

A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS

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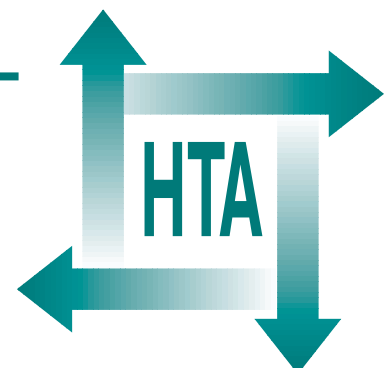
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**Health Technology Assessment
NHS R&D HTA Programme**





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List of abbreviations

AMI	acute myocardial infarction	MAST-I	Multi-centre Acute Stroke Trial – Italy
ASK	Australian Streptokinase trial	MR	magnetic resonance
CCT	controlled clinical trial	MRS	Modified Rankin Scale
CCTR	Cochrane Controlled Trials Register	MRI	magnetic resonance imaging
CI	confidence interval	NINDS	National Institutes of Neurological Disorders and Stroke
CT	computed tomography	NS	not significant
df	degrees of freedom	OR	odds ratio
ECASS	European Co-operative Acute Stroke Study	PICH	primary intracerebral haemorrhage
FAST	Field Assessment of Stroke Treatment	PROACT	Prolyse in Acute Cerebral Thromboembolism
FDA	Food and Drug Administration	QALY	quality-adjusted life-year
GP	general practitioner	RCT	randomised controlled trial
IST	International Stroke Trial	SAH	subarachnoid haemorrhage
ITT	intention to treat	rt-PA	recombinant tissue plasminogen activator
LAPSS	Los Angeles Prehospital Stroke Screen	SK	streptokinase
LOS	length of stay	TIA	transient ischaemic attack
LSR	Lothian Stroke Register		
MAST-E	Multi-centre Acute Stroke Trial – Europe		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or has been used only once, or is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Background

There is strong evidence that, for patients with acute stroke, admission to a stroke unit providing organised stroke care and rehabilitation saves lives and reduces disability. Medical treatments such as thrombolysis or neuroprotective agents, given within the first few hours of onset of ischaemic stroke, offer the prospect of at least moderate additional benefit. Most of the evidence of benefit of thrombolysis came from trials performed in healthcare systems that are rather different to the NHS. This review therefore aims to assess whether, when used in the NHS, these new agents are likely to be effective and cost-effective.

Objectives

The objectives of the current report are:

- to assess the effectiveness of thrombolytic drugs
- to assess the effectiveness of neuroprotective drugs
- to map current pathways of acute stroke care, identify barriers to implementation of emergency drug treatments for acute stroke in the NHS, and to suggest solutions to overcome these barriers
- to model the health economic impact of thrombolytic therapy.

Methods

Data sources and study selection

Multiple bibliographic sources were searched to identify: all unconfounded randomised trials comparing either a thrombolytic or a neuroprotective agent with placebo (or open control) in patients with acute stroke; and all published reports of studies identifying barriers to effective acute stroke care. A panel developed an economic model of acute stroke care from the Lothian Stroke Register, and by consensus discussion between the research team members supplemented by data on outcome after stroke derived from relevant publications where necessary.

Data extraction

For the review of thrombolysis, the data included in the analyses were checked where possible with the original trialists. For the review of neuroprotection completed systematic reviews were sought. For the review of barriers to acute care and interventions to overcome them, two reviewers independently selected studies meeting the inclusion criteria and extracted the data; differences were resolved by discussion.

Data synthesis

Standard Cochrane quantitative systematic review methods were used (Cochrane Revman 4.1 software); a fixed-effect model was used and results were expressed as odds ratios (ORs). For the economic analyses, a Markov model was created to estimate the number of life-years and quality-adjusted life-years (QALYs) gained with thrombolytic therapy. Sensitivity analyses were used to test the robustness of the estimates.

Results

Efficacy of thrombolysis

Seventeen trials (5216 patients) of urokinase, streptokinase, recombinant tissue plasminogen activator (rt-PA) or recombinant pro-urokinase were included. About 50% of the data came from trials testing intravenous rt-PA, mostly given within 6 hours of stroke onset. Thrombolytic therapy significantly increased the odds of fatal intracranial haemorrhage (OR = 4.15; 95% confidence interval (CI), 2.96 to 5.84). Thrombolytic therapy also increased the odds of death at the end of follow-up (OR = 1.31; 95% CI, 1.13 to 1.52). However, despite the increase in deaths, (because it markedly reduced the degree of disability in survivors), thrombolytic therapy within 6 hours significantly reduced the proportion of patients who were dead or dependent at the end of follow-up (OR = 0.83; 95% CI, 0.73 to 0.94). There was heterogeneity between the trials that could have been due to: the thrombolytic drug used, variation in the concomitant use of aspirin and heparin, severity of the stroke, and time to treatment. The most widely tested agent, rt-PA, may be associated with slightly less hazard and more benefit than other agents.

Efficacy of neuroprotective drugs

No agent has yet been proven to be sufficiently effective in man to be granted a product licence. Useful economic analyses were therefore not possible.

Barriers to acute stroke treatments

The key barriers identified were:

- the patient's or family's inability to recognise stroke symptoms or failure to seek urgent help
- patient or family calls general practitioner instead of an ambulance
- inefficient process of emergency stroke care in hospital, and
- delay in neuroimaging.

Some interventions to overcome specific barriers had been evaluated:

- education programme for the public and healthcare workers
- training programme for paramedical staff to improve the accuracy of diagnosis, and
- reorganisation of in-hospital systems to streamline acute stroke care.

None of the evaluation studies provided reliable estimates of effect.

Cost-effectiveness of thrombolysis with rt-PA

The model suggested that if eligible patients were treated with rt-PA there was a 78% probability of a gain in quality-adjusted survival during the first year, at a cost of £13,581 per QALY gained. Over a lifetime, rt-PA was associated with a cost-saving of £96,565 per QALY. However, the estimates were imprecise and highly susceptible to the assumptions employed in the economic model; under several plausible assumptions, rt-PA was much less cost-effective than standard care and under others, a great deal more cost-effective.

Conclusions

Implications for healthcare

Thrombolytic drugs

The data available are limited and the estimates of effectiveness and cost-effectiveness are imprecise. The data were judged to be insufficient to provide reliable estimates of the cost of modifying NHS services for patients with acute stroke to enable rt-PA to be delivered safely and effectively within the NHS. In the authors' opinion, the data do not, therefore, support the widespread use of thrombolytic therapy in routine clinical practice in the NHS.

Neuroprotective drugs

An agent associated with even modest benefit is likely to be cost-effective, but none is available yet.

Barriers

The cost of overcoming the known barriers to acute stroke treatment is likely to vary from centre to centre and will depend chiefly on the baseline level of stroke service provision.

Recommendations for research

There is a case for further research to:

- determine reliably the effects of rt-PA on short- and long-term survival and to identify which patients are most likely to benefit (and which to be harmed); this would require new large-scale randomised trials comparing thrombolytic therapy with control
- determine the nature (and costs of) the changes in NHS services that would be needed to deliver rt-PA therapy safely and effectively to patients with acute stroke (if rt-PA is licensed in the UK); this would include the costs of service changes that would be necessary to ensure that patients with suspected acute ischaemic stroke are admitted to hospital much more quickly than is currently the norm.

Chapter I

Background

This section aims to provide a brief introduction to the main research questions to be covered in the report and to summarise the evidence already available to answer those questions. The aim is therefore to clarify: whether the questions are still important; whether others have already answered those questions reliably from an NHS viewpoint; and, if not, to identify the gaps that this study could address.

The current burden of stroke

Stroke is a major cause of death and disability in both the more-developed and the less-developed world.^{1,2} In the UK, the burden of stroke on patients, their carers, the NHS and on society is substantial: each year there are about 125,000 strokes;¹ stroke causes about one in ten of all deaths and about 25% of men and 20% of women can expect to suffer a stroke if they survive to 85 years.³ The incidence and lifetime prevalence of stroke are far higher than for any other neurological disorder.⁴ By contrast to cancer and coronary heart disease, the major burden of stroke is chronic disability rather than death.⁵ About a third of stroke survivors are functionally dependent after 1 year; survival with any degree of impairment is likely to be associated with a reduction in health-related quality of life. In the UK, there are about 250,000 disabled stroke survivors, and stroke is the commonest cause of neurological disability in the community.^{3,4,6} A review of studies of the cost of stroke indicated that stroke consumes about 2–4% of total health-care costs (i.e. excluding social care and indirect costs) in Europe and the USA.⁷ The cost of stroke in the UK is high: costing £2.3 billion per year, it accounts for about 6% of the total NHS and Social Services expenditure, nearly twice the expenditure for coronary heart disease.^{2,8} Despite this high disease burden and high cost, there are few reliable comparisons of the process of acute stroke care, the outcomes and the costs associated with different ways of delivering acute stroke care between countries.⁹ Furthermore, research into stroke prevention, treatment and rehabilitation has been very under-funded in the UK and elsewhere.² New medical treatments for acute stroke are becoming available, yet few have been

subject to economic evaluation. A systematic review of cost-effectiveness research for stroke up to 1999 identified about 2000 potential publications, but only 26 studies met the eligibility criteria.¹⁰ Of the 26 studies in the review, only one related to acute stroke and it considered thrombolytic treatment with recombinant tissue plasminogen activator (rt-PA).¹¹

The burden of stroke is projected to increase

In most developed countries, stroke mortality has declined over the past two decades, but a large proportion of this fall has been due to a reduction in case fatality, rather than in incidence.¹² For the next two decades, with the proportion of older people in the population set to rise, the total number of new strokes each year is projected to increase considerably.^{1,13,14} By the year 2020, stroke will account for 6.2% of the total burden of illness in the developed world.¹⁴

Medical treatment of acute stroke

The only medical treatment that is of proven benefit for routine use in patients with acute ischaemic stroke is aspirin.¹⁵ Although a large variety of other medical and (a few) surgical interventions are now potentially available for the treatment of acute stroke, thrombolytic treatment with rt-PA is the only agent supported by evidence from randomised trials that is also licensed for use in clinical practice (at least in some parts of the world). By contrast, though many neuroprotective agents that were beneficial in animal models have been evaluated in randomised trials in man, none has been shown to be sufficiently effective and safe to gain a product licence. It appears, therefore, that thrombolysis is the intervention most likely to become relevant to the NHS within the next few years.

How strong is the evidence to support the use of thrombolysis for acute ischaemic stroke?

The Cochrane systematic review of the 17 completed randomised trials of thrombolysis in stroke, included 5216 patients, and showed that thrombolysis significantly reduced the proportion of

patients who were dead or dependent. However, for every 1000 patients treated, 45 die from intracranial bleeding.¹⁶ This is a cause for significant concern. Critics of the review note that it includes trials of several different agents and prefer to focus on the data relating to rt-PA, the one agent that is licensed for clinical use. If analysis is restricted to the trials of rt-PA, it is evident that not all trials were as positive as the National Institutes of Neurological Diseases and Stroke (NINDS) trial¹⁷ and secondly, though the 16% increase in the odds of death with rt-PA did not reach statistical significance, it was certainly potentially clinically very important.¹⁶ Nonetheless, despite the clear risk of fatal intracranial haemorrhage and the uncertainty about its effects on death, the analysis showed that intravenous rt-PA (within 6 hours of onset) was associated with a significant 21% reduction in the odds of being dead or dependent at the end of trial follow-up (at about 3 months); for every 1000 patients treated, 57 avoided death or dependency. This appears a clinically worthwhile benefit. However, there are some caveats: rt-PA is a relatively expensive drug and the trials in which it was evaluated were conducted in well-resourced, largely non-UK, centres (so these estimates of its effects and cost-effectiveness may not apply when thrombolysis is used in routine NHS practice).

Is thrombolysis likely to be feasible as routine treatment for NHS patients with acute stroke?

It can only be used where licensed

Although thrombolysis appears to be a very promising treatment, there is considerable debate about its place in routine clinical practice. This debate perhaps explains why it has not been licensed for routine use worldwide. It has been granted a full licence only in the USA and Canada (and the countries of the European Union are in the process of responding to a recommendation from the European regulatory authorities to grant a restricted licence subject to further trials being undertaken), for intravenous administration in the treatment of patients with acute ischaemic stroke within 3 hours of onset. The experience of countries where rt-PA is licensed for clinical use give some indication of the problems that would face NHS decision-makers should thrombolysis be licensed in the UK.

Even where it is licensed, rt-PA usage varies with several factors

A study in Copenhagen, in an area where 88% of all strokes occurring in the community were admitted to hospital, registered 1197 patients with

acute stroke.¹⁸ Only 170 (14.2%) patients arrived in hospital within 3 hours and only 64/1197 (5.3%) would have been eligible for thrombolysis. If all 1197 patients had been admitted within 3 hours, then 539 (45.0%) would have been eligible for thrombolysis on current criteria.¹⁸ Surveys of actual use of rt-PA (almost exclusively within 3 hours of onset) in clinical practice tend to confirm this estimate. A study of the 29 hospitals in the Cleveland area of the USA registered 3948 patients admitted with ischaemic stroke, of whom only 70 (1.8%) were given rt-PA.¹⁹ Interestingly, the proportion treated varied considerably between hospitals (range, 0–10%), partly because of variations between hospitals in the proportion arriving within 3 hours of onset, and partly by random variation because of small sample sizes in each hospital. However, among those patients admitted within 3 hours, the relative variation in the proportion treated was even greater (0–40%). A similar study restricted to patients with ischaemic stroke (of whom a higher proportion will be eligible for thrombolysis than unselected stroke patients) conducted across 42 academic medical centres in the USA found 49/1195 (4.1%) were given thrombolytic treatment; in this study, a significantly smaller proportion of African-Americans were treated than white Americans (1.1% versus 5.3%).²⁰ The largest study to date reported the use of rt-PA among 23,058 patients with acute stroke from 137 community hospitals in the USA.²¹ Overall 1.6% were given rt-PA, but again there was large variation in the proportion treated; in 35% of hospitals none of the patients received the treatment at all. There were highly significant trends of decreasing rt-PA use with increasing age, among blacks and among females. If the patient was treated by an attending neurologist (rather than a general physician) the odds of being treated were increased.²¹ A single-centre study in a specialised acute stroke unit in Germany reported much higher usage. They treated 14.9% of all patients with acute ischaemic stroke (or 9.4% of all admitted acute stroke patients).²²

Even in Germany, some acute hospitals do not have the facilities to give rt-PA

In Germany, as in the USA, there is variation in use, and some centres do not use rt-PA at all (or do not have the facilities to deliver it). The key facility required is computed tomography (CT) scanning or magnetic resonance imaging (MRI) to rule out brain haemorrhage before treatment is started.²³ A study of stroke patients admitted to one of four rural general hospitals in southern Germany found that none of the hospitals had an on-site CT or MRI scanner, so that although 59% of patients

were admitted within 6 hours, only 36% of patients had a CT scan and only half of those scans were performed within 24 hours of admission.²⁴ It did not appear from the report that any patient received rt-PA. These data suggest that thrombolysis could well be currently practicable in a small proportion of patients in the UK, but the precise proportion eligible for treatment would depend critically on the local level of acute stroke service provision.

Is thrombolysis definitely (or potentially) cost-effective?

The first fully published economic analysis of rt-PA for acute stroke was published in 1998.¹¹ From the perspective of the US healthcare system (which includes nursing home costs), for every 1000 patients treated, rt-PA increased hospitalisation costs by US\$1.7 million but decreased rehabilitation costs by \$1.4 million and nursing home costs by \$4.8 million. Multiway sensitivity analyses indicated a greater than 90% probability of cost savings. The estimated impact on long-term health was 564 (95% confidence interval (CI), 3 to 850) quality-adjusted life-years (QALYs) saved over 30 years of the model per 1000 patients treated. However, the study is of limited value to current decision-making in the NHS because:

- the estimate of efficacy was based on a single, unusually positive trial in 624 patients – the NINDS study¹⁷ – yet there is now a great deal more efficacy data available
- the US healthcare system is different (and it is difficult to judge how closely the estimates of the extra costs of introducing the treatment would apply in the UK)
- the possibility that treatment might increase mortality was not modelled
- the estimate of the gain in QALYs was very imprecise (and included the possibility of almost no benefit), and
- as several of the authors were closely involved in the NINDS trial, the possibility of conflict of interest cannot be ruled out.

Drummond has highlighted how important it is to exclude conflict of interest in studies of new drugs.²⁵ A more recent decision analysis, applying efficacy estimates derived from three randomised trials, and locally collected patient utility data, concluded – from the perspective of the few patients who did fulfil the medical inclusion criteria – that, on average, rt-PA is superior to standard therapy.²⁶ However, the sensitivity analyses suggested that the model's preferred choice was highly susceptible to changes in many of the model parameters.²⁶

A further study, commissioned by a pharmaceutical company but conducted by an independent economist has recently been published in full.²⁷ A study by the National Stroke Research Institute of Australia has taken a more rigorous approach and based its estimates of treatment effect on the NINDS trial (but modelling that the treatment effect might be 100%, 50%, 33% or only 25% of that observed in the trial).²⁸ The model was populated with data from a local community-based epidemiological study of acute stroke, enhancing its generalisability. The authors concluded that treatment with rt-PA did increase hospital costs but this increase was offset by long-term savings in nursing home costs, though these benefits were not realised within the first year.²⁸

Should thrombolysis be implemented in the UK now?

This decision should ideally be informed by a methodologically rigorous guideline document. Two self-appointed non-governmental guideline groups from outside the UK have recommended that thrombolysis should be implemented.^{23,29} Both groups placed particular emphasis on the results of the single 'positive' NINDS trial of rt-PA,²³ as sufficient evidence to justify its use in routine clinical practice and, hence, recommend thrombolysis with intravenous rt-PA for all patients with acute ischaemic stroke presenting to hospital within 3 hours of onset who meet certain criteria.^{23,29} Hoffman has criticised the guideline for being over-optimistic and for placing undue emphasis on the results of a single small positive trial.³⁰

Furthermore, it is notable that most of the North American Guideline document authors had been involved in the NINDS trial as investigators, and so there may have been significant conflicts of interest during the process of guideline development; it may not have been as methodologically rigorous and independent as it might have appeared. The methods for development of the consensus statement by the European Ad Hoc Group were not stated, so, again, there must be doubts about its methodological rigour.

Health service provision in the UK is organised and funded differently from the USA and most of Europe, so it is not clear how much these recommendations should apply to the UK anyway. Other expert groups have placed greater emphasis on estimates of the effect of treatment derived from a systematic review of all of the relevant randomised trials, as such estimates are likely to be less biased and more precise.²⁵ A recent

methodologically rigorous, UK national stroke guideline, which took all of these factors (and the reality of UK stroke care) into account, recommended the use of thrombolysis only in the context of randomised controlled trials (RCTs).³¹ The Canadian Association of Emergency Physicians have recently issued guidelines that make the same recommendation.³² At present, in the light of these recommendations, and the fact that rt-PA is not yet licensed in the UK for the treatment of acute stroke, it appears appropriate that it is only being used in a handful of patients per year and in a few highly specialised UK stroke centres at present (Dennis MS, University of Edinburgh, Western General Hospital, Edinburgh: personal communication, September 2002).

Economic modelling

Economic modelling could help inform the NHS on how to act:

- do nothing (which might deny patients an effective treatment and be more costly to society)
- seek to implement thrombolysis in the UK within existing services (which might be harmful to at least some patients and be costly to society)
- invest resources to improve acute stroke services (difficult in the current NHS financial situation)
- fund studies to collect more primary research data (e.g. by conducting further RCTs, which could provide more precise estimates of risk, benefits and cost-effectiveness).

Jørgensen and co-workers¹⁸ have done some limited modelling and they concluded their paper thus:

If all 1,197 patients had been admitted in due time, then 539 (45%) would have been eligible for rt-PA and an estimated 48 = 4% (95% CI, 0.1–8%) would have benefited. These estimates may be too generous, as we could not exclude patients with rapidly improving symptoms, a criterion excluding 10% in the US trial. In conclusion, alteplase (rt-PA) may benefit single patients, but will have no impact on the general prognosis of stroke. Because time is crucial and because evaluation of paraclinical data requires a specialist setting, treatment with rt-PA will need large investments and reorganisation of the care for stroke patients. Before it is decided to offer this expensive, potentially harmful and possibly only marginally effective treatment, we suggest that another, much larger European trial is needed to test the results of the US trial.

If, as Jørgensen suggests, further primary research is justified, modelling may also help to inform the design and sample size of any future studies.³³ Furthermore, an economic modelling study of hypothetical treatments for acute stroke has indicated that even modest clinical benefits may be cost-effective in the long run.³⁴ However, to detect such moderate benefits reliably requires very large trials.³⁵

The situation for acute stroke now (i.e. a lack of evidence from randomised trials large enough to detect moderate benefits reliably) appears analogous to that seen at the early stages of the evolution in the treatment of acute myocardial infarction (AMI). Between 1960 and the early 1980s a large number of small trials of thrombolysis for the treatment of AMI were conducted. Some suggested benefit and others harm, so that the treatment was hardly used in routine clinical practice. A systematic review of the available randomised AMI trials in 1985 provided very strong evidence that thrombolysis reduced the odds of death after AMI by about 22%,³⁶ but clinicians were not persuaded to change their habits by this mere meta-analysis. However, the analyses led to several very large scale trials, and when the results of those trials were published, there followed an extremely rapid change in clinical practice within 2 years.³⁷ However, mega-trials are costly and time-consuming. A funding agency considering an application for such a trial in acute stroke would be more likely to support it if the cost of the research was concordant with the potential health gain (and the plausible range of cost-effectiveness of the intervention predicted from the modelling). In other words, the prospect of substantial health gain or cost-savings makes a large-scale trial easier to justify.

Models of the economic impact of introducing thrombolysis must account for existing stroke services

Economic modelling has many uses, but it is, by nature, an abstract process, several steps away from the realities of the care of patients with acute stroke in the NHS. A very important parameter for any model is the extra service costs (e.g. the extra investigations, equipment and staff) required to deliver the new intervention.²⁵ There appears to be general agreement that, if stroke patients are to be treated safely and effectively with thrombolysis, the treatment should be given in the context of a well-organised acute stroke service. However, it is difficult to estimate the extra costs required to get to an agreed high level of organisation, and how much the extra cost will vary between UK

hospitals. There are several difficulties and these are discussed below.

There are no nationally or internationally agreed standards of general care for acute stroke

The configuration of acute services that would be appropriate in Europe or the UK are not well defined. However, several consensus panels have at least agreed that acute stroke care should be well organised,^{29,38,39} In particular, the experts recommend that thrombolytic treatment needs to be delivered in a particularly well-organised setting.^{23,29} How well organised do acute stroke services need to be in general? How many additional resources are needed to deliver thrombolytic treatment effectively and safely? The configuration of stroke rehabilitation services is becoming well defined by evidence from reliable trials and systematic reviews. There is good evidence that admission to an organised stroke unit reduces the number of deaths and increases the number of patients alive and free of disability.⁴⁰ To try to define an evidence-based process of care for patients with acute stroke, stroke units can broadly be subdivided into those that provide care from the moment of admission until discharge (comprehensive care), and those that admit patients after the acute phase (stroke rehabilitation). The Cochrane systematic review suggests that admission to a unit offering comprehensive care is associated with greater benefit than admission to a stroke rehabilitation unit, but the components of the organisation of acute stroke care that contribute to that benefit have yet to be identified reliably.⁴⁰

How intensive (or costly) should acute stroke care be?

There is now limited evidence on some potentially beneficial components of acute stroke care, chiefly monitoring of physiological parameters (e.g. temperature, blood pressure, oxygenation and blood glucose level), with protocol-based correction of any deviations from normal.⁴¹⁻⁴⁷ There is little agreement on the key evidence-based elements of care for acute stroke, or the resource input required. The European Ad Hoc Group recommend very intense resource use, with treatment of patients in intensive care units.³⁸ While this model is neither evidence-based nor affordable in the UK, the accumulating evidence on the benefits of well-organised acute stroke care does suggest that there may be a case to increase the intensity of services for acute stroke care, whether or not thrombolysis is introduced.^{48,49} At the time this review was commissioned, there

were no nationally agreed standards of care for patients with acute stroke. By the time this report was in draft form, a National Service Framework for Older People had been published, which has set some standards of care for stroke, with specific mention of some aspects of acute stroke care in England and Wales, though it was published too late to be included in the analyses for this study.⁵⁰ In any event, it is not sufficiently detailed to cost the resource implications reliably.

Variations in the process of, and resource cost of, acute stroke care and variations in outcome

How then can one estimate the costs and benefits of investing extra resources in acute stroke care? Routine health service data might provide some clues. The healthcare services for patients with acute stroke (and their costs) vary enormously both between and within countries, and so do the outcomes.^{9,51-54} One might hope that countries (or hospitals) with better-organised stroke services or those that invest greater resources in acute stroke services might have better clinical outcome after stroke. Several studies comparing outcomes after stroke between and within countries have found substantial variations, which are not fully explained either by the quality or costs of care.^{9,53,54} Nonetheless, these studies do at least give estimates of the cost of an episode of care for a patient with acute stroke, and estimates of the variability in resource use and the key determinants of cost.

How much does it cost to raise service standards enough to deliver thrombolysis safely?

If a new medical treatment for acute stroke, such as thrombolysis, is to be introduced, the cost of introducing it in a particular hospital will depend on:

- the nationally agreed level of service that is needed to deliver the treatment effectively, safely and efficiently
- the resources already available for acute stroke care in that hospital
- the variation in the difference (i.e. level of service needed minus resources already available) between different hospitals.

If the service is to be introduced across the whole NHS and is to be delivered equitably, the extra resources required to introduce the service will therefore vary enormously between hospitals. In some hospitals, where acute stroke services are

already well developed, the extra investment needed is likely to be small, whereas in others with poorly developed stroke services, much greater investment will be required. Surveys and audits of the current provision of acute stroke care in the UK confirm that there are substantial variations in the level of service provision for patients with acute stroke and in the quality of stroke care; and many stroke patients are treated in hospitals without a designated stroke physician or a stroke rehabilitation unit.^{6,54-56} There is therefore much to be done to improve stroke services across the country.^{6,54-56}

How urgently should the NHS handle patients with acute stroke?

The duration of the 'therapeutic time window' for effective treatment of acute stroke is likely to be a major determinant of the configuration and cost of acute stroke services. If it is just 3 hours or less, services are likely to require much greater resources than if it is longer, say 6 hours or more. Unfortunately, the precise time window for safe and effective medical treatment of any type is not known.⁵⁷ Even for a specific treatment, such as intravenous thrombolysis, there is considerable debate about the time window. One view is that the window is precisely 3 hours.²³ Baron argues that such a fixed and rigid time window is implausible on pathophysiological grounds.⁵⁷ The data from a sub-group analysis of the NINDS trial and the data from the use of thrombolytic therapy in myocardial infarction both argue against an 'all-or-nothing' change from benefit to risk at precisely 3 hours and instead show a declining benefit with increasing delay.^{58,59} The sub-group analysis of the NINDS trial is not very reliable, as it is based on very small numbers of events.⁵⁸ Figure 1 shows the data from a robust and reliable individual patient data meta-analysis of the trials in myocardial infarction.

The time window in AMI (at least in patients with electrocardiographic changes showing ST (sinus tachycardia) elevation or bundle branch block) is at least 12 hours, though the benefit is greatest within the first hour.⁵⁹ In view of the likely time dependency of any treatment benefit, the

uncertainties about exactly how time-dependent it is makes costing services even more challenging.

Summary

It appears that the place of neuroprotective and thrombolytic therapy in the routine treatment of acute ischaemic stroke has not yet been established. Of the two interventions, it appears thrombolysis is the more likely to be relevant to the NHS in the near future. This report seeks to summarise the available evidence and its implications for clinical practice and research in the NHS.

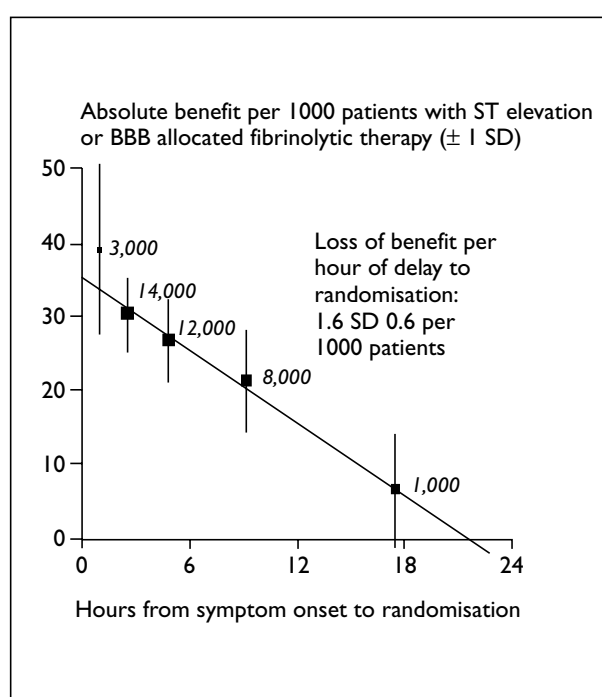


FIGURE 1 Absolute reduction in 35-day mortality versus delay from symptom onset to randomisation (estimated from a meta-analysis of data on 45,000 patients with AMI with ST elevation or bundle branch block, randomised to thrombolytic therapy or control). Area of black square and the extent to which it influences the line drawn through five points is approximately proportional to the number of patients it is based on. The vertical line above and below the square is one standard deviation. (Figure from Fibrinolytic Therapy Trialists' Collaborative Group overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. (Reproduced with permission⁵⁹) (BBB, bundle branch block; SD, standard deviation; ST, sinus tachycardia)

Chapter 2

Systematic review of effectiveness of thrombolytic therapy in acute ischaemic stroke

Background

Acute ischaemic stroke is a major cause of death and disability worldwide. Most strokes are due to blockage of an artery in the brain by a blood clot. Clot-dissolving (or thrombolytic) drugs may reduce brain damage from a stroke by restoring the blood flow if given rapidly enough after stroke, but may also cause serious bleeding in the brain. An overview of the literature on thrombolysis in acute ischaemic stroke in 1992⁶⁰ identified six randomised trials, which included a total of only 700 patients. A Cochrane Review updated the review and included the more substantial information that became available from larger trials in 1995/96 (total 3478 patients). The present version adds the trials completed in 1998/99, and also more complete data from the earlier trials. Thus, the total number of patients now randomised (and made public) in trials of thrombolytic therapy in acute ischaemic stroke is 5216 (data available on 5210), still a relatively small amount of trial data compared with that available for the use of thrombolysis for AMI.*

Methods

Objectives

The objectives of this review are to determine whether (and in what circumstances) thrombolytic therapy might be an effective and safe treatment for acute ischaemic stroke. Three main hypotheses are tested:

- that thrombolytic therapy increases the risk of death within the first 2 weeks, and reduces the risk of death at long-term follow-up
- that thrombolytic therapy increases the risk of early symptomatic or fatal intracranial haemorrhage
- that, at long-term follow-up, the reduction in the proportion of patients alive but dependent more

than offsets any early hazard, so that there is an overall net benefit and a reduction in the proportion with a poor outcome (i.e. dead or dependent)

- we also wished to undertake exploratory analyses to examine whether:
 - thrombolytic therapy interacts with anti-thrombotic therapy to increase the hazard
 - the balance of risk and benefit with thrombolytic therapy may vary with the pre-treatment severity of the stroke
 - there is a ‘therapeutic time window’ for effective treatment.

Inclusion and exclusion criteria

Types of studies

We sought to identify all truly randomised trials of thrombolytic therapy compared with placebo or open control in patients with acute ischaemic stroke. Trials that were not truly random (e.g. dose range finding studies) were not included. Trials in which the exact method of randomisation was unknown, even after correspondence with the authors, were included for the present. Trials that were not originally analysed on an intention-to-treat (ITT) basis were included if information on outcome could be obtained on all randomised patients thus allowing an ITT analysis to be performed.

Types of participants

Trials that included patients of any age or sex with a definite acute ischaemic stroke (confirmed by CT scanning to exclude cerebral haemorrhage prior to randomisation) were eligible.

Types of interventions

All types of thrombolytic drug given in any dose, by the intravenous or intra-arterial route, were included:

- urokinase (also known as u-PA)
- recombinant pro-urokinase

* Cochrane Reviews are regularly updated as new information becomes available and in response to comments and criticisms. The reader should consult The Cochrane Library for the latest version of a Cochrane Review. Information on The Cochrane Library can be found at www.update-software.com

- streptokinase (SK)
- rt-PA, or
- lumbrokinase.

Trials that were confounded by the treatment or control group receiving another active therapy which had not been factored in to the randomisation (e.g. thrombolytic drug plus another agent versus placebo, or thrombolytic drug versus another agent) were excluded.

Types of outcome measures

We sought to extract data on a variety of outcomes:

- deaths from all causes within the scheduled treatment period (usually the first 7–10 days after treatment)
- symptomatic intracranial haemorrhage: either symptomatic (i.e. associated with a deterioration in the patient's neurological state), or fatal (i.e. leading directly to death). Note that symptomatic intracranial haemorrhage includes haemorrhagic transformation of the infarct, haemorrhage elsewhere in the brain, and haemorrhage into the spaces surrounding the brain
- deaths from all causes during the whole trial follow-up period
- poor functional outcome at the end of follow-up; this was defined as death or dependency, measured by the Rankin or Barthel scales, at the end of the trial follow-up period. Poor functional outcome is the most clinically relevant and important measure of outcome as the aim of treatment should be not merely to avoid death but to increase the proportion of independent survivors and conversely to reduce the risk of survival with serious disability. Dependency in the present analysis was defined as a score of between 3 and 5 inclusive on the Modified Rankin Scale (MRS). Some would prefer a definition of good outcome (independence) including Rankin 0 and 1 only; therefore wherever possible we sought data on the number of patients in each individual Rankin category.

Search strategy for identification of studies

This review has drawn on the search strategy developed for the Cochrane Stroke Group as a whole. All possibly relevant trials were identified in the Group's Specialised Register of Controlled Trials (see appendix 1 and the Stroke Group's Review Group Details for more information; these are published in the section of the Cochrane

Library entitled *About the Cochrane Collaboration*). The Register was last searched by the Review Group in May.

The version of the review published on The Cochrane Library was supplemented by an additional search of EMBASE (Ovid) through the Bath Information and Data Services (BIDS) between 1980 and February 1997 using the following strategy (for this current version of the review, we used a very much more extensive strategy (details available on request) and last ran the search in April 2001, though this latter search did not identify any new relevant trials):

- (b) exp cerebrovascular disease/
- (b) stroke\$.tw
- (b) cerebrovasc\$.tw
- (b) 1 or 2 or 3
- (b) urokinase/
- (b) prourokinase/
- (b) streptokinase/
- (b) tissue plasminogen activator/
- (b) lumbrokinase/
- (b) thrombol\$.tw
- (b) (urokinase or pro?urokinase or streptokinase).tw
- (b) (tissue plasminogen activator or lumbrokinase).tw
- (b) 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
- (b) 4 and 13.

A handsearch of the following journals (1979 to April 1994) was carried out:

- *Japanese Journal of Stroke*
- *Clinical Evaluation*
- *Japanese Journal of Pharmacology & Therapeutics*
- *Rinsho Ketsueki*.

Translations of the non-English language publications were obtained from people in whose native language the paper was published.

We contacted pharmaceutical companies ($n = 321$) for more information about trials known to exist from the above efforts, and for information on any trials that were so far unknown to the reviewers (last systematic contact December 1997). All companies except one (who was known to be doing a trial in any case) responded, and no new trials were identified that had not already been identified.

References quoted in thrombolytic therapy papers were also examined, and direct contact was made with principal investigators of trials in Europe, the USA, Japan and China.

Attendance at and screening of abstracts presented at the following conferences was also included in the search strategy.

- 1st and 2nd International Conferences on Acute Stroke (Geneva, Switzerland 1991 and 1993)
- 2nd to 10th European Stroke Conferences (Lausanne, Switzerland 1992; Stockholm, Sweden 1994; Bordeaux, France 1995; Munich, Germany 1996; Amsterdam, The Netherlands 1997; Edinburgh, Scotland 1998; Venice, Italy 1999; Vienna, Austria 2000; Lisbon, Portugal 2001)
- 2nd, 3rd, 4th, 5th and 6th International Symposia on Thrombolysis in Acute Ischaemic Stroke (La Jolla, USA 1992; Nara, Japan 1994; Copenhagen, Denmark 1996; Bethesda, Maryland 1998; Hamilton Island, Australia 2000)
- 1st and 3rd Annual Advances in Stroke Management Meetings (Barcelona, Spain 1995; Crete, Greece 1998; Sardinia, Spain 1999)
- International Stroke Conference (Melbourne, Australia 2000)
- International Conference on Acute Stroke and Thrombolysis (Hamilton Island, Australia 2000).

A full list of journals searched can be found in appendix 1.

Data collection and extraction

Trials were selected for inclusion in the review after seeking additional unpublished information from the principal investigators of all the trials that appeared to meet our inclusion criteria. We aimed to extract from each trial the number of patients originally allocated to each treatment group to allow an ITT analysis, if the trial had not already been presented in this way.

For each included trial information was collected on:

- the method of randomisation
- blinding of treatment administration
- blinding of outcome assessment
- whether an ITT analysis was done (or could possibly be done).

The numbers of patients in the treatment and control groups were extracted who had:

- died within the first 7–10 days
- developed symptomatic or fatal intracranial haemorrhage early after the stroke (within the first 7–10 days)
- died by the end of the trial follow-up
- were dependent on others in activities of daily living by the end of the trial follow-up period.

In addition, data were extracted to allow a number of exploratory sub-group analyses, as follows:

- the proportion of patients given aspirin or heparin within the treatment period
- the number of patients who died or were dependent at the end of follow-up according to whether they had been treated within 3 hours of the stroke or later than 3 hours (in trials that randomised patients beyond 3 hours after the stroke).

A tabulation of the extracted data was cross-checked and then verified with the principal investigator of each trial and any errors were corrected. In Haley and co-workers⁶¹ and Morris and co-workers⁶² the outcomes were very clearly described in the original texts and verification with the principal investigators was not necessary.

Our definition of symptomatic intracranial haemorrhage included patients who died or deteriorated clinically as a result of intracranial haemorrhage. This could be either secondary bleeding into the infarct or new bleeding at an anatomically separate site elsewhere in the brain or its surrounding spaces, after randomisation confirmed by CT scanning or post-mortem. We have defined early after the stroke as within the first 7–10 days, as the trials each tended to use a slightly different time point, but all had collected information on intracranial haemorrhage certainly within the first 10 days. Many symptomatic haemorrhages actually occurred within the first few days of the stroke. It is difficult to estimate the exact number of symptomatic intracranial haemorrhages because some patients died without a CT scan or post-mortem. Thus, the true number with symptomatic intracranial haemorrhage may be higher than that suggested by these data. On the other hand, heightened awareness of an association between haemorrhagic transformation and thrombolysis may mean that the investigators too readily attributed any neurological deterioration following treatment to intracranial haemorrhage, even if the amount of blood was small. Review of published CT scans suggests that at least for some trials, symptomatic intracranial haemorrhage included patients with very large swollen and oedematous infarcts with trivial amounts of haemorrhage within them.⁶³ Therefore, it is also possible that the risk of intracranial haemorrhage has been overestimated. The European Co-operative Acute Stroke Study (ECASS) trial⁶³ did not report the number of patients with symptomatic intracranial haemorrhage, but instead whether the radiological appearance

of the haemorrhage suggested haemorrhagic transformation of an infarct or parenchymatous haematoma (and its size). Most parenchymatous haemorrhages were associated with symptoms, so we used the number of patients with parenchymatous haematoma as the number with symptomatic haemorrhages.

Both proportional and absolute risk reductions were calculated for each outcome. Heterogeneity between trial results was tested for using a standard chi-squared test. The results reported in the text are odds ratios (ORs) (i.e. the ratio of the odds of an unfavourable outcome among treatment-allocated patients to the corresponding odds among controls), which were calculated using the Peto fixed-effects method.

Details of studies included

Seventeen trials, which included 5210 patients are included,^{17,61–76} (six patients are missing from the ATLANTIS B trial publication⁶⁴). Additional details of these studies are available in the electronic version of this review, published on the Cochrane Library.¹⁶ Note that the NINDS trial¹⁷ was conducted in two consecutive parts, A and B, but published in one paper, so is included as one trial in this review. The three trials performed in the 1980s^{65–67} were methodologically very different to the rest of the trials, which were performed in the 1990s. The trials of the 1980s used very low doses of intravenous thrombolytic drug, given daily for several days, and started up to 5 or 14 days after the stroke. The trials of the 1990s used a single large dose of thrombolytic drug (in the region of 80–100 mg rt-PA), given intravenously in most trials, within 3 or at most 6 hours of the stroke. The 1980s trials did not collect data on functional outcome and therefore only the trials of the 1990s contribute to the analysis of death or dependency. All trials however contribute to analyses of intracranial haemorrhage and death by the end of follow-up (although very few deaths or intracranial haemorrhages occurred in the trials in the 1980s). However, it is possible to see from the figures what effect the exclusion of these early trials would have on the overall results.

The Multi-centre Acute Stroke Trial – Italy (MAST-I) trial,⁶⁸ which tested intravenous SK and oral aspirin given within 6 hours of stroke onset in a two-by-two factorial design, was the only trial so far to test for an interaction between thrombolytic and antithrombotic drugs in a randomised trial – the comparison of SK plus aspirin versus aspirin

alone from MAST-I is included in this review (separated from the MAST-I data in the absence of aspirin) because it represents the only available randomised evidence on this important interaction. As there was a significant adverse interaction between SK and aspirin, which we felt was important to highlight, the data for the patients receiving SK in the presence or absence of aspirin are presented separately (i.e. SK versus control, and SK plus aspirin versus aspirin alone).

Types of stroke patient included

The selection of patients was based initially on clinical criteria to diagnose the stroke sub-type (cortical versus lacunar versus posterior circulation):

- five trials randomised all types of ischaemic stroke – cortical, lacunar and posterior circulation^{17,61,64,68,69}
- one trial included cortical and lacunar strokes⁷⁰
- four trials included only patients with symptoms of hemispheric cortical ischaemia (see below for additional CT scan criteria)^{62,63,71,72}
- four trials included patients with angiographically proven occlusion of the internal carotid or middle cerebral artery^{73–76}
- three trials included presumed thrombotic stroke of most severities and excluded presumed cardio-embolic strokes (though it is not clear whether artery-to-artery embolism counted as ‘embolic’ in this context).^{65–67}

Stroke severity

Most trials used a stroke severity scale, such as the National Institutes of Health Stroke Scale or Scandinavian Stroke Scale, or developed their own neurological stroke severity scale to measure the severity of the stroke at baseline. All trials excluded patients in coma (i.e. unconscious); most trials did not randomise many patients who were drowsy except the Multi-centre Acute Stroke Trial – Europe (MAST-E),⁷² in which 50% of the patients were drowsy or stuporose at randomisation.

Age-related exclusion criteria

- Only five trials had no upper age limit and included very elderly patients.^{65–68,72}
- Three trials had an upper age limit of 85 years.^{70,75,76}
- The NINDS trial¹⁷ initial protocol stated an upper age limit of 80 years, although patients over the age of 80 were randomised (the actual age of the oldest patient was not stated in the primary publication, but a patient of 87 years is referred to in the subsidiary paper on intra-

cranial haemorrhage by the NINDS Stroke Study Group).⁷⁷

- All the remaining trials had an upper age limit of 80 years.

Visible infarction on the CT scan at randomisation

- Two trials specified that the pre-randomisation CT had to be normal.^{73,74}
- Three trials specified that the pre-randomisation CT scan had to be normal or only show ischaemic changes in less than one-third of the middle cerebral artery supply territory.^{63,64,71}
- Two trials excluded patients with mass effect and midline shift on CT.^{75,76}
- None of the other trials specified that patients with a CT scan that showed an infarct (which was likely to be symptomatic) should be excluded, although individual doctors may have excluded these patients in some centres depending on local opinion.

Time to randomisation

The maximum time interval allowed between the onset of the stroke and the start of the treatment administration varied from within 3 hours to up to 2 weeks.

- Two trials randomised patients within 3 hours.^{17,61}
- One trial randomised patients within 4 hours.⁷⁰
- One trial randomised patients within 3–5 hours – part of ATLANTIS B.⁶⁴
- Ten trials randomised patients within 6 hours.^{62,63,68,69,71–76}
- Two trials randomised patients within 5 days.^{65,66}
- One trial randomised patients within 2 weeks.⁶⁷ (Note that these latter three trials^{65–67} do not contribute data to the analysis of early deaths or of death and dependency, as early deaths were not recorded and a functional outcome measure was not used in these trials. They do contribute data to the analyses of intracranial haemorrhages and deaths by the end of follow-up.)

Thrombolytic agent tested

The thrombolytic agents tested in the 17 trials were as follows.

- Four trials used SK.^{62,68,70,72}
- Eight trials used rt-PA.^{17,61,63,64,69,71,73,74}
- Three trials used urokinase.^{65–67}
- Two trials used rpro-urokinase.^{75,76}

Thus trials using intravenous rt-PA contribute 2889/5144 patients – 56% of the data in this review.

Dose range tested and route of administration

The dose range tested and the route of administration in the 17 trials were as follows.

- The SK dose was 1.5 MU (as used to treat AMI) in four studies.^{62,68,70,72}
- The rt-PA dose was similar to that used to treat AMI at 1.1 mg/kg to a maximum of 100 mg in one study,⁶³ about 20% less at 0.9 mg/kg to a maximum of 90 mg in five studies,^{17,61,64,69,71} and about one-third of that in two studies.^{73,74} All SK and rt-PA doses were administered by intravenous infusion through a peripheral arm vein, over 1 hour.
- The urokinase dose in Abe and co-workers,⁶⁷ Atarashi and co-workers⁶⁶ and Ohtomo and co-workers⁶⁵ was much lower than the equivalent for AMI and was administered intravenously once daily for 7 days.
- The rpro-urokinase dose was 6 mg in the Prolyse in Acute Cerebral Thromboembolism (PROACT) study⁷⁵ and 9 mg in PROACT 2;⁷⁶ in both trials the dose was administered intra-arterially, through a catheter with its tip embedded in the occluding thrombus.

Concomitant use of antithrombotic treatment

One trial⁶⁸ compared aspirin with SK and control, starting within 6 hours of stroke onset, in a factorial randomisation (i.e. patient were randomised to SK, aspirin, aspirin plus SK or to neither). In the groups randomised to receive aspirin, treatment was continued for 10 days.

Antithrombotic use was not randomly assigned in any other trial and its permitted use varied.

- In the Australian Streptokinase (ASK) trial,⁷⁰ all patients were to receive 300 mg aspirin starting within 4 hours of the SK infusion and continued daily thereafter.
- In PROACT,⁷⁵ all patients received intravenous heparin 1000 U/hour during the trial angiogram, reduced to 500 U/hour halfway through the trial.
- In PROACT 2,⁷⁶ all patients received intravenous heparin 500 U/hour for 4 hours starting at the time of the angiogram infusion.
- In MAST-E,⁷² aspirin and intravenous heparin were allowed to start at any time and continue for any time (about 25% of patients received aspirin or heparin within 24 hours and 75% within the first week of the stroke).

- In the ECASS⁶³ and ECASS II⁷¹ studies, subcutaneous heparin was allowed within 24 hours of the stroke (and thereafter) and aspirin after 24 hours. (In ECASS II, about 20% of patients were taking aspirin at the time of their stroke, and 54% of rt-PA-treated patients received subcutaneous heparin within the first 24 hours, but we are unsure of the corresponding numbers for ECASS, or the number of patients in either trial receiving aspirin or heparin after 24 hours.)
- In Haley and co-workers⁶¹ a few patients received antithrombotic drugs within 24 hours and thereafter.
- In several trials no antithrombotic drugs were allowed within 24 hours but aspirin was allowed thereafter.^{17,64,69,73}
- In three trials^{65–67} antithrombotic drugs were not allowed during the 7 days of treatment infusion, but could be used thereafter.
- The antithrombotic drug used was not stated clearly in two trials.^{62,74}

Follow-up

Early outcome assessments were made at around 7–10 days in most trials. Some trials also performed more frequent assessments in the first few hours and days after the trial treatment. In the present review, outcome events occurring within the first 7–10 days (whichever was the later date at which data were collected) have been used to determine the effect of thrombolytic therapy on early outcome. The final outcome assessment was at:

- about 1 month after the stroke^{62,65–67,73,74}
- 3 months^{17,61,63,64,69–71,75,76}
- 6 months.^{68,72}

Note that follow-up at 6 months and 1 year have recently been reported for NINDS,⁷⁸ although the 3-month outcome, the primary outcome originally reported, is used in the present review. Note also that because of the difficulty of blinding the biological effect of thrombolytic therapy, it is important to ensure that outcome assessment is objective (unbiased). Follow-up should therefore be performed by individuals unaware of the trial treatment allocation either because they have not been involved in the administration of the trial treatment, or in the care of the patient during at least the first few days. In MAST-I,⁶⁸ the 6-month follow-up was by telephone by a trained observer blind to the treatment allocation. The MAST-E⁷² and ASK⁷⁰ trials did not specify who performed the follow-up or that they should not have been involved in the trial treatment administration or patient care in the first 24 hours. In NINDS,¹⁷

ATLANTIS A⁶⁹ and ATLANTIS B,⁶⁴ follow-up at all stages was to be by a doctor (blinded) who had not been involved in the randomisation or care of the patient in the first 24 hours. In ECASS,⁶³ ECASS II,⁷¹ PROACT⁷⁵ and PROACT 2,⁷⁶ follow-up was by a mixture of individuals – where possible by someone who had not been involved in the patient's care within the first 24 hours but this may not always have been the case.

Assessment of functional outcome

Functional outcome was assessed by a variety of measures:

- the Barthel Scale^{62,70,73,74}
- an undefined scale (no, mild, moderate or severe limitation)⁶¹
- the Rankin Scale^{68,72}
- the MRS^{17,63,64,69,71,75,76}
- or was not assessed at all.^{65–67}

Some trials used more than one scale to measure outcome. The trials by Abe and co-workers,⁶⁷ Ohtomo and co-workers⁶⁵ and Atarashi and co-workers⁶⁶ used the Global Improvement Rating, which measures change in neurological status and safety outcome as a composite surrogate for functional outcome.

There are differences in the primary outcome measure used between trials, in that some used a poor functional outcome and some used a good outcome. The following trials sought 'dependency' as a measure of poor functional outcome: MAST-I⁶⁸ and MAST-E,⁷² which defined dependency as Rankin 3 or worse, and Morris and co-workers⁶² and ASK,⁷⁰ which defined dependency as Barthel 60 or worse.

The following trials sought 'good functional outcome': ECASS,⁶³ ECASS II,⁷⁹ NINDS,¹⁷ ATLANTIS A⁶⁹ and ATLANTIS B,⁶⁴ which defined good outcome as MRS 0 or 1. For most trials, it has been possible to obtain data on patients in each individual Rankin (or Barthel) group, or data dichotomised on Rankin 0–2 versus 3–6, or 0 and 1 versus 2–6, so that dependency in this review refers to Rankin (or MRS) 3–5 (6 being dead) unless otherwise stated. The only trials for which the number of patients in individual Rankin groups were not available (and therefore the data shown are for Rankin 2 or worse) are ATLANTIS A⁶⁹ and PROACT.⁷⁵

Methodological quality of included studies

Seventeen trials have been included: eight recent trials from 1995 to 1999, seven earlier trials all using intravenous thrombolytic therapy, and two trials

using intra-arterial thrombolytic therapy. A trial by Naito (Naito, 1984) was excluded after discussion with Professor Abe (co-investigator), as it was not possible to account for 11/101 randomised patients (most of whom were in the control group). Another trial (Edinburgh, 1991) was excluded because it stopped prematurely after randomisation of only four patients. Three trials conducted in China were excluded, two because of confounding (Don-Cai Yuan, 1995; Zhang Yuan Xiang, 1995) and one because the duration of follow-up was only 3 weeks (Pang Shi-Qi, 1993) (see *Table 1*).

Randomisation method

Randomisation was generally well described. The methods used were as follows.

- Five trials used central telephone randomisation.^{68,70,72,75,76} In MAST-I⁶⁸ and PROACT 2,⁷⁶ the allocated treatment was then given unblinded without a placebo. In MAST-E⁷² and ASK,⁷⁰ sealed pre-packs of SK or identical-appearing placebo were selected according to the randomisation instructions.
- Three trials randomised patients at the participating hospital by selection of a sealed, sequentially-numbered pre-pack (of active drug or identical-appearing placebo) followed within 2 hours by a telephone call to the Central Trial Co-ordinating Office to notify them of the patient and the number of the drug pack.^{17,64,69} The pack numbering was done according to a randomisation list.
- Two trials randomised patients by selection of a sequentially numbered, sealed drug pre-pack at the participating centre provided by the sponsor from a randomisation schedule drawn up centrally.^{63,71}
- Five trials used sealed drug pre-packs of active drug or identical-appearing placebo.^{65–67,73,74}
- One trial used sealed envelopes.⁶¹
- The method of randomisation was not stated in one trial.⁶²

Blinding

Due to its effects on the coagulation system at high doses, thrombolysis is difficult to administer completely blind, as there are often quite obvious signs of minor bleeding (prolonged bleeding at venepuncture sites, easy bruising, gingival or conjunctival haemorrhages, etc). Thus, provision of an identical-appearing placebo (in the syringe) may not fully blind investigators to treatment allocation.

Analysis

Only the ITT results are included here. In any trials where there have been exclusions, these

were made prior to the breaking of the randomisation code. A strict ITT analysis was used in ten trials,^{17,63,64,68–70,72,75,76,79} but not in any of the earlier trials. However, for the earlier trials, with additional information from the principal investigators where necessary, we have attempted to find a final outcome for all randomised patients, rather than simply relying on the published data from which some randomised patients may have been excluded. Note the ECASS trial was published as ITT and as a target population after about 20% of the randomised patients had been excluded.⁶³

Premature closure of recruitment

Randomisation in MAST-E (all patients) and ASK (in the > 3-hour group) stopped on the advice of their respective data monitoring committees after only about half of the originally intended number of patients had been randomised. MAST-I was suspended by its steering committee (in view of the adverse climate for continuing thrombolytic trials at the time, due to the stopping of MAST-E and ASK) to examine its interim results after randomisation of about one-third of its originally intended number. Four trials^{17,63,71,76} all reached their planned targets. PROACT⁷⁵ stopped after completing two of its planned three dosage arms. ATLANTIS A⁶⁹ was stopped on publication of the NINDS trial, and continued in modified form as ATLANTIS B,⁶⁴ which in turn stopped in 1998 following a futility analysis prompted by results from ECASS II.⁷¹

Results

Results are presented in *Figures 2–6*. Note that in each figure, trials are grouped according to which thrombolytic drug was used, with a subtotal OR for that agent. The overall OR for all trials appears at the bottom of each figure.

Death from all causes within the first 7–10 days

Data on deaths occurring within the first 7–10 days were available for seven trials (*Figure 2*). There was a significant excess of early deaths with thrombolysis. A total of 16.6% of those allocated to thrombolytic therapy died compared with 9.8% of those allocated to control (OR = 1.85; 95% CI, 1.48 to 2.32; $2p < 0.000001$). In absolute terms, if confirmed, this is an increase of 68 (95% CI, 44 to 93) early deaths per 1000 patients treated with thrombolysis. There was borderline significant heterogeneity ($\chi^2 = 15.05$, degrees of freedom (df) = 7; $p < 0.05$). Data on early deaths were available for four of the trials of intravenous rt-PA. The

TABLE 1 Studies excluded from the systematic review of effectiveness

Study	Reason for exclusion
<p>Don-Cai Yuan <i>et al.</i> High dose urokinase in the treatment of acute ischaemic stroke. <i>J Brain Neurol Dis</i> 1995;3(2):111</p> <p>Chinese – abstracted by Dr Ming Liu</p>	<p>A randomised trial of intravenous urokinase 8000–10000 U/kg (total 600,000–900,000 U) plus nimodipine, vitamin E and C, aspirin, mannitol, dexamethasone, nidocain and snake venom, versus ‘conventional treatment’ (i.e. everything except urokinase) given over 40 minutes within 2 days of onset of ischaemic stroke</p> <p>Urokinase 10,000–15,000 repeated the following day if no improvement</p> <p>Follow-up was using the Chinese Neurological Scale at only 2 weeks after treatment. No long-term follow-up. This scale does not appear to measure dependency. A total of 80 patients were randomised, 40 per treatment arm. There is no mention of the number who died or had symptomatic intracranial haemorrhage</p> <p>The trial was excluded because of the short follow-up period</p>
Edinburgh, 1991	<p>This unpublished study terminated prematurely because of the impracticality of intra-arterial thrombolytic treatment. Four patients were randomised between SK (250,000 MU into the occluded cerebral artery) or placebo during the year that the trial ran (1991). It had been intended to randomise at least ten patients. Three received SK and one received the placebo. One patient (SK) died within a week of the stroke of a massive cerebral infarct; 6-month outcome in the other three was: 1 (SK) Rankin 2; 1 (SK) Rankin 3; 1 (placebo) Rankin 4</p> <p>These results have not been included because the number is so small and the randomisation (because of the premature termination) so imbalanced</p>
Hong Kong, 1994	<p>This unpublished trial of intravenous SK stopped prematurely after randomisation of only a few patients because of concerns about the use of SK arising from termination of MAST-E, ASK and MAST-I</p>
Meyer, 1963	<p>Although randomised and controlled, this trial was conducted in the pre-CT era. Thus there was no means to ensure that only ischaemic stroke patients were included. (It is quite possible that several of the patients had a haemorrhagic stroke at entry to the trial; such patients are now vigorously excluded from current trials)</p>
Meyer, 1964	<p>Although randomised and controlled, this trial was – like Meyer 1963 – conducted in the pre-CT era and was therefore excluded for the same reason</p>
Naito, 1984	<p>The data are presented in two, possibly three, different publications. Many patients were lost to follow-up during the 4-week trial period. Dr Naito has died and Professor Abe is unable to supply further information on those lost to follow-up. Although there were no deaths or cerebral haemorrhages among the patients who completed the trial, the data are incomplete and may be badly skewed by lack of information on what happened to the patients who dropped out</p>
<p>Pang Shi-Qi <i>et al.</i> Clinical study of therapeutic effectiveness in treating ischaemic cerebrovascular disease with lumbrokinase. <i>Chinese J Neurol Psychiatry</i> 1993;26(4): 229–231</p> <p>Data extracted by Dr Ming Liu</p>	<p>This appears to be a randomised trial (method uncertain) of lumbrokinase two tablets daily for 21 days versus placebo. A total of 303 patients received lumbrokinase and 150 received placebo; both groups received dextran</p> <p>Very little is known about outcome. Follow-up was at 3 weeks only and therefore this trial was excluded. No information on deaths or intracranial haemorrhages. There is thought to have been conflict between the authors and the pharmaceutical sponsor so no further details have been published (Ming Liu, personal communication)</p>
<p>Zhang Yuan Xiang <i>et al.</i> Thrombolytic therapy and external counterpulsation in acute cerebral infarction. Proceedings of the Fourth Chinese Stroke Con- ference. Chengdu, Oct 1995, p44 (abstract)</p> <p>Data extracted by Dr Ming Liu</p>	<p>Randomised trial (method unknown) of intra-arterial urokinase 300,000–1,000,000 units for 1 hour plus heparin, plus a ‘physical therapy’ (nature uncertain) plus ‘conventional treatment’ versus ‘conventional treatment’ (nature uncertain) started within 6 hours of onset of acute ischaemic carotid territory stroke. A total of 67 patients were included, 32 in the active and 35 in the placebo arms. Follow-up was at 3 months using a neurological deficit score. The number of deaths and intracranial haemorrhages was not mentioned</p> <p>The trial was excluded because of the confounding of treatment allocation</p>

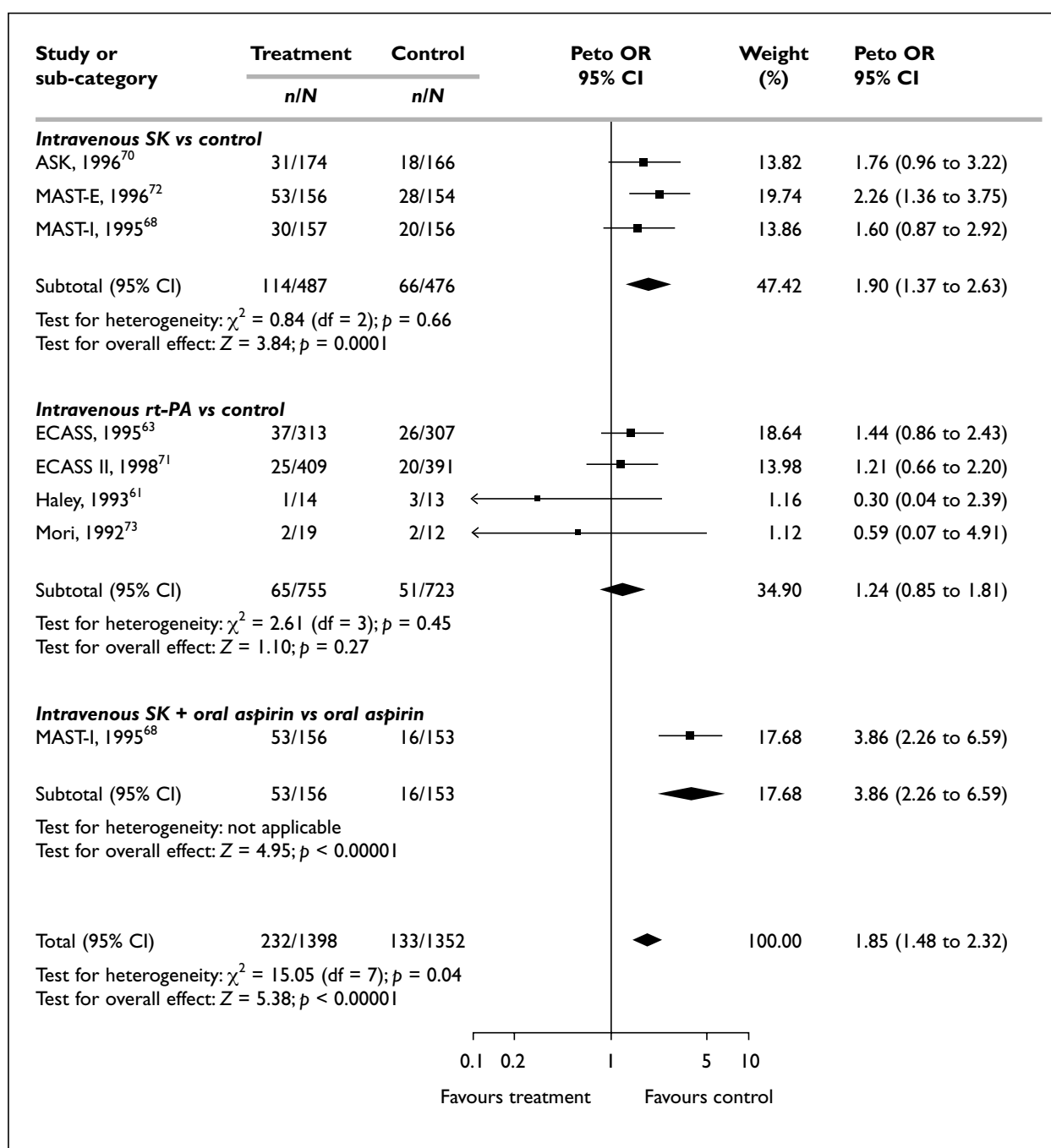


FIGURE 2 Effects of thrombolytic therapy on death from all causes within the first 7–10 days

numerical (tabular) data on early deaths for the NINDS trial¹⁷ have not been published, but the NINDS investigators did publish a survival curve, which suggested that fewer deaths occurred in the rt-PA-treated patients from 24 hours after treatment onwards. The tabular data available from the other rt-PA trials showed a non-significant excess of early deaths: the OR was 1.24 (95% CI, 0.85 to 1.81; $2p =$ not significant (NS)) with no significant heterogeneity. In the trials using SK, there was a significant excess of early deaths (OR = 1.90; 95% CI, 1.37 to 2.63).

Fatal intracranial haemorrhage

Data were available from eleven trials on fatal intracranial haemorrhage (Figure 3). This outcome may underestimate the frequency of intracranial haemorrhage as some of the patients who died without a post-mortem or CT scan may have died of intracranial haemorrhage. There was a significant five-fold increase in the rate of fatal intracranial haemorrhage with thrombolysis (5.5% of patients allocated to thrombolysis compared with 1.0% of those allocated to control: OR = 4.33; 95% CI, 3.12 to 6.03; $2p < 0.000001$). There was no heterogeneity

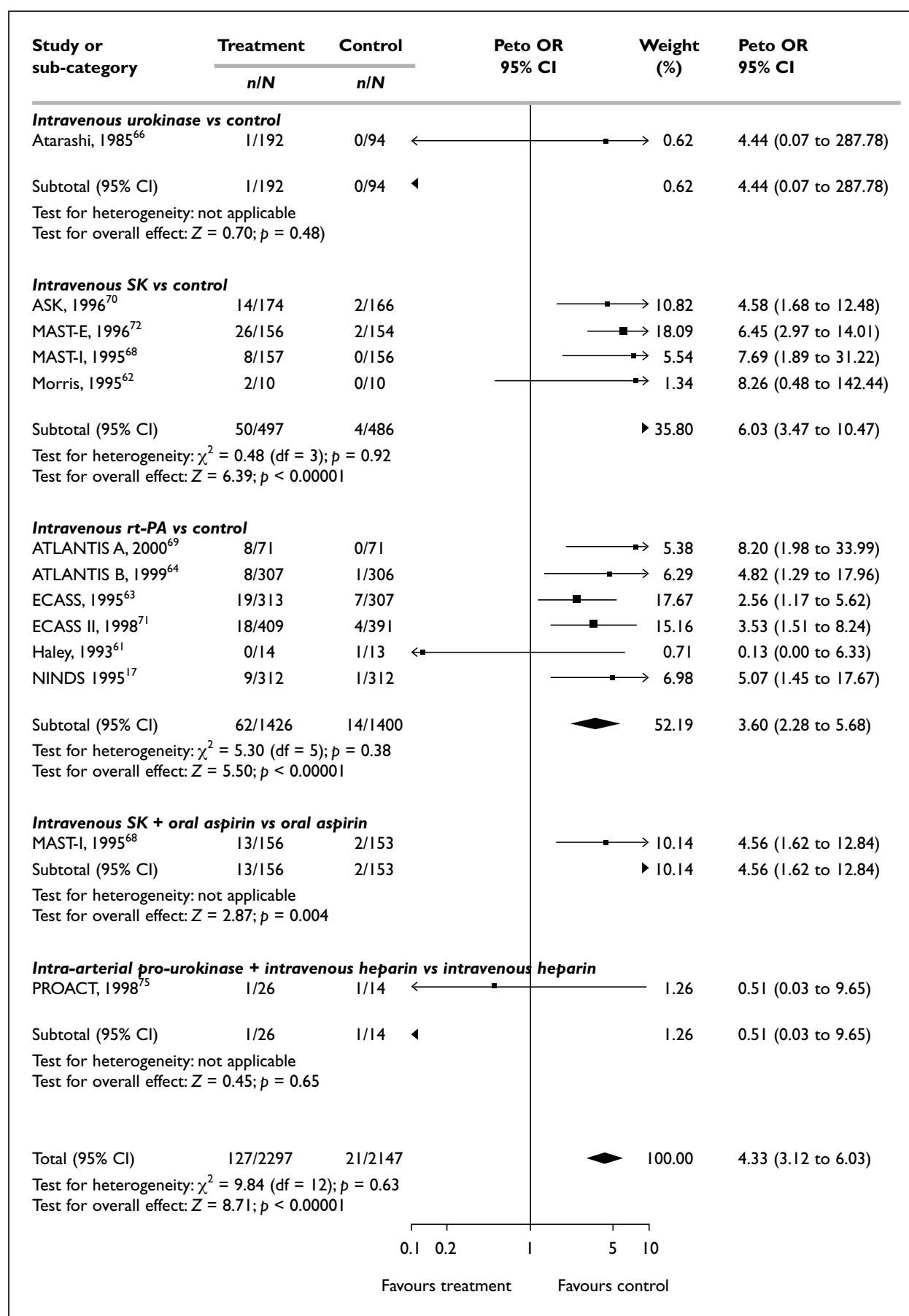


FIGURE 3 Effects of thrombolytic therapy on fatal intracranial haemorrhage

(χ^2 for heterogeneity = 9.84 (df = 12); p = NS). In trials of rt-PA, there were 33 (95% CI, 22 to 45) extra fatal intracranial haemorrhages per 1000 patients treated (OR = 3.60; 95% CI, 2.28 to 5.68; $2p < 0.000001$) with no heterogeneity between trials ($\chi^2 = 5.30$ (df = 5); p = NS). In trials of SK, there were 92 (95% CI, 65 to 120) extra fatal intracranial haemorrhages per 1000 treated (OR = 6.03; 95% CI, 3.47 to 10.47). The combination of SK with aspirin in MAST-I⁶⁸ significantly increased total deaths from cerebral causes (OR = 2.0; 95% CI, 1.1 to 3.7), fatal intracranial haemorrhage (OR = 4.56; 95% CI, 1.62 to 12.84), and more patients died of cerebral causes without a CT scan or post-mortem who may therefore also have had intracranial haemorrhage, than in the group who received SK alone.

Symptomatic (including fatal) intracranial haemorrhage

All trials provided data on intracranial haemorrhage and most provided them in a form that made it clear how many patients had suffered a neurological deterioration associated with the appearance of new haemorrhage in the brain on a CT brain scan or at post-mortem (data available in electronic versions of this review¹⁶). There was a highly significant four-fold increase in symptomatic intracranial haemorrhage with thrombolysis in 9.3% of those allocated to thrombolysis versus 2.5% of those allocated to control (OR = 3.46; 95% CI, 2.75 to 4.37; $2p < 0.000001$). This represents an extra 69 (95% CI, 57 to 82) symptomatic intracranial haemorrhages per 1000 patients treated. In trials using rt-PA, there were 70 (95% CI, 53 to 88) extra symptomatic intracranial haemorrhages per 1000 patients treated (OR = 3.13; 95% CI, 2.34 to 4.19; $2p < 0.000001$) with no heterogeneity between trials ($\chi^2 = 11.84$ (df = 7); p = NS). The exclusion of trials that used lower doses of thrombolysis and had lower rates of fatal and symptomatic intracranial haemorrhage had little effect on the overall result as they contributed relatively few of the data to this analysis. Poor blinding of the radiologists interpreting the scans may have biased these estimates, as small areas of petechial haemorrhage within a large infarct may be over-reported in patients known to have received thrombolysis.

Deaths from all causes within the scheduled follow-up (including the early deaths)

Data were available for all 17 trials, which included 5210 patients (Figure 4). There was a modest but significant increase in deaths within scheduled follow-up, from 15.7% in controls to 19.1% in the patients allocated to thrombolysis (OR = 1.32; 95% CI, 1.13 to 1.53; $2p = 0.0008$). In absolute terms,

this represented an extra 37 (95% CI, 17 to 56) deaths at the end of follow-up per 1000 patients treated with thrombolysis. There was considerable heterogeneity between the trials ($\chi^2 = 38.8$ (df = 17); $p < 0.01$); two trials^{17,68} (patients allocated to SK alone) showing a non-significant reduction, and three trials^{68,70,72} (patients allocated to SK plus aspirin) showing a significant increase in case fatality with thrombolysis. In the trials of intravenous rt-PA there was a non-significant increase in deaths (OR = 1.17; 95% CI, 0.95 to 1.45) equivalent overall to 19 more deaths per 1000 patients treated. There was significant heterogeneity of treatment effect among the trials of rt-PA ($\chi^2 = 14.42$ (df = 7); $p < 0.05$).

Death or dependency at the end of trial follow-up

Analysable data from 12 trials on functional outcome were available for 4342 patients (Figure 5). A further two trials also assessed functional outcome but the data from one⁶¹ were incomplete (3/27 patients were alive but were lost to follow-up), and in the other,⁷⁴ the Barthel scores have not been published. There was a significant reduction in death or dependency with thrombolysis; 55.1% of those allocated to thrombolytic therapy compared with 59.2% of those allocated to control (OR = 0.83; 95% CI, 0.73 to 0.94; $2p = 0.003$). This would be clinically important if confirmed, as it is equivalent to 43 (95% CI, 15 to 72) fewer dead or dependent patients per 1000 treated. This substantial absolute benefit is comparable to that achievable with thrombolysis for AMI.⁵⁹ There was no significant heterogeneity of treatment effect between the trials ($\chi^2 = 19.96$ (df = 12); p = NS) (i.e. broadly speaking, the treatment effect in all trials was in the same direction). For the six trials using intravenous rt-PA (2830 patients), the OR was 0.80 (95% CI, 0.69 to 0.93; $2p = 0.002$), equivalent to 55 (95% CI, 19 to 91) fewer patients being dead or dependent. There was significant heterogeneity of treatment effect among the trials using rt-PA ($\chi^2 = 13.23$ (df = 5); $p < 0.05$). If an alternative definition of poor outcome (Rankin 2–6) is used in this analysis, the effect of thrombolysis is unchanged, with a significant reduction in the number of patients with a poor outcome (OR = 0.79; 95% CI, 0.69 to 0.90), with no significant heterogeneity. For the six trials using rt-PA, the OR was 0.76 (95% CI, 0.65 to 0.89), with significant heterogeneity ($\chi^2 = 14.84$ (df = 5); $p < 0.05$).

Analyses to explore source of heterogeneity

To attempt to identify possible causes for the heterogeneity of the effect of treatment on death from all causes, we have ordered the trials by:

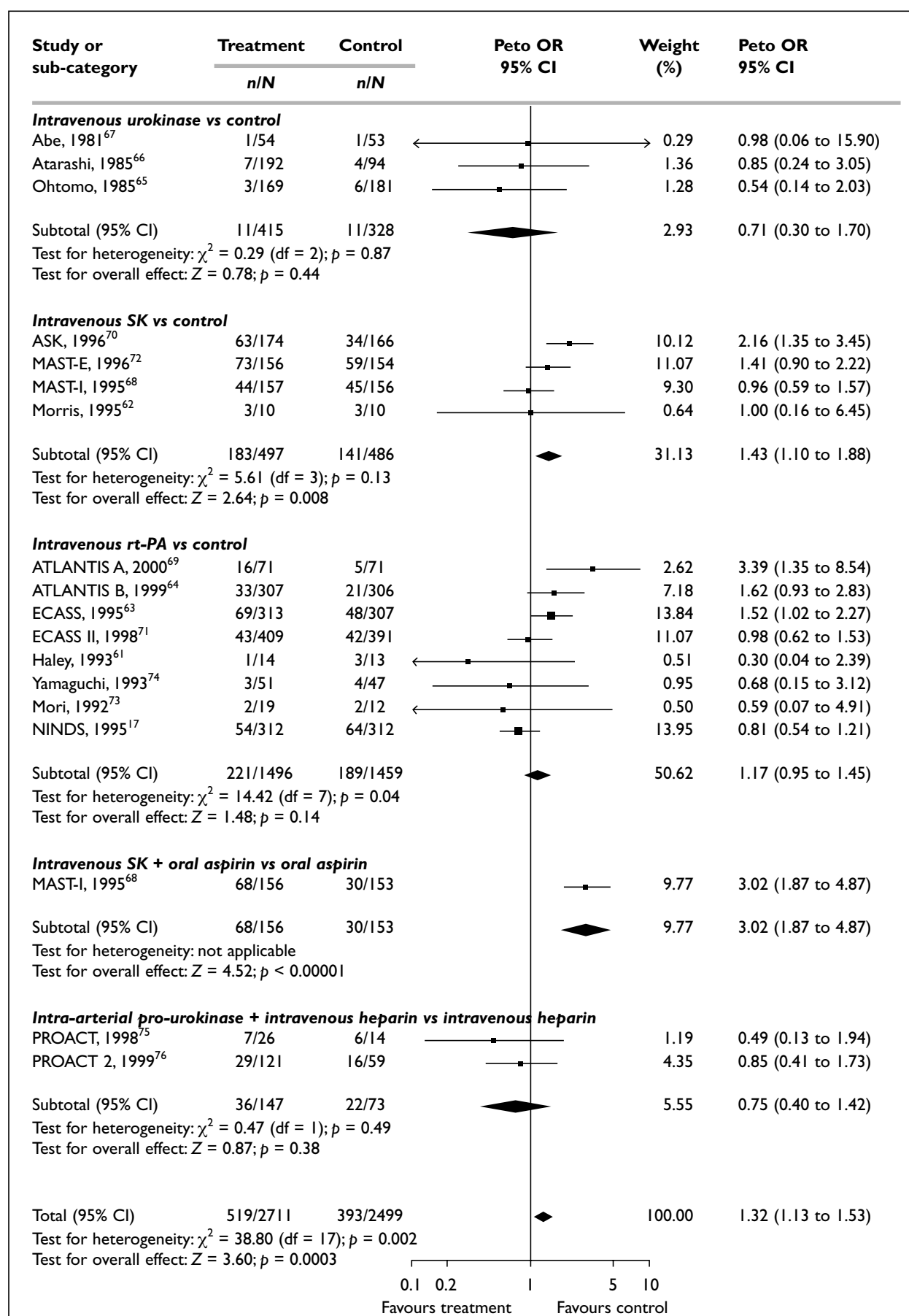


FIGURE 4 Effects of thrombolytic therapy on deaths from all causes within the scheduled follow-up (including the early deaths)

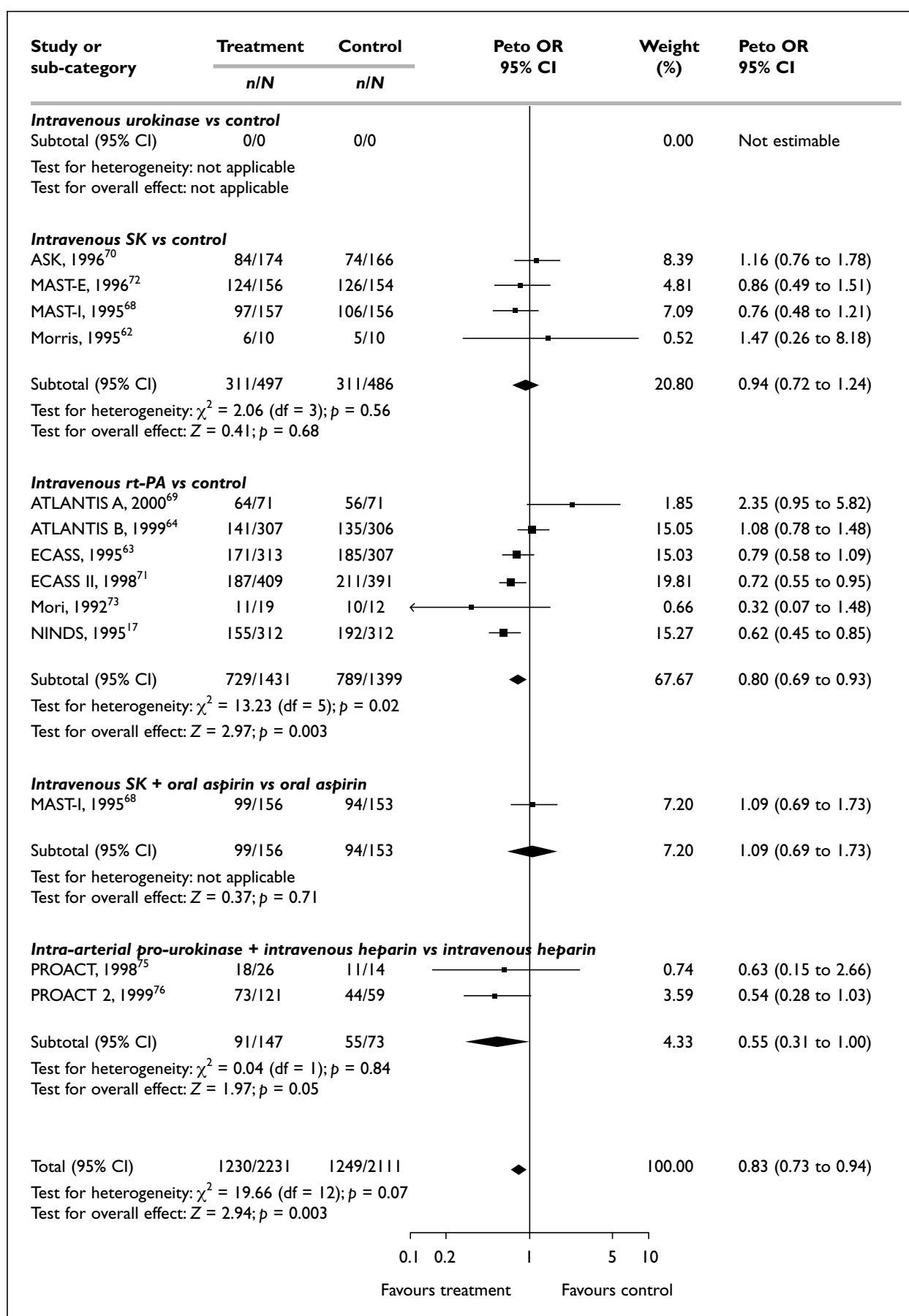


FIGURE 5 Effects of thrombolytic therapy on death or dependency at the end of trial follow-up

- thrombolytic drug used
- concomitant antithrombotic drug usage
- pre-randomisation severity of stroke among patients randomised based on the case fatality in the control group.

We also examined the extent to which time to treatment modified the estimates of treatment effect on death or dependency, and death by the end of follow-up.

Thrombolytic drug

Indirect comparisons of the treatment effect did not show statistically significant differences (on case fatality at the end of follow-up) between trials of urokinase (OR = 0.71), SK (OR = 1.43) and rt-PA (OR = 1.17). However the CIs were wide, reflecting the relatively small sample sizes. It is possible that the heterogeneity was due to factors other than thrombolytic drug used, as there are numerous other important methodological differences between these trials. For example, the dose and drug administration regimens differed, mainly between trials using UK and those using SK and rt-PA, but this precluded the analysis of the effect of dose. Direct randomised comparisons would be required to decide which drug at which dose has least hazard (and most benefit). Alternatively, an integrated comparison based on individual patient data might help.

Concomitant antithrombotic drug use

It is not possible to comment on the effect of aspirin use prior to the stroke; although some trials recorded prior aspirin use, data could not be extracted from the publications. The interaction between thrombolytic drugs and antithrombotic drugs given simultaneously (or the latter very soon after the former) was only tested by random allocation in the MAST-I trial,⁶⁸ which therefore provides the only valid evidence. In MAST-I there was a clinically important adverse interaction between aspirin and SK when given simultaneously, resulting in a substantial increase in case fatality (early and late), which was not offset by a reduction in the number of dead or dependent patients by the end of follow-up (28% of those allocated to SK alone versus 43% of those allocated to SK plus aspirin were dead by the end of follow-up ($p < 0.001$), and 62% and 63% were dead or dependent, respectively (versus 68% in the control group)). The actual cause of the increase in early and total deaths with SK and aspirin appears largely to be due to neurological events. Aspirin with SK significantly increased the number of deaths in hospital from all causes (OR = 2.2; 95% CI, 1.3 to 3.8), from neurological causes (OR = 2.0;

95% CI, 1.1 to 3.7), and intracranial haemorrhage on CT scan or at post-mortem (OR = 2.2; 95% CI, 1.0 to 5.0) when compared with the group that received SK alone. There was no difference in deaths from neurological causes without intracranial haemorrhage, but note also that more patients in the SK plus aspirin group died of neurological causes without a CT scan or post-mortem, so could also have had an intracranial haemorrhage (i.e. the increase in intracranial haemorrhage with aspirin and SK may be even greater^{68,80}). Valuable information is also available on antithrombotic drug use in eleven other trials,^{17,61,63,64,69,70,72,73,75,76,79} and some further data in three other trials.⁶⁵⁻⁶⁷ There is a trend towards increased case fatality the more frequent and nearer to the administration of thrombolysis the concomitant antithrombotic drug is administered (OR = 1.95 when all patients received antithrombotic drugs within 24 hours of thrombolysis; OR = 1.27 when some patients received antithrombotic drugs within 24 hours; OR = 1.14 when no patients received antithrombotic drugs within 24 hours but some thereafter; and OR = 0.89 for no antithrombotic drugs within the first 10-14 days). Although these data are based mainly on non-randomised comparisons, they do support the evidence of a clinically significant adverse interaction between thrombolysis and antithrombotic drugs given concurrently as found in MAST-I,⁶⁸ and may go some way towards explaining the heterogeneity between the trials for case fatality.

Severity of stroke among randomised patients

There was no obvious statistically significant difference in the effect of thrombolysis on case fatality between trials with a case fatality rate less than 19% in the control group (OR = 1.3) and those with a case fatality rate greater than 20% in the control group (OR = 1.13). However this may mask an important relationship between stroke severity and hazard with thrombolysis, as the risk of thrombolytic treatment was much greater in the trials that randomised a greater proportion of patients with severe strokes based on the case fatality rate in the control group (e.g. MAST-E,⁷² OR = 1.41) compared with those where there was a greater proportion of mild strokes (e.g. Abe and co-workers,⁶⁷ OR = 0.98). The relationship with stroke severity requires individual patient data for proper analysis.

Does time to randomisation modify effect on death or dependency?

Two trials included only patients who could be randomised and start treatment within 3 hours of

the stroke.^{17,61} Data are available from five other trials on the sub-group of patients randomised within 3 hours.^{63,68,70,72,79} The data are limited and strongly influenced by the NINDS trial, which contributed more patients to the analysis of treatment within 3 hours of stroke than the other trials combined. There are also likely to be imbalances in baseline variables between the thrombolysis and control patients as evidenced by the small and uneven numbers of patients. These data should therefore be regarded with extreme caution and require confirmation in future trials. There was a significant reduction in the number of patients dead or dependent with thrombolysis within 3 hours (54.8% of those allocated to thrombolysis were dead or dependent compared with 67.2% of those allocated to control: OR = 0.59; 95% CI, 0.46 to 0.74; $2p = 0.00002$). In absolute terms, if confirmed, this would be equivalent to 125 (95% CI,

71 to 178) fewer dead or dependent patients per 1000 treated with thrombolysis, and would be highly important clinically.

To compare these data on the effects of treatment given within 3 hours with the effects when given after 3 hours, we examined only those trials that reported data for both time windows.^{63,68,70,72,79} There was no significant difference in the proportion dead or dependent with thrombolytic treatment given within 3 hours (OR = 0.70; 95% CI, 0.50 to 0.97) and between 3 and 6 hours (OR = 0.98; 95% CI, 0.84 to 1.14), although there is a trend towards better outcome with earlier treatment. In trials using rt-PA alone, there was a similar non-significant trend to greater benefit when given within 3 hours (OR = 0.69; 95% CI, 0.44 to 1.09), compared with after 3 hours (OR = 0.88; 95% CI, 0.73 to 1.06) (Figure 6). The fact

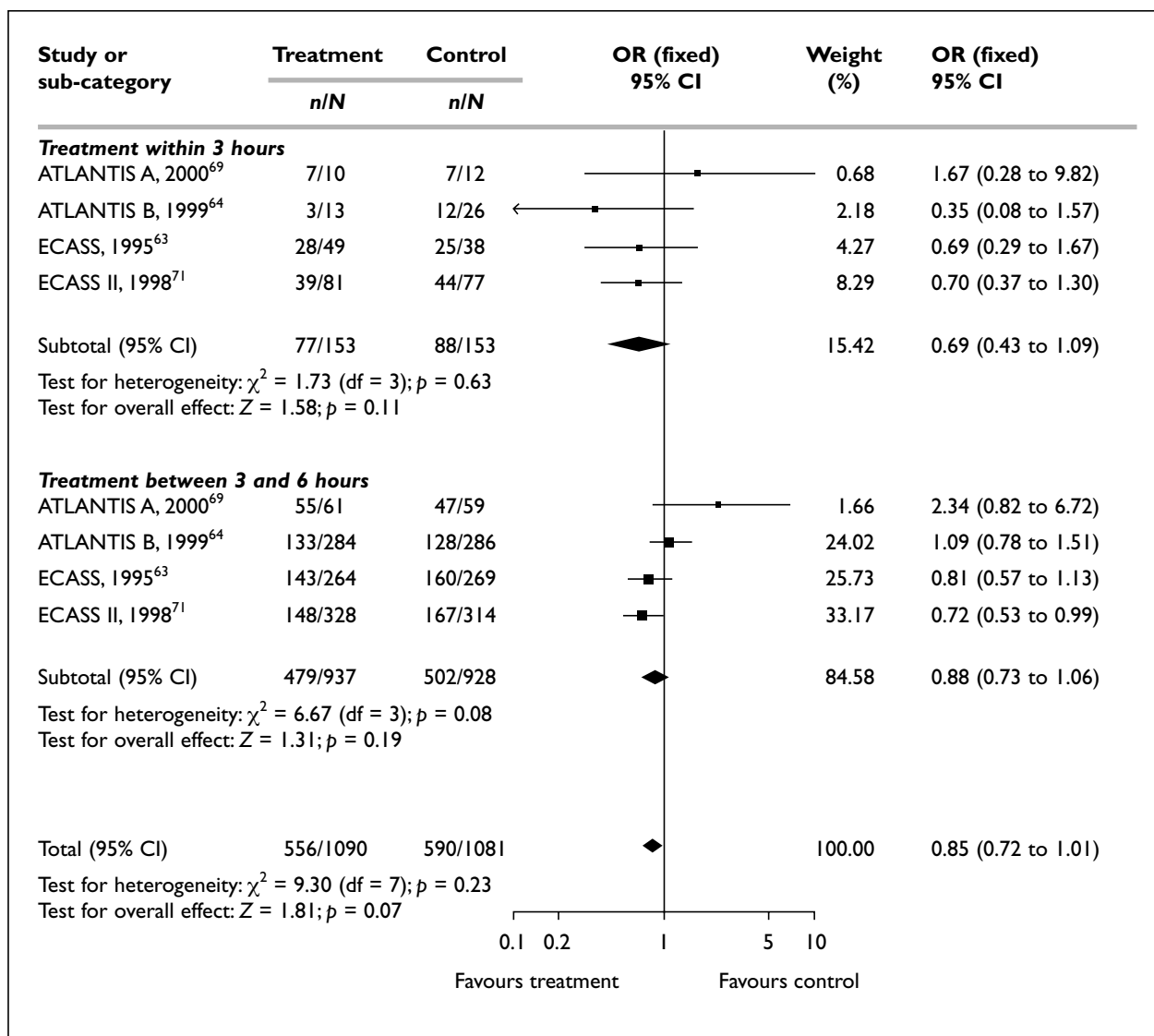


FIGURE 6 Effect of thrombolytic therapy on death or dependency among patients included in trials of rt-PA with inclusion criteria of 0–6 hours, subdivided by time to randomisation. (This criterion excludes the NINDS trial, which only recruited patients 0–3 hours after onset¹⁷)

that this trend did not reach statistical significance should not be interpreted to mean that time to treatment, within 6 hours, is unimportant, but rather that some third factor may have partly confounded the association between time and outcome, or interacted with the effect of thrombolytic treatment and with time.

This type of analysis, based on summary data, has the major limitation in that it does not adequately adjust for co-variables (such as time and baseline stroke severity). An analysis based on individual patient data could provide better (but still incomplete) adjustment for potential confounders and for baseline imbalance. We were not permitted access to the individual patient data from the trials of rt-PA, so were unable to perform such an analysis ourselves. However, an individual patient data meta-analysis of the rt-PA trials has recently been presented, but not published. The detailed final results therefore cannot be cited at present, but they did provide stronger evidence that the benefits of rt-PA are indeed time-dependent, even after adjustment for co-variables. However, the authors noted that it would require a further trial recruiting patients 0–6 hours, including at least 5440 patients, 1400 of whom should be recruited under 3 hours, to confirm or refute their findings (Brott T, University of Jacksonville, Florida: personal communication, February 2002). In that analysis (which included the NINDS trial), the CI for the effects of treatment within 3 hours were wide, and included the possibility of only modest benefit.

Methodological weaknesses and problems with execution of NINDS trial

The NINDS trial suffered from some technical mishaps and methodological problems, which only came to light in the final editorial stages of preparing this review. Details of the trial analyses were made available at (<http://www.fda.gov/cber/products/altegen061896.htm>) on the Food and Drug Administration (FDA) website. The problems are detailed below.

- The documents show that the 1995 publication was not, as stated in the manuscript, an unbiased ITT analysis, but a potentially more biased on-treatment analysis (such analyses generally produce a more favourable estimate of treatment effect).
- There was considerable imbalance in stroke severity at baseline with the placebo group including a larger proportion of severe strokes. Unfortunately, the analyses presented by the NINDS investigators in their 1995 and sub-

sequent reports have not adequately adjusted for baseline imbalance.

- Each centre held envelopes with the unblinded treatment allocation, and hence did not assure adequate concealment of treatment allocation, a well-known further potential source of bias.
- The trial did not employ an effective system of stock control and delays in restocking centres lead to centres using the wrong type of treatment (e.g. active instead of placebo) in at least 13 patients and, in a further 18, a box from the wrong time stratum. This represents a treatment error rate of at least 3.5%. This further complicates the interpretation of the trial results.

In our view, these problems do not invalidate the trial results, but they do indicate that some biases may have been introduced which may have led the NINDS trial to over-estimate the benefits of rt-PA. In the light of these problems a sensitivity analysis, which excludes the trial, is justified (*Figure 6*).

Does time to randomisation modify effect on death?

Data are available for nine trials. The NINDS trial contributes 50% of the data (624/1256 patients). There was a very modest, non-significant excess of deaths during follow-up with thrombolysis, of 22.1% of patients allocated to thrombolysis versus 19.8% of those allocated to control (OR = 1.14; 95% CI, 0.87 to 1.51). If confirmed in future trials, this would be equivalent to 22 extra deaths per 1000 patients treated with thrombolysis (95% CI, 22 less to 65 more). In trials using rt-PA, the equivalent figure was four fewer deaths per 1000 (95% CI, 52 fewer to 44 more). To compare treatment within with treatment after 3 hours, a similar analysis to *Figure 6* above was performed. There was no difference in treatment effect between those treated within 3 hours (OR = 1.66; 95% CI, 1.12 to 2.45) and between 3 and 6 hours (OR = 1.57; 95% CI, 1.30 to 1.91) after the stroke. For trials testing intravenous rt-PA, the relative excess of deaths was similar for patients treated within 3 hours (OR = 1.75; 95% CI, 0.91 to 3.36) and between 3 and 6 hours (OR = 1.38; 95% CI, 1.05 to 1.82).

Discussion

There is now substantial evidence on the immediate hazards and the apparent net benefit of thrombolytic therapy in the treatment of acute ischaemic stroke. Overall, thrombolytic therapy was associated with significant excesses of:

- deaths within the first 7–10 days
- symptomatic and fatal intracranial haemorrhages
- deaths by the end of follow-up.

However, disability was reduced in survivors, so overall there was a significant net benefit in terms of the outcome dead or dependent. For every 1000 patients treated with thrombolysis, 43 avoided death or dependency. Trials of intravenous rt-PA contributed the most data to this review, and in indirect comparisons, rt-PA appeared somewhat more favourable. Treatment with rt-PA was associated with a non-significant excess of early deaths and deaths by the end of follow-up, and a significant excess of symptomatic intracranial haemorrhages, but significantly more patients avoiding dependent survival – for every 1000 patients treated with intravenous rt-PA, 55 avoided death or dependency when treated up to 6 hours after stroke. This result is statistically and clinically highly significant.

The excess of early deaths with thrombolytic therapy appears to be due mainly to intracranial haemorrhage. Fatal intracranial haemorrhage was increased about five-fold by thrombolytic therapy and symptomatic intracranial haemorrhage about four-fold.

The effects of thrombolysis on death at the end of follow-up were less clearly consistent between trials. Early case fatality was increased by about two-fold in trials for which the data were available. But, by the end of follow-up, in eleven trials (including the MAST-I patients allocated to SK alone) thrombolysis was associated with a (non-significant) reduction in case fatality, and in six trials (including the MAST-I patients allocated to SK plus aspirin) with an increase (some significant) in case fatality. Overall thrombolysis significantly increased case fatality (about an extra 37 deaths per 1000 patients treated). The data were rather scanty, but the excess with intravenous rt-PA or intra-arterial rpro-urokinase was rather smaller, and with intravenous SK plus aspirin somewhat larger. The limited exploration of reasons for this heterogeneity, which has been possible with the data available so far, suggest that case fatality (the hazard) with thrombolytic treatment may be increased by concomitant use of antithrombotic drugs within 24 hours of thrombolysis and randomisation of mainly severe strokes with a high case fatality in the control group. For patients randomised within 3 hours of onset, the data are scanty and the estimates of the effect of treatment on death are imprecise. The point estimate is consistent with little or no net effect on death,

but also one cannot reliably exclude the possibility of an increase in deaths. Given this degree of uncertainty, even among patients randomised within 3 hours, it is difficult to support the routine use of thrombolysis within 3 hours of stroke onset suggested in several guidelines.

Furthermore, only one trial has reported effects on survival up to 1 year; the remainder related to survival up to 3 or 6 months. Longer-term follow-up data on survival and disability would help to provide better estimates of the cost-effectiveness of the treatment. For example, if the advantage of thrombolysis over control, in terms of survival free of disability was still evident a few years later (rather than just a few months) then the greater potential health gain would make the early hazard easier to accept.

The interaction between aspirin and thrombolytic therapy (SK) was only tested by random allocation in the MAST-I⁶⁸ trial. Although the number of patients was small (about 155 patients in each treatment group), there was a highly statistically and clinically significant adverse interaction between aspirin and SK, which increased case fatality at all stages. Although it appears that aspirin and SK given within a short time of each other are hazardous, there is no information on the effect of thrombolysis if patients are taking aspirin at the time of their stroke, or on when it might be safe to start aspirin after the stroke.

The time window beyond which there is unlikely to be any benefit (or too much hazard) with thrombolytic therapy is unclear. The NINDS rt-PA trial, which randomised patients within 3 hours of the stroke, showed a significant reduction in the number of patients dead or dependent and a non-significant reduction in case fatality during follow-up (but the data on early case fatality have not been published). Treatment with rt-PA has been licensed by the US FDA (and in countries that follow the US FDA guidelines) and recently in Canada (with application under consideration in Europe) for treatment of acute ischaemic stroke if given within 3 hours and only in patients similar to those included in the NINDS trial. However, the 3-hour time window is only one possible factor to explain the NINDS trial result. Other possibilities being considered are:

- minor imbalances in baseline stroke severity between the treatment groups
- strict avoidance of antithrombotic drugs within 24 hours of rt-PA

- use of a slightly lower dose of rt-PA than the dose of thrombolytic drugs used in the other recent trials
- rigorous control of the patient's blood pressure during the treatment infusion
- the particular type of hospital setting in which the trial was conducted
- or simply the play of chance.

There is no way of knowing what the trial result might have been if patients had been randomised between 3 and 6 hours using the same protocol. The sub-group of patients randomised within 3 hours of the stroke in the MAST-I⁶⁸ (patients allocated to SK alone), ASK,⁷⁰ ECASS I,⁶³ and ECASS II^{71,79} showed a similar reduction in the proportion of dead or dependent patients to the NINDS trial.¹⁷ In these trials, patients randomised between 3 and 6 hours after stroke showed some reduction in the number of dead or dependent patients (albeit non-significant). Thus the time window for benefit might extend to, or even beyond 6 hours in selected patients. There are several strands of evidence to indicate that the benefits of thrombolytic therapy are likely to be greater, the earlier the treatment is given:

- the pathophysiology of acute cerebral infarction in animals and man
- the limited evidence from trials of thrombolysis in stroke
- the very strong evidence of time dependency of benefit of thrombolysis for AMI.

There is general agreement that if thrombolysis is to be given for cerebral infarction, it should – as for myocardial infarction – be given as soon as possible. If rt-PA is licensed for acute ischaemic stroke in Europe, it is likely that the licence will stipulate that its use will be limited to patients who can be treated within 3 hours of onset. Therefore the debate is now more centred on:

- whether there is scope for benefit for patients who present more than 3 hours after onset
- the exact size of the benefit under 3 hours
- the effects on death from all causes
- among patients who present within 3 hours, but do not meet the criteria set out in some guidelines (e.g. aged over 80 years), whether there is scope for net benefit.

There is little information on which thrombolytic drug and at what dose might have most benefit and least hazard. Direct randomised comparisons would be required.

There is little information yet on the effect of thrombolytic therapy in the elderly, in whom stroke is most common. Of the recent trials, only three^{17,68,72} did not have an upper age limit. All the other rt-PA trials had an upper age limit of 80 years, and the NINDS trial included very few patients older than 80 years.

There is a suggestion that the presence of a visible recent infarct on the CT scan prior to randomisation may be related to increased hazard (risk of intracranial haemorrhage and death) but this was based on a *post hoc* analysis of the CT scans in ECASS I in which the baseline CT scans were not read blind to follow-up CT scans. Some trials had CT-visible infarction exclusion criteria and some, including the NINDS study, did not. The reported rate of CT-visible infarction varied between trials, either reflecting differences in patient selection, observer sensitivity, or definition of visible infarction signs. There is no information on other possible risk factors on the CT scan for intracranial haemorrhage with thrombolytic therapy (such as evidence of small-vessel disease), which should be addressed in future trials.

The trials included in this review are small in comparison with the trials of thrombolytic therapy in myocardial infarction. Trials with small sample sizes are prone to imbalances in important prognostic factors. In this review, it appears there may be imbalances between the treatment groups in baseline variables, which might contribute to the apparent treatment effect and overall trial result (particularly as three of the trials stopped early and well short of their planned sample size targets). For example, in MAST-E more patients allocated to SK treatment received antithrombotic drugs than those allocated to control.⁷² Individual patient data would be required to examine the interaction of these and other baseline variables with the effect of thrombolytic therapy, which may help to overcome some of the problems with imbalances between the treatment groups.

A more detailed individual patient data meta-analysis of the SK trials using data from MAST-E, MAST-I and ASK has been published by the Thrombolysis in Acute Stroke Pooling Project.^{81,82} The authors commented that, from the indirect comparisons available in the Cochrane review, SK appeared rather less promising than rt-PA. Their analyses suggested only a few factors that might modify the effect of SK, and that if further trials of the agent were planned, a number of

design features would be important: earlier administration, avoidance of concomitant aspirin and the use of lower doses.⁸² A similar meta-analysis is planned of data from the rt-PA trials by the ECASS, NINDS and ATLANTIS investigators.

This Cochrane review of thrombolysis for ischaemic stroke is based on data from just over 5000 patients – a very small number in relation to the global burden of the disorder (perhaps six million ischaemic strokes per year worldwide). The centres that took part in the trials reviewed were particularly interested in, and familiar with, the investigation and management of acute stroke. To extrapolate these results to thrombolysis when used more widely in routine clinical practice in less-specialist centres could result in much greater hazard and thereby reduce or completely negate any potential benefit. Much more information is needed on:

- how to select patients (to maximise benefit and minimise hazard)
- the influence of stroke severity, stroke sub-type, age, time from onset, concomitant use of

antithrombotic drugs, choice of thrombolytic drug, dose and route of administration

- which CT scan appearances before thrombolytic drugs should be used to guide patient selection.

Randomised trials to specifically examine the effect of age, stroke severity, prior aspirin use, CT scan appearance, the interaction with time from stroke, and in different care delivery environments are the best means of providing such data.

This present version of the review is the result of an ongoing process involving the collaborative effort of many researchers worldwide and the principal investigators of many of the thrombolysis trials. It should be noted that it has not been possible to achieve a consensus among all of the reviewers on the inclusion of the earlier thrombolysis studies because of their methodological differences (they tended to use lower doses of thrombolytic drug and randomised up to 2 weeks after stroke onset).⁶⁵⁻⁶⁷ At present this review represents all of the evidence from the RCTs on the effects of thrombolytic therapy on acute ischaemic stroke.

Chapter 3

Systematic review of trials of neuroprotective agents

Background

Rationale for neuroprotection

There are many points in the pathophysiological cascade between the occlusion of a cerebral artery and irreversible neuronal cell death where pharmacological intervention might be beneficial.^{83,84} There is no generally agreed definition of a neuroprotective drug, but in the context of acute stroke, the aim of this class of agents is to limit the volume of brain damaged by ischaemia.⁸⁴ When a specific neuroprotective agent is used in animal models, it is possible to show that the agent reduces the volume of brain damaged by infarction.^{83,85} In animal models, the effect of treatment is generally assessed by pathological examination of the brain, to measure the boundary of the infarcted area and so calculate the infarct volume. Assessed this way, the effects of these agents seem large.⁸³ The pharmaceutical industry has been able to identify a very large number of compounds for clinical development and testing in human acute stroke.^{86,87} Some agents may be effective both in patients with primary intracerebral haemorrhage and in those with cerebral infarction (in which case, treatment could be started immediately, while brain CT is awaited, or even before admission to hospital). Some agents are relatively simple to administer, with a short intravenous infusion lasting only a few hours, whereas others may require infusions to be maintained for several days or require careful electrocardiographic monitoring to detect prolongation of the QT interval, which may herald serious cardiac arrhythmias.

Methodological considerations

The problem, however, comes in assessing neuroprotective drugs in humans, where the measure of outcome is clinical and there are many factors that could cloud the assessment of the effect of the drug.⁸⁶ Three specific points are worth making.

- There are a number of steps to be taken between first identifying a promising agent during pre-clinical testing in animals and man before any large scale clinical trials are

mounted; greater attention to achieving these milestones might increase the chances of a successful clinical development and licensing of a neuroprotective drug.⁸⁷

- There may be a good case for testing agents in both ischaemic and haemorrhagic stroke.⁸⁶
- Trials should have sufficient power to detect moderate treatment effects, as even modest short-term benefits may yield surprisingly large gains in quality-adjusted survival in the long term. Such gains could make neuroprotective agents potentially very cost-effective.^{34,88}

No products licensed for clinical use by January 2001: implications for this review

At the time the topic for this review was identified in 1998, it seemed likely that at least one neuroprotective agent would be licensed for use in man within a year or so, indicating the need for a systematic review of the available evidence of any agents likely to enter clinical use in the near future. However, this has not occurred, and at the time the main searches for this review were completed (19th January 2001), no licensed compound was identified. At the time the report was submitted for final editorial approval, in March 2002, no compound was licensed (or likely to be licensed). There does not appear to be any immediate prospect of a compound gaining a licence.⁸⁹ This has several implications for this section of the review.

- As none of the compounds identified and tested in commercially-sponsored completed Phase III trials are to be licensed, none will be available soon for use in the NHS for the treatment of acute stroke. It would therefore be of little value to assemble detailed quantitative reviews of trial data for compounds that are no longer in clinical development.
- Even if each individual trial of a particular agent did not demonstrate net benefit at the level pre-specified in the protocol, it is possible that a quantitative systematic review might show evidence of overall net benefit (though smaller than had been anticipated at the planning stage of the trial).

- If a meta-analysis of several inconclusive trials of a neuroprotective agent whose clinical development had been terminated showed evidence of moderate benefit, it is possible that it might eventually be licensed. However, even if estimates of efficacy were available for such an agent, it would be difficult to obtain realistic estimates of costs, making reliable economic modelling impractical.

We therefore concluded that the most practicable approach was to:

- provide a qualitative summary of the field, citing quantitative systematic reviews, where available, to illustrate future possibilities
- make the results of our searches publicly available by electronic means in the Cochrane Controlled Trials Register (CCTR) in the Cochrane Library (we have exported the records from the Cochrane Stroke Group's Specialist Register of Trials to CCTR).

Hypotheses tested in the review

In patients with acute stroke, can a licensed neuroprotective drug (or other neuroprotective strategy) reduce the proportion of patients with a poor outcome (outcome assessed at least 3 months after stroke onset) without unacceptable side-effects?

Methods

Search strategy

The Cochrane Stroke Group's Specialised Register of Trials was searched for reports that met the following criteria:

- report of an RCT or controlled clinical trial (CCT), and
- the trial included patients with acute stroke, and
- evaluated agents that were coded as either neuroprotective or calcium antagonists.

(See chapter 2 *Methods* for a description of the methods used to assemble the trials register.)

Details of interventions included in review

The agents that appear to have been evaluated in clinical trials are listed in *Table 2*. Some of the studies have not been published, but some details of these may be found at <http://www.strokecenter.org/trials/>. Systematic reviews were available for several agents (see below).

Results

Completed systematic reviews of specific agents

21-aminosteroids (*tirilazad*)

Tirilazad is a non-glucocorticoid, 21-aminosteroid that inhibits lipid peroxidation. Studies in experimental models of ischaemic stroke had suggested that tirilazad has neuroprotective properties. As a result, clinical studies were undertaken to assess the safety and efficacy of tirilazad in the treatment of acute ischaemic stroke. A systematic review of the RCTs that assessed the safety and efficacy of tirilazad in patients with acute ischaemic stroke has been published.^{90,91} Trials of tirilazad were identified from searches of The Cochrane Library and communication with Pharmacia & Upjohn, the manufacturer of tirilazad. Data relating to early and end-of-trial case fatality, disability (Barthel Index and Glasgow Outcome Scale), phlebitis, and corrected QT interval were extracted by treatment group from published data and company reports and analysed by using the Cochrane Collaboration meta-analysis software Revman. Six trials (four published, two unpublished) assessing tirilazad in 1757 patients with presumed acute ischaemic stroke were identified; all were double-blind and placebo-controlled in design. Tirilazad did not alter early case fatality (OR = 1.11; 95% CI, 0.79 to 1.56) or end-of-trial case fatality (OR = 1.12; 95% CI, 0.88 to 1.44). A just-significant increase in death and disability, assessed as either the expanded Barthel Index (OR = 1.23; 95% CI, 1.01 to 1.51) or Glasgow Outcome Scale (OR = 1.23; 95% CI, 1.01 to 1.50) was observed. Tirilazad significantly increased the rate of infusion-site phlebitis (OR = 2.81; 95% CI, 2.14 to 3.69). Functional outcome (expanded Barthel Index) was significantly worse in pre-specified sub-groups of patients: all females (OR = 1.46; 95% CI, 1.08 to 1.98) and patients receiving low-dose tirilazad (OR = 1.31; 95% CI, 1.03 to 1.67); a non-significantly worse outcome was also seen in patients with mild-to-moderate stroke (OR = 1.40; 95% CI, 0.99 to 1.98). Tirilazad mesylate increases death and disability by about one-fifth when given to patients with acute ischaemic stroke. The reviewers concluded that there is no indication to use tirilazad and that further trials of tirilazad are not warranted. However, analysis of individual patient data from the trials might help elucidate why tirilazad appears to worsen outcome in acute ischaemic stroke.

Corticosteroids

Much of the brain swelling in ischaemic stroke is due to cytotoxic oedema, which is related to cell membrane dysfunction. Early treatment with

TABLE 2 Neuroprotective agents

Class of agent	Name
Calcium channel antagonists	DP-b99 Nimodipine Flunarizine
Free radical scavengers – antioxidants	Ebselen Tirilazad
GABA agonists	Clomethiazole Diazepam
Glutamate antagonists AMPA antagonists	GYKI 52466 NBQX YM90K YM872 ZK-200775 (MPQX) SYM 2081
Kainate antagonist	
Competitive NMDA antagonists CGS 19755 (Selfotel) NMDA channel blockers	AR-R15896 Aptiganel (Cerestat) Dextrorphan Dextromethorphan Magnesium Memantine MK-801 NPS 1506 Remacemide
Glycine site antagonists	ACEA 1021 GVI50526
Polyamine site antagonists	Eliprodil Ifenprodil
Growth factors	Fibroblast Growth Factor
Leukocyte adhesion inhibitor	Anti-ICAM antibody (Enlimomab) Hu23F2G
Nitric oxide inhibitor	Lubeluzole
Opioid antagonists	Naloxone Nalmefene
Phosphatidylcholine precursor	Citicoline (CDP-choline)
Serotonin agonists	Bay x 3072 Repinotan
Sodium channel blockers	Fosphenytoin Lubeluzole 619C89
Potassium channel opener	BMS-204352
Mechanism unknown or multiple actions	Cerebrolysin Piracetam Lubeluzole

Note: The Cochrane Stroke Group is in regular communication with the register of ongoing trials held at the Stroke Center at Washington University website. Interested readers who wish to obtain further details of current studies on-line should go to: <http://www.strokecenter.org/trials/>
(Date website last accessed 30th March 2001)
GABA, gamma-aminobutyric acid; AMPA, alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; NMDA, N-methyl-D-aspartate

corticosteroids may help reduce the swelling and hence improve the outcomes after a stroke. High-dose corticosteroids may also have neuroprotective effects. A Cochrane systematic review has been published, which last had a substantive amendment on 27 October 1998. Scrutiny of the Cochrane Stroke Group trials register in January 2001 when the searches for this report were prepared, did not identify any additional relevant studies. The objective of this review was to assess the effect of corticosteroids in acute presumed ischaemic stroke. The authors searched the Cochrane Stroke Group trials register and contacted investigators in the field. Published randomised trials comparing corticosteroids with placebo or control in people with acute (presumed or definite) ischaemic stroke were included. Trials were included if treatment began within 48 hours of stroke onset and if clinical outcome was assessed. Two reviewers independently applied the inclusion criteria, assessed trial quality and extracted the data. Seven trials involving 453 people were included. Details of trial quality that may relate to bias were not available from most trials. No difference was shown in the odds of death within 1 year (OR = 1.08; 95% CI, 0.68 to 1.72). Treatment did not appear to improve functional outcome in survivors. Six trials reported neurological impairment but pooling the data was impossible because no common scale or time interval was used. The results were inconsistent between individual trials. The only adverse effects reported were small numbers of gastrointestinal bleeds, infections and deterioration of hyperglycaemia across both groups.

The reviewers concluded that there is not enough evidence to evaluate corticosteroid treatment for people with acute presumed ischaemic stroke. (Note: high-dose corticosteroids (intravenous methylprednisolone) are currently being evaluated as a treatment for patients with acute traumatic brain injury;^{92,93} if they prove effective and safe in that setting, then further trials in patients with ischaemic stroke may be warranted.)

Calcium antagonists

The sudden loss of blood supply in ischaemic stroke is associated with increased levels of calcium ions within neurones. Inhibiting this increase could protect neurones and is thought to reduce neurological impairment, disability and handicap after stroke. The Cochrane systematic review on the topic sought to determine whether calcium antagonists reduced the risk of death or dependency after acute ischaemic stroke.⁹⁴ The influence of different drugs, dosages, routes

of administration, time intervals after stroke and trial design on the risk of poor outcome was investigated. Relevant trials were identified in the Specialised Register of Controlled Trials (last searched in March 1999). All truly randomised trials comparing a calcium antagonist with control in patients with acute ischaemic stroke were included. Two authors assessed all trials and extracted the data. Poor outcome, defined as death or dependency in activities of daily living, was used as the main outcome. Analyses, where possible, were ITT analyses. Forty-six trials were identified, of which 28 were included (7521 patients). No effect of calcium antagonists on poor outcome at the end of follow-up (OR = 1.07; 95% CI, 0.97 to 1.18), or on death at end of follow-up (OR = 1.10; 95% CI, 0.98 to 1.24) was found. Intravenous administration of calcium antagonists was associated with an increase in the number of patients with poor outcome compared with oral administration (indirect comparisons). Comparisons of different doses of nimodipine suggested that the highest doses were associated with poorer outcome. Administration within 12 hours of onset was associated with an increase in the proportion of patients with poor outcome, but this effect was largely due to the poor results associated with intravenous administration. A subgroup analysis restricted to trials of nimodipine (given orally, at a dose of 120 mg/day) started within 12 hours of stroke onset, did not show a beneficial effect. The reviewers concluded there was no evidence to justify the routine use of calcium antagonists in patients with acute ischaemic stroke.

Piracetam

Piracetam has neuroprotective and antithrombotic effects that may help to reduce death and disability in people with acute stroke. A published Cochrane systematic review sought to assess the effects of piracetam in acute presumed ischaemic stroke.^{95,96} The authors searched the Cochrane Stroke Review Group trials register, MEDLINE (from 1965), EMBASE (from 1980), and BIDS ISI (from 1981), contacted manufacturers and handsearched 15 journals. A substantive amendment to this systematic review was last made on 26 January 1999. Randomised trials comparing piracetam with control, with at least mortality reported and entry to the trial within approximately 48 hours of stroke onset were included. Two reviewers extracted data and assessed trial quality and this was checked by the other two reviewers. Study authors were contacted for missing information. Three trials involving 1002 people were included, with one trial

contributing 97% of the data. Participants' ages ranged from 40 to 85, and both sexes were equally represented. Piracetam was associated with a statistically non-significant increase in death (31% increase; 95% CI, 81% increase to 5% reduction). This trend was no longer apparent in the large trial after correction for imbalance in stroke severity. Limited data showed no difference between the treatment and control groups for functional outcome, dependency or proportion of patients dead or dependent. Adverse effects were not reported. The reviewers concluded that there was some suggestion of an unfavourable effect of piracetam on early death, but this may have been caused by baseline differences in stroke severity in the trials. Piracetam does not appear to reduce dependency for stroke patients. A second Cochrane review, in preparation, is assessing the role of potentially neuroprotective drugs (including piracetam) on the recovery of language function after stroke.⁹⁷

Methylxanthines

The methylxanthine derivatives (pentoxifylline, propentofylline and pentifylline) are vasodilators. They also inhibit platelet aggregation and thromboxane A₂ synthesis, decrease the release of free radicals and may be neuroprotective. A Cochrane systematic review of these agent has been published and a substantive amendment to the review was last made on 11 June 1996.⁹⁸ However, the Cochrane review covers an area where no active research is taking place. It will be updated if relevant information becomes available, but scrutiny of the Cochrane Stroke Group trials register in January 2001 when the searches for the current report were prepared, did not identify any additional relevant studies. The Cochrane review of methylxanthines sought to assess the effect of intravenous or oral methylxanthines (pentoxifylline, propentofylline or pentifylline) in patients with acute ischaemic stroke. The reviewers searched the Cochrane Stroke Group trials register, MEDLINE (from 1965), EMBASE (from 1981), ISI (from 1981) and the Ottawa stroke trials registry and contacted drug companies. Randomised trials comparing pentoxifylline, propentofylline or pentifylline with placebo or control in patients with definite or presumed acute ischaemic stroke were included. Trials were included if treatment was started within 1 week of stroke onset. Two reviewers independently applied the inclusion criteria. Trial quality was assessed. Five trials were included. Four trials tested pentoxifylline in 763 people, and one tested propentofylline in 30 people. No trials of pentifylline were found. Early death (within

4 weeks) occurred in 34/408 (8%) patients given a methylxanthine drug compared with 49/385 (13%) given placebo (OR = 0.64; 95% CI, 0.41 to 1.02). This non-significant trend to fewer deaths was due mainly to one pentoxifylline trial that found a highly significant reduction in early deaths. Two trials reported early death or disability and found a non-significant reduction (OR = 0.49; 95% CI, 0.20 to 1.20). Late death (beyond 4 weeks) was reported in the propentofylline trial involving 30 patients, with no difference between treatment and placebo (OR = 0.70; 95% CI, 0.13 to 3.68). Data for neurological impairment and disability were not in a form suitable for analysis. Data on quality of life, stroke recurrence, thromboembolism and bleeding were not reported. The reviewers concluded that there was not enough evidence to assess the effectiveness and safety of methylxanthines after acute ischaemic stroke.

Vinpocetine

Vinpocetine, a vasoactive vinca alkaloid, is a synthetic derivative of apovincamine, and reported to be neuroprotective.⁹⁹ The Cochrane systematic review of the topic sought to assess the effect of vinpocetine in acute ischaemic stroke. The authors searched the Cochrane Stroke Group trials register (last searched in August 1999) and MEDLINE, and contacted researchers in the field and drug companies. Unconfounded randomised trials of vinpocetine compared with placebo, or any other reference treatment, in people with acute stroke were included. Trials were included if treatment started no later than 14 days after stroke onset. Two reviewers independently applied the inclusion criteria. One reviewer extracted the data that was then checked by the second reviewer. Trial quality was assessed. One trial involving 40 patients was included. Data for 33 patients were reported. No deaths occurred in the trial and no significant difference in dependency was shown between the treatment and placebo groups. No adverse effects were reported. The reviewers concluded there was not enough evidence to evaluate the effect of vinpocetine on survival or dependency of patients with acute stroke and that there was no indication to use it routinely (though the authors reported it is used quite widely for this purpose in eastern Europe, despite the lack of good evidence).

Cooling therapy

Observational studies in patients with acute stroke have shown an association between high body temperature and poor prognosis. The Cochrane review sought to assess the neuroprotective effects of cooling¹⁰⁰ when applied to patients with

acute ischaemic stroke or primary intracerebral haemorrhage.¹⁰¹ The authors searched the Cochrane Stroke Group trials register (last searched in March 1999), MEDLINE up to November 1998, EMBASE from January 1980 to November 1998. They contacted investigators, pharmaceutical companies and manufacturers of cooling equipment in this field. All had completed RCTs or CCTs, published or unpublished, where cooling therapy (therapy given by physical devices or antipyretic drugs primarily to lower body temperature independently of basal temperature at the beginning of treatment) was applied up to 2 weeks of an acute ischaemic stroke or primary intracerebral haemorrhage were to be included. Two reviewers independently searched for relevant trials. No randomised trials or controlled trials were identified; one placebo-controlled trial of metamizol is currently underway. The reviewers concluded there was no evidence from randomised trials to support the routine use of physical or chemical cooling therapy in acute stroke. As experimental studies showed a neuroprotective effect of hypothermia in cerebral ischaemia,¹⁰⁰ and hypothermia appears to improve the outcome in patients with severe closed head injury,¹⁰² trials with cooling therapy in acute stroke are warranted.^{100,103,104}

Gangliosides

Gangliosides may have a protective effect on the central and peripheral nervous systems. This Cochrane systematic review sought to assess the effect of exogenous gangliosides in acute ischaemic stroke.¹⁰⁵ The authors searched the Cochrane Stroke Group trials register (last searched in March 1999) and contacted drug companies. Randomised trials of gangliosides compared with placebo or standard treatment in people with definite or presumed ischaemic stroke and started within 15 days of symptom onset, were included. One reviewer applied the inclusion criteria. Two reviewers independently extracted the data. Trial quality was assessed. Eleven trials involving 2257 people were included. All the trials tested purified monosialoganglioside GM1. Only three trials described the randomisation procedure. Follow-up was between 15 and 180 days. Death at the end of follow-up showed no significant difference (OR = 0.91; 95% CI, 0.73 to 1.14). There was no difference shown between early (within 48 hours) and delayed treatment. For disability, two trials showed an improved Barthel Index score with gangliosides (weighted mean difference, 8.6; 95% CI, 1.2 to 16.0). In two trials, eight patients experienced adverse effects that led to discontinuation of ganglioside treatment, seven

had skin reactions and one developed Guillain–Barré syndrome. The reviewers concluded that there was not enough evidence to determine whether gangliosides are beneficial in acute stroke. Caution is warranted because of reports of sporadic cases of Guillain–Barré syndrome after ganglioside therapy. No further studies are warranted at present, until a comprehensive meta-analysis of individual patient data from the completed trials, examining the effects of treatment on disability and case fatality is available.¹⁰⁵

Nitric oxide donors (nitrates)

Nitric oxide has several effects on the brain and vascular system that may be beneficial in ischaemic stroke and useful in the management of hypertension in acute stroke. Some forms of nitric oxide synthase inhibition may also be beneficial. These agents are considered to be potentially neuroprotective.¹⁰⁶ However, high concentrations of nitric oxide are likely to be toxic to brain tissue. The objective of the Cochrane systematic review was to assess the effects of nitric oxide donors, L-arginine, or nitric oxide synthase-inhibitors in people with acute ischaemic stroke. A substantive amendment to this systematic review was last made on 29 August 1997. The authors searched the Cochrane Stroke Group trials register (July 1997), MEDLINE (for trials from 1965), EMBASE (from 1980) and ISI (from 1981), and contacted drug companies and researchers in the field. Randomised and quasi-randomised trials comparing nitric oxide donors, L-arginine, or nitric oxide synthase-inhibitors in patients within 1 week of onset of confirmed ischaemic stroke. Two reviewers independently applied the inclusion criteria. No completed trials were found. One small placebo-controlled trial of glyceryl trinitrate patches is underway. There is currently no evidence from randomised trials on the effects of nitric oxide donors, L-arginine, or nitric oxide synthase-inhibitors in patients with acute ischaemic stroke. However, a large-scale trial – the Efficacy of Nitric Oxide in Stroke (eNOS) trial – is now under way (Bath PM, University of Nottingham: personal communication, September 2002).

Details of systematic reviews in progress

A number of Cochrane systematic reviews of potential neuroprotective agents are in progress. Published protocols are available in The Cochrane Library for the following:

- antioxidants for acute stroke¹⁰⁷
- choline precursors for acute and subacute ischaemic and haemorrhagic stroke¹⁰⁸

- excitatory amino acid modulators for acute ischaemic stroke,¹⁰⁹ and
- lubeluzole for acute ischaemic stroke.^{110*}

Discussion

Many trials have been completed, but no neuroprotective drug has yet been found to have a sufficiently favourable balance of risk and benefit to be licensed for clinical use. This may have occurred for a number of reasons: the animal studies were not adequate,⁸⁷ benefits were smaller than predicted from the animal studies and hence the clinical trials were not powered to detect moderate effects,^{86,88} and unexpected toxicity. Neuroprotective drugs have a wide variety of adverse effects ranging from the minor (e.g.

small changes in blood pressure, or thrombophlebitis) to major (e.g. severe hallucinations, psychosis, major cardiac problems or severe hypotension, Guillain–Barré syndrome).^{84,105} However, the situation may change, and one of the neuroprotective compounds currently undergoing trials may gain a licence for use in acute ischaemic stroke in the next few years. It is probable that the extremely large reductions in cerebral infarct volumes achieved with neuroprotective agents in experimental animal models will translate into only moderate reductions in disability when used in human acute stroke. Nonetheless, modelling the effects of short-term benefits suggests that long-term gains in quality-adjusted survival could make neuroprotective agents very cost-effective, even if the immediate benefits appear quite small.³⁴

* This report has now been published in full.¹¹⁰

Chapter 4

Systematic descriptive study of barriers to effective acute stroke care

Background

Before an emerging medical treatment can be administered to a patient with acute stroke, a chain of events must take place. The sequence starts with the recognition of symptoms by the patient and ends when the administration of the agent is complete (and any complications from the treatment have been dealt with). Efficient acute stroke care and administration of early medical treatments within the time window may not be possible if there are undue delays or difficulties in the pathway of patient care. Delays can occur at any point along the pathway. Difficulties may arise through lack of expertise or simply lack of resources. In a particular hospital's stroke service, there may be several points where such barriers to effective care can be identified.¹¹¹ For example, undue delay in transferring a stroke patient to hospital and in performing a CT brain scan might mean that the patient was no longer eligible to receive thrombolytic therapy.¹¹² Efficient implementation of acute medical treatments such as thrombolysis will only be possible if the specific barriers are identified and dealt with in each hospital seeking to provide acute stroke care.

Methods

Objectives of this review

This section of the systematic review has two main objectives:

- to describe the reported barriers to early treatment of acute stroke patients, and
- to assess the effectiveness of any interventions designed to overcome specific barriers.

Criteria for considering studies for this review

Type of study

To identify potential barriers to efficient acute stroke care, prospective and retrospective observational studies were sought. All studies that assessed the nature or duration of the delays within the pathway of care were considered. Only studies published in English were considered due to

limited resources. The following types of publications were excluded:

- studies that were not original research (e.g. review articles)
- studies that observed or followed-up selected cohorts of patients who only received rt-PA or other specific acute medical treatment
- surveys of opinions (e.g. of paramedical staff)
- studies of very specialised groups of stroke patients (e.g. stroke patients with onset in hospital or who required helicopter transfer)
- observational studies of stroke patients where no data on delays or barriers were reported (e.g. cost-analysis studies, stroke registers).

To assess the effectiveness of interventions designed to overcome specific barriers, unconfounded RCTs were sought that compared an intervention versus none, or one intervention versus another. However, quasi-randomised trials, CCTs, before-and-after studies, and interrupted time series were also considered with due allowance for the large number of biases that are likely to be associated with non-randomised designs.^{113,114} Observational studies with no comparison group were also considered. However, only studies with an adequate description of their methodology were to be included.

Type of participant

All studies that recruited patients who had been admitted to hospital with new neurological deficit consistent with a clinical diagnosis of stroke were included in this part of the review. Studies that recruited all types of ischaemic and haemorrhagic strokes (including subarachnoid haemorrhage) were included, but studies that recruited **only** patients with subarachnoid haemorrhage were excluded, as the management of these patients (who often require neurosurgical intervention) would have been very different to the generality of stroke patients.

Categorising reported barriers to efficient acute stroke care

We anticipated that the published literature on this subject would use a very wide range of methods

and be of very variable quality. We also anticipated that many of the barriers identified in countries outside the UK might not be particularly relevant to the NHS. Thus we aimed to examine these publications and draw out the main themes that appeared to be common and potentially relevant, and then group results under these headings. We developed a classification by drawing up a list, circulating it among the authors, then modifying the list of categories in the light of the data.

Evaluation of interventions to overcome specific barriers

The aim was to assess the effectiveness of any intervention, compared with none or other interventions, in overcoming specific barriers to efficient acute stroke care. Therefore, all studies that attempted to evaluate such interventions, irrespective of research design were considered. We anticipated that there would be several types of interventions, for instance, educational programmes for the public and healthcare staff, training for paramedical staff to improve their accuracy of stroke diagnosis, and organisational interventions to streamline acute stroke care. In a study evaluating a specific intervention, the choice of outcome measure will depend on the nature of intervention tested and the types of barriers that they were designed to overcome. We therefore aimed to record outcomes which might provide a measure of the efficiency of an acute stroke service. For example, time delay from stroke onset to transfer to hospital, to obtain a CT scan, or to ward admission would be relevant. Other outcome measures of interest might include patients' knowledge of stroke or the proportion of patients treated with thrombolytic therapy within 3 hours.

Search strategy for identification of studies

Descriptive studies of barriers (and uncontrolled studies of interventions to overcome barriers)

To identify descriptive studies of barriers, MEDLINE (1990–2000) and EMBASE (1990–2000) were searched. MEDLINE and EMBASE databases were searched from 1990 onwards because emergency treatments for stroke such as thrombolysis only began to be implemented from the early 1990s and the first large RCT was published in 1995.¹⁷

Controlled trials of interventions to overcome barriers

To identify controlled trials, the trials register of the Cochrane Stroke Group,¹¹⁵ which, at that time, contained over 3800 references to 1900 CCTs was

searched (appendix 1). This trials register is a comprehensive register of all published and unpublished stroke trials that have been identified through overlapping electronic search strategies and handsearching. We also performed electronic searches of five major biomedical databases using the on-line information source the Scientific and Technical Network. Separate detailed search strategies were developed for each database, and a combined multifile search was run simultaneously, from the first available year of each database, using the advanced facility of automatic de-duplication across databases. Furthermore, the Central/CCTR of The Cochrane Library (year 2000, issue 3),¹¹⁶ which contains over 270,000 reports of trials, was searched. Titles, keywords and abstracts of all downloaded citations were screened and paper copies of those meeting pre-defined selection criteria were assessed in detail. Reference lists of relevant articles were also scanned. The following electronic search strategies were used.

- **Cochrane Stroke Group trials register.** In August 2000, we searched the Cochrane Stroke Group trials register using the following two intervention codes: 'service provision' and 'thrombolysis'. For more information on the search strategies used for the trials register, please visit the Cochrane Stroke Group module of The Cochrane Library (URL: <http://www.update-software.com/Cochrane/default.HTM>). This search identified a total of 200 possibly relevant studies.
- **Central/CCTR year 2000, issue 3.** Details of the search strategy and search terms used are given in appendix 2. This search identified a total of 3032 possibly relevant publications.
- **MEDLINE (Ovid) 1990–2000.** Details of the search strategy and search terms used are given in appendix 2. This search identified a total of 8856 possibly relevant publications.
- **EMBASE (Ovid) 1990–2000.** Details of the search strategy and search terms used are given in appendix 2. This search identified a total of 6473 possibly relevant publications.

Selection of papers for review

Two reviewers screened all the titles, abstracts and keywords of publications identified by the searches to assess their eligibility. Publications that clearly did not meet the inclusion criteria were excluded at this stage. Paper copies of the full publications that were possibly relevant were obtained. Two reviewers then assessed them according to our pre-specified selection criteria. We resolved any disagreement by discussion.

Assessment of methodological quality and data extraction

Two reviewers independently assessed the methodological quality of all included studies and recorded their findings on a data form, which recorded the important aspects of methodology such as study design and type of intervention and control. We did not use an overall scoring system to evaluate methodological quality. One reviewer then extracted data onto a pre-defined data extraction form.

Data analysis

This was a descriptive review and no formal quantitative analysis was planned. All information was presented in tables.

Details of studies included in the review

A total of 18,561 titles and abstracts were scanned and 112 publications were retrieved in full text. From these, a total of 61 studies published in English were included, 54 of which reported data on barriers to acute care and seven were studies of interventions to overcome barriers. Eight publications were abstracts and the remainder were full journal articles.

Details of studies of barriers to efficient acute stroke care

Fifty-four observational studies with a total of 39,030 patients were found. Of these, 23 studies were conducted in the USA or Canada, 20 in Europe, six in Asia, two in Israel, two in Australia or New Zealand, and one in South America. Fifteen studies stated that patients were consecutively recruited.¹¹⁷⁻¹³¹ Three studies recruited only patients with ischaemic strokes¹³²⁻¹³⁴ and one study recruited only patients with first-ever strokes.¹³⁵ The populations in all studies were hospital-based except in two studies which were community-based.^{127,136} The earliest study was published in 1991¹³⁷ and the most recent was in 2001.¹²⁰

The studies were divided into three main groups:

- studies that evaluated delay times (e.g. from stroke onset to arrival at hospital)
- studies that assessed the proportion of patients potentially eligible for thrombolysis
- studies that examined other parameters such as the accuracy of stroke diagnosis by paramedical staff or patients' knowledge of stroke.

Delay times were presented as means, medians, or percentages within a specified time (e.g. in one study, 61% of stroke patients arrived at hospital within 3 hours of onset¹³⁸).

There were several major deficiencies in the identified studies. First, there was a variation in the definition of the time of onset. The time of onset was defined in most studies as the time when symptoms were first noticed. However, if symptoms were noticed on waking, the time of onset was variably defined, for example as the time of waking, the midpoint between asleep and awakening, the time when the patient had no symptoms, or the time when the patient fell asleep. Some studies excluded these patients from analysis. Second, even in patients whose symptoms started while awake, the exact time of onset was not determinable or recorded. Again, the method of handling these missing data varied between studies. Third, delay times were truncated at different points in different studies (e.g. for one study 0-3, 4-6, 6-12, and over 12 hours, and for another study 0-12, 12-24, and over 24 hours). Furthermore, delay times were often reported as means without standard deviations, or as medians without interquartile ranges, making useful comparison between studies impossible. Finally, in most studies, there was little detailed description of the organisational setting within which acute stroke patients were managed, for example, whether stroke patients were admitted to an emergency department or directly to a stroke unit, or whether a specialist stroke team was involved in patient care. This information is important in order for the reader to understand the stroke management system and how barriers could be overcome.

Details of studies evaluating interventions to overcome barriers

There were no RCTs. Seven studies evaluated interventions but used a weaker research design, with a total of at least 3154 patients (one study published in abstract form did not state the number of recruited patients and so was not counted in the total¹³⁹). Of the seven non-randomised studies, two were uncontrolled before-and-after studies,^{139,140} two were comparative studies,^{121,141} and three were observational studies without a comparison group.¹⁴²⁻¹⁴⁴ Six studies were carried out in the USA and one in the UK, and all were hospital-based. Only one study stated that the patients were consecutively recruited.¹²¹ The earliest study was published in 1992¹⁴⁰ and the most recent in 1999.^{141,144}

None of the included studies were randomised. The reporting of methodology was generally satisfactory although again, the organisational setting within which acute stroke patients were managed was poorly reported. In general, the

interventions were adequately defined but, in the comparative studies, the control intervention was poorly defined or not defined at all. For example, in one comparative study, a new pager system was implemented to reduce delay in alerting the stroke team (the 'code stroke' system).¹²¹ In this study, the code stroke system and the method of its implementation were described in some detail, but there was no description of the alerting system that was in place prior to the implementation of the code stroke system.

None of the comparative studies reported patient characteristics in the treatment or control groups. Patient characteristics were reported in only two observational studies.^{143,144} Furthermore, it was unclear whether the implementation of the intervention was independent of other organisational changes over time, such as changes in the stroke referral system, opening of a new stroke unit, or implementation of a new CT scanner.

Details of excluded studies

Forty-nine publications were excluded for the following reasons:

- publications were not original research reporting new data (16 publications)
- no data on delays or barriers included (ten publications)
- studies included only patients treated with thrombolytic or other acute medical treatments (nine publications)
- dual publications (seven publications)
- surveys (three publications)
- studies of very specialised groups of stroke patients (two publications)
- studies of patients who did not have stroke (one publication)
- publication not in English language (one publication).

See appendix 3 for a list of excluded references.

Results

Barriers to efficient acute stroke care

Forty-five of the 54 studies described delays between one point in the path of care to another (Figure 7 and Table 3).

The commonest points of care for which delays were reported (in various combinations and permutations) were from stroke onset to arrival at hospital, from arrival to first medical assessment, CT brain scan, neurologist assessment, ward

admission, or administration of thrombolytic therapy. Some studies concentrated on the pre-hospital phase and identified delays involved in calling an ambulance, its arrival at the location of stroke onset, and transfer to hospital.

Studies usually reported delay times using means, medians and the proportions of patients within various delay time categories (most commonly 0–3, 4–6, 6–12 and more than 12 hours). For example, ten studies reported mean delay time from stroke onset to arrival at hospital.^{112,125,126,138,142,153–157} This ranged from 1.4 hours¹⁴² to 29 hours.¹²⁶ Ten studies reported mean delay time from arrival at hospital to CT brain scan.^{112,132,134,139,142,154,155,157–159} This ranged from 40 minutes¹³⁴ to 58 hours.¹³² In 25 studies, it was possible to perform a cumulative analysis of the proportion of patients in various delay time categories.^{112,117,120,123,124,126–128,131,135,136,138,143,155,156,160–169} For example, the proportion of patients who arrived within 6 hours of stroke onset was determinable for 20 of these 25 studies; this ranged from 35%¹¹⁷ to 80%.¹³⁸

Nine main categories of barriers were identified. The studies examining these barriers were assessed. Some studies analysed the strength of association between the presence of particular barriers and delay, and reported the results as ORs with 95% CIs. For the purpose of this review, we concentrated on the potentially modifiable barriers (e.g. patient's knowledge of stroke, use of ambulance) rather than the non-modifiable barriers (e.g. symptom onset on waking). Moreover, we only noted barriers for which data were reported; we excluded barriers for which the investigators did not provide explicit data.

The patient or family did not recognise symptoms of stroke or recognised them but did not seek urgent medical help:

Public knowledge about stroke is generally poor.¹⁷⁰ The patient or family are often unaware of the significance of symptoms or the urgency with which medical help should be sought. Moreover, the onset of stroke may occur during sleep and hence the symptoms will only be noticed when the patient awakes. In such patients, the precise time of onset is hard to categorise. Twenty-one studies identified this barrier.^{117,119,122–124,126,129,138,148,153,155–157,160,162,164,165,167,168,171,172}

These studies found substantial pre-hospital delays as a result of the patient or family not recognising the symptoms of stroke or not seeking urgent medical help. The commonest factors associated with this type of barrier were:

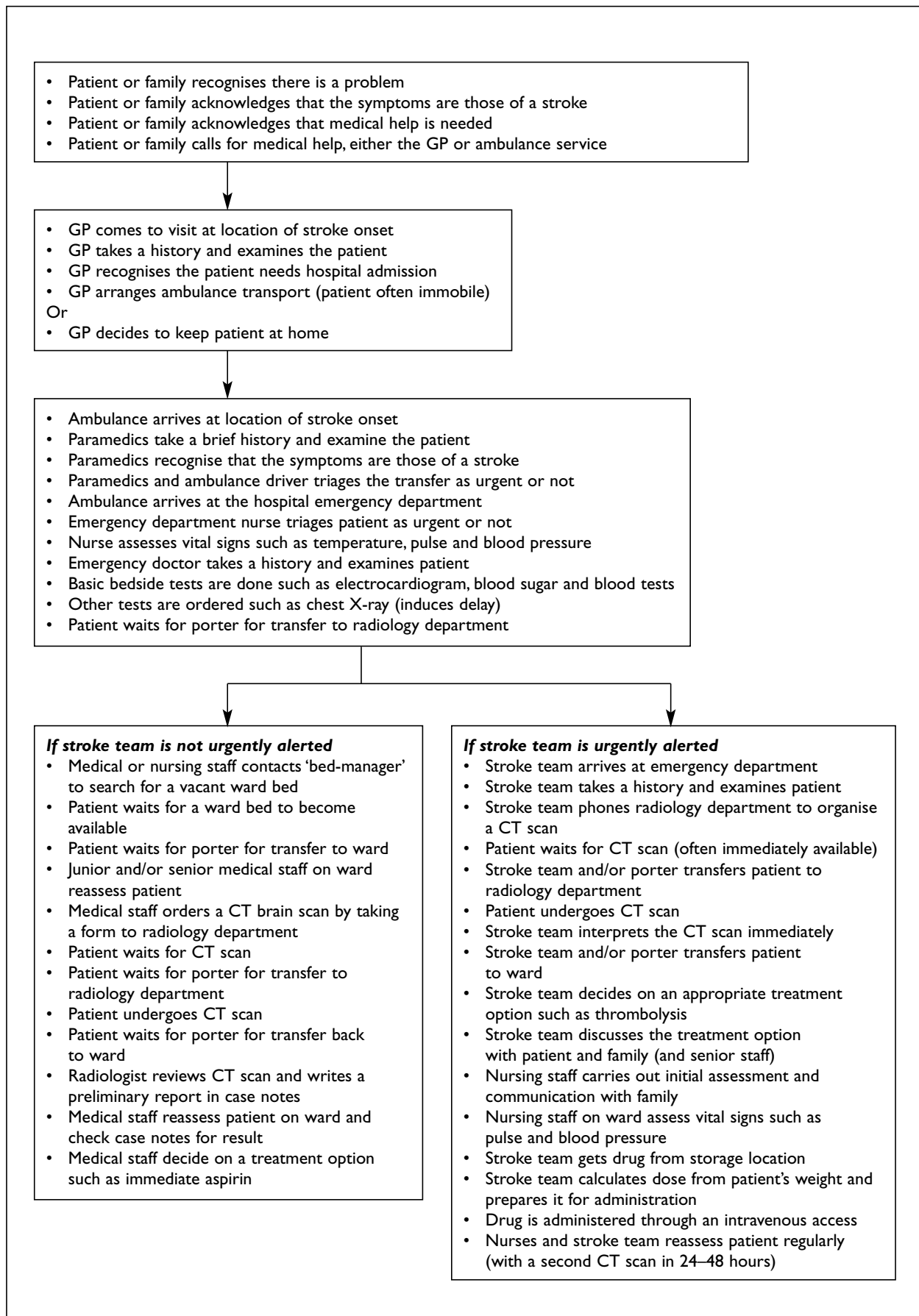


FIGURE 7 The pathway of acute stroke care (using thrombolysis as an example of acute treatment)

TABLE 3 Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Alberts et al., 1990 ⁶⁵ USA	Observational study	Hospital-based	457 stroke and TIA patients	Onset to arrival	Cumulative: 192/457 (42%) arrived < 24 h; 67% < 48 h; 92% < 7 days; 95% < 14 days Reasons for delay: stay at home hoping symptoms would get better; not realising it was a stroke; GP concludes 'nothing wrong' or does not admit to hospital	1 & 2
Herderschee et al., 1991 ¹³⁷ The Netherlands	Observational study	Hospital-based	120 stroke patients	Onset to ward admission	Median delay from first medical assessment to ward admission was 1 h; median total delay from onset to ward admission was 4 h Delay was less if onset in the morning	4 & 6
Harper et al., 1992 ¹⁶⁴ UK	Observational study	Hospital-based	535 stroke patients	Onset to first medical assessment	Delay times were known for 374/535 patients. Cumulative: delay from onset to first medical assessment: 101/374 (27%) < 3 h; 49% < 6 h; 74% < 12 h; 88% < 24 h; and 95% < 48 h; median delay was 6 h Delay was more if admitted via GP; onset at night, living alone, or patient older	1, 2 & 4
Kay et al., 1992 ¹⁶⁸ Hong Kong	Observational study	Hospital-based	773 stroke patients (excluding TIA, SAH or subdural haemorrhage)	Onset to CT scan	Cumulative: 63% arrived < 12 h; 76% < 24 h; and 85% < 48 h Delay was less if haemorrhage and more if lacunar stroke; delay also probably less because the older often live with the younger generations 51% of CT done < 24 h after arrival	1 & 5
Feldmann et al., 1993 ¹¹⁹ USA	Observational study	Hospital-based	100 consecutive stroke patients	Onset to first medical assessment	96% had known time of onset; mean delay from onset to first medical assessment was 13.4 ± 2.3 h (median 4 h) and from onset to neurologist assessment was 21.2 ± 2.9 h Delay to arrival was less if older, sudden onset of symptoms that remain stable, symptoms recognised by a bystander, and interpreted as stroke 69% arrived directly at emergency department, 28% via GP and 2% directly to neurologist	1, 4 & 6
Biller et al., 1993 ¹⁶⁷ USA	Observational study	Hospital-based	30 stroke patients	Onset to ward admission	Cumulative: 16/30 (53%) arrived < 3 h; 63% < 6 h; 73% < 22 h; and 83% < 24 h. 0/30 (0%) admitted to stroke ward < 3 h; 13% < 6 h; 47% < 12 h; and 73% < 24 h; mean delay from arrival to ward admission was 8.6 h Reasons for delay were lack of awareness by patients (only 33% thought they were having a stroke) and non-urgent approach by medical staff	1, 4 & 6
Malik et al., 1993 ¹⁷⁶ USA	Comparative study (no intervention introduced)	Hospital-based	170 stroke patients – 39 patients from 1986 and 131 patients from 1992	Arrival to first medical assessment	In 1992, mean delay from arrival to first medical assessment was 1.4 h (vs 0.5 h in 1986)	4

continued

TABLE 3 contd Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Ferro <i>et al.</i> , 1994 ¹²⁶ Portugal	Observational study	Hospital-based	309 consecutive stroke patients	Onset to CT scan	Delay times were known for 278/309 patients. Cumulative: 117/278 (42%) arrived < 6 h; 54% < 12 h; and 69% < 24 h Mean delay from onset to arrival was 29 ± 53.8 h (median 9.5); from arrival to first medical assessment was 0.7 ± 0.5 h (median 0.7); from arrival to neurologist assessment was 1.7 ± 1.2 h (median 1.7); and from neurologist assessment to CT was 3.3 ± 2.4 h (median 3.2)	1, 2, 3, 4, 5 & 6
Panayiotou <i>et al.</i> , 1994 ¹⁴⁷ UK	Observational study	Hospital-based	410 stroke patients	% eligible for acute stroke therapy < 12 h	Reasons for exclusion: 188/410 (46%) had delay > 12 h; 21% had pre-morbid disability; 20% too mild; 15% had other severe illness; 12% were drowsy or coma; 6% had haemorrhage on CT; 4.5% had brainstem stroke; 4% had abnormal electrocardiogram; and 3% had abnormal electrolytes; only 6% were eligible for acute stroke therapy < 12 h after onset	None
Anderson <i>et al.</i> , 1995 ³⁶ New Zealand	Observational study	Community-based	1803 stroke events (not stroke patients)	Onset to CT scan	Delay time from onset to arrival was known for 1008/1803 (83%) events. Cumulative: 216/1008 (21%) arrived < 1 h; 52% < 4 h; 76% by 24 h; and 85% by 48 h; median delay from onset to arrival was 3.5 h (2 h for haemorrhages and 4.3 h for infarcts)	5
Bratina <i>et al.</i> , 1995 ¹⁵⁴ USA	Observational study	Hospital-based	112 stroke patients arriving < 6 h of onset	Onset to neurologist assessment	545/1008 (42%) had CT (only 442 events had delay times to CT documented). Cumulative: 1% had CT < 1 h, 11% < 4 h, 37% < 24 h and 52% < 48 h. Median delay to CT was 66 h for infarcts, 14 h for PICH and 6 h for SAH Mean delay from onset to arrival was 1.9 ± 1.3 h, from arrival to triage was 0.2 ± 0.4 h, from arrival to first medical assessment was 1.2 ± 4.4 h, from arrival to CT was 1.7 ± 1.1 h, and from arrival to neurologist assessment was 2.1 ± 3.5 h Delays were less if stroke team involved	4, 5 & 6
Kothari <i>et al.</i> , 1995 ¹⁴⁵ USA	Observational study	Hospital-based	151 stroke patients	Onset to arrival	Delay times were known in 119/151 patients. Overall median delay from onset to arrival was 5.7 h. For those who called ambulance, median delay from onset to ambulance arrival was 1.7 h and from onset to arrival at emergency department was 2.9 h. Cumulative: 21/151 (14%) patients arrived < 1 h, 30% < 3 h, 40% < 6 h, 50% < 12 h, 61% < 24 h (21% unknown). Median delay from arrival at emergency department to first medical assessment was 0.3 h, from arrival to CT scan was 1.2 h, and from arrival to ward admission was 5.3 h. 50% arrived by ambulance Delay was less if ambulance transfer or white-race; 40% of patients sought medical help only after being advised by family or friend	1, 2, 3, 4, 5 & 6

continued

TABLE 3 contd Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Bartolini et al., 1995 ⁴⁶ Italy	Observational study	Hospital-based	150 stroke patients	% eligible for rt-PA	Using MASTI protocol, 8/150 (5.3%) received rt-PA within 6 h of onset. Reasons for excluding the remaining 142 patients were: delay in arrival > 6 h (32%); organisational problems (18%); haemorrhage on CT (13%); pre-morbid disability (25%); coma at onset (7%); and signs resolving (5%). Organisational problems included availability of CT scan and access to a ward willing to administer rt-PA	3, 4, 5 & 6
Liu et al., 1995 ³¹ China	Observational study	Hospital-based	187 consecutive stroke patients	Onset to arrival	Cumulative: 93/187 (50%) arrived < 3 h; 65% < 6 h; 78% < 12 h; 83% < 24 h; and 88% < 48 h Delay was less if haemorrhage	None
Jorgensen et al., 1996 ¹⁷ Denmark	Observational study	Hospital-based	1059 consecutive stroke patients. (1197 stroke patients screened but 40 excluded for unknown onset time and 98 for symptoms on waking)	Onset to arrival	Cumulative: 74/1059 (7%) arrived < 1 h; 25% < 3.5 h; 35% < 6 h; 48% < 12 h; and 68% < 24 h. Median delay from onset to arrival was 14 h Delay was less if stroke more severe or history of TIA; delay was more if living alone and retired status ORs reported	1
Pistoliato & Ermani 1996 ³⁸ Italy	Observational study	Hospital-based	348 stroke patients	Onset to ward admission	Mean delay from onset to arrival was 4.9 ± 8.9 h (median 2 h) and delay from onset to ward admission was 5.6 ± 9 h (median 2.5 h). Cumulative: 20% arrived < 1 h; 61% < 3 h; 80% < 6 h; and 90% < 12 h Delay to arrival was less if stroke more severe (reduced consciousness, greater handicap), greater awareness, and daytime onset, and haemorrhages; 12% had symptoms on waking	1
Fogelholm et al., 1996 ³⁵ Finland	Observational study	Hospital-based	363 first-ever stroke patients	Onset to arrival	Cumulative: 159/363 (43%) arrived < 6 h; 60% < 12 h; 71% < 24 h; and 84% < 48 h Delay from onset to arrival was less for SAH (median 3 h) or PICH (median 4 h) than infarct (median 10 h); delay was also less if patient arrived directly at emergency department, reduced consciousness, severe headache, vomiting at onset, or onset during afternoon or weekday	2
Tilley et al., 1997 ¹⁸ USA	Observational study	Hospital-based	17324 consecutive stroke patients (admitted < 24 h of onset)	Onset to rt-PA	Using the NINDS criteria, 1511/17324 (8.7%) were eligible for rt-PA < 3 h of onset, but only 620/17324 (3.6%) were treated Reasons for ineligibility were: onset too late (52%), symptoms improving rapidly (10%), haemorrhage on CT (8%), and others including (descending frequency): symptoms too mild, patient too old, co-morbidity, seizure at onset, and non-stroke diagnosis	4 & 5 Plus: 1. No old medical records 2. Delays in phlebotomy 3. Getting and mixing drug at pharmacy

continued

TABLE 3 contd Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Azzimondi et al., 1997 ⁶⁶	Observational study	Hospital-based	189 stroke patients	Onset to arrival	Cumulative: 81/189 (43%) arrived < 3 h; 56% < 6 h; 70% < 12 h; 90% < 24 h Delays were less if symptom onset when awake or in daytime, reduced consciousness, and paralysis of more than one limb; ORs with CIs reported	None
Italy						
Wang et al., 1997 ⁶⁹	Observational study	Hospital-based	833 stroke patients	Onset to arrival	Cumulative: 199/833 (24%) arrived < 3 h; 35% < 6 h; 48% < 12 h; 61% < 24 h In one hospital, 24% of CT done < 3 h and 40% < 6 h after arrival	5
China						
Williams et al., 1997 ⁶⁸	Observational study	Hospital-based	67 stroke patients	Patient knowledge of stroke	Only 25% knew they were having a stroke and 38% knew warning signs of stroke. 42/49 (86%) patients who arrived > 3 h thought symptoms were not serious, and 14% were unable to call for help. 50% arrived by ambulance Delay was less if ambulance transport or more severe stroke	1 & 2
USA						
Rosamond et al., 1998 ⁶⁵	Observational study	Hospital-based	152 suspected stroke patients	Onset to arrival	Overall median delay from onset to seeking help was 1 h and median delay from onset to arrival was 3 h; means were 4.3 ± 6.9 h and 6.4 ± 7.7 h, respectively Delay was less if a witness recognised symptoms, if patient felt more urgent, or if called emergency services or ambulance; 49% arrived by ambulance Non-strokes accounted for 45%; ORs with CI reported	1 & 2
USA						
Streifer et al., 1998 ²³	Observational study	Hospital-based	216 consecutive stroke patients	Onset to arrival	Cumulative: 39/216 (18%) arrived < 1.5 h; 26% < 3 h; 54% < 6 h; 70% < 12 h; and 77% < 24 h Delay from onset to arrival was less if severe neurological deficit or onset in afternoon	1
Israel						
Menon et al., 1998 ⁷³	Observational study	Hospital-based	241 stroke patients	Onset to neurologist assessment	Median delay from onset to arrival was 4.5 h, from arrival to first medical assessment was 0.2 h and from arrival to neurologist assessment was 1.7 h Delays were less if ambulance transfer, bypassing GP, haemorrhage, and female	2, 4 & 6
USA						
Salisbury et al., 1998 ⁶²	Observational study	Hospital-based	181 stroke patients	Onset to arrival	Delay times were known for 151/181 patients. Cumulative: 4/151 (31%) patients arrived < 3 h and 46% < 6 h 56% initially called GP vs 41% called ambulance. Cumulative: delay from GP call to visit was 68% < 1 h; and 90% < 2 h (median 0.5); median delay from onset to seeking help was 0.3 h; median delay from arrival to first medical assessment was 1.1 h Delays were less if ambulance transfer, onset not at home, symptoms resolving rapidly, and reduced consciousness; delay was more with initial contact with GP	1, 2, 3 & 4
UK						
						continued

TABLE 3 contd Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Meier-Reichenauer et al., 1998 ⁵⁷ Austria	Observational study	Hospital-based	266 stroke patients arriving < 24 h	Onset to rt-PA	Mean delay from onset to seeking help was 0.7 ± 3.5 h; from onset to arrival was 2.5 ± 3.7 h; from arrival to first medical assessment was 0.1 ± 0.2 h; from arrival to CT was 0.3 ± 0.3 h; and from arrival to rt-PA was 0.8 ± 0.5 h; 25% had delay from arrival to rt-PA of 0.5 h Delays were less if ambulance transport	1, 2, 4 & 5
Smith et al., 1998 ⁶⁵ USA	Observational study	Hospital-based	1895 stroke patients	Onset to arrival	Delay times were known for 1334/1895 patients. Cumulative: 50% arrived < 3 h; 66% < 6 h; 80% < 12 h; and 90% < 24 h Delays were more if dependent pre-stroke or ethnic minority; delays were less if admitted via emergency department, seizure or syncope at onset, and previous myocardial infarction or abnormal mental status	None
Andre et al., 1998 ⁴⁹ Brazil	Observational study	Hospital-based	56 stroke patients	% eligible for rt-PA	Using NINDS criteria, reasons for exclusion were: late diagnosis (82%), refused consent (10%), medical contraindication (6%) and CT signs of mass effect (2%) Reasons for late diagnosis were late arrival, medical staff's lack of recognition or inappropriate response, transfer delay and late CT scan Overall, 9% received rt-PA	4, 5, 6 & 7
Grond et al., 1998 ³⁰ Germany	Observational study	Hospital-based	453 consecutive stroke patients	Onset to rt-PA and % eligible for rt-PA	Reasons for ineligible for rt-PA were: non-strokes (11%); haemorrhage (19%); signs resolving (17%); arrival > 3 h or unknown onset time (22%); medical exclusion criteria (10%); and refusal to give consent (0.4%) Overall, 22% received rt-PA, 26% of whom < 1.5 h from onset; mean delay from onset to rt-PA was 0.8 h	7
Zweifler et al., 1998 ⁸⁰ USA	Observational study	Hospital-based	245 stroke patients	% eligible for rt-PA	Of 245 patients, 185 were activated as code stroke and 60 were non-urgent; 33/245 (13%) were non-strokes; 48 patients arrived < 3 h and were infarcts; 25 were ineligible due to signs resolving; five were on warfarin, and others (e.g. CT abnormalities, seizure) Using NINDS criteria, 3.7% received rt-PA	None
Chiu et al., 1998 ⁵⁰ USA	Observational study	Hospital-based	1035 stroke patients	% eligible for rt-PA	Using NINDS criteria, 3% received rt-PA. Reasons for exclusion were: delay > 3 h from onset (37%), haemorrhage (22%), too mild or resolving symptoms (19%), and non-stroke (12%)	None

continued

TABLE 3 contd Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Hodgson, 1998 ¹⁵⁹ Canada	Observational study	Hospital-based	537 stroke patients	Arrival to CT scan	For patients managed through emergency department: mean delay from arrival to first medical assessment was 0.7 h (< 2 h in 74%), and from arrival to CT scan was 15.1 h (< 3 h in 15%); 60% of patients arrived by ambulance	4 & 5
Wester et al., 1999 ¹² Sweden	Observational study	Hospital-based	329 consecutive stroke and TIA patients	Onset to CT scan	For stroke patients, median delay from onset to arrival was 4.8 h; from onset to stroke unit admission was 8.8 h; from onset to CT scan was 22 h; for TIA patients, median delay times were 4 h, 7.5 h and 17.5 h, respectively Delay from onset to arrival was less if haemorrhage, sudden onset of symptoms, severe neurological deficit, presence of bystander, and ambulance transfer; delay from arrival to admission or CT scan was less if severe neurological deficit or earlier medical assessment; 51% arrived by ambulance; 33% were non-strokes	1, 2, 4, 5 & 6
Siu et al., 1999 ²⁴ Hong Kong	Observational study	Hospital-based	201 consecutive possible stroke patients	Onset to CT scan	192/201 patients had CT (10% non strokes). Cumulative: 80/192 (42%) arrived < 2 h; 52% < 3 h; and 71% < 12 h; median delay from onset to seeking medical help was 2.9 h; from seeking help to ambulance arrival was 0.17 h; from ambulance arrival to arrival at emergency department was 0.28 h, from arrival at emergency department to CT scan was 4.2 h Using NINDS criteria, 5/192 (2.6%) were eligible for rt-PA; eligibility for rt-PA was more likely if delay from onset to seeking help of < 0.25 h and CT scan performed < 1 h after assessment; 58/192 (30%) patients were categorised as semi-urgent at triage on arrival ORs reported	1, 2, 3, 4, 5 & 6
Charleston et al., 1999 ⁶¹ Australia	Observational study	Hospital-based	184 stroke events in 179 patients (SAH excluded)	Onset to CT scan	Delay times were known for 109/179 patients. Overall median delay from onset to arrival was 3 h (2 h for haemorrhages and 3 h for infarcts) Cumulative: delay from onset to arrival: 35/109 (32%) patients arrived < 1 h; 52% < 3 h; 64% < 6 h; 87% < 24 h; and 94% by 48 h; median delay from onset to CT was 19 h (11 h for haemorrhages and 21 h for infarcts) Cumulative: delay from onset to CT scan: 111/109 (10%) scanned < 3 h; 22% < 6 h; 50% < 24 h; and 69% < 48 h Delay was less for haemorrhages	4, 5, 6 & 8
Using NINDS criteria, 5% of patients were potentially eligible for rt-PA; reluctance to use rt-PA because of conflicting trial results and difficulty starting rt-PA < 3 h						continued

TABLE 3 contd Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Lin et al., 1999 ¹³² Taiwan	Observational study	Hospital-based	157 ischaemic stroke patients (arriving < 48 h of onset)	Onset to laboratory investigations	Mean delays from arrival to first medical assessment was 3 ± 3 h; from arrival to CT ordered was 22 ± 34 h; from arrival to CT was 58 ± 41 h; from arrival to lab tests ordered was 12 ± 13 h; from arrival to lab tests done was 61 ± 24 h; and from arrival to neurological assessment was 174 ± 225 h Delays were less if history of previous stroke or referred from other hospital ORs with CIs reported	4, 5 & 6 Plus: Referral from other hospitals increases delay
Lannehoa et al., 1999 ¹⁵⁵ France	Observational study	Hospital-based	317 stroke patients	Onset to CT scan	237/317 patients had known delay times to arrival. Cumulative: 142/237 (60%) patients arrived < 3 h; 77% < 6 h; 80% < 12 h; mean delay from onset to arrival was 4.5 h (median 2.3); from arrival to CT was 3.7 h (median 3); from arrival to first medical assessment was 0.5 h (median 0.5); from medical assessment to CT was 2.8 h (median 2.1) 82% of patients arrived by ambulance; delay from onset to arrival was less if haemorrhage, presence of witness at onset, severe neurological stroke, and use of ambulance; delay from arrival to CT was less if haemorrhage, severe stroke, or request in afternoon ORs with CIs reported	1, 2, 4 & 5
Collins et al., 1999 ¹²⁵ Ireland	Observational study	Hospital-based	100 consecutive stroke patients	% eligible for rt-PA	78/100 patients had infarcts (data analysed). Mean delay from onset to arrival was 12.2 ± 15.7 h; 21% arrived < 2 h; and 25% < 3 h Using NINDS criteria, 6% of patients were potentially eligible for rt-PA (assuming CT done < 1 h after arrival)	5
O'Connor et al., 1999 ¹³³ USA	Observational study	Hospital-based	214 ischaemic stroke patients	% eligible for rt-PA	Using NINDS criteria, 95/214 (44%) patients were ineligible due to delay to treatment > 3 h; 14% to signs resolving; 10% to haemorrhage on CT; 9% to symptoms too mild; 7% to co-morbidity (and few for other reasons) Overall, 6 (2.8%) were eligible for rt-PA	None
Morris et al., 1999 ¹⁵⁸ USA	Observational study	Hospital-based	170 stroke patients arriving < 36 h of onset	Arrival to neurologist assessment	Mean delay from arrival to first medical assessment was 0.59 h (median 0.42); from arrival to CT scan was 2.1 h (1.9); from arrival to neurologist assessment was 2.8 h (2.4) Delays were less if ambulance transfer; 49% arrived by ambulance	4, 5 & 6

continued

TABLE 3 contd Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Casetta <i>et al.</i> , 1999 ¹⁵⁶ Italy	Observational study	Hospital-based	894 stroke patients	Onset to arrival	Delay times were known for 760/894 patients. Cumulative: 188/760 (25%) arrived < 1 h; 41% < 2 h; 54% < 4 h; 73% < 12 h; and 83% < 24 h; mean delay from onset to arrival was 21 ± 2 h (median 3.5) Using NINDS criteria, 16% were potentially eligible for rt-PA Delays were less if patient older, living with partner, sudden onset of symptoms, stroke more severe, and positive family history of stroke ORs reported	I
Kothari <i>et al.</i> , 1999 ¹⁶⁰ USA	Observational study	Hospital-based	86 patients with possible stroke or TIA	Accuracy of paramedic diagnosis	Sensitivity of paramedic diagnosis was 52%, specificity was 67% and likelihood ratio was 1.5; positive predictive value was 80%	Low accuracy of paramedic diagnosis of stroke or TIA
Johnston <i>et al.</i> , 1999 ¹⁷⁴ UK	Before-and-after study (no intervention introduced)	Hospital-based	132 stroke patients – 32 consecutive prospective stroke patients and 100 retrospective patients	Onset to ward admission	Prospective evaluation: cumulative: 8/32 (25%) arrived at emergency department < 3 h and 47% < 6 h; median delay from arrival to nurse assessment was 0 h; to first medical assessment was 0.7 h; to CT was 2 h; to ward admission was 3.4 h; median time spent in emergency department was 2.8 h Reasons for delay: GP contact, non-urgent ambulance transport, physicians delay in emergency department, uncertain diagnosis, poor physician training in stroke, no care pathway Retrospective evaluation: similar results	2, 3, 4, 5, 6 & 8 Plus: Physicians (especially juniors) had poor training in stroke
Fiorelli <i>et al.</i> , 1999 ²⁸ Italy	Observational study	Hospital-based	104 consecutive stroke patients	Onset to CT and % eligible for rt-PA	Cumulative: 34% arrived < 3 h and 54% < 6 h; 60% of CT done < 3 h after arrival; 51% arrived by ambulance Using NINDS criteria, 14% were potentially eligible for rt-PA	2 & 5
Schroeder <i>et al.</i> , 2000 ¹⁷¹ USA	Observational study	Hospital-based	1851 brain attack patients	Onset to neurologist assessment	617/1851 (33%) patients were strokes. Of these seven had missing information and 51 had pre-hospital delay of > 48 h, leaving 559 for analysis Median delay from onset to arrival was 3.5 h; from arrival to first medical assessment was 0.3 h; from arrival to CT scan was 1.5 h; and from arrival to neurologist assessment was 2.4 h Patients who were more likely to use ambulance were: haemorrhages, older people, those living with someone else, someone else first noticing symptoms, and a heightened sense of urgency ORs with CIs reported	I, 2, 4 & 6

continued

TABLE 3 contd Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Morris et al., 2000 ¹² USA	Observational study	Hospital-based	1207 stroke patients	Onset to CT scan	Mean delay from onset to arrival was 5.4 ± 7.6 h (median 2.6); from onset to CT scan was 6.8 ± 7.7 h (median 4); cumulative: 290/1207 (24%) arrived < 1 h, and 56% < 3 h; median delay from arrival to neurologist assessment was 3.1 h Delays from onset to arrival or to CT scan were less if ambulance transfer or symptom onset while awake Using NINDS criteria, 22 (1.8%) received rt-PA ORs reported	2, 4, 5 & 6
Engelstein et al., 2000 ¹⁷⁵ USA	Observational study	Hospital-based	201 stroke patients	Onset to first medical assessment and % eligible for rt-PA	Using NINDS criteria for rt-PA, 188/201 (94%) were ineligible due to delay from onset to arrival > 2 h; 12% to haemorrhage on CT; 11% to signs resolving; 8% to coma at onset; and 6% to CT signs of mass effect; overall, no patient was eligible Mean delay from ambulance arrival to arrival at emergency department was 0.4 h; from arrival to triage was 0.1 h; and from triage to first medical assessment was 0.6 h; 6.5% arrived < 2 h; 51% arrived by ambulance	3 & 4
Rasmussen et al., 2000 ²⁷ Denmark	Observational study	Community-based	123 consecutive stroke patients	Onset to arrival	37% arrived by ambulance, 54% via GP and 9% by other means Cumulative: 47/123 (38%) arrived < 3 h; 53% < 6 h; and 72% < 24 h Delay was less if ambulance transfer; for ambulance group: 78% arrived < 3 h and 87% < 6 h; for GP group: 13% arrived < 3 h and 30% < 6 h Patients arriving by ambulance were more severe	2
Ravindrane et al., 2000 ²⁹ UK	Observational study	Hospital-based	136 consecutive stroke patients	Onset to first medical assessment	68/136 (50%) arrived at emergency department via ambulance and 49% arrived directly at ward via GP admission Mean delay from onset to first medical assessment was 2.1 h (ambulance) vs 8.6 h (GP); mean delay from onset to seeking help was 0.5 h (ambulance) vs 2.4 h (GP); mean delay from seeking help to arrival was 0.2 h (ambulance) vs 2.7 h (GP); mean delay from arrival to first medical assessment was 0.8 h (ambulance) vs 2 h (GP)	1, 2 & 4
Duncan et al., 2000 ⁷² USA	Observational study	Hospital-based	459 stroke patients	Onset to arrival	Delay times were known for 360/459 patients. 180/360 (50%) arrived < 3 h and 65% < 6 h Delay was less if stroke more severe, weakness or numbness in limbs, dysarthria, or white race; delay was more if history of stroke or TIA; 50% had knowledge of stroke symptoms and signs	1 & 2

continued

TABLE 3 contd Review of studies of barriers to efficient acute stroke care

Study	Design	Population	Patients	Delays	Results	Barriers identified*
Bornstein & Karepov 2000 ¹⁵¹ Israel	Observational study	Hospital-based	267 stroke patients	Accuracy of paramedic diagnosis	Ambulance staff diagnosis of stroke had 82% sensitivity, 95% specificity, 73% positive predictive value and 97% negative predictive value; false-positive rate was 27% and false-negative rate was 3%	Low accuracy of paramedic diagnosis of stroke or TIA
Yoneda et al., 2000 ¹³⁴ Japan	Observational study	Hospital-based	154 ischaemic stroke patients arriving < 7 days	Onset to CT and % eligible for rt-PA	Cumulative: 34% arrived < 3 h and 70% < 24 h; mean delay from arrival to CT was 0.7 h Delay was less if ambulance transport or cardioembolic stroke Using NINDS criteria, 9% were potentially eligible for rt-PA	2 & 5
Wein et al., 2000 ¹⁵² USA	Observational study	Hospital-based	429 stroke patients	Predictors for calling ambulance	Patients more likely to call ambulance after stroke if employed; 38% called ambulance	2
Lacy et al., 2001 ²⁰ USA	Observational study	Hospital-based	553 consecutive stroke patients	Onset to first medical assessment	Delay times were known in 483/553 patients. Cumulative: 154/483 (32%) arrived < 1.5 h; 46% < 3 h; 61% < 6 h; 70% < 12 h; and 79% < 24 h Delay from onset to arrival > 6 h was less likely if female, ambulance transfer, and history of atrial fibrillation, myocardial infarction or heart failure; delays from arrival to first medical assessment was less if ambulance transfer Patients > 75 years were more likely to use ambulance; 325/553 (65%) patients arrived by ambulance ORs with CIs reported	2 & 4

* Key to barrier numbers

1. The patient or family did not recognise symptoms of stroke or recognised them but did not seek urgent medical help
2. Patient or family calls GP instead of the emergency services (ambulance)
3. Ambulance policy categorises stroke as a non-urgent condition
4. Emergency department triages stroke as a non-urgent condition
5. Delay in neuroimaging
6. Inefficient process of acute stroke care
7. Difficulties with informed consent for thrombolysis
8. Physicians' opinion

PtCH, primary intracranial haemorrhage; SAH, subarachnoid haemorrhage; TIA, transient ischaemic attack

- patient living alone or retired^{117,126,156,164,168,171}
- symptoms not recognised or not interpreted as stroke^{119,126,138,165,167,172}
- no bystander witness of stroke symptoms at onset^{119,122,155,171}
- patient or family did not seek medical help^{124,129,160}
- patient or family had no sense of urgency to seek help when symptoms started^{126,129,153,157,171}
- stroke onset at home¹⁶²
- patient refused to go to hospital¹²⁶
- patient or family thought symptoms would improve spontaneously and so waited before seeking medical help.^{126,165}

Patient or family calls general practitioner (GP) instead of the emergency services (ambulance):

In the UK or other countries where primary care is well developed, patients often call the GP first rather than the emergency service, even after a severe stroke. There is potentially significant delay with this practice as GPs do not usually rush to assess the patient. After assessment, many GPs choose to keep the patient at home rather than arranging for prompt hospital admission. Twenty-three studies identified this type of barrier.^{112,120,122,124,126-129,134,135,148,152,153,155,157,160,162,164,165,171-174}

These studies found that ambulance transfer or direct admission to the emergency department was associated with a shorter delay from onset to arrival at hospital, whereas first contacting the GP increased the delay. In one study, GPs were found to have advised the patient to stay at home rather than be admitted to hospital.¹²⁶ In another study, GPs misdiagnosed the condition and advised the patient to stay at home as there was “nothing wrong”.¹⁶⁵ One study¹⁷¹ observed that the following groups of patients were more likely to arrive at hospital by ambulance:

- patients living with someone else
- if a witness was present at stroke onset
- there was a heightened sense of urgency
- increasing age
- if the stroke was haemorrhagic.

Fourteen studies reported the proportion of patients who arrived by ambulance.^{120,122,126,128,129,143,148,152,153,158-160,162,175}

This was generally about 50%, ranging from 38%¹⁵² to 65%.¹²⁰

Ambulance policy categorises stroke as a non-urgent condition: Even when the emergency service is called, stroke is often not regarded as a true emergency (‘blue light’) except occasionally when the patient has signs of severe neurological damage such as reduced consciousness or

convulsions. Consequently, there may be a delay before the ambulance reaches the patient and then in transferring the patient to hospital. We included studies that evaluated delay times from calling the emergency services to the time of ambulance arrival, and from ambulance arrival at the patient to reaching the hospital door. Seven studies identified this type of barrier.^{124,126,146,160,162,174,175} Although studies found that patients who called the emergency services arrived at hospital much earlier than if GPs were first contacted,^{126,162,174} ambulance policy appeared to classify stroke as a non-urgent condition, so leading to slower transfer to hospital.

Emergency department triages stroke as non-urgent: At the hospital emergency department, stroke is often not regarded as an urgent condition so that patients are of moderate-to-low priority to be assessed, investigated and treated. We included studies that examined delay from stroke onset (or arrival at hospital) to first medical assessment, neurologist’s assessment, or alerting the acute stroke team. Studies that examined time to obtaining neuroimaging or ward admission were excluded in this category but included in the categories below. Twenty-seven studies identified this type of barrier.^{112,118-120,122,124,126,129,132,137,146,149,154,155,157-162,164,167,171,173-176} The delay from arrival at hospital to first medical assessment varied considerably. For example, in one study, the median delay was 20 minutes,¹⁷¹ compared with 4 hours in another study.¹¹⁹ In the emergency department, acute stroke is often not handled as an emergency medical condition and patients may have to wait a long time before nursing and medical assessments are completed. In one study, one-third of acute stroke patients were categorised as semi-urgent at triage on arrival at hospital.¹²⁴

Delay in neuroimaging: In most hospitals, there is a delay in obtaining neuroimaging such as CT or magnetic resonance (MR) brain scans. Radiology departments rarely perform CT scans out of normal office hours (usually between 5 p.m. and 9 a.m.) except for very urgent cases (e.g. head injury). Stroke is often not regarded as such an urgent condition. We included studies that have evaluated delay from stroke onset (or arrival at hospital) to the first CT or MR brain scan. Twenty-two studies assessed or identified this type of barrier.^{112,118,122,124-126,128,132,134,136,146,149,154,155,157-161,168,169,174} All studies assessed delay times to CT rather than MR brain scans. None of the studies evaluated delay times to other forms of neuroimaging

such as catheter or MR angiography, carotid duplex or transcranial Doppler studies. This type of barrier could be a result of:

- scanning facilities being unavailable (especially out-of-office hours)
- delay in requesting the scan
- delay in transporting the patient to the radiology department
- delay in carrying out the scan
- delay in reporting the scan by a radiologist.

Only two studies examined the possible reasons for delay.^{118,146}

Inefficient process of acute stroke care: Despite the robust evidence to support management of stroke patients in stroke units, recent observational studies have found that many stroke patients in the UK still receive care in general medical wards.¹⁷⁷ We included studies that evaluated delay times from stroke onset (or arrival at hospital) to first medical assessment, neurologist's assessment, or ward admission (e.g. stroke unit or general medical ward). Eighteen studies assessed or identified this type of barrier.^{112,119,122,124,126,132,137,146,149,154,158–161,167,171,173,174} Delay in ward admission could be due to:

- a bed not being available
- delay in getting a porter to transfer patient to the ward
- delay in decision-making by the medical or specialist team.

Only one study examined the possible reasons for delay.¹⁴⁹ In another study, one of the barriers to urgent thrombolytic therapy was that some wards were not prepared or willing to administer the drug; this organisational barrier might have involved nurses, doctors or policy makers.¹⁴⁶

Difficulties with informed consent for thrombolysis: Most acute medical treatments may be associated with potential harm (e.g. haemorrhagic complications) as well as potential benefit (e.g. reduced disability). In the acute phase, a large proportion of stroke patients have language impairment or reduced consciousness, so they cannot give their informed consent to receive acute interventions or to enter randomised trials of acute interventions. Some patients and relatives may refuse to give consent for these interventions. Two studies identified this barrier concerning thrombolysis. In one study, 10% of patients did not receive the treatment because they refused

consent,¹⁴⁹ whereas this reason only accounted for 0.4% in another study.¹³⁰

Physicians' opinion: There is a large variation in UK consultants' opinion regarding thrombolysis for acute ischaemic stroke. In the early 1990s, a survey showed that only 2% of consultants believed thrombolysis was definitely beneficial, 14% believed it was definitely harmful, and 79% were uncertain.¹⁷⁸ A more recent Stroke Association Survey suggested that these opinions have not changed significantly.¹⁷⁷ Even in the USA, where rt-PA is licensed for use in stroke, only 16% of neurologists have ever administered it and many neurologists were uncertain of its benefits.¹⁷⁹ One study reported that some physicians were reluctant to administer rt-PA because of conflicting trial results and difficulty in starting treatment within 3 hours of stroke onset.¹⁶¹ Another study found that some physicians were uncertain of the diagnosis of acute stroke and this uncertainty was responsible for delaying treatment in the emergency department.¹⁷⁴ It was not practicable to design a search strategy to reliably detect (with reasonable sensitivity and specificity) all the studies that mentioned physicians' uncertainties, so we accept we will have missed important studies.

Other barriers: Six studies reported other types of barrier. One study identified delays in retrieving old medical records, performing phlebotomy, and acquiring the rt-PA drug from pharmacy.¹¹⁸ The need to transfer the patient from another hospital was a source of delay.¹³² One study found that poor training in stroke for doctors was a potentially modifiable barrier.¹⁷⁴ Two studies assessed the accuracy of stroke diagnosis by paramedical staff; one study¹⁴⁵ found the diagnostic methods used by these individuals had low sensitivity (52%) and specificity (67%) but another study¹⁵¹ found high sensitivity (82%) and very high specificity (95%). Improvement in stroke diagnosis by paramedical staff may reduce pre-hospital delay.

Studies that did not identify any modifiable barriers: Seven studies did not identify any modifiable barriers.^{131,133,147,150,163,166,180} These studies could be divided into three main groups: those that only assessed delay from onset to arrival at hospital (but did not assess possible reasons for the delay); those that only assessed the proportion of patients who were eligible for thrombolytic therapy; and those that only identified non-modifiable barriers. Identified non-modifiable barriers included the clinical features of acute stroke that have been found

to correlate with delayed acute stroke care, such as stroke sub-type,^{122,131,135,136,138,155,161,171,173} stroke severity,^{117,122,138,148,155,156,162} and conscious state.^{135,138,162,166}

Proportion of stroke patients eligible for thrombolysis: Nine studies assessed the proportion of stroke patients who were actually treated with rt-PA (six studies), or potentially eligible (three studies) for rt-PA, within 3 hours of stroke onset.^{125,128,130,133,134,149,150,175,180} One other study assessed the actual proportion of patients eligible for SK therapy within 6 hours of onset.¹⁴⁶ Overall, the proportion ranged from 0%¹⁷⁵ to 22%.¹³⁰ Practice guidelines proposed by the American Heart Association were followed in the studies involving rt-PA therapy,²³ whereas the MAST-I protocol was followed in the study involving SK therapy.⁶⁸ In the five studies that evaluated the proportion of patients treated with rt-PA within 3 hours,^{130,133,149,150,175} the five commonest reasons for being ineligible for rt-PA therapy are shown in *Table 4*.

Interventions to overcome barriers

Seven studies have evaluated the effectiveness of interventions designed to overcome barriers to efficient acute stroke care (*Table 5*).^{121,139–144} From these studies, three types of interventions could be identified:

- an education programme for the public and healthcare workers^{140,143}
- a training programme for paramedical staff to improve the accuracy of diagnosis^{141,142,144}
- reorganisation of in-hospital systems to streamline acute stroke care.^{121,139}

Education programmes for the public and healthcare workers

In the two studies by Alberts and co-workers¹⁴⁰ and Barsan and co-workers,¹⁴³ the educational programmes were designed to promote the use of rt-PA within 3 hours after stroke. The programme was aimed at the public via the media (television, radio, newspaper) and at the healthcare workers through teaching sessions and advertisements.

The objective was to promote early recognition of stroke symptoms, use of the emergency service, rapid ambulance transfer, and early hospital treatment of acute stroke patients. The programme in the Alberts study also involved a rapid referral system that included helicopter transfer of patients. This before-and-after study showed that, after the introduction of the education programme, delay from stroke onset to arrival at hospital was reduced for patients with ischaemic strokes; the proportion of patients with ischaemic stroke arriving within 24 hours of onset increased from 37% (pre-education) to 86% (post-education). No difference was found for patients with haemorrhagic stroke.¹⁴⁰ The Barsan study (an open study) of the education programme showed that, during the course of the study (2 1/2 years), the mean delay time from stroke onset to arrival at hospital was reduced from 3.2 to 1.5 hours. At the same time, the use of emergency services (calling 911) among admitted stroke patients increased from 39% in the first quartile of the study to 60% in the fourth quartile. The increased use of emergency services was found almost exclusively in patients with non-haemorrhagic stroke.¹⁴³

Training programmes for paramedical staff to improve accuracy of diagnosis

In the three studies by Kidwell and co-workers,¹⁴² Smith and co-workers,¹⁴¹ and Harbison and co-workers,¹⁴⁴ the training programmes were designed to improve the accuracy of stroke diagnosis by paramedical staff and to reduce the delay in transferring the patients to hospital. The programmes taught the paramedical staff to take an accurate history and examine the patient properly for clinical signs of stroke. One programme also taught the pathophysiology of stroke and how to perform the National Institutes of Health Stroke Scale.¹⁴¹ If stroke was suspected, the patient was to be transferred to hospital urgently and the staff at the emergency department should be alerted of the patient's arrival. The programme was called the Los Angeles Prehospital Stroke Screen (LAPSS) in the

TABLE 4 Commonest identified reason for being ineligible for rt-PA therapy

Reason	Range (%)
Delay to treatment of more than 3 hours or onset time unknown	22–94
Haemorrhage or mass effect found on CT scan	10–22
Clinical signs of stroke too mild or resolving rapidly	9–19
Medical contraindications to rt-PA	6–10
Refusal to consent to treatment	0.4–10

TABLE 5 Results of studies of interventions to overcome specific barriers to acute stroke care

Study	Design	Delay	Patients	Intervention	Results
Alberts <i>et al.</i> , 1992 ⁴⁰ USA	Before-and-after study	Onset to arrival	479 stroke patients (290 patients pre- and 189 patients post-intervention)	Treatment: Education programme about rt-PA for the public (television, radio and newspaper) and healthcare workers (medical and paramedical); rapid referral system including helicopter transfer Control: Pre-education	Delay from onset to arrival was reduced post-intervention Infarcts presented < 24 h: post-intervention 139/159 (86%) vs pre-intervention 70/187 (37%) No difference with haemorrhagic strokes
Gomez <i>et al.</i> , 1994 ²¹ USA	Comparative study	Onset to drug treatment	98 consecutive stroke patients	Treatment: Code stroke using a centralised pager system to ensure members of stroke team alerted of new stroke patient (for emergency treatment) Control: Patients not treated with code stroke protocol during the study period	12/98 patients were treated with code stroke protocol vs 86/98 controls Mean delay from onset to arrival: code 2 h vs control 1.6 h; delay from arrival to code stroke activation: code 0.69 h vs control 1.3 h; mean delay from code stroke to first assessment: code 0.08 h vs control 0.42 h; mean delay from assessment to drug treatment: code 0.5 h vs control 0.7 h
Barsan <i>et al.</i> , 1994 ⁴³ USA	Observational (open) study of an intervention	Onset to arrival	2099 stroke patients arriving < 24 h of onset	Treatment: Educational programme (at start of NINDS trial, Feb. 1987) for medical, nursing and paramedical staff, stressing need to recognise symptoms and signs, and rapid transport and assessment; public education via radio, television, newspaper etc. to educate on symptoms and signs of stroke, and need to call ambulance	Delay times were known in 1116/2099 patients; using NINDS criteria 74/2099 (3.5%) received rt-PA Cumulative: 432/1116 (39%) arrived < 1.5 h, 59% < 3 h, 77% < 6 h; delay from onset to arrival was less if ambulance transfer, treatment at community (rather than university) hospital, and onset in afternoon; after starting educational programme, use of emergency services (91) increased from 39% to 60%; mean delay from onset to arrival declined from 3.2 to 1.5 h during course of study (2 1/2 years)
Kidwell <i>et al.</i> , 1998 ⁴² USA	Observational (open) study of an intervention	Onset to trial drug administration (< 6 h) and accuracy of paramedic diagnosis	83 retrospective stroke patients	Treatment: LAPSS was a diagnostic instrument based on history (age, past medical history e.g. epilepsy, duration of symptoms and premorbid disability), blood glucose, and examination (asymmetry of face, grip and arm strength); if patient fulfilled criteria then treated as code stroke for emergency transfer	Mean delay from onset to arrival was 1.4 h, from onset to CT was 3.3 h, from onset to drug was 3 h (some did not need CT); LAPSS had 92% sensitivity for identifying stroke
Englander <i>et al.</i> , 1998 ³⁹ USA	Before-and-after study	Arrival to rt-PA	Not stated	Treatment: Continuous quality improvement where multidisciplinary team designed algorithms and evaluation forms for acute stroke assessment Control: Before implementation	Mean delay from arrival to first medical assessment improved from 0.75 ± 0.57 h to 0.17 ± 0.18 h; delay from arrival to CT improved from 1.95 ± 2.1 h to 0.77 ± 0.28 h; delay from arrival to neurologist assessment improved from 1.27 ± 0.7 h to 0.77 ± 0.38 h; after intervention, delay from arrival to rt-PA (or decision not to) was 0.77 ± 0.6 h

continued

TABLE 5 contd Results of studies of interventions to overcome specific barriers to acute stroke care

Study	Design	Delay	Patients	Intervention	Results
Smith et al., 1999 ⁴¹ USA	Comparative study	Accuracy of paramedic diagnosis	84 stroke patients	Treatment: Education programme (FAST) for paramedics consisting of training on pathophysiology and symptoms and signs of stroke; teaching on how to test and observe language, visual fields, motor function and gait (using National Institutes of Health Stroke Scale) Control: No specific instruction	Sensitivity of paramedic diagnosis was 90% in each group and positive predictive value was FAST 60% vs control 70%; no data on true negative to calculate specificity or likelihood ratio; for all paramedics (both groups), sensitivity increased from 60% (pre-treatment period) to 90% (treatment period) but positive predictive value decreased from 80% to 60–70%
Harbison et al., 1999 ⁴⁴ UK	Observational (open) study of an intervention	Onset to arrival	311 stroke patients (123 via ambulance and 188 via GP)	Rapid Ambulance Protocol with paramedic training to improve stroke diagnosis (Face, Arm and Speech Test) and instruction to divert all suspected stroke patients to one hospital	Paramedics correctly diagnosed stroke in 102/123 (83%) patients; median delay from onset to arrival was 1.2 h for ambulance transfer and 6 h for GP admission; median delay from onset to seeking medical help was 0.6 h, from seeking help to ambulance arrival was 0.1 h, from ambulance arrival to arrival at emergency department was 0.4 h; delay was less if ambulance transfer

Kidwell study,¹⁴² the Field Assessment of Stroke Treatment (FAST) in the Smith study,¹⁴¹ and Rapid Ambulance Protocol in the Harbison study.¹⁴⁴ The study by Kidwell of the training programme showed that stroke diagnosis by paramedical staff had a sensitivity of 92%; however, specificity was not reported.¹⁴² The study by Harbison of the ambulance protocol found that the trained paramedical staff correctly diagnosed stroke or transient ischaemic attack in 83% of patients, and that delay to arrival at hospital was much greater if the patient or family contacted a GP initially.¹⁴⁴ The study by Smith assessed the accuracy of stroke diagnosis, comparing a training programme with no training programme. This study showed no significant improvement in the sensitivity (90% in each group) or positive predictive value (FAST 60% versus control 70%) of stroke diagnosis. However, compared with before the training began, the sensitivity of stroke diagnosis increased from 60% (pre-training) to 90% (post-training).¹⁴¹

Re-organisation of in-hospital systems to streamline acute stroke care

In the two studies by Gomez and co-workers¹²¹ and Englander and co-workers,¹³⁹ the in-hospital systems were reorganised to reduce delay and promote efficient acute stroke care. The intervention in Gomez was called code stroke, which was a centralised pager system that ensured all members of the stroke team were alerted simultaneously when a new acute stroke patient arrived at the emergency department. The intervention in the Englander study was a continuous quality improvement scheme applied across many components of the stroke service. It involved using new algorithms and evaluation forms, which were designed by the multidisciplinary stroke team, for acute stroke assessment. The study by Gomez assessed in-hospital delays, comparing the code stroke system with standard management. Delay time from arrival at hospital to first medical assessment was significantly shorter with the code stroke system (46 minutes versus 101 minutes; $p < 0.05$). There was, however, no difference in delay times from stroke onset to arrival, or from first medical assessment to acute treatment.¹²¹ The before-and-after study by Englander showed that, after the introduction of the continuous quality improvement scheme, all in-hospital delays were significantly reduced. Mean delay from arrival at hospital to first medical assessment reduced from 45 ± 34 minutes to 10 ± 11 minutes ($p < 0.001$); mean delay from arrival to CT scan reduced from 117 ± 126 minutes to 46 ± 17 minutes ($p < 0.05$); and mean delay from arrival to neurologist

assessment reduced from 76 ± 42 minutes to 46 ± 23 minutes ($p < 0.05$).¹³⁹

Discussion

Generalisability of the results

We have attempted in this qualitative synthesis to describe the main themes and broad categories of barrier to efficient acute stroke care. However, the studies we assessed were enormously variable in quality, sample size, study population, and methods. Relatively few data were available from the UK. In one sense, the consistency with which certain barriers were noted (e.g. delay in the recognition of symptoms) gives them both internal and external validity, as they occurred in a wide variety of healthcare settings. However, the importance of each of these potential barriers to efficient stroke care in the NHS is less clear. Nonetheless, this review may provide a framework for clinicians and healthcare planners to assess the components of their local acute stroke service.

Reliability of the results

Many of the studies had methodological weaknesses and hence were open to substantial bias. We have kept discussion of these problems brief as they have been reviewed in some detail by Evenson and co-workers.¹⁸¹ These weaknesses preclude, as anticipated, a reliable quantitative synthesis of the impact of specific barriers. Similarly, the heterogeneity of the interventions employed to overcome barriers also precluded a quantitative analysis.

Pre-hospital barriers

The most consistently reported barrier was the patient's or family's poor knowledge of stroke, which delayed their request for urgent medical help. About 60% of people in the USA know the main presenting symptoms of stroke,¹⁸² compared with below 10% in Germany.^{183,184} There is weak evidence that education of the public via the mass media may indeed improve knowledge of stroke, increase the use of emergency medical services, and so reduce delay in arriving at hospital.^{140,143} A recent study also provided some evidence that community-based education campaigns using newspapers and television can improve knowledge of stroke; after the education programme, people were 35% more likely to know a symptom of stroke, although less than half of people could actually name a stroke symptom.¹⁷⁰ The impact on delay to arriving at hospital in the study area was not assessed.

Knowledge alone is not sufficient. The public must also be convinced that stroke symptoms indicate a medical emergency and that they should actively seek medical attention, as declared by the US National Stroke Association consensus statement.¹⁸⁵ This education can take two main forms; targeting the entire population or targeting only the high-risk groups and their relatives. Targeting the entire population is extremely costly (hence the intensity of education may be low), but it is more likely to cover all the people at risk. In contrast, targeting only the high-risk groups (e.g. the elderly) may mean that the intensity of education can be higher, but many of the people in the lower-risk groups (who might have a stroke) may be missed. Two studies suggest that high-risk groups, such as the older population and stroke survivors, have a poor knowledge of stroke and the appropriate secondary preventative measures.^{186,187} A recent review showed that methods of providing information to stroke patients and carers currently used in clinical practice are largely ineffective and need to be improved.¹⁸⁸ On the other hand, a Cochrane systematic review concluded that promotion via the mass media could encourage the use of effective services and should therefore be considered.¹⁸⁹

Any education about stroke should aim to improve public knowledge of how to recognise the main symptoms of stroke and of the need to call the emergency service (and not the GP) without delay.¹⁹⁰ We found evidence that when the patient bypasses the GP, this appears to reduce the delay in reaching hospital.¹¹² Encouraging the public to call the emergency services whenever stroke is suspected may increase the demands on ambulance services and emergency departments, many of which are already at full stretch and struggling to cope.¹⁹¹ Furthermore, this may theoretically impact badly on other patient groups, such as those with acute coronary syndromes, for which proven and licensed acute treatments already exist and the necessity for emergency ambulance transfer is unquestionable. Ideally, all paramedical staff should receive training in stroke to improve the accuracy of their pre-hospital diagnosis, so that the right patients are rapidly transferred to hospital for acute treatment. It is also arguable that a low specificity of diagnosis by paramedical staff (i.e. many false-negatives) may be acceptable as long as the sensitivity can be improved. However, we should aim to develop paramedical systems with a high positive predictive value for the diagnosis of acute stroke to avoid inundating emergency departments with patients who could be appropriately managed less urgently.

In this review, we did not find enough evidence to conclude that education and training of paramedical staff produced any significant improvement on the accuracy of stroke diagnosis.^{141,142,144}

Even with the most effective education programme, many stroke patients will still never reach hospital. In the UK, it has been estimated that between 25% and 50% of stroke patients are managed at home by primary healthcare teams and not admitted to hospital.¹⁹² Any educational programme might need to include information for GPs to encourage a swifter response when presented with a diagnosis of acute stroke. In the many parts of the world where thrombolysis is not licensed for routine use in acute stroke, policy makers can argue that, although stroke patients should be admitted to hospital promptly, there is not enough reason to admit them immediately.¹⁹³ Until thrombolysis is licensed worldwide, it may be a difficult task to justify the cost and effort of such extensive education programmes.

In-hospital barriers

Once the patient arrives at hospital, acute stroke care should be efficient, streamlined and comprehensive.¹¹¹ This systematic review has identified many in-hospital barriers, starting from the moment the patient arrives through the emergency department door. The commonest and most consistently reported sources of delay were in medical assessment (first medical assessment and specialist assessment by neurologist or stroke team), in performing neuroimaging, and in ward admission. There is weak evidence that interventions to reduce in-hospital delays may be effective. However, large-scale randomised trials and well-conducted observational studies will be needed to assess the best way to improve practice. Stroke patients are often assessed as low priority in the emergency department, so are frequently made to wait for a long time for clinical assessment, investigation and treatment.^{174,194} Measures to improve efficiency of acute stroke care can be multifaceted involving interventions at various points within the pathway of care. For example, a quality improvement programme could involve one or more of the following:

- training of triage emergency department nurses and physicians to recognise stroke and triage it for urgent treatment
- education of nurses and physicians to alert the stroke specialists (stroke team or neurologist) as soon as possible after hospital arrival
- streamlining access to CT scanning and allow for 24-hour emergency scanning

- setting up of an acute stroke unit with staff who are trained in caring for stroke patients and administration of acute stroke treatments such as thrombolysis.

On arrival at the hospital, acute stroke patients should be triaged as high priority to be assessed and treated urgently.⁴⁹ Without such a triage, any modern acute treatment such as thrombolysis is unlikely to have a major impact on stroke recovery.¹⁹⁵ For this to happen, the emergency department needs a well-organised acute stroke protocol with which every member of the team is familiar. A 'reflex response' action is what is required if barriers are to be overcome. This reflex response might entail, for example, immediately alerting the acute stroke team, informing the radiology department, and checking the availability of a vacancy on the stroke unit. In the USA, national guidelines state that a stroke patient should be evaluated by a physician within 10 minutes of arrival at the emergency department.¹⁹⁶ However, prioritising stroke patients to be assessed first would mean other patients have to wait longer. This might again increase demand on an already fully stretched emergency department service,¹⁹⁷ but involving the stroke team early may actually reduce the demand on the emergency department staff.

Acute treatments such as thrombolysis cannot be administered until the results of brain imaging are known. The availability of CT scanning varies around the world and within the UK; in some parts of Europe, particularly among the eastern European countries, only a low proportion of stroke patients is investigated with a CT scan.¹⁹⁸ A recent survey of UK and Italian hospitals found that Italian doctors expected CT brain scans to be done more quickly than UK doctors, their hospitals were more likely to have a CT scanner operating all the time, and a porter was used less frequently to transport the patient to the CT scanner. The authors proposed that a few simple changes in the way CT scanning is organised for stroke patients in the UK could speed access to CT scanning considerably.¹⁹⁹ For most parts of the world, stream-

lining access to CT scanning for stroke patients may be difficult to achieve in practice because of limited resources. However, in places where thrombolysis is already licensed and routinely administered, neuroradiology services might be better organised and more efficient.²⁰⁰ In the USA, national guidelines state that a CT scan should be carried out within 25 minutes of the patient arriving at the emergency department, and the scan should be reported by a neuroradiologist within 45 minutes.¹⁹⁶

Giving priority to stroke patients without increasing resources may also impact on patients with other diagnoses as it means they have to wait longer, but it should not affect the overall waiting list or waiting time as the CT scan (for a stroke patient) is merely shifted from 2 days to a few hours. However, if 24-hour access to the CT scan is required, extra radiographers and radiologists, and hence extra resources, may well be needed.

Although information provision and education is useful, there is evidence that education alone has a limited effect on physician's behaviour.²⁰¹⁻²⁰³ The introduction of guidelines and protocols may help change behaviour. In the UK, national guidelines such as The Royal College of Physicians' National Clinical Guidelines for Stroke²⁰⁴ and the Scottish Intercollegiate Guidelines Network guidelines (URL: <http://www.show.scot.nhs.uk/sign/guidelines/index.html>) for stroke are useful high-quality resources. A systematic review showed that the use of explicit guidelines can indeed improve clinical practice, although the size of benefit may be small and costs may be high.²⁰⁵ Guidelines and protocols that are designed and implemented by the local multidisciplinary stroke team can potentially ensure consistently high standards of early assessment and acute treatment. As documentation of stroke assessment and progress of recovery is often poor,²⁰⁶ stroke protocols can also include standardised documentation such as an assessment pro forma. This may allow more uniform and complete documentation, although its effectiveness remains to be proven.²⁰⁷

Chapter 5

Cost-effectiveness of thrombolysis with rt-PA for acute ischaemic stroke

Background

If the NHS is to use rt-PA as a routine treatment for patients with acute ischaemic stroke, the treatment must be worthwhile from several perspectives. Firstly, for individual patients, the long-term benefits should, on average, outweigh the short-term risks. Secondly, for the NHS, the clinical benefits gained (in terms of life-years, or QALYs) should justify the costs of treating the relatively few patients that are currently eligible for rt-PA. It is relatively straightforward to assemble the evidence needed to judge whether or not rt-PA is 'worthwhile' from these two fairly limited perspectives.

However, if the NHS judges rt-PA to be 'worthwhile' from the first two perspectives, it must then decide whether it would be cost-effective (and feasible) to deliver the treatment equitably to all the NHS patients that might benefit from it. On present evidence, perhaps 1–5% of patients with acute ischaemic stroke could be treated and potentially derive benefit from rt-PA. Thrombolysis is a treatment that should be given within the context of a well-organised acute stroke care service, but it appears that few centres in the UK currently meet this criterion and can deliver the treatment safely and effectively. It would therefore require substantial NHS investment to improve acute stroke services to the point where they can deliver rt-PA. Such investment might be easier to justify:

- if there was proof **beyond reasonable doubt** of the benefits of the treatment (measured perhaps in terms of life-years gained), or
- if there was evidence that improving the quality of acute stroke services was cost-effective (just as improved organisation of stroke rehabilitation improves outcome and reduces cost), or
- if external evidence established that a larger proportion of patients could be treated with rt-PA.

We have performed a systematic review to assemble the evidence on the efficacy of thrombolysis in general and rt-PA in particular. Some clinicians and patients already regard this evidence as sufficient to justify the use of rt-PA in a small

proportion of patients. However, the evidence falls short of providing proof beyond reasonable doubt of the benefits of rt-PA. The value of an economic model in this situation is then to explore the plausible range of cost-effectiveness of the treatment. This knowledge would inform the decision whether or not to use rt-PA more widely in the NHS or, if not, whether to invest in further research on it. If the plausible range of the estimates of cost-effectiveness were very wide, then the limits of the estimates of the cost of implementing thrombolysis for stroke in the NHS would be correspondingly wide (and hence uninformative).

This section of the report describes the results of an economic model that has several key features which distinguish it from the earlier cost-effectiveness analyses of rt-PA:

- the estimates of efficacy were based on a systematic review of all relevant randomised trials
- the costs used are applicable to the NHS
- the model was populated with data from a large prospective register of stroke patients treated in the NHS
- a number of approaches were used to explore the plausible range of cost-effectiveness of rt-PA in the NHS.

Methods

This economic evaluation has been designed to inform the decision on whether or not to introduce thrombolytic treatment for NHS patients with acute ischaemic stroke.

Study question

From the perspective of the NHS, is thrombolytic treatment for acute ischaemic stroke (compared with standard care), cost-effective over 1 year and over a lifetime as judged by the incremental cost per QALY gained?

Perspective

We have performed analyses from the perspective of the NHS healthcare and personal social services.

The costs of care in the initial phase of acute stroke fall on the NHS acute hospital sector, but long-term care may fall either to the NHS continuing care sector or to the social service budget.^{208,209} We have aggregated the latter two costs, so that any cost reductions in the long term (due to reduced disability and reduced need for long-term care, whoever funds it) can offset the higher acute care costs associated with treatment. We have therefore included the direct costs of hospital stay, rehabilitation and long-term care. We have not included an assessment of any indirect economic costs, such as loss of work-related earnings.

Assessment of alternatives to thrombolytic treatment

At present the only effective medical treatment for patients with acute ischaemic stroke is aspirin.^{15,210} In clinical practice, patients with confirmed ischaemic stroke who do not receive thrombolysis would be given aspirin immediately, whereas those treated with thrombolysis would generally be started on aspirin about 24 hours later.²¹⁰ A meta-analysis of the trials of aspirin in acute stroke showed that the benefits of aspirin were comparable, whether started within 24 hours or between 24 and 48 hours of stroke onset; thus there should be no material difference in outcome attributed to the delay in starting aspirin among patients given thrombolysis.²¹⁰ It is difficult to define a standard package of general care for patients with acute stroke, and even more so to define one for patients treated with thrombolysis (see chapter 1). We have therefore assumed for the analyses in this report that the alternative treatments being compared are 'standard care' and 'standard care plus thrombolysis'.

Form of evaluation

We have adopted both a cost-effectiveness approach, assessing health gain in terms of life-years gained, and a cost-utility approach, assessing gains in QALYs. We have modelled costs and effectiveness over the short term (1 year) and the long term (lifetime).

Choice of thrombolytic agent

The most reliable estimate of the efficacy of thrombolysis is obtained from a systematic review of all the relevant randomised trials, including several different thrombolytic regimens (see chapter 2). A Cochrane systematic review of the trials directly comparing one thrombolytic regimen with another did not find sufficient evidence to draw reliable conclusions about which was the most effective (date of last substantive amendment

1998).²¹¹ The searches performed in chapter 2 did not identify any new trials that had become available since 1998 to add to that review. The data presented in chapter 2 therefore provide only indirect comparisons of different regimens, which are more prone to bias than direct randomised comparisons. However, we decided that our economic analyses should be based on a single regimen, intravenous rt-PA, for the following reasons:

- about 50% of the evidence in the review comes from trials of this regimen
- it is the only regimen which has any form of product licence for use in stroke (in USA, Canada and Germany)
- the indirect comparisons suggest rt-PA is somewhat more promising than other regimens.

However, the patients included in the trials of thrombolysis were highly selected and were largely recruited from non-UK centres. So, to produce results that are more relevant to the NHS, we undertook a modelling approach, applying data on efficacy from the trials to a population of stroke patients treated within the NHS.

Choice of measure of benefit

The health outcome summary measure is the number of QALYs gained. A cost-effectiveness analysis based on life-years gained would be of limited value, as it takes no account of the problem that many stroke patients survive in a disabled state. One of the key factors that patients (and their relatives) consider when deciding on thrombolytic treatment is how highly they value survival free of dependency relative to death or survival in a dependent state. The use of QALYs as the measure of benefit enabled us to encompass the value (utility) to stroke patients of death or survival in a dependent or independent state after stroke. While it may be difficult to assess health-related quality of life after stroke and to measure the utility patients attach to different states of disability after stroke, there are strong arguments for assessing the benefits in terms of QALYs rather than just life-years gained.^{212,213}

The decision analysis model

We constructed a decision analysis model of the pathways that acute stroke patients follow after being admitted to hospital. The model was constructed by discussion among the reviewers, analysis of our own stroke registry data, and review of the literature. The model was entered into a software package (Data 3.5 software, TreeAge Software Inc., Williamstown, MA, USA) and is shown in *Figure 8*. We defined five groups of

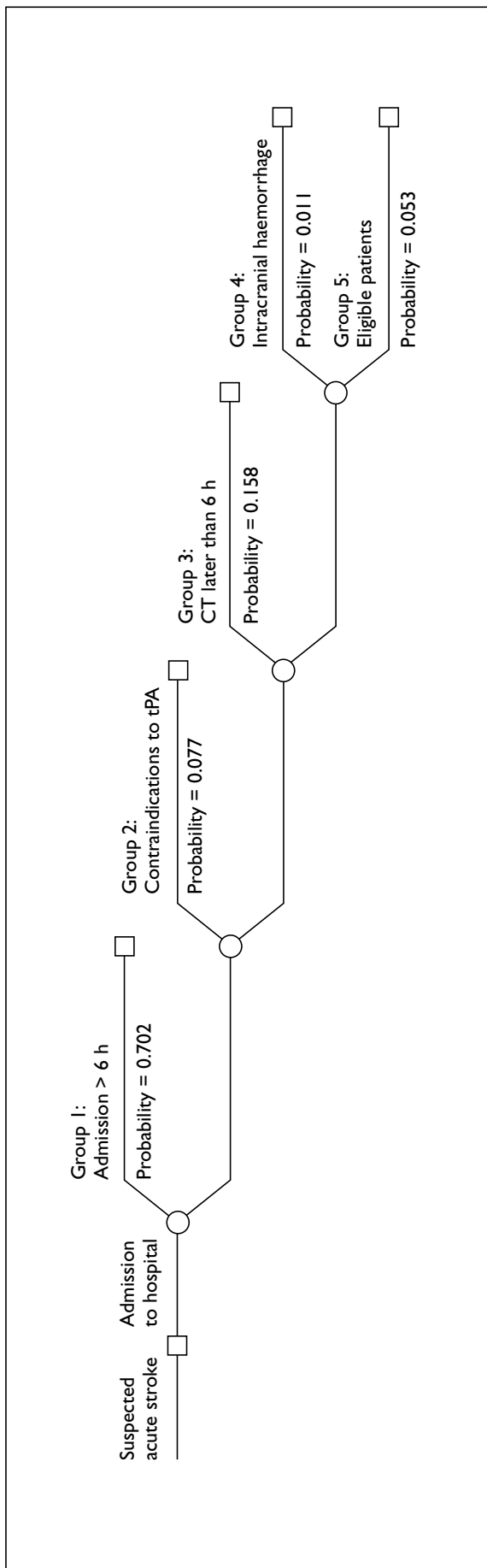


FIGURE 8 Care pathways and base-case probabilities

patients (the proportions of patients in each group are shown in the figure).

- **Group 1: Patients admitted to hospital more than 6 hours after stroke onset.** Patients who had symptoms on waking were included in Group 1.
- **Group 2: Patients with contraindications to rt-PA.** Patients were assumed to have contraindication to rt-PA if they had a pre-stroke MRS score of 3 or more, or were on long-term oral anticoagulants.
- **Group 3: Patients whose CT scan was performed later than 6 hours after stroke onset.** The time from symptom onset to CT scanning was known for a subset of patients and extrapolated to all patients in the dataset. Patients known to have been CT scanned later than 6 hours from stroke onset were included in Group 3.
- **Group 4: Patients with intracranial haemorrhage on CT scan.** If an intracranial haemorrhage was seen on the first CT scan after stroke onset the patient was included in Group 4.
- **Group 5: Patients eligible for thrombolysis.** All those who remain after exclusion of Groups 1–4.

The underlying pathway probabilities are shown in *Table 6*. *Table 6* also lists all the other base-case values (with plausible ranges) used in the model, and the sources of the estimates.^{16,214–220}

To predict the health and economic outcomes of rt-PA after the first year, we used a Markov modelling approach (*Figure 9*).^{221–223} The Markov model used age-specific mortality, risk of recurrent stroke, and stroke-specific case fatality to estimate the probabilities of being dead, dependent, and independent at the beginning of each year. The Markov process was run repeatedly in 1-year cycles till the end of the cohort life-time, and totals were computed for the accumulated health outcomes and costs.

The patient data set

We used data from the Lothian Stroke Register (LSR) in order to provide a more ‘realistic’ estimate of the type of stroke population that might be offered rt-PA in the NHS. The methods of this register have been reported elsewhere.^{214,224} At the time of these analyses, the LSR contained data from 1779 prospectively identified consecutive patients with a definite or probable stroke who had required inpatient care from September 1989 to June 2000. The LSR data items used in the analysis included: length of hospital stay (LOS), functional outcome according to the MRS,²²⁵ and

the occurrence of recurrent stroke, death from recurrent stroke and death from all causes up to 12 months after the index stroke.

Assumptions about health outcomes

We examined the follow-up data in the LSR to ascertain MRS score at 6 and 12 months after stroke onset, and surviving patients were then categorised as dependent (MRS ≥ 3) or independent (MRS < 3). The distribution of the different functional outcomes at 6 and 12 months is presented in *Table 7*.

We estimated survival during the first year by calculating the median survival in each functional outcome category, for those who survived up to 6 months, and for those who survived up to 12 months, using figures from *Table 6*. The assumptions made about various parameters are listed below.

Survival after 1 year: We assumed that after the first year, deaths occurred at an equal rate in dependent and independent survivors.²²⁶ We used published estimates of all-cause mortality, adjusting for age²²⁷ and history of previous stroke, assuming that the overall death rate after the first year was 2.5 times the age-adjusted mortality of the UK population.²¹⁶ Among patients who had a recurrent stroke after the first year, we calculated survival from the rate of recurrent stroke and the case fatality of patients with recurrent stroke in the LSR, assuming the risks to be equal in dependent and independent patients.¹¹ We also assumed that patients remaining alive after the recurrent stroke were reallocated equally to the independent and dependent functional outcome category. For example, in a particular model year, the number of independent patients that had a recurrent stroke and remained alive were allocated in equal numbers to the independent and dependent functional outcome category.

Efficacy of rt-PA: Group 5 in the LSR consists of patients who are eligible for rt-PA treatment. We assumed that this group was given rt-PA, and named this Group 5a. We used the estimate of effect from the Cochrane systematic review¹⁶ (see chapter 2 and *Table 6*) to calculate the proportions of independent, dependent, and dead patients in Group 5a, and compared the outcomes with Group 5, which received standard treatment. The method of calculation of outcomes among patients treated with rt-PA is illustrated in appendix 4 (see *Figure 17*).

Patient values/preferences: Patient utility values for the dependent and independent states were

TABLE 6 Base-case values and range of plausible values

Model parameter	Base-case value	Plausible range	Source/comments
Pathway probabilities			
Admission within 6 hours	0.2981	0.2981–0.7000	LSR ($1/3$ of patients with symptoms present on waking) ²¹⁴
No contraindications to rt-PA	0.7424	–	LSR ²¹⁴
CT performed within 6 hours	0.2857	0.2857–1.0000	LSR ²¹⁴
No haemorrhage	0.8304	–	LSR ²¹⁴
Distribution of patients at 6 and 12 months by functional outcome	See Table 7		
Median survival within the first year			
Patients dying within 6 months	21 days	–	LSR ²¹⁴
Patients dying 6–12 months	300 days	–	
Survival after the first year			
Annual age-specific mortality rates	–	–	LSR, ²¹⁴ National Statistics (average cohort starting age: 69 years) ²¹⁵
Multiplier age-specific mortality among stroke patients	2.5		Perth community stroke study ²¹⁶
Survival after the first year among patients who have had recurrent stroke			
Annual risk of stroke recurrence after 1 year	0.05	–	LSR ²¹⁴
Annual stroke mortality among patients with recurrent stroke	0.25	–	LSR ²¹⁴
Efficacy of rt-PA			
OR for 'death'	1.16	0.94–1.44	Cochrane systematic review ¹⁶
OR for 'death or dependency'	0.79	0.68–0.92	Cochrane systematic review ¹⁶
Utility values			
Independence	0.74	0.69–0.79	LSR ²¹²
Dependence	0.38	0.29–0.47	LSR ²¹²
Death	0.00	–	LSR ²¹²
Mean unit cost per inpatient day	£200	£150–500	Scottish Health Service Costs 1998–99 for Western General Hospital, Edinburgh; range for Scotland ²¹⁷
Mean LOS			
Independent survivor	14 days	14–31 days	LSR ^{209,214}
Dependent survivor	51 days	51–78 days	LSR ^{209,214}
Non-survivor	33 days	33–34 days	LSR ^{209,214}
Cost of rt-PA treatment	£480	£480–1000	Base case assumes drug costs only ²¹⁸ (see Table 8)
Cost of (ambulatory) rehabilitation			
Independent survivor	£40	–	MEDTAP model ^{219,220}
Dependent survivor	£763	–	
Average annual cost of long-term care			
Independent survivor	£876	–	MEDTAP model ^{219,220}
Dependent survivor	£11,292	–	
Discount rate for (future) costs and outcomes (QALYs)	0.06	0.03	National rate

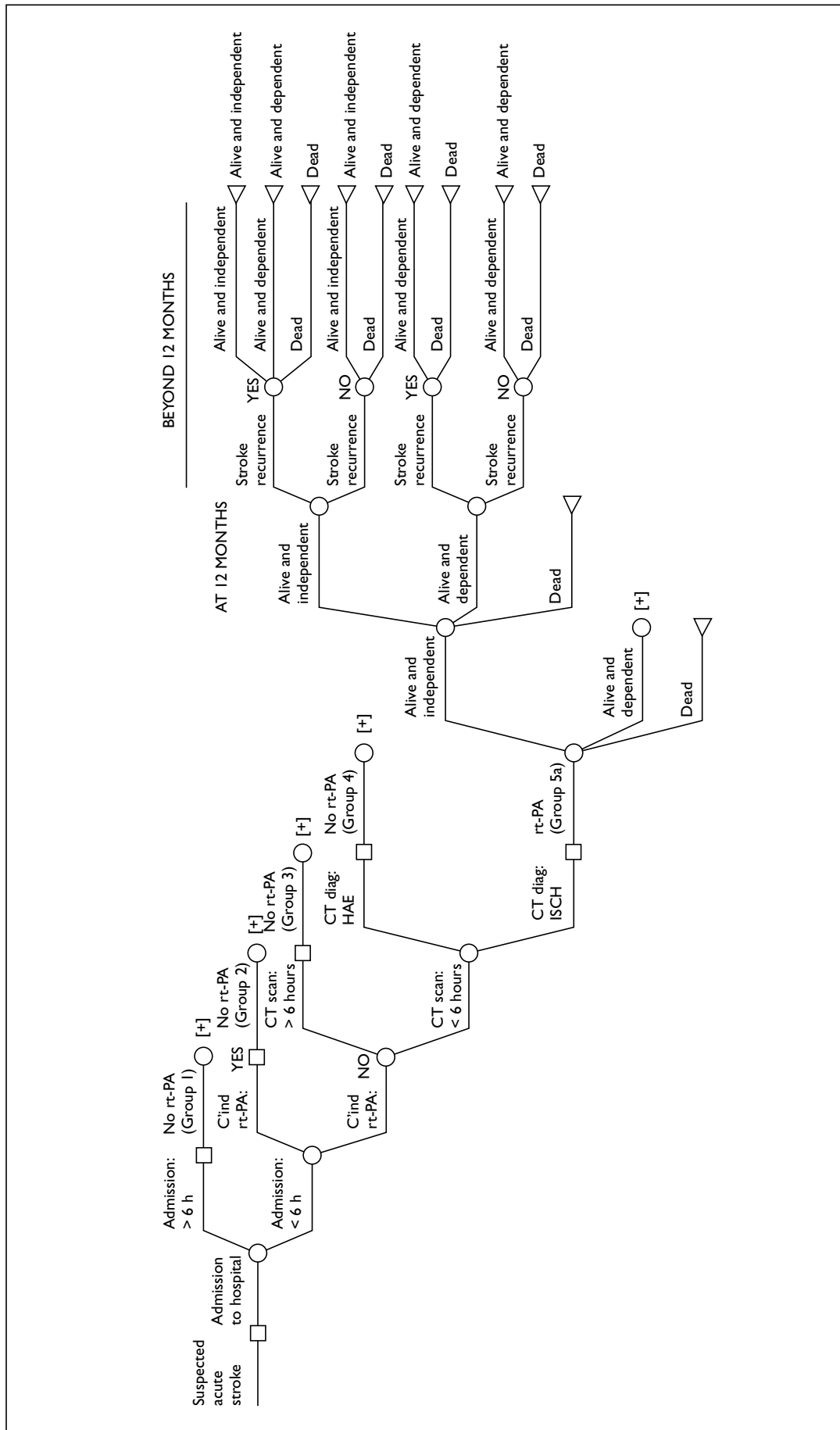


FIGURE 9 The Markov model. The Markov model is displayed only for patients who are in the independent health state after rt-PA treatment. The Markov model is identical at every node ending with [+] (C'ind, contraindication; CT diag, CT diagnosis; HAE, intracranial haemorrhage; ISCH, ischaemic stroke)

TABLE 7 Probabilities of different functional outcomes after acute ischaemic stroke. Data from the LSR^{214,224}

Cohort sub-group*		Outcome		
		Independent	Dependent	Dead
Group 1	6 months	0.4079	0.3827	0.2094
	12 months			
	Independent	0.8813	0.1359	–
	Dependent	0.0799	0.7646	–
Group 2	6 months	0.1066	0.3770	0.5164
	12 months			
	Independent	0.7500	0.0930	–
	Dependent	0.1667	0.7674	–
Group 3	6 months	0.3673	0.3714	0.2612
	12 months			
	Independent	0.8837	0.1573	–
	Dependent	0.0930	0.7753	–
Group 4	6 months	0.2778	0.3889	0.3333
	12 months			
	Independent	0.8000	0.1429	–
	Dependent	0.2000	0.8571	–
Group 5	6 months	0.3953	0.3256	0.2791
	12 months			
	Independent	0.8750	0.1111	–
	Dependent	0.0938	0.7407	–
Group 5a [†]	6 months	0.4529	0.2373	0.3099
	12 months			
	Independent	0.8750	0.1111	–
	Dependent	0.0938	0.7407	–
	6 months	0.0313	0.1481	–
	12 months			
	Independent	0.8750	0.1111	–
	Dependent	0.0938	0.7407	–
	6 months	0.0313	0.1481	–
	12 months			
	Independent	0.8750	0.1111	–
	Dependent	0.0938	0.7407	–
	6 months	0.0313	0.1481	–
	12 months			
	Independent	0.8750	0.1111	–
	Dependent	0.0938	0.7407	–
	6 months	0.0313	0.1481	–
	12 months			
	Independent	0.8750	0.1111	–
	Dependent	0.0938	0.7407	–
	6 months	0.0313	0.1481	–
	12 months			
	Independent	0.8750	0.1111	–
	Dependent	0.0938	0.7407	–
	6 months	0.0313	0.1481	–
	12 months			
	Independent	0.8750	0.1111	–
	Dependent	0.0938	0.7407	–
	6 months	0.0313	0.1481	–
	12 months			
	Independent	0.8750	0.1111	–
	Dependent	0.0938	0.7407	–

* Group 1: patients admitted after 6 hours; Group 2: patients admitted within 6 hours, but with contraindications to rt-PA; Group 3: patients admitted within 6 hours and without contraindications, but CT scan performed after 6 hours; Group 4: patients admitted within 6 hours, no contraindications, CT scan performed within 6 hours, but haemorrhage on CT scan; Group 5: patients admitted to hospital in time, no contraindications, CT scan performed within 6 hours, no haemorrhage on CT scan; Group 5a: Group 5 now receiving rt-PA

[†] Outcomes at 6 and 12 months in patients receiving rt-PA is calculated by effect estimates in chapter 2

derived from EuroQol-5 dimensions (EQ-5D) categorical scores measured in a sample of 147 LSR patients. Utilities were generated from these responses, using the preferences of the general public.²¹² These patients had also been assessed by standard measures of dependence, so relative preferences for the three different health states could be assigned: of 0.74 for independence, 0.38 for dependence, and 0.00 for death.²¹² These estimates are remarkably similar to the utilities obtained with the same method in 867 IST patients²¹² and to those derived from a systematic review of the relevant literature, which was published after these analyses were prepared.²¹³

Costs

The economic outcome summary measure is the difference in estimated healthcare costs between the two treatment alternatives (5 and 5a). All cost estimates (*Table 6*) reflect 1999–2000 prices. Health sector costs were identified, measured and valued from a NHS public sector perspective.^{209,215}

Assumptions about costing

We calculated the cost of hospital admission by multiplying the expected cost per hospital day by the LOS for patients in different functional outcome categories at 12 months.²⁰⁹ We did not assume extra costs due to increased numbers of intracranial haemorrhage with rt-PA, and the list

price of rt-PA of £480 was taken as the base-case estimate of the cost of rt-PA. We classified stroke care after discharge into ambulatory rehabilitation (use of therapists and residential facilities) and long-term care (nursing home, carer/sheltered home, and own home), according to a model developed by MEDTAP International (London, UK).^{219,220} In this model, resource use for disabled and non-disabled patients were estimated by an expert panel of clinicians, and combined with unit costs obtained from standard national sources.^{228,229} We assumed that the costs of hospital admission for recurrent stroke (cost per hospital day and LOS) were the same as the costs of the initial admission. We also assumed that patients would not be re-treated with rt-PA on subsequent admissions with recurrent stroke.

We sought to assess the typical additional costs of implementing rt-PA treatment in an ‘average’ district general hospital. However, we were unable to define either a nationally agreed level of resource use required to deliver thrombolysis for acute stroke or to obtain reliable measures of the variation in the current level (and cost) of acute stroke care in UK hospitals. We therefore sought to identify in a qualitative way the specific extra resources we considered necessary to deliver thrombolysis (in the context of an RCT) in our own hospital (*Table 8*).²¹⁷ However, as the Western General Hospital is probably not ‘typical’ and we suspect the variations in resources allocated to acute stroke care vary enormously in the UK, any quantitative estimates derived from these data could not be reliably extrapolated to other hospitals in the UK.

The health-economic summary measure

The chosen economic summary measure in this study is the incremental cost-effectiveness ratio among patients eligible for rt-PA. The possible outcomes of economic evaluations can be illustrated by using a permutation matrix.²³⁰ *Figure 10* shows the nine different permutations and uses shading to show the strength of each permutation of costs and effects in terms of decision-making. The chosen health-economic outcome measure in this study, the incremental cost-effectiveness ratio, is calculated by dividing the difference in mean costs by the difference in mean health effects (life-years gained or QALYs). A positive incremental cost-effectiveness ratio indicates an increase in cost per QALY gained (cell *A*), a zero value means that there is no increase in cost per QALY gained, and a negative value signifies a decrease in cost per QALY gained (cell *G*). When there is no increase in QALYs,

however (cells *B*, *E*, *H*), or when there is a loss in QALYs (cells *C*, *F*, and *I*), the incremental cost-effectiveness ratio has no meaningful interpretation.

Adjustment for timing of costs and benefits

We assessed the cost-effectiveness of thrombolysis at 12 months and at the end of the cohort lifetime. We took account of the longer time horizon over which costs and health benefits may accrue by discounting outcomes and cost at an annual rate of 6%.

Allowance for uncertainty Simple sensitivity analyses and threshold analyses

We performed a number of sensitivity analyses and threshold analyses to explore the impact of varying key parameters in the model, by systematically varying parameters throughout their range of values:

- rt-PA efficacy (i.e. ORs for ‘death’ and ‘death or dependency’)
- system efficiency (i.e. speed of patient admission and assessment)
- utility values
- costs of rt-PA treatment
- length of hospital stay
- unit cost per inpatient day.

We systematically varied each assumption throughout its range of values.

Extreme scenario analyses

We explored the impact of varying rt-PA efficacy by using the lower and upper 95% CIs of the OR for the effect of rt-PA on ‘death’, and ‘death or dependency’ (see chapter 2). We defined a ‘best-case’ scenario by assuming a minimum probability of ‘death or dependency’ (or, in other words, maximum probability of ‘independence’) and minimum probability of ‘death’, and vice versa for ‘worst-case’. To ensure that probability coherence was maintained in the model, the probability of ‘dependency’ was then calculated by subtracting these probabilities from 1.0. Using the ranges of ORs for rt-PA efficacy in *Table 6*, we obtained the following ranges of probabilities for the three different outcomes at 6 months:

- Independence 0.4155–0.4902
- Death 0.2668–0.3579
- Dependency 0.2266–0.2430.

We were also interested to see whether a more efficient system able to deliver rt-PA to a larger

TABLE 8 Examples of extra resources required to deliver thrombolytic therapy safely and effectively

Patient status	Regular assessment	Time to assessment	For rt-PA: additional effort	Extra costs required
Patient arrives in ARU	Nurse triage	0 minutes	Nurse triage	
	Non-urgent ARU doctor assessment (senior house officer level)	40 minutes (median delay)	Nurse activates stroke team	5 minutes additional nurse time
	Non-urgent bloods	Next day	Urgent stroke team assessment (registrar grade)	30 minutes registrar time
			Urgent bloods + clotting (within 1 hour)	Extra lab effort Additional blood test
Patient goes to CT scan	Non-urgent	Within 24 hours	Urgent (within 1 hour)	
	Accompanied by a nurse		Accompanied by the registrar	60 minutes registrar time
			Registrar waits for scan, reviews results	
			Consultant reviews scan, patient, discusses with relatives	30 minutes consultant time
Patient to stroke ward	Nurse assessment – routine observations	Junior nurse Non-urgent	Nurse assessment (senior nurse) Immediate neuro observations	Same time, just immediate and by more senior nurse
			rt-PA infusion: Drawn up, bolus injected, commence infusion	75 minutes registrar time
Care over first 24 hours	Routine observation four times per day	Four observations/ 24 hours	15-minutely observation for 60 minutes 1-hourly observation for 4 hours 2-hourly observation for 8 hours, then four times per day	12 additional sets of observations Senior nurse requires 1:1 care for 5 hours
	Routine junior staff review	Once in 24 hours	Registrar review twice in next 24 hours	25 minutes registrar time
	Consultant review at 24 hours	15 minutes	Overnight junior staff review Consultant review after infusion Consultant review at 24 hours	Additional 10 minutes 20 minutes additional consultant time

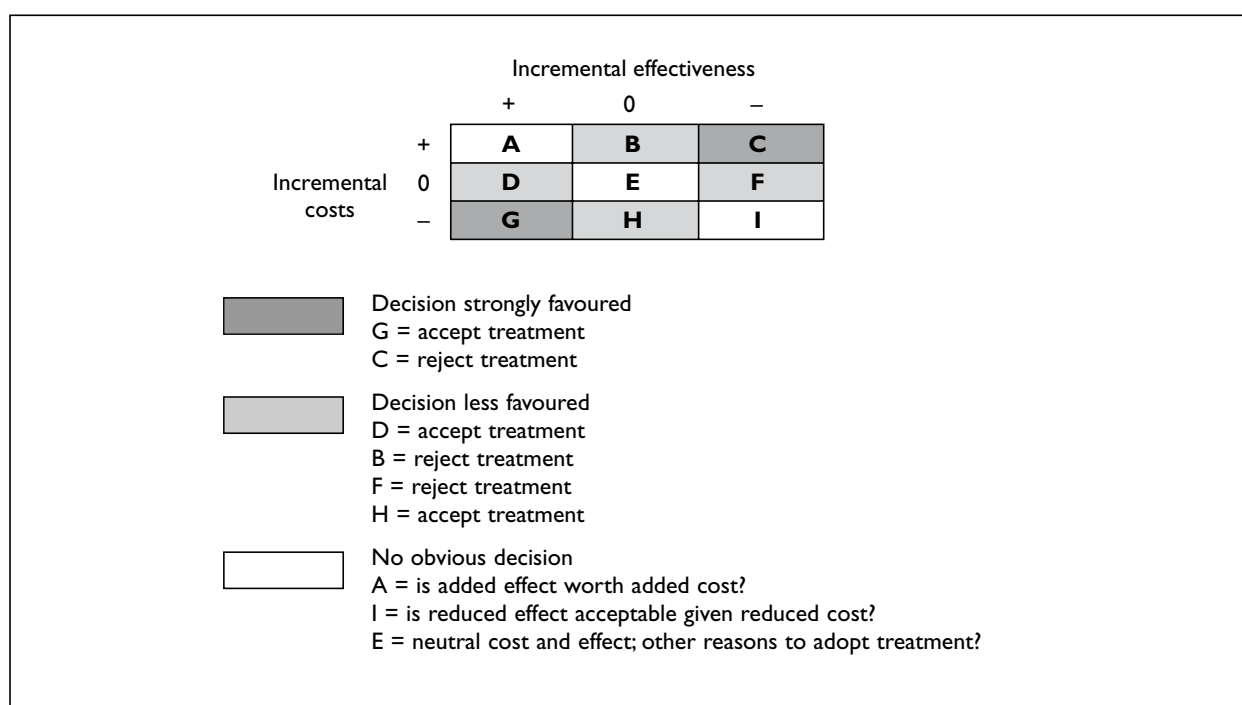


FIGURE 10 Permutation matrix for possible outcomes of economic evaluations for study of intervention versus comparator

proportion of patients would make any difference to the impact of rt-PA. In the base-case analysis just over 5% of patients admitted to hospital were eligible for rt-PA (i.e. Group 5). We now assumed that the speed of admission to hospital and CT scanning could be increased so that that some patients, who were previously ineligible because of delayed admission (Group 1) or delayed CT scanning (Group 3), could become eligible for thrombolytic treatment. These two ‘new’ groups are named Group 5(1) and Group 5(3), respectively (*Figure 11*).

Figure 11 also shows the pathways probabilities in a system where 70% of all patients are admitted within 6 hours (allowing for the fact that about 30% of all patients will have symptoms on waking), and where all of these patients are scanned without delay. Ideally, we should also have performed sensitivity analyses taking into account variation in discharge dispositions and a plausible range of costs of long-term care, but these data were not available to us. Furthermore, current NHS data on the costs of long-term care are distorted by two factors which tend to prolong hospital stays: firstly, there is a lack of nursing home places, and secondly, there are often delays in setting up complex packages of home care for many patients.

Probabilistic sensitivity analysis (Monte Carlo simulation)

The sensitivity analyses explore the impact on the cost-effectiveness ratio of varying each parameter

across its range of possible values, but it does not consider the frequency distribution of the different values. In Monte Carlo simulation each parameter is assigned a frequency distribution (e.g. normal distribution or a uniform distribution).²³¹ The analysis randomly draws a new value from within the distribution during each of 10,000 iterations, and this results in a probability distribution of outcomes (health outcomes, costs, or cost-effectiveness ratios) that can be used to construct the 5th and 95th percentiles.

We performed several ‘one-way’ Monte Carlo simulations to assess the uncertainty due to variation in individual parameters. We also performed a multi-way Monte Carlo simulation to determine how likely certain levels of cost-effectiveness were when we simultaneously incorporated all ranges of values for variables listed in *Table 6*. We again performed 10,000 iterations; in each iteration, we used newly selected values from within the ranges. When a Monte Carlo simulation is performed, a proportion of the iterations may show a loss in QALYs. As the incremental cost-effectiveness ratio is not applicable in those cases, the percentiles for the incremental cost-effectiveness ratios can not be calculated for the proportion of iterations showing a loss in QALYs. In such cases, percentiles are calculated for the proportion of iterations showing a gain in QALYs, and reflect the 5th and 95th percentiles **assuming** that there is a gain in QALYs.

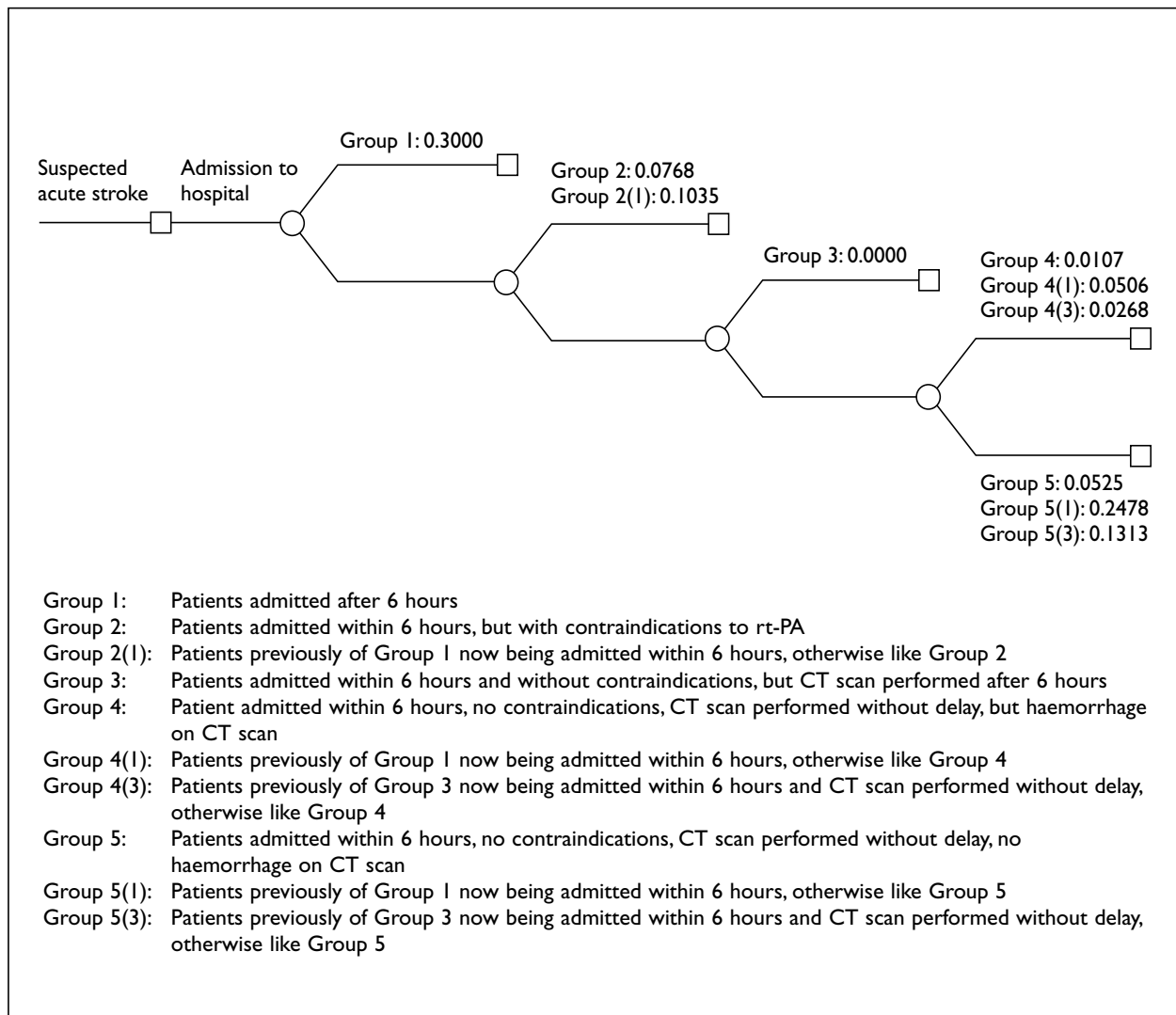


FIGURE 11 Pathway probabilities in a system that is optimal for rt-PA treatment

Results

Cost-effectiveness at 12 months

Table 9 presents the costs and outcomes at 12 months per 100 patients treated with rt-PA. The base case analysis assumes that only 5.3% of the patients admitted to hospital were eligible for rt-PA treatment, and shows that treatment with rt-PA costs an additional £11,001 and results in a QALY gain of 0.81 per 100 patients treated (and a loss of 2.7 life-years, data not shown). This gives a marginal cost-effectiveness ratio for rt-PA treatment of £13,581 per QALY gained. The multi-way Monte Carlo simulation showed that the 5th and 95th percentiles for the increase in costs at 12 months were -£44,065 and £47,095, respectively, and that the corresponding percentiles for the impact on health outcomes were -0.4020 and 1.8259 QALYs, respectively. The analysis also showed that there was a 85.5% probability of an increase in QALYs

by rt-PA treatment. If we assume that rt-PA increases QALYs, the 5th and 95th percentiles for the incremental cost-effectiveness ratio for this group (8550/10,000 trials) are -£81,680 (cost savings) and £142,505 (additional costs) per QALY gained.

Varying the efficacy of rt-PA

Table 9 also shows the impact of varying a selection of key parameters in the model, and the 5th and 95th percentiles reflecting the uncertainty that stems from the variation of those parameters. The impact of assuming the most optimistic estimate of rt-PA efficacy is to increase the number of QALYs gained from 0.81 to 3.68 and to reduce the costs from £11,011 to £1129 per 100 patients treated. This results in a considerable improvement in the marginal cost-effectiveness ratio, from £13,581 to £307. When we assume the least favourable estimate of rt-PA efficacy, rt-PA is no longer

TABLE 9 Costs (£), health outcomes (QALYs) and costs per QALY gained at 12 months per 100 patients eligible for rt-PA

	Costs per 100 patients		QALYs		Incremental costs (5th and 95th percentiles)*	Incremental QALYs (5th and 95th percentiles)*	Incremental costs per QALY gained (5th and 95th percentiles)*
	rt-PA	Standard	rt-PA	Standard			
Base-case analysis	625,965	614,964	41.05	40.24	11,001 (-44,065, 47,095)	0.81 (-0.4020, 1.8259)	13,581 [†]
Variation of parameter values							
rt-PA efficacy							
'Best-case' efficacy	616,093	614,964	43.92	40.24	1129 (1826, 19,262)	3.68 (-1.36, 2.82)	307 [†]
'Worst-case' efficacy	634,755	614,964	37.99	40.24	19,791 (1826, 19,262)	-2.25 (-1.36, 2.82)	Not applicable
System efficiency[‡]							
70% admitted within 6 hours (12% of patients eligible for rt-PA)	629,446	618,102	43.03	42.18	11,344 (11,041, 11,352)	0.85 (0.81, 0.86)	13,346 (13,140, 13,580)
No delay to CT (18% of patients eligible)	637,793	625,994	41.42	40.74	11,799 (11,001, 11,927)	0.68 (0.66, 0.73)	17,351 (15,753, 17,353)
50% admitted within 6 hours and no delay to CT (31% of patients eligible)	635,579	623,850	42.73	41.96	11,729 (11,537, 11,745)	0.77 (0.71, 0.80)	15,232 (14,479, 16,521)
70% admitted within 6 hours and no delay to CT (43% of patients eligible)	634,644	622,946	43.29	42.48	11,698 (11,537, 11,745)	0.81 (0.71, 0.80)	14,441 (14,479, 16,521)
Utility values							
Dependent state: decreased to 0.29	625,965	614,964	39.00	37.52	11,001 (i.e. no impact)	1.48 (0.21, 1.41)	7433 (7812, 54,234)
Dependent state: increased to 0.47	625,965	614,964	43.10	42.96	11,001 (i.e. no impact)	0.14 (0.21, 1.41)	78,579 (7812, 54,234)
Independent state: decreased to 0.69	625,965	614,964	38.86	38.29	11,001 (i.e. no impact)	0.57 (0.59, 1.03)	19,300 (10,707, 18,812)
Independent state: increased to 0.79	625,965	614,964	43.23	42.18	11,001 (i.e. no impact)	1.05 (0.59, 1.03)	10,477 (10,707, 18,811)
Cost of rt-PA treatment							
Doubled (to £1000)	673,965	614,964	41.05	40.24	59,001 (13,740, 56,578)	0.81 (i.e. no impact)	72,841 (16,461, 70,339)
LOS							
Dependent survivor increased to 78 days	743,799	765,212	41.05	40.24	24,771 (11,736, 24,076)	0.81 (i.e. no impact)	-26,436 (-24,539, 11,728)
Independent survivor increased to 31 days	769,651	744,880	41.05	40.24	-21,413 (-19,660, 9320)	0.81 (i.e. no impact)	30,581 (14,481, 29,873)
Unit cost per inpatient day							
Reduced to £150	481,474	461,223	41.05	40.24	20,251 (-31,232, 14,671)	0.81 (i.e. no impact)	25,001 (-38,993, 18,343)
Increased to £500	1,492,912	1,537,411	41.05	40.24	-44,499 (-31,232, 14,671)	0.81 (i.e. no impact)	-54,937 (-38,993, 18,343)

* 5th and 95th percentiles for the frequency distribution of incremental costs, incremental QALYs, and incremental cost-effectiveness ratios, based on ranges of possible values and assumptions given in Tables 6 and 7 (Monte Carlo one-way, two-ways (system efficiency) and three-ways (rt-PA efficacy) sensitivity analysis with 10,000 iterations). It does not represent the CI (reflecting random error) surrounding the point estimates in the table

[†] The Monte Carlo simulations were consistent with a (small) risk of loss of QALYs, in which case the costs per QALY gained is not applicable. The 5th and 95th percentiles for the incremental cost-effectiveness ratios, given that there is a gain in QALYs, are provided in the text

[‡] Analyses include patients who were excluded in the base-case analysis because of delayed admission, delayed CT scan, or both

the treatment of choice. The extra cost of treating patients with rt-PA instead of standard therapy increases from £11,011 to £19,791, and is associated with a loss of 2.25 QALYs.

The threshold analyses in *Figures 12a* and *12b* show that the utility of rt-PA treatment is sensitive to the probabilities of different functional outcomes 12 months after treatment ('sensitive' meaning that standard care becomes the dominant treatment option for some value within the plausible range of the parameter). *Figure 12a* shows that rt-PA is the preferred treatment when the value of the probability of death at 6 months following rt-PA is lower than 0.32996 (i.e. the threshold value for this variable), a value which lies within our plausible range (see *Table 6*). Similarly, *Figure 12b* shows that as long as the probability of independence following rt-PA at 6 months exceeds 0.4267, the rt-PA strategy remains more effective.

Monte Carlo simulation involving all three probability ranges showed that there is a 78.4% probability of increased QALYs. If we assume that rt-PA

increases QALYs, the 5th and 95th percentiles are £1812 and £101,500, respectively, per QALY gained.

Varying the efficiency of the healthcare system

This analysis is difficult to interpret, as we were unable to cost the resources required to give hospitals sufficient capacity to handle patients if 70% were admitted within 6 hours. There was only moderate impact of increasing the efficiency of the healthcare system. Raising the proportion of patients admitted within 6 hours from 30% to a maximum of 70%, or assuming no delay to CT, reduced the costs per QALY gained only slightly (from £13,581 to £13,346, or to £17,351, respectively). *Table 9* also shows costs and outcomes assuming 70% probability of admission to hospital within 6 hours and no delays to CT scan, which represent an upper limit of the probability of rt-PA treatment (i.e. 43%). The overall impact of treating these three (slightly different) groups of patients with rt-PA (Group 5, 5(1), and 5(3)) was very similar to the base-case analysis (where only Group 5 was given rt-PA), yielding an incremental cost-effectiveness ratio of £14,441 per QALY

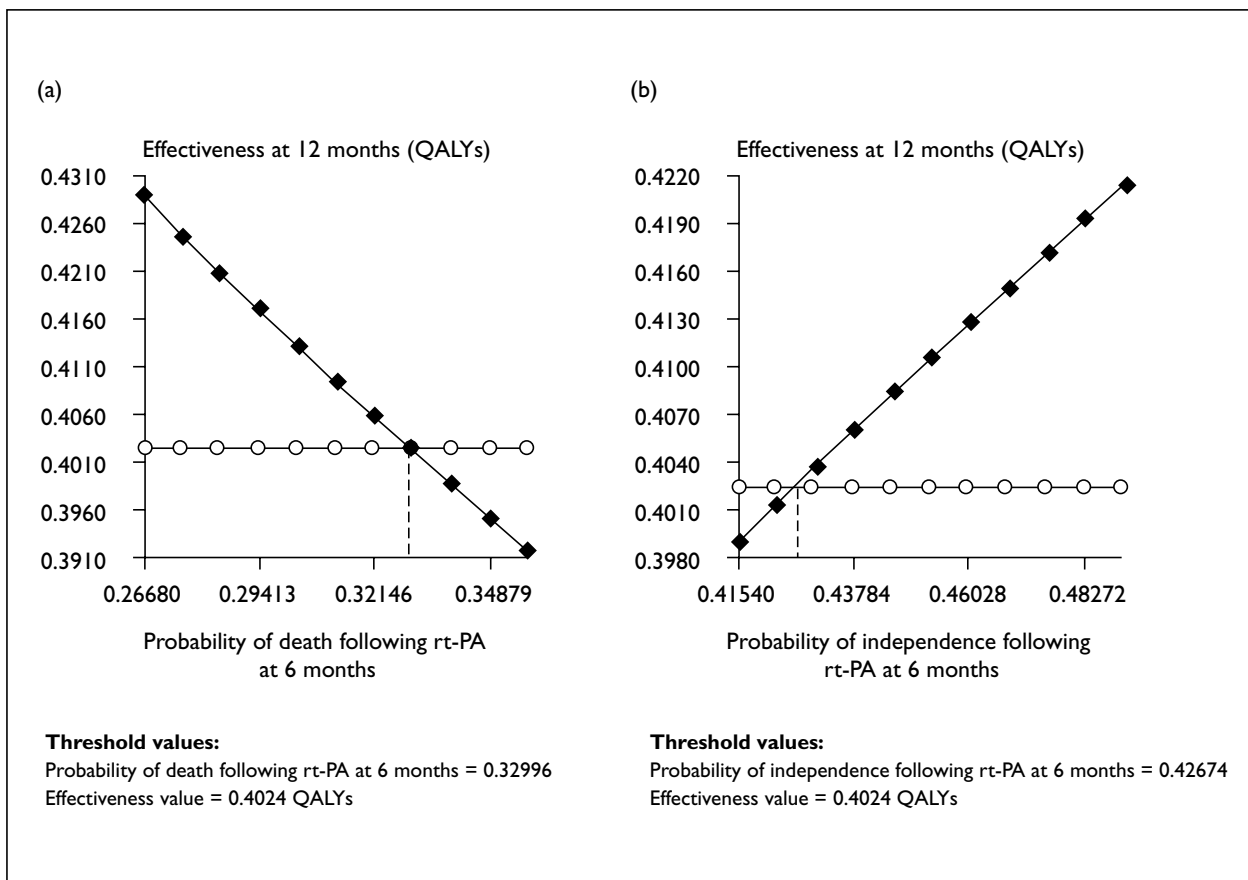


FIGURE 12 Sensitivity analysis: impact of varying the effect of rt-PA on a) death and b) independence. In 12a the x-axis represents the probability of being dead at 6 months with rt-PA; in 12b it represents the probability of being dependent at 6 months with rt-PA (○, No rt-PA (Group 5); ◆, rt-PA (Group 5a))

gained. The 5th and 95th percentiles also showed that the incremental cost-effectiveness ratio was relatively insensitive to variation in admission rate, delay to CT, and the combination of the two parameters (5th and 95th percentiles 14,479 and 16,521, respectively).

Varying both rt-PA efficacy and system efficiency

We also wanted to explore the range of marginal cost-effectiveness when varying more than one variable in Table 9 at the same time. For example, the combined impact of assuming a best-case scenario with respect to both rt-PA effectiveness and system efficiency (70% admitted within 6 hours and no delays to CT scanning) is an increased costs of £566 and a gain of 3.50 QALYs per 100 patients treated (marginal cost-effectiveness £162 per QALY gained, data not shown). On the other hand, if we assume the most unfavourable estimate of rt-PA effectiveness and that only 10% are admitted within 6 hours (i.e. only 1.8% of patients admitted to hospital receive rt-PA), there will be an increase in cost of £19,791 and loss of 2.25 QALYs (data not shown), which means that standard therapy

is the dominant strategy (i.e. more effective and less costly than rt-PA treatment).

Varying health state utility values

The utility values assigned to the two functional outcomes ('independence' and 'dependence') were varied within the plausible ranges shown in Table 6. A lower utility for the dependent health state (from 0.38 to 0.29) increased effectiveness (from 0.81 to 1.48 QALYs gained), while a higher utility (of 0.47) had the reverse impact (i.e. lowering effectiveness from 0.81 to 0.14 QALYs gained, Table 9). The threshold analysis illustrated in Figure 13a shows that as long as the utility for the dependent health state is lower than 0.489 the rt-PA strategy is more effective. This value lies just outside our plausible range of 0.29–0.47, which means that rt-PA is always the more effective treatment. The 5th to 95th percentiles interval for the marginal cost-effectiveness ratio is wide, however, ranging from £7812 to £54,234 per QALY gained.

A lower utility for the independent health state (from 0.74 to 0.69) reduced effectiveness (from 0.81 to 0.57) while a higher utility (of 0.79)

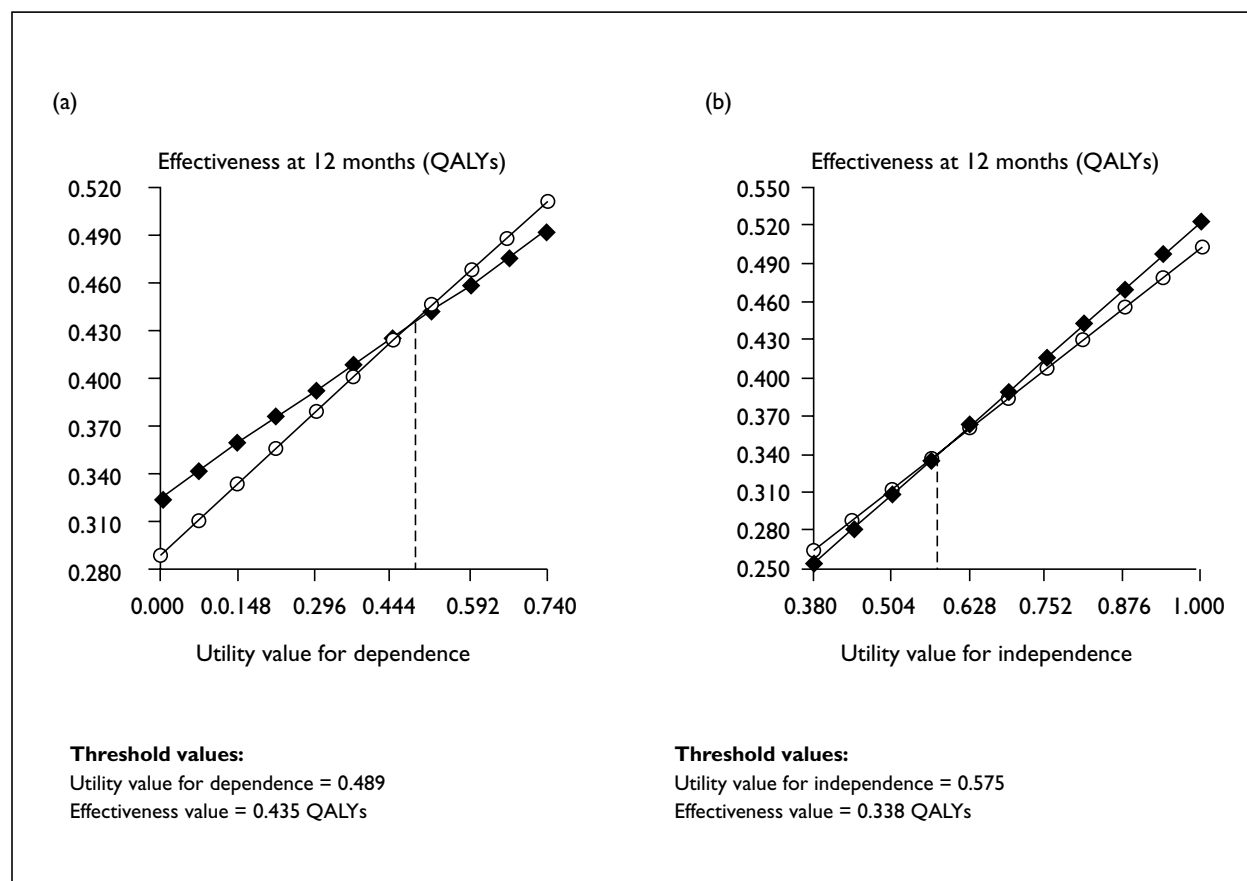


FIGURE 13 Sensitivity analysis: impact of varying utility values of a) the dependent and b) the independent health states after stroke. The x-axis is the utility value assigned to that health state (○, No rt-PA (Group 5); ◆, rt-PA (Group 5a))

increased effectiveness (from 0.81 to 1.05 QALYs gained, *Table 9*). The threshold analysis illustrated in *Figure 13b* shows that as long as the utility for the independent health state exceeds 0.575, rt-PA is more effective. Again, the value for this variable lies just outside our plausible range of 0.69–0.79, which means that rt-PA is always the more effective treatment. The cost-effectiveness across this interval ranges from £19,300 to £10,477 per QALY gained, and the 5th and 95th percentiles are 10,707 and 18,811, respectively.

Varying the unit cost of rt-PA

The cost-effectiveness estimates for treatment with rt-PA increases (worsens) as the unit cost of rt-PA rises. For example, a doubling of the unit cost used in the base case from £480 to nearly £1000 increases the marginal cost-effectiveness ratio more than five-fold (i.e. from approximately £13,581 to £72,841 per QALY gained – 5th and 95th percentiles 16,461 and 70,339, respectively). *Figure 14* shows that even an increase in the unit cost by 10% (to £528) results in a rise in the cost-effectiveness ratio to almost £20,000 per QALY gained (an increase of approximately 45%).

Varying LOS

Increasing the LOS of dependent survivors from 51 to 78 days results in a cost saving of £21,413 (*Table 9*) and a reduction in cost per QALY gained of £26,436 (5th and 95th percentiles £24,539 reduction and £11,728 increase, respectively).

A cost saving is first observed when the LOS exceeds approximately 62 days (*Figure 15*). Increasing the LOS of independent survivors from 14 to 31 days increases the marginal cost-effectiveness ratios of the rt-PA strategy from £13,581 to £30,581 (5th and 95th percentiles £14,481 and £29,873, *Table 9*).

Varying the unit cost per inpatient day

Lowering the unit cost per inpatient day from £200 to £150 increases the marginal cost-effectiveness estimates from £13,581 to £25,001. Raising the unit cost of this variable to £500 results in a cost saving of £44,499 (see also *Figure 16*). Indeed a cost saving is achieved when the unit cost exceeds approximately £290. The 5th and 95th percentiles of the incremental cost-effectiveness ratio, when allowing for variation in unit cost per inpatient day, were £38,993 reduction and £18,343 increase per QALY gained.

Cost-effectiveness at end of the cohort lifetime

Costs accrue in the short term (e.g. initial acute care), while survival gains accumulate over a far longer period, and analyses performed at 12 months therefore underestimate expected yield (e.g. in terms of QALYs gained) relative to costs. We therefore also wanted to estimate the likely cost-effectiveness of rt-PA over the longer term. *Table 10* presents the costs and outcomes at the end of the cohort life-time. The base-case

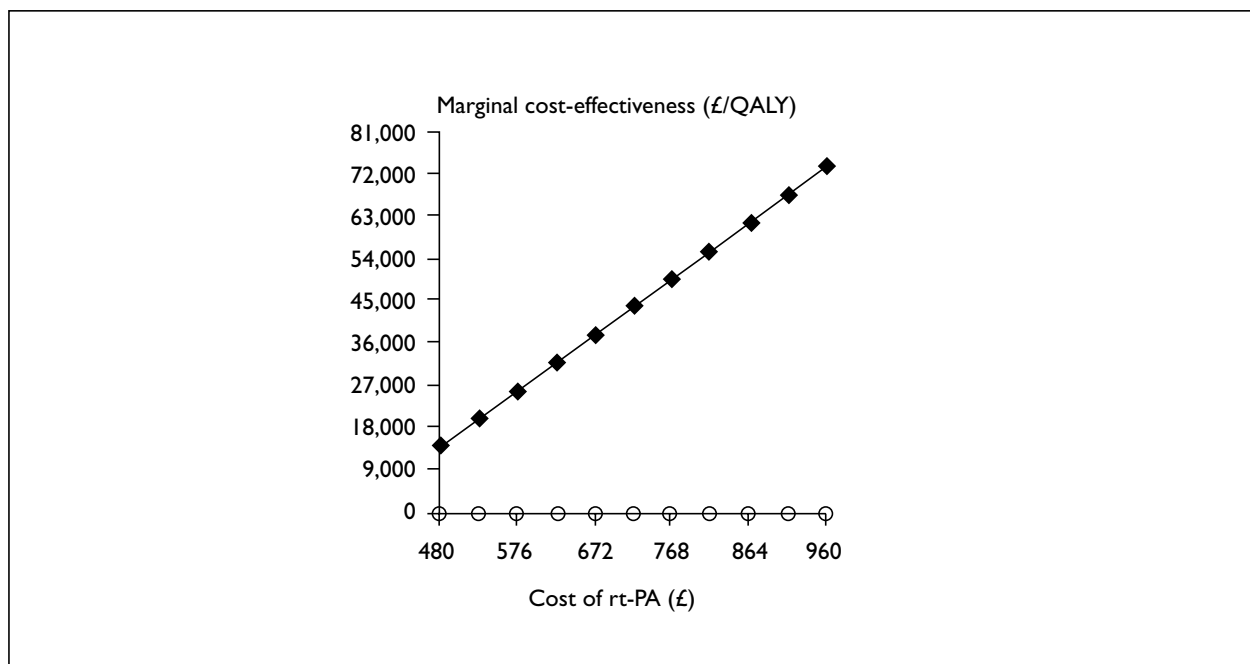


FIGURE 14 Sensitivity analysis: impact of varying the unit cost of rt-PA treatment. Cost of rt-PA (○, No rt-PA (Group 5); ◆, rt-PA (Group 5a))

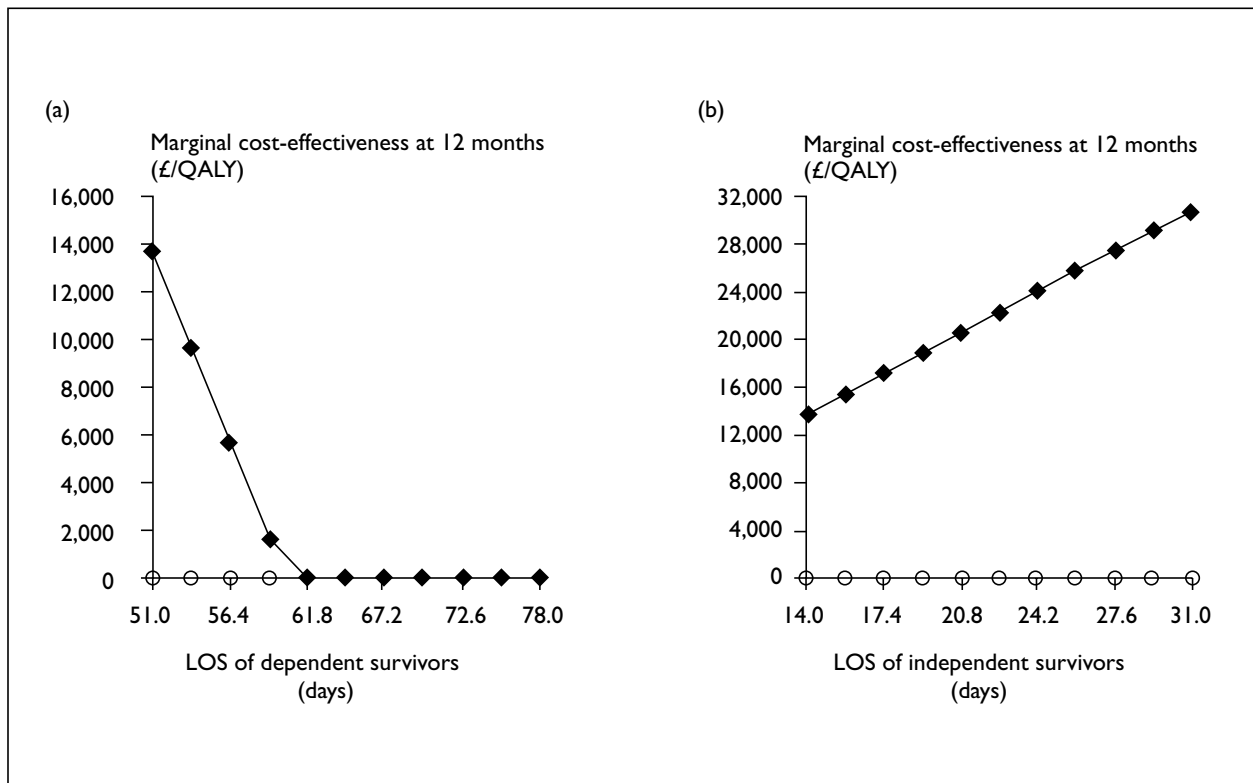


FIGURE 15 Sensitivity analysis: impact of varying the LOS for a) dependent and b) independent survivors (○, No rt-PA (Group 5); ◆, rt-PA (Group 5a))

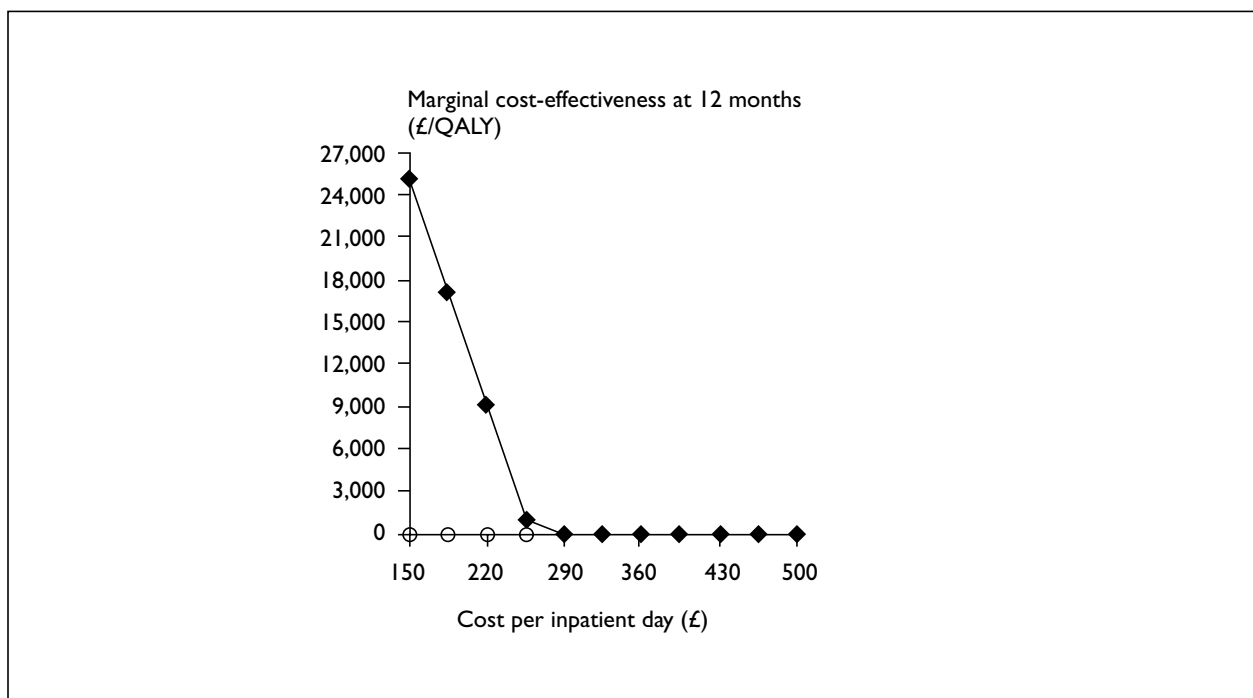


FIGURE 16 Sensitivity analysis: impact of varying the cost per inpatient day (○, No rt-PA (Group 5); ◆, rt-PA (Group 5a))

analysis shows that rt-PA then becomes the dominant strategy. Treatment with rt-PA is more effective (gain in QALYs of 3.63 per 100 patients treated) and less expensive than standard treatment (cost savings of £350,532), and results in a reduced cost of £96,565 per QALY gained. However, rt-PA was less effective in terms of life-years, with a loss of 1.22 years relative to standard treatment (data not shown).

The multi-way Monte Carlo simulation showed that there was a 76.6% probability of increased QALYs; the 5th and 95th percentiles for the reduction in costs were -£443,596 and -£306,685, respectively, and that the corresponding percentiles for the impact on QALYs were -3.32 and 8.48 QALYs, respectively. If we assume that rt-PA increases QALYs, the 5th and 95th percentiles for the incremental cost-effectiveness ratios for this group (7660/10,000 trials) are -£908,153 (net savings) and -£37,858 (net savings) per QALY gained.

Including or excluding costs of ambulatory rehabilitation and long-term care

Table 10 shows that by including only costs associated with re-hospitalisation for recurrent stroke (not costs of ambulatory rehabilitation and long-term care) rt-PA is still cost-effective with a marginal cost-effectiveness of £722 per QALY gained.

Varying the discount rate for future costs and QALYs

We also re-estimated the cohort lifetime results by discounting costs and benefits at a lower rate than in the base-case analysis (3% as opposed to 6% per annum). A lower discount rate increased the cost saving of £350,352 to £395,001 and generated a higher number of QALYs gained from 3.63 to 4.00 per 100 patients treated (marginal cost-effectiveness ratio of -£98,753 per QALY gained).

Varying the efficacy of rt-PA

The impact of assuming the most optimistic estimate of rt-PA efficacy was to increase the number of QALYs gained from 3.63 to 19.41, reduce the costs from £350,532 to £267,713 per 100 patients treated (Table 10), and change the marginal cost-effectiveness ratio from £96,565 to £13,793 saved per QALY gained. When we assume the least favourable estimate of rt-PA effectiveness, rt-PA results in a loss of 13.21 QALYs, and the incremental cost-effectiveness ratio can not be calculated. Monte Carlo simulation involving all three probability ranges showed that there was a 74.6% probability of increased QALYs. If we assume that rt-PA increases QALYs, the 5th and

95th percentiles are -£724,604 and -£25,237, respectively, per QALY gained.

Varying the efficiency of the healthcare system

Treatment with rt-PA was the dominant strategy for all values of the system efficiency parameters (admittance within 6 hours and no delay to CT). The incremental cost-effectiveness ratio varied from £96,534 to £157,869 saved per QALY gained, and the 5th and 95th percentiles showed that the incremental cost-effectiveness ratio was robust to variation of the system efficiency parameters.

Varying health state utility values

Treatment with rt-PA was also the dominant strategy for all utility values assigned to the independent and dependent state. The gain in QALYs ranged from 0.49 to 6.77, and all the 5th percentiles were consistent with a gain in QALYs.

Varying the unit cost of rt-PA

The cost-effectiveness estimates for treatment with rt-PA increases (worsens) only slightly as the unit cost of rt-PA rises, and doubling of the unit cost used in the base case from £480 to nearly £1000 is still associated with large benefits in terms of both costs and effectiveness (incremental cost-effectiveness ratio £83,342 saved per QALY gained).

Varying LOS

Increasing the LOS of dependent or independent survivors still results in large cost savings and incremental cost-effectiveness ratios of £92,432 and £105,366 saved per QALY gained, respectively.

Varying the unit cost per inpatient day

The analyses also showed that rt-PA is the dominant treatment strategy when the unit cost per inpatient day is varied within its range of possible values. The incremental cost-effectiveness ratio is robust to changes in the unit cost per inpatient day, varying from £93,440 to £115,317 saved per QALY gained.

Discussion

The base-case analysis showed that treatment with rt-PA was associated with an additional cost of £13,581 per QALY gained during the first 12 months after treatment. This estimate is considerably higher than the published estimates for treatment with rt-PA for myocardial infar-

TABLE 10 Costs (£), health outcomes (QALYs) and costs per QALY gained at the end of the cohort life-time per 100 patients eligible for rt-PA

	Costs		QALYs		Incremental costs (5th and 95th percentiles)*	Incremental QALYs (5th and 95th percentiles)*	Incremental costs per QALY gained (5th and 95th percentiles)*
	rt-PA	Standard	rt-PA	Standard			
Base-case analysis	2,620,862	2,971,394	227.01	223.38	-350,352 (-443,596, -306,685)	3.63 (-3.32, 8.48)	-96,565 [†]
Variation of parameter values							
Cost of stroke care							
Costs of ambulatory rehabilitation and long-term care omitted	769,350	766,729	227.01	223.38	2621 (-67,426, 36,813)	3.63 (-3.32, 8.48)	722 (-48,800, 18,416)
Discount rate (costs and QALYs)							
Reduced to 3%	3,296,580	2,901,569	254.98	250.98	-395,001 (-392,415, -352,429)	4.00 (3.64, 3.98)	-98,753 (-98,608, -96,716)
rt-PA efficacy							
'Best-case' efficacy	2,703,681	2,971,394	242.79	223.38	-267,713 (-447,037, -272,929)	19.41 (-8.18, 14.71)	-13,793 [†]
'Worst-case' efficacy	2,511,447	2,971,394	210.17	233.38	-459,457 (-447,037, -272,929)	-13.21 (-8.18, 14.71)	Not applicable
System efficiency[‡]							
70% admitted within 6 hours (12% of patients eligible for rt-PA)	2,831,410	3,178,934	239.82	236.22	-347,524 (-350,211, -347,589)	3.60 (3.60, 3.62)	-96,534 (-96,616, -96,583)
No delay to CT (18% of patients eligible)	2,837,413	3,197,354	232.21	229.93	-359,940 (-359,830, -356, 394)	2.38 (2.30, 2.79)	-157,869 (-156,621, -127,964)
50% admitted within 6 hours and no delay to CT (31% of patients eligible)	2,898,050	3,252,076	239.12	236.32	-354,026 (-357,878, -351,600)	2.80 (2.50, 3.09)	-126,438 (-143,321, -113,975)
70% admitted within 6 hours and no delay to CT (43% of patients eligible)	2,923,629	3,275,160	242.04	239.01	-351,531 (-357,878, -351,600)	3.03 (2.50, 3.09)	-116,016 (-143,321, -113,975)
Utility values							
Dependent state: decreased to 0.29	2,620,862	2,971,394	213.63	206.86	-350,352 (i.e. no impact)	6.77 (0.81, 6.43)	-51,777 (-433,922, -54,201)
Dependent state: increased to 0.47	2,620,862	2,971,394	240.39	239.90	-350,352 (i.e. no impact)	0.49 (0.81, 6.43)	-715,371 (-433,922, -54,201)
Independent state: decreased to 0.69	2,620,862	2,971,394	215.49	213.00	-350,352 (i.e. no impact)	2.49 (2.60, 4.65)	-140,776 (-134,610, -75,427)
Independent state: increased to 0.79	2,620,862	2,971,394	238.53	233.76	-350,352 (i.e. no impact)	4.77 (2.60, 4.65)	-73,487 (-134,610, -75,427)
Cost of rt-PA treatment							
Doubled (to £1000)	2,668,862	2,971,394	227.01	223.38	-302,532 (-384,140, -304,994)	3.63 (i.e. no impact)	-83,342 (-95,989, -84,039)

continued

TABLE 10 contd Costs (£), health outcomes (QALYs) and costs per QALY gained at the end of the cohort life-time per 100 patients eligible for rt-PA

	Costs		QALYs		Incremental costs (5th and 95th percentiles)*	Incremental QALYs (5th and 95th percentiles)*	Incremental costs per QALY gained (5th and 95th percentiles)*
	rt-PA	Standard	rt-PA	Standard			
Variation of parameter values							
LOS							
Dependent survivor increased to 78 days	2,777,416	3,112,945	227.01	223.38	-335,529 (-349,793, -336,268)	3.63 (i.e. no impact)	-92,432 (-96,404, -92,698)
Independent survivor increased to 31 days	2,773,565	3,156,042	227.01	223.38	-382,477 (-380,838, -352,076)	3.63 (i.e. no impact)	-105,366 (-104,981, -97,091)
Unit cost per inpatient day							
Reduced to £150	2,440,525	2,779,712	227.01	223.38	-339,187 (-402,246, -345,931)	3.63 (i.e. no impact)	-93,440 (-110,795, -95,377)
Increased to £500	3,702,887	4,121,488	227.01	223.38	-418,601 (-402,246, -345,931)	3.63 (i.e. no impact)	-115,317 (-110,795, -95,377)

* 5th and 95th percentiles for the frequency distribution of incremental costs, incremental QALYs, and incremental cost-effectiveness ratios, based on ranges of possible values and assumptions given in Tables 6 and 7 (Monte Carlo one-way, two-ways (system efficiency) and three-ways (rt-PA efficacy) sensitivity analysis with 10,000 iterations). It does not represent the CI (reflecting random error) surrounding the point estimates in the table

† The Monte Carlo simulations were consistent with a (small) risk of loss of QALYs, in which case the costs per QALY gained is not applicable. The 5th and 95th percentiles for the incremental cost-effectiveness ratios, given that there is a gain in QALYs, are provided in the text

‡ Analyses include patients who were excluded in the base-case analysis because of delayed admission, delayed CT scan, or both

tion,^{232,233} but it is still well within the range of cost-effectiveness for healthcare interventions offered within the NHS.²³⁴ The base-case estimate at 12 months is also comparable to some interventions for ischaemic stroke, such as ticlopidine for secondary prevention, surgery in asymptomatic carotid stenosis, and anticoagulation in low-risk patients with atrial fibrillation.¹⁰ However, the base-case estimate was very imprecise; the Monte Carlo simulations indicated that there was a 15% probability of a loss of QALYs with rt-PA treatment. Even if we assume that rt-PA increases QALYs, the 5th and 95th percentiles for the incremental cost-effectiveness ratio for this group (8550/10,000 trials) were –£81,680 (cost savings) and £142,505 (additional costs) per QALY gained. With such uncertainty it is difficult to justify widespread implementation in the NHS.

When the model was run to the end of the cohort lifetime, there appeared to be a substantial cost **saving** of £96,565 per QALY gained. This is consistent with the findings of other studies that have modelled the long-term health-economic impact of rt-PA.^{11,28,220} However, such non-standardised comparisons of cost-effectiveness are fraught with methodological difficulties, and should therefore be interpreted with extreme caution.^{234,235} First both the short- and long-term cost-effectiveness estimates were very imprecise. At 12 months, the 5th and 95th percentiles for the impact on costs ranged from a cost saving of £44,065 on the one hand, to an extra cost of £47,095 on the other. Likewise, the 5th and 95th percentiles for the impact on health outcomes were a loss of 0.4020 QALYs and a gain of 1.8259 QALYs, respectively. There is therefore considerable uncertainty about the exact size of the incremental cost-effectiveness ratio for rt-PA in acute stroke. The cost-effectiveness estimates were sensitive to rt-PA efficacy and costs of rt-PA. Other parameters thought to be important, such as ‘system efficiency’ and patient values did not have any significant impact on the incremental cost-effectiveness ratio.

Second, the cost-effectiveness estimate at 12 months is heavily influenced by the source of the data in the model.²³⁴ This may invalidate the comparison between our study and previous studies of cost-effectiveness of rt-PA in stroke,^{11,28,220} and may explain the different short-term results. In contrast to earlier studies, we found that the cost savings were not realised within the first 1–2 years after treatment. One likely explanation is that the other studies were based on the more optimistic estimates of rt-PA effectiveness from

the single NINDS trial¹⁷ or the three major rt-PA trials.^{17,63,71} They also used more favourable values for patients’ preferences.^{236,237} We based our estimates of the effectiveness of rt-PA on the results of a systematic review of all the available evidence from RCTs performed to date (see chapter 2). Furthermore, we used more conservative estimates of the patient valuation of the dependent state which, as it turned out, were close to the estimates derived from a recent systematic review of patient utilities after stroke.²¹³ We believe therefore that our overall assessment of cost-effectiveness is closer to that likely to be found in clinical practice.

Third, the uncertainty in the long-term results relates not only to the data variability and the source of the data, but also to the appropriateness of the methods used.²³⁴ We are aware that the assumption (also applied by Fagan¹¹) that long-term survival is equal in dependent and independent survivors may not hold true. Samsa and Matchar used a model with input from various sources, which suggested that among stroke patients who survived 6 months, disability level at 6 months was an important determinant of subsequent survival (i.e. survival was worse with increasing disability).⁸⁸ This finding should ideally be replicated by analysis of independent data sets. However, had we incorporated such a differential effect on survival for dependent and independent patients, this would have favoured rt-PA, as thrombolytic treatment increases the number of independent, and decreases the number of dependent survivors. We also had no access to sample data about the resource use in the long term, and therefore used estimates from a panel of experts.^{219,220} The validity of the model relies heavily on the accuracy of these estimates, and an analysis based on actual sample data would have been preferable.²³⁸

Another uncertainty relates to the generalisability of the findings.²³⁴ It is likely that both resource use (e.g. LOS) and the valuation of resources (e.g. mean unit cost per inpatient day) will vary considerably within the NHS. However, we have used national official figures to ‘average out’ local differences in unit costs,²¹⁵ and we believe that the resources used by patients registered in the LSR is reasonably representative of the resources use by stroke patients admitted to other UK hospitals. The sensitivity analysis points to several key parameters that affect the incremental cost-effectiveness ratio of rt-PA, and can be used to estimate the costs associated with different levels of resource use in different locations.

Our analysis did not include the costs of implementing rt-PA in NHS hospitals. We have assumed

that there are no capacity constraints in the healthcare system, and that there are no extra costs associated with giving rt-PA to more patients. For example, we have assumed that:

- all admissions are equal, regardless of when they occur
- CT scanning equipment is always readily available
- the correct number and mix of healthcare professionals and hospital beds are always in place.

We sought to assess these additional costs of rt-PA treatment by identifying the specific service components we considered likely to be required to deliver thrombolysis in our hospital, over and above those required for 'standard' acute stroke care (*Table 8*). However, we were unable to find a nationally agreed level of resource use required to deliver thrombolysis for acute stroke and no reliable measures of the variation in the current level (and cost) of acute stroke care.

Chapter 6

Conclusions

Implications for practice

Thrombolysis

- The data available are limited. However, with the thrombolytic agents tested in recent trials there was, overall, proof beyond all reasonable doubt of a substantial excess risk of fatal intracranial haemorrhage and death from all causes. This hazard appeared to be increased if anti-thrombotic drugs were given concurrently.
- After a few months, the immediate risks are offset by reductions in dependent survival, so that at 3–6 months there was a net benefit. There was a significant reduction in the proportion of patients who were dead or dependent at the end of follow-up (i.e. significantly more patients were alive and independent).
- Despite the substantial net benefit, the available data did not provide sufficient evidence to determine reliably how much the treatment effect was modified by various factors: age, time from stroke onset, the clinical deficit, or the radiological features on a pretreatment scan. This makes it difficult to identify the patients most likely to be benefited (or harmed) by thrombolysis.
- The greatest amount of data were available for intravenous rt-PA. Indirect comparisons suggested it was associated with fewer deaths and more patients benefiting than other agents.
- In the light of these considerations, although rt-PA is not yet licensed in the UK, some clinicians may choose to use it in highly selected patients. Others, who are concerned about the definite risks, may choose not to use the treatment.

Neuroprotection

- In early 2002, there were no data to support the use of any neuroprotective intervention routinely for patients with acute stroke.
- Furthermore, none of the agents had a product licence for use in acute stroke. Even if neuroprotective drugs do become licensed, they are unlikely to be a panacea, and will need to be given in the context of a well-organised acute stroke service.
- The features of a service that can deliver neuroprotective treatment quickly, effectively and efficiently to patients with acute stroke in the NHS have yet to be defined.

Barriers to acute stroke care

- The included studies were very heterogeneous with respect to design, methodological quality, measures of outcome and study population. It was not possible to justify substantial changes to the delivery of acute stroke care on the basis of the evidence reviewed.
- However, this report does provide a checklist of potential barriers that could provide a framework for an audit of local acute stroke services. Such an audit could identify interventions needed to make the service more efficient.

Cost-effectiveness of thrombolysis

- From the perspective of the NHS, thrombolysis for acute stroke holds the promise, under favourable assumptions, of being cost-effective in terms of QALYs gained, particularly when the longer-term cost and health outcomes were considered.
- However, the range of possible incremental cost-effectiveness ratios was considerable, and the conclusions from the economic modelling were very sensitive to the assumptions made and a number of parameters, including the effectiveness of rt-PA. The less favourable estimates indicated that rt-PA could be either only marginally cost-effective, or even harmful (i.e. standard therapy is the preferred option).
- Thus, in the authors' opinion, because of the possibilities of net harm and only marginal cost-effectiveness, albeit under some quite plausible assumptions, the evidence does not currently support the use of thrombolysis in **routine** NHS practice.

Recommendations for research

Thrombolysis

The above uncertainties suggest that further large-scale randomised trials comparing thrombolytic therapy with control in patients with acute ischaemic stroke are justified:

- to confirm whether the advantage of thrombolytic therapy in terms of the reduction in death and dependency at 3 months does indeed persist to 6 months and beyond, as suggested by one trial

- to determine reliably the effects on short- and long-term survival
- to identify which categories of patient are most likely to benefit (and which to be harmed)
- to identify means of minimising the hazards without reducing the benefit
- to provide clearer evidence that, when used in a wider range of hospitals, thrombolytic therapy is associated with a definite net benefit.

Neuroprotection

- The trials in acute stroke to date have been relatively small (compared with the trials in AMI) and therefore it is possible that some agents with only moderate clinical benefits may have been abandoned prematurely.
- Hence, although some further efficacy trials may be justified to identify the most promising neuroprotective agents, some much larger megatrials with a few tens of thousands of patients may be justified to determine whether neuroprotective therapy is beneficial in routine clinical practice. Such trials could also help to define which categories of patient are most likely to gain from treatment and which are the most likely to suffer adverse effects (confusion, hallucinations and agitation have been common in the early trials). Large-scale trials could also help define the therapeutic time window; whether it is just a few hours or perhaps as long as 24 or even 48 hours for some particular categories of patients.
- If a neuroprotective agent is found to be effective, it would be worthwhile to update this review and perform a cost-effectiveness analysis. If, in addition, the agent is not toxic to patients who turn out not to have a stroke, and can safely be given before CT scanning, then pre-hospital treatment by paramedical staff would become an important way to deliver treatment with minimal delay (and hence maximal potential benefit).
- Further Health Service Research will be needed to identify:
 - the key components of effective acute stroke care
 - the specific components required to deliver neuroprotective therapy quickly and safely (e.g. pre-hospital treatment by paramedical staff), and
 - the likely costs and benefits of investing more NHS resources into acute stroke (whether or not a neuroprotective drug is licensed).

Barriers to acute stroke care

(not necessarily ranked in order of importance)

- There is evidence that public understanding of stroke is limited. Research is needed to identify the most cost-effective way to improve public knowledge of stroke sufficiently to ensure the proportion of patients seeking urgent medical help is increased and delay in reaching hospital is reduced.
- Further Health Service Research studies are justified to evaluate the most effective way to organise acute stroke care.
- If thrombolysis or neuroprotection were to be licensed in the UK, additional research will be needed to inform the design of acute stroke care services that can deliver acute treatment quickly, effectively, efficiently and equitably.

Cost-effectiveness of thrombolysis

- The cost-effectiveness of rt-PA could not be assessed reliably because of the imprecise estimates of its efficacy. Large-scale randomised trials would be needed to provide sufficiently precise estimates.
- If trials establish reliably that thrombolysis is effective, then better estimates of the costs of implementing thrombolysis for acute stroke in the NHS will be needed. A more ‘dynamic system approach’ to explore the relationships between different system components and their impact on patient treatment strategies would be informative.
- As the cost-effectiveness estimates were very sensitive to a relatively small set of parameters, future research could focus on the relationship between thrombolytic therapy, resource consequences and health effects. This could be done using techniques that permit estimates of the joint distribution of incremental costs and effectiveness. Bayesian resampling methods with Markov simulation could be an appropriate approach.
- More data are needed on the effect of the level of disability at 6 months after stroke on subsequent survival. If survival is greater and the degree of disability is less, this would improve the long-term cost-effectiveness of rt-PA. Research might profitably examine existing cohorts of stroke patients to estimate the size of this effect.



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Contributions of authors

Peter Sandercock designed the project, wrote the protocol, was the principal applicant for the grant, and the first author of this monograph. He also coordinated the design conduct, analysis and reporting of the work described in this monograph. He wrote the first drafts of the *Executive summary* and chapters 1 and 3, and takes final editorial responsibility for all aspects of the report and its publication.

Aileen Neilson developed the decision-analytic model, implemented the model on computer, entered all of the data and ran the models. She commented on the draft report.

Eivind Berge helped to develop the decision-analytic model, worked closely with Aileen Neilson to develop the analysis plan, and drafted the text and tables for chapter 5. He commented on the other sections of the report.

Martin Dennis helped to develop the protocol. Throughout the project he advised on aspects of the report to do with stroke service delivery and the use of thrombolysis in clinical practice. He commented on the draft report.

John Forbes commented on the protocol and advised Aileen Neilson on the cost-effectiveness analyses. He commented on the draft report.

Peter Hand helped to develop the decision-analytic model, contributed to the work of the systematic review of the barriers to effective stroke care and commented on the draft report.

Joseph Kwan helped to develop the decision-analytic model. He set up and ran the searches, entered the data and wrote the first draft of chapter 4. He commented on the draft report.

Brenda Thomas advised on and ensured that all the bibliographic searching was comprehensive, efficient and as cost-effective as possible. She commented on the draft report.

Steff Lewis helped to develop the decision-analytic model. She extracted the data from a variety of sources (including the LSR) to provide the parameter estimates for the model. She advised on the statistical aspects of the project and commented on the draft report.

Richard Lindley helped to develop the protocol. Throughout the project he advised on the aspects of the report to do with stroke service delivery and the use of thrombolysis in clinical practice. He commented on the draft report.

Joanna Wardlaw performed the systematic review of the trials of thrombolytic therapy and wrote the first draft of chapter 2. Throughout the project she advised on the aspects of the report to do with imaging in stroke patients. She commented on the draft report.

Declared competing interests of the authors

Peter Sandercock was the Principal Investigator of the Second International Stroke Trial (IST-2) to evaluate a neuroprotective compound (619c89). The trial was to be conducted independently of the manufacturer (GlaxoWellcome). He received a grant from GlaxoWellcome for the initial phases of the study, but the compound was withdrawn from clinical development and IST-2 was terminated before any patients had been

randomised. He is the Chairman of the Steering Committee for the Third International Stroke Trial (IST-3) of thrombolysis in acute stroke. The start-up phase of the trial is currently funded by a grant from the Stroke Association. Boehringer Ingelheim have donated trial drug and placebo for the 300 patients to be included in the start-up phase. He is also a member of the Trial Steering Committee for the Medical Research Council IMAGES trial (of Magnesium, a potentially neuroprotective agent).

Richard Lindley is Principal Investigator of IST-3 for thrombolysis in acute stroke. He is the editor of *Stroke Matters*, a journal published with an unrestricted educational grant from Boehringer Ingelheim, the manufacturers of rt-PA. He has received a grant from Boehringer Ingelheim for a qualitative study of ethical aspects of thrombolytic therapy.

Joanna Wardlaw is the contact reviewer for the Cochrane systematic review of thrombolytic treatment for acute stroke. She is a member of the IST-3 Management Group and leads a collaborative neuroradiological group assessing the scans of patients entered in the trial. She is director of the SHEFC Brain Imaging Research Centre for Scotland at the University of Edinburgh. The Centre houses an MRI scanner, which was funded by the UK Research Councils Joint Research Equipment Initiative, supplemented by grants and donations from various other sources (including Boehringer Ingelheim). She has also attended meetings (as an unpaid independent external adviser) held by Boehringer Ingelheim to discuss the licensing of rt-PA.

Martin Dennis has received grants from UCB Pharma for work on risk of seizures after stroke, from Sanofi to support work on stroke prevention, and from GlaxoWellcome to establish a series of clinical training fellowships in stroke medicine. He is a member of the IST-3 Steering Committee and

is participating as a collaborator in IST-3. He is responsible for running stroke services at the Western General Hospital, which has received patient leaflets supported by Boehringer Ingelheim. He was also founding president of the British Association of Stroke Physicians; Boehringer donated towards the cost of establishing the Association.

Eivind Berge is the national coordinator of IST-3 Norway.

Stephanie Lewis is the trial statistician for IST-3.

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Appendix I

Publications searched

The following journals (with details of years being searched) were searched for all RCTs and CCTs by the Cochrane Stroke Group:

- Acta Medica Portuguesa* (1996–)
Age and Ageing (1995–)
American Journal of Clinical Nutrition (1991–)
Annals of Neurology (1979–)
Annals of the Academy of Medicine, Singapore (1972–)
Archives of Neurology (1959–)
Archives of Physical Medicine and Rehabilitation (1980–)
Arquivos de Medicina (1996–)
Canadian Journal of Neurological Sciences (1983–)
Canadian Journal of Occupational Therapy (1980–95)
Cerebrovascular Diseases (1991–)
Chinese Journal of Internal Medicine (1989–95)
Chinese Journal of Nervous and Mental Diseases (1980–95)
Chinese Journal of Neurology and Psychiatry (1978–95)
Chinese Journal of Neurosurgery (1985–95)
Chinese Medical Journal (1983–)
Clinical Neuroscience/Ideggyogyaszati Szemle (1948–)
Clinical Rehabilitation (1987–)
European Journal of Neurology (1994–)
European Neurology (1968–71, 1985–)
Health Bulletin (1977–)
Heart Disease and Stroke (1992–94)
International Journal of Rehabilitation Research (1985–)
Journal of Clinical Neuroscience (1994–)
- Journal of Neurologic Rehabilitation* (1987–)
Journal of Neurology (1974–)
Journal of Neurology, Neurosurgery and Psychiatry (1948–)
Journal of Neuroscience Nursing (1979–)
Journal of Neurosurgery (1948–)
Journal of Speech and Hearing Research (1958–)
Journal of Stroke and Cerebrovascular Disease (1991–)
Neurological Research (1979–)
Neurology (1970–)
Neurology India (1976–80)
Neuropsychological Rehabilitation (1991–)
Neurosurgery (1977–)
Rehabilitation Nursing (1988–)
Revista Portuguesa de Cardiologia (1990–)
Revista Portuguesa de Neurologia (1992–)
Revue Neurologique (1988–93)
Scandinavian Journal of Rehabilitation Medicine (1986–90, 1995–)
Stroke (1970–)
Surgical Neurology (1973–)
Tohoku Journal of Experimental Medicine (1980–92)
Topics in Stroke Rehabilitation (1994–)
- Systematic retrospective handsearching of five Japanese journals (for stroke trials only):
Clinical Evaluation (1980–April 1994)
Japanese Journal of Stroke (1980–April 1994)
Kiso To Rinshyo (1980–April 1994)
Rinsho Ketsueki (1980–April 1994)
Yakuri To Chiryō (Japanese Journal of Pharmacology and Therapeutics) (1980–April 1994)

Appendix 2

Search strategy employed in study of barriers to effective acute stroke care

Central/CCTR: year 2000, issue 3

1. cerebrovascular-disorders*:me
2. (stroke* or cva*)
3. (cerebrovascular or (cerebral next vascular))
4. (((cerebral or cerebellar) or brain*) or vertebrobasilar)
5. (((infarct* or ischaemi*) or ischemi*) or thrombo*) or apoplexy)
6. (emboli* or occlusion)
7. (#5 or #6)
8. (#4 and #7)
9. (((cerebral or intracerebral) or intracranial) or parenchymal)
10. ((brain* or intraventricular) or cerebellar)
11. ((infratentorial or supratentorial) or subarachnoid)
12. ((#9 or #10) or #11)
13. (((haemorrhage or hemorrhage) or haematoma*) or hematoma*)
14. (bleed* or aneurysm*)
15. (#13 or #14)
16. (#12 and #15)
17. thrombo*
18. ((intracranial or sinus) or sagittal)
19. (#17 and #18)
20. (ruptured near aneurysm*)
21. aneurysm-ruptured*:me
22. ((ischaemic or ischemic) or apoplectic)
23. ((event or events) or insult)
24. (#22 and #23)
25. (((((((#1 or #2) or #3) or #8) or #16) or #19) or #20) or #21) or #24)
26. emergency-medical-services*:me
27. emergencies*:me
28. emergency-treatment*:me
29. hospitalization:me
30. patient-admission:me
31. intensive-care-units:me
32. referral-and-consultation:me
33. patient-acceptance-of-health-care:me
34. health-services-accessibility*:me
35. hotlines*:me
36. time-factors*:me
37. time-management*:me
38. delay*
39. (emergency or emergencies)
40. barriers

41. (time near ((presentation or arrival) or admission))
42. (hospital near ((admission or arriv*) or presentation))
43. (rapid next response)
44. emergency-medical-technicians*:me
45. ((((((((((((((((((#26 or #27) or #28) or #29) or #30) or #31) or #32) or #33) or #34) or #35) or #36) or #37) or #38) or #39) or #40) or #41) or #42) or #43) or #44)
46. (#25 and #45)

MEDLINE (Ovid): 1990–2000

1. exp cerebrovascular disorders/
2. (stroke\$ or poststroke\$ or cva\$).tw.
3. (cerebrovascular\$ or cerebral vascular).tw.
4. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
5. (infarct\$ or isch?emi\$ or thrombo\$ or apoplexy or emboli\$).tw.
6. 4 and 5
7. (cerebral or intracerebral or intracranial or parenchymal).tw.
8. (brain or intraventricular or brainstem or cerebellar).tw.
9. (infratentorial or supratentorial or subarachnoid).tw.
10. 7 or 8 or 9
11. (haemorrhage or hemorrhage or haematoma or hematoma).tw.
12. (bleeding or aneurysm).tw.
13. 11 or 12
14. 10 and 13
15. thrombo\$.tw.
16. (intracranial or sinus or (venous adj5 sinus\$) or (sagittal adj5 venous) or (sagittal adj5 vein)).tw.
17. 15 and 16
18. 1 or 2 or 3 or 6 or 14 or 17
19. exp transportation of patients/ or Emergency medical service communication systems/ or Emergency medical services/ or Emergency service, hospital/ or Triage/
20. Emergencies/
21. ambulances/
22. exp emergency treatment/
23. hospitalization/

24. patient admission/
 25. "referral and consultation"/
 26. patient acceptance of healthcare/
 27. health services accessibility/
 28. hotlines/
 29. time factors/
 30. time management/
 31. delay\$.tw.
 32. (emergency or emergencies).tw.
 33. barriers.tw.
 34. (time adj5 (presentation or arrival or admission)).tw.
 35. (hospital adj5 (admission or arriv\$ or presentation)).tw.
 36. rapid response.tw.
 37. Emergency medical technicians/
 38. (time adj10 (treatment or therapy)).tw.
 39. or/19-38
 40. 18 and 39
 41. limit 40 to (human and english language)
 42. Thrombolytic therapy/
 43. exp streptokinase/ or Fibrinolytic agents/ or Plasminogen activators/ or Tissue plasminogen activator/ or Urinary plasminogen activator/
 44. thromboly\$.tw.
 45. tissue\$ plasminogen activator.tw.
 46. (streptokinase or urokinase or alteplase or prourokinase or anistreplase).tw.
 47. or/42-46
 48. (18 and 47) not 41
 49. limit 48 to (human and english language)
- EMBASE (Ovid): 1990–2000**
1. exp cerebrovascular disease/
 2. (stroke\$ or cva\$ or poststroke).tw.
 3. (cerebrovasc\$ or cerebral vascular).tw.
 4. (cerebral or cerebell\$ or brain\$ or vertebrobasilar).tw.
 5. (infarct\$ or isch?emi\$ or thrombo\$ or emboli\$ or apoplexy).tw.
 6. 4 and 5
7. (cerebral or intracerebral or intracranial or parenchymal or brain or intraventricular or brainstem or cerebellar or infratentorial or supratentorial or subarachnoid).tw.
 8. (haemorrhage or hemorrhage or haematoma or hematoma or bleed\$ or aneurysm\$).tw.
 9. 7 and 8
 10. thrombo\$.tw.
 11. (intracranial or (venous adj5 sinus\$) or (sagittal adj5 venous) or sagittal vein).tw.
 12. 10 and 11
 13. 1 or 2 or 3 or 6 or 9 or 12
 14. emergency health service/
 15. hospital admission/
 16. emergency ward/
 17. patient transport/
 18. early diagnosis/
 19. patient referral/
 20. hospitalization/
 21. emergency treatment/
 22. ambulance/
 23. health care access/
 24. health care utilization/
 25. time/
 26. emergency/
 27. emergency health service/
 28. emergency health service/
 29. time management/
 30. delay\$.tw.
 31. (emergency or emergencies).tw.
 32. barriers.tw.
 33. (time adj5 (presentation or arrival or admission)).tw.
 34. (hospital adj5 (presentation or arrival or admission)).tw.
 35. rapid response.tw.
 36. rescue personnel/
 37. (time adj10 (treatment or therapy)).tw.
 38. or/14-37
 39. 13 and 38
 40. limit 39 to human
 41. limit 40 to english language

Appendix 3

Studies excluded from study of barriers to effective acute stroke care

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Appendix 4

Supplementary details for chapter 5

Details of estimation of rt-PA effect

The calculation of the effect of rt-PA, if applied to the patients in the LSR, are given in *Figure 17*.

The probabilities used to estimate the effect of increasing system efficiency so that patients could be treated without delay are given in *Table 11*.

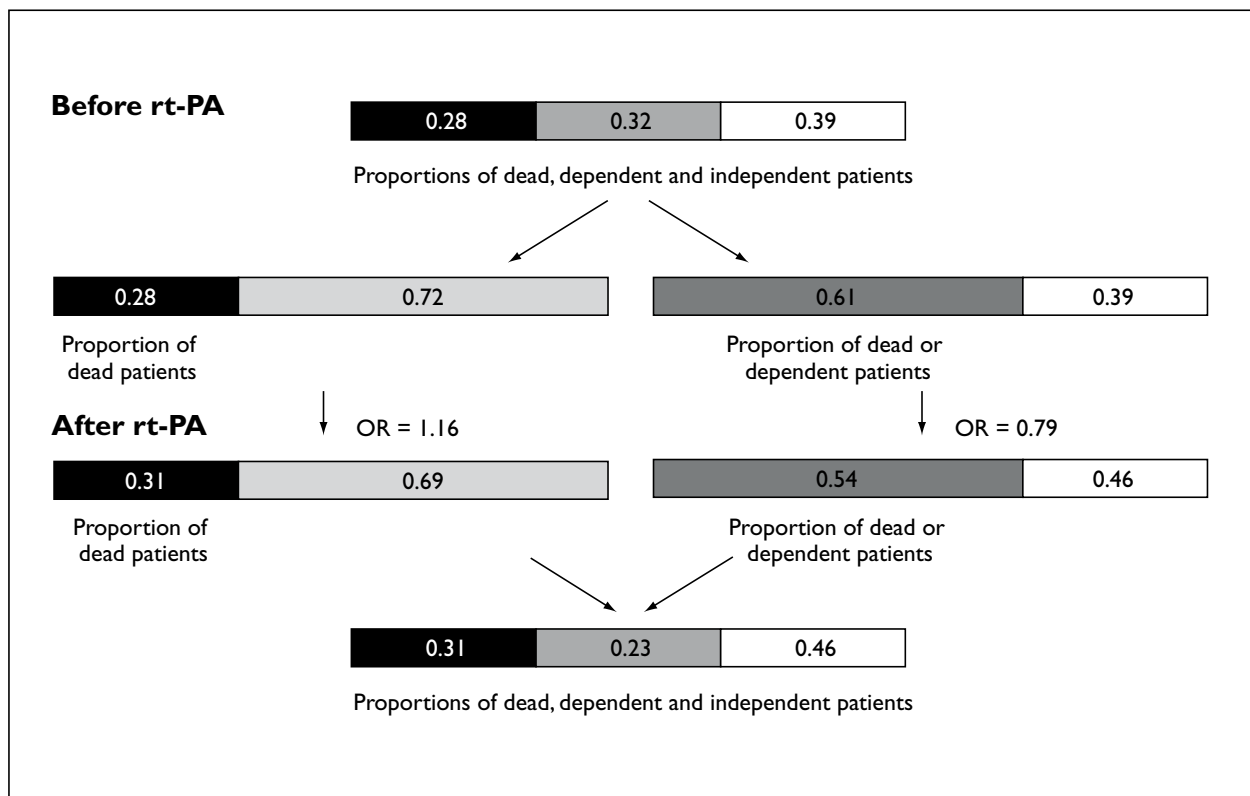


FIGURE 17 Estimation of proportion of dead, dependent and independent patients in the LSR who had been given tPA (■, Proportion of dead patients; ▨, proportion of dead or dependent patients; ▩, proportion of dependent patients; □, proportion of independent patients)

TABLE 11 Probabilities of different functional outcomes after acute ischaemic stroke in a service system without delays. Data from the LSR²¹⁴ and the systematic review of the efficacy of rt-PA for acute ischaemic stroke¹⁶

Sub-group		Functional outcome		
		Independent	Dependent	Dead
Group 1a (base case)	At 6 months	0.4658	0.2992	0.2350
	At 12 months			
	Independent	0.8813	0.1359	–
	Dependent	0.0799	0.7646	–
Group 1a (best case)	At 6 months	0.5033	0.2974	0.1933
	At 12 months			
	Independent	0.8813	0.1359	–
	Dependent	0.0799	0.7646	–
Group 1a (worst case)	At 6 months	0.4282	0.2957	0.2761
	At 12 months			
	Independent	0.8813	0.1359	–
	Dependent	0.0799	0.7646	–
Group 3a (base case)	At 6 months	0.4237	0.2855	0.2908
	At 12 months			
	Independent	0.8837	0.1573	–
	Dependent	0.0930	0.7753	–
Group 3a (best case)	At 6 months	0.4607	0.2899	0.2494
	At 12 months			
	Independent	0.8837	0.1573	–
	Dependent	0.0930	0.7753	–
Group 3a (worst case)	At 6 months	0.3870	0.2757	0.3374
	At 12 months			
	Independent	0.8837	0.1573	–
	Dependent	0.0930	0.7753	–
	Dead	0.0233	0.0674	–

For definition of Groups 1–5, see text and Figure 8
Group 1a = Group 1 now receiving rt-PA because of admission to hospital within 6 hours
Group 3a = Group 3 now receiving rt-PA because of CT scan within 6 hours
Outcomes at 6 and 12 months in patients receiving rt-PA are calculated by effect estimates obtained from Wardlaw et al.¹⁶
Base-case estimates: 16% increase in death, 21% decrease in death/dependency
Best-case estimates: 6% decrease in death, 32% decrease in death/dependency
Worst-case estimates: 44% increase in death, 8% decrease in death/dependency



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<p>Mrs Stella Burnside, Chief Executive, Altnagelvin Hospitals Health & Social Services Trust, Londonderry</p>	<p>Dr David Elliman, Consultant in Community Child Health, St. George's Hospital, London</p>		
<p>Dr Paul O Collinson, Consultant Chemical Pathologist & Senior Lecturer, St George's Hospital, London</p>	<p>Dr Tom Fahey, Senior Lecturer in General Practice, University of Bristol</p> <p>Dr Andrew Farmer, General Practitioner & NHS R&D Clinical Scientist, Institute of Health Sciences, University of Oxford</p>		
<p>Dr Barry Cookson, Director, Laboratory of Hospital Infection, Public Health Laboratory Service, London</p>	<p>Professor Jane Franklyn, Professor of Medicine, University of Birmingham</p>		

Pharmaceuticals Panel

Members

<p>Chair, Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital</p>	<p>Dr Christopher Cates, GP & Cochrane Editor, Bushey Health Centre, Bushey, Herts</p> <p>Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff</p> <p>Dr Felicity J Gabbay, Managing Director, Transcrip Ltd, Milford-on-Sea, Hants</p> <p>Mr Peter Golightly, Director, Trent Medicines Information Services, Leicester Royal Infirmary</p> <p>Dr Alastair Gray, Director, Health Economics Research Centre, Institute of Health Sciences, University of Oxford</p>	<p>Mrs Sharon Hart, Managing Editor, <i>Drug & Therapeutics Bulletin</i>, London</p> <p>Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust</p> <p>Mrs Jeannette Howe, Deputy Chief Pharmacist, Department of Health, London</p> <p>Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton</p> <p>Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London</p>	<p>Dr Eamonn Sheridan, Consultant in Clinical Genetics, St James's University Hospital, Leeds</p> <p>Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool</p> <p>Professor Terence Stephenson, Professor of Child Health, University of Nottingham</p> <p>Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry, London</p> <p>Professor Jenifer Wilson- Barnett, Head of Florence Nightingale School of Nursing & Midwifery, King's College, London</p>
<p>Professor Tony Avery, Professor of Primary Health Care, University of Nottingham</p>			
<p>Professor Iain T Cameron, Professor of Obstetrics & Gynaecology, University of Southampton</p>			
<p>Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London</p>			

Therapeutic Procedures Panel

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<p>Ms Tracy Bury, Head of Research & Development, Chartered Society of Physiotherapy, London</p>	<p>Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester</p>	<p>Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester</p>	
<p>Mr Michael Clancy, Consultant in A & E Medicine, Southampton General Hospital</p>	<p>Professor Gene Feder, Professor of Primary Care R&D, St Bartholomew's & the London, Queen Mary's School of Medicine & Dentistry, University of London</p>	<p>Professor Rajan Madhok, Medical Director & Director of Public Health, North & East Yorkshire & Northern Lincolnshire Strategic Health Authority, York</p>	
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continued

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We look forward to hearing from you.

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