Thrombolytic therapy for acute ischaemic stroke

Damian Jenkinson

Recombinant tissue plasminogen activator (rt-PA, also known as alteplase; Actilyse®) is the first and only licensed thrombolytic approved for use in acute ischaemic stroke in the UK. This article reviews the evidence for the role of rt-PA in acute stroke management and how it may improve long-term clinical outcome for selected patients as part of a comprehensive stroke service.

Stroke is a syndrome of rapidly developing clinical symptoms and signs of focal (or global) loss of cerebral function, with symptoms lasting 24 hours or longer, or leading to death with no apparent cause other than that of vascular origin (Wolfe, 2000). Stroke is the leading cause of adult disability and a major cause of death in the UK. A stroke can occur at any age, although half of all strokes occur in those over 70 years of age. Almost one in four men and one in five women aged 45 years can expect to have a stroke if they live to their 85th year.

Evidence for the effectiveness of interventions in acute stroke has, until recently, been confined to organized stroke care and the use of aspirin after ischaemic stroke. However, several large placebo-controlled randomized trials have suggested that thrombolytic therapy is a promising treatment for acute ischaemic stroke. If administered within 3 hours of stroke onset to carefully assessed and selected patients, thrombolysis can reduce long-term disability and improve clinical outcome.

Alteplase (Actilyse®, Boehringer-Ingelheim Ltd, Germany) received its licence for use in acute ischaemic stroke in the UK in April 2003. It is the first licensed thrombolytic for use within the 3-hour window in this indication. This review examines the clinical evidence base for the use and role of alteplase in acute ischaemic stroke.

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ACUTE ISCHAEMIC STROKE

Acute ischaemic stroke accounts for 76% of all strokes, with 10% being attributed to primary intracerebral haemorrhage and 4% to subarachnoid haemorrhage. *Table 1* indicates the proportions of first strokes that can be expected according to the Bamford classification.

Approximately 19% of patients who suffer an acute ischaemic stroke will die within 30 days of stroke onset (Bamford et al, 1990). However, of those who survive the initial acute event, the cumulative risk of a recurrent stroke over 5 years remains high, ranging from 15–42% (Hankey et al, 1998; Wolf et al, 1999), with the greatest risk of recurrence being within the first 6 months. Some survivors will also experience continuing disability after 6 months, with the main neurological deficits being contralateral paralysis, or weakness on one side of the body (hemiplegia or hemiparesis) and impairment or loss of speech (aphasia). One year after a stroke, 65% of survivors are functionally independent.

The need to improve acute stroke services was exemplified by a survey carried out by the Stroke Association which showed that provision of stroke services throughout the UK was largely inconsistent and substandard (Ebrahim and Redfern, 1999). Despite the admirable model standards of stroke care described in the National Service Framework for Older People (Department of Health, 2001), evidence from the

TABLE 1.
Proportion of first strokes

Cerebral infarction (76%)	Partial anterior circulation (56%)
	Lacunar (20%)
	Total anterior circulation (15%)
	Posterior circulation (8%)
	Unclassified (1%)
Primary intracerebral haemorrhage (10%)	
Subarachnoid haemorrhage (4%)	
Not known (10%)	

From Bamford et al (1991)

Royal College of Physicians' National Sentinel Audit of Stroke suggests that progress in development of stroke services across the UK is unacceptably slow (Royal College of Physicians, 2002a), with marked variation across the UK in terms of the organization and process of care (*Figure 1*). In 1999, 25% of stroke patients spent most of their time on a stroke unit and by 2002 this had risen to only 27%. Although there are more stroke units, they remain of insufficient capacity, and although there are more stroke clinicians, they have insufficient time to provide appropriate care.

The National Clinical Guidelines for Stroke state that all stroke services should include a coordinated multidisciplinary team, staff with specialist expertise in stroke and rehabilitation, educational programmes for staff, patients and carers, and facilities for the rapid assessment of transient ischaemic attack and minor stroke with access to brain and vascular imaging services (Royal College of Physicians, 2002b). Planning for the delivery of a comprehensive service for patients with acute stroke should now also incorporate the capacity to safely implement thrombolysis for highly selected patients. Importantly, developments in service, catalysed by the introduction of thrombolysis, would ultimately benefit all patients presenting with acute stroke.

THE USE OF THROMBOLYSIS IN STROKE

The two thrombolytic agents that have been most studied in stroke are recombinant tissue plasminogen activator (rt-PA) and streptokinase. The three main trials involving streptokinase have been disappointing, reporting an early increased risk of cerebral haemorrhage and death with no net benefit at final follow up (Lees, 2000). The poor outcomes in the streptokinase-treated patients might be explained by the inclusion of patients with more severe strokes, greater use of antithrombotic drugs, higher doses, and the longer time to treatment compared with the trials that used rt-PA. The four main trials involving rt-PA are described individually below and then in meta-analysis. Lastly, clinical experience with thrombolysis for stroke since licensing of rt-PA is described.

RT-PA

rt-PA is a recombinant DNA-derived version of a naturally occurring tissue plasminogen activator (t-PA) protein normally secreted by human endothelial cells. Upon intravenous infusion, rt-PA is relatively inactive in the systemic circulation. It has a low affinity for plasminogen but a high affinity for fibrin and binds rapidly to an existing blood clot. Once bound to fibrin, its affinity for plasminogen is increased and plasminogen is converted to plasmin resulting in local fibrinolysis (*Figure 2*). rt-PA has a short system half-life and is rapidly eliminated via the liver.

rt-PA was launched under strict licensing guidelines. It should only be used by a physician specialized in stroke care, experienced in the use of thrombolytic treatments and with the facilities to monitor its use and complications. Brain imaging must be conducted before administration to exclude haemorrhagic stroke or the very early signs of massive infarction.

rt-PA is contraindicated in certain circumstances: if there is a suspicion of intracranial or subarachnoid haemorrhage, a history of stroke

Figure 1. Royal College of Physicians' National Sentinel Audit of Stroke (2002a). The organization and process of stroke care in 235 trusts across the UK.

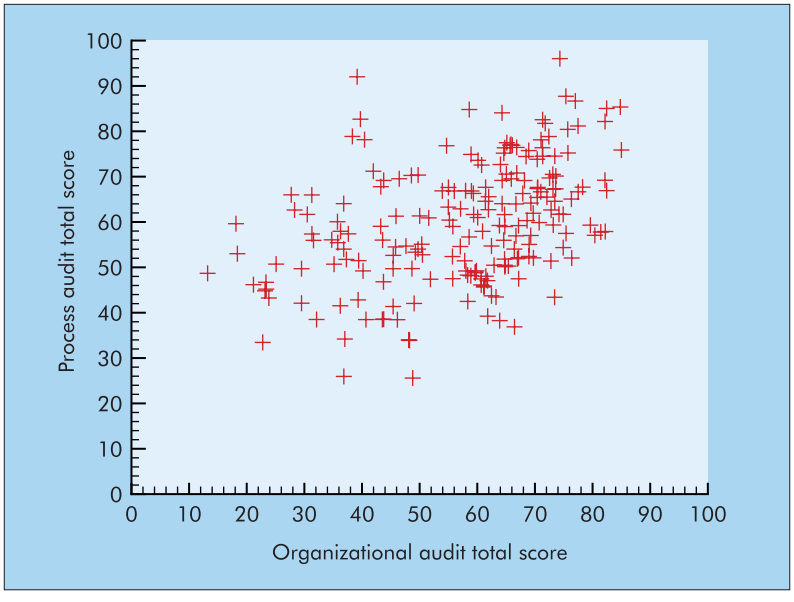
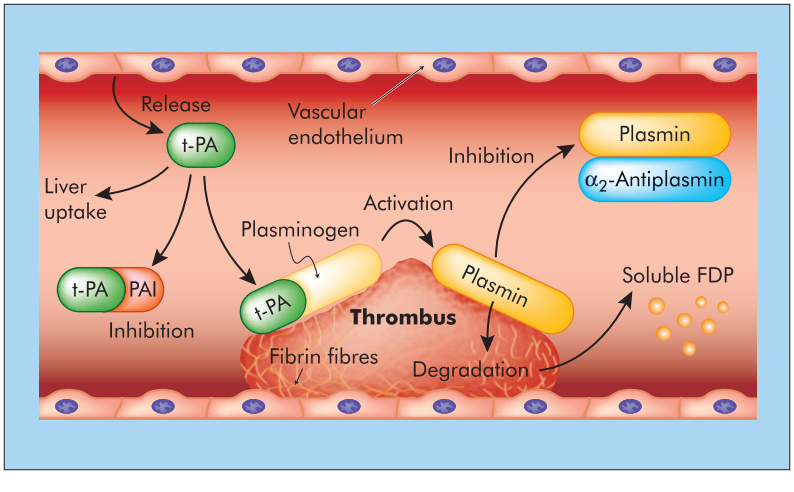


Figure 2. Mode of action of alteplase. FDP = fibrin degradation products; PAI = plasminogen activator inhibitor; t-PA = tissue plasminogen activator.



within 3 months, recent intracranial neoplasm, arteriovenous malformations or aneurysm, use of oral anticoagulants such as warfarin, severe uncontrolled arterial hypertension, uncontrolled diabetes, severe liver disease, or if the patient has had major surgery in the preceding 3 months. rt-PA is not indicated for use in those under 18 years or over 80 years of age, although one study found no increased risk in elderly patients (>80 years) treated with rt-PA (Tanne et al, 2000). The stroke physician must carry out a risk/benefit evaluation before administering rt-PA to elderly patients. Patients with very mild or very severe strokes appear not to benefit from thrombolytic treatment with rt-PA.

Individual trials

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS) published their findings for thrombolytic therapy in acute ischaemic stroke in 1995 (NINDS, 1995). Patients within 3 hours of onset of acute stroke were randomized to receive rt-PA 0.9 mg/kg or placebo, after brain haemorrhage had been excluded by computed tomography (CT) brain scan. Patients with systolic blood pressure (BP) >180 mmHg or diastolic BP >110 mmHg were excluded. Concomitant use of all antithrombotic agents was prohibited for 24 hours after treatment with rt-PA and there was rigorous control of BP within the pre-specified limits mentioned above. The NINDS trial consisted of two parts, 1 and 2.

The part 1 study sought to determine neurological outcomes 24 hours after treatment in 291 patients randomized to rt-PA or placebo. The primary end point, indicated by an improvement of 4 points or more in the National Institutes of Health Stroke Scale (NIHSS) or complete recovery (NIHSS score = 0), was not significantly different between the treatment groups. However, secondary analysis suggested that treatment with rt-PA was associated with an improved outcome at 3 months using the Barthel Index, modified Rankin Scale, Glasgow Outcome Scale and NIHSS.

The part 2 study evaluated neurological outcomes at 3 months in 333 patients randomized to rt-PA or placebo. A favourable outcome was defined as minimal or no disability using the four stroke assessment scales; the Barthel Index (≥ 95), Glasgow Outcome Scale (score = 1), modified Rankin Scale (score of ≤1), and NIHSS (score ≤1). As compared with patients given placebo, patients treated with rt-PA were at least 30% more likely to have minimal or no disability at 3 months on all four outcome scales (NINDS, 1995). Symptomatic intracranial haemorrhage within 36 hours after stroke onset occurred in 6.4% of patients given rt-PA compared with 0.6% of patients given placebo. Despite this, mortality at 3 months was lower in the rt-PA group at 17%, compared with 21% in the placebo group.

The first European Cooperative Acute Stroke Study (ECASS I) was a European multicentre trial that evaluated neurological outcomes at 3 months in 620 patients, randomized to either rt-PA or placebo. A higher dose of rt-PA was used (1.1 mg/kg) with a maximum interval of 6 hours between onset and treatment. Although no benefit for treatment with rt-PA was seen in the intention-to-treat group, a post-hoc analysis of the 'target population' (after exclusion of about 20% of the randomized patients with protocol violations, mostly as a result of visibility of early signs of cerebral infarction on the randomization CT brain scan) suggested that thrombolysis with rt-PA was effective in improving some functional measures and neurological outcomes in a defined subgroup of stroke patients with moderate to severe neurological deficit and without extended infarct signs on the initial CT scan (Hacke et al, 1998).

The second European Cooperative Acute Stroke Study (ECASS II) was designed to specifically exclude those patients with visible infarction in more than a third of the middle cerebral artery (MCA) territory, in addition to those with intracranial haemorrhage, on CT. A lower rt-PA dose was administered (0.9 mg/kg, to match that used in the NINDS trial) within 6 hours of symptom onset (Hacke et al, 1998). ECASS-II evaluated neurological outcomes at 3 months in 620 patients, randomized to alteplase or placebo. The outcome of the trial was neutral on its pre-stated end points.

The last major trial published using rt-PA was the ATLANTIS (Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischaemic Stroke) trial (Clark et al, 1999). The initial overall objective of ATLANTIS A was to test the efficacy and safety of rt-PA in acute ischaemic stroke patients up to 6 hours after stroke onset, with patient selection criteria that were similar to those in the NINDS trial. CT brain scan was mandatory before randomization to exclude cerebral haemorrhage, but there were no exclusion criteria based on visible infarction. In November 1993, the protocol was modified on the basis of the results from the NINDS trial,

after 142 patients had been randomized. ATLANTIS B initially had a 5-hour time window, changed in 1996 to a 3–5-hour window, and CT exclusion criteria were introduced (visible infarction in more than one third of the MCA territory).

Intravenous rt-PA 0.9 mg/kg was administered to an intent-to-treat population of 613 patients, of whom 547 were treated within 3–5 hours of symptom onset with 39 treated within 3 hours and 24 after 5 hours. Clark et al (1999) only presented data on the patients randomized between 3 and 5 hours. The study found no significant rt-PA benefit on the 90-day efficacy end points (NIHSS score of <1) in patients treated between 3 and 5 hours (Clark et al, 1999).

The NINDS trial is therefore the only trial to date which has yielded positive results for rt-PA in acute ischaemic stroke using the predefined study end point. Factors which may have contributed to this success are shown in *Table 2*.

TABLE 2.
Factors possibly contributing to NINDS trial success

3-hour window
Imbalance in baseline severity
Antithrombotic avoidance for 24 hours
Lower recombinant tissue plasminogen activator dose
Rigorous blood pressure control
Type of recruiting hospitals
Chance

NINDS = National Institute of Neurological Disorders and Stroke

Meta-analysis of the trials

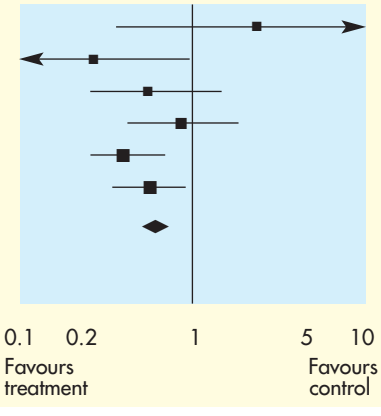
A Cochrane review of thrombolysis in stroke was published in 2003 and involved an analysis of eighteen randomized trials of any thrombolytic agent compared with control in patients with definite ischaemic stroke. The review included 5727 patients, in trials testing urokinase, streptokinase, rt-PA or recombinant prourokinase. Approximately 50% of the data analysed came from trials testing intravenous rt-PA. Overall, thrombolytic therapy administered up to 6 hours after ischaemic stroke significantly reduced the proportion of patients who were dead or dependent (modified Rankin 3–6) at 3–6-month follow-up. Trials results involving rt-PA suggested that it may have more benefit and be less hazardous than other thrombolytics when given up to 6 hours after stroke onset. The review concluded that thrombolytic therapy results in a significant net reduction in the proportion of patients dead or dependent during daily living, with the data supporting the use of rt-PA in specialized stroke centres in selected eligible patients (Wardlaw et al, 2003).

A meta-analysis of the effect of thrombolysis with rt-PA in those patients treated within 3 hours of stroke (*Figure 3*) provides further support for this concept. The absolute risk reduction in poor outcomes is 13%. The number needed to treat with rt-PA to prevent one poor outcome is 8, and the benefit remains graded over time. Between onset and 1.5 hours, rt-PA treatment increases the odds of favourable outcome by 2.8 (95% confidence interval = 1.8–9.5) and between 1.5 and 3 hours by 1.5 (95% confidence interval = 1.1–2.1).

Figure 3. Effect of thrombolysis with recombinant tissue plasminogen activator within 3 hours of stroke. Outcome: death or dependency (modified Rankin 3–6) at 3months (Brott, 2002). See text for full details and references for studies. CI = confidence interval; df = degrees of freedom.

Study	No. showing poor outcome/no. at follow up: Treatment	Control	Odds ratio	Weight (%)	Odds ratio (95% CI)
Atlantis A	8/10	7/12		2.3	2.59 (0.45–15.08)
Atlantis B	4/13	17/26		4.2	0.26 (0.07–0.96)
ECASS I	30/49	26/36		9.1	0.57 (0.24–1.4)
ECASS II	47/81	48/77		17.9	0.84 (0.44–1.58)
NINDS trial 1	76/144	107/147		32.1	0.43 (0.26–0.68)
NINDS trial 2	103/168	122/165		34.4	0.56 (0.36–0.69)
Total (95% CI)	266/465	329/465		100.0	0.565 (0.42–0.73)

Test for heterogeneity χ^2=7.07, df=5, *P*=0.22
Test for overall effect z=4.29; *P*=0.00002



Clinical practice

The outcome of these trials led to the licensing of rt-PA for stroke by the US Food and Drug Administration and, conditionally, in the European Union – the first ever treatment approved for acute ischaemic stroke. The NINDS trial also prompted the Stroke Council of the American Heart Association to recommend that, if haemorrhagic stroke is excluded, thrombolytic therapy with rt-PA should be started in patients within 3 hours of a stroke (Wolf et al, 1999).

The Standard Treatment with Alteplase to Reverse Stroke (STARS) study was undertaken to assess the safety profile and to document clinical outcome and adverse events in rt-PA-treated patients. The study concluded that favourable clinical outcomes and low rates of symptomatic intracerebral haemorrhage can be achieved with rt-PA treatment when treatment protocols are strictly adhered to (Albers et al, 2000).

Other studies have investigated the use of rt-PA in routine clinical practice with less positive results than in the controlled trial setting. A retrospective cohort study in Connecticut showed overall inhospital mortality (25%) was higher than that obtained in the NINDS trial (13%). However, a significant proportion of patients in the Connecticut cohort that displayed the higher mortality had major protocol deviations. Patients without such deviations had outcomes similar to the NINDS cohort (Bravata et al, 2002).

A similar situation was seen in a study carried out in Cleveland, with 50% of the 70 patients treated with rt-PA having deviations from national guidelines. In these patients the mortality rate was higher than in those not treated with rt-PA (15.7% *vs* 5.1%) with 11 seen to develop symptomatic intracranial haemorrhage resulting in six deaths (Bravata et al, 2002). Both of these studies clearly demonstrate the need to closely follow guidelines when using rt-PA for acute stroke (Lenzer, 2003).

Finally, a comparison of clinical outcomes in the first 180 patients receiving rt-PA in routine clinical practice across Europe and registered in the observational safety monitoring study Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) (see below), with clinical outcomes from the trials, gave evidence of similar benefit (Wahlgren, 2002). Rates of symptomatic intracranial haemorrhage were also similar to those seen in the trials.

A corollary of strict adherence to guidelines in thrombolysis, which is important for service planning, is that the proportion of patients with acute stroke who are likely to be eligible for treatment is only around 1–5%.

SAFE IMPLEMENTATION OF THROMBOLYSIS IN STROKE MONITORING STUDY

As part of the licensing agreement for rt-PA, an observational safety monitoring study called SITS-MOST has been set up, embedded within the Safe Implementation of Thrombolysis in Stroke International Thrombolysis Register (SITS-ISTR). SITS-ISTR is an internet-based, international monitoring registry for auditing the safety and efficacy of routine therapeutic use of thrombolysis in acute ischaemic stroke (www.acutestroke.org). The registry is available to clinicians across Europe and was established by the ECASS investigators and is now owned by the International Collaborative Group, represented by the SITS Scientific Committee.

The role of SITS-MOST is to demonstrate that rt-PA can be at least as safe and beneficial in routine clinical practice as in the clinical trials. The register will provide continuing follow up for patients who have met the defined inclusion criteria for rt-PA treatment and who receive thrombolysis within 3 hours of symptom onset. Centres participating must have appropriate acute stroke facilities and be based in Europe, including Iceland, Norway and Switzerland. Entry requires the agreement of the National Coordinator, based at the Karolinska Hospital in Stockholm in Sweden. Stroke physicians using rt-PA should register with SITS-MOST and provide data on patients who have received rt-PA within their acute stroke centre. These data will focus on time delays in management, baseline and demographic data, baseline stroke severity (NIHSS score), baseline imaging studies and follow-up NIHSS score and imaging, with an evaluation of results using the modified Rankin score at 3 months together with details of any complications such as haemorrhage.

These data will be available online and in annual statistical reports, allowing centres to compare their own data with national and international data. Boehringer Ingelheim, as the marketing authorization holder for rt-PA, has a legal obligation to provide regular periodic safety update reports to the European Medicines Evaluation Authority's Committee for Proprietary Medicinal Products.

CONCLUSIONS

Future trials are needed to identify those patients who are most likely to benefit and least likely to be harmed by thrombolysis. In particular, the evaluation of the contribution of age, sex, stroke severity, blood pressure and its con-

trol, CT scan appearance, stroke subtype, concurrent administration of other neuroprotective treatments, prior and post-antiplatelet and post-anticoagulation therapy is critical. Patients are currently being recruited into two randomized placebo-controlled studies further investigating the efficacy and safety of rt-PA after acute stroke. First, the Third International Stroke Trial (www.dcn.ed.ac.uk/IST3) is recruiting patients of all ages up to 6 hours after stroke. Second, the Third European Cooperative Acute Stroke Study (ECASS III) is recruiting patients 3–4 hours from the onset of symptoms, in order to further explore the available treatment window. Other studies using diffusion and perfusion magnetic resonance imaging are in progress, and more intra-arterial thrombolysis trials are planned.

Thrombolytic treatment with rt-PA is an effective and evidence-based treatment for acute ischaemic stroke when administered to appropriately selected patients. Although there is a risk of early fatal or symptomatic intracranial haemorrhage, the randomized clinical trials show that rt-PA administered within the 3-hour time window results in one or more independent survivor for every eight patients treated.

The safe introduction of thrombolytic therapy in the UK should be in the context of an organized and integrated stroke service. By promoting the rapid recognition of stroke symptoms in the community, and the prompt transport of such patients to specialized stroke units for early investigation, stabilization and treatment, there would be a substantial net benefit for all patients with stroke, and not just for the small proportion who would be eligible for thrombolysis. The later group of patients treated with rt-PA should be entered onto the SITS-MOST registry, to ensure that safety and efficacy of thrombolysis in clinical practice is at least as good as in the trials. **HM**

Conflict of interest: Dr Jenkinson has received financial sponsorship to attend scientific conferences and lecturers' fees from various pharmaceutical companies, including Boehringer Ingelheim.

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KEY POINTS

- Stroke is one of the leading causes of morbidity and mortality and is the leading cause of disability in the developed world.
- Between 80 and 85% of all acute strokes are caused by cerebral infarction, usually resulting from partial or complete occlusion of a cerebral artery.
- Recombinant tissue plasminogen activator (rt-PA) is the first and only licensed thrombolytic treatment for acute ischaemic stroke and treatment of appropriate patients reduces disability and morbidity.
- rt-PA should only be administered by stroke physicians after computed tomography or magnetic resonance imaging scanning has exclude intracranial haemorrhage.
- All patients treated with rt-PA should be enrolled within the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST).
- Strict adherence to treatment protocol is essential to ensure maximum benefit from treatment with minimum hazard.