever be performed in the future. Regarding methodology, the transfer of structured clinical data between the EMS team at the emergency site and the hospital stroke team could also be optimized by the use of personal digital assistants (58) or smart phones (59).

Interestingly, one study found that combining the concept of prenotification with additional improvements in in-hospital stroke management resulted in a ‘door-to-needle’ time of only 20 mins (56). The philosophy behind these very short door-to-needle times is, according to the Finnish authors, ‘to do as little as possible after the patient has been arrived in the clinic, and as much as possible when the patient is on the way to the clinic’ (56).

Telemedicine interaction between regional hospital and stroke center and perspectives for communication between emergency site and stroke center

By using systems for bidirectional audiovisual videoconferencing and exchange of videos of the examination of the patient and of CT scans, nonspecialized regional hospitals can already obtain guidance in stroke treatment from hospitals designated as stroke centers [(60), Fig. 1]. Previous studies not only showed that such telemedicine interaction between two hospitals is reliable and safe (61–64), but also that it exerts positive effects on thrombolysis rates and clinical outcome (65).

Importantly, such telemedicine technologies could in principle also allow bidirectional communication between the EMS team at the emergency site and the stroke center. Such strategies have been investigated for many years (66,67); however, technical problems such as the temporary loss of signals still today impair reliable interaction between ambulance and hospital (68,69).

Prehospital stroke treatment: an alternative strategy for reducing delay to treatment?

To achieve the goal of enabling more than a minority of stroke patients to profit from recanalization therapies in the future, the concept of prehospital stroke treatment has been elaborated upon in the last decade [(70), Fig. 1]. This concept is based on the use of an otherwise conventional ambulance that, additionally, contains a small CT scanner and a point-of-care laboratory {mobile stroke unit [(71), Fig. 2]}. This ambulance also contains equipment that allows telemedicine interaction with the hospital, thereby making possible bidirectional communication and transfer of videos or CT scans of patients from the emergency site to the hospital.

A first randomized trial involving 100 patients recently showed that, compared with optimized conventional stroke management, prehospital stroke treatment reduces the time between alarm and therapy decision from 76 to 35 mins (72). A therapy decision was made within 60 mins after symptom onset (the ‘golden hour’) for 57% of the patients treated in the mobile stroke unit but for only 4% of the conventionally treated patients. This and other studies of stroke treatment directly at the emergency site already document a broad spectrum of additional novel medical options, especially the option of triaging patients to the most appropriate hospital on the basis of a diagnosis clarified before the patients are transported. For example, patients with large-vessel occlusion demonstrated by prehospital CT angiography could specifically be triaged to specialized stroke centers that offer endovascular treatment (73). Moreover, this strategy allows organization of further specialized treatments and etiology-specific blood pressure management already in the prehospital phase of stroke management (73–75). The latter could be specifically clinically relevant because there are indications that differential adjustment

Table 3 Studies on the effect of prenotification on stroke management quality

References	Site (number of stroke centers)	Study design	Year	Number of stroke patients with and without intervention	Intervention	Onset-to-door time (min) with and without intervention	Thrombolysis rates (%) with and without intervention
Belvis <i>et al.</i> (50)	Barcelona, Spain (1)	Parallel observation	2001–2002	39 vs. 181	Prenotification	Mean (SD): 64.6 (37.8) vs. 69.4 (44.6), $P = 0.542$	19 vs. 4.5, $P = 0.003$
Abdullah <i>et al.</i> (51)	Boston, United States (1)	Before vs. after implementation	2004–2005	44 vs. 74	Prenotification	Median (IQR): 66 (42–126) vs. 90 (42–174), $P = 0.42$	41 vs. 21, $P = 0.04$
Quain <i>et al.</i> (52)	Newcastle, Australia (1)	Before vs. after implementation	2005–2007	232 vs. 205	Prenotification plus bypass protocol	Median (IQR): 90.5 (63–185) vs. 150 (93–339), $P = 0.004$	21.4 vs. 4.7, $P < 0.001$
Kim <i>et al.</i> (53)	Busan, Korea (1)	Before vs. after implementation	2006–2007	328 vs. 678	Prenotification plus in-hospital reorganization	Mean (SD): 121.5 (34.8) vs. 74.7 (38.5), $P < 0.01^*$	14.3 vs. 6.5, no P values indicated
Köhrmann <i>et al.</i> (54)	Erlangen, Germany (1)	Longitudinal observation	2006–2009	246* (without control group)	Prenotification, plus EMS education, in-hospital reorganization	Median (IQR): 72.5 (52–99)	–
Gladstone <i>et al.</i> (49)	Toronto, Canada (3)	Before vs. after implementation	2004–2005	290 vs. 217	Prenotification plus EMS screening tool, ambulance destination decision rule with bypass protocol	Median (IQR): 63 (30) vs. 46 (7), $P = 0.83$	23.4 vs. 9.5, $P = 0.01$
O'Brien <i>et al.</i> (55)	Gosford, Australia (1)	Before vs. after implementation	2006–2008	115 vs. 67	Prenotification plus prehospital assessment tool, bypass protocol, in-hospital reorganization	Mean†: 76 vs. 59, $P = 0.18^*$	19 vs. 7, $P = 0.03$
Meretoja <i>et al.</i> (56)	Helsinki, Finland (1)	Before vs. after implementation	1998–2011	167 in 2011 vs. 7 in 1998*	Prenotification plus EMS education, use of stroke recognition tools, in-hospital reorganization	Median (IQR): 89 (62–138) vs. 75 (45–145)*	31 in 2011, no earlier data
Casolla <i>et al.</i> (57)	Lille, France (1)	Parallel observation	2008–2011	191 vs. 56	Prenotification	Median (IQR): 81 (61–120) vs. 97 (49–144), $P = 0.628$	–

*Only rt-PA-treated patients were included.

†No SD displayed.

EMS, emergency medical services; IQR, interquartile range; rt-PA, recombinant tissue plasminogen activator.

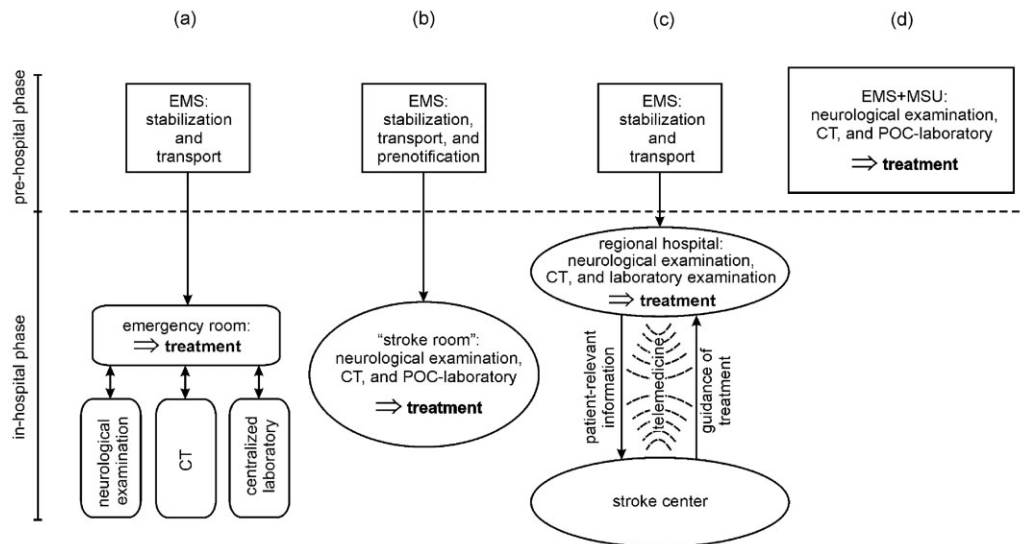


Fig. 1 Strategies of acute stroke management. (a) Conventional stroke management; (b) optimized stroke management with prenotification of the receiving hospital and in-hospital reorganization with diagnostic workup and treatment at one site; (c) telemedicine interaction between regional hospital and stroke center, allowing the stroke center to provide guidance in acute treatment; (d) prehospital stroke treatment in an ambulance equipped with a CT scanner, point-of-care laboratory, and telemedicine interaction with the stroke center. CT, computed tomography; EMS, emergency medical services; MSU, mobile stroke unit; POC, point-of-care.

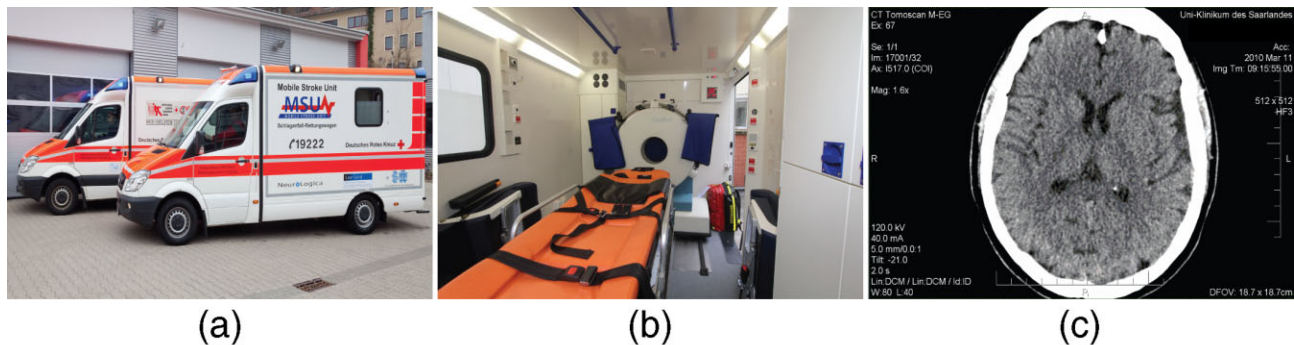


Fig. 2 Ambulance for prehospital stroke treatment. (a) External view of the second-generation mobile stroke unit (in front) with integrated multimodal CT scanner, point-of-care laboratory, and telemedicine capability; the unit is sized as a conventional ambulance (in back). (b) Interior view. (c) Exemplary computed tomography scan obtained at the emergency site.

of blood pressure can be beneficial for patients with ischemic stroke (tolerating higher blood pressure values) or hemorrhagic stroke (reducing elevated blood pressure) (76).

In the future, the concept of prehospital stroke treatment could be complemented by the inclusion of other diagnostic and therapeutic strategies, such as further imaging procedures, neuroprotective strategies, or future hemorrhage therapies. However, currently, prehospital stroke treatment is still a potential perspective rather than clinical reality, and further research is still needed with regard to the medical efficacy of and the best setting for this concept. Finally, although many arguments suggest that increased allocation of resources in the golden hour of stroke could save the much higher costs of long-term care of disabled patients, the cost-effectiveness of prehospital stroke treatment remains to be demonstrated.

As limitation, this review on the different links of the prehospital stroke rescue chain did not completely follow a systematic approach as articles found by PubMed search were selected and

weighted based on their originality and their relevance to the topic of prehospital stroke management.

In summary, this review indicates that prehospital delay is a major reason that only a minority of patients obtain recanalizing therapy today. Options for the improvement of prehospital stroke management include, on the patient's side, target-specific and continual public awareness campaigns. On the EMS side, frequently repeated training in the use of tools for symptom recognition, prioritized transport to experienced stroke centers, and, probably most important, prenotification of the receiving hospital can improve time to treatment and treatment rates. In the future, even prehospital stroke treatment could contribute to better stroke management.

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