Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2012, **37**, 399–409 doi: 10.1111/j.1365-2710.2011.01329.x

Review Article

Barriers to the utilization of thrombolysis for acute ischaemic stroke

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Received 03 July 2011, Accepted 22 November 2011

Keywords: **alteplase, barriers, cerebrovascular accident, stroke, thrombolysis, tissue plasminogen activator**

SUMMARY

What is known and Objective: **Thrombolysis is currently the only evidence-based pharmacological treatment available for acute ischaemic stroke (AIS); however, its current utilization is suboptimal (administered to <3% of AIS patients). The aim of this article was to identify the potential barriers to the use of thrombolysis via a review of the available literature.**
Methods: **Medline, Embase, International Pharmaceutical Abstracts and Google Scholar were searched to identify relevant original articles, review papers and other literature published in the period 1995–2011.**
Results and Discussion: **Several barriers to the utilization of thrombolysis in stroke have been identified in the literature and can be broadly classified as 'preadmission' barriers and 'post-admission' barriers. Preadmission barriers include patient and paramedic-related factors leading to late patient presentation for treatment (i.e. outside the therapeutic time window for the administration of thrombolysis). Post-admission barriers include in-hospital factors, such as suboptimal triage of stroke patients and inefficient in-hospital acute stroke care systems, a lack of appropriate infrastructure and expertise to administer thrombolysis, physician uncertainty in prescribing thrombolysis and difficulty in obtaining informed consent for thrombolysis. Suggested strategies to overcome these barriers include public awareness campaigns, prehospital triage by paramedics, hospital bypass protocols and prenotification systems, urgent stroke-unit admission, on-call multidisciplinary acute stroke teams, urgent neuroimaging protocols, telestroke interventions and risk-assessment tools to aid physicians when considering thrombolysis. Additionally, greater pharmacists' engagement is warranted to help identify the people at risk of stroke and support preventative strategies, and provide the public with information regarding the recognition of stroke, as well as facilitate the access and use of thrombolysis.**
What is new and Conclusion: **The most effective interventions appear to be those comprising several strategies and those that target more than one barrier simultaneously. Therefore, optimal utilization of thrombolysis requires a systematic, integrated multidisciplinary approach across the continuum of acute care.**

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WHAT IS KNOWN AND OBJECTIVE

Stroke is one of the leading causes for death and disability in developed countries[1] yet is both preventable and treatable. Although preventive strategies have been successfully implemented, leading to a reduction in age-standardized stroke incidence in countries like Australia[2] and the UK[3], they have had less impact on the incidence of stroke in the United States.[4] This is likely due to the increasing prevalence of stroke risk factors[4], particularly diabetes and hyperlipidaemia.[5] Annually, 780 000 people in the United States experience a new or recurrent stroke, which translates to one stroke attack every 40 s.[6] In Australia, stroke is the second largest 'killer' after ischaemic heart disease, with approximately 60 000 attacks per year.[7] Acute ischaemic stroke (AIS) accounts for greater than 80% of stroke presentations, with approximately 680 000 strokes per year in the United States and 49 000 stroke per year in Australia.[6,7] Acute stroke management has dramatically improved in the past two decades, following the introduction of dedicated stroke units and the use of acute interventions such as aspirin treatment for AIS[8] and decompressive surgery[9], leading to a reduction in dependency, mortality and disability, from stroke.[10,11] A less invasive intervention for less severe strokes is the administration of thrombolysis using recombinant tissue plasminogen activator (tPA), which facilitates rapid reperfusion of the brain tissue via lysis of occluding thrombi and which is currently the only evidence-based pharmacotherapeutic treatment currently available for AIS.[12]

Evidence shows that patients, selected according to eligibility criteria, who are treated with thrombolysis, are at least 30% more likely to have minimal or no disability at 3 months.[13] Furthermore, in routine clinical practice, utilization of thrombolysis has been proven to be safe and effective, affording reductions in patient disabilities after stroke.[14] Consequently, national and international clinical guidelines recommend the use of thrombolysis in the acute management of ischaemic stroke.[12,15–17]

Despite overwhelming evidence to support the use of thrombolysis, only a small proportion of patients with AIS currently receive this treatment. In the United States, about 2% of ischaemic stroke patients receive thrombolysis.[18] Similarly, in Australia approximately 3% of ischaemic stroke patients receive thrombolytic therapy.[7] Therefore, the aim of this review was to identify the barriers to the utilization of thrombolysis in AIS, as well as possible strategies to overcome these.

METHODS

Data sources

A comprehensive search of the literature was performed, using the following electronic databases to retrieve relevant papers: Medline via Web of Knowledge (1950–present), Embase (1966–present), International Pharmaceutical Abstracts (IPA) via OvidSP (1950–present) and Google Scholar. Reviews, prospective and retrospective observational studies and clinical audits, identifying potential barriers to thrombolysis for AIS, were sought.

Search strategies

A two-tiered search strategy was employed. A general search of the topic in question was performed in Tier 1 using the key words 'thrombolysis' and 'tPA'. To narrow down the search to focus on the review objectives, relevant key words were used in Tier 2, such as 'stroke', 'cerebrovascular accident', 'barrier', 'intervention' and 'utilization'. Search results from both tiers were combined using the appropriate Boolean operators. Reference lists in all retrieved articles were further examined to identify additional papers. Inclusion criteria for selecting the publications were as follows: English language, studies involving human subjects, original articles and review papers.

The time period from January 1995 to June 2011 was selected to retrieve all relevant articles since the publication of the NINDS trial[13], being the first positive randomized controlled trial (RCT) for thrombolysis in stroke.

RESULTS AND DISCUSSION

Thrombolysis significantly decreases disability from AIS.[13,19] Furthermore, observational trials such as STARS[20], CASES[21] and SITS-MOST[14] have reported acceptable safety and efficacy in clinical practice. Despite the overwhelming evidence to support the effectiveness of thrombolysis, as well as national and international guidelines[16,22,23] recommending the use of thrombolysis in selected patients, only a small proportion of patients with AIS receive thrombolysis.[24]

Patient selection for thrombolysis is principally based on the protocols used in those RCTs that have demonstrated a significant benefit from this treatment, with patients deemed eligible for thrombolysis when the benefit of treatment outweighs the risk (as for any other pharmacological intervention). For thrombolysis, a risk of bleeding, particularly intracerebral haemorrhage (ICH), is the main risk. Two major RCTs that have given support for thrombolysis, and have consequently shaped the guidelines for its use, both reported a 10-fold increase in the incidence of symptomatic ICH (SICH) associated with thrombolysis. The NINDS trial[13] reported a rate of 6·4% for SICH (vs. 0·6% for placebo; $P < 0{\cdot}001$), while the ECASS-3 trial[19] reported a rate of 2·4% (vs. 0·2% for placebo; $P = 0{\cdot}008$), with both trials reporting no significant difference in mortality or any other major adverse event.

As expected, thrombolysis is contraindicated in patients with a high risk of bleeding, including patients on therapeutic anticoagulation, recent gastrointestinal or urinary tract haemorrhage, recent major surgery and a history or evidence of ICH.[16,22,23] Patients with minor or rapidly improving symptoms are also ineligible for thrombolysis because the risks of treatment in these patients generally outweigh the benefit. A study of 2165 stroke patients found that 13·6% of AIS patients presenting within the therapeutic time window to receive thrombolysis were considered to be ineligible because of contraindications.[25]

In clinical practice, sites that are supported by efficient in-hospital systems and experienced stroke teams committed to providing evidence-based stroke care have demonstrated optimal utilization of thrombolysis. Overall, they have reported relatively high treatment rates >21%[26,27], resulting in 43% of treated patients having minimal or no disability at 3 months, which is comparable (if not superior) to the results of the RCTs.[26] However, such centres do not reflect main stream practice in this regard, with thrombolysis utilization generally suboptimal.

Barriers to the utilization of thrombolysis in stroke

Several barriers to the utilization of thrombolysis in stroke have been identified in the literature[28–32] and can be broadly classified as preadmission barriers and post-admission barriers (Fig. 1). Consequently, many strategies and interventions have been proposed to help overcome these barriers in an attempt to optimize the utilization of thrombolysis in stroke.

Preadmission barriers

Patient-related barriers. Late patient presentation is a major barrier to the utilization of thrombolysis in stroke. Several studies in the United States have reported that fewer than 20% of AIS patients are admitted to a hospital within 3 h of stroke onset.[18,33–36] A prospective cohort study by Katzan *et al.*[18], conducted in 29 hospitals and involving 3948 patients, reported that only 17% of AIS patients presented within 3 h. Another retrospective audit of 42 academic medical centres (1195 AIS patients) by Johnston *et al.*[34] reported that approximately 18% of AIS patients presented within 3 h of stroke onset. This means that, given the annual incidence of AIS in the United States (approximately 680 000)[6], more than 540 000 patients would be ineligible for thrombolysis because of late presentation. In Australia, the proportion of AIS patients who are admitted to hospital within 4·5 h of stroke onset is reportedly 39% (35% within 3 h).[7] This translates to 30 000 AIS patients annually being ineligible for thrombolysis because of late presentation when using the extended time window of 4·5 h or 32 000 patients being ineligible according to a time window of 3 h. There are several reasons for late patient presentation for treatment:

Poor recognition of stroke symptoms and failure to react appropriately: The inability of the stroke patient or bystanders to recognize stroke symptoms is because of their limited awareness of the clinical presentation, particularly early signs, of stroke such as facial numbness, slurring of speech and arm or leg weakness. Consequently, relatively few patients are initially recognized as having had a stroke, and this causes delays in seeking help. Mosely *et al.* reported that only 22% of emergency callers did so within 1 h of stroke symptom onset.[37] There are many reasons for the delay in seeking medical help, including stroke symptoms being perceived at first as mild; the patient waiting to see whether symptoms would improve; and the general practitioner being contacted first rather than the emergency service.[31] In some cases, medical attention is not sought at all.[31] One of the common reasons for a delay in seeking medical help relates to patients living alone, and it has been reported that approximately

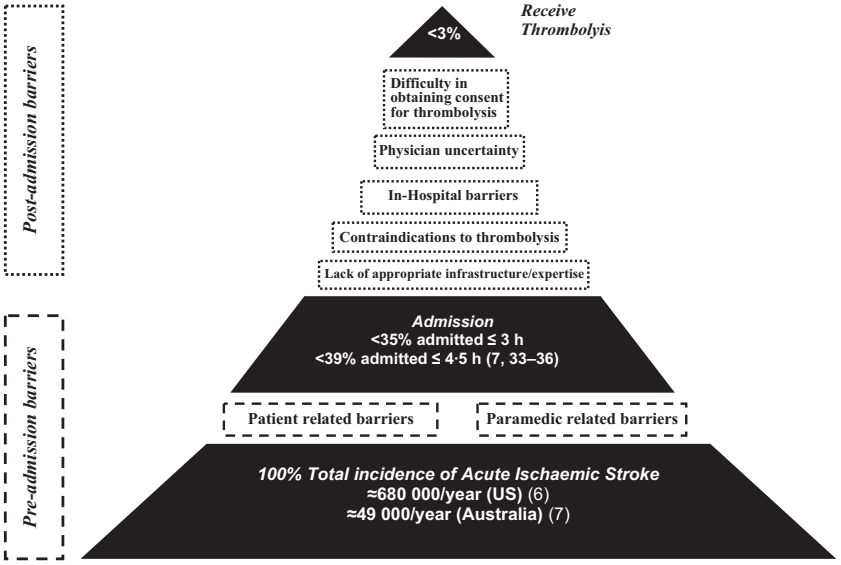

Fig. 1. Barriers to the utilization of thrombolysis for acute ischaemic stroke.

33% of stroke patients live alone.[38] This is important given that only 3% of patients are reportedly able to call for an ambulance themselves[37] because of the fact that a patient's consciousness level is reduced during a stroke attack.[31] Patients who are at high risk of stroke but who cannot avoid living alone can seek assistance by having an emergency communication network set up for them at home. This involves the use of a personal alarm (necklace-style) that can be easily activated by the patient to promptly alert a family member or a neighbour that emergency medical attention is needed. Contact with the emergency service results in the rapid transfer of the patient by ambulance, and several studies have suggested that transport by ambulance reduces prehospital and in-hospital delays and increases the likelihood of admission to a stroke unit and subsequent thrombolysis treatment.[32,39,40]

The main strategy undertaken to address the poor recognition of stroke symptoms and failure to react appropriately is better patient education. Several public awareness campaigns have been undertaken worldwide, for example the Brain Attack campaign in the United States and the F.A.S.T campaign in Australia.[41,42] Such campaigns aimed to increase community knowledge of stroke, risk factors, warning signs and symptoms and the importance of promptly contacting an emergency service.[31] Public awareness campaigns employ several techniques to reach and educate the general public, including mass media using television advertisements.[43,44] Furthermore, targeted stroke education programmes have employed websites, patient education tool-kits and brochures, including specific brochures targeting high-risk patients or high-risk ethnic groups, for example, African Americans.[45] Unfortunately, the impact of these educational programmes has not been evaluated in clinical practice.

Despite these campaigns, knowledge of stroke has not noticeably improved. In the United States, Kleindorfer *et al.*[46] conducted a community-based survey over three different time periods, 5 years apart (1995, 2000 and 2005), and found that knowledge of stroke warning signs and risk factors had not improved in recent years. They also reported extremely poor knowledge of thrombolysis as a treatment option; only 3·6% of respondents were able to name tPA or 'clot buster' as a treatment for stroke. Many reasons for the lack of improvement in public knowledge have been proposed, and among these are the existence of a theoretical limit as to how much information the public can absorb; the type of educational message delivered; not targeting the correct audience; and failing to test the messages for efficacy before implementation.[46] Furthermore, for the patient to sense the relevance of the message being delivered, the patient must be aware of their own stroke risk.[46] Yoon *et al.*[47] found that patients who had been told that they were at risk of stroke were more concerned about having a stroke than those who were not.[47] Furthermore, it is also likely that knowing that a time-sensitive treatment is available would have a strong impact on patients' behaviour. This critical information would help the patient translate knowledge into appropriate action (i.e. immediately contacting the emergency services) in order to be eligible to receive the treatment.[46] Therefore, future campaigns should focus not only on the warning signs and risk factors of stroke, but also on the availability of thrombolysis as a potential treatment and that this treatment is time sensitive.[46] For mass media campaigns to be effective, they must involve the prolonged exposure of a single, clear and efficacious message.[44] Taking into account the large proportion of patients who are not considered for therapy because of late presentation, overcoming this barrier may be the approach that has the greatest impact on thrombolysis utilization rates.[46]

Narrow time window for the administration of thrombolysis: Until recently, thrombolysis has been approved for use as a treatment administered within a therapeutic time window of 3 h from the onset of a stroke. This necessitates that the patient or bystander recognizes the symptoms, calls an ambulance, presents to a hospital, gets assessed and is formally diagnosed within this narrow time frame to be considered for thrombolysis.

There are a limited number of strategies available to facilitate earlier patient presentation, but the simplest solution is to extend the therapeutic window for administration of treatment. Fortunately, following very recent results from clinical trials, the therapeutic time window for the administration of thrombolysis has been extended from 3 to 4·5 h from stroke onset, principally based on the results of the ECASS-3 trial[19], and this has been incorporated into clinical guidelines in United States[16], Europe[22] and Australia.[23] To date, there is no evidence to support the use of thrombolysis beyond 4·5 h in ischaemic stroke, and it is unknown whether patients would benefit from late thrombolysis administration and/or whether the risk of ICH would outweigh the benefit. Current on-going trials, such as the third International Stroke Trial (IST-3)[48], aim to determine whether the therapeutic time window can be further extended to 6 h. Additionally, trials have explored methods to assist in better identifying patients who may benefit from the late administration of thrombolysis. A magnetic resonance imaging (MRI)-based imaging technique (MRI of perfusion diffusion mismatch) has been used to specifically select patients who may benefit from thrombolytic therapy in an extended time window[49], with the demonstrated potential to select specific patients for treatment even up to 9–12 h from stroke onset.[50] A large Phase III trial, the EXTEND trial, is currently being undertaken to validate the selection of patients for thrombolysis based on MR mismatch.[51]

Paramedic-related barriers. Paramedics (ambulance services) are responsible for the rapid transfer of patients to an appropriate hospital. Therefore, where paramedical staff are not appropriately trained and equipped with proper screening tools and specific protocols for managing thrombolysis-eligible patients (including possessing precise knowledge of the narrow therapeutic time window), the paramedic services may themselves present a barrier to thrombolysis use.[31] Barriers may either be related to unnecessary time delays in transferring patients to hospitals or in transferring patients to hospitals that do not offer thrombolysis.

Time delays by the paramedics: Failure of emergency dispatchers and/or paramedical staff to accurately identify stroke and triage stroke patients as an emergency has been recognized as the major reason for delays caused by the paramedics.[30] As many as 28% of stroke patients are not identified by paramedics as having had a stroke, because of a lack of knowledge regarding the signs and symptoms.[52] Furthermore, a survey conducted in the United States by Crocco *et al.*[53] suggested that paramedics were unaware of the therapeutic time window for administration of thrombolysis, and hence do not sufficiently appreciate the need to triage stroke patients as being 'highly acute'.

Two main strategies have been considered to overcome this problem. Firstly, providing appropriate education and training for paramedical staff to improve the accuracy and speed of stroke diagnosis, including providing relevant resources, such as specific web-based training opportunities.[54] Secondly, developing and implementing prehospital stroke screening tools and other appropriate ambulance stroke protocols to assist paramedics. Prehospital stroke screening tools, such as the Face Arm Speech Test[55], the Los Angeles Prehospital Stroke Scale[56] and the Cincinnati Prehospital Stroke Scale, have been developed, evaluated and widely implemented to help paramedical staff appropriately identify potential stroke patients.[57] Another innovative approach, which more specifically targets transient ischaemic attack, is the use of risk stratifying tools (for example ABCD[58] and ABCD2[59,60]) to facilitate hospital admission for high-risk patients.

Admission to hospitals not offering thrombolysis: Given current practice guidelines, acute stroke patients should be preferentially admitted to hospitals offering thrombolysis.[45,61] A study in Switzerland by Engelter *et al.*[61] reported that 20% of stroke patients are admitted to hospitals not offering thrombolysis. To address this, hospital by-pass protocols for thrombolysis-eligible patients have been trialed and supported by adequate training of paramedical staff on the implementation of such protocols. A study by Silliman *et al.*[62] successfully developed and evaluated a hospital by-pass protocol where paramedical staff used a helicopter to transfer potentially thrombolysis-eligible patients to a specialist stroke centre. Up to 71% of eligible patients arrived at the centre within 3 h and 21% received thrombolysis.

Hospital by-pass protocols in conjunction with other ambulance stroke protocols (such as prenotification systems) have been shown to increase the access of patients to thrombolysis.[54] An Australian intervention by Quain *et al.*, which comprised several ambulance-based tools, significantly increased the proportion of patients receiving thrombolysis from 4·7% to 21·4% ($P < 0·001$). This study also reported a significant reduction in the time between symptom onset and emergency department arrival from 150 to 90·5 min ($P = 0·004$) and between emergency department arrival and stroke unit admission from 361 to 232·5 min ($P < 0·001$). Furthermore, the study reported superior long-term clinical outcomes for treated patients: 43% of treated patients had minimal or no disability at 3 months.[26] This intervention comprised the PAST (Pre-hospital Acute Stroke Triage) protocol, consisting of a prehospital stroke assessment tool, an ambulance protocol for hospital bypass for potentially thrombolysis-eligible patients and a prehospital notification system of an acute stroke team.[26]

This highlights the critical role of paramedical staff in providing optimal acute stroke care and must be incorporated within comprehensive approaches to address current barriers.[63] Paramedics are responsible for accurately identifying potential thrombolysis-eligible patients in the field, rapidly transporting them to an appropriate stroke care facility and prenotifying the hospital prior to arrival.[57] In the future, the role of paramedical staff might even expand to include the administration of neuroprotective agents to stroke patients prior to admission.[31,64]

Post-admission barriers

Having a patient present to a hospital within the narrow time window for thrombolysis significantly increases their chances of receiving treatment. However, there are considerable barriers to the administration of thrombolysis post-admission. These can be broadly classified as in-hospital barriers and a lack of appropriate infrastructure/expertise to administer thrombolysis.

In-hospital barriers. Inefficient in-hospital evaluation and treatment can be a barrier to administering thrombolysis to eligible patients.

Suboptimal triage of stroke patients in the emergency department: A previous systematic review of the barriers to thrombolysis found that the delay from patient arrival to first medical assessment varied considerably from 20 min to 4 h[30] because of suboptimal triage of stroke patients. To overcome this delay, it is necessary to educate and train emergency department nurses to

quickly and accurately identify stroke. Education requirements for emergency department nurses should include early stroke recognition triggers, but also an awareness of critical care pathways involving thrombolysis, highlighting its narrow time window, and the necessary critical care of the patient.[65]

The most effective interventions with regard to triage of patients are those that integrate a prehospital assessment by paramedics with subsequent appropriate triage in the emergency department. A study by Behrens *et al.*[66] assessed the impact of a programme that trained paramedical and emergency department staff in how to accurately identify potential stroke patients in the field, rapidly transfer them to hospital and appropriately triage them in the emergency department. The study reported a reduction in the mean delay from onset of symptoms to hospital arrival from 5·2 to 3·3 h. In addition, the delay from diagnosis to administration of thrombolysis decreased from 2·6 to 1·6 h. The percentage of patients arriving within 3 h of symptom onset considerably increased from 2% to 15% and access to thrombolysis noticeably increased from 2% to 11%.

Another successful approach was moving the triage step from the hospital setting to the ambulance (prehospital triage) and implementing a protocol for prehospital notification. This approach has been shown to effectively reduce in-hospital delays. In a study of 189 patients, Mosley *et al.*[63] found that stroke recognition and hospital prenotification by paramedics were associated with significantly shorter times from ambulance call to first medical assessment ($P = 0{\cdot}001$ and $P < 0{\cdot}001$).

Inefficient in-hospital acute stroke care systems: A lack of medical systems and protocols in place in the emergency department, such as an on-call acute stroke team or urgent neuroimaging protocols for acute stroke patients, can cause significant in-hospital delays to treatment. Several innovative strategies have been proposed to overcome these delays, such as the reorganization of in-hospital systems and the introduction of a stroke team emergency call system.

Reorganizing in-hospital systems: The standard procedures for organizing access to medical equipment within a hospital can cause unnecessary delays in the diagnosis of patients with AIS. One strategy to overcome this is to reorganize the access points to medical equipment to facilitate rapid patient assessment. A study in Finland by Lindsberg *et al.*[67] moved the computed tomography (CT) scanner to the emergency department and streamlined triage via prenotification systems from the ambulance. This reorganization resulted in reduced in-hospital delays and increased patient access to thrombolysis. The CT delay time decreased markedly from approximately 63 to 7 min ($P < 0{\cdot}0001$) and the 'door-to-needle' time decreased from approximately 88–50 min ($P < 0{\cdot}001$).

Introduction of an acute stroke team emergency call system: An Australian study by Nazir *et al.*[68] presented another effective approach to speed up the assessment and management of stroke in the emergency department. The study investigated the effect of implementing an emergency call system activated by the triage nurse when a potential stroke patient was identified, which resulted in the rapid deployment of an acute stroke team to the emergency department. The 'onset-to-needle' (165 vs. 140 min; $P < 0{\cdot}05$) and 'door-to-needle' (80·5 vs. 71 min; $P < 0{\cdot}05$) times were significantly improved, and there was a twofold increase in the proportion of patients receiving thrombolysis as a result of implementing this system.

Lack of appropriate infrastructure/expertise to administer thrombolysis. For a patient to successfully receive thrombolysis, the patient must not only present in time but the hospital must be fully equipped to administer thrombolysis.[69] In many countries, a large percentage of the population does not have access to hospitals utilizing thrombolysis. For example, in the United States, a nationwide study reported that 64% of hospitals did not utilize thrombolysis at all within the 2-year period covered by the study.[69]

Similarly, in a recent Australian national survey of hospitals, only 28% were reported to offer thrombolysis.[70] Rural and suburban hospitals are not usually fully equipped to administer thrombolysis, and many do not have stroke units and/or stroke physicians; therefore, stroke patients admitted to these hospitals are not usually considered for therapy.[32] Furthermore, there is considerable discrepancy between the stroke care provided to patients in rural vs. metropolitan areas. A recent retrospective cohort study by Cadilhac *et al.*[71] comparing stroke care in rural vs. metropolitan areas found that for 2254 stroke patients (55% of whom were treated in metropolitan hospitals) stroke unit access varied significantly (rural 3% vs. 77% metropolitan). Additionally, it was found that stroke patients treated in rural hospitals had significantly worse health outcomes.[71] This barrier can be overcome by transferring thrombolysis-eligible patients to an appropriate facility, by utilizing paramedical stroke screening tools and hospital by-pass protocols as described earlier.

Increasing patient access to the limited specialist expertise, especially for rural and remote areas, can also be achieved in a cost-effective manner through the use of telemedicine.[64] Telemedicine is defined as '*the use of telecommunications technologies to provide medical information and services*'.[72] The application of telemedicine in stroke is sometimes referred to as 'telestroke' and is an increasingly important part of clinical practice in some regions.[73] Telemedicine involves the use of videoconferencing, which incorporates a dedicated, high-quality, interactive, bidirectional audiovisual system, alongside the use of teleradiology that enables the remote inspection of brain scans. This system allows the bedside and distant (expert neurologist) clinicians to clearly see and hear each other in full colour via the use of appropriate cameras and display screens.[64]

One of the largest studies evaluating the utility of telemedicine in the administration of thrombolysis was the Telemedical Pilot Project for Integrative Stroke Care (TEMPiS), which commenced in 2003.[74] This study used telemedicine to connect 12 community hospitals (with very limited or no thrombolysis experience) with two stroke centres. During the first 22 months, TEMPiS found no significant difference in mortality rates and functional outcomes between patients given thrombolysis via telemedicine (170 patients) and those given thrombolysis conventionally in stroke centres (132 patients). Mortality rates were 11·2% vs. 11·5% ($P = 0{\cdot}55$) at 3 months, and 14·2% vs. 13% ($P = 0{\cdot}45$) at 6 months. Similarly, at 6 months a good functional outcome was observed, defined by a modified Rankin scale (mRS) ≤1 (39·5% vs. 30·9%; $P = 0{\cdot}10$) and a Barthel Index ≥95/100 (47·1% vs. 44·8%; $P = 0{\cdot}44$). Furthermore, the clinical outcomes of both groups were comparable to those reported in randomized trials.

Another recent study by Pervez *et al.*[75] utilized telemedicine to administer thrombolysis to eligible stroke patients before transferring them to a regional stroke centre, that is, the so-called drip and ship approach. This study also did not find any

significant differences in mortality, SICH and functional outcomes between those 181 patients given thrombolysis via the telemedicine 'drip and ship' method and the 115 patients given thrombolysis by the conventional manner at a regional stroke centre. This study suggests that telemedicine can also be used to shorten the time to thrombolysis, and subsequently, the patient can be transferred to receive optimal stroke care at a stroke centre.

The American Stroke Association gives a *Class I, Level of Evidence B*[64] recommendation to the use of telemedicine by stroke specialists to provide expert medical opinion on the use of thrombolysis in patients with AIS, when on-site stroke expertise is not immediately available. Although relatively large funds are required to establish stroke units or enable telemedicine nationwide, any expenses directed to this area would be compensated by the long-term savings in rehabilitation and nursing home costs. Health economic analyses of thrombolysis show considerable net cost savings, as much as US$600 per thrombolysis-treated patient.[76]

Despite the long-term cost savings associated with thrombolysis, the direct usage cost of thrombolysis can be a significant barrier to its utilization, especially in developing countries where the cost of tPA is approximately twice the annual income per capita.[77] Even among developed countries, the reimbursement from insurance providers for acute stroke care does not necessarily cover the costs of thrombolysis.[78]

Physician uncertainty in prescribing thrombolysis. Proper assessment of the risks vs. benefits of thrombolysis in an acute setting can be challenging, and physician uncertainty of the impact of thrombolysis is an important barrier to the utilization of thrombolysis in routine clinical practice.[30] This uncertainty is partly due to a lack of awareness regarding the role of thrombolysis.[42] A survey of 266 resident physicians in Los Angeles (1998) found that only 60% recognized that thrombolysis should be administered within 3 h, and 28% reported that they did not even consider the use of thrombolysis in AIS.[42]

Emergency physicians usually have limited experience with thrombolysis and therefore are not comfortable routinely prescribing it. In a survey of 2600 emergency physicians, 40% reported that they were not likely to use thrombolysis in stroke, even in an ideal setting.[79] Of these, 65% reported that this was because of the risk of SICH, 23% reported lack of benefit and 12% reported both reasons. The survey also found that previous experience with thrombolysis was independently associated with the willingness to use thrombolysis.[79] Emergency physicians' attitude towards thrombolysis greatly affects the future implementation of this therapy, as this is a key step in the administration of first-line therapies for stroke. These physicians set the policies and procedures in the emergency department, and their attitude towards thrombolysis is likely to influence other personnel involved in the acute treatment of stroke patients.[42]

Collaborative decision-making between emergency physicians and neurologists has been shown to be successful in stroke treatment. Akins *et al.*[80] compared the clinical outcomes of stroke patients who received thrombolysis treatment from a neurologist or an emergency physician following a telephone discussion with a consultant neurologist and radiologist. The functional outcomes, SICH rates and mortality rates were found to be similar in patients treated by a neurologist or by an emergency physician. The mean 'door-to-needle' times were also similar. Another observational study by Batmanian *et al.*[81] was designed to assess the safety and efficacy of a 24-h comprehensive protocol-driven model for thrombolysis in the emergency department, where the initial assessment was undertaken by the emergency physician but the decision to treat was made by an attending neurologist. The study reported a 15% utilization rate of thrombolysis and superior clinical outcomes at 3 months; 67% of the treated patients were independent (mRS = 0–2) and 47% had excellent functional recovery (mRS ≤ 1). Furthermore, SICH was not observed.

Essential to the proper implementation of thrombolysis in routine clinical practice is the presence of appropriate staff to monitor and manage suspected complications. To help diminish worries related to the risk of ICH after thrombolysis, the Brain Attack Coalition and the American Academy of Neurology recommend that a neurosurgeon be available to facilitate the administration of thrombolysis.[82]

One of the reported reasons for underutilization of thrombolysis relates to the risk vs. benefit assessment undertaken to determine the appropriateness of therapy. With regard to the relative benefit of treatment, patients are sometimes not considered for therapy because the physician underestimates the severity of stroke symptoms (i.e. assesses them to be mild). This deprives the patient of rapid reperfusion of the affected area in the brain, leading to permanent disability. A study by Barber *et al.*[25] reported that 31% of stroke patients were excluded from treatment because their symptoms were either considered too mild or were rapidly improving. As a result of not being treated, a third of these patients were left dependent or dead.

Two main strategies have been proposed to provide the necessary support to emergency physicians. The first is the use of telemedicine; a survey conducted by Moskowitz *et al.*[83] found that emergency physicians reported positive beliefs regarding the role of telemedicine in optimizing stroke management and its superiority over conventional telephone consultation. The second is the use of decision-making tools that aid physicians in the risk/benefit assessment for thrombolysis. Several evidence-based tools that predict good and bad functional outcomes with and without thrombolysis have been developed (Table 1). Unfortunately, the utility of these tools and their influence on physician decision-making and patient outcomes has not been evaluated in clinical trial settings.

An additional factor compounding physician uncertainty about thrombolysis relates to concerns about the influence of the pharmaceutical industry on the endorsement of this treatment and potential conflicts of interest (as is the case for any pharmaceutical product). Financial contributions from pharmaceutical companies to organizations that set the therapeutic guidelines for stroke may have an impact on their recommendations, and it has been highlighted that some experts have ties to the manufacturer of tPA.[89,90] It is also worth mentioning here that the major RCT (ECASS-3) that led to the expansion of the therapeutic time window of tPA from 3 to 4·5 h was sponsored by the pharmaceutical manufacturer of tPA and that this sponsor was responsible for the monitoring and data management of the trial.[19]

Difficulty in obtaining informed consent for thrombolysis. Once the physician has weighed the risks and benefits of thrombolysis in a particular setting, they then must involve the patient or their family in the decision-making process. Obtaining the patient's or, more realistically, the family's consent for thrombolysis is the final barrier to the administration of thrombolysis, as consent

Table 1. Decision-making tools for thrombolysis in stroke

Tool	Description	Outcome	Utility/computer or paper based	Strengths	Limitations
Kent *et al.*[84] Stroke-TPI (stroke–thrombolytic predictive instrument)	Provides patient-specific predictions of the probability of a normal or near-normal outcome, catastrophic outcome (death or very severe disability), with without thrombolysis	Presents proportions of: mRS ≤ 1 (placebo) mRS ≤ 1 (tPA) mRS ≥5 (placebo or tPA)	Patient selection for thrombolysis and patient counselling Computer based	Provides patient-specific prognoses (both good and bad functional outcomes)	Not validated Strictly computer based Applicable only to patients receiving IV thrombolysis within 3 h (i.e. ≠ >3 h, ≠ IA thrombolysis) Predictions may not be valid for patients in routine clinical practice or patients not well represented in the database (age >85, systolic blood pressure >200 mmHg, with pre-existing disability)
Lou *et al.*[85] The HAT Score (haemorrhage after thrombolysis)	Diabetes mellitus or baseline blood glucose >200 mg/dL (11·1 mM) upon admission, 1 point; baseline NIHSS score, 15–20 (1 point), ≥20 (2 points); Presence of easily visible hypodensity on CT scan; <1/3 of MCA territory (1 point), ≥1/3 of MCA territory (2 points)	HAT score ≤2 low risk of ICH HAT score >3 higher rates of SICH and catastrophic outcomes at 3 months	Patient selection for thrombolysis and patient counselling Paper based	Simple, practical, quick, and easy-to perform scale Score Validated in two independent cohorts	Further validation required Retrospective nature Applicable only to patients receiving IV thrombolysis within 3 h (i.e ≠ >3 h, ≠ IA thrombolysis) Predictions may not be valid for patients not well represented in the database (patients with SICH)
Cucchiara *et al.*[86] A risk score to predict ICH	One point for each: age >60 years, baseline NIHSS score >10, glucose >8·325 mM (150 mg/dL), and platelet count<150 000/mm^3	Rate of ICH: 0 points, 2·6%; 1 point, 9·7%; 2 points, 15·1%; ≥3 points, 37·9%	Patient selection for thrombolysis and patient counselling Paper based	Simple, practical, quick, and easy-to perform scale	Not validated Applicable only to patients receiving IV thrombolysis within 3 h (i.e ≠ >3 h, ≠ IA thrombolysis) Predicts only the risk of ICH (not functional outcome)
Cunningham[87] The outcome wheel	The tool kit generates a visual presentation of the risks and benefits of thrombolysis that is easily interpreted by both patients and clinicians to allow for rapid, informed decision-making	Patient eligibility according the Canadian Guidelines 1998 and NIHSS score Outcome figures with and without thrombolysis displays percentages of: 1. Minimal or no disability 2. Intracranial bleed 3. Disability and death	Patient counselling only Computer based but may be adapted for paper-based use	Completed forms may be saved and subsequently audited Visual displays: permit patients to rapidly understand response patterns to therapy	Not validated Applicable only to patients receiving IV thrombolysis within 3 h (i.e ≠ >3 h, ≠ IA thrombolysis) The outcome figures are based on a study that was not powered to detect subgroup differences and hence found no statistical evidence that the thrombolysis treatment effect differed among patient subgroups

Table 1. (Continued)

Tool	Description	Outcome	Utility/computer or paper based	Strengths	Limitations
Gadhia *et al.*[88] Figures visually convey benefit and risk of stroke thrombolysis	Four different figures (visual displays) that compare outcomes with and without thrombolysis	Figures representing functional outcomes with and without thrombolysis	Patient counselling only Paper based	Visual displays: permit patients to rapidly understand response patterns to therapy	Not validated Applicable only to patients receiving IV thrombolysis within 3 h (i.e ≠ >3 h, ≠ IA thrombolysis)

mRS, modified Rankin Scale; tPA, tissue plasminogen activator; IV, intravenous; IA, intra-arterial; NIHSS, National Institutes of Health Stroke Scale; SICH, symptomatic intracerebral haemorrhage; ICH, intracerebral haemorrhage; MCA, middle cerebral artery; CT, computed tomography.

will only be sought after the physician has completed the patient assessment and found that the patient is eligible for treatment. Most patients and carers prefer to be given accurate information and be actively involved in the decision-making process. A study found that 93% of its participants wanted exact information regarding the risks vs. benefits of thrombolysis and that 91% favoured shared patient–doctor decision-making.[91] The patient's lowered consciousness level, the patient's and family's poor understanding of medical terminology, and the considerable time pressures, are all factors that can hinder informed decision-making in a time-sensitive manner.

To overcome this obstacle, decision-making tools that generate visual displays of the risks/benefits of thrombolysis treatment have been developed to give patient and family members realistic expectations of thrombolysis. These tools help physicians counsel patients and families on the risks of thrombolysis in an unbiased and time-effective manner[86–88] (Table 1). The impact of these tools on physician–patient interaction and patient/family comprehension of the treatment options has not been evaluated in a clinical practice setting.

WHAT IS NEW AND CONCLUSION

The current utilization of thrombolysis for stroke treatment is suboptimal because of several inter-related reasons. This article has presented the common barriers and the proposed strategies to overcome these. Because of the considerable underutilization of thrombolysis, interventions that have targeted any of these barriers have usually been successful. Below are the key interventions that have been demonstrated to increase the utilization of thrombolysis in clinical practice:

- Public awareness campaigns that focus on the availability of a time-sensitive treatment (thrombolysis)
- Paramedical prehospital triage using prehospital stroke screening tools
- Hospital by-pass protocols coupled with hospital prenotification systems
- Efficient in-hospital acute stroke care systems including urgent stroke-unit admission, an on-call multidisciplinary acute stroke team and urgent neuroimaging protocols
- Utilization of telestroke in rural and remote areas: 'drip and ship'/'drip and keep' procedures
- Wider physician endorsement of thrombolysis and use of appropriate risk-assessment tools

Addressing physicians' concerns regarding the utilization of thrombolysis is of critical importance. Compared with other barriers to the utilization of thrombolysis, overcoming this barrier will have a relatively rapid impact on thrombolysis utilization rates. Furthermore, any improvement realized in other areas, such as late patient presentation, ambulance service delays or lack of resources, will only be reflected in an increase in utilization rates through the physicians' adoption and implementation of thrombolysis. In addition, overcoming this barrier will have a progressive and sustained impact, because once policies and procedures are put in place and proper implementation of thrombolysis is established, future physicians will be trained in an environment where thrombolysis is a reality and priority.

The findings of this review also highlight that greater engagement of pharmacists (i.e. the pharmacotherapeutics experts) is warranted in different aspects of stroke care including stroke prevention, acute stroke care and post-discharge rehabilitation.

Pharmacists are relatively seldom included in interventions targeting stroke care, yet pharmacists have a potential role to play in many facets where pharmacotherapy is central to this care. For example, pharmacist-led interventions have been shown to be successful in optimizing prophylactic antithrombotic therapy and in helping control modifiable risk factors, such as blood pressure[92,93], and pharmacists are also recognized as essential members of contemporary stroke rehabilitation units.[94] In particular, within the hospital setting, pharmacists can potentially play a more proactive role in facilitating access to thrombolysis for acute treatment, and supporting clinicians in their risk/benefit assessments for this treatment. In the primary care setting, community pharmacists are in a unique position to identify patients at risk of stroke through specifically developed screening programmes[95] and educate at-risk patients and their families regarding the early recognition of stroke symptoms and appropriate action at the onset of stroke.[96] The involvement of the pharmacist in patient education can have a significant impact on thrombolysis utilization rates, given that late patient presentation is the most significant barrier to the utilization of thrombolysis in stroke.[46] The potential role of pharmacists in acute stroke care, however, remains speculative and evidence through further research is needed to support the efficacy of their involvement.

In conclusion, the most effective approaches reported in the literature to facilitate the use of thrombolysis are those which target more than one barrier simultaneously. Therefore, optimal utilization of thrombolysis requires a systematic, integrated multidisciplinary approach across the continuum of acute care, from prehospital assessment, to admission to specialized stroke units, and then to optimal in-hospital stroke care systems. Greater pharmacist involvement is needed in different aspects of stroke care from patient education to facilitating access to thrombolysis. Increasing the utilization rates for this important therapy will eventually result in decreased rehabilitation costs and improvement in patient outcomes in terms of reduced disability and improved quality of life. There is still a need for more research to find the most effective and cost-effective interventions to improve the use of thrombolytic therapy in stroke.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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