What is the place of thrombolysis in acute stroke? A review of the literature and a current perspective

Peter O Jenkins, Martin R Turner and Paul F Jenkins

ABSTRACT – The global burden of stroke, the undisputed success of intravenous thrombolysis in the management of myocardial infarction and subsequent evidence from animal models of cerebral infarction have all fuelled intense interest in the potential role for thrombolytic agents in the acute management of stroke in clinical practice. Before any clinical treatment is introduced universally its safety and efficacy must be demonstrated in the routine clinical environment and not just within the ideal conditions of controlled clinical trials. Similarly, the cost effectiveness of a new treatment modality is an essential consideration before its use is promulgated. This paper reviews the current scientific evidence for thrombolysis in stroke with reference to issues of safety, efficacy and cost effectiveness.

KEY WORDS: cerebral haemorrhage, cerebral infarction, cost effectiveness, stroke, thrombolysis, tissue plasminogen activator

Introduction

Intravenous (iv) thrombolytic agents are an established and effective treatment in acute myocardial infarction (AMI), a disease with some similarities to acute ischaemic stroke. Additionally there have been several animal stroke models, which demonstrate that thrombolysis results in reduced infarct size and improved neurological function.[1–3] These findings have provided a rationale to implement the use of thrombolysis in the management of human acute ischaemic stroke. Its use has, however, been delayed due to concerns over increased risk of intracerebral haemorrhage and the cost of providing an infrastructure capable of providing this treatment in an acute setting.

To justify the use of a treatment it must be shown to be safe, effective (under the ideal conditions of a randomised controlled trial (RCT) and in the community) and economically efficient. This article reviews the evidence for the use of thrombolysis in acute ischaemic stroke and poses the question as to whether its widespread use is justified.

Randomised controlled trials

As of July 2007, there were eight major RCTs studying the safety (indicated by the early death or haemorrhage rate) and efficacy (using the end-points of death or dependency at the end of the trial follow-up period) of iv thrombolytic therapy. Table 1 summarises this data and includes figures for a large Cochrane meta-analysis.[4] The aim of this paper is not to provide an exhaustive review of all the trials conducted into the safety and efficacy of thrombolysis and so seven trials included in the Cochrane review have been omitted. Three of the trials were conducted during the 1980s (Ohtomo 1985,[5] Atarashi 1985,[6] Abe 1981[7]) and were methodologically different to the others – very low doses of urokinase were given over several days, starting 5–14 days after the stroke. In addition, functional data was not recorded – merely rates of haemorrhage and death by end of follow up. The four other trials omitted from the table (Japanese Thrombolysis Study Group 1993,[8] Mori 1992,[9] Haley 1993,[10] Morris 1995[11]) were small studies with only 98, 31, 27 and 20 patients respectively. The size of these studies therefore means that they lack the statistical power of those included in the table and this paper.

Streptokinase (SK) did not show the benefit so readily observed in the setting of AMI, perhaps highlighting early important differences in the pathogenesis of stroke and its optimal acute treatment. All three of the SK trials were terminated early due to

Trials

ASK: Australian Streptokinase Trial Study Group

ATLANTIS: Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischaemic Stroke

COST: Copenhagen Stroke Study

DEDAS: Dose Escalation of Desmoteplase for Acute Ischaemic Stroke

DIAS: Desmoteplase in Acute Ischaemic Stroke Trial

ECASS: European trial

MAST-E: Multicenter Acute Stroke Trial Europe Study Group

MAST-I: Multicenter Acute Stroke Trial Italy

NINDS: National Institute of Neurological Disorders and Stroke

PROACT: Prolyse in Acute Cerebral Thromboembolism

SITS-MOST: Safe Implementation of Thrombolysis in Stroke-Monitoring Study

Peter O Jenkins
MA BMBCh, Foundation Year 1, Guys and St Thomas' Hospital, London

Martin R Turner
MBBS MRCP PhD, Specialist Registrar in Neurology, John Radcliffe Hospital, Oxford; Clinical Tutorial Fellow to Green College, Oxford

Paul F Jenkins
MA MB BChir FRCP FRCPE, Professor of Medicine, University of Western Australia and Joondalup Health Campus, Perth, Australia

Clin Med 2008;8:253–8

interim analyses that demonstrated significantly increased mortality in the drug-treated patients. Post hoc analysis of the ASK trial suggested that the increased risk of adverse outcomes was due to those treated beyond three hours, and that those treated within three hours were at no greater risk than the control group.[21] The MAST-E trial showed a significant increase in haemorrhage and early death, although this result was worsened by the concomitant use of heparin.[22] In all these trials, the use of SK was found to be hazardous and of little or no long-term benefit.

The trials with recombinant tissue plasminogen activator (rtPA) were more hopeful. The NINDS alteplase stroke study is the only large, randomised trial that has demonstrated a benefit of iv thrombolytic therapy in the treatment of acute ischaemic stroke.[16] It showed that patients treated with thrombolysis were 30% more likely to have minimal or no disability at three months and that this benefit was carried through to one year.[23] It did, however, result in a significant increase in the risk of symptomatic intracranial haemorrhage but this did not produce a significant increase in the early death rate. The success of the NINDS trial has been attributed to its stringent exclusion criteria and to its three-hour treatment window.

Table 1. Randomised controlled trials of thrombolysis in acute stroke showing rates of early death up to 30 days, dependency (usually defined as a Rankin score greater than 2 (inclusive)) or death at up to six months and rates of symptomatic intracranial haemorrhage. Adapted with permission from the BMJ Publishing Group.[4]

Trial	n	Drug/time	Thrombolytic (%)	Control (%)	p values
ASK[12]	340	SK/<4 hours			
Early death (7 days)*			17.8	10.9	not stated
Death/dependency (3 months)			42.3	44.6	
Haemorrhage*			12.6	2.4	p<0.01
MAST-E[13]	310	SK/<6 hours			
Early death (10 days)*			34.0	18.2	p=0.002
Death/dependency (6 months)			79.5	81.8	
Haemorrhage*			21.2	2.6	p<0.001
MAST-I[14]	622	SK/<6 hours			
Early death (10 days)*			26.5	11.7	p<0.00001
Death/dependency (6 months)			62.6	64.7	
Haemorrhage*			8.0	1.3	p<0.01
ECASS 1[15]	620	rtPA/<6 hours			
Early death (30 days)			17.9	12.7	
Death/dependency (3 months)			63.3	71.7	
Haemorrhage*			19.8	6.5	p<0.001
NINDS[16]	624	rtPA/<3 hours			
Early death (30 days)			12.8	15.7	
Death/dependency (3 months)*			57.4	73.4	p<0.05
Haemorrhage*			6.4	0.6	p<0.001
ECASS 2[17]	800	rtPA/<6 hours			
Early death (7 days)			6.1	4.9	
Death/dependency (3 months)			59.7	63.4	
Haemorrhage*			8.8	3.4	not stated
ATLANTIS[18]	613	rtPA/3–5 hours			
Early death (30 days)			7.6	4.2	
Death/dependency (3 months)			58.3	59.5	
Haemorrhage*			6.7	1.3	p<0.001
Chinese UK 2003[19]	465	Urokinase/6 hours			
Early death (10 days)			7.3	5.4	
Death/dependency (3 months)			40.0	41.2	
Haemorrhage			3.8	2.0	
Cochrane meta-analysis[20]	5675	SK/rtPA			
Early death*			14.9	9.4	p<0.00001
Death/dependency*			53.3	58.0	p=0.004
Haemorrhage*			8.7	2.5	p<0.0001

*Significant difference (p<0.05). n = number of subjects; rtPA = recombinant tissue plasminogen activator; SK = streptokinase.

The ECASS 1 trial, published at a similar time to the NINDS study, found no significant improvement in the final outcome after three months but did demonstrate a significant increase in early mortality and haemorrhage.[15] On review of the data, however, 17.4% of the patients included in the trial were found to have major protocol violations. Excluding these violators from the subsequent re-analysis revealed improved neurological recovery and improvement in some functional measures. There was still, however, a threefold increased risk of symptomatic haemorrhage. This form of post-event reanalysis is however biased. The ECASS 2 study demonstrated no significant difference in the 90-day mortality rate, or favourable neurological outcome between the groups – this disappointing result could be explained by the strict inclusion criteria creating a population of stroke patients with less severe strokes.[17]

The ATLANTIS study failed to show any benefit for thrombolysis over placebo for patients randomised between three and five hours after stroke.[18] A small subset (of just 61) was, however, randomised within three hours of onset. Patients treated in this group showed a significant increase of 35% in the number of patients with a favourable outcome.[24]

These large RCTs dominated the 1990s and the beginning of this decade. The favourable results from the NINDS study and subsequent meta-analyses have, however, shifted the attention towards finding ways of improving safety and efficacy, and lengthening the treatment time window by using different

imaging techniques, different thrombolytic agents or intra-arterial routes for administering thrombolysis. The recent DIAS[25] and DEDAS[26] trials used desmoteplase (a thrombolytic derived from bat saliva) administered within three to nine hours of the onset of symptoms. It has been claimed that desmoteplase is superior to rtPA due to its high fibrin specificity and a reduced propensity to promote neuronal damage in ischaemic brain tissue.[27,28] These studies also employed the use of magnetic resonance imaging (MRI) diffusion/perfusion mismatches to determine eligibility – this could be a more sensitive method of determining the size of the central infarct and that of the surrounding (and potentially salvageable) ischaemic penumbra. It also demonstrated that a longer 'stroke-to-treatment' time interval was not associated with reduced treatment effect, suggesting that the diffusion/perfusion mismatch as a marker of tissue at risk may be a better predictor of therapeutic response than duration of symptoms. The use of intra-arterial thrombolysis has produced some promising results in the PROACT I[29] and PROACT II[30] trials (the Cochrane meta-analysis showed an 18% relative risk reduction for death and dependency at the end of the follow up[20]). Intra-arterial administration has the benefit of allowing reduced doses of thrombolytic agent to be used and the possibility of mechanical disruption of the clot. This still remains a specialist procedure and is yet to gain regulatory approval.

In 1996, based on the results of the NINDS study, the US Food and Drug Administration approved the use of rtPA for stroke thrombolysis if given within three hours of the onset of symptoms. Since then the regulatory authorities of Canada and Europe have followed suit.

Since these recommendations were made the basis of this approval, the NINDS study, and more generally the efficacy of this treatment in usual clinical practise have come under intense scrutiny. Several concerns have been raised concerning the trial and the implementation of the treatment in the community.[31–34] Outlined below are the main arguments relating to the efficacy of this treatment:

1 It is true that most of the RCTs show an increase in mortality with the use of thrombolysis in acute stroke. Several meta-analyses have, however, demonstrated the possibility of an improved longer term disability outcome from this treatment. The most recent version of which, the 2003 Cochrane review,[20] analysed 5,675 patients from 18 trials. This study confirmed the early hazard from thrombolysis (mainly due to the SK trials) but also demonstrated that significantly fewer patients were dead or dependent at three to six months (53.9% compared with 58.0%). The reliability of a meta-analysis that combines such variations in trial design is, however, questionable.

2 Questions have been raised as to the validity of the data used in the NINDS trial. The patients in the treatment arm had milder stroke baseline scores than those in the placebo arm.[35] Doubters claimed that this invalidated the results but an independent analysis of the primary data was performed and confirmed the original findings,[36] as did a subsequent post-hoc analysis.[37] Other critics argue, however, that no amount of statistical analysis can eradicate this inherent bias in the raw trial data.

3 There is a concern that thrombolysis mortality might occur in the more severe stroke patient group, hence skewing the results in terms of long-term functional status by removing those patients less likely to do well.

4 There has been concern over the safety and efficacy of thrombolysis when it is used in normal clinical practice and not by stroke experts in RCTs. In 2000 a report was published based on 3,948 stroke patients who were admitted to hospitals in the Cleveland, Ohio, area.[38] This survey showed that half of the patients treated with thrombolysis deviated from the national treatment guidelines and that the incidence of symptomatic intracerebral haemorrhage was 15.7%, much higher than that reported in the RCTs. For this reason the European Agency for the Evaluation of Medicinal Products (EMEA) approved the use of thrombolysis in acute stroke under the condition that all treated patients must be included in a register, SITS-MOST, to allow determination of its safety and efficacy in clinical practice. The SITS-MOST study,[39] which included 6,483 patients from 285 centres in 14 countries between 2002 and 2006, was released in January 2007. It concluded that 'intravenous alteplase is safe and effective in routine clinical use when used within three hours of stroke onset, even by centres with little previous experience of thrombolytic therapy for acute stroke'. The proportion of patients with symptomatic intracerebral haemorrhage at seven days (7.3%) and the mortality rate at three months (11.3%) were both lower in the SITS-MOST study than in the pooled RCTs (8.6% and 17.3% respectively), leading the authors of the SITS-MOST study to encourage the wider use of thrombolytic therapy for suitable patients treated in stroke centres.

5 Numerous ethical issues have also been raised. Although the NINDS trial showed no significant change in the death rate between those treated and the control group, other trials, eg MAST-I, ECASS 1, MAST-E and ASK have done. Thrombolytic therapy therefore exposes the patient to an increased acute risk of haemorrhage, which may result in increased disability or death. In addition, it was discovered that one fifth of patients initially diagnosed with stroke by expert stroke teams were subsequently found not to have strokes.[40] Exposing such patients to thrombolysis would be potentially disastrous. It is important to ask if the gain warrants the risk in the broader acute setting, as well as addressing whether patients are competent to provide informed consent regarding this therapy.

6 Evidence of publication bias, whereby unfavourable studies go unreported is a recognised issue, as are concerns over potential conflicts of interest.[41]

7 Finally, even assuming effectiveness, the clinical impact can be argued to be marginal when taken in the whole with consideration of cost issues. Do the benefits justify the

expenses, which include specialist stroke teams, rapid access to neuroimaging services (which optimally seems to be MRI rather than computed tomography) and radiologists? This issue of cost effectiveness is discussed below.

In conclusion, iv treatment of ischaemic stroke with thrombolysis within a three hour time window has been shown to be safe and effective in RCTs. Overall the studies show a 30% increase in the chance of suffering little or no disability at three months, with the number needed to treat to identify clinical benefit being just three. The SITS-MOST study confirmed that this benefit was also shown in the community but there are still concerns as to its cost efficiency despite its proven efficacy.

Cost effectiveness

Even if we assume that thrombolysis is effective when used in the community, it has been argued that it provides minimal actual benefit due to the small percentage of patients eligible for treatment within the strict entry criteria. In most stroke centre guidelines the indications and contraindications for thrombolysis have been based upon the inclusion and exclusion criteria of the NINDS study. Several recent survey studies have shown that the proportion of patients treated with thrombolysis ranges from only 3% to 7%.[42–45] In addition, a retrospective analysis, applying the exclusion criteria and treatment effect reported in the NINDS trial to the unselected stroke population of the COST, demonstrated that only 5% of the 1,197 stroke patients would have been eligible for thrombolysis.[46] Eliminating those that died or had a full recovery, this resulted in a net benefit of only 0.4% of the stroke population as a whole. The three hour time limit was recognised to be the biggest constraining factor in recruiting patients and the study therefore also examined the ideal situation where all patients were treated within this timeframe. In this ideal scenario the authors concluded that thrombolysis would still only benefit 4% of the stroke population as a whole. We must not forget, however, that stroke affects approximately 80,000 people per year in the UK and therefore even a modest improvement percentage of 4% translates into a population of 3,600 people benefiting from this therapy annually. This is comparable to the number of newly diagnosed cases of some high profile cancers such as cervical, oral and central nervous system tumours and the value of thrombolysis in stroke in terms of absolute numbers of patients with improved outcome should not be dismissed.

Stroke is also the leading cause of adult disability in the developed world and due to the costs of hospitalisation and rehabilitation it creates a huge financial burden on the NHS. The National Audit Office in England produced data showing that the annual cost of stroke to the UK was £7 billion with £2.6 billion attributable to direct health costs.[47] For this reason even a small improvement in the treatment of stroke, for relatively few patients, can create a huge financial benefit.

Several studies have been conducted using mathematical models to estimate the health economic impact of using thrombolysis in the treatment of stroke. When studied in the North American healthcare system, thrombolysis was shown to be cost saving due to the reduction in rehabilitation and nursing home costs.[48] The only study conducted into the cost efficiency of thrombolysis use in the NHS,[49] however, concluded that although the benefits appeared promising, the estimates of effectiveness and cost effectiveness were imprecise. This imprecision resulted in a huge variability in outcomes, ranging from large cost savings under favourable assumptions to large expenditures using less favourable estimates. Treatment with thrombolysis was associated with a cost of £13,581 per quality-adjusted life years (QALY) gained during the first 12 months (significantly less than the £30,000 figure used by the National Institute for Health and Clinical Excellence as a rough estimate of cost effectiveness), over a lifetime this resulted in a substantial cost saving of £96,565 per QALY gained. The 5th and 95th percentiles for cost effectiveness at 12 months were, however, £81,680 (cost savings) and £142,505 (additional costs) per QALY gained, hence demonstrating the large variability in results and the potential dangers of drawing conclusions from this data.

The use of economic health models to determine cost effectiveness warrants further discussion since they may dictate future use of this and other treatments. These models are mathematical interpretations of real life scenarios and are therefore estimates in their very definition. Some authors have already highlighted the limitation of such analyses; namely that if a new treatment requires more resources, misuse of the cost-effectiveness ratios may result in the adoption of inefficient treatments.[50] This applies to the use of thrombolysis since all these models fail to take into account the cost of providing an acute stroke thrombolysis service. To safely and effectively apply this treatment, huge expense will be required to provide a round-the-clock specialist team of physicians capable of identifying and treating eligible patients; a radiological service that is able to provide rapid imaging and specialist review of the results; the education of both emergency services in the hospital to recognise the necessity for urgent management, and the general public in recognising the importance of seeking immediate help. It must also be recognised that a large proportion of the potential future savings arise from reduced nursing home and rehabilitation costs. If health economics are considered from the view of the NHS then it must be remembered that they will assume the cost of the intervention whereas it will be the social services and the patients' families that will receive a large proportion of the financial benefits. Finally, the results from these models are highly dependent on the long-term benefits of thrombolysis. The costs accrued over a lifetime can be large. Do the benefits of thrombolysis extend beyond the one-year time period, a variable which is yet to be investigated but has been assumed by some studies?

In conclusion, data from healthcare models must be treated with caution as the real costs of thrombolysis will come with the implementation and maintenance of an infrastructure capable of delivering this therapy. It must also be remembered that even a treatment with a substantial effect on stroke outcome (such as thrombolysis) can have no more overall effect in the population than a much weaker treatment (such as aspirin) if it cannot be given to more than a small minority.

Conclusion

There is good evidence to support the safety and efficacy of thrombolysis in acute ischaemic stroke both in RCTs (demonstrated in the Cochrane review) and in the community (as shown by the SITS-MOST trial). Its cost effectiveness is still debatable, however. Economic models suggest that thrombolysis may provide significant cost savings but such models do not necessarily reflect real life and for that reason they must be interpreted with caution.

Unlike AMI, ischaemic stroke has a variable natural history. The future lies in determining which stroke patients are more likely to benefit from thrombolysis, and which are at greater risk of complications. Current advances in imaging, particularly using diffusion and perfusion-weighted MRI, may allow improved selection of those patients most likely to benefit from therapy.[51]

Although effectiveness has been demonstrated it is important to consider the view of the patient. Thrombolysis is a high-risk strategy, with an increased chance of intracerebral haemorrhage offset by the possibility of reduced neurological disability. Just as some people are willing to risk their savings in a 'high risk, high gain' stock market, others would rather invest in low yield risk-free bonds. Physicians will have a critical role in presenting the evidence to patients and must endeavour to present a balanced argument. This requires specific training and knowledge of the field.

Despite the controversy and conflicting data surrounding this treatment, the drive to implement thrombolysis has acted as a catalyst to improve the care of all patients after stroke. It has drawn attention to the need for specialist stroke care and the advent of specialist stroke centres has had the largest beneficial effect in reducing death and disability of all the therapies for stroke.[52] Continuing advances in neuroimaging and the improvement in the acute stroke management infrastructure will improve both the efficacy and the safety of this and other future treatments.

References

1 Del Zoppo GJ, Poeck K, Pessin MS *et al.* Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol* 1992;32:78–86.
2 ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17187 of acute myocardial infarction. *Lancet* 1988;ii:349-60.
3 Papadopoulos SM, Chandler WF, Salamat MS *et al.* Recombinant human tissue-type plasminogen activator therapy in acute thromboembolic stroke. *J Neurosurg* 1987;67:394–8.
4 Pereira AC, Martin PJ, Warburton EA. Thrombolysis in acute ischaemic stroke. *Postgrad Med J* 2001;77:166–71.
5 Ohtomo E, Araki G, Itoh E *et al.* Clinical efficacy of urokinase in the treatment of cerebral thrombosis. Multi-centre double-blind study in comparison with placebo (Translated from Japanese). *Clin Eval* 1985; 15:711–31.
6 Atarashi J, Ohtomo E, Araki G *et al.* Clinical utility of urokinase in the treatment of acute stage cerebral thrombosis: Multi-centre double blind study in comparison with placebo (Translated from Japanese). *Clin Eval* 1985;13:659–709.
7 Abe T, Kazama M, Naito I *et al.* Clinical evaluation for efficacy of tissue cultured urokinase on cerebral thrombosis by means of multi-centre double-blind study (Translated from Japanese). *Blood Vessel* 1981;12:321–41.
8 Yamaguchi T, Hayakawa T, Kiuchi H, Japanese Thrombolysis Study Group. Intravenous tissue plasminogen activator ameliorates the outcome of hyperacute embolic stroke. *Cerebrovasc Dis* 1993;3:269–72.
9 Mori E, Yoneda Y, Tabuchi M *et al.* Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology* 1992;42:976–82.
10 Haley EC, Brott TG, Sheppard GL *et al.* Pilot randomized trial of tissue plasminogen activator in acute ischaemic stroke. *Stroke* 1993; 24:1000–4.
11 Morris AD, Ritchie C, Grosset DG, Adams FG, Lees KR. A pilot study of streptokinase for acute cerebral infarction. *Q J Med* 1995;88:727–31.
12 Donnan GA, Davis SM, Chambers BR *et al*, and for the Australian Streptokinase (ASK) Trial Study Group. Streptokinase for acute ischaemic stroke with relationship to time of administration. *JAMA* 1996;276:966.
13 Multicenter Acute Stroke Trial Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med* 1996;335:145–50.
14 Multi-centre Acute Stroke Trial Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin and combination of both in treatment of acute ischaemic stroke. *Lancet* 1995;346:1509–14.
15 Hacke W, Kaste M, Fieschi C *et al*, and for the ECASS Study Group. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA* 1995;274:1017–25.
16 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–7.
17 Hacke W, Kaste M, Fieschi CW *et al.* Randomised double-blind placebo controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 1998;352: 1245–51.
18 Clark WM, Wissman S, Albers GW *et al*, and for the ATLANTIS Study Investigators. Recombinant tissue-type plasminogen activator (alteplase) for ischaemic stroke 3 to 5 hours after symptom onset. *JAMA* 1999;282:2019–26.
19 Chen QT, He M. Intravenous thrombolysis with urokinase for acute cerebral infarction. *Chin J Neurol* 2002;35:210–8.
20 Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Revi* 2003;3CD000213.
21 Donnan GA, Davis SM, Chambers BR *et al.* Trials of streptokinase in severe acute ischaemic stroke. *Lancet* 1995;345:578–9.
22 International Stroke Trial Collaborative Group. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischaemic stroke. *Lancet* 1997;349:1569–81.
23 Kwiatkowski TG, Libman RB, Frankel M *et al.* Effects of tissue plasminogen activator for acute ischaemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med* 1999;340: 1781.
24 Albers GW, Clark WM, Madden KP, Hamilton SA. ATLANTIS Trial: results for patients treated within three hours of stroke onset. *Stroke* 2002;33:493.
25 Hacke W, Albers G, Al-Rawi Y *et al.* The Desmoteplase in Acute Ischaemic Stroke Trial (DIAS): A phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005;36:66.
26 Furlan AJ, Eyding D, Albers GW *et al.* Dose Escalation of Desmoteplase for Acute Ischaemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke* 2006;37:1227.
27 Liberatore GT, Samson A, Bladin C *et al.* Vampire bat salivary plasminogen activator (desmoteplase): a unique fibrinolytic enzyme that does not promote neurodegeneration. *Stroke* 2003;34:537.

28 Reddrop C, Moldrich RX, Beart PM *et al.* Vampire bat salivary plasminogen activator (desmoteplase) inhibits tissue-type plasminogen activator-induced potentiation of excitotoxic injury. *Stroke* 2005;36:1241.

29 del Zoppo GJ, Higashida RT, Furlan AJ *et al.* PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke* 1998;29:4.

30 Furlan AJ, Higashida RT, Wechsler L *et al.* Intra-arterial pro-urokinase for acute ischaemic stroke. The PROACT II study: a randomised controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA* 1999;282:2003.

31 Lenzer J. Alteplase for stroke: money and optimistic claims buttress the 'brain attack' campaign. *BMJ* 2002;324:723.

32 Mann J. Truths about the NINDS study: setting the record straight. *West J Med* 2002;176:192.

33 Trotter G. Why were the benefits of tPA exaggerated? *West J Med* 2002; 176:194.

34 Wardlaw JM, Lindley RI, Lewis S. Thrombolysis for acute ischaemic stroke: still a treatment for the few by the few. *West J Med* 2002;176:198.

35 Marler JR, Tilley BC, Lu M *et al.* Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology* 2000; 55:1649–55.

36 Ingall TJ, O'Fallon WM, Asplund K *et al.* Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischaemic stroke treatment trial. *Stroke* 2004;35:2418–24.

37 Kwiatkowski T, Libman R, Tilley BC *et al.* The impact of imbalances in baseline stroke severity on outcome in the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study. *Ann Emerg Med* 2005;45:377.

38 Katzan IL, Furlan AJ, Lloyd LE *et al.* Use of tissue-type plasminogen activator for acute ischaemic stroke: the Cleveland area experience. *JAMA* 2000;283:1151.

39 Wahlgren N, Ahmed N, Davalos A *et al*; SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007;369:275–82.

40 Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department: Implications for acute stroke trials. *Arch Neurol* 1995;52:1119–22.

41 Liebeskind DS, Kidwell CS, Sayre JW, Saver JL. Evidence of publication bias in reporting acute stroke clinical trials. *Neurology* 2006;67:973–9.

42 Schenkel J, Weimar C, Knoll T *et al.* R1 – systemic thrombolysis in German stroke units – the experience from the German Stroke data bank. *J Neurol* 2003;250:320–4.

43 Szoeke CE, Parsons MW, Butcher KS *et al.* Acute stroke thrombolysis with intravenous tissue plasminogen activator in an Australian tertiary hospital. *Med J Aust* 2003;178:324–8.

44 Katzan IL, Hammer MD, Hixson ED *et al.* Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol* 2004;61:346–50.

45 California Acute Stroke Pilot Registry (CASPR) Investigators. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. *Neurology* 2005;64:654–9.

46 Jorgensen HS, Nakayama H, Kammersgaard LP, Raaschou HO, Olsen TS. Predicted impact of intravenous thrombolysis on prognosis of general population of stroke patients: simulation model. *BMJ* 1999; 319:288–9.

47 National Audit Office/Department of Health. *Reducing brain damage: faster access to better stroke care*. London: Stationery Office, 2005.

48 Fagan S, Morgenstern L, Pettita A *et al.* Cost-effectiveness of tissue plasminogen activator for acute ischaemic stroke. *Neurology* 1998;50: 883–90.

49 Sandercock P, Berge E, Dennis M *et al.* Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischaemic stroke assessed by a model based on UK NHS costs. *Stroke* 2004;35:1490–7.

50 Donaldson C, Currie C, Mitton C. Cost-effectiveness analysis in health care: contraindications. *BMJ* 2002;235:891–4.

51 Albers GW. Expanding the window for thrombolytic therapy in acute stroke. The role of acute MRI for patient selection. *Stroke* 1999;30: 2230–7.

52 Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. *Lancet* 1999;354:1457–63.