The chain of care enabling tPA treatment in acute ischemic stroke: a comprehensive review of organisational models

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Abstract

Introduction
Protracted and partial implementation of treatment with intravenous tissue plasminogen activator (tPA) within 4.5 hours after acute stroke onset results in potentially eligible patients not receiving optimal treatment. The goal of this study was to review the performance of various organisational models of acute stroke care delivery, and subsequent attempts to improve implementation of tPA treatment.

Methods
Publications comprehensively reporting on organisational models to improve implementation of i.v. tPA treatment of acute ischemic stroke patients were selected. The efficacy of organisational models was assessed using process outcome measures: thrombolysis rates, time dependent operational endpoints (time delays), functional outcomes: safety (rate of symptomatic intracranial hemorrhage, mortality rates) and clinical outcome at 90 days (modified Rankin Scale).

Results
Fifty-eight published studies assessing organisational models were identified. Four dominant models of acute stroke care delivery were discerned, i.e., primary and comprehensive stroke centres, telemedicine, and the mobile stroke unit. Performance reported for these models suggest a large variation in administration of thrombolytic therapy (0.7% – 30%). Time delays and functional outcomes found varied considerably, just like safety and mortality (0.0% – 11.5%, and 3.4% – 31.9%, respectively).

Discussion
These findings suggest that improving organisational models for tPA treatment may improve acute stroke care. However, implementation may be hampered by regional variation in acute stroke care capacity, expertise, and a fragmented approach towards organising stroke care.
Introduction

Acute ischemic stroke has become a medical emergency since the introduction of intravenous (i.v.) tissue plasminogen activator (tPA) as an effective treatment for acute ischemic stroke within 4.5 hours after onset [1-3]. Only 1-7% of eligible patients receive thrombolytic therapy [4, 5], however, 25% may be attained in optimized settings [6]. This reflects considerable under treatment, which is directly related to patient unawareness (e.g. unfamiliarity with stroke symptoms and how to act), delayed hospital arrival, inefficient organisation of hospital stroke services, the narrow therapeutic time window, and scepticism among physicians about the scientific evidence of tPA treatment such as emergency physicians [7-10]. Apparently, integration of individual services into coordinated stroke care systems has proven difficult leading to suboptimal treatment and inefficient use of resources [11]. Implementing all-inclusive organisational models for efficient delivery of acute stroke care requires long term and broad commitment. Typically, they build on the cooperation between various organisations (e.g. general practitioners, emergency medical services, hospital services), dedicated staff (e.g. trained stroke personnel), and specific resources (e.g. brain imaging, and hospital beds) [9, 12].

To improve and facilitate acute stroke treatment new organisational models for acute care have been developed. Among others, the Brain Attack Coalition proposed two levels of coordinated hospital-based systems for acute stroke treatment, namely primary and comprehensive stroke centres [13, 14]. In addition, the American Heart and Stroke association has recommended telemedicine as an effective organisational model to increase access to acute stroke care for geographically remote areas with limited stroke expertise. A novel concept is prehospital thrombolysis by a mobile stroke unit [15].

The aim of this study was to review organisational models and summarise the evidence of efficacy to enhance implementation of tPA treatment in acute ischemic stroke.

Methods

Literature search

An online literature Pubmed, Embase, Web of Science, search was performed by one author (M.L.) for studies published from January 2000 to May 2012. Pubmed was searched using a combination of the following terms: [models, theoretical OR organisation OR management] AND [stroke OR brain infarction] AND [thrombolytic therapy OR actilyse OR thrombolysis] AND [randomised clinical trials]. The Embase search combined the following terms: [acute AND stroke OR brain] AND [infarction OR ischemic] AND [stroke] AND [blood clot lysis OR fibrinolytic therapy OR alteplase OR actilyse OR thrombolysis] AND [theoretical model OR organisation OR management] AND [randomised clinical trials]. The Web of Science was searched using a combination of the following words: [acute stroke] AND [brain infarction] AND [ischemic stroke]
AND [thrombolytic therapy] OR [alteplase] OR [actilyse] AND [management] AND [organisation] AND [theoretical model] AND [randomised clinical trials]. An additional search for randomised clinical trials was performed using the websites http://clinicaltrials.gov/ and http://www.controlled-trials.com/. Both websites were searched using a combination of the following terms: [stroke] AND [thrombolysis]. Other relevant articles were identified through cross reference searches. The first selection of the literature was made based on Medical Subject Headings (MESH) terms, text words in the title, and the abstract of the selected literature. This selection was screened for relevance by reading abstracts or, if necessary, full articles. Finally, all selected literature was read in full. Articles not specifically on the delivery of i.v. tPA for acute ischemic stroke, organisational models for acute ischemic stroke, abstracts, scientific comments, scientific advisories, and publications without abstract were excluded. Only original contributions (clinical studies) were included. Related (review) articles were used for cross reference searches. All selected literature was in English.

Outcome measures
The effectiveness of organisational models was considered using the following outcome measures: thrombolysis rates, time dependent operational endpoints, safety (rate of symptomatic intracranial hemorrhage (sICH) defined to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study [16], mortality rates and functional outcome at 90 days, defined as excellent (modified Rankin Scale 0-1) and good (modified Rankin Scale 0-2). Articles published on the topic of cost-effectiveness of organisational models were not collected in this review; this is covered in a paper published elsewhere [17]. Also descriptions of stroke units were not included in this review because they represent standard care [18].

Definitions
The following definitions for organisational models were identified: stroke centres and telemedicine.

Stroke centres are meant to improve treatment by applying uniform criteria for standardised stroke practice. Two main subcategories of stroke centres were distinguished: primary stroke centres (PSCs), which have the necessary staffing, infrastructure, and programs to stabilize and treat most acute stroke patients [13], and comprehensive stroke centres (CSCs), equipped with the essential personnel, infrastructure, expertise and programs to diagnose and treat stroke patients who require a high intensity of medical and surgical care, specialised tests, or interventional therapy [14].

Telemedicine or telestroke services can be defined as the exchange of medical information from one site to another using electronic communication, such as telephone, internet, or teleconference [19]. So-called ‘hub and spoke’ models operate as urban located regional stroke centres (the hub) that provide 24-hour centralized support to satellite rural hospitals (spokes).
lacking specific stroke expertise, in an effort to enhance the administration of acute stroke therapies in rural areas [20].

**Results**

Fifty-eight articles were included in the final review (Figure 1). Findings of the literature on organisational models for the delivery of i.v. tPA for acute ischemic stroke and their main outcome measures are summarised in Table 1.

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**Figure 1.** Results of search strategy
Table 1. Studies reporting on organisational models

<table>
<thead>
<tr>
<th></th>
<th>Primary stroke centres</th>
<th>Comprehensive stroke centres</th>
<th>Telemedicine</th>
<th>Mobile stroke unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA rate (%)</td>
<td>0.7 – 20.8</td>
<td>2.0 – 21.9</td>
<td>2.1 – 30.0</td>
<td>22.6</td>
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<tr>
<td>Safety (%)</td>
<td>2.7 – 5.6</td>
<td>0.0 – 9.2</td>
<td>0.0 – 11.5</td>
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<td>Mortality rate</td>
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<td>Hospital (%)</td>
<td>10.1 – 19.0</td>
<td>5.7 – 22.0</td>
<td>3.4 – 14.9</td>
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<td>30 days (%)</td>
<td>10.1</td>
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<tr>
<td>90 days (%)</td>
<td>6.0 – 15.0</td>
<td>12.5 – 16.1</td>
<td>11.0 – 31.9</td>
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<td>1-year case fatality (%)</td>
<td>19.1</td>
<td>16.6</td>
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<tr>
<td>90 day functional outcome</td>
<td></td>
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<tr>
<td>Excellent (mRS 0-1) (%)</td>
<td>36.4 – 40.0</td>
<td>34.0 – 74.2</td>
<td>29.4 – 47.0</td>
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<tr>
<td>Favourable (mRS 0-2) (%)</td>
<td>37.7 – 45.5</td>
<td>43.0 – 77.4</td>
<td>42.0 – 49.1</td>
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<tr>
<td>Efficacy (process times)</td>
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<td>Onset to door time</td>
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</tr>
<tr>
<td>Median (min)</td>
<td>60.0 – 142.0</td>
<td>52.0 – 84.0</td>
<td>50.0 – 60.0</td>
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<tr>
<td>Mean (min)</td>
<td>49.0 – 106.0</td>
<td>53.0</td>
<td>30.4 – 144.2</td>
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<tr>
<td>Door to neurological examination</td>
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<tr>
<td>Median (min)</td>
<td>15.0</td>
<td>0.0</td>
<td></td>
<td>8.6</td>
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<tr>
<td>Mean (min)</td>
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<tr>
<td>Door to CT evaluation</td>
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<tr>
<td>Median (min)</td>
<td>32.0 – 60.0</td>
<td>8.0 – 67.0</td>
<td>15.0 – 25.0</td>
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<tr>
<td>Mean (min)</td>
<td>27.0</td>
<td>59.0</td>
<td>17.0 – 86.3</td>
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<td>Door to needle time</td>
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<tr>
<td>Median (min)</td>
<td>20.0 – 98.0</td>
<td>35.0 – 84.0</td>
<td>61.0 – 90.0</td>
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<tr>
<td>Mean (min)</td>
<td>28.0 – 120.0</td>
<td>86.0 – 95.0</td>
<td>49.1 – 104.9</td>
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<tr>
<td>Onset to needle time</td>
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<td></td>
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<tr>
<td>Median (min)</td>
<td>119.0 – 134.0</td>
<td>96.0 – 165.0</td>
<td>125.0 – 151.8</td>
<td>72.0</td>
</tr>
<tr>
<td>Mean (min)</td>
<td>133.0 – 169.0</td>
<td>119.0 – 155.0</td>
<td>113.0 – 170.2</td>
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Abbreviations: tPA, tissue plasminogen activator; mRS, modified Rankin Scale; CT, computed tomography.

**Stroke centres**

Primary stroke centres: the literature search identified 11 articles including 199760 patients. Seven studies were prospective [21-27], 4 were retrospective [28-31]. Treatment with thrombolytic therapy ranged from 0.7% – 20.8% [22-31].
Rate of sICH rate ranged from 2.7% – 5.6% [26, 27]. Hospital mortality ranged from 10.1% – 19.0% [26, 29, 30]. Reported thirty day mortality rate was 10.1% [22], 90 day mortality rate ranged from 6.0% – 15.0% [21, 27], and one-year mortality 19.1% [25].

Excellent functional outcome was 40.0% [27]. Reported good functional outcome was 37.7% [21].

Time from stroke onset to hospital arrival ranged from a median of 60.0 – 142.0 minutes [21, 23, 24], and a mean of 49.0 – 106.0 minutes [21, 27, 30]. Median time from hospital arrival to computed tomography (CT) imaging was 60.0 minutes [23], at a mean of 27.0 minutes [27]. Time from hospital arrival to treatment with tPA ranged from a median of 20.0 – 68.0 minutes [21, 23], and a mean of 28.0 – 120.0 minutes [21, 26, 27, 30]. Median time from stroke onset to tPA treatment was 119.0 – 127.0 minutes [21, 23], mean time ranged from 133.0 – 169.0 minutes [21, 26, 27, 30].

Three studies including 2948 patients reported outcomes before and after implementation of acute stroke care [32-34].

The proportion of patients treated with tPA increased ranging from 2.8% – 17.7% [32-34]. The median time from hospital arrival to neurological consultation decreased to 15 minutes [33], from hospital arrival to CT imaging to 32 minutes [33], and from hospital arrival to tPA treatment to 98 minutes [33].

Comprehensive stroke centres: the literature search identified 14 articles including 39001 patients. Eight studies were prospective [25, 35-41], and 6 retrospective [42-47]. Treatment with thrombolytic therapy ranged from 2.0% – 21.9% [25, 35-40, 43, 44, 46].

Rate of sICH ranged from 0.0% – 9.2% [36, 37, 42-44, 46-48]. Hospital mortality rate ranged from 5.7% – 22.0% [36, 38, 46, 47], 90 day mortality rate from 12.5% – 16.1% [36, 37, 43, 44]. One-year mortality was 16.6% [25].

Excellent functional outcome ranged from 34.0% – 74.2% [37, 41-44], reported good functional outcome from 43.0% – 77.4% [36, 39, 42, 43, 48].

Time from stroke onset to hospital arrival ranged from a median of 52.0 – 84.0 minutes [36, 38, 43], reported mean time was 53.0 minutes [41]. Median time reported for hospital arrival to neurological examination was 0.0 minutes [36]. Time from hospital arrival to CT imaging ranged from a median of 8.0 – 67.0 minutes [36, 38, 47], and a mean of 59.0 minutes [41]. Time from hospital arrival to treatment with tPA ranged from a median of 35.0 – 84.0 minutes [36, 37, 47], and a mean of 86.0 – 95.0 minutes [35, 41, 43]. Time from stroke onset to tPA treatment ranged from a median of 96.0 – 165.0 minutes [36-38, 42, 44, 47, 48], and a mean of 119.0 – 155.0 minutes [41, 43, 46].

**Telemedicine**

The literature search identified 26 articles including 34339 patients. Fifteen studies were prospective [49-63], 11 studies were retrospective [45, 64-73].
Treatment with thrombolytic therapy ranged from 2.1% – 31.0% [49, 50, 53, 54, 56, 58-60, 66, 67, 70, 72, 73]. Rate of sICH ranged from 0.0% – 11.5% [45, 50-52, 55, 59-61, 64, 65, 67, 69, 71]. Hospital mortality rate ranged from 3.4% – 14.9% [45, 50, 54, 55, 58-61, 64, 66, 69, 71], and 90 day mortality rate from 11.0% – 31.6% [49, 51, 52, 57, 58, 65, 67, 68].

Excellent functional outcome ranged from 29.4% – 47.0% [49, 51-53, 56, 57, 68], reported good functional outcome from 42.0% – 49.1% [51, 52, 65, 67].

Time from stroke onset to hospital arrival ranged from a median of 50.0 – 60.0 minutes [50, 59, 65], and a mean of 30.4 – 144.2 minutes [49, 59-62, 71]. The mean time from hospital arrival to neurological examination was 8.6 minutes [49]. Time from hospital arrival to CT imaging ranged from a median of 15.0 – 25.0 minutes [59, 65], and a mean from 17.0 – 86.3 minutes [49, 59]. Time from hospital arrival to treatment with tPA ranged from a median of 61.0 – 90.0 minutes [50, 59, 64, 65, 67, 69], and a mean of 68.0 – 104.9 minutes [52, 59, 60, 62, 71]. Time from stroke onset to tPA treatment ranged from a median of 125.0 – 151.8 minutes [45, 50, 59, 64, 65, 69], and a mean of 113.0 – 164.8 minutes [49, 52, 53, 55-57, 59-62, 68, 71].

Three studies including 676 patients reported outcomes before and after implementation of acute stroke care [74-76]. The proportion of patients treated with tPA increased ranging from 5.6% – 21.0% [74-76].

Mobile stroke unit
The literature search identified 1 prospective study including 53 patients [15]. Treatment with thrombolytic therapy was 22.6%. Median time from symptom onset to tPA treatment was 72.0 minutes.

Qualitative results
Improvements in acute stroke care reported in the selected literature are largely influenced by the implementation of guidelines on acute stroke care. For example, using (national) guidelines for the development of primary and comprehensive stroke centres resulted in substantial improvements over time in the proportion of patients treated with thrombolysis, time dependent operational endpoints, safety, referral rates to primary care and local emergency departments, and the overall level of stroke care [25, 26, 29, 32, 34, 39].

Guideline driven telemedicine systems can lead to an increase the proportion of patients treated with thrombolysis, lower mortality, and the rapid and safe use of tPA in rural community hospitals [57, 58, 61, 68]. In addition, developing telemedicine initiatives may lead to similar outcomes as on-site treatment at a primary or comprehensive stroke centre [51].
DISCUSSION

To our knowledge, this is the first systematic review that addresses the efficacy of different stroke care systems in relation to thrombolytic therapy in acute stroke. Within the scope of this review, four organisational models of acute stroke care were identified. Three models (primary and comprehensive stroke centres, telemedicine) share a primary focus on in-hospital care, one model on prehospital stroke care (mobile stroke unit). The mobile stroke unit is a very promising approach to reduce delay in acute stroke therapy; however its efficacy still has to be proven.

All models achieved increases in the rate of thrombolytic therapy, time delays and functional outcome albeit with considerable variation. These models can be viewed as equivalent, with stroke centres predominantly serving urban areas, and telemedicine applied in rural areas where stroke centres provide expertise to outlying hospitals.

In the literature numerous guidelines on how to improve the level of acute stroke care are published. The most important are from the American Stroke Association [77], and the European Stroke Organisation [78]. These guidelines recommend several important factors on prehospital and emergency department aspects regarding acute stroke care. Prehospital factors include calling 911 in response to stroke symptoms, priority dispatch, field use of stroke screening tool, and prehospital notification. Emergency department factors include rapid triage, laboratory, and neuroimaging testing. Adherence to these guidelines may improve the quality of acute stroke care in areas with low tPA utilization [32, 75]. Recommendations are made how guidelines for acute stroke care can be implemented [79]. The Brain Attack Coalition provides action plans for stroke pathways to implement or improve acute stroke care [80].

Comparability and pooling across studies was difficult because of methodological differences, variation in patient selection, and regional differences in stroke systems [81]. In addition, it proved difficult for regions to formulate an optimal model in relation to the region. Large differences were observed in pre- and intra-hospital delays between studies. This may primarily reflect geographical inequalities with differences in resources, stroke expertise, and subsequent stroke technology leading to suboptimal generalisation to other regions.

How to go forward? There will always be a need for randomised controlled trials (RCTs) to provide evidence in support of particular interventions along the stroke care pathway. RCTs are, however, expensive and time consuming and their focus on particular interventions may not make them the best options to identify critical success factors along the entire stroke pathway. An alternative method to study the entire stroke pathway is that applied in simulation modelling. For example, a discrete event simulation model indicated that a National Institutes of Neurological Disorders and Stroke (NINDS)-compliant iv-TPA treatment strategy would result in a higher proportion of patients treated, whilst remaining cost-effective [82]. As currently used in efforts to streamline patient flow and facilitate budget analysis, simulation modelling offers a
tool to study the entire chain of care, identify the weakest links and directing limited budgets to interventions that are most likely to improve stroke system outcomes.

As for the robustness of our findings we acknowledge that our systematic review may have some shortcomings. Any literature search can miss some articles regarding organisational models in acute ischemic stroke. Besides the existence of stroke units we found it difficult to extract the concept of an organisational model for acute ischemic stroke. We nevertheless feel that the overall observation of fragmented approaches towards organising stroke care is compelling.

In conclusion, current literature on organisational models has a predominant focus on intra hospital stroke care and shows better outcome when stroke care is organised in regional stroke centres and/or applies telemedicine initiatives. There is a need for a targeted approach to eliminate bottlenecks in the entire pre- and intra hospital stroke care pathway, such as may be provided by simulation modelling.

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**Competing interests**
None.
References

10. CAEP Committee on Thrombolytic Therapy for Acute Ischemic Stroke. Thrombolytic therapy for acute ischemic stroke [position statement].(2001) . CEJM 3:8-12


American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Circulation 115:e478-534


