Early Thrombolysis for the Treatment of Acute Myocardial Infarction

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ABOUT HOME UNIT

The Liverpool Reviews and Implementation Group (LRIG) was established within the Department of Pharmacology and Therapeutics in April 2001. It is a multi-disciplinary research group whose purpose, in the first instance is to conduct systematic reviews commissioned by the Health Technology Assessment Programme.

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The views expressed in this publication are those of the authors and not necessarily those of the review panel, the HTA Programme, NICE or the Department of Health.

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To examine the clinical and cost-effectiveness of available drugs for early thrombolysis in the treatment of acute myocardial infarction (AMI) in hospital and pre-hospital settings.

Background
Coronary heart disease (CHD) is a major cause of morbidity and mortality in the UK accounting for around 125,000 deaths a year. AMI affects an estimated 274,000 people each year. Of these, approximately 50% (137,000) die within 30 days of AMI and over half these deaths occur prior to reaching hospital or other medical assistance.

The development and introduction of new pharmacological agents has made it necessary to review the clinical and cost effectiveness of older and newer agents used for early thrombolysis. Those reviewed in this document include: streptokinase, alteplase, reteplase and tenecteplase.

Methods
The search incorporated a number of strategies for clinical effectiveness and economic evaluation. The search strategy covered the period from 1980 to 2001 and included the following electronic databases MEDLINE, EMBASE, Science Citation Index/Web of Science, Cochrane Trials Register, Health Technology Assessment (HTA), Database of Abstracts of Reviews of Effectiveness (DARE) and NHS Economic Evaluation Database (NHSEED). Search terms included were myocardial infarction/heart infarction combined with specific drug terms including alteplase, reteplase, streptokinase, tenecteplase, anistreplase and urokinase. Reference lists of included studies and pharmaceutical company submissions were searched to identify other relevant studies. In addition, a number of medical journals were hand searched to identify any newly published papers that might not yet have been indexed in electronic databases.

Study selection
Randomised controlled trials that include comparison of included drugs (alteplase, reteplase, streptokinase and tenecteplase) in the early stages of AMI delivered in the pre-hospital or hospital setting were included in the review. Studies that examine the use of anistreplase or urokinase were identified but not included in the analysis. Data on the following outcome measures were included in the review: mortality, bleeding, stroke, reinfarction, allergy and anaphylaxis.

Economic evaluation included studies reporting efficacy data primarily based on drug versus drug randomised controlled clinical evidence, explicit synthesis of costs and outcomes in a cost effectiveness ratio, full economic evaluation.

Quality assessment
The methodological quality of studies for clinical effectiveness was assessed using the criteria based on the NHS Centre for Reviews and Dissemination (CRD) Report 4.

The quality of cost-effectiveness was assessed using a checklist updated from that developed by Drummond and colleagues, 1997.

Results

Clinical effectiveness

Hospital

A total of 162 references were identified to which the inclusion criteria were applied. Of these, 20 studies reported in 50 articles fulfilled the inclusion criteria. These included 14 comparative studies involving a total study population of 142,907 patients. Data from two studies were combined in the study reports and this combination of data is maintained in the review.

Definitive conclusions on efficacy (30-35 day mortality) are that streptokinase is as effective as non-accelerated alteplase, that tenecteplase is as effective as accelerated alteplase, and that reteplase is at least as effective as streptokinase.

Some conclusions require interpretation of data, i.e. whether streptokinase is as effective as, or inferior to accelerated alteplase; and whether reteplase is as effective as accelerated alteplase or not.

Depending on these, two further conclusions on indirect comparisons arise, whether tenecteplase is superior to streptokinase or not, and whether reteplase is as effective as tenecteplase or not.

That these questions remain to be resolved illustrate that any differences in mortality between drugs is small.

There seem to be significant differences between drugs in incidence of stroke with streptokinase having the lowest rate.

Streptokinase causes more allergic reactions than other drugs.

Pre-hospital

The search failed to identify any studies conducted in the pre-hospital setting that compared the effectiveness of different drugs. There is no reason to believe that the effectiveness of a drug will be altered by administration in the pre-hospital setting.

Nine randomised controlled studies that examine the efficacy and safety of pre-hospital thrombolysis were identified and are discussed. The required use of heparin with either of the bolus products does not seem to provide any practical barrier to their widespread use.

Cost-effectiveness and modelling

A detailed review of the economic literature was undertaken. Of the 107 articles assessed, only eight met the quality criteria that led them to be evaluated in detail. The general quality of economic analyses undertaken in this area was disappointing and largely focussed on evaluating cost-effectiveness in healthcare environments outside the NHS.

A critique and re-analysis were also undertaken of the two detailed economic models contained in the industry submissions. Both models were rerun using the assumptions

contained in the competitor model. In addition, they were re-analysed using a preferred set of coefficients that reflected, as far as possible, the weight of the available evidence.

Variations in QALYs gained between the individual drugs were small. Supposed advantages presented in the industry submissions largely relate to comparatively minor variations in efficacy or minor improvements in aspects of the side-effect profile associated with each individual drug. Streptokinase was clearly the most cost effective drug and other drugs were compared to it. Costs per QALY for newer drugs compared to streptokinase ranged up to £17,000. Given the similarity in outcome, cost-effectiveness becomes largely determined by the acquisition costs of the drug. This conclusion was robust to a variety of variations in assumptions. In contrast to this robust conclusion, differences between alteplase, tenecteplase and reteplase were small and their relative ranking in cost effectiveness changed according to the assumptions used.

Implementation

There are substantial opportunities for refining hospital thrombolysis procedures to meet NSF targets. Changing drugs is a very minor element in achieving improved door to needle time.

Pre-hospital thrombolysis will be necessary in some areas to allow NSF targets to be met. The choice of drug for pre-hospital thrombolysis is determined by acquisition cost and by convenience. Our experts did not wish to consider the use of infusion products (e.g. alteplase or streptokinase) but preferred bolus administration (reteplase and tenecteplase).

The cost impact of switching to the more expensive bolus drugs could be as much as £50 million per year, over and above existing costs of approximately £30-40 million for the NHS in England and Wales.

Conclusion – clinical effectiveness

The decision regarding which agent to use is therefore a balance of risks and benefits related to mortality and stroke. No clear conclusion, based on statistical comparison, can be drawn.

Conclusion – economic evaluation

Given the similarity in outcome, cost-effectiveness becomes largely determined by the acquisition costs of the drug. This conclusion was robust to a variety of variations in assumptions. Streptokinase was therefore the most cost effective drug.

ABBREVIATIONS

A&E	Accident and Emergency
ACC	American College of Cardiology
ACCP	American College of Chest Physicians
AHA	American Heart Association
AMI	Acute myocardial infarction
APPT	Activated partial thromboplastin time
APSAC	Anisoylated plasminogen-streptokinase activator complex
ASA	Aspirin, acetylsalicylic acid
ASSENT	Assessment of the Safety of a New Thrombolytic
BHF	British Heart Foundation
CAD	Coronary artery disease
CCU	Coronary Care Unit
C-E	Cost-effective(ness)
CEA	Cost-effectiveness analysis
CEEU	Clinical Effectiveness and Evaluation Unit (Royal College of Physicians – British Cardiac Society)
CHD	Coronary heart disease
CRD	The NHS Centre for Reviews and Dissemination
CHF	Congestive heart failure
COBALT	Continuous Infusion versus Double-Bolus Administration of Alteplase
ECG	Electrocardiogram
ECSG	European Cooperative Study Group
EF	Ejection fraction
EMIP	European Myocardial Infarction Project
EMS	Emergency Medical Services
FDA	Food and Drug Administration, U.S. Department of Health and Human Services
FTT	Fibrinolytic Therapy Trialists'
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico

GP	General practitioner
GREAT	Grampian Region Early Anistreplase Trial
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
IC	Intracoronary
ICER	Incremental cost effectiveness ratio
ICH	Intra-cranial haemorrhage
INJECT	International Joint Efficacy Comparison for Thrombolytics
ISG	International Study Group
ISIS	International Study of Infarct Survival
ITT	Intention to treat analysis
JRCALC	Joint Royal Colleges Ambulance Liaison Committee
KAMIT	Kentucky Acute Myocardial Infarction Trial
LVF	Left ventricular function
MIMS	Monthly Index of Medical Specialties
MIN	Minutes
MINAP	Myocardial Infarction National Audit Project
MITI	Myocardial Infarction Triage and Intervention trial
NAOMI	National Audit of Myocardial Infarction
NSF	National Service Framework
NTG	Nitroglycerin, glyceryl trinitrate
PAIMS	Plasminogen Activator Italian Multicenter Study
PE	Pulmonary embolism
PTCA	Percutaneous transluminal coronary angioplasty
RAAMI	Randomized Angiographic trial of recombinant tissue-type plasminogen Activator (alteplase) in Myocardial Infarction
RAPID 1	Reteplase Angiographic Phase II International Dose-Finding trial
RAPID 2	Reteplase versus Alteplase Patency Investigation during Myocardial Infarction trial
RCT	Randomised controlled trial
r-PA	Reteplase

QALY	Quality adjusted life year
SA	Sensitivity analysis
SC	Subcutaneous
SK	Streptokinase
TIMI	Thrombolysis in Myocardial Infarction
TNK	Tenecteplase
t-PA/rt-PA	Alteplase, tissue plasminogen activator
VF	Ventricular fibrillation
IV	Intravenous
U	Unit
UKHAS	UK Heart Attack Study

DEFINITIONS OF TERMS

Arrythmias	Irregular heart rhythms
Door to needle time	Time from arrival of patient in hospital to delivery of thrombolysis
Ejection fraction	The percentage of blood pumped out of the ventricle with each contraction
Haemorrhage	The escape of blood from the vessels, bleeding
Ischaemia	Lack of oxygen (usually from blockage of blood vessel)
Infarct	Death of tissue due to ischaemia
Killip class	Classification of severity of heart failure
Recanalization	Joining of capillaries within a thrombus establishing a way for blood to traverse the thrombus
Reinfarction	Any new myocardial infarction occurring after the index infarct, irrespective of the mechanism and location of infarction
Reperfusion	The restoration of blood flow in a blocked artery
Thrombosis	Process of clotting
Thrombus	Blood clot
Time to treatment	Time from onset of symptoms of AMI until delivery of thrombolysis
TIMI flow rate	A measure of coronary blood flow

1. AIM OF THE REVIEW

To examine the comparative clinical and cost effectiveness of available drugs for early thrombolysis in the treatment of acute myocardial infarction (AMI) in hospital and pre-hospital settings.

2. BACKGROUND

2.1 Description of underlying health problem

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the UK accounting for more than 125,000 deaths per year.(1) Although rates of coronary heart disease have been decreasing over the past three decades, this has not been consistent across age groups, gender or socio-economic class. A more rapid reduction has been seen in younger age groups (45-54 years), in men and in higher socio-economic groups. In addition, the rate of decline in the UK has been slower then that in other developed counties (e.g. Denmark, Norway, Australia).(1)

Coronary heart disease is usually due to atherosclerotic narrowing of the coronary arteries supplying the muscle of the heart (the myocardium). It may be silent or manifest itself as angina pectoris (typically chest pain on exertion, when the myocardial oxygen demands rise above the ability of the narrowed arteries to deliver). Its first presentation can be an acute myocardial infarction (AMI). AMI is the result of a thrombus or clot forming on top of a ruptured atherosclerotic plaque, blocking the blood flow through the artery. Unless the blood flow can be quickly restored, the muscle supplied by that artery "infarcts", or dies because of lack of oxygen (ischaemia). This muscle damage weakens the heart, and may cause heart failure either early (within a matter or hours) or later (over a period of months or years). It may also lead to other events such as fatal heart rhythm disturbances and death.

Typical symptoms of AMI include chest pain (often described as crushing), pallor and shortness of breath. Pain is often severe enough for the sufferer to seek help. Older patients or diabetics may experience atypical symptoms and relatively little or less severe pain. (2)

In the UK, AMI affects an estimated 274,000 people each year (237,000 in England and Wales). Of these, approximately 50% (137,000) die within 30 days of AMI and over half of these deaths occur prior to the patient reaching hospital or other medical assistance. Onset of symptoms of AMI is usually sudden and the highest risk of death is within the first hour of experiencing an AMI. International data show a 28-day case fatality rate for all AMI of about 50% and about a third of patients experiencing AMI die within the first hour of the onset of their symptoms.(3, 4)

The Oxford Myocardial Infarction Incidence Study (OXMIS) provides an analysis of fatality rates (at one month) for all cases, hospitalised cases and sudden death (i.e. *"coronary deaths before patient was seen by a doctor"*).(5) For males, "all cases" fatality rates were 41 per 100,000, "hospitalised cases" 15, and "sudden death" 27. For females, the corresponding figures were 44, 22 and 26. The OXMIS survey also indicated an incidence/mortality ratio of 2.43:1 in males and 2.14 in females when mortality is defined by non-survival to 28 days. The BHF summary indicates that of those dying within 28 days, three-quarters die within 24 hours. The British Regional Heart Study data checked on 198 persons who had heart attacks between 1978 and 1985 but survived 28 days. Of these, 77% survived five years and 63% ten years (controls surviving 96% and 91% over the same period).(6) Approximately one-third of all AMIs remain clinically unrecognised at the time of the acute event (7).

Diagnosis

According to the World Health Organisation, the diagnosis of AMI requires that at least two of the following three criteria be met: 1) a clinical history of ischaemic-type chest discomfort, 2) changes on repeated electro-cardiographic (ECG) tracings usually over two to three days, and 3) a rise and fall in serum cardiac markers (typically over 1-2 days but new sensitive markers may allow a diagnosis within 6-12 hours). However, these criteria may not be suitable for the diagnosis of AMI, within the first 6 hours when interventions to restore blood flow, such as drugs to dissolve the thrombus, may be of most value. Changes in ECG readings are useful in the diagnosis of AMI and ST segment elevation is very specific in identifying patients requiring reperfusion therapy. These changes may occur in the "anterior" ECG leads (generally indicating an occlusion in the left coronary artery, the main supply to the myocardium and hence affecting more myocardium, with a worse prognosis) or inferior (generally implying a smaller infarct with a better outlook, possibly due to obstruction in the right coronary artery or some smaller branches of the left artery) ECG leads. However, as many as 50% of patients with AMI may not exhibit ST elevation in the early stages (2) and assessment of change in ST abnormalities has been proposed as a more sensitive diagnostic marker. Changes in traditional serum cardiac markers also often occur too slowly to be of immediate value. Newer, more rapidly available tests are being evaluated.

Current practice for early identification of patients experiencing an AMI, and who might benefit from reperfusion therapy, therefore includes a combination of clinical symptoms and ECG changes. Serial ECG changes are monitored if initial readings appear normal but clinical symptoms persist or become worse. Serial readings may also be needed if initial readings are abnormal but not diagnostic of AMI.

Treatment

Medical care for patients experiencing AMI has changed over the past 40 years. Care in the 1960s and 70s focused on the treatment of life threatening arrhythmias. This included the development of specialist coronary care units to monitor these patients. The 1980s saw the conduct of large clinical trials to assess the effectiveness of drugs that broke down the clot causing the infarct (thrombolysis).

If the clot blocking the artery can be dissolved, then the ischaemic tissue can be reperfused and death of muscle (infarct) avoided. The earlier this can be done, the more muscle can be salavage. Reperfusion can be achieved by mechanical means (physically disrupting the clot) or by chemical means, by using drugs which hasten the dissolution of the clot. If reperfusion is delayed, then the muscle will infarct and die before it can be reperfused. The time without reperfusion to cause infarction can be as little as 1 hour, but there is still benefit from reperfusion therapy for up to at least 12 hours, decreasing as time goes by.

The first reports of the use of thrombolysis in AMI (e.g. with streptokinase) appeared in the late 1950s. However, the first meta-analysis of studies comparing the use of thrombolysis to placebo and indicating its positive impact on mortality was not published until 1985.(8) This analysis indicated the highly significant 22% (+/- 5%) reduction in odds of death. In addition it revealed somewhat larger decreases in re-infarction rates and only small numbers of adverse events.

Clinical practice in the use of these drugs did not change until the results of some key large studies were published in the late 1980s (9, 10). These trials showed a reduction in 30-day mortality of around 20%, which was a decrease in actual rates from 10% to 8%. This is lower

than the 25% case fatality rate typically reported around this time, and reflected perhaps the effects of selection criteria for the clinical trials. Nevertheless, this was a considerable improvement in outcome and thrombolytic therapy for patients seen within 12 hours of onset of AMI became the expected standard of care.

Some adjunctive therapies are also beneficial, in particular the antiplatelet agent aspirin. The ISIS-2(10) study showed a reduction in mortality of around 3% in patients treated with streptokinase alone, but of 6% in those treated with both streptokinase and aspirin. Other studies and meta-analyses have confirmed the benefits of aspirin(11, 12), which has become standard recommended therapy. Studies of other antiplatelet agents are ongoing and suggest a cumulative benefit with that of aspirin in certain settings.

Treatment regimes for patients experiencing AMI have been presented out in evidence based clinical guidelines established through a combination of professional and voluntary bodies.(2, 3, 13, 14). Not all patients are suitable for treatment with thrombolytic treatment. In the first instance delay on the part of the patient following the onset of symptoms may mean that they are not eligible for treatment. Even for patients seeking help early may not be suitable for treatment. The increased risk of bleeding means that all patients need to be screened. Appendix I and II) include current criteria used in this screening process. However, even those appropriately screened who receive treatement may bleed. One of the most severe bleeds can be within the brain perhaps causing a catastrophic intracranial haemorrhage. Thrombolysis is therefore a balance of the benefits and risks, each of which must be carefully weighed.

2.2 Description of new intervention

The list of thrombolytic agents licensed for use in the UK, their method of administration and listed costs are presented in Table 1. Two other drugs, not available in the UK, are also described. Some key clinical features of these drugs are described here (13) but differences in their *in vitro* clot specificity are omitted. These drugs activate plasminogen, a naturally occurring protein in the blood, to plasmin, which breaks down fibrin. Fibrin is a key structural protein in thrombus and hence the drugs "dissolve" the clot. All of these drugs are delivered intravenously (IV).

Streptokinase

This was the first widely used fibrinolytic agent. It has a short half-life and is delivered in a continuous infusion over one hour. It is derived from Group A streptococci. Patients may have antibodies to these common microorganisms or may develop antibodies following administration of this agent. If a patient has antibodies, they are at increased risk of an allergic reaction (including the most severe form, anaphylaxis) to streptokinase. Alternatively the presence of antibodies may diminish the thrombolytic effect of streptokinase. These effects mean that streptokinase is used only once in any given patient, and repeated administration is discouraged. In some areas, up to 50% of patients presenting with AMI have already received streptokinase once and are therefore not suitable for this drug.

Alteplase

Alteplase is essentially the same as the naturally occurring activator of plasminogen in the human body, produced by recombinant DNA technology. As a human product, it does not cause antibody formation and is therefore less far less likely than streptokinase to cause allergic reactions. It can also be administered on more than one occasion. Initially it was

delivered in an infusion over 3 hours. Further investigation suggested that it might be more effective when delivered in what has come to be known as an accelerated manner, which includes a bolus dose, followed by infusion over 90 minutes.(15, 16) This is the currently recommended treatment protocol.

Reteplase

This is a more recent drug, a recombinant plasminogen activator similar to alteplase, but with a prolonged half-life. It is delivered through two IV bolus injections 30 minutes apart.

Tenecteplase

This drug is newly available in the UK. It is also a recombinant plasminogen activator similar to alteplase but with a prolonged half-life, increased fibrin specificity and increased resistance to inhibition by plasminogen activator inhibitors. Administration is through a single IV bolus injection. Tenecteplase is currently a black triangle drug.

Anistreplase

This drug was a derivative of streptokinase which could be administered as a single bolus injection instead of an infusion. This made it acceptable in particular for pre-hospital thrombolysis. The drug is no longer available in the UK since sales were inadequate to justify its continued manufacture.

Urokinase

Similar to alteplase but had been subjected to less evaluation. Its manufacture was also abandoned for commercial reasons.

All of these drugs are administered with aspirin and with heparin, as shown in the Table 1. Although it is not within the remit of this review to assess the effectiveness of heparin therapy, it will be discussed briefly later.

Table 1: Characteristics of drugs included in the review

Generic name:	Proprietary name	Supplier	Dosage	Administration	Heparin Dose(17-20)	Approximate cost**
Alteplase (t-PA) Tissue-type plasminogen activator rt-PA	*Actilyse®*	Boehringer Ingelheim	**Standard**: 100 mg over 3 h (10 mg IV followed by 50 mg over 60 mins then 4 infusions of 10 mg over 30 mins **Accelerated**: 15 mg bolus 50 mg over 30 min 35 mg over 60 min	IV bolus/infusion	5000 U bolus followed by 1000 U/hour	£600
Reteplase (r-PA)	*Rapilysin®*	Roche	10 units followed by further 10 U in 30 min	IV bolus	5000 U bolus followed by 1000 IU/hour	£720
Streptokinase (SK)	*Streptase®* *Kabikinase® (No longer produced)* Non-proprietary *(to be withdrawn)*	Aventis Behring Pharmacia & Uphohn B. Braun	1.5 million units over 60 min	IV infusion	5000 U bolus followed by 1000 IU/hour 12500 U SC twice daily	£80-85
Tenecteplase (TNK) TNK-tPA	*Metalyse®*	Boehringer Ingleheim	30-50 mg over 10 seconds	IV bolus	5000 U bolus followed by 1000 IU/hour	£700-800
Agents no longer available:						
Anistreplase Anisoylated plasminogen-streptokinase activator complex (APSAC)	N/A	N/A	30 U	IV bolus		£495 (1995)
Urokinase	N/A	N/A	2.0 million units	IV bolus		£460 (1995)

** Based on list prices stated in the British National Formulary (21)

These drugs may differ in their beneficial and in their adverse effects, and the benefits and risks have to be considered in each patient. There are guidelines for the identification of the appropriate population of patients to receive treatment.(2, 13, 14, 22) These guidelines have been transferred into checklists to be used to screen patients prior to administration of treatment. Examples of such lists for use in the hospital and pre-hospital setting are presented in Appendices I and II.

2.3 Current service provision

Current provision of service

The exact number of patents treated with thrombolysis in England and Wales is uncertain: the number is probably between 80-100,000 per year, at a current cost of around £35 million (see Chapter 7). Although thrombolysis is standard treatment for patients presenting with AMI in the NHS, there is evidence that many patients are receiving sub-optimal therapy with variation in the delivery of thrombolysis treatment in hospital settings in the UK. In relation

to the use of thrombolysis, data from 39 UK hospitals (1992-95) revealed a range of 49-85% of patients with a confirmed diagnosis of AMI received thrombolysis.(23) In relation to timing of treatment, survey data from three British health districts in 1994-95 indicated that 2% of patients had received thrombolysis within 60 minutes of presentation while 25% received treatment within two hours.(24, 25)

Thrombolysis is almost always delivered to patents after arriving in hospital, possibly losing valuable time (and hence heart muscle). Meta-analysis of trials has shown that early thrombolysis is more effective and that the treatment is of limited value once irreversible myocardial damage has occurred.(26-28) Advances in the speed of action and ease of administration of newer drugs combined with recognition of improved outcomes with earlier administration have prompted further attempts to decrease the time from symptom onset to treatment delivery.

The period of greatest risk for patients experiencing AMI is in the first few hours after onset of symptoms and delays in this time period are a result of a number of factors.(29). The major delay is in patients' seeking help. However other delays occur after this and require attention. Directions to address this in England are outlined in the National Service Framework (NSF) and NHS Plan.(30, 31) Specifically, in the National Service Framework for Coronary Heart Disease, standards five and six, stipulate that,

> *"People with symptoms of a possible heart attack should receive help from an individual equipped with and appropriately trained in the use of a defibrillator within eight minutes of calling for help, to maximise the benefits of resuscitation should it be necessary and...*
>
> *People thought to be suffering from heart attack should be assessed professionally and, if indicated, receive aspirin. Thrombolysis should be given within 60 minutes of calling for professional help."*

There has been recognition that a goal of providing thrombolysis within this 60-minute time window may be difficult when transport distances (or times) are long. To address this issue the NSF states:

> *"…usually hospital will be the best place to give thrombolysis. However, where the 'call-to-hospital' time cannot be reduced below 30 minutes, it may be more appropriate to plan to give thrombolysis before admission to hospital."*

The NHS Plan therefore has stipulated that:

> *"There will be a three year programme to train and equip ambulance paramedics to provide thrombolysis an hour sooner than if they were taken to hospital first, saving up to 3,000 lives a year once fully implemented"*

The implementation of these standards of care requires the assessment of current service provision by both hospitals and ambulance services. It requires an assessment of patient populations, geography, transport times, pre-hospital service equipment and expertise and in-hospital services for the delivery of thrombolysis.

MINAP and Hospital Care

The establishment of the NSF prompted the Royal College of Physicians to develop the Myocardial Infarction National Audit Project (MINAP) in late 1998.(32) This is a joint

project of the Clinical Effectiveness and Evaluation Unit (CEEU) of the Royal College of Physicians and the British Cardiac Society. The working group overseeing this project has been tasked with

> "*developing a mechanism that would allow clinicians to examine the management of myocardial infarction within their hospitals in order to meet the standards specified by the National Service Framework for Coronary Heart Disease".*

The MINAP project aims to have all hospitals in England and Wales collecting data by 2002.(33) By the end of 2001, 70% of hospitals had begun transmitting data to the project.

The core data set of the MINAP project comprises all aspects of "*the process and outcome of the management of patients admitted to hospital with myocardial infarction*". However, those related to early thrombolysis include: demography, delay to treatment, cardiac arrest and resuscitation and thrombolytic and anti-thrombotic therapy. The data collection method was pilot tested in nine sites in 2000.(34) Initial data quality assessment from ten hospitals is now available.(33)

Variation in service

Initial work of CEEU also included a baseline survey of UK facilities that provide care to patients with AMI.(35) Ninety-seven percent of hospitals had a written policy regarding the use of thrombolysis. The location of delivery of treatment varied. Approximately 25% of 211 hospitals had a fast-track system to transfer patients from A&E to the CCU to receive treatment. Over half provided treatment primarily in the A&E department transferring patients to the CCU, while half of all hospitals had a mechanism whereby AMI patients could be admitted directly to the CCU without assessment anywhere else in the hospital. In those hospitals that provided thrombolysis in the A&E department, 16% used the services of specially trained nurses.

Drug choice in thrombolysis

Accurate cumulative reports of the proportion of patients receiving various agents in the UK and Wales do not exist. As mentioned previously, the work by the Royal College of Physicians(35) identified that almost all hospitals have a written policy regarding the use of thrombolysis. Overall, 82% stated that streptokinase was used for eligible patients experiencing their first AMI. However, additional data indicated that approximately half of the hospitals recommend the use of alteplase for younger patients. Almost 60% of hospitals indicated that their choice of drug was limited by cost. Data in pharmaceutical company submissions suggest that in the NHS, streptokinase was used in 55% of thrombolysis episodes, alteplase in 33% and reteplase in 11%.

Pre-hospital care in AMI

At present, pre-hospital care is often limited to getting the patient quickly to hospital. The Department of Health Emergency Services Report for 2000-2001(36) indicates that there is a variation in the ability of the ambulance services to meet the NSF standards. Although performance is improving, this report indicates that only three services responded to 75% of *Category A* (immediately life threatening, including probable AMI) calls within eight minutes.

Pre-hospital thrombolysis may increasingly be provided where NSF targets on speed of thrombolysis cannot be met using only hospital administration. It is currently available in two

(out of 30) ambulance trusts in England (East Midlands and Staffordshire).(37, 38) The 2001 report of NHS Wales includes mention of provision of aspirin to patients of AMI by members of the ambulance service but makes no mention of the delivery of pre-hospital thrombolysis.(39)

A recent survey conducted in 2001 by the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) indicates that a number of other ambulance trusts are considering implementing pre-hospital thrombolysis. A larger group indicated that they would be moving towards paramedics performing ECGs and transmission of this data to alert receiving hospitals and reduce delay after arrival at hospital (Chamberlain D, JRCALC: personal communication, 2002). This is consistent with other information provided to the review group regarding implementation of independent projects in eight different ambulance trusts. The aim of these projects will be to reduce time to thrombolysis through the transmission of pre-admission ECG data (Quinn T, Cardiac Care Advisor: personal communication, 2002). Draft reports and presentation of the findings of these projects are beginning to appear.(40)

2.4 Summary

The primary purpose of this review is to examine the effectiveness and cost effectiveness of various drugs used in early thrombolysis for AMI. It therefore includes evaluation of the clinical studies of drug effectiveness and the evaluation of existing economic evaluations. It goes on to present the results of the analysis of the economic models submitted in the company submissions.

The economic conclusions are based on an assumption that the clinical environment (hospital and pre-hospital) is currently able to provide appropriate treatment. This of course is not the case. Hospital care currently includes thrombolytic treatment but treatment times are not optimal and variations in provision exist. Provision of pre-hospital care in the UK is limited. Although outside the remit of this review the authors provide a discussion regarding the factors influential in the implementation of appropriate treatment.

3. METHODS

3.1 Methods for reviewing clinical effectiveness

3.1.1 Search strategy: clinical effectiveness

The search incorporated a number of strategies. Search terms for electronic databases included were: myocardial infarction/heart infarction and thrombolysis combined with specific drug terms (e.g. alteplase (t-PA), reteplase, streptokinase tenecteplase, anistreplase and urokinase

Electronic searches included the following databases:

MEDLINE (1980-2001)
EMBASE (1980-2001)
Science Citation Index/Web of Science (1988-2001)
Cochrane Trials Register (2001, 4)
Health Technology Assessment (HTA) (1992-2001)
Database of Abstracts of Reviews of effectiveness (DARE) (1998-2001)

Specific search strategies and the number of references retrieved for each search is provided in Appendices III, IV and V.

Searching was limited to English language reports

Reference lists of included studies and pharmaceutical company submissions were searched to identify other relevant studies. In addition, hand searching of American Heart Journal, Circulation, American Journal of Cardiology, British Medical Journal, Circulation, European Heart Journal, Heart, Emergency Medicine Journal, International Journal of Cardiology, Journal of the American College of Cardiology, Journal of the American Medical Association, Lancet, New England Journal of Medicine and Stroke was carried out for the period of January 2001 to January 2002 to identify any newly published papers that might not yet have been indexed in electronic databases.

All the references were exported to *Endnote* reference database, ISI Research Soft, Cal., USA, version 5.

3.1.2 Inclusion and exclusion criteria: clinical effectiveness

The identified citations were assessed for inclusion through two stages and disagreements were settled by discussion at each stage. Two reviewers independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved (YD, ABol). Full text copies of the selected papers were obtained and assessed independently by two reviewers for inclusion (YD, RD). Studies were considered eligible for inclusion if they met the following criteria:

Study design

Randomised controlled trials (RCTs) that include comparison of included drugs and any or all of the listed outcomes.

Interventions

Comparison of currently available intravenous thrombolytic therapies administered in the early stages of AMI in the hospital or pre-hospital setting. Drugs included in the review were: tissue plasminogen activator (t-PA), reteplase, streptokinase and tenecteplase. Studies that examine the use of anistreplase (not currently available) or urokinase (not currently licensed for use in thrombolysis in the UK) were also identified and used to inform the background of the review but not included in the analysis.

Participants

Patients with recent on-set AMI without contraindications to thrombolytic therapy. Diagnosis of AMI to be made through clinical assessment or ECG.

Outcomes

Data on the following outcome measures were included:
Mortality
Patency of coronary arteries
Left ventricular function
Stroke
Reinfarction
Bleeding
Allergy
Anaphylaxis

3.1.3 Data extraction: clinical effectiveness

Hospital

Data extraction was carried out by three reviewers (YD, RD, RH). Data were independently extracted by one reviewer and checked by a second into a pre-designed data extraction form. Data from multiple reports of single trials were extracted onto a single data extraction form.

Pre-hospital

Data for information tables were extracted by one reviewer (RD) and checked by a second (YD).

3.1.4 Quality assessment: clinical effectiveness

Hospital

Three reviewers (YD, RD, RH) independently evaluated the included primary studies for methodological quality. This involved methodological assessment for clinical effectiveness based on Centre for Reviews and Dissemination, York, Report 4 (41)(see Appendix VI). Any discrepancies were resolved through consensus.

Pre-hospital

Since no studies comparing drugs used in the pre-hospital setting were identified, there were no studies to be assessed. Descriptive comment is provided regarding trials that evaluated pre-hospital care.

3.2 Methods for reviewing cost-effectiveness

3.2.1 Search strategy: cost-effectiveness

The following databases were searched for English language papers.

MEDLINE
EMBASE
NHS Economic Evaluation Database (NHSEED)
Database of Abstracts of Reviews of Effectiveness (DARE)
Science Citation Index/Web of Science
Cochrane Trials Register
Health Technology Assessment (HTA)

Search strategies and results of the searches undertaken are presented in Appendix VI.

3.2.2 Inclusion and exclusion criteria: cost-effectiveness

Using explicit, predetermined criteria, two reviewers (ABol, AH) independently identified studies for inclusion in the cost-effectiveness review process. Decisions were compared. Where there was disagreement, both reviewers discussed the paper together and a final decision was made. The inclusion and exclusion criteria used in the review are presented below.

Inclusion criteria for economic evaluation papers

Active comparator (streptokinase, alteplase, reteplase or tenecteplase)
Efficacy data primarily based on published drug versus drug randomised controlled clinical trial evidence
Explicit synthesis of costs and outcomes in a cost effectiveness ratio
Full economic evaluation
Primary paper

Exclusion criteria for economic evaluation papers

Non-drug comparator (e.g. placebo or conservative therapy) or aspirin, urokinase, anistreplase
Source of clinical efficacy data from non-randomised clinical trial or not explicitly stated
No attempt to synthesise costs and benefits
Letters, editorials, reviews, commentaries or methodological papers

All the references were exported to *Endnote* reference database, ISI Research Soft, Cal., USA, version 5.

3.2.3 Data extraction: cost-effectiveness

All cost-effectiveness data was abstracted by a single reviewer (ABol) and then checked by a second reviewer (RM). Both reviewers are health economists with expertise in economic evaluation. Given that several of the cost-effectiveness papers included in the review incorporated the use of modelling techniques, it was appropriate to extract additional data from these papers.

The data extracted from the published cost-effectiveness analyses are presented in four sections.

Firstly, there is a section on study design where the following information is stated:
- Type of economic evaluation and measure of synthesis
- Intervention
- Study population
- Time period of analysis and extrapolation details

The second section summarises the key cost and cost data sources used in the studies:
- Cost items
- Cost data sources
- Country, currency and year

The third section summarises the range of outcomes and efficacy data sources used in the studies:
- Range of outcomes
- Efficacy data sources
- Utility values and data sources
- Modelling method and data sources

Finally, the fourth section explores the results of the cost-effectiveness studies:
- Cost-effectiveness ratio
- Subgroup analysis and results
- Sensitivity analysis and results
- Authors conclusions

3.2.4 Quality assessment: cost-effectiveness

The quality assessment of cost-effectiveness analyses was based on the Drummond 10-point checklist.(42) All studies were scored (ABol, RM) according to the checklist detailed in Appendix VIII.

4. RESULTS: CLINICAL EFFECTIVENESS - HOSPITAL

4.1 Included studies

Selection of included studies

A total of 162 references were identified to which the inclusion criteria were applied. Of these, 20 studies reported in 50 articles fulfilled the inclusion criteria (Section 11.1) A total of 21 papers were reports of studies examining the effectiveness of thrombolytic agents not currently available in the UK. These were excluded on this basis and are listed (by drug) in the References, Section 11.2**.**

No studies relating to the use of thrombolytic agents in a pre-hospital setting fulfilled the inclusion criteria. These 28 references, which are described, are listed in the References, Section 11.3.

Reports of studies relating to agents under consideration in this review (Table 1), utilised within hospital, but which did not fulfil the inclusion criteria are detailed in References, Section 11.4. Reason for exclusion is given for each of these excluded references.

Details of the hospital studies included in the review follow below.

Hospital based studies:

Twenty studies reported in 50 articles met the inclusion criteria (Table 2). These included 14 studies comparing two or more drugs,(17-20, 43-49, 51-53, 60) four dose ranging trials (54-57) and two trials of various regimes of the same drug.(58, 59) Dose ranging trial is defined as a clinical trial in which two or more doses of an agent are tested against each other to determine which dose works best and is least harmful. Data from two included studies GISSI-2 and ISG(46, 47) were combined in the study reports and this combination of data was maintained in this review.

Table 2: Summary of included clinical studies:

Alteplase/ Streptokinase	Alteplase/ Tenecteplase	Alteplase/ Reteplase	Streptokinase/ Reteplase	Dose Ranging & mixed regimes
GUSTO I(18)*[Acc t-PA] Central Illinois(43) Cherng(44) ECSG(45) GISSI-2/ISG(46, 47) ISIS-3(48) KAMIT(49) PAIMS(51) TIMI-1(52) White(60)	ASSENT-2(20) *[Acc t-PA]	GUSTO III(19)*[Acc t-PA] RAPID-2(17) *[Acc t-PA]	INJECT(53)	COBALT(58)(t-PA) *[Acc t-PA] Xu (59)(SK) SIX(54)(SK) ASSENT-1(55)(TNK) TIMI 10B(56)(TNK)*[Acc t-PA] RAPID-1(57) (r-PA)

*[Acc t-PA] Involved accelerated alteplase. SK, streptokinase; t-PA alteplase; r-PA, reteplase; TNK, tenecteplase.

4.2 Quantity and quality of research available

Quality assessment of included trials

Methodological quality of studies is summarised in Table 3 using the criteria based on CRD Report 4 (Appendix VII).

Of the 14 included studies nine reported a truly random method of sequence generation (i.e. use of centralised or computerised random numbers), in all other trials the method was not stated. Eight studies appeared to have adequately concealed allocation of treatment.

All studies reported the number of randomised participants and presented the participant eligibility criteria. The co-interventions for each treatment group were identified in all studies.

The baseline comparability for each treatment group was presented and achieved in13 trials, whereas in one study (ISIS-3) it was not presented.

Eleven studies reported the blinding of outcome assessors. None of the studies reported the assessment of the blinding procedure. All studies appeared to include an intention to treat analysis and reported the number and reason for withdrawals.

Table 3: Quality assessment of included clinical studies

Checklist items:*	Randomisation:			Baseline comparability:		Eligibility criteria specified	Co-interventions identified	Blinding:				Withdrawals:		Intention to treat
	Truly Random	Allocation concealment	Number stated	Presented	Achieved			Assessors	Administration	Participants	Procedure assessed	>80% randomised in final analysis	Reasons stated	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Alteplase/Streptokinase:														
GUSTO I(18)	✔	✔	✔	✔	✔	✔	✔	✔	✘	✘	ns	✔	✔	✔
Central Illinois(43)	ns	ns	✔	✔	✔	✔	✔	✔	✘	✔	ns	✔	✔	✔
Cherng(44)	ns	ns	✔	✔	✔	✔	✔	ns	✘	✘	ns	✔	✔	✔
ECSG(45)	✔	✔	✔	✔	✔	✔	✔	✔	ns	ns	ns	✔	✔	✔
GISSI-2/ ISG(46, 47)	✔	✔	✔	✔	✔	✔	✔	✘	✘	✘	ns	✔	✔	✔
ISIS-3(48)	✔	✔	✔	ns	ns	✔	✔	✔/✘	✔/✘	✔/✘	ns	✔	✔	✔
Kamit(49)	✔	✔	✔	✔	✔	✔	✔	✔	ns	ns	ns	✔	✔	✔
PAIMS(51)	ns	ns	✔	✔	✔	✔	✔	✔	ns	ns	ns	✔	✔	✔
TIMI-1(52)	✔	ns	✔	✔	✔	✔	✔	✔	✔	✔	ns	✔	✔	✔
White(60)	ns	ns	✔	✔	✔	✔	✔	✔	✔	✔	ns	✔	✔	✔
Alteplase/Tenecteplase:														
ASSENT-2(20)	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	ns	✔	✔	✔
Alteplase/Reteplase:														
GUSTO III(19)	✔	✔	✔	✔	✔	✔	✔	✔	✘	✘	ns	✔	✔	✔
RAPID II(17)	ns	ns	✔	✔	✔	✔	✔	✔	✘	✘	ns	✔	✔	✔
Streptokinase/Reteplase:														
INJECT(53)	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	ns	✔	✔	✔

Items graded: ✔ **yes** (item adequately addressed), ✘ **no** (item not adequately addressed), ✔/✘ **partially** (item partially addressed) or **ns not stated**.
Quality assessment checklist items in are described in full in Appendix VII.

Characteristics of trials

The 14 included trials involved a total study population of 142,907 patients. Characteristics of these studies are presented in Table 4. In addition, six were dose ranging trials and trials of various regimes of the same drug, involving in total 12,189 patients. These are listed within the Reference section of the included studies.

The size of studies varied from the smallest with 122 patients to the largest involving 41,299 patients. Six trials had fewer than 300 patients in total whereas five trials had more than 10,000 patients in total.

Eight trials were carried out in more than one country. The remainder were conducted in a single country (Taiwan, New Zealand, Italy and USA-three trials).

Ten studies compared alteplase with streptokinase. Seven studies used the standard doses of streptokinase (1.5 MU) and alteplase (100 mg). One of these utilised accelerated administration of alteplase. Two studies compared accelerated alteplase with reteplase. One study compared streptokinase to reteplase, and one alteplase with tenecteplase.

Inclusion criteria were consistent across the trials and were based on age, ECG changes and duration of AMI symptoms. Patients presenting up to six hours of onset of AMI symptoms with duration of at least 30 minutes were included in seven trials. Eleven trials excluded patients with current contraindications to thrombolysis comparable to those described by the European Society of Cardiology (Appendix IX). Other criteria for exclusion included shock, hypotension, history of previous MI, malignancy and childbearing age or pregnancy.

The primary endpoints used in the trials include 30-35 day mortality, efficacy, 90-minute artery patency/flow rates and left ventricular function. A range of secondary outcomes have been reported in trials such as bleeding, stroke, reinfarction, allergy and anaphylaxis.

All trials used various adjunct treatments. Of these, 11 studies reported the use of aspirin and heparin, two studies used a combination of heparin and nitroglycerin and one further study used a combination of heparin, aspirin and nitroglycerin.

Table 4: Characteristics of clinical studies

Study	**Interventions**	**N**	**Location**	**Participant inclusion**	**Participant exclusion**	**Primary endpoint**	**Other Outcomes**	**Adjunct treatment(s)**
	Alteplase/Streptokinase							
GUSTO I (18) *Acc t-PA	Acc t-PA SK SK+t-PA SK 1.0 MU/1 hour, t-PA 1.0 mg/kg/one hour	10396 20251 10374	International 1081 hospitals 15 countries	AMI symptoms within previous 6 h; chest pain for 20 minutes; ECG changes	Contraindications to thrombolysis previous treatment with SK or anistreplase, previous participation in the trial; non-compressible vascular punctures	Mortality 30-day	Combined 30-day mortality: or nonfatal stroke, or nonfatal haemorrhagic stroke, combined 30-day mortality or nonfatal disabling stroke	Aspirin Heparin
Central Illinois(43)	t-PA 10 mg bolus, followed by 50 mg in the first hour, and 20 mg/hour for the next 2 hours SK 375,000 IU bolus, followed by 1,125,000 IU/ 1 hour	123 130	USA 30 hospitals	Treatment within 4 hours of onset of chest pain; ECG changes; age ≤75 yrs with first AMI	Contraindications to thrombolysis; ST-segment depression or non-Q wave infarction, or both, left bundle branch block, prior coronary artery bypass surgery;	Not stated	LVF Mortality, Bleeding, Stroke Allergic reactions	Aspirin IV heparin
Cherng(44)	t-PA SK	59 63	Taiwan	Chest pain ≥30 minutes; less than 6 hours, ECG changes; age <70 yrs	Contraindications to thrombolysis; Shock (BP <80 mmHg); child-bearing age	Unclear	Patency LVF Bleeding Mortality	Aspirin IV nitroglycerin IV heparin
ECSG(45)	t-PA 0.75 mg/kg/90 minutes SK	64 65	Europe 7 hospitals	Severe chest pain 30 minutes; randomisation within 6 hours of onset of symptoms; ECG changes; Age 20-70; no previous AMI	Contraindications to thrombolysis; hypotension (Systolic BP <90 mmHg); heart rate >110 min; previous infarction; major hepatic or renal disease, cancer or proliferate diabetic retinopathy; pregnancy	Not stated	Patency Mortality Adverse events - used their own criteria	IV heparin SK group also got aspirin
GISSI-2/ISG (46, 47)	t-PA SK 1.5 MU/ 30-60 min	10372 10396	International 14 countries	AMI admit to CCU within 6h from symptom onset; ECG changes	Contraindications to thrombolysis; uncontrolled hypertension (systolic ≥200 mm Hg, diastolic ≥ 110 mm Hg); previous treatment with SK within past six months	Mortality In- hospital	Mortality – (discharge + 6 months) Major adverse events	Aspirin Heparin (50%)

*Acc t-PA Involved accelerated alteplase. *Current contraindications to thrombolysis* are detailed in Appendix IX. t-PA= alteplase, SK = streptokinase, APSAC = anistreplase, TNK= tenecteplase, r-PA= reteplase

Table 4 (continued): Characteristics of clinical studies

Study	**Interventions**	**N**	**Location**	**Participant inclusion**	**Participant exclusion**	**Primary endpoint**	**Other Outcomes**	**Adjunct treatment(s)**
	Alteplase/Streptokinase							
ISIS-3(48)	t-PA SK APSAC 30 units over minutes	13746 13780 13773	International 914 hospitals 17 countries	Symptoms of AMI within previous 24 hours	Contraindications to thrombolysis	Mortality 35-day	Allergy ↓BP Stroke Shock PE VF Cardiac arrest Reinfarction	Aspirin (all patients) Heparin (half of patients)
PAIMS(51)	t-PA SK	86 85	Italy 8 Hospitals	Chest pain for 30 minutes, unrelieved by SB nitroglycerin; < 3 h from onset of symptoms to recruitment; ECG changes; age: 20-70 yrs;	Contraindications to thrombolysis; previous MI; cardiogenic shock; left bundle branch block; uncontrolled hypertension (diastolic ≥110 mm Hg, systolic ≥200 mm Hg); major liver or renal disease; childbearing age	Thrombolytic efficacy and effects on LVF	Time to reperfusion ECG output Intensity of chest pain Adverse events	Heparin NTG
TIMI-1(52)	t-PA SK	157 159	USA 13 hospitals	Chest pain 30 minutes; ECG changes; age <75 yrs.	Contraindications to thrombolysis; pain >7 hours, patients with less than 50 reduction in artery post IC NTG	Recanalizatio n[n] at 90 min	LVF EF Adverse events	IV heparin, IC nitroglycerin
White(60)	t-PA SK 1.5 MU/30 minutes	135 135	New Zealand 4 hospitals	Chest pain 30 minutes; ECG changes; First AMI;	Age > 70 years; Q-wave infarction; hypertension (systolic pressure >200 mmHg)	LVF	Patency rates at 3 weeks Reinfarction, Adverse events Mortality	Aspirin IV heparin
	Alteplase/Alteplase and Streptokinase							
KAMIT(49)	t-PA t-PA (half dose - 10 mg bolus the 40 mg/1 hour) + SK (1.5 MU)	107 109	USA	Chest pain within previous 6 hours; ECG changes; age <75 yrs.	Contraindications to thrombolysis	Patency at 90 min	In-hospital reocclusion LVF Bleeding, Recurrent ischemic events	Aspirin Heparin

Table 4 (continued): Characteristics of clinical studies

Study	**Interventions**	**N**	**Location**	**Participant inclusion**	**Participant exclusion**	**Primary endpoint**	**Other Outcomes**	**Adjunct treatment(s)**
	Alteplase/Tenecteplase							
ASSENT-2 (20) *Acc t-PA	Acc t-PA TNK 30-50 mg, single bolus, weight-adjusted	8488 8461	International 29 countries 1021 hospitals	AMI symptoms within previous 6 h; ECG changes; age ≥18 years;	Contraindications to thrombolysis; use of abciximad or other glycoprotein IIb/IIIa antagonists within preceding 12 h; biopsy of a parenchimal organ, transient ischaemic attack, or dementia; any structural damage to CNS	Mortality 30-day	Non- fatal stroke major non-fatal cardiac events stroke	Aspirin IV heparin
	Alteplase/Reteplase							
GUSTO III (19) *Acc t-PA	Acc t-PA r-PA	4921 10138	International 20 countries 807 hospitals	Chest pain > 30 minutes; symptoms < 6 hours	Contraindications to thrombolysis; systolic bp > 200 mm Hg, diastolic BP 110 mm Hg, recent non-compressible vascular pressure	Mortality 30-day	Net clinical benefit (freedom from death or disabling stroke) Death or stroke Adverse events	Aspirin Heparin
RAPID II (17) *Acc t-PA	Acc t-PA r-PA	155 169	USA 20, Germany 5 Hospitals	Chest pain ≥ 30 minutes, not relieved by nitroglycerin; presenting within ≤ 12 hours of symptom onset; ECG changes; age >18 years	Prior coronary angioplasty within 2 weeks; previous q-wave MI in the same anatomic region; women with child bearing potential; contraindications to thrombolysis	Patency at 90 min	Patency rates, left venricular function, stroke, reinfarction, bleeding, death	Aspirin IV heparin
	Streptokinase/Reteplase							
INJECT (53)	SK r-PA	3006 3004	Europe 9 countries 208 hospitals	Chest pain ≥ 30 minutes; treatment within 12 hours of onset of symptoms; ECG changes or bundle branch block	Intracranial neoplasm, arteriovenous malformation, or aneurysm; pregnancy or breastfeeding; contraindication to SK; treatment with SK or anistreplase within 12 months; administration of any other investigational drug within 30 days; previous enrolment in the study	Mortality 35-day	Intracerebral events Bleeding Cerebrovascular events Allergic reactions, Reinfarction	Aspirin IV heparin

*Acc t-PA Involved accelerated alteplase. *Current contraindications to thrombolysis* (22) are detailed in Appendix IX. t-PA= alteplase, SK = streptokinase, APSAC = anistreplase, TNK= tenecteplase, r-PA= reteplase

Participant characteristics

The baseline characteristics of the participants are presented in Table 5. Five studies reported the proportion of participants aged over 70-75 years, ranging between 11.6% to 26.1%. The TIMI-1 study reported the proportion of participants over 65 years of age (t-PA 22%, SK 28%). The proportion of females among the studies varied between 8.5% and 28.2%. In nine studies the proportion of females was at least 19%. The proportion of patients with an anterior infarct varied from 32% to 61.9%. Two studies reported time to treatment in intervals (recording proportions of people treated with various time bands over 0-24 hours in ISIS-3 and 0-6 hours in GISSI-2). The other studies reported median or mean time to treatment, ranging from 2.1 (PAIMS) to 5.2 hours. Time to treatment varied somewhat between the treatment arms. The proportion of participants with a history of previous MI was between 6% to 18.4%. Follow-up was within hospital in six studies, and 30-35 days in the others.

Table 5: Characteristics of clinical study participants

Study	**Number randomised**	**Age years**	**> 70-75 years, %**	**Sex female %**	**Systolic BP mm Hg**	**Anterior infarct, %**	**Time, hours, symptom onset to treatment**	**Previous AMI, %**	**Follow-up**
	Alteplase/Streptokinase								
GUSTO I(18) ***Acc t-PA**	41021	Median Acc t-PA 62 (52,70) SK 62 (52,70) SK+ t-PA 61 (52,70)		25	Median Acc t-PA+ IV Hep 130 (113, 144) SK+ SC Hep 130 (111, 144) SK+ IV Hep 129 (112, 144) SK+ tPA+IV Hep 130 (112, 143)		Median, Minutes Acc t-PA+ IV Hep 165 (120, 230) SK+ SC Hep 164 (115, 232) SK+ IV Hep 165 (120, 230) SK+ tPA+IV Hep 170 (121, 237)	Acc t-PA 17 SK 16.5 SK+ t-PA 6	30 days
Central Illinois(43)	253	Mean t-PA 59 (10) SK 59 (11)		t-PA 28 SK 28		t-PA 44 SK 36	Mean, Minutes t-PA 146 (61) SK 148 (59)		Hospital
Cherng(44)	122	Mean 57.6 (9.5)		14.8		t-PA 57.6 SK 61.9	Mean t-PA 5.2 (3.7) SK 4.9 (2.3)		30 days
ECGS(45)	129	Median t-PA 55.1 (32.4, 70.7) SK 54.3 (36.2, 70.4)		t-PA 9.3 SK 8.5	Median t-PA 130 (70, 195) SK 130 (90, 195)	t-PA 53 SK 48	Median t-PA 3.0 (1.1, 5.5) SK 2.6 (0.8, 5.9)		Hospital
GISSI-2/ISG (46, 47)	20891	Not reported	t-PA 22.9 SK 23.0	t-PA 21.7 SK 21.1			% ≤1 t-PA 14.4 SK 14.9 ≤3 t-PA 63.9 SK 63.7 >3-6 t-PA 34.5 SK 34.7	t-PA 17.4 SK 16.9	Hospital

Mean (SD), Median (range)

Table 5 (continued): Characteristics of clinical study participants

Study	**Number randomised**	**Age years**	**> 70-75 years, %**	**Sex female %**	**Systolic BP mm Hg**	**Anterior infarct, %**	**Time, hours, symptom onset to treatment**	**Previous AMI, %**	**Follow-up**
	Alteplase/Streptokinase (continued)								
ISIS-3(48)	41299	Not reported	26.1 (>70 years)	27.1		34.9	% 0-6 78.2 7-12 14.4 13-24 7.4	21.7	35 days
PAIMS(51)	171	Mean t-PA 57 (8) SK 58 (8)		t-PA 12.8 SK 22.3	Mean t-PA 133 (22) SK 135 (21)	t-PA 51.2 SK 43.5	Mean, Minutes t-PA 124 (40) SK 127 (41)		Hospital
TIMI-1(52)	316	Mean t-PA 56 SK 57	t-PA 22 SK 28 (>65 years)	t-PA 20 SK 21	Mean t-PA 132 SK 134	t-PA 45 SK 52	Mean, Minutes t-PA 286 SK 287	t-PA 17 SK 18	Hospital
White(60)	270	Mean t-PA 55 (9) SK 56 (9)			Mean t-PA 132 (27) SK 133 (26)	t-PA 36 SK 32	Mean t-PA 2.5 (0.6) SK 2.5 (0.6)		30 days
	Alteplase/Alteplase and Streptokinase								
KAMIT(49)	216	Mean t-PA 55(11) t-PA/SK 53(11)		t-PA 17 t-PA/SK 17	Mean t-PA 130 (21) t-PA/SK 129 (26)	t-PA 42 t-PA/SK 42	Mean t-PA 3.0 (1.2) t-PA/SK 2.9 (1.2)	t-PA 13 t-PA/SK 12	Hospital

Mean (SD), Median (range)

Table 5 (continued): Characteristics of clinical study participants

Study	**Number randomised**	**Age years**	**> 70-75 years, %**	**Sex female %**	**Systolic BP mm Hg**	**Anterior infarct, %**	**Time, hours, symptom onset to treatment**	**Previous AMI, %**	**Follow-up**
	Alteplase/Tenecteplase								
ASSENT-2(20) ***Acc t-PA**	16949	Median t-PA 61 (51, 70) TNK 62 (52, 70)	t-PA 12.6 TNK 12.4	t-PA 23.3 TNK 22.9	Median t-PA 133 (119, 150) TNK 133 (120, 150)	t-PA 40.2 TNK 39.4	Median t-PA 2.8 (1.9, 3.8) TNK 2.7 (1.9, 3.8)	t-PA 16.1 TNK 15.8	30 days
	Alteplase/Reteplase								
GUSTO III(19) ***Acc t-PA**	15059	Median t-PA 63.0 (53, 72) r-PA 62.9 (53,71)	t-PA 13.5 r-PA 13.6	t-PA 27.2 r-PA 27.5	Median t-PA 134 (119, 150) r-PA 135 (119, 150)	t-PA 47.7 r-PA 47.4	Median t-PA 2.7 (1.9, 3.9) r-PA 2.7 (1.8, 3.8)	t-PA 18.4 r-PA 18.4	30 days
RAPID II(17) ***Acc t-PA**	324	Median t-PA 62 (30, 89) r-PA 58 (24, 87)		t-PA 19 r-PA 24	Unclear	t-PA 37 r-PA 39	Median t-PA 2.4 r-PA 2.5	t-PA 18 r-PA 17	35 days
	Streptokinase/Reteplase								
INJECT(53)	6010	Mean SK 61.9 (11.7) r-PA 61.8 (11.5)	SK 12.1 r-PA 11.6	SK 27.1 r-PA 28.2	Mean SK 134.7 (23.4) r-PA 135.8 (23.1)	r-PA 41.4 SK 44.0	Mean SK 4.1 (2.4) r-PA 4.2 (2.8)	SK 14.7 r-PA 14.5	35 days

Mean (SD), Median (range)

Thrombolytic drug comparisons

Data on selected clinical outcomes from studies comparing thrombolytic agents are detailed in Table 6. Outcomes include mortality up to 35 days, any stroke, hemorrhagic stroke**,** reinfarction, bleeding, allergy and anaphylaxis.

All of the 14 included studies presented data on mortality up to 35 days, although there was variation in the time scale underpinning the mortality values. Only three of the studies did not report stroke data, although a total of six studies did not give figures for haemorrhagic stroke. Again, the majority of studies (10/14) reported numbers of study participants determined to have experienced reinfarction. Information on major bleeding was provided in most trials (13/14), however, the categorisation and reporting of bleeding events varied. The review team were unable to confidently match the description of bleeds in the GUSTO I report with the bleeding categories used in this review. Therefore, bleed data are only presented for twelve studies. Incidences of allergy and anaphylaxis were less frequently reported. Eight studies reported on allergy. With the exception of the INJECT study, these were all trials investigating alteplase/streptokinase. Five reports provided data on anaphylaxis. This included three studies comparing alteplase/streptokinase and one for each of the alteplase/tenecteplase and alteplase/reteplase studies.

Where available, data on the compared outcomes were used in the meta-analyses (presented later in this chapter).

Table 6: Thrombolytic drug comparisons

Study	**Interventions**	**Number randomised**	**Mortality 0-35 days**	**Stroke any**	**Haemorrhagic stroke**	**Reinfarction**	**Bleeding total**	**Bleeding major**	**Allergy any**	**Anaphylaxis**
	Alteplase/Streptokinase									
GUSTO I(18)	SK sc hep	9841	705/9796 (7.2)[i]	118/9709 (1.22)	46/9709 (0.49)	295/8669 (3.4)	Unclear	Unclear	494/8669 (5.7)	61/8669 (0.7)
	SK iv hep	10410	767/10377 (7.4)[i]	144/10314 (1.40)	56/10314 (0.54)	370/9260 (3.99)	Unclear	Unclear	537/9260 (5.8)	56/9260 (0.6)
	Acc t-PA	10396	652/10344 (6.3)[i]	159/10268 (1.55)	74/10268 (0.72)	369/9235 (3.99)	Unclear	Unclear	148/9235 (1.6)	18/9235 (0.2)
	SK + t-PA	10374	723/10328 (7.0)[i]	168/10248 (1.64)	96/10248 (0.94)	368/9193 (4.0)	Unclear	Unclear	496/9193 (5.4)	55/9193 (0.6)
Central Illinois(43)	t-PA	123	6/123 (5)				26/123 (21)	18/123 (14.6)	0/123	0/123
	SK	130	9/130 (7)				36/130 (28)	25/130 (19.2)	3/130 (2)	SK 0/130
Cherng(44)	t-PA	59	2/59 (3.4)				8/59 (13.6)	3/59 (5.1)		
	SK	63	5/63 (7.9)				7/63 (11.1)	3/63 (4.8)		
ECGS(45)	t-PA	64	3/64 (4.7)[a]	0/64		2/64 (3.1)		4/64 (6.2)	0/64	
	SK	65	3/65 (4.6)[a]	1/65 (1.5)		4/65 (6.1)		5/65 (7.7)	1/65 (1.54)	
GISSI-2/ISG (46, 47)	t-PA	10372	929/10372 (8.9)[j]	138/10372 (1.3)	44/10372 (0.4)	274/10372 (2.6)		64/10372 (0.6)		
	SK	10396	887/10396 (8.5)[j]	98/10396 (0.9)	30/10396 (0.3)	314/10396 (3.0)		96/10396 (0.9)		
ISIS-3(48)	t-PA	13746	1418/13746 (10.3)	188/13569 (1.39)	76/13569 (0.56)7	397/13569 (2.93)		109/13569 (0.80)	109/13569 (0.80)	
	SK	13780	1455/13780 (10.6)	141/13607 (1.04)	25/13607 (0.18)7	472/13607 (3.47)		118/13607 (0.87)	490/13607 (3.60)	
PAIMS(51)	t-PA	86[d]	4/86			0/86	10/86	0/86	0/86	
	SK	85[d]	7/85			2/85 (2.35)	06/85	1/85	4/85	
TIMI-1(52)	t-PA	143-157	7/143 (4.9)[e]	0/290		19/143 (13)[f]	47/143 (32.9)	22/143 (15.4)	7/143 (5)	0/290
	SK	147-159	12/147 (8.2)[e]			17/147 (12)[f]	46/147 (31.3)	23/147 (15.6)	25/147 (17)	
White(60)	t-PA	135	5/135 (3.7)[i]	2/135 (at least)	2/135 (at least)	7/135 (5.2)[i]		0/135	3/135 (2)	
	SK	135	10/1357.4)[i]			7/135 (5.2)[i]		3/135 (2.2)	0/135	

Percentages in parenthesis. [a] Events from 3rd day until discharge, [b] Patency at 75-90 minutes post treatment=0-3, [c] 9 months, [d] 147 treated, 159 randomised, [e] in hospital stay, [f] 21 days data; 6 months t-PA 24/143, SK 19/147; 12 months t-PA 26/143, 21/147, [g] Definite only, [h] with IV heparin, [i] data for 30 days, [j] in-hospital data, with and without heparin

Table 6 (continued): Thrombolytic drug comparisons

Study	**Interventions**	**Number randomised**	**Mortality 0-35 days**	**Stroke any**	**Haemorrhagic stroke**	**Reinfarction**	**Bleeding total**	**Bleeding major**	**Allergy any**	**Anaphylaxis**
	Alteplase/Alteplase and Streptokinase									
KAMIT(49)	t-PA/SK	109	6/109 (5.5)[e]	2/109 (2)	1/109 (1)	0/109		13/109 (12)		
	SK	107	4/107 (3.7)[e]	2/107 (2)	0/107	4/107 (4)		11/107 (11)		
	Alteplase/Tenecteplase									
ASSENT-2(20)	**Acc t-PA**	8488	522/8488 (6.15)[i]	141/8488 (1.66)	80/8488 (0.94)	323/8488 (3.8)	2457/8488 (28.95)	504/8488 (5.94)		17/8488 (0.2)
	TNK	8461	523/8461 (6.18)[i]	151/8461 (1.78)	79/8461 (0.93)	347/8461 (4.1)	2236/8461 (26.43)	394/8461 (4.66)		8/8461 (0.1)
	Alteplase/Reteplase									
GUSTO III(19)	**Acc t-PA**	4921	356/4921 (7.24)[i]	88/4921 (1.79)	42/4921 (0.87)	207/4921 (4.2)		59/4921 (1.20)		3/4921 (0.06)
	r-PA	10138	757/10138 (7.47)[i]	166/10138 (1.64)	92/10138 (0.91)	426/10138 (4.2)		96/10138 (0.95)		5/10138 (0.05)
RAPID II(17)	**t-PA**	155	13/155 (8.4)	4/155 (2.6)						
	r-PA	169	7/169 (4.1)	3/169 (1.8)						
	Streptokinase/Reteplase									
INJECT(53)	**SK**	3004	285/2992 (9.53)	30/2992 (1.00)	11/2992 (0.37)		458/2992 (15.3)	141/2992 (4.7)	54/2992 (1.8)	
	r-PA	3006	270/2994 (9.02)	37/2994 (1.23)	23/2994 (0.77)		449/2994 (15)	138/2994 (4.6)	33/2994 (1.1)	

Percentages in parenthesis.[e] in hospital stay, [i] 30-day data, [l] serious bleed

4.3 Quality assessment of included studies

Quality assessment was carried out using a checklist designed by Centre for Reviews and Dissemination.(41) The checklist includes key aspects of RCT design and quality. However, this is a recently developed tool and when used to assess studies that pre-date it, provides some challenges to reviewers in interpretation of the terminology (e.g. double blind, concealment of allocation). A discussion of these issues has been published by Schulz and Grimes.(61)

Overall methodological quality of included studies was excellent. Results of the assessment were presented earlier in Table 3. The three large studies that compared accelerated alteplase (GUSTO I, ASSENT-2, GUSTO III) and the single large study comparing streptokinase and reteplase (INJECT) were international studies that scored well on all criteria except assessment of their blinding techniques. Two of these large studies (GUSTO I and GUSTO III) were open label studies, and therefore those administering the drugs and presumably the patients were aware of the treatment being administered. However, in each, treatment allocation was randomised, the outcome assessors were blind to the treatment allocation, and the treatment outcome (death at 30 days) was objective. Follow-up of patients in all studies was excellent.

4.4 Meta-analysis

The primary endpoints and major secondary endpoints of the trials comparing at least two drugs in particular related to hazards of drugs are presented here and a meta-analysis undertaken. The trials compare: alteplase to streptokinase (Table 7 for all alteplase and Table 8 for alteplase other than in accelerated infusions), accelerated alteplase to tenecteplase (Table 9, based only on one study), accelerated alteplase to reteplase (Table 10), and reteplase to streptokinase (Table 11, one study).

The meta-analysis are presented in the tables using odds ratios (OR) with 95% CI and, where appropriate, using a random effect model. Data extracted and included in the analysis are mortality (30-35 day), stroke (total and hemorrhagic), major bleed and re-infarction. Data related to congestive heart failure did not lend itself to meta-analysis and was extracted for use in the economic model and is presented there.

There has been extensive debate over the evaluation of the effectiveness of alteplase provided as an infusion and accelerated alteplase which is provided as a bolus followed by an infusion.(11) We expand on this controversy in the discussion. We therefore present the analysis in two tables, one including the GUSTO I trial and one not. There is no statistical evidence of heterogeneity between trials in either. The data for GUSTO I is the more commonly presented comparison of the two streptokinase only arms compared to the accelerated alteplase arm.

These provide direct comparisons where they are available: however not all the possible drug comparisons have been made in randomised controlled trials and it is necessary to draw indirect comparisons. The justifications and conclusions of the direct and indirect comparisons are made in the discussion.

The main results are as follows:

- *All alteplase versus streptokinase*: No difference in mortality or reinfarction (Table 7). Total stroke and haemorrhagic stroke rates were lower in streptokinase grouping.
- *Alteplase excluding accelerated alteplase versus streptokinase*: No difference in mortality (Table 8). In the streptokinase group there was a lower incidence of total stroke and haemorrhagic stroke. Major bleed and reinfarction rates were lower in the alteplase group.
- *Accelerated alteplase versus tenecteplase*: No differences in mortality, total stroke, haemorrhagic stroke or reinfarction. Fewer major bleeds with tenecteplase (Table 9).
- *Accelerated alteplase versus reteplase*: No difference in mortality, total stroke, haemorrhagic stroke, major bleed or reinfarction (Table 10).
- *Reteplase versus streptokinase*: No difference in mortality, total stroke, major bleeds. There was a lower incidence of haemorrhagic strokes in the streptokinase group (Table 11).

Table 7: All alteplase versus streptokinase

Outcome	Study	Alteplase	Streptokinase	OR random effect (95% CI)
Mortality up to 35 days	CENTRAL ILLINOIS	6/123	9/130	0.69 (0.24, 2.00)
	CHERNG	2/59	5/63	0.41 (0.08, 2.18)
	ECSG	3/64	3/65	1.02 (0.20, 5.23)
	GISSI-2/ISG	929/10372	887/10396	1.05 (0.96, 1.16)
	GUSTO I	652/10344	1472/20173	0.85 (0.78, 0.94)
	ISIS-3	1418/13746	1455/13780	0.97 (0.90, 1.05)
	PAIMS	4/86	7/85	0.54 (0.15, 1.93)
	TIMI 1	7/143	12/147	0.58 (0.22, 1.52)
	WHITE	5/135	10/135	0.48 (0.16, 1.45)
	Total	3026/35072	3860/44974	0.94 (0.85, 1.04)
				Test for Heterogeneity x^2=13.96, *df*=8, P=0.083
Stroke (total)	ECSG	0/64	1/165	0.33 (0.01, 8.34)
	GISSI-2/ISG	138/10372	98/10396	1.42 (1.09, 1.84)
	GUSTO I	159/10268	262/20023	1.19 (0.97, 1.45)
	ISIS-3	188/13569	141/13607	1.34 (1.08, 1.67)
	Total	485/34273	502/44091	**1.29 (1.13, 1.46)**
				Test for Heterogeneity x^2=1.99, *df*=3, P=0.58
Hemorrhagic stroke	GISSI-2/ISG	44/10372	30/10396	1.47 (0.92, 2.34)
	GUSTO I	74/10268	102/20023	1.42 (1.05, 1.91)
	ISIS-3	76/13569	25/13607	3.06 (1.95, 4.81)
	Total	194/34209	157/44026	**1.83 (1.14, 2.93)**
				Test for Heterogeneity x^2=8.30, *df*=2, P=0.016
Reinfarction	ECSG	2/64	4/65	0.49 (0.09, 2.79)
	GISSI-2/ISG	274/10372	314/10396	0.87 (0.74, 1.03)
	GUSTO I	369/9235	665/17929	1.08 (0.95, 1.23)
	ISIS-3	397/13569	472/13607	0.84 (0.73, 0.96)
	PAIMS	0/86	2/85	0.19 (0.01, 4.08)
	TIMI 1	19/143	17/147	1.17 (0.58, 2.36)
	WHITE	7/135	7/135	1.00 (0.34, 2.93)
	Total	1068/33604	1481/42364	0.93 (0.81, 1.07)
				Test for Heterogeneity x^2=9.91, *df*=6, P=0.13

Table 8: Alteplase *excluding accelerated alteplase* versus streptokinase (GUSTO I omitted)

Outcome	Study	Alteplase	Streptokinase	OR random effect (95% CI)
Mortality-up to 35 days	CENTRAL ILLINOIS	6/123	9/130	0.69 (0.24, 2.00)
	CHERNG	2/59	5/63	0.41 (0.08, 2.18)
	ECSG	3/64	3/65	1.02 (0.20, 5.23)
	GISSI-2/ISG	929/10372	887/10396	1.05 (0.96, 1.16)
	ISIS-3	1418/13746	1455/13780	0.97 (0.90, 1.05)
	PAIMS	4/86	7/85	0.54 (0.15, 1.93)
	TIMI 1	7/143	12/147	0.58 (0.22, 1.52)
	WHITE	5/135	10/135	0.48 (0.16, 1.45)
	Total	2374/24728	2388/224801	1.00 (0.94, 1.06)
				Test for Heterogeneity x^2=6.87, *df*=7, P=0.44
Stroke (total)	ECSG	0/64	1/165	0.33 (0.01, 8.34)
	GISSI-2/ISG	138/10372	98/10396	1.42 (1.09, 1.84)
	ISIS-3	188/13569	141/13607	3.06 (1.95, 4.81)
	Total	326/24005	240/24068	**1.37 (1.16, 1.62)**
				Test for Heterogeneity x^2=0.84, *df*=2, P=0.66
Hemorrhagic stroke	GISSI-2/ISG	44/10372	30/10396	1.47 (0.92, 2.34)
	ISIS-3	76/13569	25/13607	3.06 (1.95, 4.81)
	Total	120/23941	55/24003	**2.13 (1.04, 4.36)**
				Test for Heterogeneity x^2=4.91, *df*=1, P=0.027
Major bleed	CENTRAL ILLINOIS	18/123	25/130	0.72 (0.37, 1.40)
	CHERNG	3/59	3/63	1.07 (0.21, 5.53)
	ECSG	4/64	5/65	0.80 (0.20, 3.13)
	GISSI-2/ISG	64/10372	96/10396	0.67 (0.48, 0.92)
	ISIS-3	109/13569	118/13607	0.93 (0.71, 1.20)
	PAIMS	0/86	1/85	0.33 (0.01, 8.11)
	TIMI 1	22/143	23/147	0.98 (0.52, 1.85)
	WHITE	0/135	3/135	0.14 (0.01, 2.73)
	Total	220/24551	274/24628	0.81 (0.68, 0.97)
				Test for Heterogeneity x^2=4.69, *df*=7, P=0.7
Reinfarction	ECSG	2/64	4/65	0.49 (0.09, 2.79)
	GISSI-2/ISG	274/10372	314/10396	0.87 (0.74, 1.03)
	ISIS-3	397/13569	472/13607	0.84 (0.73, 0.96)
	PAIMS	0/86	2/85	0.19 (0.01, 4.08)
	TIMI 1	19/143	17/147	1.17 (0.58, 2.36)
	WHITE	7/135	7/135	1.00 (0.34, 2.93)
	Total	699/24369	816/24435	0.86 (0.77, 0.95)
				Test for Heterogeneity x^2=2.29, *df*=5, P=0.81

Table 9: Accelerated alteplase versus tenecteplase

Outcome	Study	Acc Alteplase	Tenecteplase	OR random effect (95% CI)
Mortality- up to 35 days	ASSENT-2	522/8488	523/8461	0.99 (0.88, 1.13)
Stroke	ASSENT-2	141/8488	151/8461	0.93 (0.74, 1.17)
Hemorrhagic stroke	ASSENT-2	80/8488	79/8461	1.01 (0.74, 1.38)
Major bleed	ASSENT-2	504/8488	394/8461	**1.29 (1.13, 1.48)**
Reinfarction	ASSENT-2	323/8488	347/8461	0.93 (0.79, 1.08)

Table 10: Accelerated alteplase versus reteplase

Outcome	Study	Acc Alteplase	Reteplase	OR random effect (95% CI)
Mortality Up to 35 days	GUSTO III	356/4921	757/10138	0.97 (0.85, 1.10)
	RAPID 2	13/155	7/169	2.12 (0.82, 5.46)
	Total	369/5076	764/10307	1.24 (0.61, 2.53)
				Test for Heterogeneity x^2=2.60, *df*=1, P=0.11
Stroke (total)	GUSTO III	88/4921	166/10138	1.09 (0.84, 1.42)
	RAPID 2	4/155	3/169	1.47 (0.32, 6.66)
	Total	92/5076	169/10307	1.10 (0.85, 1.43)
				Test for Heterogeneity x^2=0.14, *df*=1, P=0.71
Hemorrhagic stroke	GUSTO III	42/4921	92/10138	0.94 (0.65, 1.36)
Major bleed	GUSTO III	59/4921	96/10138	1.27 (0.92, 1.76)
Reinfarction	GUSTO III	207/4921	426/10138	1.00 (0.84, 1.19)

Table 11: Reteplase versus streptokinase

Outcome	Study	Reteplase	Streptokinase	OR random effect (95% CI)
Mortality- up to 35 days	INJECT	270/2994	285/2992	0.94 (0.79, 1.12)
Stroke (total)	INJECT	37/2994	30/2992	**1.24 (0.76, 2.00)**
Hemorrhagic stroke	INJECT	23/2994	11/2992	**2.10 (1.02, 4.31**)
Major bleed	INJECT	138/2994	141/2992	0.98 (0.77, 1.24)

4.5 Other adverse effects

Several studies report rates of allergy or anaphylaxis. Reported rates for allergy are often different suggesting different diagnostic criteria, but in general the rates of allergy and anaphylaxis on streptokinase are approximately 3-4 times those on alteplase (e.g. GUSTO I reports 5.7% allergy and 0.7% anaphylaxis on streptokinase compared to 1.6%

and 0.2% respectively on alteplase). The differential rates with reteplase are not so large - INJECT reports 1.8% allergy on streptokinase compared to 1.1% on reteplase. There seems little difference in rates of allergy between the newer drugs in comparative studies.

4.6 Subgroup analysis of included studies

Six included studies conducted subgroup analysis of mortality at 30-35 days. The three most common subgroups of patients were identified according to age, location of infarction and time from onset of symptoms to treatment. Thrombolytic drug comparisons by subgroups are presented in Table 12.

There are no differences in the comparative efficacy of different drugs at different ages. Older patients typically have higher mortality rates regardless of drug. The GUSTO I study which shows an advantage of accelerated alteplase over streptokinase shows the advantage consistently in all age groups.

When the time to treatment was categorised at different time intervals, the GUSTO I study seemed to show a better outcome with acclerated alteplase in those treated within 6 hours, but a better outcome with streptokinase in those treated after 6 hours.(18) On re-analysis, this was not statistically significant.(62) In ASSENT-2, the 30-day mortality in patients treated after four hours from symptom onset was significantly lower with tenecteplase than with alteplase (absolute difference 2%) and in GUSTO III alteplase showed a significantly better mortality benefit in late-treated patients (greater than four hours) than reteplase.

In GUSTO I, although statistically not significant, 30-day mortality benefit from accelerated alteplase was consistent compared with streptokinase regardless of location of infarct. However, the absolute benefit was greater in patients with anterior wall infarctions.

Table 12: Thrombolytic drug comparisons by subgroups

Study	**Number randomised**	**Age (years)**	**Infarct location**	**Time from symptom onset to treatment (hours)**
	Alteplase/Streptokinase			
GUSTO 1(18) ***Acc t-PA**	41021	*30-day mortality* % <65 t-PA 2.7; SK 3.3; 65-74 t-PA 8.3; SK 10.4; 75-85 t-PA 18.2; SK 19.7; >85 t-PA 30.0; SK 29.2	*30-day mortality* % Anterior t-PA 8.6; SK 10.5; Inferior t-PA 4.7; SK 5.3	*30-day mortality* % 0-2 t-PA 4.3; SK 5.4; 2-4 t-PA 5.5; SK 6.7; 4-6 t-PA 8.9; SK 9.3; >6 t-PA 10.4; SK 8.3
GISSI-2/ISG (46, 47)}	20891	*In-hospital mortality* % ≤70 t-PA 5.8; SK 5.4; >70 t-PA 19.4; SK 19.1	Not reported	*In-hospital mortality* % ≤3 t-PA 8.2; SK 7.9; >3 t-PA 10.2; r-PA 9.5
ISIS-3(48)	41299	Not reported	Not reported	*35-day mortality* % 0-6 t-PA 9.6; SK 10.0
	Alteplase/Tenecteplase			
ASSENT-2(20) ***Acc t-PA**	16949	*30-day mortality* % ≤75 t-PA 4.3; TNK 4.6; >75 t-PA 19.3; TNK 17.4	*30-day mortality* % Anterior t-PA 8.2; TNK 8.0; Other t-PA 4.8; TNK 5.0	*30-day mortality* % 0-2 t-PA 4.9; TNK 5.0; >2-4 t-PA 5.5; TNK 6.3; >4 t-PA 9.2; TNK 7.0
	Alteplase/Reteteplase			
GUSTO III(19) ***Acc t-PA**	15059	*30-day mortality* % ≤75 t-PA 5.2; r-PA 5.5; >75 t-PA 20.2; r-PA 21.6	*30-day mortality* % Anterior t-PA 9.4; r-PA 10.1; Inferior t-PA 5.2; r-PA 4.8; Other t-PA 7.5; r-PA 9.7	*30-day mortality* % 0-2 t-PA 6.1; r-PA 5.8; 2-4 t-PA 6.9; r-PA 7.2; >4 h t-PA 7.9; r-PA 9.7
	Stereptokinase/Reteteplase			
INJECT(53)	6010	*35-day mortality* % <51 r-PA 1.7; SK 2.9; 51-65 r-PA 5.3; SK 6.4; >65 yr r-PA 16.4; SK 15.4	Not reported	*35-day mortality* % <3 r-PA 6.7; SK 7.5; 3-6 r-PA 9.1; SK 9.4; >6 h r-PA 13.2; SK 13.6

4.7 Discussion

Equivalence and non-equivalence

Before discussing the results and their interpretation, and the indirect comparisons, it is important to consider how we may determine whether two drugs are similar in their efficacy, and how clinical trials are designed to prove that drugs are either different or equivalent. This is a key issue with which appraisers of this evidence must be familiar.

Broadly, non-equivalence studies (often referred to as superiority studies) are powered to demonstrate a difference between two treatments. They are based on a null hypothesis that there is no difference, which may then be disproved. It is standard in such studies to use an intention to treat analysis (i.e. to analyse all patients according to their randomised allocation to treatment, and not according to whether they ever received the therapy or whether they perhaps changed at some point to the alternative therapy). The ITT is by its nature conservative and tends to demonstrate *no difference* rather than *difference*(63), and is the most rigorous analysis.

Equivalence trials are used when the existing standard therapy is considered effective and a placebo controlled trial would not be appropriate. One might then wish to prove that a new therapy is at least as good as the existing standard. Equivalence studies are also used to assess frequency of side effect, cost, or the ease of administration of one drug versus another. Equivalence studies aim therefore to demonstrate that the treatment effects are equal, not different. But the two drugs are unlikely to produce exactly the same results (this would be the case even if we compared exactly the same drug in two arms of a study): so we must define *a priori* what we mean by equivalence – e.g. what is the range of difference in efficacy between two therapies, within which the therapies may be considered clinically equivalent.

A key question therefore is what is this range of difference in efficacy (i.e. in 30-day mortality) between two thrombolytic agents within which we may consider them equivalent. There is the view held by some research groups(64) and presented in the American College of Chest Physicians (ACCP) guidelines that the range of difference (i.e. the 95% confidence intervals of any difference) must be less than 1% absolute difference in mortality at 30 days.(13) This means that the confidence intervals of any difference in efficacy must lie within -1% to +1% if the two drugs are to be considered clinically equivalent. This is based on the extent of the difference seen in the GUSTO I study between alteplase and streptokinase, where a difference greater than this is considered to indicate that alteplase and streptokinase are clinically different.

Other studies have used other criteria: for instance, the COBALT study,(58) examining two methods of dosing with alteplase, used an extremely rigorous level of not more than 0.4% difference based on the lower confidence interval of the difference seen in GUSTO I. This was subsequently considered excessively rigorous by many, and Ware and Antman(63) suggest a difference of up to 1.5%. Other studies have used a difference of no more than 50% relative mortality difference compared to streptokinase (an interval that could equate to roughly 1% in absolute mortality, on the basis that streptokinase shows a 2% reduction compared to placebo).

The American drug licensing agency, the Food and Drugs Administration (FDA) proposes a boundary based on the relative risk ratio between two drugs, where the upper 95% confidence interval should not exceed 14.3% relative difference (also based on the relative difference in GUSTO I).(65) The European Medicines Evaluation Agency (responsible for licensing thrombolytic drugs in Europe) has not yet determined what it considers equivalence but it seems likely to be similar to the ACCP guidance (F. Rotblat, Medicines Control Agency: personal communication, 2002).

This definition of equivalence relates only to efficacy in 30-day mortality. Some argue that the correct figures on which to base equivalence should also include a measure of adverse effects such as stroke.(66) However, there is no consensus around this, nor any consensus on what the limits for equivalence for any end point other than 30-day mortality should be.

Analysing Equivalence Trials

Even if there was agreement on the definition of equivalence, there remain issues regarding how we analyse equivalence trial data. It can be argued that intention to treat analysis (essential in superiority trials where it is deliberately conservative in tending to reject a difference between therapies) is less appropriate in equivalence studies where it might hide true differences. The more conservative approach would be a 'per protocol' analysis (i.e. analysing only those patients who received a particular therapy and who continued on it) which tend to emphasise differences). An ideal would be to consider both forms of analysis (as is done in the report of the INJECT study).(67)

Problems that may produce differences between ITT and per protocol analyses include loss of data (e.g. due to patient drop outs) and of handling cross-overs (where patients originally assigned to one arm actually switch at some point to the alternative). Fortunately, these problems do not apply in studies of thrombolytics: data ascertainment for 30-day mortality are usually of very high standard, and the nature of the acute treatment means that there is rarely any crossover.

We therefore believe it is methodologically sound to interpret the confidence intervals produced in superiority studies of thrombolytic therapies as if they had been produced in true equivalence studies, with both ITT and per protocol analysis. This is a view supported by others.(68, 69) The results of the INJECT study also lend confidence to this approach where the results of the ITT are similar to those of the per protocol analysis.

Direct Comparisons Between Drugs

The evidence base is dominated by a small number of large clinical trials and these require careful critical review. In addition the previous discussion regarding the establishment of criteria for judging equivalence will be included here.

Data presented in this section is a combination of the Odds Ratio data from the earlier table and absolute risk differences provided from other reports

Alteplase and Streptokinase

There have been a number of studies that have compared these two treatments, as outlined in Tables 7 and 8. Three major studies influence the comparisons. The first two, GISSI-2/ISG and ISIS-3 compare the standard regimen of a slow infusion and show no clear benefit of alteplase over streptokinase. The third is GUSTO I using a frontloaded or accelerated infusion showing mortality benefit at 30 days.

The GUSTO I study has been the source of much controversy. It had four arms with approximately 10,000 patients in each. The arms were: a) streptokinase with subcutaneous heparin; b) streptokinase with intravenous heparin; c) accelerated alteplase with intravenous heparin; d) standard alteplase with streptokinase. It has been argued that the frontloading or accelerated regimen improves the efficacy of alteplase, and achieves earlier artery patency and hence loss of myocardium. This seemed to be supported by the RAAMI study(16) which showed that at 60 min after initiation of the alteplase infusion, the observed angiographic patency rates were 76% in the accelerated regimen group and 63% in the control group ($p = 0.03$). At 90 min these rates were 81% and 77% respectively ($p = 0.21$). On this basis, it might be expected that accelerated regiments might produce better mortality results than standard alteplase, although this has not been tested adequately.

GUSTO I showed an absolute decrease in mortality of 1% (95% CI: 0.37%, 1.6%) at 30 days favouring accelerated alteplase given with intravenous heparin over streptokinase (two arms merged, one with subcutaneous heparin and one with intravenous heparin). However, there have been numerous criticisms of this study. These can be briefly summarised as follows:-

- That the benefit in alteplase over streptokinase was largely seen in those patients in GUSTO I treated in North America (i.e. the bulk of the patients in the trial). Results indicate a 1.2% absolute reduction in mortality in US patients versus 0.7% reduction in mortality in non-US patients.(70) This may reflect American familiarity with alteplase based regimens and relative unfamiliarity with streptokinase, particularly since the trial was not blinded.
- That there were substantial numbers of protocol violations in the subcutaneous heparin arm of streptokinase (up to 11% in total but more common in patients treated in the USA).
- That there were differences in management of patients between centres, for instance, the larger proportion of alteplase patients who received coronary artery bypass grafting and differences in post infarct management in US compared to non-US study sites.
- That differences in long term outcomes between US and non-US study participants may be due to long term management of these patients.(71)
- That the merging of the two streptokinase regimes was not scientifically valid, while choosing not to merge the two alteplase arms.

The GUSTO investigators(72) responded that although not blinded, allocation to treatment was randomised; there was an intention to treat analysis reported; and that the primary endpoint of death was collectable in an unbiased and impartial way. They pointed to an angiographic sub-study of GUSTO which also showed a higher patency rate of infarct-related artery at 90 minutes compared to streptokinase: this provided a logical

pathophysiological explanation for the effects of alteplase in decreasing mortality. Lee and colleagues(73) further reported that among GUSTO patients who did not have coronary artery bypass surgery during the hospitalisation, 30-day mortality was 6.5% in those treated with alteplase compared to 7.6% in those treated with streptokinase, still a clinically and statistically significant difference.

Another criticism relates less to the GUSTO I study itself and more to how it has been interpreted, i.e. that there has been excessive emphasis on GUSTO I to the exclusion of other trials of streptokinase versus alteplase.

Collins and colleagues (11) argue that any differences between thrombolytic regimens are likely to be small compared to the overall benefits of thrombolysis and that studies need to be compared as a whole, without selective emphasis on one trial or on particular subgroups. This group therefore conducted a meta-analysis of ISIS-3, GISSI-2 and GUSTO I(11) (note that in our meta-analysis, we have merged the results of GISSI-2 with ISG).

They argue that the biological effect of alteplase was only to achieve earlier patency but by no more than 30-60 minutes. The evidence they quote for this is the angiographic substudy referred to which showed greater TIMI-3 flow rates at 90 minutes but not at 180 minutes (they express some concern that this is reported as TIMI-3 flow rates, and not as the TIMI-2 or 3 rates originally envisaged in the protocol). Accepting earlier patency by 30-60 minutes, and based on the mean time of symptom onset to treatment, and the rate of decreased mortality arising from earlier reperfusion as demonstrated in the Fibrinolytic Therapy Trialists' (FTT) meta-analysis,(28) they argue that it could be expected that no more than 1 to 2 lives per 1000 would be saved (0.2% absolute decrease in mortality at 30 days) by using alteplase rather than streptokinase. They therefore consider the extent of benefit seen in GUSTO-I to be implausible and more likely to be a statistical outlier than an accurate definitive result.

The time course of benefit from thrombolysis is an important topic here and will be discussed in more depth later. Collins and colleagues(11) use the conservative FTT time course and dismiss the alterative time course put forward by Boersma and colleagues(26) as being the result of selective emphasis on certain small trials. Whatever the case, given the mean time to thrombolysis in GUSTO I of two hours, the differences in mortality by either graph would be small as is made clear later in this review.

Collins and colleagues(11) merged the two alteplase arms and compared them to the merged streptokinase-only arms, even though only one of the alteplase arms used the accelerated regimen. This has been controversial but they justify this by arguing that the accelerated nature of alteplase in one arm was not crucial, since the total dose of alteplase actually received by patients in the first hour of treatment was almost identical in both alteplase arms (82mg in the accelerated arm versus 78mg in the alteplase/streptokinase arm).

Accordingly they felt justified merging GUSTO I with GISSI-2 and ISIS-3 in a meta-analysis. This showed a statistically significant difference of 0.49% (4.9/1000 patients

treated) in 30-day non-stroke mortality between alteplase and streptokinase, with no evidence of heterogeneity between the trials. This is substantially less than the 1% benefit claimed for most analyses of GUSTO I which compare the two streptokinase-only arms to the alteplase-only arm alone.

The balance between risk and benefit is also uncertain and while there may be benefits in coronary patency and mortality with earlier treatment, the risks in particular of intracranial haemorrhage will be similar across all time bands. Collins and colleagues(11) estimate a statistically significant excess risk of total stroke from alteplase over streptokinase of 3.3/1000 patients treated, and of intracranial haemorrhage of 2.9/1000 patients treated in their meta-analysis: GUSTO I showed an increased stroke risk in the alteplase group of 3/1000.

Merging these two endpoints of 30-day death and stroke in their meta-analysis, Collins and colleagues(11) conclude that there is no convincing benefit of alteplase over streptokinase (only 1.6 strokes or deaths per 1000 patients treated, and not statistically significant). They concluded that there was no clinically significant difference between the drugs.

Others have argued about this interpretation. A criticism is the assumption that a meta-analysis is superior to the evidence presented in one (very) large trial. Specific points of conflict are whether accelerated alteplase used in GUSTO I but not in the other studies is superior (it is in the angiographic RAAMI study, but such angiographic findings may not exist in clinical event reduction e.g. see the RAPID studies which suggested a benefit of reteplase over alteplase, not borne out in the GUSTO III study), and that it was inappropriate to merge the two alteplase arms because of the different regimens and because of the confounding by the presence of streptokinase in one arm. It is therefore argued that it is inappropriate to include GUSTO I in a meta-analysis of studies of comparing alteplase to streptokinase.

We therefore present two tables comparing streptokinase to alteplase, based on all the studies identified which compared these drugs, one without and one with GUSTO I. The first excluding GUSTO I indicates no clear benefit for alteplase over streptokinase (difference 0.02% in favour of alteplase, 95% CI: –0.47, 0.5). The second including GUSTO I show similar results (difference 0.06% in favour of alteplase, 95% CI: –0.3, 0.44).

Alteplase and Reteplase

Two trials are considered in this comparison, GUSTO III and RAPID 2. Both trials used a regimen of accelerated alteplase.

RAPID 2 was a relatively small angiographic study which showed better coronary arterial patency (TIMI 2/3 flow rates of 82% on reteplase versus 66% on accelerated alteplase at 60 minutes).(17) This led to a postulation of a 20% clinical benefit in 30-day mortality for reteplase over alteplase, based on an expectation of better outcomes with earlier and more complete reperfusion.(74) This was tested in the large GUSTO III study

which was planned and powered as a superiority trial, to detect a putative clinical superiority of reteplase over alteplase.

In fact, GUSTO III failed to show the superiority of reteplase with an absolute difference in mortality between the two treatments of 0.23% in favour of alteplase with 95% confidence intervals of –1.1% to 0.66% (i.e. that reteplase could be up 1.1% worse or 0.66% better than alteplase). A later report of one year follow up from GUSTO III shows a difference in mortality of 0.14% in favour of alteplase (with 95% CI: -1.21%, 0.93%).(75)

The failure to show a benefit in mortality despite benefits in reperfusion may mean that the reperfusion results arose by chance and were not typical of what might be expected, or that the correlation between TIMI flow rates and clinical outcomes are not as secure as previously believed (with implications for the interpretation of streptokinase and alteplase in RAAMI and GUSTO I). We should therefore be cautious in accepting surrogate data such as patency rates in relation to thrombolysis but seek trials with true clinical outcomes such as 30-day mortality.

The results of the analysis indicate that there is no statistically significant difference in 30-day mortality. However, if limits of equivalence are set at 1% absolute difference, then the results of this trial cannot be used to say that reteplase is as effective as alteplase. This is a view supported by the American College of Chest Physicians (ACCP)(13).

However another recent review(65) interprets the GUSTO III study as showing the equivalence of reteplase and alteplase. It does this by merging the outcomes of mortality and disabling stroke, so that the combined event rate is (alteplase) 7.91% versus (reteplase) 7.89% (difference -0.02% 95% CI: -0.9%, +0.8%), and not the 7.24% versus 7.47%. This, the authors comment, is within the preset 1% definition, but this is strictly incorrect since the definition refers to mortality only and not to the combined endpoint of mortality and disabling stroke.

Reteplase and Streptokinase

The INJECT study shows a 0.5% absolute difference in 35-day mortality in favour of reteplase (not statistically significant). However, the 95% confidence intervals of -1.98% (reteplase better) to +0.96% (reteplase worse) require interpretation. These confidence intervals imply that reteplase may be marginally better (0.5%) than streptokinase but unlikely to be better than a 1.98% improvement in mortality over streptokinase and unlikely to be worse by more than 0.96% compared to streptokinase.

At the lower extreme therefore, this fits within the defined 1% confidence intervals of equivalence and therefore it may be said that reteplase is not worse than streptokinase (non-inferior) and could be superior.

The ‘per protocol’ analysis of this study confirms this result (absolute difference in mortality of 0.53% versus ITT analysis of 0.51%). The similarity between the two analyses is of course not surprising, since 98.8% of patients actually received randomised treatment.

Alteplase and Tenecteplase

ASSENT-2 was designed as an equivalence trial comparing tenecteplase to alteplase in relation to 30-day mortality. The results indicate equivalence in that the clinical efficacy is within the bounds of 1% equivalence. There was however a statistically significant difference in the rate of major bleed (5.94% on alteplase v 4.66% on tenecteplase), but there are no guidelines on what constitutes equivalence or inequivalence for this endpoint. There is a suggestion in a company submission that this trial underestimates the effectiveness of tenecteplase because of the double dummy approach used but this seems to us to be unlikely.

Indirect Comparisons

The lack of evidence from head to head trials between some thrombolytics necessitates some indirect comparisons. Conclusions drawn from such indirect comparisons are more tenuous. This is particularly so when one tries to quantify any degree of superiority. Nevertheless when we turn to an attempt to evaluate the economics of using different drugs in Chapter 6, we are forced into making some estimate of the extent of any such differences.

Streptokinase versus Tenecteplase

Here we must extrapolate from trials such as ASSENT-2 showing equivalence of tenecteplase with alteplase (although with less heart failure and more major bleeds in the alteplase group) and GUSTO I possibly showing superiority of alteplase over streptokinase or equivalence, depending on the interpretation of the alteplase/streptokinase comparison discussed above. Therefore, tenecteplase is either superior to streptokinase (by the same degree as alteplase in GUSTO I), or equally effective and possibly more hazardous. Crudely adding together rates of difference in heart failure between alteplase and streptokinase in GUSTO I (2%) and between alteplase and tenecteplase in ASSENT-2 (0.9%) to produce a reduction in heart failure rates of 2.9%, as in one company submission, is particularly tenuous.

Reteplase versus Tenecteplase

As there have been no direct clinical trial comparisons between tenecteplase and reteplase, we are therefore forced to draw conclusions based on the GUSTO III study and ASSENT-2. This is perhaps the issue where company interests are most divided. If reteplase is equivalent to accelerated alteplase, then it would be considered the equivalent of tenecteplase. If the strict interpretation of the confidence intervals in GUSTO III is adopted however, then reteplase cannot be considered equivalent to alteplase or tenecteplase. This is perhaps a matter for appraisal rather than strict evidence, as outlined below.

4.7.2 Adverse Events

The major adverse events differ between the drugs. Allergy or even anaphylaxis occurs with streptokinase but is rare with the other drugs. Although there are substantial differences in the definitions of bleeding and hence the rates of bleeding in different studies, the risk of major bleed is slightly higher on streptokinase than on the other drugs directly compared to it. This may be because streptokinase is less fibrin specific and can cause a more generalised coagulopathy than the other drugs. Some argue this effect is

possibly more marked than the clinical trial data alone show, since the other drugs are usually given with intravenous heparin. However, the analysis by Collins and colleagues(11) casts doubt on this as a significant source of difference.

There was a significant increase in the risk of stroke for alteplase compared to streptokinase. This was largely accounted for by an increase in the incidence of haemorrhage stroke. The meta-analysis shows an absolute risk increase of 2 per 1000 and a relative increase of 83%. GUSTO I alone showed an increase of 42% but the absolute effect was similar. This is an extremely important adverse event that seems clearly related to the drug chosen. It offsets some of the difference in mortality between drugs since patients with intracranial haemorrhages are more likely to suffer severely disabling strokes. This will have an effect on the long-term costs of thrombolysis.

Reteplase also showed an increased tendency to stroke and a significant increase in haemorrhage stroke compared to streptokinase. In contrast there was no difference between alteplase and reteplase in GUSTO III nor between alteplase and tenecteplase in ASSENT-2.

There was no significant difference in re-infarction rates between any of the drugs.

No equivalence definitions have been produced to compare adverse effects nor does the existing definition include provision for difference in adverse effects, except those demonstrated in 30-day mortality.

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4.7.3 Risk of intracranial haemorrhage with bolus therapy

It is clear that the newer drugs are associated with an increased risk of intracranial haemorrhage compared to streptokinase. A meta-analysis by Mehta and colleagues(76) suggests that the rate of intracranial haemorrhage in patients receiving bolus thrombolytics such as reteplase, anistreplase, or tenecteplase may be unduly high without any gain in efficacy (odds ratio 1.25 (95% CI: 1.08, 1.45, P=0.003). We have considered this and agree with the rebuttals by Armstrong and colleagues (77) and Collen and Sobel.(78) The pooling of results from disparate drugs, which have different rates of adverse effects and possibly of primary efficacy, simply on the basis of routes of administration, may be inappropriate. The meta-analysis includes one agent, lanoteplase, which has been withdrawn specifically because of a high rate of ICH. Our meta-analysis shown earlier demonstrates no increased risk of total stroke rates with reteplase or tenecteplase compared with alteplase. We have therefore not taken this into account in the economic evaluation, other than where differences in point estimates of the event can be derived from the trials.

4.7.4 Subgroup analysis

No trial has been set up to specifically examine subgroups and therefore all conclusions drawn must be treated with great caution. Differences between subgroups may have arisen entirely by chance. The best-known example of this is the analysis from ISIS-1, showing marked differences in outcome depending on patients' astrological sign. Collins

and colleagues warn of the risks of excessive subgroup analysis of studies that compare stretokinase and alteplase also.(11)

There are no consistent differences in response to drug by age, by time to thrombolysis or by site of infarct. Where differences occur in trials, eg in GUSTO III between reteplase and alteplase, or in ASSENT-2 between tenecteplase and alteplase, they seem likely to have arisen as a result of subgroup analysis. Further evidence of any differental benefits in subgroups is required

There is no convincing evidence of relative difference in benefit of different drugs by site of infarct – the absolute benefit of alteplase is greater in treating anterior infarcts in GUSTO I but this only reflects their greater mortality.

There is an increase in reinfarction rate on streptokinase compared to alteplase in ISIS-3, but in no other study. This influences the results in the analysis without GUSTO I, but its clinical significance, if real, is small.

There is therefore no evidence in the subgroup analysis to assist in differentiation between drugs.

4.7.5 Heparin

A study of co-therapies used with thrombolytic drugs, such as the heparins and their route of administration, is outside the scope of this review but the question of heparin use in particular requires some comment, since it affects the feasability of the use of the drugs outside hospital.

Collins and colleagues(11) consider the use of co-therapies with thrombolysis. It is widely accepted that all patients should receive aspirin, based on the ISIS 2(10) study. GUSTO I used intravenous heparin in the alteplase arm, but subcutaneous (unfractionated) heparin in one streptokinase arm and intravenous heparin in the other. Collins and colleagues (11), again as part of their meta-analysis of interventions after myocardial infarction examined the question of whether high dose subcutaneous heparin regime would be comparable to intravenous regimes. They conclude that in GUSTO I the rate of death in patients on intravenous heparin was 7.4% compared to 7.3% in those on subcutaneous heparin (consistent with a conclusion of equivalence based on ACCP(13) definitions) with similar lack of difference in other endpoints including stroke or haemorrhagic stroke. They therefore conclude that high dose subcutaneous heparin is as effective as intravenous heparin. In common practice, streptokinase is not given with intravenous heparin, whereas alteplase (based on GUSTO I) regime is.

The ASSENT-3 study(79) is also strictly outside the terms of this study since it does not consider comparisons between thrombolytic drugs. However it does allow a comparison between patients treated with tenecteplase and either intravenous unfractionated heparin or the subcutaneous low molecular weight heparin enoxaparin.

This study used a composite endpoint of 30-day mortality, in hospital refractory ischaemia or in hospital reinfarction and found a rate of 11.4% on enoxaparin and 15.4%

on unfractionated heparin. There was no statistically significant difference in mortality at 30 days (5.4% on enoxaparin v 6.0% on unfractionated heparin (difference 0.64%, 95% CI: -0.8%, 2.1%) Applying ACCP(13) criteria, this suggests that enoxaparin is not inferior to unfractionated heparin and may be superior.

While treatment of AMI is not yet a licensed indication for enoxaparin, this trial combined with the Collins review,(11) would seem to indicate that the use of subcutaneous heparin, and in particular a low molecular weight subcutaneous heparin may be as effective as intravenous heparin in AMI. It would seem from the evidence presented by Collins that this result was not surprising and could be anticipated to apply to all other thrombolytics in the same way, despite the absence of firm trial evidence for the combination with thrombolytics other than tenecteplase. This would simplify the administration and facilitate the use of thrombolytic agents. One company submission comments that the GRACE registry(80) indicates that 41% of patients with acute MI already receive a low molecular weight heparin with thrombolytics other than tenecteplase. This figure is likely to increase in the light of the results of ASSENT-3, especially (but not exclusively) in conjunction with tenecteplase.

This might be of particular value in pre-hospital thrombolysis as discussed in the next section.

The role of other possible co-therapies in AMI (eg glycoprotein IIb/IIIa inhibitors) is under extensive study but is not considered further here.

4.7.6 Conclusions

Differences in the benefit in 30-35 day mortality between drugs are less than the benefit of thrombolysis as a whole.
The scientific evidence comparing the comparative effects of drugs on 30-35 day mortality is open to interpretation, depending on the definitions of equivalence chosen. Direct comparisons lead to the following firm conclusions:

A Streptokinase is as effective as non-accelerated alteplase
B Tenecteplase is as effective as accelerated alteplase
C Reteplase is at least as effective as streptokinase

Depending on interpretation of equivalence and of some major trials, the following conclusions are also possible:

D Concerning streptokinase and alteplase
Streptokinase is as effective as all alteplase, including accelerated alteplase
Or
Streptokinase is inferior to accelerated alteplase

E Concerning reteplase and alteplase
Reteplase is as effective as accelerated alteplase
Or
Reteplase is not (shown to be) as effective as accelerated alteplase

The following indirect comparisons may also be drawn, and depend on the answers to D and E (obviously any conclusions drawn here are tentative):

F Concerning streptokinase and tenecteplase, depending on the interpretation of point D
Tenecteplase is as effective as streptokinase
Or
Tenecteplase is superior to streptokinase

G Concerning reteplase and tenecteplase, depending on the interpretation of point E
Reteplase is as effective as tenecteplase
Or
Reteplase is not as effective as tenecteplase

In the absence of further evidence, the resolution of these is a matter for appraisal rather than for strict scientific interpretation. That the scientific evidence leaves this open to debate is an illustration of the uncertainty of such small differences.

The benefits of thrombolysis have to be set against the potential hazards: in particular stroke is more common on the newer drugs than on streptokinase, but the newer drugs have a negligible incidence of allergy.

The effects of any clinical differences between the drugs on their cost effectiveness are considered later.

5. RESULTS: CLINICAL EFFECTIVENESS - PRE-HOSPITAL

5.1 Included studies

The literature search failed to identify any studies conducted in the pre-hospital setting that compared the effectiveness of different drugs. That is, there were no drug versus drug comparison studies conducted in the pre-hospital setting. Rather, studies conducted in the pre-hospital setting have focused on the feasibility and safety of the delivery of thrombolysis in this setting. In these studies, patients were randomised to receive treatment either in the pre-hospital or hospital setting and all patients received the same drug. Primary outcome measures were time saved and mortality, with additional outcomes of adverse events.

We identified nine such randomised controlled trials in our search(81-89) that examine the efficacy and safety of pre-hospital thrombolysis. Six of these were also included in a recent systematic review and meta-analysis that examined the effectiveness on mortality of pre-hospital thrombolysis compared to hospital thrombolysis.(90)

We also consider a number of other non-randomised or audit type reports that may provide further information on the likely issues regarding the implementation of pre-hospital thrombolysis within the NHS. These are included in the discussion portion of this section and in the section dealing with implementation (Chapter 7).

5.2 Characteristics of pre-hospital studies

The characteristics of the nine RCTs are presented in Table 13

Table 13: Characteristics of trials: pre-hospital

Study	Design	Drug	N	Location	Diagnosis/decision	Administration
Barbash 1990(81)	RCT	Alteplase	Pre = 43 In = 44	Israel	History ECG	Physician
Castaigne 1989(82)	RCT	APSAC	Pre = 57 In = 43	France MCU	ECG	Physician
EMIP 1993(83)	RCT Stratified by ECG and centre	Anistreplase	Pre = 2570 In = 2719	Europe – 15 countries Canada – 1 centre, 163 centres in all	ECG	Physician
GREAT 1992(84)	RCT	Anistreplase	Pre = 163 In = 148	Scotland 29 GP practices	GP observation ECG done – not used for diagnosis	GP
McAleer 1992(85)	RCT open	Streptokinase	Pre = 43 In = 102	Northern Ireland MCCU	ECG	Physician
McNeill 1989(86)	RCT	Alteplase	Mix of Pre (49) and A&E (8) versus CCU N=57	Northern Ireland MCCU	ECG	Physician
MITI 1993(89, 91)	RCT	Alteplase	Pre= 175 In =185	USA 19 hospitals	ECG transmitted to physician by paramedic	Paramedic
Roth 1990(87)	RCT	Alteplase	Pre = 74 In = 44 Last 29 patients not randomly allocated	Israel MICU	ECG – ST elevation	Physician
Schofer 1990(88)	RCT Double blind	Urokinase	Pre = 40 In = 38	Germany MICU	ECG – ST elevation	Physician

Pre = Pre-hospital; In = In Hospital data

The studies were carried out in Europe, Canada, Israel, Northern Ireland and the UK. The trial sizes are small except for one large multi-centred study(83) that randomised more than 5000 patients. Diagnosis and decision to treat in the studies was by ECG and clinical signs in all of the studies but the one carried out in the UK(84) where although ECGs were recorded they were not used in the decision to treat. Thrombolysis was given by a physician in all the studies except the USA study(89) where it was provided by paramedics after consultation with a physician.

Morrison and colleagues(90) used six of these studies in their meta-analysis(82-84, 87-89). They excluded three(81, 85, 86) which did not meet their outcome inclusion criteria of mortality data available at discharge. Since the most common endpoint in effectiveness studies is 30-35 day mortality we have included all nine trials in the characteristics table (Table 13).

The trials included in the meta-analysis used a variety of drugs (anistreplase in three, alteplase in two and urokinase in one). Morrison(90) considered that it was reasonable to group these disparate drugs together on the grounds of their broad clinical similarities. This ignores any possible differences in effectiveness between drugs as discussed in the previous section. In that section, we did not disucss comparisons between anistreplasee since it is no longer available, but at least one small (hospital based) study suggested that anistreplase, the drug most widely used in existing pre-hospital studies was less effective than accelerated alteplase.(92)

The merging of trials is based on the argument that benefits arising from differences between drugs (maximum 10 lives saved at one month/1000 patients treated) may be less important than benefits from differences in time to thrombolysis.(93)

The administrators of the thrombolytic and the criteria under which it was administered varied considerably between trials. In most cases (n=7) assessment and treatment were provided by a physician. In the only UK study (84), this was carried out by a GP. The only study in which treatment was provided by a paramedic was in the USA MITI study (89) where paramedics assessed the patient, communicated that information to a physician in the hospital and provided treatment as directed by the physician.

Individually these trials failed to show a statistically significant difference between all cause in-hospital mortality, although the point estimates all favoured pre-hospital thrombolysis. Time to administration of pre-hospital thrombolysis ranged from 85-130 minutes from onset of pain. Pre-hospital thrombolysis was initiated approximately 58 minutes quicker than hospital thrombolyis, and this ranged from a 33 minute reduction in the MITI study(89) to a reduction of 130 minutes in the GREAT study.(84)

The Morrison(90) review shows a pooled benefit in mortality of a relative reduction of 17% with pre-hospital thrombolysis compared to hospital thrombolysis (95% CI: 2%, 30%, P=0.03). In these studies, this translates into an absolute risk reduction of 1.6% (95% CI: 0.2%, 3% - the paper quotes 2% as the risk reduction but based on the actual figures, the correct reduction is 1.6%), i.e. 16 more patients alive at hospital discharge per thousand patients treated pre-hospital compared with in hospital.

The authors of the Morrison paper were unable to comment on complication rates or need for

other medical or surgical therapy. They conclude that the benefits of pre-hospital thrombolysis are convincing and argue that the choice of drug is far less important than making a correct diagnosis and providing rapid and safe administration of thrombolysis.

5.3 Discussion

The effectiveness of pre-hospital thrombolysis in improving outcomes would seem to have been resolved by the Morrison meta-analysis.(90) However, none of the methods of treatment administration of the studies included in the meta-analysis correspond exactly to how pre-hospital thrombolysis might be used in the NHS and therefore there are difficulties in interpreting these diverse studies and their applicability to the wider NHS.

None of the identified studies of pre-hospital care met the inclusion criteria of our review. We have broadly described the existing studies which compare pre-hospital thrombolysis with hospital thrombolysis, but which do not provide direct comparisons between drugs. The underlying assumption therefore is that the relative benefits (or lack of benefits) of one drug over another are proportionately maintained in the different settings, and at different times of administration.

The drugs used in the studies were anistreplase, urokinase and alteplase. Two of these drugs (urokinase and anistreplase) are no longer available in the UK. The third (alteplase) has been considered as unsuitable by individual ambulance services for use in the pre-hospital setting (see discussion in Section 7.4). Cohort studies have shown the feasibility of using reteplase, but have not provided any outcome data comparing it to other agents in well-designed trials. To date, we have no data related to the use of tenecteplase in the pre-hospital setting.

Since none of the studies met the inclusion criteria of the review, a formal assessment of their quality has not been carried out. However, these studies do provide important information regarding the implementation of pre-hospital thrombolysis and highlights aspects of relevance to the NHS.

These issues are discussed here in relation to each of the major trials.

European Myocardial Infarction Project Group

EMIP(83)was the largest trial to date with over 5000 patients. It was multinational, and compared pre-hospital versus hospital anistreplase. Patients with or without typical ECG changes and typical history were randomised within 6 hours of onset of chest pain. Patients were stratified by their degree of ECG change, and also investigators were allowed to exclude patients at their discretion.

The time saving was 55 minutes and the reduction in 30-day mortality was 13% (mortality 9.7% v 11.1%, benefit 1.4%, 95% CI: -0.1%, 3.1%, P= 0.08). All participating ambulances (‘mobile coronary care units’) were staffed by a doctor. A total of 32.7% of all patients screened were actually entered into the study, the majority (87.2%) with ST elevation in the ECG. Complications were more common out of hospital and included (early) ventricular fibrillation (1% of cases), and shock including severe allergy (1%).

An important point here is how participation in the trial decreased the hospital door-to-needle time. In this study this time was 15 minutes. This was more rapid than anticipated and may

have reduced the anticipated added benefits of pre-hospital administration used in the power calculation, resulting in a non-significant result.

Myocardial Infarction Triage and Intervention trial

MITI(89) was a smaller trial (n=360) conducted in Seattle, an urban area with a long history in excellence of emergency cardiac care. Patients had typical pain and ECG changes. The drugs used were alteplase (over 3 hours) and aspirin delivered by random allocation in either the pre-hospital or hospital setting. In the pre-hospital setting paramedics provided the drug following transmission of ECG results and clinical assessment to a doctor. This may have allowed discretionary application of exclusion criteria and have introduced a selection bias that may limit the generalisability of this study.

The patients included were only 4% of all patients with chest pain screened and 21% of all AMIs. There was a non-significant decrease in 30-day mortality (5.7 versus 8.1%, 2.7% difference, 95% CI: -3%, 7.8%,) in favour of pre-hospital treatment. There was no difference in 2 year survival (89% for pre, and 91% for hospital treated patients).(91)

Patients contacted emergency services relatively quickly compared with British standards – typically only 27 minutes after the onset of symptoms. The median time to pre-hospital treatment was 77 minutes, and to hospital treatment was 110 minutes, a saving of 33 minutes. Delivering an alteplase infusion in the field delayed transfer time to hospital by 15 minutes. The time saved was modest by comparison with most studies, reflecting the urban nature of the service provided. However, the study also showed a remarkable improvement in hospital door-to-needle time of 40 minutes for patients in the trial. Door-to-needle time for randomised patients was 20 minutes for MITI patients, as opposed to 60 minutes for concurrent patients seen in the emergency departments of the participating hospitals. This illustrates the potential timesavings that can be achieved with active management of the service in the hospital setting.

Grampian Region Early Anistreplase Trial

GREAT(84) is perhaps the most important study from an NHS perspective since it was performed in the UK. In it, 311 patients were randomised either to receive anistreplase or placebo from their (specially trained) GP or the alternative drug/placebo on arrival at hospital. GPs selected patients on the basis of a history of chest pain of 20 minutes to 4 hours duration, and treatable within 6 hours of onset of pain. Although ECGs were recorded, they were not used in the decision to administer thrombolysis.

Seventy-eight percent of patients entered did in fact have a subsequently proven AMI. However, only 51% of patients assessed had ECG changes (ST elevation) that would have meant that they met inclusion criteria for standard trials assessing effectiveness of thrombolytic therapy. The relative rarity of AMI was illustrated by the fact that each GP recruited a patient on average every eleven months.

Timesavings were impressive. The median time to treatment from onset of pain was 101 minutes pre-hospital compared to 240 minutes in the hospital group. There were substantial delays in administering thrombolysis in hospitals – hospital door-to-needle time was not specifically measured but was estimated at around 87 minutes.

The all cause mortality outcomes are shown in the table (Table 14) below (data are not available to fill all cells).

Table 14: Mortality at discharge and selected time points

	Pre-hospital	In hospital	Relative Difference	Absolute difference	P value
Hospital discharge(90)			44% (+23—75)		NS
1 month(94)				6% (–0.5 to 12.7)	NS
3 months(84)	8%	15.5%	49%	7.6% (-14.7 to -0.4)	0.04
1 year(94)	10.4	21.6%	52% (14 –89)	11.2%	0.007
5 years(95)	25%	36%		11%	<0.025

These benefits from GREAT are very impressive but there are grounds for caution in interpreting them. GREAT differs from all other trials of thrombolysis in several respects. Firstly, it was a feasibility study – it was never designed nor powered to show a mortality benefit. The fact that it has must be regarded as hypothesis generation rather than hypothesis testing. The benefits seen in GREAT were substantially greater than those seen in other studies of pre-hospital thrombolysis or indeed in hospital treatment. The pattern of increasing divergence of mortality up to two years (14% absolute difference in mortality) followed by a (predictable) convergence from five years onwards is unusual in thrombolytic trials and has not been seen in other trials with long term follow up such as ISIS-2 or GUSTO I.

GREAT may therefore represent a statistical outlier, with extreme results such as are commonly seen in very small trials. As elsewhere, we should examine the whole of the available evidence and not be unduly swayed by one small study.

A contrary view is that few other studies have demonstrated such large timesavings between pre-hospital and hospital treatments, and that the greater benefit may be explained by this.(96) In subsequent subgroup analysis and follow up to ten years, Rawles claims that the benefit of pre-hospital thrombolysis was confined to patients with ST elevation or bundle branch block, and in these patients the average survival was 7.4 years (pre-hospital) versus 5.9 years (in hospital), difference 1.6 years, 95% CI: 0.5, 2.6 (Rawles J, Lead Investigator GREAT study/Consultant cardiologist (Retired), Aberdeen, personal communication: 2002).

In the absence of other studies supporting the extent of the benefit seen in GREAT, it is therefore unclear how to synthesise the findings with other research. Even if correct, there are difficulties in applying such data to other parts of the UK where the transport times and distances are likely to be shorter. The model of administration of thrombolysis on suspicion alone of AMI is not one generally favoured, and the role of the GP is not as prominent in most models of care currently under consideration. These issues are explored more fully in Chapter 7 on implementation.

Two other studies(85, 86) have been conducted in the UK, both in Northern Ireland. Both were relatively small and used mobile coronary care units with medical staff. McNeil and colleagues assessed the use of alteplase, and McAleer and colleagues evaluated streptokinase.

McAleer and colleagues used an open allocation, the basis for which was not reported. The reported time saving by pre-hospital administration was 34 minutes. The results reported dramatic but not statistically significant reductions in mortality at 14 days in favour of pre-hospital treatment, 2.3% versus 11.7% (difference 9.4%, 95% CI: -1.5%, 17.3%). This difference was still evident at the one-year follow-up. McNeill and colleagues(86) showed a time saving of 68 minutes, no mortality benefit but an improvement in left ventricular function favouring pre-hospital thrombolysis. The benefit in the McAleer study is extraordinarily large and seems unlikely: the open allocation may explain the results. The model of mobile coronary care units is uncommon in the NHS outside Northern Ireland.

Non-randomised, Audit or Observational studies

The review team did not carry out a comprehensive search or apply stringent inclusion criteria in the search for non-randomised studies. Those studies presented here have been selected to identify factors to be addressed in relation to the implementation of pre-hospital care.

Pre-hospital thrombolysis has been widely used in the Netherlands for some years. Lamfers and colleagues(97, 98) report a small observational study of pre-hospital thrombolysis with anistreplase offered in one Dutch city (n=227), versus retrospective records of hospital patients (n=269) treated with alteplase or streptokinase. Their comparisons reported a time saving of 63 minutes as a result of pre-hospital administration of treatment. GPs or paramedics in the community provided treatment after transmitting ECG and clinical findings to the hospital. They report that a total of 13% of pre-hospital patients were considered to have had their AMI aborted (as evidenced by predefined decreases in ST segment elevation on ECG) compared to 4% of hospital patients. However there was no reported difference in 12-month mortality rates (pre-hospital 11% versus 10% in patients receiving hospital treatment).

Hand searching identified one recent abstract authored by Lamfers and colleagues(99) which claims to compare reteplase (120 patients) with anistreplase or streptokinase (130 patients) out of hospital. In fact this was an observational study: patients were sequentially and openly assigned to either drug regimen (anistreplase was the preferred comparator in one trial centre, streptokinase in the other) given pre-hospital. The results were a time saving of 23 minutes for the double bolus reteplase, no difference in 30-day mortality or other outcome measures. The authors report that reteplase seemed to be as effective as the older drugs but acknowledge the weaknesses of the study design.

An observational study by Herlitzand and colleagues(100) from Sweden describes a process of administration using reteplase out of hospital, in ambulances staffed by (for the most part) a nurse in addition to ambulance staff. The number of patients reported is relatively small (n=154) and there is no comparator group. ECG interpretation was by a base hospital and the time to thrombolysis from arrival of the ambulance was approximately 31 minutes. The time to thrombolysis was 91 minutes in densely populated areas, up to 156 minutes in more sparsely populated areas. The latter group are perhaps analogous to the population treated in the GREAT study. There are no outcome measures reported or any comparisons of times saved by pre-hospital thrombolysis.

A further study of reteplase in the pre-hospital setting is available in abstract format in the public domain (a slightly more detailed report is available from in confidence information

data in the Roche company submission).(101) This is a study which tests the safety and feasibility of pre-hospital administration of reteplase and tries to determine the time saved. It is not directly comparative and only uses historical controls. Results to date include 315 patients. The median time from arrival of ambulance to thrombolysis is the same as in the Swedish study, i.e. 31 minutes, compared to 64 minutes in a control, i.e. a saving of 33 minutes.

An Italian study(102) reports the use of anistreplase in a rural emergency room (n=102) with no immediate coronary care unit support, perhaps analogous to a community hospital in the UK, compared to patents transferred directly to a hospital with a coronary care unit (n=178). The method of allocation was not described, and like the McAleer study, doubts are raised about the quality of the results. The decision to thrombolyse was based on an ECG transmitted to a local coronary care unit, and the time saving achieved was 75 minutes. Mortality at 35 days was 7.5% in those treated in the emergency room, compared to 10.7% of those treated in the coronary care unit (3.2% reduction, 95% CI: –4%, 10% not statistically significant).

Finally, we have received reports from the two ambulance services (East Midlands and Staffodshire)(37, 38) currently implementing programmes of pre-hospital thrombolysis in the UK. In these trusts, the USA model of paramedic assessment and transmission of findings to a physician has been adopted. They have confirmed the feasibility of the delivering thrombolysis in the pre-hospital setting. However, phasing in of the programme means that the number of patients being treated is small (14 in the first year in one area). This is consistent with reports from one of the few rural centres in Canada that implemented a policy of pre-hospital thrombolysis and did not administer the treatment to any patient in the first year (Shuster M, Director A&E Banff Mineral Springs Hospital, personal communication: 2002). The impact of a pre-hospital thrombolysis service and likely volume of patients are discussed in Section 7.

Other pre-hospital thrombolysis studies underway

The ASSENT-3 Plus study is an RCT comparing tenecteplase with enoxaparin versus tenecteplase with intravenous heparin in pre-hospital thrombolysis and may allow comparison. It does not compare two different thrombolytic drugs and would allow only indirect comparisons with those patients who have received tenecteplase and possibly alteplase in hospital as in ASSENT 3. Recruitment of 1600 patients is due to be completed in late 2002 and results will be available in early 2003 (Boehringer Ingelheim submission).

5.4 Conclusion

There is no evidence regarding the comparative effectiveness of each drug in the pre-hospital setting. Therefore conclusions regarding choice of drug must be drawn from studies conducted in the hospital setting. Additionally the choice of drug in this situation will also be influenced by convenience and ease of administration, and possibly cost.

We conclude that pre-hospital thrombolysis is feasible and reduces the time to thrombolysis, though the estimate varies from 30 minutes to two hours, the best estimate we believe being the pooled figure of 58 minutes in the Morrison analysis.(90) Given that this saving was achieved in the context of clinical trials, real world savings may be greater. The NSF has laid down guidelines for the provision of thrombolysis and the need to consider pre-hospital thrombolysis when time delays are expected (either due to transport time or distance).(30)

The meta-analysis of existing studies shows a mortality benefit, although this is not shown in any individual trial.

It is tempting to extrapolate the results of the GREAT study as providing the best evidence in the NHS but there are several reasons why this should not be done.

The absolute benefit to be expected from the earlier administration of pre-hospital thrombolysis will also depend on the time to administration and on whether one follows the Boersma(26), Newby(27) or FTT(28) or other plots which are discussed in detail later in the next section.

6. RESULTS: ECONOMIC ANALYSIS

6.1 Introduction to economic evidence

The aim of this chapter is to assess the relative cost-effectiveness of thrombolytic agents currently available in the UK for treatment of AMI in either a hospital or pre-hospital setting. The chapter begins with a review of published literature on the economics of different thrombolytics in hospital, focusing on eight studies. These are limited to the comparison between streptokinase and alteplase and date from either before GUSTO I or after. Their conclusions depend on whether it is accepted that alteplase is superior to streptokinase, i.e. the studies are appropriately driven by the clinical evidence.

A detailed critique is provided of the economic evaluation of the GUSTO I study which compared accelerated alteplase and streptokinase, and also of the GREAT study for the general principles which can be drawn in relation to considering pre-hospital thrombolysis.

A detailed critique and reanalysis was also undertaken of the economic models submitted as part of the industry submissions. To address potential bias, a more independent set of assumptions was incorporated into the models to assess their impact on the results gained. A key issue is the importance of time to initiation of thrombolysis and this is explored in depth.

6.2 Review of economic literature

The aim of this section is to summarise those published cost-effectiveness analyses of thrombolysis which are based primarily on the results of drug versus drug randomised controlled trials. Two reviewers (ABol & AH) searched the economic literature and applied inclusion and exclusion criteria to identify relevant cost-effectiveness evidence. Two reviewers (ABol and RM) then independently assessed the studies which were included in the review. The generalisability of such results to the specific circumstances of clinical practice in the NHS is discussed in a later section. The methods used for this review are described in Section 3.2.

Identification of studies

One reviewer (ABol) examined at the titles and abstracts of the 798 articles identified by electronic search, and 98 were considered relevant. In addition, the reviewer looked through all of the articles identified by the clinical effectiveness search strategies and selected a further five papers. Finally, by searching the references of all of the papers obtained, a further four articles were identified for possible inclusion in this review. These 107 articles were then assessed for inclusion in the review using the criteria previously described. Eight met the criteria and are considered further here.(103-110)

6.3 Quantity and quality of research available

Of these eight studies, three papers(103, 107, 108) are linked as the economic evaluations described are primarily based on the same cost-effectiveness model. However, for the purposes of data extraction, these studies have been summarised as individual studies as they address different questions. One paper(105) is based on a previously published clinical model.(111) All of the studies were considered comparisons of different drugs in hospital based thrombolysis - none addressed the cost-effectiveness of different drugs in pre-hospital

thrombolysis. The results of the quality assessment exercise are presented in Table 15 below. Details of the quality checklist items are provided in Appendix VIII.

Overall the studies were of good quality, except in three areas. First, most of the studies did not measure costs and benefits from the same study population i.e. cost data were often estimated whereas benefit information was taken from a previously published trial. Second, the reader often had to refer to the original efficacy study in order to be sure of the comparator as the descriptions of alternative interventions were often not sufficiently detailed. Finally the derivation of utility values was not fully explained in any of the studies containing cost utility ratios.

Table 15: Quality assessment of published economic evaluations

Checklist items:	Well-defined question	Comprehensive description of alternatives	Effectiveness established	Costs & consequences: Identified	Measured accurately	Valued credibly	Adjusted for differential timing	Incremental analysis	Sensitivity analysis (SA)	Issues of concern to users included
	1	2	3	4	5	6	7	8	9	10
Goel and Naylor 1992[a]; Naylor and Bronskill 1993; Massel D 1999(103, 107, 108)	✔ perspective explicitly stated	✔/✘ method of drug administration vague at times	✔	✔/✘ differences in side effects not specifically modeled, long term costs not incorporated into analysis	✔	✔	✔ where appropriate	✔	✔	✔/✘ no subgroup analyses were conducted around age, infarct location or time from onset of symptoms to treatment. Naylor(108) and Massel(107) did not address long term costs or benefits and so a full discussion of key issues was lacking
Kalish et al., 1995(104)	✔	✔	✔	✔	✔	✔/✘ derivation of utility values is unclear	✔	✔	✔ extensive SA undertaken	✔
Kellet J, 1996(105)	✔ perspective explicitly stated	✔	✔/✘ 20% relative rate of reduction in mortality for tPA over SK is assumed rather than the conventional 14%	✔	✔	✔/✘ derivation of utility values is unclear	✔ results presented with and without discounting	✔	✔	✔
Lorenzoni et al., 1998(110)	✔	✔	✔	✔/✘ authors explicitly only consider the crude cost of thrombolytic therapy and number of lives saved at 30 days	✔	✔	N/A	✔	✔/✘ discussion of SA results in text was poor	✔/✘ the authors achieve their stated objectives but in doing so leave key issues undiscussed
Mark et al., 1995(106)	✔/✘ inaccurate perspective stated	✔	✔	✔ medical costs after one year are excluded but introduced in sensitivity analysis	✔	✔/✘ derivation of utility values is unclear	✔ Results presented with and without discounting	✔	✔ extensive SA undertaken	✔/✘ the trial data collected comes from 15 different countries, yet the discussion of results is distinctly US focussed
Pelc et al., 1997(109)	✔	✔	✔	✔/✘ only medical costs up to one year are considered	✔	✔	N/A	✔	✔/✘ discussion of SA results was more qualitative than quantitative	✔/✘ the authors achieve their stated objectives but in doing so leave key issues undiscussed

✔=dimension appropriately addressed; ✔/✘ dimension partially/maybe addressed; N/A dimension not applicable

Study design

All of the studies were incremental cost-effectiveness analyses (see Table 16). A range of cost effectiveness measures was described but cost per life year saved was the most common. Three papers also included incremental cost utility analyses and used quality adjusted life years (QALYs) as a measure of utility. All of the studies considered only one comparison between thrombolytics – that between alteplase and streptokinase - standard alteplase in the pre-GUSTO I studies, and accelerated alteplase in studies published after GUSTO I.

The time period of analysis varied across studies. The time period chosen was primarily determined by the source of efficacy data. Where the studies used modelling techniques to estimate survival, the time horizon of the model was much longer than the time period of the study for which real data were available. Some studies only calculated costs until the end of the first year post MI whilst others calculated costs over the entire remaining life expectancy of the patient. Although incremental costs were calculated by all of the studies, few of the studies provided enough cost information to replicate the calculations to check the robustness and reliability of their calculated incremental cost-effectiveness ratios.

Table 16: Characteristics of economic studies

Study	Type of evaluation and synthesis	Interventions	Study population	Time period of study
Goel and Naylor , 1992(103)	Cost-effectiveness analysis Cost per life year gained	SK, intravenous t-PA	Hypothetical cohort of nonelderly patients with uncomplicated myocardial infarctions. Sensitivity analysis allowed extrapolation to higher risk subgroups	Trial data – 4 weeks after AMI Extrapolated data – 5 years
Kalish et al., 1995(104)	Cost-effectiveness analysis and cost-utility analysis Cost per QALY gained	intravenous SK, accelerated t-PA	Hypothetical patients with acute MI who were candidates for thrombolytic therapy and who presented within 6 hours of symptom onset	Trial data – 1 year Extrapolated data – over remaining lifetime
Kellett, 1996(105)	Cost-effectiveness analysis and cost-utility analysis Cost per QALY gained	accelerated t-PA, SK	Hypothetical 65 year old man with a definite acute MI presenting< 4 hours after the onset of symptoms.	Trial data – 30 days after AMI Extrapolated data – over remaining lifetime
Lorenzoni et al., 1998(110)	Cost-effectiveness analysis Cost per extra life saved	recombinant t-PA, SK	Hypothetical population of 1000 patients with AMI with the clinical characteristics of the patients enrolled in the GUSTO trial(18)	Trial data – 30 days after AMI
Mark et al., 1995(106)	Cost-effectiveness analysis and cost-utility analysis Cost per life year gained, cost per QALY gained	accelerated tPA, SK	Patients enrolled in the GUSTO trial (18)	Trial data – 1 year after MI Extrapolated data – over remaining lifetime
Massel, 1999(107)	Cost-effectiveness analysis Cost per additional short run survivor	SK + aspirin, accelerated t-PA+ aspirin	Hypothetical cohort of nonelderly patients with uncomplicated MI who have resistance to SK	Trial data – 5 to 6 weeks after MI
Naylor and Bronskill, 1993(108)	Cost-effectiveness analysis Cost per additional short run survivor	Alteplase, intravenous SK	Hypothetical cohort of nonelderly patients with uncomplicated MI. Sensitivity analysis allowed extrapolation to higher risk subgroups	Trial data – 5 to 6 weeks after MI
Pelc et al., 1997(109)	Cost-effectiveness analysis Cost per life year saved	accelerated t-PA v SK	602 patients who survived initial MI in Feb 1993 and 102 patients who did not survive initial MI during this period	Trial data – 1 year after AMI

t-PA= alteplase, SK = streptokinase

Costs

Cost data and their source are presented in Table 17. Some authors used both primary and secondary cost data sources and both national and local sources of cost data were used in the studies. Individual patient costing was not used and none of the studies adopted a societal perspective.

The key categories of costs were similar across all of the studies and can be divided into hospital costs and post-discharge continuing care costs. Hospital costs included the thrombolytic drug therapy costs as well as cardiac procedures, length of stay and professional charges. Post-discharge costs included follow up clinics and the treatment of adverse events. There was significant variation in the estimation of costs related to adverse events with some studies including the continuing cost of strokes and heart failure while others did not.

Table 17: Cost data and cost data sources

Study	Cost items	Cost data sources	Country, currency and year
Goel and Naylor, 1992(103)	Thrombolytic drugs, cardiac procedures and other treatment of AMI episode. Long term model did not include differences in costs of medical care in added years of life	Procedural costs based on a comprehensive costing study carried out in 4 Canadian teaching hospitals from 1986-88. Professional costs from Ontario Health Insurance Plan fee schedule which includes visit and fee charges. Drugs costs from manufacturers	Canada; Canadian dollars (Can $); 1986-1988 (all costs were adjusted to represent constant 1988 dollars using the Canadian Consumer Price Index)
Kalish et al., 1995(104)	Thrombolytic therapy, hemorrhage, anaphylaxis and procedures. Long term costs of managing coronary heart disease and disabling stroke were calculated	Thrombolytic therapy – medication costs (Brigham and Woman's hospital); hospitalization – DRG reimbursement rates including professional fees (Brigham and Woman's hospital); miscellaneous – national and published figures, patient driven data	US; US dollars ($US); 1992
Kellett, 1996(105)	Thrombolytic therapy, anaphylaxis, major bleed, major stroke, acute MI and heart failure. Long term costs of nursing home care for major stroke and medical care for CHF were calculated	Irish hospital costs based on DRGs (1988). Drugs costs – list price. Stroke costs – telephone survey. Medical care for CHF-personal communication and estimates	Ireland; Irish pounds (IR £); 1996 (1988 costs were inflated to 1996 prices using a 5% per annum inflation rate). Costs are also presented in pounds sterling (1996)
Lorenzoni et al., 1998(110)	Only changes in thrombolytic therapy costs were discussed	Drug costs from national forumularies: Rote Liste (Germany), L'informatore Farmaceutico (Italy), British National Formulary (UK), Red Book (USA)	Germany (marks 1995), Italy (lire 1996), UK (pounds sterling 1996) and US (US dollars 1996). Relevant costs were estimated in ECUs and in US dollars. Exchange rates as 1/12/97
Mark et al., 1995(106)	Thrombolysis therapy, cardiac procedures, length of stay in ICU, rehospitalization, follow up hospital days and outpatient visits. No cost differences in treatment groups were calculated after one year	Initial hospitalisation - Duke Transition One cost-accounting system and Medicare fee schedule (North Carolina); Drugs – list price and average cost of 16 randomly selected GUSTO hospitals; Follow up – Medicare DRG reimbursement rates (North Carolina); Physician's fees –Medicare fee schedule	US; US dollars ($US); 1993
Massel, 1999(107)	Thrombolytic drugs, cardiac procedures and other treatments of acute MI	Procedural costs based on a costing study in 4 Canadian teaching hospitals from 1986-88. Professional costs were obtained from Ontario Health Insurance Plan fee schedule which includes visit and fee charges. Drugs costs from manufacturers	Canada; Canadian dollars (Can $). All costs were inflated to 1997 Canadian dollars with the Health and Personal Care component of the Canadian Consumer Price Index
Naylor and Bronskill, 1993(108)	Thrombolytic drugs, cardiac procedures and other treatments of acute MI	Procedural costs based on a comprehensive costing study carried out in 4 Canadian teaching hospitals from 1986-88. Professional costs were obtained from Ontario Health Insurance Plan fee schedule which includes visit and fee charges. Drugs costs from manufacturers	Canada; Canadian dollars (Can $); 1986-1988; all costs were adjusted to represent constant 1991 dollars using the Canadian Consumer Price Index
Pelc et al., 1997(109)	Days in CCU, thrombolysis, cardiac procedures, drug treatments, rehospitalisation. Costs were only estimated up until 1 year after treatment	Treatment –Treatment Strategy in Myocardial Infarction register which included data from 327 active general hospitals and 1828 patients (Feb 1993) + 1 year extension of this register which involved more than 700 of these patients. Hospital and patient surveys	France; french francs (FF); 1994

Outcomes

All of the studies analysed used a reduction in mortality as their primary outcome measure. The time-scale over which mortality improvements was measured and the metric used (number of lives saved, life years gained, QALY improvements) varied between the studies. The efficacy data sources described vary depending on the publication date of the study (Table 18). Two pre-GUSTO I studies used efficacy data from a range of five randomised controlled clinical trials that directly compared streptokinase and alteplase. Both of these papers used sensitivity analysis to address the uncertain efficacy of alteplase over streptokinase. One study (105) used a reduced mortality rate of 20% from the GUSTO I study instead of the conventional 14% reduction. A range of outcomes was stated in the studies. Several papers quoted similar efficacy data from the GUSTO I study including 30-day mortality, one year mortality, number of life years and quality adjusted life years gained. Adverse event outcomes of interest included stroke, reinfarction, major bleed, anaphylaxis, and congestive heart failure.

Where cost utility analysis was undertaken, the source of the utility values was usually derived from previously published papers.(104, 105) Only one study attempted to calculate utility values directly from real subjects.(106) However, little detail was provided regarding the elicitation of values, making their accuracy and appropriateness uncertain.

Table 18: Outcome data and data sources

Study:	Range of outcomes	Efficacy data sources	Utility values and data sources	Modeling method and data sources	Probabilities and assumptions of model
Goel and Naylor , 1992(103)	Mortality, life years gained	5 RCTs that compared directly SK and tPA (1985-1990)	N/A	Sensitivity analysis was used to project differences in outcome. Short term mortality based on data from 5 RCTs. Long term survival was modelled using data from the ISAM trial (48 months)	Baseline case assumes short term mortality with SK is 8% and the annual hazard rate post SK is 4% allowing combinations of varying short term and long term advantages for alteplase to be considered. Short term reinfarction rate of 6% for SK was also used. Non fatal events were not considered in the long term model
Kalish et al., 1995(104)	Death within 30 days, death within one year, survival with stroke, survival with reinfarction, survivial with stroke and reinfarction	GUSTO study (18) (1993)	Published trial (GISSI-2) where the time-trade off method was used. Paper published in 1994	Life expectancy after MI and after stroke was calculated using the declining exponential approximation of life expectancy (DEALE) method. Other life expectancy estimates were based on a consensus of the authors. Baseline probabilities from published trials	Extrapolation via assumption of constant mortality rate. Baseline case: 9% alteplase mortality, SK 10.1%; cost of alteplase $2216, SK$ 313; life expectancy after MI 14.6 yrs, stroke rate with alteplase 0.9%, SK 0.8%, reinfarction rate 4% alteplase, SK 3.7%
Kellett, 1996(105)	Death from MI, life years gained, quality adjusted life years gained, stroke, major bleed, analphylaxis, congestive heart failure	GUSTO study (18); risk of stroke for patients was taken from a review of 13 major trials of thrombolytic therapy (1993)	Previously published studies (1985, 1991, 1995). Perfect health (1), alive with major disabling stroke (0.5), alive with congestive heart failure (0.9)	Life expectancy estimated using a Markov process. Probability of death from AMI, reduction in mortality from MI due to thrombolytic therapy - published literature. Risk of stroke after thrombolysis taken from a review of 13 major trials of thrombolytic therapy	Reduction in probability of dying from MI if accelerated alteplase given <4hrs = 20%; additional risk of major disabling stroke with alteplase 0.3%-0.4%; reduction in risk of developing CHF with alteplase=10%
Lorenzoni et al., 1998(110)	Number of lives saved after 30 days	GUSTO study (18) (1993)	N/A	Data sources based on GUSTO(18)	Data sources based on GUSTO(18)
Mark et al., 1995(106)	Mortality at 30 days, mortality at one-year, life years gained, quality of life, disabling nonfatal stroke	GUSTO study (18) (1993)	Prospective random sample of GUSTO patients (n=2600). Based on telephone interviews 12 months after treatment. Mean utility weights were same for both groups (0.9)	A Cox proportional hazards model was constructed and included a Gompertz parametric survival function. Survival model was based on the experience of 4379 patients in the Duke Cardiovascular Disease Database	(i) Hazard of death after 1 yr did not depend on the thrombolytic agent received (ii) patients' pattern of long-term survival was typical of the chronic, stable phase of CHD. SK survival at 30 days = 92.7%, alteplase = 93.7%; SK survival at 1 yr = 89.9%, alteplase =91% from GUSTO study (18)
Massel, 1999(107)	Short-term (5 to 6 wks) survivor	5 RCTs that compared directly SK and tPA; GUSTO study(18) (1985-1993)	N/A	Potential benefits from treatment were estimated only with respect to short term survival	N/A
Naylor and Bronskill, 1993(108)	Short-term (5 to 6 weeks) survivor	5 RCTs that compared directly SK and tPA. Preliminary results from GUSTO (18) (1985-1993)	N/A	Long term survival is not incorporated into the analysis	N/A
Pelc et al., 1997(109)	Mortality at one-year, life years gained	GUSTO (18) (1993)		Data sources based on GUSTO (18)	Data sources based on GUSTO(18)

Cost-effectiveness ratios

Most studies were undertaken outside the UK, thus using different cost data and assumptions that were not directly relevant to the NHS.

Five out of the studies explicitly conducted subgroup analyses (Table 19), usually based on age, location of infarct and time to treatment. Some studies explored these subgroups in isolation,(104, 110) others in combination. Where subgroup analyses were performed, the results demonstrated that more favourable cost effectiveness ratios were achieved by treating older people, patients with anterior infarcts and those patients who present early for treatment.

All of the studies conducted sensitivity analysis to some extent. One-way, two-way and three-way approaches to sensitivity analysis were described. The three linked papers (103, 107, 108) described in this review used sensitivity analysis to investigate the impact of differences in efficacy between alteplase and streptokinase on their results.

One study was supported by a research grant from a pharmaceutical company.(104) Only two studies did not acknowledge funding sources.(109, 110) The authors of the six remaining papers acknowledged some form of support from manufacturers of thrombolytic drugs.

Table 19: Results presented in included studies

Study:	Cost-effectiveness ratio	Subgroup analysis and results	Sensitivity analysis and results	Authors conclusion
Goel and Naylor , 1992(103)	If alteplase is superior to SK, cost per life year gained would be $58,600; if no immediate survival advantages but greater left ventricular preservation, cost per life year gained would be $37,400	Not stated	One-way and two-way SA were undertaken. Results were relatively insensitive to changes in any factors apart from short and longer term mortality rates with alteplase, cost of alteplase and the relative procedure volume ratio	SK is a more cost effective choice than alteplase without proven short term mortality advantages
Kalish et al., 1995(104)	$30,300 per additional QALY gained for use of alteplase versus streptokinase (based on 30-day mortality from GUSTO); $27,400 per additional QALY using 1 y ear mortality data	Cost-effectiveness ratios were more favourable in older patients (<$50,000/QALY for a projected life expectancy of >=5 years), in patients treated <6hrs ($34,000/QALY) and in anterior myocardial infarctions ($16,300/QALY)	One-way SA was conducted using one year GUSTO mortality data. ICER was sensitive to the difference in mortality seen between SK and alteplase (however, even if relative mortality advantage of alteplase is only half that shown by GUSTO, cost per QALY remains <$60,000), cost of thrombolytic therapy and life expectancy after MI	Despite its higher cost compared to streptokinase, alteplase is a cost-effective therapy for myocardial infarction under a wide range of assumptions regarding clinical outcomes and costs
Kellett, 1996(105)	Incremental cost-effectiveness ratio of accelerated alteplase over streptokinase was IR £6290.29 per life year or IR £6176.72 per QALY	Older patients and those with anterior infarctions had improved C-E ratios. Higher risk of stroke worsens C-E ratio (inversion point >1.9%) and higher probability of dying from MI (no treatment) (inversion point <6.4%) improves the C-E ratio	Threshold analysis using the IR £10,000 per QALY critical value; results were sensitive to incremental cost of tPA over SK, discount rate used for survival benefits, time of treatment after onset of symptoms, patient age, probability of dying from MI, probability of stroke	Accelerated alteplase, if given early after symptom onset in specific patient groups, could be a highly efficient use of scarce healthcare resources
Lorenzoni et al.,1998(110)	Incremental cost (ECUs) per extra life saved: 132,199 (Germany); 146,652 (Italy), 100,757 (UK), 198,254 (US)	C-E ratios were more favourable in older patients and in anterior myocardial infarctions. Best C-E ratios found in the UK	Based on GUSTO study 95% confidence intervals of risk reduction. SA results are poorly explained. At the lower extreme of the confidence interval, alteplase can result in higher costs and lower efficacy than SK)	Cost-efficacy of alteplase Vs SK varies greatly among countries due to differences in drug costs. Selective use of thrombolytics for some sites of infarction is more cost-effective than the exclusive use of alteplase
Mark et al., 1995(106)	Incremental C-E ratio for the use of alteplase instead of SK was $32,678 per life year gained, incremental cost per QALY was $36,402 Undiscounted cost per life year gained = $20,468	C-E ratios were more favourable in older patients and in anterior myocardial infarctions. For anteriors, >$50,000/QALY for patients 40 yrs of age or under. For inferiors, >$50,000/QALY for patients up to 60 years	One-way SA (including threshold analysis). Results were most sensitive to a lowering of the long-term survival benefits of alteplase (cost/life year gained >$50,000 if life years saved <7 undiscounted years per 100 patients) and to increases in the projected medical costs for alteplase patients after the 1st year (if alteplase group had extra costs of $1,100 per year past the 2nd year of follow up, cost per life year gained > $50,000)	C-E of treatment with accelerated alteplase rather than streptokinase compares favourably with that of other worthwhile therapies
Massel, 1999(107)	Alteplase is a C-E alternative to SK when resistance is high ($54, 158 per short run survivor with 50% resistance) assuming a 1% absolute risk reduction in mortality. As the level of resistance decreases, alteplase becomes a less cost effective choice	Not stated	Two-way SA varying (i) percentage of patients with resistance to streptokinase (ii) additional absolute reduction in mortality form alteplase use instead of streptokinase. Alteplase was C-E when rates of SK resistance were high, even with modest absolute risk reductions in mortality	Using alteplase in patients previously treated with streptokinase is a cost-effective strategy but becomes less cost effective as resistance increases

Naylor and Bronskill, 1993(108)	Alteplase is C-E as a substitute for SK if clinically superior. For a 1% mortality advantage, the cost per additional short-term survivor is $277,860.	Not stated	One-way SA shows that by varying the absolute risk reduction in mortality from 4% to 0.5%, incremental cost per additional short run survivor varies from $69,465 to $555, 721	The final verdict on the cost-effectiveness of alteplase versus SK must wait for empirical data from the GUSTO trial
Pelc et al., 1997(109)	Incremental cost effectiveness of alteplase (versus streptokinase) was F70 128 per life year saved	C-E ratios are less favourable in younger patients and those with inferior infarctions	One-way SA. Costs were substituted with exact (highest possible) unit-cost data from a single specialised cardiology centre (F107 450/life year gained)	Clinical and C-E data demonstrate that alteplase is a C-E first line option for the management of acute MI in french general hospitals

Overall assessment of published economic evidence from randomised controlled trials

Incremental cost-effectiveness analysis was the appropriate approach to adopt in all of the studies as it is the change in costs and the corresponding change in benefits which is of interest to the decision maker. All of the studies justified their choice of comparator. Given the publication dates of the included studies, all of the studies included comparators that were relevant alternatives for the treatment of acute myocardial infarction at that time. The majority of studies used efficacy data from the GUSTO I study.(18) This was an international trial but the estimated use of medical resources was derived only from US patients, and are unlikely to translate into other health services. Authors in Europe applied the results of the GUSTO I study to their own settings in an attempt to compare the cost-effectiveness of alteplase versus streptokinase. Consequently, cost-effectiveness ratios were expressed in several currencies, a reflection of the international interest in the choice between alteplase and streptokinase. Clearly the range of costs identified, estimated and valued in an economic evaluation influences the calculation of the cost-effectiveness ratio. Unfortunately some studies did not sufficiently explore the true cost of complications over the lifetime of the patient. Nor was this addressed fully by sensitivity analysis.

As it is uncommon for quality of life data to be routinely included as part of a randomised controlled trial, it is perhaps not surprising that only three studies considered issues that can be addressed by cost-utility analyses. Given that both alteplase and streptokinase have been demonstrated to improve both patient quality and quantity of life, the use of cost utility analysis in this context would have been informative.

Subgroup analysis was appropriately performed in many of the studies with age, location of infarct and time from onset of symptoms to treatment being the three most important groups. However, it should be noted that subgroup analysis by age based on the results of the GUSTO I study should be handled with care as only 30-day efficacy data were available at the time when study results were published. The results of the sensitivity analyses revealed that the mortality differential between streptokinase and alteplase was the factor that consistently influenced the cost-effectiveness ratio. The cost differential between drugs was also important.

Conclusions

Pre-GUSTO I studies that compared alteplase with streptokinase were in agreement that until any mortality advantage could be identified for alteplase, streptokinase would continue to be the preferred choice of thrombolytic. However, with the publication of the GUSTO I study results and the demonstrated mortality benefit of alteplase over streptokinase, subsequent economic studies have shown that alteplase appears to be more cost-effective than streptokinase. The outcome of this review of the economic studies is therefore dependent on whether one accepts the results of the GUSTO I study as illustrating a credible clinical advantage over streptokinase, a matter for appraisal (see Section 4).

6.4 Detailed critique of major sources of economic evidence

6.4.1 Economic analysis of the GUSTO I trial

Cost-effectiveness analysis

The GUSTO I clinical trial incorporated an economic sub-group analysis to determine the comparative cost-effectiveness of alteplase and streptokinase. Effectiveness was expressed as the number of additional years of life saved calculated by taking the number of lives saved, multiplied by an estimate of remaining life expectancy. Complex modelling was required to estimate the impact of the short-term benefit on long-term outcome as long-term patient survival was unknown. To translate the survival data (11 extra survivors at one year per 1000 patients treated on alteplase) into additional years of survival, the Duke cardiovascular disease database was combined with statistical techniques to estimate lifetime survival. From these calculations, it was estimated that each alteplase patient would gain an average of 0.14 life years from alteplase relative to streptokinase.

The treatment groups had the same rate of bypass surgery (13%) and angioplasty (31%) during the initial hospitalisation. Overall, the first year health costs excluding the difference in the cost of the thrombolytic agent were $24,990 per patient treated with alteplase and $24,575 per patient treated with streptokinase. The estimated cumulative increase in medical costs (hospital cost plus physician fees) at one year therefore averaged $415 for alteplase patients in comparison to streptokinase. When the relative costs of the two thrombolytic agents were added in, the resulting incremental cost for the alteplase arm rose to $2,845. Because the non-drug cost-differential at one year was not significant, the primary analysis assumed that there would be no incremental cost for alteplase after the first year. Thus, $2,845 was also held to represent the incremental lifetime costs of a patient treated on alteplase, rather than streptokinase.

Using this estimate and a discount rate of 5%, the GUSTO I trial investigators concluded that the cost-effectiveness ratio of using alteplase instead of streptokinase was $32,678 per year of life saved. As part of the sensitivity analysis, the costs typically paid by hospitals for thrombolytic agents were substituted for their list price. This alteration reduced the cost per life year to $27,115. Although it was stated that a societal perspective had been employed, indirect and non-medical costs were not included in the analysis.

There was consideration of the utility of patients who have had an AMI in the GUSTO study: patients in the study were generally willing to trade 10 years of life in their post-AMI state of health for 9 years of excellent health. Applying this weighting factor to both alteplase and streptokinase recipients rescaled the cost-effectiveness ratio in the baseline case to $36,402 per QALY.

Subgroup analysis in GUSTO I

Assessment of the comparative costs and benefits arising for selected sub-groups (by age and location of infarct) of patients were performed in GUSTO I. This analysis might enable thrombolytic therapy to be targeted upon patients in whom it is most

effective or cost-effective. However, as the authors stress, the results of the sub-group analyses should be interpreted cautiously.

In general, cost effectiveness was greater in patients at higher risk of absolute mortality, i.e. the older patients and those with anterior infarcts. For example, the additional cost per life year gained of alteplase over streptokinase was estimated to be $13,410 for patients older than 75 years with anterior MI, and $16,246 for patients older than 75 years with inferior MI. In contrast, in a low risk patient such as a patient younger than 40 with an inferior infarction, the cost effectiveness ratio was $203,071 per year of life saved.

In summary, the economic analysis performed alongside GUSTO I demonstrated that alteplase expanded survival at an acceptable cost within the context of a clinical trial undertaken in the USA healthcare system.

6.4.2 Critique of economic analysis of GUSTO I trial

The GUSTO study has been criticised from many viewpoints. Other investigators have commented on the small size of the difference in outcome, differences in the results obtained within and outside of the USA, the open nature of the trial, the high cost differential between the drugs studied, the increased stroke rate with alteplase and other factors that are held to prevent acceptance of the conclusions.(93) All of these factors must be taken into consideration when interpreting the cost-effectiveness ratios presented by the authors of the economic analysis as their implications might affect the magnitude of the clinical effect and/or limit the relevance of study findings to specific settings.

Cost differences in the first year

The authors only report cost differences between the groups during the first year post-infarct as they estimated that the cost differences in the second six months of the first year were not significantly different. In addition, cost data after the first 12 months were not available. By far, the two most expensive cost items during the initial hospitalisation period were coronary angioplasty and coronary bypass surgery which were performed with equal frequency in both groups. However, given the acknowledged higher rate of aggressive and invasive interventions in the USA compared to other countries,(112) it would have been useful to explore the impact of changing the procedural rates to reflect those of non-USA countries on the estimated cost-effectiveness ratios.

Cost differences after one year

If the non-significant cost differential identified between the two groups between six and twelve months ($508) was annualised and maintained for the entire period of increased survival, then an unacceptable cost effectiveness ratio of $147,333 would have been estimated.(113) Even if this cost differential were maintained for a period of only three years, the incremental cost per life year gained would be $55,300. Clearly inclusion or exclusion of this cost differential has significant implications for the cost-effectiveness of alteplase versus streptokinase.

Increased risk of stroke

Alteplase resulted in significantly more non-fatal disabling strokes than streptokinase, but the additional cost of care for patients who experienced stroke was only incorporated into the economic analysis for the first year post-infarct, after which costs were assumed to be equivalent for both groups. This approach to costing is subject to criticism as it is likely that health services incur costs for a much longer period for this group of patients. The authors, to some extent, addressed this issue using sensitivity analysis. In the sensitivity analysis, a patient with a disabling stroke was assumed to have the same life expectancy as a non-stroke patient but was assumed to require lifetime (15 years) institutionalised care. This assumption reduced the comparative cost-effectiveness of alteplase to $42,400 per life year saved.

Quality of life issues

The methods used to elicit utility values to explore patient quality of life issues were not clearly described by the authors. The elicitation of utility values from patients does not lend itself to telephone interviews given the complex nature of the questions and concepts under discussion. In addition, comparative quality of life data in sub-groups of patients receiving alteplase or streptokinase was not analysed. This is an important omission in view of the difference in the rate of strokes between the two groups.

Implications for the UK

The generalisability of the GUSTO results has been intensively scrutinised. With regard to the economic study, the only concession to differences between non-US countries and the US was the use of typical European prices for the drugs in a sensitivity analysis; substitution of European prices, lead to a substantially improved cost effectiveness ratio ($13,943 per year of life saved). Unfortunately in the economic analysis, there was no similar reflection of the different patterns of care between non-USA countries and the US. Evaluation of the GUSTO data has at least shown that alteplase is more cost-effective than streptokinase in the USA, whether or not these results have less relevance for non-US countries is the subject of much debate.

6.4.3 Economic analysis of the GREAT study

The cost effectiveness of pre-hospital versus in hospital thrombolysis is not the subject of this review. Nevertheless, it is important to review one trial which addressed this issue, the Grampian Regional Early Anistreplase Trial (GREAT)(84) study, as it considers several important areas within the context of the NHS. The clinical details of this trial have already been discussed in Chapter 5; this current section considers the economic evaluation associated with that study.(114, 115)

The authors compared the costs and benefits of anistreplase (see Chapter 2 – this drug is no longer available in the UK for commercial reasons) administered by GPs before the patient was admitted to hospital versus hospital thrombolysis in a randomised controlled trial. This paper was excluded from the detailed review of economic evidence outlined above because the trial was not a direct drug versus drug comparison (anistreplase may be considered a more convenient bolus administered equivalent of streptokinase) but rather a setting to setting comparison.

Relative to hospital thrombolysis, analysis of the GREAT trial has shown that pre-hospital community thrombolysis versus hospital thrombolysis leads to a significantly enhanced probability of survival at 4 years of 11%, at a very modest additional cost (£425 per patient). This gives a marginal cost per life saved of £3,890. The cost per life year saved by pre-hospital thrombolysis is modest compared with, for example, the cost of switching from streptokinase to alteplase in the hospital setting(114, 115).

It was estimated that if all eligible patients had received early thrombolysis, then the total additional cost to the health service would have been £77,000.(114) Therefore it would appear that the benefits of early thrombolysis could be obtained for a comparatively insignificant increase in cost. However there would be additional costs to the health service as a whole because such early thrombolysis would cause an estimated 1.5% increase in the number of patients surviving AMI until admission to hospital.(114, 115)

6.4.4 Critique of the economic analysis of the GREAT study

A criticism of the economic analysis of the GREAT study is that the economic evaluation was not carried out at the same time as the randomised controlled trial. The economic analysis (115) was conducted four years later and relies on very limited follow-up data. The economic evaluation would have benefited from some consideration of quality of life issues. Although no study viewpoint was explicitly stated, it can be assumed that the evaluation adopted a NHS perspective that included costs incurred in both hospital and pre-hospital settings.

From the published economic evaluation, it was difficult to determine the exact nature of the two interventions being compared. In particular, a detailed description of hospital thrombolysis was lacking.

Costs included in the economic evaluation were appropriately described in terms of the range of costs included in the analysis. However, physical quantities of costs and unit costs in monetary terms were not presented. It would be impossible for the analysis to be replicated using different parameter values more suited to the reader's setting.

The authors conducted sensitivity analysis to a limited extent. In their cost analysis of pre-hospital thrombolysis, the authors used low and high estimates regarding the additional length of GP visits and capital equipment. No parameters were varied in the analysis of hospital costs. The probability of survival after pre-hospital thrombolysis compared to hospital thrombolysis was based on the latest data from the GREAT trial and at four years, the additional probability of survival was 0.11 (95% CI: 0.01, 0.21). As the GREAT study was not designed with a cost-effectiveness question in mind, the confidence intervals around the cost per life saved were very wide. Low estimates revealed a range of £1,990 to £42, 820 whereas high estimates revealed a range of £4,100 to £88,100. In summary, the cost per life saved by community thrombolysis headlined in the paper by the authors was modest and ranged between £3,890 and £8,000 (figures from low estimate calculations). It would have been appropriate for the authors to present the results of their economic analysis in terms of cost per life years saved in keeping with other economic studies.

Although impressive, the results of GREAT need to be tempered by comparison with other trials that have shown a lesser benefit, as discussed in Chapter 5. The applicability of the GREAT study to the NHS as a whole is therefore uncertain, as are the results of its cost-effectiveness analysis.

6.5 Discussion of key issues highlighted by reviews of economic evidence

6.5.1 Perspective

The perspective from which economic analyses of AMI are undertaken is crucial as the viewpoint adopted influences the range of costs to be identified, measured and valued. No studies have addressed the indirect costs to patients or their families of an AMI nor of a disabling stroke following thrombolysis. There is debate about the most appropriate way of measuring such indirect costs and whether and how they should include loss of productivity. Most studies therefore adopt a simple health service or payer perspective.

6.5.2 Treatment costs

The treatment cost of an uncomplicated AMI in the NHS is estimated at £903 (116) and this figure is based on an average of five in-patient days. The figures provided in the industry submissions are higher (around £1900 for an uncomplicated MI, excluding costs of thrombolysis) and seem more plausible to us. In either event, the costs of thrombolysis other than streptokinase are a very significant element of the costs of AMI. Most previous published economic evaluations considered the cost of drug treatments for AMI small by comparison with the associated costs of in-patient stay. This may be correct if subsequent follow-up care is included, especially when expensive diagnostic and treatment techniques are utilised or if the patient suffers serious adverse events. Several studies in North America and Europe suggest that the contribution of the thrombolytic drug to the total cost of care ranges from approximately 0.5% (streptokinase) to 5% (alteplase).(93)

The biggest costs are perhaps those of rehabilitation and support following disabling stroke. Attributing a single cost to stroke is complicated by the many different levels of care associated with different severities of stroke. The impact of variations in the incidence of stroke on the comparative cost-effectiveness of different thrombolytics will depend on the comparative incidence and lifetime support costs associated with this adverse outcome. In general, this aspect of long term costs has not been well managed in economic studies published to date.

6.5.3 Generalisability of economic evaluations conducted alongside clinical trials

Economic evaluations are likely to be strengthened by being linked to clinical trials as this provides scientifically credible data on which to base economic analysis. However, real world clinical practice is not as controlled as in the clinical trial framework, and the issues around generalisability of trials to real world clinical practice has been discussed above. Major problems occur in comparing the results due to differences in methodology, clinical setting, assumptions made and study perspective. Jonsson(117) discusses methods of addressing the problems that arise in economic evaluations linked to international trials of AMI. Clinical trials generally enrol patients who have a lower mortality than expected in a general population and

therefore the benefits of a therapy in high risk patients such as the elderly may be underestimated. Conversely, a clinical trial may not enrol patients with co-morbidity and thus may underestimate the adverse effects of a therapy if it were given routinely in a community hospital. In addition, cost structures vary in different environments and patterns of care, including indications, threshold for interventions, duration of hospital stay and readmission rates will vary widely. Some costs may occur because of protocol driven costs which are outside the normal clinical care of the patient. It is important therefore that these be distinguished from standard care.

In economic evaluations based on multicentre studies e.g. thrombolytic trials, some of these difficulties are compounded by the fact that many patients will be cared for in health services where the care received and its cost are substantially different from those in the NHS. For instance, in the economic evaluation of the GUSTO study the one concession made to translating the American cost to a European setting was a sensitivity analysis around the cost of the drug. This ignored different patterns of medical care and different costs for procedures or staff in Europe and makes the results unreliable for this reason. Such studies, although they lack generalisability, may provide the data that allow translation to other settings.(117)

6.6 Summary from review of economic evidence

Any estimate of the relative cost-effectiveness of accelerated alteplase compared with streptokinase depends critically on the weighting of evidence between GUSTO I and previous trials. However, the data on thrombolysis in acute myocardial infarction is evolving and more clinical and economic data are required to demonstrate benefits both in the pre-hospital and hospital settings. A range of factors on both the cost and effectiveness side will considerably influence cost-effectiveness into the future. The price of thrombolytic drugs may decrease, practice patterns may change and there may be further improvements in pharmacological therapy. For thrombolysis, as in other situations, effectiveness data in routine clinical practice will be crucial with such factors as bleeding complications, stroke rates, and timing of intervention likely to vary from those identified in the efficacy data identified in clinical trials.

The comparative cost-effectiveness of the different drug regimes appear to be uncertain from current available evidence, especially regarding the use of reteplase and tenecteplase. In addition, comparative drug costs must be placed in the context of the total cost imposed on the health service by each of the therapeutic options.

6.7 Critique and re-analysis of industry submitted economic models

6.7.1 Introduction

Review of the economic evidence on early thrombolysis for the treatment of acute myocardial infarction reveals that very little up-to-date evidence of cost-effectiveness exists in the published literature. Upon further investigation, it is clear that those studies that do exist are limited in their relevance to the UK NHS. No economic evaluations of reteplase or tenecteplase were identified by the literature search. However, in the industry submissions both these drugs together with streptokinase and alteplase were the focus of detailed cost-effectiveness analyses. We felt that it was appropriate to appraise the economic models as presented in the industry

submissions and offer our own conclusions on the relative cost effectiveness of thrombolytics based on exploration of a range of potential scenarios reflecting uncertainty in the underlying model assumptions and parameter values.

Industry submissions

Submissions to the National Institute of Clinical Excellence were received from the following manufacturers/sponsors:

a. Aventis Behring Ltd
b. Boehringer Ingelheim Ltd
c. Roche Products Ltd

Two of the three industry submissions include detailed cost-effectiveness models in support of the clinical evidence presented (Boehringer Ingelheim and Roche). All three companies included a cost-impact analysis for the extended use of their product. This critique focuses on the submissions offered by Boehringer Ingelheim and Roche as they comprehensively address the cost-effectiveness of thrombolysis in both hospital and pre-hospital settings. In doing so, they assess the relative costs and benefits of streptokinase, alteplase, reteplase and tenecteplase. In contrast, the Aventis Behring submission is a brief cost minimisation study, and does not present detailed analysis of costs or benefits of any of the drugs. Valid comparisons of cost-effectiveness can only therefore be made based on the Boehringer Ingelheim and Roche submissions.

Introduction to industry models

Table 20 offers a brief overview of the models submitted by Roche and Boehringer Ingelheim which highlights the main differences between them.

In both of these submissions, results are presented for both pre-hospital and hospital thrombolysis comparisons. Each model has been carefully appraised both in terms of the appropriateness of its structure and the specific assumptions concerning parameter values made when generating cost-effectiveness results. In the following sections, key aspects are discussed in relation to evidence available. Also the relative impact of alternative assumptions on the results presented has been assessed.

Table 20: Main features of submitted cost-effectiveness models

Feature	**Roche model**	**Boehringer Ingelheim model**
Type of model	Basic accounting tables of costs and outcomes at 30 days, with simple projection of mortality gains beyond 30 days.	Decision-analytic model with time-points at 30 days, 1 year and 10 years.
Short-term survival	All survival benefit accrued by 30 days.	Most survival benefit accrued by 30 days. Some additional benefit results from reduction in CHF among 30-day survivors.
Long-term survival	General assumption of mean survival of 10 years for all 30-day survivors.	Survival projected separately for patients with/without CHF from 30 days to 1 year and 10 years.
Thrombolysis administration time	Assumed pre-hospital administration time is 60 mins earlier than in-hospital time. Also bolus products assumed to be given 20 mins earlier than infused products.	Assumed pre-hospital administration time is 60 mins earlier than in-hospital time. Also bolus products assumed to be given 15 mins earlier than infused products.
Time-dependent mortality	Assumption of 2 life-years gained per hour of reduced delay to thrombolysis. No functional model of time delay - efficacy assumed.	Boersma non-linear model of time delay - efficacy assumed. This is combined with distribution of delay times to estimate mortality changes. Delay times are represented in the model in time bands.
Costing	Costs only calculated for 30 days. Costs not discounted. List prices of drugs used. All adverse events attributed the same average cost. Additional drug wastage cost included to reflect 'saved doses' for some patients with adverse events.	Detailed costing model for 10 years. Costs discounted at 6%. List prices of drugs used. Adverse events costed separately in detail. Long-term costs and events differentiated for patients with/without CHF, restricted to cardiac events and care. Long-term stroke care costs also included.
Life-years & utility	Single utility value used for all survivors at all times. Discounting applied at 1.5% to long-term survival.	Different utilities for reinfarcts and strokes (with and without disability). Life-years discounted at 1.5%.
Efficacy of thrombolysis	All four drugs assumed to be equivalent in efficacy.	Alteplase & tenecteplase assumed to be superior to reteplase, which is better than streptokinase.

The basis of each company's claim to cost-effectiveness can be summarised as follows:

(i) Hospital thrombolysis

Roche consider all four products to be equally efficacious in reducing 30-35 day mortality, but claim that earlier administration of reteplase and tenecteplase yields

some additional benefit in reducing mortality further compared to non-bolus products (streptokinase and alteplase). By combining differences in list price, drug use and adverse event costs, Roche claim an overall cost slightly less than that for alteplase and tenecteplase. Thus Roche use a cost-minimization argument to suggest that reteplase should be considered the preferred treatment for hospital thrombolysis.

Boehringer Ingelheim claim a slightly better efficacy (30-day mortality) for tenecteplase than the other thrombolytics, and also a reduced incidence of post-infarct heart failure. By projecting these effects over ten years, they claim slightly reduced discounted costs compared to alteplase and reteplase. Thus, they claim that tenecteplase dominates other treatments in both costs and effectiveness.

(ii)Pre-hospital thrombolysis

Only the two bolus-administered products are considered suitable for pre-hospital use in the industry submissions, and so streptokinase and alteplase are not assessed here for use outside the hospital environment.

Roche use similar arguments to those for hospital thrombolysis to claim reduced costs compared to tenecteplase (assuming equivalent clinical efficacy). Boehringer Ingelheim again rely on a supposed mortality benefit (deduced from indirect comparison) together with reduced incidence of heart failure leading to lower long-term costs, as the basis for claiming superiority for tenecteplase over reteplase.

6.7.2 Mortality, survival and the impact of thrombolysis

Long-term follow-up studies of thrombolytic use show a consistent pattern of effect. Cohorts receiving thrombolysis suffer fewer early deaths in the days immediately following their acute infarction, and the difference is sustained at a constant level thereafter for up to ten years. The maximum divergence between survival curves in trials occurs at times ranging from one month (GISSI-1) to six months (ISIS-2), the majority of benefit occurring within the first two weeks. Thus the two most appropriate measures of survival benefit are the case-fatality rates at one month and twelve months, representing immediate and maximum survival benefit. There is no convincing evidence that thrombolysis affects survival after this period, despite the unusual results of the GREAT study.

6.7.3 Effect of time to thrombolysis on mortality

A study to deliberately randomise patients to treatment at different times would be unethical, and therefore in assessing time to benefit we are forced to conduct retrospective analyses of existing trials set up for other purposes. Since the general effect of thrombolytic therapy is to prevent fatal damage in the early hours and days post-infarct, it is reasonable to expect that quicker administration of thrombolysis should lead to larger numbers of patients receiving benefit. However, this effect may be confounded by an increasing chance that patients thrombolysed very soon after the onset of symptoms will include some whose prognosis is very poor. Thus the relationship between mortality reduction and time of administration may not be simple, or even monotonic in form.

This ambiguity is evident in three published studies:

- the FTT Collaborative Group(28) presented a meta-analysis of 45,000 patients from large trials (greater than 1000 patients) of hospital-administered thrombolysis, analysed by time from onset of symptoms to randomisation. Collins and colleagues (11)on behalf of the FTT group concluded that *"the slope of absolute gradient plotted against increasing delay is fairly gradual and is not significantly steeper in the first few hours"*. As a consequence they fitted a linear function of time by regression.
- Newby and colleagues (27) described a time-based analysis of GUSTO I results, and derived an observational trend line which exhibits three phases: a gradual near-linear increase in mortality with increasing delay from four hours upwards, a steeper near-linear increase in the 2-4 hour delay period, and a reverse trend (reducing mortality with increasing delay) for delays of less than two hours.
- Boersma and colleagues (26) carried out a further meta-analysis adding in additional smaller trials of over100 patients. This included many of the trials in the Morrison pre-hospital thrombolysis meta-analysis, most notably the EMIP study. They reported evidence of a non-linear relationship with time delay, and fitted a curve involving a hyperbolic component (though without offering any justification for this choice).

These differences in 30-day mortality are compared in Figure 1, and the corresponding reductions in mortality suggested by an improvement in time to thrombolysis of one hour are shown in Figure 2.

Figure 1 Alternative models of mortality as a function of delay of treatment

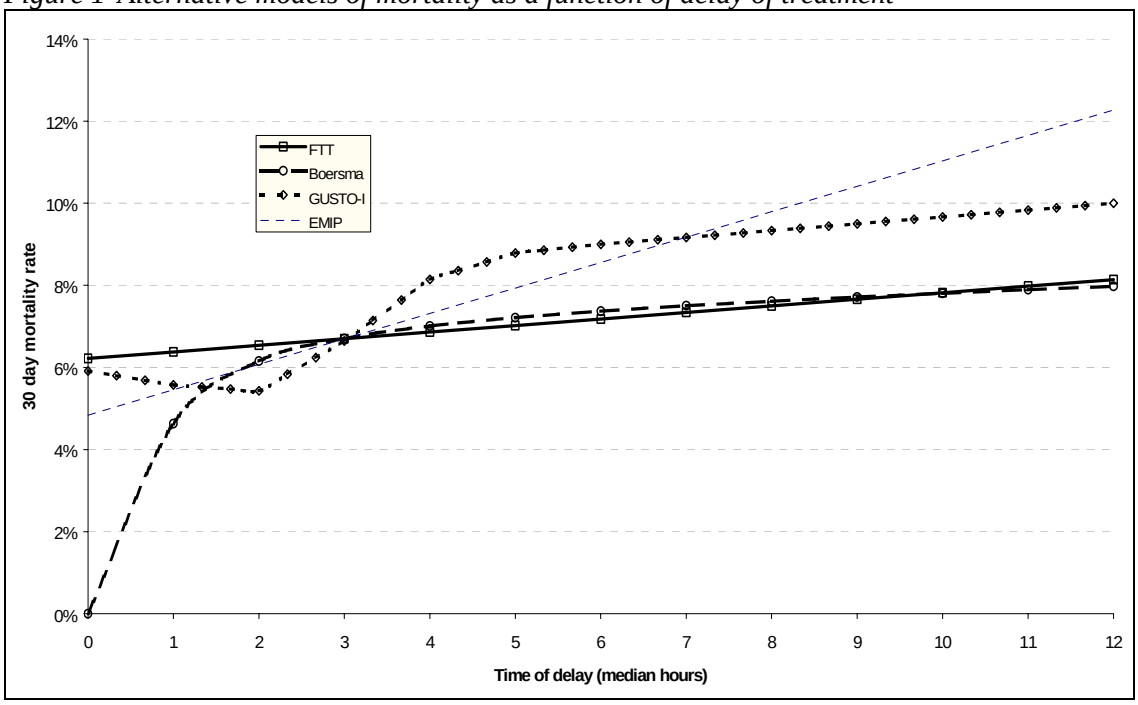
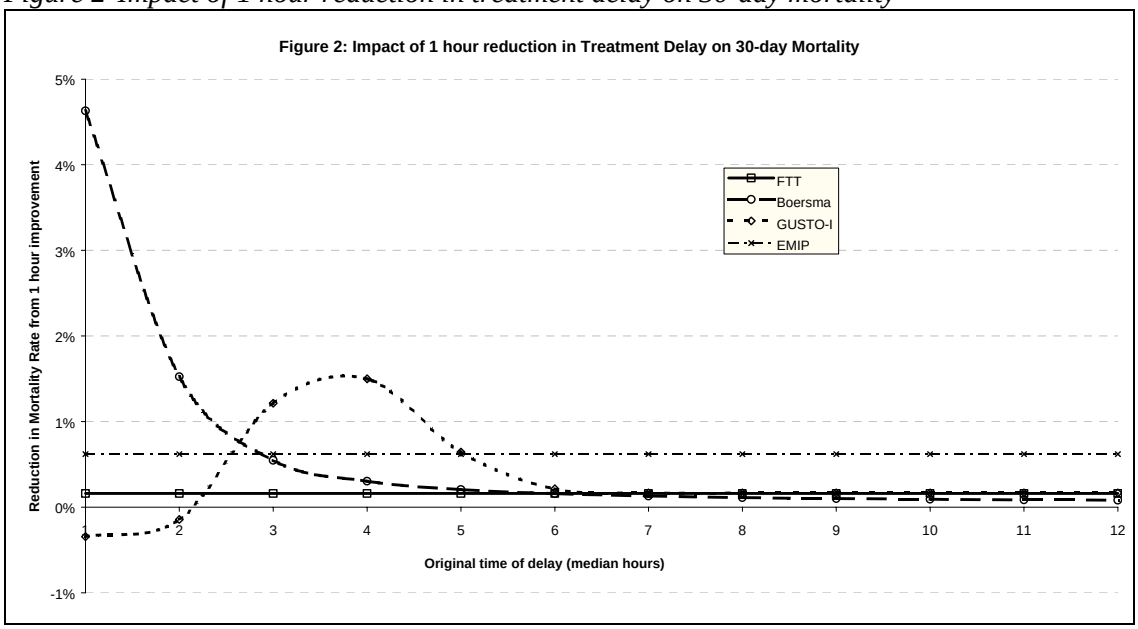


Figure 2 Impact of 1 hour reduction in treatment delay on 30-day mortality



The different models provide similar results in the mid-ranges of their estimates, but significantly different results (particularly in the case of the two non-linear models) at the extremes of both very short or very long delays.

There is no definitive basis for selecting between these models, based as they are on different data sets and with different assumptions. However, we may offer some observations. The FTT line has the strength of simplicity, and is based on good quality large-scale trials. However, it has small numbers of patients at the extremes of the time delay distribution, and is therefore not sensitive to any deviations from linearity. The FTT result suggests that no mortality benefit should arise from thrombolysis when the time delay from onset of symptoms exceeds 21 hours. This

may or may not be clinically reasonable, but there is no strong evidence to support this inference.

Newby(27) does not attempt to fit a pre-defined functional form to her data, but presents a stylised representation of a non-linear fit to observational data. The result is intuitively appealing, suggesting that there is a sizeable sub-population whose prognosis is so poor that thrombolysis is irrelevant to the fatal outcome, but that within the 12 hour time horizon of the trial data, benefit continues to accrue slowly even among those groups treated very late. In particular, Newby's(27) results suggest that the primary operational aim should be to thrombolyse within 2.5 hours of onset of symptoms, with a secondary aim to treat within four hours. The greatest incremental advantage arises from speeding patients to treatment who are currently thrombolysed between 2.5 and four hours of onset of symptoms.

The choice of non-linear function by Boersma and colleagues(26) is arbitrary, but implies an extreme relationship with time delay that probably cannot be supported by either evidence or clinical experience. Projecting backwards toward zero delay in thrombolytic administration, the fitted function implies that immediate treatment would completely eliminate AMI mortality. This seems to be unduly optimistic, as clinical experience suggests that many patients die within minutes of symptoms beginning, well before any thrombolysis could take effect. In addition, the Boersma function implies that no mortality benefit should accrue when the time delay exceeds 34 hours (compared with 21 hours for FTT(28)). Boersma and colleagues(26) also used eight pre-hospital studies to conclude that the benefit from earlier thrombolysis in these studies was of the order of 21/1000 treated per hour saved, based only on two time points and dominated by the evidence from the largest trial, EMIP. Since these results and the Morrison(90) meta-analysis have most studies in common it is unsurprising that they reach similar conclusions.

Both the meta-analysis undertaken by Morrison(90) and that reported by Boersma(26) of pre-hospital studies are heavily dependent on a single trial (EMIP(83)) which contributed 85% and 83% respectively of the aggregate patient populations. To assess the confidence that may be placed in these meta-analyses it is therefore important to look in detail at the results of the EMIP(83) trial. Although EMIP(83) reports an important (non-significant) reduction in absolute mortality risk at 30 days of 1.4%, it is less helpful in determining the nature of the influence of time to treatment on outcome. Of the figures shown in *'Table 4'* of the EMIP(83) paper, only those for time to first injection for the pre-hospital group provide reliable evidence of a direct temporal effect (all other results involve multiple time intervals without any indication of inter-period temporal correlations). Plotting these data against time suggests a simple linear relationship (at least up to 6 hours from onset of symptoms), with a gradient equivalent to an absolute risk reduction of 0.62% per hour saved in reaching treatment. The difference between this and Boersma's(26) 2.1% is attributable to the inclusion of some small studies with relatively extreme results in the latter analysis, as well as the apparent compounding of inter-arm differences with underlying temporal trends. In the absence of better evidence we offer a fourth option for estimating mortality risk due to earlier treatment based on the more reliable component of the EMIP(83) results: this is exhibited on a common basis to the other options in Figures 1 and 2.

We must consider why the overall benefit of 1.4% associated with a difference in time of 55 minutes from EMIP(83) is greater than the time effect derived from *'Table 4'* of the report. This is not clear: however, it seems likely that the overall effect of 1.4% is due not only to time but also to additional confounding factors which differ systematically between the pre-hospital and hospital settings. To take only two estimates of difference (e.g. 1.4% in EMIP(83), or 1.6% in the Morrison(90) meta-analysis or 2.1% in the pre-hospital meta-analysis of Boersma, both of which draw heavily on EMIP(83)) and to attribute all of the difference to time alone is clearly a questionable assumption.

Rawles(94) examined time to thrombolysis and outcome in the GREAT(84) study and reported a saving of 21 (2.1%) lives at 30 days per thousand (95% CI: 1, 94) treated per hour, and 69 lives (95% CI: 16, 141) at 30 months per 1000 treated. Although this calculation agrees with that from Boersma and colleagues,(26) this is probably only because they both utilize the same approach of attributing all differences to time alone, which has already been questioned above. With regard to the Rawles(94) results, it is also important to acknowledge that the results of the GREAT(84) study itself appear to be exceptional, as outlined in Chapter 5: it has shown a mortality benefit, though never intended or powered to test the hypothesis of reduced mortality; the benefit is greater than for most other studies of thrombolysis; and the mortality benefit continues to diverge up to two years in contrast to the fixed benefits after 30 days in all larger studies. The reasons for such exceptional are likely to relate to the small size of the study and the atypical trial environment in which the data was collected.

Rawles questioned why the benefits observed in the pre-hospital settings are greater than those in Newby's data or in either the FTT model or in the main Boersma model.(26) He argues that existing models are flawed,(96) confounded by the fact that sicker patents will seek help and be thrombolysed sooner; such patients will always have a higher mortality. Newby(27) in particular seems to illustrate this from the GUSTO I(18) study (see Figure 1) – i.e. that patients treated very early had a worse prognosis than those treated later and this was also seen to some extent in the GREAT(84) study where presentation at one hour was associated with twice the mortality of those presenting at four hours (96). This, Rawles(96) argues, would confound the post hoc analysis of mortality related to time in all studies. Rawles(96) argues that pre-hospital versus hospital trials would come closest to the design of a study set up to examine time differences alone. Despite these arguments, the EMIP(83) data clearly suggests that there are other differences between settings, apart from the time to thrombolysis.

We have therefore questioned the often quoted figure of 2% extra benefit per hour saved in time to thrombolysis in the following calculations and have attempted to isolate a more accurate relationship between these two crucial elements of the economic evaluation.

This issue is important when considering whether or not to undertake pre-hospital thrombolysis (which is not the subject of this appraisal). In comparing the efficacy of two products equally suitable for pre-hospital thrombolysis, and which are both

administered at the same time, the specific timing has no impact in differentiating by efficacy between the candidate drugs. In the context of in-hospital thrombolysis, timing of administration is only important if we have evidence that one drug can be administered more quickly than another in a real-life environment. Then the four relationships described above can each be used to estimate mortality differences attributable to differences in time of administration.

Both the Roche and Boehringer Ingelheim submissions make similar assumptions about the timing of bolus delivered drugs compared to infused drugs (15-20 minutes quicker) on the basis of published audit studies. Consultations with specialist staff suggest that this difference may now be overstated in the UK, where differences of only 5-6 minutes have been reported (see Section 7). Applying these figures to the four proposed relationships with a 20 minute time advantage FTT (28) yields 0.5 fewer deaths per 1000 and EMIP(83) 2.1 per 1000 regardless of timing, Boersma(26) projects 0.3 fewer deaths per thousand at twelve hours delay, increasing to 0.9 per thousand at four hours, 3.1 per thousand at two hours and 11 per thousand at 40 minutes. Newby(27) suggests a benefit of 0.6 per thousand fewer deaths for longer time delays (over six hours), and a maximal benefit from the 20 minute advantage of 4-5 per thousand in the 2-4 hour delay time window. If instead we prefer the 5-6 minute estimate of timing advantage for bolus-administered drugs, then the quoted incremental improvements in mortality should be divided by four. On this basis we conclude that the proposed gains in health outcomes from faster administration of bolus drugs in the in-hospital context are generally very small, regardless of the chosen relationship between mortality reduction and time delay from onset of symptoms.

A further related issue may be whether the speed of onset of thrombolysis for a bolus product may be faster than for an infusion, and manifest by higher coronary artery patency rates. This is not considered separately here since any such benefit should be present implicitly in clinical efficacy in comparative clinical trials, and any additional allowance would amount to double counting.

6.7.4 Comparative efficacy

As described in the chapter on clinical evidence, it is difficult to rank the four drugs in terms of their relative effects on mortality and morbidity. In particular there are no direct head-to-head trials involving reteplase and tenecteplase. Attempts to estimate differences between these two drugs rely on inference from trials where each is compared to alteplase, and inferences on such a basis may not be reliable. As mentioned above, Roche claim that there is no basis to assume any meaningful difference between the four products on mortality, whereas Boehringer Ingelheim hold that tenecteplase and alteplase yield similar benefits, but that reteplase is significantly less efficacious. In the absence of any basis in evidence to choose between these positions we are obliged to evaluate the consequences of each on overall cost-effectiveness to assess the impact of this uncertainty on the relative ranking of the drugs.

6.7.5 Short-term adverse events and long-term sequelae of acute myocardial infarction

A range of adverse events may occur in the hours and days immediately following an acute myocardial infarction. Most of these are quite rare and lead either to early death or to recovery following additional emergency intervention. The impact of these on mortality is largely accounted for through 30-35 day mortality rates, but the additional costs incurred must be explicitly calculated where drugs differ in their adverse events profile. Table 21 summarises the short-term adverse events included in either model, and the rates assumed for each product.

Both company submissions cite GUSTO I & III and ASSENT-2 as sources for their figures. Despite this apparent commonality, both definitions and parameter values derived do not generally correspond. Only Boehringer Ingelheim provide any details of the manner of derivation of their figures: those for alteplase and streptokinase are obtained directly from GUSTO I, tenecteplase figures for haemorrhagic strokes (directly) and serious bleeding and reinfarctions (indirectly) are obtained from ASSENT-2, with all other figures assumed equal to GUSTO I rates for alteplase. Some figures in the Roche submission can be traced directly to GUSTO III, but others are not readily verified. The most significant discrepancies evident in Table 21 relate to episodes of bleeding, and to incidence of congestive heart failure. Both submissions therefore appear to be selective in their choice of adverse drug effects and corresponding parameter values.

Table 21: Incidence Rates of adverse events assumed in submitted models

	Streptokinase		Alteplase		Reteplase		Tenecteplase	
Short-term adverse event	Roche	Boehringer Ingelheim	Roche	Boehringer Ingelheim	Roche	Boehringer Ingelheim	Roche	Boehringer Ingelheim
Bleeding requiring transfusions	8.43%	12.90%	6.20%	11.10%	5.90%	11.10%	**4.86%**	**8.66%**
Re-infarction	-	**3.71%**	-	4.00%	-	4.00%	-	4.32%
Hypotension	22.25%	-	19.50%	-	20.60%	-	**19.26%**	-
Cardiogenic shock	5.87%	-	4.40%	-	4.60%	-	**4.29%**	-
Tamponade or cardiac rupture	0.90%	-	0.90%	-	0.80%	-	**0.77%**	-
Asystole	4.20%	-	4.20%	-	4.20%	-	4.20%	-
Anaphylaxis	0.09%	-	0.06%	-	0.05%	-	**0.03%**	-
Pulmonary embolism	0.13%	-	**0.10%**	-	**0.10%**	-	0.23%	-
Events with possible long-term sequelae	Roche	Boehringer Ingelheim	Roche	Boehringer Ingelheim	Roche	Boehringer Ingelheim	Roche	Boehringer Ingelheim
Congestive heart failure	19.17%	15.39%	17.50%	13.50%	**17.20%**	13.50%	**17.20%**	**11.75%**
Intra-cranial haemorrhage	-	**0.58%**	-	0.80%	-	0.80%	-	0.80%
Ischaemic stroke	-	**0.71%**	-	0.75%	-	0.75%	-	0.75%
All strokes	**1.33%**	**1.29%**	1.80%	1.55%	1.60%	1.55%	1.93%	1.55%

Bold = best performing product for each model/event

6.7.6 Long term effects of thrombolysis

Two conditions (disabling stroke and congestive heart failure) have enduring consequences which persist and tend to worsen throughout the remaining lifetime of sufferers, and which adversely affect future risk of further cardiac events, the costs of health and social care, and the patient's quality of life. Potentially, small differences in incidence of these conditions among survivors of AMI could lead to substantial differences in both costs and outcomes, and it is therefore important to assess carefully how these conditions are treated in the two submitted models.

Stroke

In the Roche model, stroke is treated in an identical manner to all other adverse events. The probability of a patient suffering a stroke is related only to an additional treatment cost, and has no impact on outcomes in the long-term. No attempt is made to assess the proportion of stroke patients left with significant disability, or to consider whether this alters their life expectancy or quality (utility) of life. This is a surprising omission in view of the claimed superiority of reteplase over both alteplase and tenecteplase concerning stroke incidence. Since disabling stroke is known to be associated with a generally poor prognosis and reduced longevity, the Roche approach to modelling stroke is clearly unsatisfactory.

The Boehringer Ingelheim model estimates the numbers of patients surviving with disabling haemorrhagic and ischaemic strokes, which are used to apply appropriate utility values to survival for these patients. Long-term mortality does not appear to be adjusted for such patients.

Congestive Heart Failure (CHF)

As in the case of stroke, the Roche model includes CHF only in a very basic manner, as another short-term adverse event. No adjustments are made to future mortality risks, nor are costs augmented to reflect additional therapies or hospital admissions consequent on the presence of CHF.

By contrast, the Boehringer Ingelheim model includes a facility to reflect differential mortality risks between those with and without CHF, projected out to 10 years. In the submission, three options are presented based on assuming different impacts of CHF on survival. Costs of long-term treatment are also included, separately for patients with and without CHF.

6.7.7 Utility Values

The application of health-related utility values to differences in life expectancy enables calculation of incremental differences in quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) as a common currency of comparison between different uses of scarce health service resources. The utility values used in the models differ, reflecting the underlying assumptions of the modellers.

The Roche model includes utility only as a common post-analysis adjustment factor (multiplied by 0.7) applied without discrimination to all changes in life expectancy, regardless of the health state of the patient, based on a single reference from 1988. As

a result, utility in the Roche model has no effect on ICERs beyond a general rescaling. This approach is consistent with the view that surviving AMI does not lead to any long-term sequelae which in any way impact on quality of life, long-term prognosis or health or social care costs. In view of the recognised risks of stroke and heart failure associated with thrombolysis, and their well-attested consequences for patient experience and resource use, this seems to be an unduly optimistic assumption.

In the Boehringer Ingelheim model some differentiation is attempted between the various outcome states following recovery from AMI:

- after full recovery without any enduring sequelae, utility is assumed to be 1.0 (i.e. full health)
- a severe bleeding episode is considered (arbitrarily) to reduce utility by 5% in the index year, but have no impact thereafter
- a reinfarction is assumed to reduce the utility of all subsequent life-years by 20%
- life after suffering a stroke is also presumed to cause a continuing loss of utility of 45% for haemorrhagic strokes and 39% for ischaemic strokes

Only the assumptions about stroke utilities are supported by a reference. In addition, the modellers have introduced a user modifiable utility variable for use with patients suffering congestive heart failure (CHF) after AMI. In one reported analysis this was used to test a possible utility reduction of 5% due to CHF.

Both models assume that patients who survive AMI without long-term sequelae are in 'perfect health'. In view of the predominance of middle-aged and elderly people among these suffering AMI, this seems to be an unduly optimistic assumption. As people advance in age, there is a rise in chronic health problems of all sorts, and a general diminution in physical activity and capability, so that the utility accorded to a year of life for the typical 70 year old would normally be somewhat diminished compared to that of the typical 25 year old. This assumption has no effect on the ranking of cost-effectiveness between different thrombolytics, but may distort comparisons with ICERs calculated for other treatments in different population sub-groups.

The Boehringer Ingelheim approach to utility calculations is to be preferred to that of Roche in that it reflects the well attested negative impact on both physical, mental and social functioning of a disabling stroke. The values assumed for other conditions are less secure.

When attempting to run identical options within the two scenarios of the Boehringer Ingelheim model, we found that the QALY calculations did not yield identical results. Having traced the sources of this anomaly, we have corrected some errors in the model logic - as a result in some cases the results obtained differ slightly from those included in the Boehringer Ingelheim submission.

6.7.8 Costing issues

Drug & Administration Costs

A central issue to determining comparative cost-effectiveness between the different products is the ascertainment of accurate estimates on the cost of the drugs and their administration. At first sight this should be a straightforward calculation, but in practice an examination of the two models and supporting text reveals subtle differences which result in important variations in the cost differences (the important parameter).

Roche begin with standard Monthly Index of Medical Specialties (MIMS) list prices, assuming the two available dosages of tenecteplase are used in equal proportions (50:50). To these are added the cost of an infusion pump. Infusion pumps are required for the administration of streptokinase and alteplase and for the heparin infusions associated with alteplase, reteplase and tenecteplase. In addition a 'wasted dose' cost is added, which aims to reflect that a proportion of patients suffering an early adverse event will have thrombolysis aborted, thus 'wasting' the whole dose, whereas some of these will only receive the first dose of reteplase, the cost of the second dose being 'saved'. Although this argument may have merit, the costing method employed is fallacious: the correct approach is to reduce the average cost of administering reteplase, leaving the cost of other products unchanged. In practice correcting this error has a minor impact on the result. A further element of the Roche calculations concerns the costs of additional infusions required for patients treated with alteplase. An excess cost of £96 is included for this derived from a paper by Seyedroudbari and colleagues(118) from a US costing study. From the results in the original paper, it appears that the findings in 'Table 5' of that paper have been misinterpreted - we estimate that a cost differential of just £16 is justifiable for extra consumables for this effect.

Boehringer Ingelheim also begin with the published list prices, though assuming that 60% of doses will be of the lower dose. To this is added a nursing cost for administration of the drug, which is varied according to the supposed nursing time required, which varies from 6 minutes for tenecteplase, 10 minutes for reteplase, 15 minutes for alteplase, to a maximum of 20 minutes in the case of streptokinase. We are of the opinion that these differences in nursing time, even if real (see Chapter 7), are not realisable in cash terms, since they represent small redeployments of resources which are already committed costs to the hospital, and in operational terms the appropriate opportunity cost is negligible.

Table 22 summarises the calculations using both methods, and shows the extent to which pairwise cost differences are affected by apparently small assumptions. We show both the original model calculations as well as amended versions based on the corrections/alterations identified. Finally we have prepared our own estimates based on our preferred method which combines the best elements of both. On this basis it appears that for the cost of thrombolysis drugs and their administration, tenecteplase is about £100 more expensive than both alteplase and reteplase, while streptokinase is very much less expensive than all other products.

Table 22: Calculation of thrombolysis and administration costs

Roche Method - as submitted **i**

Component	Streptokinase	Alteplase	Reteplase	Tenecteplase
Drug list price	£81.18	£600.00	£716.25	£735.00
Infusion pumps	£98.00	£196.00	£98.00	£98.00
Wasted dose	£24.00	£153.00	£96.00	£185.00
Total	£203.18	£949.00	£910.25	£1,018.00

Roche Method - amended for dose saving and source figures **ii**

Component	Streptokinase	Alteplase	Reteplase	Tenecteplase
Drug list price	£81.00	£600.00	£716.00	£735.00
Infusion consumables	£23.03	£39.04	£23.03	£23.03
Saved doses	£0.00	£0.00	-£95.62	£0.00
Total	£104.03	£639.04	£643.41	£758.03

Boehringer Ingelheim Method - as submitted **iii**

Component	Streptokinase	Alteplase	Reteplase	Tenecteplase
Drug list price	£81.00	£600.00	£716.00	£728.00
Nurse time	£12.54	£9.50	£6.35	£3.80
Total	£93.54	£609.50	£722.35	£731.80

Preferred method **iv**

Component	Streptokinase	Alteplase	Reteplase	Tenecteplase
Drug list price	£81.00	£600.00	£716.00	£728.00
Infusion consumables	£23.03	£39.04	£23.03	£23.03
Saved doses	£0.00	£0.00	-£95.62	£0.00
Total	£104.03	£639.04	£643.41	£751.03

Cost differences **v**

Comparison drugs	Roche method		Boehringer Ingelheim method		**Preferred method**
	Original	Amended	Original	Amended	
Alteplase - Streptokinase	£745.82	£535.01	£515.96	£519.00	£535.01
Reteplase - Streptokinase	£707.07	£539.38	£628.81	£635.00	£539.38
Tenecteplase - Streptokinase	£814.82	£654.00	£638.26	£647.00	£647.00
Reteplase - Alteplase	-£38.75	£4.37	£112.85	£116.00	£4.37
Tenecteplase - Alteplase	£69.00	£118.99	£122.30	£128.00	£111.99
Tenecteplase - Reteplase	£107.75	£114.62	£9.45	£12.00	£107.62

Adverse event costs

In the Roche model a very simple method is adopted to costing adverse events. A list of ten adverse events is presented with an estimated incidence rate for each (see Table 21). The incidence rates are summed and the expected number of events is estimated from this total and costed at a single average cost of £2,000 per adverse event. Not only does this approach obscure differences between the adverse event profiles of the various thrombolytics, it also confuses events with short and long-term consequences. In particular, patients who suffer a disabling stroke or develop congestive heart failure are accorded only a single additional health cost, ignoring altogether the heavy and continuing long-term health and social care costs of these serious conditions. For

these reasons we consider the Roche model seriously deficient in this aspect of costing care.

The Boehringer Ingelheim model is much more detailed in dealing with adverse events. The costing model for the immediate AMI event can be expressed in terms of the following equation:

Cost of AMI hospital treatment (excluding thrombolysis) per patient

=	£1940.60	
-	£102.10	if patient dies
+	£6720.45	if suffering intra-cranial haemorrhage
+	£4423.98	if suffering ischaemic stroke
+	£3833.76	if suffering reinfarction
+	£1184.36	if suffering from major bleeding

Other adverse events occurring within the index hospital episode are implicitly costed by inclusion within the basic cost.

Long-term care for surviving patients is costed as the sum of two components:

- patients who have suffered a stroke, and not fully recovered incur health costs of £824 per annum (pa) if not disabled, and £10632 pa if disabled;
- patients who do not have CHF cost £2356.56 pa in their first year, and £1144.50 pa thereafter;
- patients who do have CHF cost £4134.70 pa in their first year, and £2337.42 pa thereafter.

Although some elements of this costing structure may be disputable, the overall impression is of credible costs reasonably well reflecting the main short and long-term drivers of health care cost.

6.7.9 Defining a Preferred Baseline

On the basis of the foregoing findings and review of available evidence, a preferred set of assumptions and parameter values was assembled, to establish a consistent baseline from which to assess relative cost-effectiveness, as set out below:

Thrombolysis drugs and administration

The net costs of thrombolytics and their administration are as set out in the 'preferred method' of Table 22.

Long-term life expectancy

A basic mean life expectancy of AMI survivors of 8.0 years is assumed (consistent with the default assumption in the Boehringer Ingelheim model, based on analysis of Capewell's results.(119)

Adverse events and 30-day mortality

Table 23 summarises the assumed outcome values, based on combining the results of GUSTO I & III and ASSENT-2 to preserve relativities between agents for each

outcome variable. The one area of contention concerns the estimation of episodes of 'major bleeding'. There is no consistency between the various trials in defining a 'major bleed', so that values are reported varying from under 1% of patients to more than 12%. Clearly, these are not comparable figures, and so we have arbitrarily adopted a rate of 12.25% for streptokinase and adjusted all other rates pro-rata to this, to preserve relativities.

To check the impact of this assumption with regard to bleeding rate, the analysis was rerun utilising a rate of 1% for streptokinase and that for the other drugs altered pro rata (data not shown). Although using such a rate slightly increased the apparent cost-effectiveness of thrombolytic therapy as a whole, it had an insignificant impact on the comparative cost-effectiveness of each individual drug.

Details of the derivation of outcome estimates used in preferred method are shown in Appendix X.

Table 23: Outcome values for preferred baseline

	30-day mortality	**Strokes (all kinds)**	**Major bleed**	**Re-infarction**	**CHF**
Streptokinase	7.65%	1.37%	1.11%	3.78%	18.00%
Alteplase	6.60%	1.63%	0.90%	4.07%	16.00%
Reteplase	6.82%	1.49%	0.71%	4.06%	15.73%
Tenecteplase	6.64%	1.75%	0.71%	4.39%	13.94%

* Congestive Heart Failure

6.7.10 Cost-effectiveness comparisons

To evaluate the relative cost effectiveness of the different drugs, we conducted economic modelling. Rather than develop a wholly new model, we chose to introduce the above key values into the two submitted models (after correction of any logic errors detected). We also introduced variants of the most contentious parameters as proposed in the company submissions, in order to test the sensitivity of the cost-effectiveness results to the interpretations of evidence most favourable to the various products (Table 24). By this means we have incorporated the alternative positions regarding the equivalence/non-equivalence of efficacy for reteplase, alteplase and tenecteplase as described earlier in this report. The findings are summarised in Table 25 in terms of incremental changes in total costs and in Quality Adjusted Life-Years (QALYs), relative to streptokinase as the current service comparator. Where appropriate, Incremental Cost-Effectiveness Ratios are calculated.

The relationship between incremental costs and incremental QALYs is shown graphically in Figure 3 (using the Boehringer model) and Figure 4 (using the Roche model). In both cases, streptokinase is used as the comparator drug with the additional costs and QALYs associated with treatment with alteplase (A), reteplase (R) and tenecteplase (T) being plotted on the graph. The results are provided for each of the three sets of assumptions (our 'preferred' assumptions, the assumptions used in the Roche model and the assumptions used in the Boehringer model) used in our modelling process. For illustrative purposes, the slope of the relationship between the

incremental cost-effectiveness of alteplase and the different set of assumptions employed is emphasised on each figure.

These figures emphasise two main factors. First, the differences in benefits in QALYs between any of the new drugs and streptokinase are small (less than 0.1 QALY over 10 years), while the difference in cost between streptokinase and the newer drugs is substantial. This means that the variability in incremental cost-effectiveness estimates is related to variations in cost far more than to variations in outcome. Secondly, the comparative position of the newer drugs show no consistency: as the assumptions behind each model changes, so too does the apparent comparative cost-effectiveness of each drug. Again, this emphasises the comparatively small and inconsistent variation in outcome derived from each drug depending on the assumptions, but the primacy of cost in determining comparative cost-effectiveness.

Although the majority of previous analyses have focussed on cost per life year gained as an outcome measure, the industry submissions comply with NICE requirements by estimating incremental cost per QALY. As this incorporates estimates of the impact of treatment on both the quality and quantity of life experienced by patients, our reanalysis of the models concentrates entirely on this outcome measure. The utility adjustments underlying the QALY calculation were entirely derived from the Boehringer Ingelheim and Roche submissions. Both models assume that all patients are in perfect health before AMI (quality adjustment of 1.0). Given the age and co-morbities associated with many such patients, this is probably an overestimate. This may overstate the number of QALYs gained through thrombolytic therapy and understate the true incremental cost per QALY. While this implies that the analysis may overstate the true cost-effectiveness of thrombolysis, it will not significantly alter the comparative cost-effectiveness exhibited by each individual drug.

Table 24: Outcome values for Variant Analyses

Outcomes:	**30-day mortality**	**Strokes (all kinds)**	**Major bleed**	**Reinfarction**	**CHF**
Roche assumptions:					
Streptokinase	*7.37%*	1.33%	8.43%	*3.75%*	19.17%
Alteplase	*6.76%*	1.80%	6.20%	*4.04%*	17.50%
Reteplase	*6.98%*	1.60%	5.90%	*4.04%*	17.20%
Tenecteplase	*6.80%*	1.93%	4.86%	*4.36%*	17.20%
Boehringer Ingelheim assumptions:					
Streptokinase	7.29%	1.29%	12.90%	3.71%	17.87%
Alteplase	6.10%	1.55%	11.10%	4.00%	15.67%
Reteplase	6.28%	1.55%	11.10%	4.00%	15.67%
Tenecteplase	6.10%	1.55%	8.66%	4.32%	13.64%

Italics = unchanged from Preferred Baseline

In all cases we see that a consistent picture emerges: differences in discounted QALYs for the four drugs used in a hospital setting are very small (less than 0.1 compared to streptokinase, equivalent to less than 1.2% of baseline expected QALYs

in the Boehringer Ingelheim model). Variations in discounted costs are also small with a maximum difference from streptokinase of £580. In general, it is evident that these model-generated cost differences are of the same order of magnitude as the pairwise differences in the costs of thrombolysis and its administration. This has implications for the robustness of rankings of cost-effectiveness for the four thrombolytic agents, in that the most important determining parameters are the relative prices of the drugs - small changes in these differences can easily alter model rankings of alteplase and the two bolus products. The most reliable result is that streptokinase is much cheaper than all other drugs, and is only a little less effective (as measured by discounted QALYs). In practice, streptokinase is currently only used as part of a protocol including alteplase as an alternative where streptokinase is contra-indicated.

These exemplications of economic models do not take account of claimed benefits from faster administration of the bolus agents over infused agents. However, we can readily estimate the impact of the assumed 15-20 minute reduction in time to treatment: assuming an overall life expectancy for survivors of about eight years, and a mean baseline delay to treatment of three hours, we calculate that the bolus agents should show additional discounted QALYs of between 0.003 and 0.014 depending on our choice of delay model (FTT,(28) EMIP,(83) Boersma(26) or Newby(27)). In most scenarios this has the effect of narrowing the gap in outcomes between the bolus agents and alteplase, further confirming these conclusions.

Of course, differences in time to angiographic reperfusion after drug administration are already included in measures of effect of differing drugs, and must not be double counted.

The results shown on Table 25 for the Boehringer Ingelheim model are based on the option with no assumption of differential relative risk of mortality for patients with heart failure. As the use of such differentials has the effect of narrowing differences in incremental cost-effectiveness ratios, this assumption is conservative.

It is evident that the claimed differences in efficacy and adverse event profiles for reteplase and tenecteplase do not translate into any consistent and reliable difference in cost-effectiveness. The largest and most influential source of these variations appears to be the relative prices of the competing agents. We therefore conclude that any choice between the two is largely governed by their relative local prices at the time of acquisition.

The final cost/QALY for the newer drugs compared to streptokinase ranges from £11,000 to £17,000 using our preferred assumptions. For broad comparison only, a headline figure for the cost effectiveness of streptokinase compared to no thrombolysis would be of the order of £800-£1,000/QALY.

Table 25: Cost-Effectiveness results using submitted models

Using Boehringer-Ingelheim model

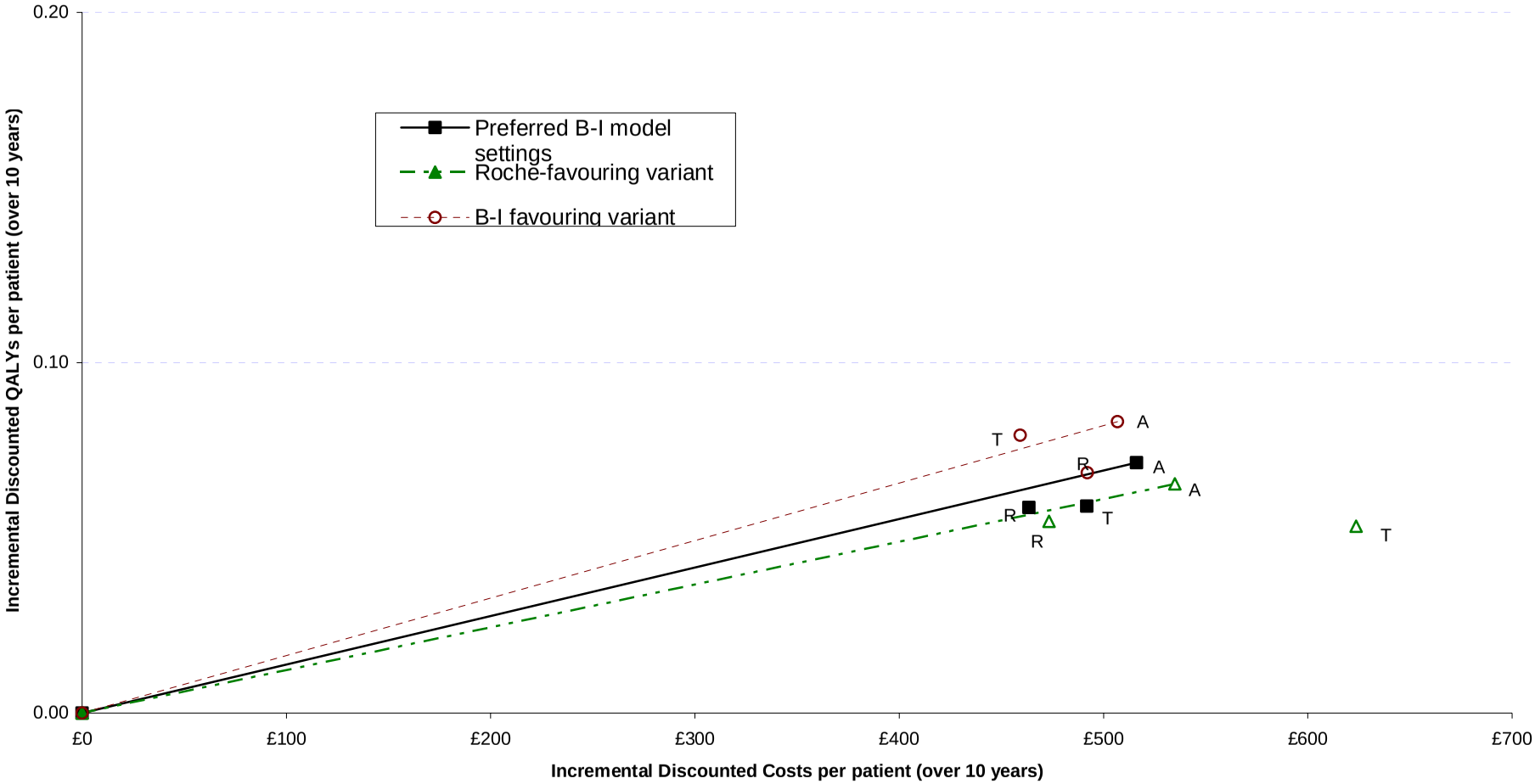
	Scenario	Streptokinase	Alteplase	Tenecteplase	Reteplase
Total discounted cost	Original model	£11,208.65	£11,672.23	£11,646.47	£11,772.97
	Preferred	£11,105.88	£11,621.98	£11,597.63	£11,569.35
	Roche variant	£11,272.02	£11,806.89	£11,895.68	£11,745.38
	B-I variant	£11,178.67	£11,685.57	£11,637.93	£11,670.74
Total discounted QALYs	Original model	7.44	7.50	7.51	7.50
	Preferred	7.37	7.44	7.43	7.43
	Roche variant	7.37	7.44	7.42	7.43
	B-I variant	7.40	7.48	7.48	7.47
Incremental cost vs Streptokinase	Original model	-	£463.58	£437.82	£564.32
	Preferred	-	£516.10	£491.75	£463.47
	Roche variant	-	£534.87	£623.66	£473.36
	B-I variant	-	£506.90	£459.26	£492.07
Incremental QALYs vs Streptokinase	Original model	-	0.06	0.07	0.06
	Preferred	-	0.07	0.06	0.06
	Roche variant	-	0.07	0.05	0.05
	B-I variant	-	0.08	0.08	0.07
ICER vs Streptokinase	Original model	-	£7,294	£5,892	£9,215
	Preferred	-	£7,219	£8,321	£7,893
	Roche variant	-	£8,176	£11,702	£8,646
	B-I variant	-	£6,095	£5,793	£7,172

Using Roche model

	Scenario	Streptokinase	Alteplase	Tenecteplase	Reteplase
Total discounted cost	Original model	£1,308.85	£1,801.20	£1,802.57	£1,727.63
	Preferred	£1,064.89	£1,504.84	£1,575.71	£1,517.26
	Roche variant	£1,233.82	£1,644.24	£1,727.59	£1,652.66
	B-I variant	£1,296.49	£1,700.64	£1,724.71	£1,725.06
Total discounted QALYs	Original model	4.93	4.93	4.93	4.93
	Preferred	4.93	4.99	4.98	4.97
	Roche variant	4.93	4.99	4.98	4.97
	B-I variant	4.93	4.99	4.99	4.98
Incremental cost vs Streptokinase	Original model	-	£492.35	£493.72	£418.78
	Preferred	-	£439.95	£510.82	£452.37
	Roche variant	-	£410.42	£493.78	£418.84
	B-I variant	-	£404.15	£428.22	£428.57
Incremental QALYs vs Streptokinase	Original model	-	0.000	0.437	0.437
	Preferred	-	0.056	0.054	0.044
	Roche variant	-	0.056	0.054	0.044
	B-I variant	-	0.063	0.063	0.054
ICER vs Streptokinase	Original model	-	N/A	£1,130	£959
	Preferred	-	£7,878	£9,509	£10,247
	Roche variant	-	£7,349	£9,192	£9,488
	B-I variant	-	£6,385	£6,766	£7,978

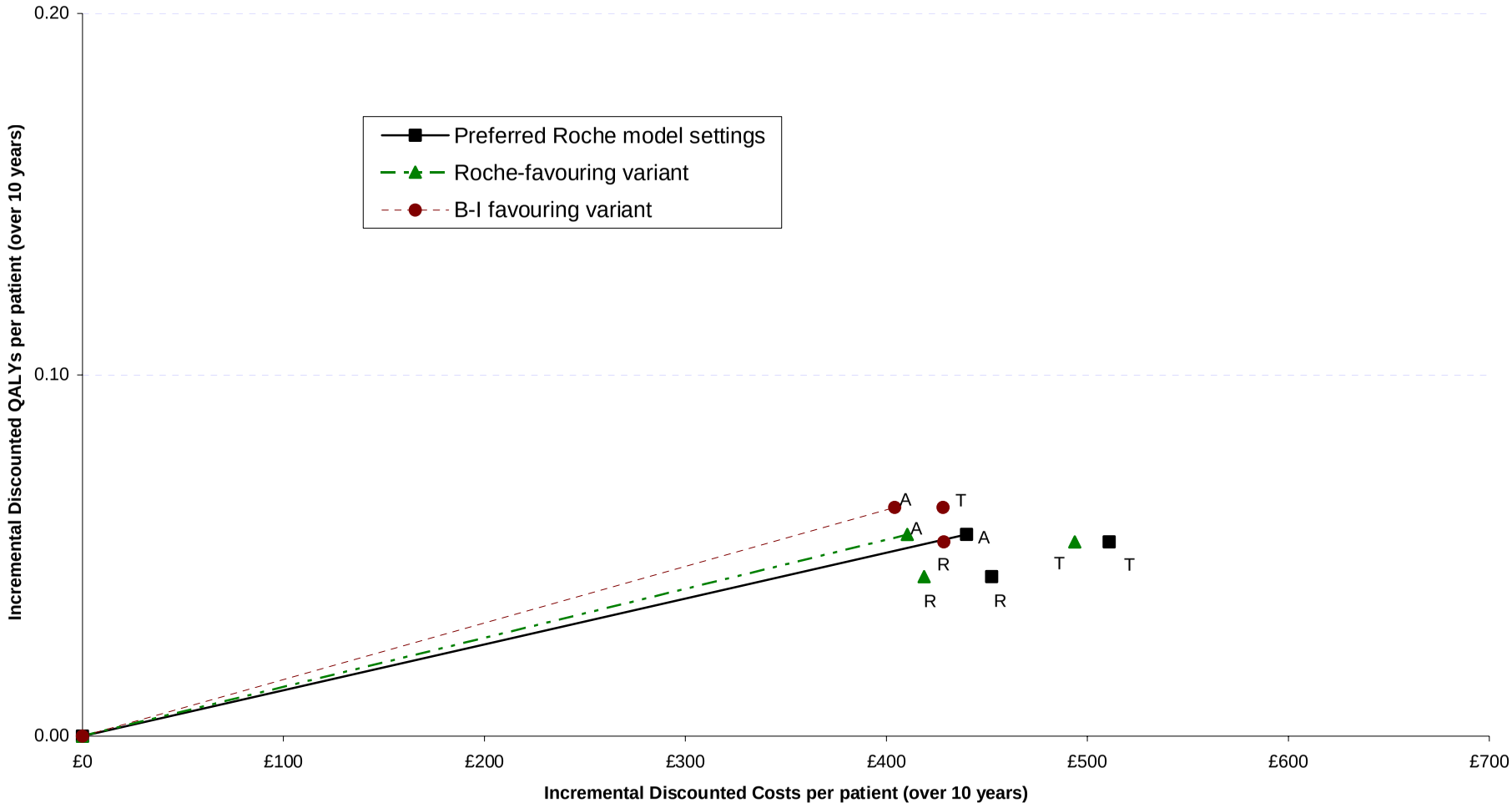
N.B. 'Original model' uses models corrected for logic and factual errors.

Figure 3: Incremental Costs and Quality-Adjusted Life Years (compared to Streptokinase) using Boehringer Ingelheim model



Referent scenario (at origin) is streptokinase. Alternatives represented as A = Accelerated Alteplase, R = Reteplase, T = Tenecteplase

Figure 4: Incremental Costs and Quality-Adjusted Life Years (compared to Streptokinase) using Roche model



Referent scenario (at origin) is streptokinase. Alternatives represented as A = Accelerated Alteplase, R = Reteplase, T = Tenecteplase

6.7.11 Pre-hospital thrombolysis

Since only the two bolus-administered drugs are considered suitable for use in a community setting, and since we may assume that the choice of which drugs has no effect on other aspects of care or outcome prior to or following hospital admission, then the previous analysis in the hospital context applies equally to pre-hospital thrombolysis. The only basis for moving away from this position would be if the time to administer the drug was significantly different between reteplase and tenecteplase in the community, but we have no basis on which to base such a presumption. We are therefore obliged to conclude that it is not possible to distinguish between the two bolus-administered products on grounds of cost-effectiveness when used for pre-hospital thrombolysis.

If the infusion products were to be used in pre-hospital thrombolysis, their cost-effectiveness would be similarly enhanced, but the relative ranking of the drugs would be unchanged.

6.8 Comparison with literature

Perhaps the most reliable conclusion in the literature review around the cost effectiveness of streptokinase compared to alteplase was that of Mark and colleagues,(106) which quotes an incremental cost of $36,000/QALY. We have criticised this study not least for its failure to consider settings other than the US. However the study of Lorenzoni and colleagues(110) compares cost effectiveness in the UK and the US, and finds that cost per QALY in the UK is approximately half that in the US. If this is correct, it would imply a UK cost per QALY in 1993 of $18,000 or approximately £13,000 using 2002 exchange rates. If a rate of inflation of 3% is allowed, this becomes £16,500.

It is not possible to draw direct comparisons between these figures from the Marks model extrapolated with several assumptions to the UK in 2002, and our figure of £11,000 to 17,000 per QALY, which we have derived in different models, using different assumptions and costings.
Nevertheless, the broad similarity of these figures tend to validate
the methodologies used in both studies

6.9 Conclusion

Given the general comparability of the drugs, any attempt to identify a comparative advantage economically for any individual drug would require large scale and robust clinical and economic analyses to be undertaken within the specific context of the NHS. With a few notable exceptions, the general quality of existing economic analyses undertaken in this area has been disappointing and largely focussed on evaluating cost-effectiveness in healthcare environments outside the NHS. Without such evidence to differentiate the cost-effectiveness analysis, the variations in outcome are insufficient to provide a conclusive result. The only consistent conclusion is that streptokinase is the most cost effective drug, judged by virtue of its lower price.

From the economic perspective, the variations in outcome between the individual drugs are so small that the economic modelling finds it difficult to come to any definitive conclusion. The case for a differential between each of the newer drugs compared to streptoinase is therefore uncertain. Supposed advantages presented in the industry submissions relate to comparatively minor variations in efficacy or minor improvements in aspects of the side-effect profile associated with each individual drug. Given such similarity in outcome, cost-effectiveness becomes largely determined by the comparative level of resources required for each drug. This largely comes down to the cost of the drug since other differences in costs of administration are small.

Considering the scenarios put forward for appraisal at the end of Section 4:

Is streptokinase as effective as alteplase (and hence other drugs)?
This is considered in the Roche model. Put simply, if streptokinase is as effective as other drugs, then its lower costs means that it dominates all other therapies.

Is reteplase equal to alteplase (and hence tenecteplase)?
In our preferred model we have assumed that reteplase is largely similar to alteplase, based on the results of GUSTO III. The ICER for reteplase compared to streptokinase then comes out worse than alteplase but better than tenecteplase – largely as a result of its purchase price. However differences are small.

In these circumstances, drug choice becomes largely determined by clinical or pragmatic preference, and by the purchase price of the individual drugs. This close relationship between acquisition price and cost-effectiveness presents a challenge to both NHS purchasers and the pharmaceutical companies involved in the manufacture of thrombolytics.

7. IMPLEMENTATION

7.1 Introduction

The context of this review has been to separate and differentiate between the provision of early thrombolysis for AMI by clinical setting (hospital or pre-hospital). Although there are physical reasons (ease of administration, ability to deal with adverse events) that mean that the delivery of treatment may be different in the pre-hospital setting there is no reason to believe that the physiological action of the agents will differ between settings.

It is not within the remit of this review to evaluate the effectiveness of pre-hospital thrombolysis or strategies related to the delivery of early thrombolysis. However, the economic analysis as presented earlier makes an assumption that there currently exist, in both settings, the mechanisms necessary to deliver care. Although these mechanisms are in place in the hospital setting, audit data indicate an inability of hospitals to meet prescribed 'door to needle' time. In the pre-hospital setting there are issues related to the appropriate model of care to be adopted to meet these standards, as well as the equipment and further training of individuals to provide the care.

The discussion in the first part of this chapter will focus on key components related to implementation of change: time to thrombolysis and selection of drug to be used. It goes on to propose three models of care that might be considered in relation to change in practice and to meeting the nationally established treatment criteria.

7.2 Time to thrombolysis

There is no debate regarding the fact that to be effective, thrombolytic therapy needs to be provided early. However, as pointed out in the previous chapter, extensive debate exists regarding the steepness of the time/treatment effectiveness curve. The various aspects of this debate have been outlined earlier and will not be repeated here. It is safe to assume that the debate will continue.

What discussion regarding the time window fails to address is the fact that the majority of people suffering from AMI do not contact medical services within that first 'golden' hour. Table 26 provides the data extracted from the RCTs of pre-hospital trials and indicates the recorded times from symptom onset to call for help.

Table 26: Time from symptom onset to call for help

Study	Contact	Time
Castaigne(82)	Mobile care unit	Average time 65 min
GREAT(84)	GP calls	Median (range) 45 min (0-340)
EMIP(83)	Ambulance	Median (range) 75 min (70-76)
MITI(89)	911/ambulance	Median (range) Pre-hosp 27 min (30-60) Hospital 28 min (11-58)
Schofer(88)	Ambulance	Mean (SD) Pre-hosp 52 min (47) Hospital 63 min (46)

As can be easily seen, with the exception of the MITI(89)study conducted in a city that has an active HeartSaver/Community awareness programme and excellent ambulance services including advanced cardiac life support since the early 1980's, the normal call time is close to an hour after the onset of symptoms. Translated into clinical practice this means that, with the exception of patients with sudden and severe symptoms (excruciating chest pain, shortness of breath, or collapse), it will be uncommon to assess patients in the first hour after the onset of their symptoms. It is not the purpose of this review to examine this issue but the general consensus of opinion is that we have not yet identified a public health initiative to change this health seeking behaviour in any sustainable way.

We therefore concentrate our efforts on areas we believe we can change – the delivery of care once the patient has sought treatment. The effectiveness of early thrombolysis has been known for some time. However, it has been the institutionalisation of the NSF (30) for Coronary Heart Disease and the NHS Plan(31) that has provided the impetus for health care professionals and health care managers to take action and implement change within health care settings to decrease what has been called 'time to needle'. This is indeed no small task and some have been so bold as to say that the goals as set are not realistic (Anonymous - at request of sources, personal communications: 2002).

However, there are a number of things that we do know about ability to impact change in time to delivery of treatment. We have evidence that we can decrease time to treatment with improved outcome in the pre-hospital setting. The meta-analysis by Morrison(90) has shown us that time to treatment can be decreased by approximately 58 minutes.

Interestingly, two pre-hospital trials (83, 89) also showed that during the trial of pre-hospital thrombolysis door to needle time for patients treated in hospital was decreased. MITI(89) showed that when they compared trial patients treated in hospital to patients who had arrived in the emergency department who were not part of the trial that time to needle for trial patients was much shorter (20 minutes versus 60 minutes).

In the UK we have examples of programmes that have been able to successfully decrease 'door to needle' time within the hospital setting. Initiatives in the early 1990s in Brighton (120) showed this was possible but that maintaining these improved treatment delivery times was difficult. When key individuals involved in the initiative were no longer involved 'door to needle' times increased (Chamberlain D, personal communication, 2002). Other initiatives, such as those implemented in Scotland(121) have successfully fast tracked patients to the CCU while others have moved treatment out of the CCU into the A&E department.

In the GREAT study (84) pre-hospital thrombolysis was administered by GPs in Scotland. After the GREAT study was completed, the rate of use of pre-hospital thrombolysis declined rapidly among GPs in Grampian. However a sustained effort of education and audit has renewed and maintained interest in this treatment.

Therefore, in terms of all time to treatment we know that providing treatment early leads to improved outcomes. It is unclear (depending on which specific time/effect model you accept) the exact impact that the minutes saved will have on morbidity and mortality. We know that we do not have an effective method for decreasing the time it takes for patients experiencing AMI to contact medical services. However, we do know that we can decrease the time from when they do make contact until they receive treatment.

7.3 Choice of drug

The evidence related to the clinical effectiveness of available drugs was presented in Chapter 4 and point estimates of effectiveness have been calculated as a part of the economic analysis in Chapter 6. Assuming 'relatively' similar effectiveness and adverse events, the choice of drug is then dependent on cost and ease of administration. The information presented here has been gathered from arguments within the literature and from clinical experts familiar with the delivery of thrombolytic treatment in both hospital and pre-hospital settings.

On the basis of cost and cost effectiveness streptokinase would be the drug of choice. In addition, this drug can be given by paramedics under the terms of the Medicines Act without any further arrangements of patient group directions and requires no pre-hospital heparin administration. However, given the problem of antigenicity, any protocol for its use would be required to include a second drug choice for patients who had previously received treatment with streptokinase. In terms of cost, all of the other alternatives are similarly priced.

The issues regarding ease of administration are less straightforward. The issues basically revolve around whether a drug is delivered as a bolus or an infusion, whether a standard dose or individually calculated dose is required and the adjunct treatments required (e.g. heparin).

Infusion versus bolus

Within the hospital setting mechanisms are already in place for the delivery of infusion medications. The uncertainty within the pre-hospital setting and the logistics of using additional equipment such as infusion pumps means that these are issues to be addressed. Our clinical experts were reluctant to consider using infusions in

patients travelling to hospital. In part this is because of inconvenience, including the storage of infusion bags, costs of infusion pumps, and also because of potential hazards problems (quoting risks of disconnecting infusions, and Medical Devices Agency concerns about difficulties with infusion pumps).

Delays due to setting up an infusion were also mentioned. We have limited evidence to compare the time required in either clinical setting for the preparation of infusions versus bolus administration of drugs. The MITI(89) studied reported an extra 15 minutes on scene to set up an alteplase infusion but have no comparator. Two company submissions suggest a 15 minute saving with bolus delivery of treatment. Seydroudbari and collegues(118) in a review of 500 patient records measured a decrease in time to treatment for reteplase over alteplase of 34 versus 51 minutes. However, 21 minutes of this delay in alteplase involved an increased amount of time to make a decision to treat patients who received alteplase, leaving the time for administration almost equal. Consultation with hospital and pre-hospital health care providers indicates, that provision of new equipment such as infusion pumps means that the difference in time to needle between infusion drugs and bolus drugs is close to negligible.

Our experts also cast doubt on whether bolus would be more than 5 minutes faster than infusion. This makes suggestions that bolus products will help hospitals meet their NSF targets less likely. Rather it implies that reorganisation of the form seen in the MITI and EMIP trials and in UK NHS practice will be more important in decreasing time to treatment than choice of drug

Trials of pre-hospital thrombolysis have successfully used drugs that were delivered by infusion. However, these trials took place prior to the availability of drugs delivered by bolus. Centres that have previously used infusions in the pre-hospital setting are currently evaluating the use of bolus reteplase.(122) Anecdotal reports also indicate a view among thrombolysis nurses that the inconvenience of providing the infusion is balanced by the ability to stop delivery of the drug should adverse events occur.

Drug dosage/Adjunct treatment

Dosages for infusion drugs are somewhat complicated but well established. Dosage for the two bolus drugs each have their own complications. In addition, each calls for the pre-administration of an IV bolus of heparin.

Reteplase is given as *'a slow infusion'* over 2 minutes. Its practicality as a drug for pre-hospital thrombolysis is demonstrated by the successes of its use by East Midlands and Staffordshire Ambulance Services NHS Trusts and also by the ER TIMI 19 (101) study, Swedish (100) and Dutch (122, 123) studies. Reteplase is given as 2 doses separated by 30 minutes. In practice, we have no data to indicate how frequently the second dose would need to be administered by the ambulance service. There has also been discussion surrounding delay in administration of the second dose if the patient is re-assessed upon arrival in hospital.

Reteplase is also administered with heparin. A bolus of heparin is administered at the time of the first bolus and an infusion started after the second. This means that the

infusion is administered in hospital rather than in the ambulance and avoids the need for infusion in the pre-hospital setting.

It has been argued in a company submission that reteplase is more difficult to give than tenecteplase because of its incompatibility with heparin. This would seem to require two intravenous lines (one for each drug), which might be difficult to secure in very ill patients. In practice where this is not readily possible, the ambulance services use one line, flushing the line carefully between administration of the two drugs . This is standard clinical practice and is consistent with recommendations in the drug company literature. This therefore does not seem to be a significant objection to the use of reteplase. Communication from the authors of the TIMI 19 trial indicates that the heparin bolus was given in some cases. They also encouraged the insertion of two intravenous lines but when that was not possible one line was used and flushed between drugs (Morrow D, TIMI study chairman: personal communication, 2002). The Dutch study of reteplase did not administer heparin in their pre-hospital evaluation (Lamfers E, Consultant Cardiologist, Nijmegen, The Netherlands: personal communication, 2002).

Administration of tenecteplase is by bolus injection over ten seconds and this would seem to make it eminently suitable for pre-hospital administration. However, it is followed by a heparin infusion, which makes it less suitable for pre-hospital use. A number of contacted experts felt this would mitigate against the acceptance of its use in the pre-hospital setting. However, the results of the ASSENT-3 study suggested that subcutaneous enoxaparin (which could be easily given in the pre-hospital setting) was as effective as an intravenous infusion of unfractionated heparin, although this is not yet a licensed regimen. The regimen of tenecteplase and enoxaparin in pre-hospital thrombolysis is being examined in the ASSENT-3 PLUS study. If this regimen were licensed, it would facilitate the use of tenecteplase with enoxaparin as a pre-hospital therapy. Given this option, our experts were divided – some would opt for tenecteplase, some to stay with reteplase with which they are familiar. One ambulance service has expressed a preference for tenecteplase, but does not make clear how it would deal with the issue of a heparin infusion. There is as yet little experience of tenecteplase in this setting but the ASSENT-3 Plus study should provide this.

The second issue of individualising dose is related to tenecteplase. It requires a weight adjustment of dose, based on evidence of increased bleeding with 50 mg doses in TIMI-10B(56). It has been suggested that this might lead to errors in dosing in the pre-hospital setting, but to counter this, evidence has been put forward that health professionals are good at assessing a patient's weight. The opinion of our experts were mixed, some indicating that weight estimation is easy, others indicating that estimation of weight by paramedics could lead to medication errors. We are inclined to accept that any minor errors that may occur are unlikely to be detrimental to patients.

The question of whether it is more appropriate to give thrombolysis based on patient weight or as 'a single dose fits all' is unresolved. The former approach has appeal and there exists some evidence to support it, but requires further definitive trial

evidence. This whole issue is not considered further here as it is beyond the remit of this review.

7.4 Models of care

Based on the results of the literature reviews, both clinical and economic, and discussions with experts in the field of thrombolysis, there appear to be three main models of care for the delivery of early thrombolysis. These models of care can be categorised as follows:

(i) Hospital thrombolysis
(ii) Collaborative care delivered jointly in the pre-hospital and hospital settings
(iii) Pre-hospital thrombolysis by an autonomous operator

Within each of these models there are a number of implementation options. For instance JRCALC(124) has outlined five different options of care within these. Our initial analysis identified ten distinct options. In this section we do not attempt to be exhaustive in our description but to outline key aspects that have been or need to be addressed by health care decision makers (clinicians or managers) who are attempting to implement changes in practice to decrease current time to treatment of patients with AMI.

Prior to discussing the models of care it is worth examining a small part of the history and evolution of the care of patients suffering from AMI in relation to who provides their care. A part of the current debate regarding early thrombolysis is the question of who should assess the patient, make the diagnosis and then provide the treatment. The shift of provision of care to patients experiencing AMI both in the hospital and in the community setting is not new. There is historical precedent and lessons that can be learned from the implementation of basic and then advanced cardiac life support (ACLS) first in hospital settings by physicians and then by hospital nurses and finally in the community by paramedics.

Similarly, there has been a parallel shift in the provision of thrombolytic therapy by hospital physicians to thrombolysis nurses in hospital and to paramedics and GPs in the community The debate that evolved in the 1980s is being repeated and the focus revolves around what happens to the role of the hospital doctor, or even GP when these roles are changed. This review does not enter into this debate. However, the position taken in the following discussion is that treatment should be delivered by health care professionals who are adequately trained and equipped to assess, diagnose, provide treatment and deal with any adverse events of that treatment. This may be a physician (GP), a paramedic or a nurse working in isolation or in collaboration with others.

The following section provides an overview of the models discussing issues that have been identified to decrease call to treatment time of patients with AMI. As might be expected, there are areas of overlap between the models and all focus on establishing an environment in which health care professionals are enabled to deliver the best quality care in the shortest period of time. Table 27 at the end of the section outlines strategies that have been identified to decrease call to treatment time within each of the models.

7.4.1 Hospital thrombolysis

In this model, all assessment and care is provided within the hospital setting. These could be patients who self-refer to the A&E department or are referred by their GP. Calls to the ambulance service, in this model, result in standard care and transport of the patient to hospital. On arrival, patient assessment may vary and handover in the A&E department would include basic information as designated by the Ambulance Trust for patients with symptoms of AMI. This model then would focus on the ability to decrease the time from when the patient arrives in the A&E until the patient receives treatment.

As discussed earlier reports exist that document the ability to decrease door to treatment time. More recently teams of thrombolysis nurses have been established to work within A&E departments as a strategy to decrease door to needle time. Initially a number of these initiatives were funded by pharmaceutical companies (personal communication, K. Rees). Later the roles were integrated within the hospital staffing. Thrombolysis nurses are typically CCU nurses who took on extended roles in the A&E department. Their roles and responsibilities vary with the norm being that they carry out initial assessment, communicate with medical staff and provide treatment and aftercare until patients are transferred to the CCU. No official training programme for these nurses was identified during this review.

7.4.2 Collaborative care delivered jointly in the pre-hospital and hospital setting

There are at least two options within this model. In the first instance, the responding GP or paramedic could assess the patient, perform an ECG and transmit the findings to the receiving hospital thus alerting hospital staff to the fact that they will be arriving with a patient who requires thrombolysis. The theory is that by alerting the hospital in advance they will be prepared to receive and treat the patient as soon as possible after arrival and therefore door to needle time will be decreased. In The Netherlands transmission of ECGs in advance of patient arrival were found to reduce the door to needle time from 84 to 36 minutes.(125)

In the second option of collaborative care, the patient receives thrombolysis on site. The GP or paramedic would first of all carry out an assessment of the patient. If the assessor is a GP then they could, if they chose, make a decision to thrombolyse the patient before transfer to hospital. If the assessor is a paramedic or a GP who is not equipped or comfortable with emergency diagnosis and treatment, they could perform an ECG, transmit the clinical findings and ECG readings to a receiving centre (normally the hospital to which the patient will be transferred) and receive direction regarding treatment. The patient would receive thrombolysis on site and be transferred to hospital.

Each of these options requires additional training of GPs and paramedics in assessment, conducting of ECGs, transmission of ECGs, delivery of treatment and dealing with any adverse events. Hooghoudt and colleagues(98) in The Netherlands have identified several barriers to collaborative pre-hospital thrombolysis including medical, legal and organisational difficulties. They found that the training of GPs and paramedics was time consuming, and that many purchasers question the value of pre-hospital thrombolysis given the lack of clear evidence of benefits (written before

Morrison meta-analysis). Delays in Holland at the time included hospital door to needle times of around 84 minutes.

Research in Wales has shown that paramedics can acquire the appropriate diagnostic skills to identify patients with AMI and that they already have the skills related to conducting patient assessments and delivering intravenous therapy.(126) A specialist training programme for paramedics and GPs to deliver thrombolysis has been jointly designed by JRCALC and Boehringer Ingleheim (personal communication Prof D. Chamberlain, JRCALC).

Research also conducted in Wales shows that the transtelephonic transmission of ECGs is problematic and is associated with a 25% failure rate.(126) Similar anecdotal experiences have been reported from the current evaluation study in Lancashire (Bastow P, Lancashire Ambulance Trust: personal communication, 2002) Given the advances in telecommunications, it would be hoped that these problems can be overcome.

Another problem that has a risen in both the Welsh and Lancashire research projects is the issue of who is responsible to receive the patient data and make treatment decisions (e.g. A&E dept, CCU). Neither project has solved these problems
The second issue regarding paramedic administration of thrombolytic therapy is whether or not paramedics actually feel that the provision of thrombolysis is within their remit and whether or not they will provide the treatment. A comparator is the implementation of the provision of aspirin to patients with symptoms of AMI presenting to the ambulance service. An audit carried out in the Ambulance Services of England and Wales found that the majority of services (26/35) were not collecting the data to assess implementation of this treatment. Of those that did collect data the survey found that between 15% and 75% of eligible patients were not receiving the drug.

The discussion regarding the use of pre-hospital thrombolysis by GPs has been discussed at great length in terms of the GREAT study.(84) Rawles and colleagues demonstrated that even in urban areas of one city in Scotland, the GP was the first point of medical contact in 68% of cases of suspected AMI (97% in rural areas), and so should not be lightly excluded as a possible medium for thrombolysis even in cities. (127) In this follow on to the GREAT study, rural GPs administered thrombolysis in 35% of cases at a median time of 45 minutes after onset of pain. Clearly in some areas with sufficient professional interest, additional training in resuscitation and administration of thrombolysis and provision of equipment such as defibrillators, the model of GP delivered thrombolysis may be worth pursing.

7.4.3 Pre-hospital thrombolysis by an autonomous operator

In this proposed model the delivery of thrombolysis would be totally under the remit of emergency response personnel. This might be GP or the ambulance service.

In this model the patient is assessed, diagnosed and treated on site without a secondary medical opinion. This means that GPs or paramedics would be acting autonomously in the pre-hospital setting. This model raises the same issues regarding training of GPs and paramedics as the second model with the added fact that they

require additional diagnostic skills. There have also been questions regarding legal responsibility for this care delivered in the community.

In relation to the UK it is worth noting the differences in health care providers, The majority of pre-hospital studies used either medical or nursing staff in the ambulance, or a mobile coronary care unit, neither of which is common in the NHS. American studies have used paramedics who participate in a significantly more extensive training and preparation programme than is provided in the UK. As noted earlier a training programme has been developed . This added training may allow paramedics to administer the thrombolytics with greater confidence.

This is a model favoured in Wales where telecommunication of patient information has been problematic.

7.4.4 Conclusions

There are a number of points within the call to treatment time continuum where changes can be initiated to decrease call to treatment time. The decision regarding the appropriate model of care to be adopted by individual trusts to meet the NSF standards will depend on the organisation of current care patterns, time/distance factors for transporting patients and the ability to decrease ‘door to needle’ time in the hospital setting. The synthesis of these data will allow current health care providers and decision makers to design appropriate implementation strategies to improve call to treatment time and ensure the provision of optimal and safe care for the patient.

Table 27: Implementation considerations

Time interval	Hospital model	Combined care	Pre-hospital model
Call to response	Appropriate triage in A&E Mechanism to fast track AMI patients to dedicated thrombolysis teams Rapid transfer of patients from A&E to CCU if appropriate	Ambulance availability Community rapid response teams GP call systems Improved organisation between ambulance services, GPs and community hospitals Improved communication between ambulance teams and receiving hospital	Ambulance availability Community rapid response teams GP call systems Improved organisation between ambulance services and GPs
Initial assessment	Suitably trained thrombolysis team Availability of appropriate equipment and skill	Suitably trained GPs and paramedics Availability of appropriate equipment (eg 12 lead ECG, telecommunication) and skills Access to remote ECG interpretation	Suitably trained GPs and paramedics Availability of appropriate equipment (eg 12 lead ECG) and skills
Assessment to decision	Professional on hand to make treatment decision quickly	Autonomous GP or paramedic able to transmit data or make treatment decision Professional on hand to make treatment decision quickly in hospital	Autonomous GP or paramedic able to make treatment decision
Decision to treatment	Appropriately trained individual to provide treatment, monitor results and deal with adverse events. Availability of appropriate drugs and equipment	Appropriately trained individual to provide treatment, monitor results and deal with adverse events. Availability of appropriate drugs and equipment	Appropriately trained individual to provide treatment, monitor results and deal with adverse events. Availability of appropriate drugs and equipment

7.5 Costs associated with the implementation of early thrombolysis models of care

7.5.1 Introduction

This section estimates the impact of different scenarios of the use of thrombolytic therapy on drug costs to the NHS. Significant international variations are evident in clinical preference for individual drugs. In the UK, the majority of patients receive Streptokinase whereas in the United States the majority receive t-PA. Such variations are likely to reflect the nature and level of budgetary constraints imposed on health services combined with the perceived relevance of the clinical evidence generated in support of each individual drug. In the UK, Streptokinase remains the drug of choice with newer drugs being largely reserved for patients who have previously received treatment, are allergic to Streptokinase or who, on the basis of sub-group analyses are most likely to benefit from Alteplase therapy.

7.5.2 Budget impact analysis

Introduction

The aim of the budget impact analysis is to estimate the costs associated with switching patients from one thrombolytic drug to another in both the hospital and pre-hospital setting. In order to carry out a budget impact assessment, accurate information is required concerning the comparative cost of the thrombolytic drugs, the market share for each drug and the total patient population.

7.5.3 Cost of the drugs

The following table (Table 28) presents the list prices of streptokinase (non-proprietary), alteplase (Actilyse®), reteplase (Rapilysin®) and tenecteplase (Metalyse®) as quoted in the British National Formulary (September 2001). The price of tenecteplase is based on the average cost of the 40mg (£700) and 50mg (£770) vials.

Table 28: List price of drugs

Product	BNF list price (£)
Streptokinase	80
Alteplase	600
Reteplase	716.25
Tenecteplase	735

7.5.4 Current market share

The current total market shares for each of the four thrombolytic drugs are discussed in the company submissions and are presented in the table below (Table 29). Aventis's market share is based on data from IMS DataView (CRPCU Hospital) only. Boehringer Ingelheim does not state the source of their information on market share but it was probably derived from the NAOMI database, and Roche's data on market share was is from company market research 2001. The differences between these

data are minor. The baseline budget impact analysis incorporates all of these market shares by calculating costs based on the range (minimum and maximum) of market shares presented.

Table 29: Total market share

	Total market share (%) as presented in each of the submissions		
Product	**Aventis**	**Boehringer Ingelheim**	**Roche**
Streptokinase	64.5	53	55.41
Alteplase	23	31	32.45
Reteplase	12.5	15	11.77
Tenecteplase	Not licensed	1	0.37

7.5.5 Patient population

Estimation of the incidence of AMI is difficult with reported estimates exhibiting large variability. Determining the size of the patient population for thrombolytic therapy is further complicated by variations in its criteria for use. The number of patients presenting with chest pain in whom thrombolytic therapy is used is typically determined by local treatment guidelines.

The company submissions include very different estimates of the total number of patients treated by thrombolysis as they consider different patient populations. Aventis estimate that approximately 105,000 patients per year are eligible for thrombolysis in the UK and state that only 86,500 patients actually receive thrombolysis. Boehringer Ingelheim estimate that approximately 46,000 administrations of thrombolytic agents are administered in England and Wales per annum. Roche estimate that approximately 54,400 receive thrombolysis in England.

Given these variations in the numbers of patients treated, we have carried out our budget impact analysis based on information derived from two recently published ambulance services documents (36, 126). Our estimates of numbers of patients eligible for thrombolysis and pre-hospital thrombolysis are presented in Table 30 (below) and are based on the analysis described by Woollard and colleagues.(126). Validation of the assumptions behind these figures is provided by Birkhead(23) who estimated that of patents with AMI, roughly equivalent numbers of patients (45% in each case) arrive at hospital as a consequence of an emergency call and GP referral with the remaining 10% of patients self-referring to hospital. Woolhard, writing from an ambulance service perspective, does not consider these ‘self referrals’ and we have omitted them here also.

Table 30: Assumptions made for numbers of patients who may be suitable for pre-hospital thrombolysis

Assumptions	*Numbers of patients*
Total number of emergency calls to Ambulance Services, England 2000-01	4.4 million
10% of emergency calls are to patients with chest pain	440,000
GPs refer the same number of chest pain patients as are seen by 999 calls	440,000
Subtotal	880,000
27% of patients with chest pain will have suffered from an AMI	237,600
49% are eligible for thrombolytic drugs	116,424
46% may be suitable for pre-hospital treatment	53,555

This figure of 49% of patients potentially receiving pre-hospital thrombolysis broadly agree with the industry submission from Boehringer which estimates that 55% of patients will be assessed for pre-hospital thrombolysis and approximately 35% will receive it.

This means that approximately 6% of all chest pain patients seen by the ambulance service may be eligible for pre-hospital thrombolysis (53,555/880,000 multiplied by 100 is 6%), or about 23% of all AMIs. The figure of 6% is similar to the percentage reported in the study with the most comparable data, the Myocardial Infarction Triage and Intervention Trial (MITI) (89) where 8863 patients with chest pain were assessed but only 360 patients were eligible for pre-hospital thrombolysis (4.1%).

7.5.6 Results

Using the list prices and the assumptions described above, the current annual cost to the NHS of thrombolytic drugs is estimated to range between £30,817,738 and £42,039,251 for all patients eligible for thrombolysis (Table 31). These are the figures used as a baseline for comparisons.

Table 31: Current cost to the NHS of thrombolytic drugs in England

Thrombolytic drug	BNF list price, 2001(£)	Low est. market share	Number patients treated	High est. market share	Number patients treated	Low cost (£)	High cost (£)
Streptokinase	80	0.53	61,705	0.645	75,093	4,936,378	6,007,478
Alteplase	600	0.23	26,778	0.3245	37,780	16,066,512	22,667,753
Reteplase	716.25	0.1177	13,704	0.15	17,464	9,814,849	12,508,304
Tenecteplase	735	0	0	0.01	1,164	0	855,716
						30,817,738	42,039,251

However, to illustrate the cost of switching eligible patients from one thrombolytic drug to another, annual costs for the following scenarios have been calculated and are presented in Table 32. As in all such scenarios it is unrealistic to assume that all patients can or should be transferred onto a single drug. However, these figures provide an indication of the cost impact of altering the patterns of thrombolytic drug

use in the hospital environment. The cost of switching all eligible patients to streptokinase has not been estimated as it is contraindicated in those patients that have already received streptokinase previously - we have arbitrarily assumed that 30% of patients would get alteplase instead. By setting the number of patients at 116000, this indicates the probable maximum but several audits have shown that many eligible patients do not receive thrombolysis – this would decease costs but we have no data to identify by how much.

Table 32: Budget impact estimates – hospital patients (100%)

Thrombolytic drug	BNF list price, 2001 (£)	Estimate of market share	Number of patients treated[a]	Total cost (£)	Additional cost based on low estimate (£)	Additional cost based on high estimate (£)
Streptokinase	80	0.7	81,499	6,519,744		
Alteplase	600	0.3	34,927	20,956,320		
			Subtotal	27,476,064	-3,341,674	-14,563,187
Alteplase	600	1	116,424	69,854,400	39,036,662	27,815,149
Reteplase	716.25	1	116,424	83,388,690	52,570,952	41,349,439
Tenecteplase	735	1	116,424	85,571,640	54,753,902	43,532,389

[a] *based on total population of 116,424*

As the organisation and delivery of pre-hospital thrombolysis is currently being developed, and is expected to be routinely available throughout England in the near future, the following annual cost estimates to the NHS have also been calculated based on expert opinion of potential market share options. The total cost of thrombolytic drugs includes the costs in both hospital and pre-hospital settings. Table 34 provides the cost implications of switching to each individual drug solely in the hospital environment. Table 33 also provides the cost implications of using a less expensive infusion drug in hospital and a more expensive bolus out of hospital.

Table 33: Budget impact estimates – hospital (54%) and pre-hospital (46%) patients

Product	Market share (hospital population =62,869)	Total cost (hospital) (£)	Product	Market share (pre-hospital population = 53,555)	Total cost (pre-hospital) (£)	Total cost (hospital + pre-hospital) (£)	Additional cost based on low estimate (£)	Additional cost based on high estimate (£)
Streptokinase + alteplase	70% + 30%	14,837,084	Reteplase	100%	38,358,768	53,195,852	22,378,114	11,156,602
Streptokinase + alteplase	70% + 30%	14,837,084	Tenecteplase	100%	39,362,925	54,200,009	23,382,271	12,160,758
Streptokinase + alteplase	70% + 30%	14,837,084	Reteplase + tenecteplase	50% + 50%	38,860,846	53,697,930	22,880,192	11,658,680

7.5.7 Impact of pre-hospital thrombolysis

If the majority of the required diagnostic and treatment procedures are common, it is only those that vary between each intervention that require detailed analysis. Pre-hospital thrombolysis requires investment in equipment and organisation and training to enable the service to be provided. However, a commitment to this has already been made by Government. In addition, drug costs may change as patient selection, choice of drug and drug costs are likely to be different between pre-hospital and hospital treatment.

The additional costs associated with the development of a pre-hospital thrombolysis in the UK are likely to be comparatively small. The service is using and adapting existing organisational structures and therefore no fundamental new structure of service is required. Provision of the service, therefore, requires additional training and a limited expansion of the service to cope with any additional workload. However, because such factors do not affect comparative drug choice in the pre-hospital environment no attempt has been made to cost them. The most significant cost is likely to be the additional drug costs resulting from a change in the choice of thrombolytic agent.

Given that the remit of the review is restricted to identifying the comparative cost-effectiveness of different drug therapies the only factor that will vary between the two identified as being suitable for use in the pre-hospital situation will be the drug acquisition costs. The infrastructure and training required for provision of both reteplase and tenecteplase is likely not to be significantly different and therefore the choice collapses to simple whichever drug can be obtained most cheaply for use in the pre-hospital environment. Currently, reteplase appears to have a price advantage and the cost penalty attached to the treatment of pre-hospital thrombolysis patients with reteplase in comparison to the current pattern of hospital provision would conserve scarce NHS resources. The precise costs would depend largely on local managers ability to negotiate favourable drug prices and the method of pre-hospital thrombolysis utilised

The list price of thrombolytics is not an accurate guide to the price that can be negotiated by large hospital purchasers. We have used list prices throughout but actual prices may be substantially less than this. In recognition of this fact, the GUSTO study incorporated an estimate of actual drug costs (rather than listed drug prices) as part of its sensitivity analysis and this significantly improved the cost-effectiveness of thrombolytic treatment. Although the details of these contracts within the NHS remain confidential, the ability to negotiate a favourable price with any of the competing suppliers represents one of the most important local variables that must be incorporated into the decision-making process.

7.5.8 Long term costs

From a long-term perspective, more extended use of thrombolytic therapy may lead the population as a whole to grow by up to 1%, the number of people with cardiac ischaemia could increase by 20% and the annual rates of AMI to also increase by about 20%. The total drugs bill may also increase by approximately 3% because of the growth in the elderly population(93).

7.5.9 Conclusion

This impact analysis does not aim to provide definitive answers, but indicates factors determining how the NHS can obtain the greatest benefit from the limited healthcare resources available for investment in thrombolysis. It is also important to recognise that the results of this impact analysis are not static and that a range of factors on both the cost and effectiveness side will considerably influence cost-effectiveness over time. The price of thrombolytic drugs may decrease, practice patterns may change and there may be further improvements in drug regimens.

8. DISCUSSION

The format of this review has included a discussion at the end of each relevant section. The final decision regarding the most appropriate drug rests on the appraisal of clinical issues (whether the evidence of difference between drugs in outcomes is considered clinically relevant), economic issues (whether the incremental cost effectiveness ratios demonstrated are considered worthwhile), and pragmatic issues (whether infusion drugs can be administered out of hospital and whether the time saving and convenience from use of bolus drugs helps meet NSF targets). The latter in particular are matters that may require local decisions within a national framework provided by NICE.

This objective of this review was to assess which is the most appropriate thrombolytic therapy in each of two settings; hospital and pre-hospital. In this it has been limited by the need to make indirect comparisons where no direct comparisons exist, and to assume that the results of hospital comparative studies would also apply in pre-hospital settings. The limitations of the available evidence have been discussed in each chapter.

In the economic evaluation of therapy, the complexity and detail of the models provided by the pharmaceutical industry submissions were superior to any that we could develop in the time and within the resources available. We therefore chose to use these models with different assumptions to test the cost effectiveness of different drugs. One drug, streptokinase, is only a fraction of the cost of any of the others, yet has all or almost all of the effectiveness of these drugs. It therefore was clearly going to be the most cost effective drug and the baseline against which all other drugs would be compared.

The resulting incremental cost effectiveness ratios for the other drugs compared to streptokinase are within the range of interventions that have been funded previously in the UK and in other health services, following assessments of this kind. The extent of the incremental benefits of other therapies, if any, and of their risks, are a matter for appraisal. However, given that we have an effective and inexpensive drug, streptokinase, which can be given in hospital and with which we have extensive experience, it seems appropriate that its use should continue to be encouraged for suitable patients.

The preferred options used in the economic evaluation are open to question. The options for comparability between drugs set out in the clinical section could only be tested to a limited degree, since no two drugs were equal in all their aspects, i.e. mortality, stroke rate, bleeding rates etc. It was necessary therefore to use point estimates which are transparently derived and which can be justified as we have presented. A range of assumptions were tested and the results in ranking order for the drugs and in their scale were robust to these. Further assumptions could be tested if necessary given more time and resource. However the key conclusions, that streptokinase is the most cost effective drug and that differences in cost effectiveness between other drugs are minor, are robust to any reasonable set of assumptions.

There are a number of points within the call to treatment time continuum where changes can be initiated to decrease call to treatment time. The decision regarding the appropriate

model of care to be adopted by individual trusts to meet the NSF standards will depend on the organisation of current care patterns, time/distance factors for transporting patients and the ability to decrease 'door to needle' time in the hospital setting. The synthesis of these data will allow current health care providers and decision makers to design appropriate implementation strategies to improve call to treatment time and ensure the provision of optimal and safe care for the patient.

Given more time, a wider range of consultation could have been undertaken in this area. Instead we depended on the opinions of a selective search of the literature and a limited number of experts in this area. Although we have sought to obtain balanced views at all times, it is possible that their prejudices are reflected in this review. It is clear that this is a rapidly changing area, and NICE's recommendations will be eagerly awaited.

9. CONCLUSION

9.1 Clinical effectiveness

Trial data are not available to provide direct comparison between all drugs included in this review. As stated in the results section the evidence for differences in clinical effectiveness of the drugs is uncertain and dependent upon *a priori* decisions regarding equivalence. The resolution of the controversies is a matter for appraisal and judgement.

Data are available from studies conducted in the hospital setting. No trials were identified that compared drug effectiveness in the pre-hospital setting. There is no reason to believe that the effectiveness of a drug will be altered by administration in the pre-hospital setting.

Definitive conclusions on efficacy (30-35 day mortality) are that streptokinase is as effective as non-accelerated alteplase, that tenecteplase is as effective as accelerated alteplase, and that reteplase is at least as effective as streptokinase.

Some conclusions require interpretation of data, i.e. whether streptokinase is as effective as, or inferior to accelerated alteplase; and whether reteplase is as effective as accelerated alteplase or not.

Depending on these, two further conclusions on indirect comparisons arise, whether tenecteplase is superior to streptokinase or not, and whether reteplase is as effective as tenecteplase or not.

That these questions remain to be resolved illustrate that any differences in mortality between drugs is small.

There seem to be significant differences between drugs in incidence of stroke with streptokinase having the lowest rate.

The decision regarding which agent to use is therefore a balance of risks and benefits related to these two factors. No clear conclusion, based on statistical comparison, can be drawn.

It is possible to use all four drugs for pre-hospital treatment but in practice bolus products seem the most convenient. The required use of heparin with both of the bolus products does not seem to provide any practical barrier to their widespread use.

9.2 Economic evaluation

Existing economic evaluations are of limited value in determining the relative cost effectiveness of drugs in the NHS. The existing studies are almost all industry funded

and depend on whether one accepts or rejects the superiority of alteplase over streptokinase.

Further economic modelling was therefore required to evaluate the cost-effectiveness of different drugs in the NHS. Company models were used as the basis of this modelling with modification of assumptions that may have favoured one drug over another. The conclusion of these modelling exercises is that differences in QALYs gained between drugs are small, and that the single most important factor in determining the incremental cost effectiveness ratio was the acquisition cost of the drug. On this basis, streptokinase was the most cost effective drug: this conclusion was robust despite several variations in assumptions of benefit or harm.

In contrast, the relative positions of alteplase, tenecteplase or reteplase varied slightly depending on the assumptions made.

Given the existing prices, the cost per QALY of newer drugs compared to streptokinase was between £12,000 to £17,000.

The benefits of earlier thrombolysis have not yet been well quantified. Minor timesavings achieved by the bolus drugs over infusion drugs do not significantly affect the incremental cost-effectiveness ratios.

9.3 Implementation

There are substantial opportunities for refining hospital thrombolysis procedures to meet NSF targets. Changing drugs is a very minor element in achieving improved door to needle time.

Pre-hospital thrombolysis will be necessary in some areas to allow NSF targets to be met. The choice of drug for pre-hospital thrombolysis is determined by acquisition cost and by convenience. Our experts did not wish to consider the use of infusion products (e.g. alteplase or streptokinase) but preferred bolus administration (reteplase and tenecteplase).

The cost impact of switching to the more expensive bolus drugs could be as much as £50 million per year, over and above existing costs of approximately £30-40 million for the NHS in England and Wales.

10. APPENDICES

I. In-hospital Thrombolysis Assessment

Countess of Chester Hospital NHS Trust, 2001

Thrombolytic Prescription – Sheet One

1 Are criteria for thrombolysis fulfilled? (see Table 1)
[2] Are there definite contraindications to thrombolysis (if 'yes' indicate in Table 2)
[3] Are there possible/treatable contraindications? (if 'yes' indicate in Table 2)
[4] Is TPA indicated? (see Table 3, if 'no' use Streptokinase)
[5] Treatment discussed with patient?

Conclusions:

6 To receive thrombolysis? Yes: Complete side 2 [Sheet Two] of this sheet. Give TPA/Strep. as appropriate; No; Review after discussion/further treatment *
7* Result of review: Give thrombolysis; Other:

[**Table 1:]**

ALL of the following: Myocardial ischaemic pain for 30 minutes or other symptoms compatible with acute MI ECG at least one of the following: 1mm ST segment elevation in 1 or more limb leads; 2mm ST elevation in 2 or more contiguous precordial leads…
Symptoms for up to 12 hours (24 hours if pain recurrent)

[**Table 2:]**

Definite contraindications: Probable aortic dissection; CVA within 3 months; Pregnancy; GI bleed with 6 months; Active peptic ulcer; Acute pericarditis; Major trauma/surgery within 6/52; Prolonged CPR.
Possible contraindications: Known bleeding diathesis; Anti-coagulation (Warfarin); Current menstruation; Other condition which may predispose to bleeding; Other serious or life-threatening disease. *Treatable contraindications:* Systolic BP more than 200mmHg; Treat BP: If *reduced* to below 200mmHg proceed with thrombolytic therapy. Discuss with cardiac team/POW if unable to reduce Below 200mmHg.

[**Table 3:**]

ONE or MORE of the following: Significant persistent hypotension (<100mmHg on several readings) Previous Streptokinase or Anistreplase (APSAC) treatment at any time Recent proven Streptococcal infection Fulfilling all of the following: Presentation within 4 hours of onset of symptoms Age ≤ 75 years Anterior MI Likelihood of invasive procedure eg temporary pacemaker insertion

Thrombolytic Prescription – Sheet Two

Door to needle time: Hours/Minutes (Time infusion started (minus) Time of admission)
Less than 30 minutes? Yes/No

Alteplase (TPA)

If not already receiving aspirin give 300mg soluble aspirin then:
Give 5000 units Heparin IV Bolus through venflon in one arm then:
Follow t-PA regime using IVAC P7000 pump through another venflon in the other arm.
Use infusion table below, set pump according to patient's approx weight using one of the categories given:

t-PA Infusion Rate (1mg/ml solution)

Weight	Bolus	50mg/50ml 0.75mg/kg over 30 min	35mg/35ml 0.5mg/kg over 60 min	Please tick the regime used
70 kg	15 ml	100 ml/hr	35mg/35ml	
60 kg	15 ml	90 ml/hr	30 ml/hr	-
55 kg	15 ml	83 ml/hr	28 ml/hr	-
50 kg	15 ml	75 ml/hr	25 ml/hr	-
45 kg	15 ml	[68] ml/hr	23 ml/hr	-
40 kg	15 ml	60 ml/hr	20 ml/hr	-

IV Heparin infusion to run concurrently and start at 1300u/hr (1.3 ml/hr as 40,000U in 40 ml)
Measure APPT at 6 hours (aim for APPT 60-80S (as in GUSTO)) Follow Heparin Protocol.
Prescribers signature/Date.
NB Heparin and TPA must be given through separate venflons.

Streptokinase

If not already receiving aspirin give 300mg soluble aspirin then:
1.5 million units Streptokinase IV over 1 hour in 100 ml of saline
Start s.c. Heparin 5000 units b.d.
Prescribers signature/Date.

Thrombolytic infusion details

Batch number; Date started; Time started; Time stopped; Time restarted; Time finished; Amount infused; Total amount infused; Nurses signature.

Please complete the Variance Analysis Sheet

Please indicate complications of thrombolysis including why treatment was stopped/interrupted: Mild Hypotension; Anaphylaxis; Haemorrhage; Urticaria; CVA; Arrhythmia; Other: Comments:

II. Pre-hospital Thrombolysis Assessment

East Midlands Ambulance Service NHS Trust

Primary Assessment:

1. Is the patient conscious, coherent, and able to understand that clot-dissolving drugs will be used?
2. Has the patient had symptoms characteristic of a coronary heart attack and did the worst pain build up over several minutes, rather than starting totally abruptly over several seconds, with a typical distribution of pain for 30 minutes duration or more?
3. Is the patient aged between 14 and 75 years of age?
4. Did the continuous symptoms start less than 3 hours ago? [modified from 6 hours]
5. Can you confirm that breathing does not influence the severity of pain?
6. Can you confirm that the heart rate is between 40-140?
7. Can you confirm that the systolic blood pressure is more than 80 mmHg and less than 160 mm Hg and that the diastolic pressure is below 95 mmHg?
8. Does the electrocardiogram show abnormal ST segment elevation of 2 mm or more (0.08 seconds after the J point) in at least standard leads or at least 2 adjacent precordial leads, not including V1? (ST elevation can sometimes be normal V1 and V2)
9. Is the QRS width 0.12 mm or less, and is bundle branch block absent from tracing?
10. Can you confirm that there is NO atrioventricular block greater than 1st degree? (if necessary after treatment with IV atropine).

Secondary Assessment (Contraindications)**:**

11. Can you confirm that the patient is not likely to be pregnant, nor has delivered within the last two weeks?
12. Can you confirm that the patient has had a peptic ulcer within the last 6 months?
13. Can you confirm that the patient has not had a stroke of any sort within the last 12 months and no permanent disability from a previous stroke?
14. Can you confirm that the patient has not been treated for any other serious brain condition? (This is intended to exclude patients with cerebral tumours)
15. Can you confirm the patient has no diagnosed bleeding tendency, has had no blood loss within the last 8 weeks (except for normal menstruation), and is not on ANY anticoagulant therapy i.e. (Heparin, Warfarin) except Aspirin?
16. Can you confirm the patient has not had any surgical operation, tooth extractions, significant trauma, or head injury within the last 3 months?
17. Can you confirm that the patient has not had chest compression for resuscitation for a period of longer than 5 minutes within the last 10 days?
18. Can you confirm that the patient is not being treated for liver failure, renal failure, or any other severe systemic illness?

III. Search for clinical studies: summary

Database	Years	Search strategy	References Identified
MEDLINE	1980-2001	See appendix IV	1387
EMBASE	1980-2001	See appendix V	1301
Science Citation Index/Web of Science	1988-2001	(alteplase or tPA or streptokinase or reteplase or tenecteplase or anistreplase or urokinase) and (thrombolysis or myocardial infarction)	2358
The Cochrane Trials Register (Central/CCTR)	2001 (4)	(alteplase or tPA or streptokinase or reteplase or tenecteplase or anistreplase or urokinase) and (thrombolysis or myocardial infarction)	621
HTA	1992-2001	Alteplase or tPA or streptokinase or reteplase or tenecteplase or anistreplase or urokinase	75
DARE	1982-2001	Alteplase or tPA or streptokinase or reteplase or tenecteplase or anistreplase or urokinase	50
		Total references identified:	**5792**

IV. Search Strategy (MEDLINE 1980-2001)

1. randomized controlled trial.pt.
2. randomized controlled trials.sh.
3. random allocation.sh.
4. double blind method.sh.
5. single blind method.sh.
6. clinical trial.pt.
7. clinical trials.sh.
8. controlled clinical trials.sh.
9. (clin$ adj25 trial$).ti,ab.
10. ((singl$ or doubl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
11. random$.ti,ab.
12. research design.sh.
13. exp evaluation studies/
14. follow up studies.sh.
15. prospective studies.sh.
16. (control$ or prospective$ or volunteer$).ti,ab.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. animal.sh.
19. human.sh.
20. 18 not (18 and 19)
21. 17 not 20
22. alteplase.ti,ab.
23. tPA.ti,ab.
24. reteplase.ti,ab.
25. streptokinase.ti,ab.
26. tenecteplase.ti,ab.
27. anistreplase.ti,ab.
28. urokinase.ti,ab.
29. 22 or 23 or 24 or 25 or 26 or 27 or 28
30. exp Myocardial Infarction/
31. (myocard$ adj4 (infarct$ or acute)).ti,ab.
32. 30 or 31
33. 21 and 29 and 32
34. limit 33 to yr=1980-2001
35. limit 34 to english language

V. Search Strategy (EMBASE 1980-2001)

1. randomized controlled trial/
2. randomisation/
3. double blind procedure/
4. single blind procedure/
5. Clinical trial/
6. Controlled study/
7. random$.ti, ab.
8. Methodology/
9. Evaluation/
10. Follow up/
11. Prospective study/
12. (control$ or prospective$ or volunteer$).ti, ab
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. limit 13 to human
15. alteplase.ti, ab.
16. tPA.ti, ab.
17. reteplase.ti, ab.
18. streptokinase.ti, ab.
19. tenecteplase.ti, ab.
20. anistreplase.ti, ab.
21. urokinase.ti, ab.
22. 15 or 16 or 17 or 18 or 19 or 20 or 21
23. Heart infarction/
24. “MYOCARDIAL INFARCTION”. mp
25. 23 or 24
26. 14 and 22 and 25
27. limit 26 to yr=1980-2001
28. limit 27 to english language

VI. Search for cost-effectiveness studies: summary

Database	Years	Search strategy	References Identified
MEDLINE	1985-2001	Alteplase or tPA or streptokinase or reteplase or tenecteplase and decision Alteplase or tPA or streptokinase or reteplase or tenecteplase and cost	88 182
EMBASE	1988-2001	Alteplase or tPA or streptokinase or reteplase or tenecteplase and decision Alteplase or tPA or streptokinase or reteplase or tenecteplase and cost	126 257
Science Citation Index/Web of Science	1984-2001	Alteplase or tPA or streptokinase or reteplase or tenecteplase and (decision or cost)	211
Cochrane Trials Register	2001 (3)	Thrombolytic therapy and cost	48
NHSEED	1995-2001	Alteplase or tPA or streptokinase or reteplase or tenecteplase	41
HTA	1995-2001	Alteplase or tPA or streptokinase or reteplase or tenecteplase	73
DARE	1995-2001	Alteplase or tPA or streptokinase or reteplase or tenecteplase	47
		Total references identified	1073
		Duplicates	275
		New total	**798**

Search stages

Search stages	References Identified
Papers identified via cost-effectiveness search	98
Papers identified via clinical effectiveness search	5
Papers identified after handsearching of references	4
Total number assessed using inclusion/exclusion criteria	107
Total number included in review	8

VII. Quality assessment checklist for clinical studies

Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No. 4, University of York (41)

1. Was the method used to assign participants to the treatment groups really random? (*Computer generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week*)
2. Was the allocation of treatment concealed? (*Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque*)
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
5. Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may influence the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who were administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?
13. Were the reasons for any withdrawals stated?
14. Was an intention to treat analysis included?

Items graded as:

✔ **yes** (item adequately addressed),
✘ **no** (item not adequately addressed),
✔/✘ **partially** (item partially addressed),
✘ **unclear** or not enough information,
na **not applicable** or **ns** **not stated**.

VIII. Quality assessment checklist for cost-effectiveness studies

1. Well-defined question
2. Comprehensive description of competing alternatives
3. Effectiveness established
4. All important and relevant costs and consequences for each alternative identified
5. Costs and consequences measured accurately
6. Costs and consequences valued credibly
7. Costs and consequences adjusted for differential timing
8. Incremental analysis costs and consequences
9. Sensitivity analyses to allow for uncertainty in estimates of costs or consequences
10. Study results/discussion include all issues of concern to users

The scores used for each dimension were as follows:

✔ Dimension appropriately addressed
✔/✘ Dimension partially/maybe addressed
N/A Dimension not applicable

IX. Current contraindications to thrombolysis

Current contraindications* to treatment are related to risk of bleeding and are divided into absolute and relative:

Absolute contraindications:
GI bleeding in the previous month
History of cerebrovascular disease especially recent events or with any residual disability
Bleeding disorder or on anticoagulant therapy
Major surgery, trauma or head injury in previous 3 weeks
Prolonged CPR (>30 minutes)
Hypertension (>180 mmHg systolic)
Aortic dissection
Acute pancreatitis
Lung cavitations

Relative contraindications:
Major hepatic or renal disease
Non-compressible puncture site
Known terminal illness
Recent retinal laser treatment

*As listed in recommendations from the European Society of Cardiology.(3)

Also, in the case of streptokinase, previous allergic reactions to either streptokinase or anistreplase or administration of either drug in the previous 2 years.

X. Derivation of 'Preferred Method' efficacy parameters

1. Mortality at 30 days

Results from three trials for 30-day mortality are combined, using Alteplase arms as the common referent. A standard mortality rate for Alteplase is calculated from GUSTO I and GUSTO-III, and then this is used, together with ASSENT-2, to estimate equivalent mortality rates for streptokinase, reteplase and tenecteplase. This method preserves the relativities of action within each individual trial whilst establishing an overall consistent ranking. The calculations are summarised in the following table, with the final parameter values highlighted in bold type.

Trial	GUSTO I	GUSTO-III	ASSENT-2
Agent	*Alteplase*	*Alteplase*	*Alteplase*
Reported mortality rates	6.303%	7.234%	6.150%
Combined rate	**6.603%**		-
Adjustment factors	x 1.048	x 0.913	x 1.074
Agent	*Streptokinase*	*Reteplase*	*Tenecteplase*
Reported mortality rate	7.302%	7.467%	6.181%
Adjusted rate	**7.650%**	**6.816%**	**6.637%**

To assess the robustness of this formulation, the calculations were repeated with the influence of GUSTO I results weighted at only 50% the weight accorded to GUSTO-III. Only very small changes in pairwise differences were found (no more than 0.007%) insufficient to have any serious effect on relative rankings on the agents. A similar recalculation was carried out including the ASSENT-2 Alteplase figures in the combined rate: although this changed the absolute risks estimated, pairwise differences changed by only a maximum of 0.014% - again insufficient to have any real impact on efficacy rankings.

2. Incidence of Any Stroke

The same method was used to calculate a set of mutually consistent stroke rates from the same three trials. The results are shown below.

Trial	GUSTO I	GUSTO-III	ASSENT-2
Agent	*Alteplase*	*Alteplase*	*Alteplase*
Reported stroke rates	1.549%	1.788%	1.661%
Combined rate	**1.626%**		-
Adjustment factors	x 1.050	x 0.909	x 0.979
Agent	*Streptokinase*	*Reteplase*	*Tenectaplase*
Reported stroke rate	1.308%	1.637%	1.785%
Adjusted rate	**1.374%**	**1.489%**	**1.747%**

Reducing the influence of GUSTO I led to pairwise changes no greater than 0.008%, and including ASSENT-2 in the alteplase combined rate led to changes of no more than 0.006%, so that the stroke estimates are also robust to various assumptions.

3. Re-Infarction

The same method was used to calculate a set of mutually consistent re-infarction rates from the same three trials. The results are shown below.

Trial	GUSTO I	GUSTO-III	ASSENT-2
Agent	*Alteplase*	*Alteplase*	*Alteplase*
Reported reinfarction rates	3.996%	4.206%	3.805%
Combined rate	**4.069%**		-
Adjustment factors	x 1.018	x 0.967	x 1.069
Agent	*Streptokinase*	*Reteplase*	*Tenecteplase*
Reported reinfarction rate	3.709%	4.202%	4.101%
Adjusted rate	**3.777%**	**4.065%**	**4.385%**

Reducing the influence of GUSTO I led to pairwise changes no greater than 0.004%, and including ASSENT-2 in the alteplase combined rate led to changes of no more than 0.010%, so that the re-infarction estimates are also robust to various assumptions.

4. Congestive Heart Failure

The same method was used to calculate a set of mutually consistent CHF rates from the same three trials. The results are shown below.

Trial	GUSTO I	GUSTO-III	ASSENT-2
Agent	*Alteplase*	*Alteplase*	*Alteplase*
Reported CHF rates	15.203%	17.496%	6.998%
Combined rate	**16.000%**		-
Adjustment factors	x 1.052	x 0.914	x 2.286
Agent	*Streptokinase*	*Reteplase*	*Tenecteplase*
Reported CHF rate	17.102%	17.203%	6.099%
Adjusted rate	**17.999%**	**15.732%**	**13.944%**

Reducing the influence of GUSTO I led to pairwise changes no greater than 0.076%. A large difference in absolute rates of CHF reported in both arms of ASSENT-2 compared to the GUSTO trials points to very different criteria being employed. Thus when ASSENT-2 data for alteplase are included in the combined rate calculation larger absolute and relative changes become evident than for the other adverse events and outcomes. The largest changes in pairwise rate differences are for those involving streptokinase (up to 0.55%), but notwithstanding the reduced confidence in individual estimates, the relative rankings of agents are unchanged and pairwise differences not involving streptokinase change by a maximum of 0.277%.

5. Major Bleeding Events

It is evident from the diversity of published outcomes on bleeding events that there is no recognised and consistent definition of what constitutes a 'major bleed' event. Published rates vary between 0% (NZ-White for alteplase) and nearly 20% (Central Illinois for atreptokinase). Clearly in many studies, many episodes, which would elsewhere be classed as 'moderate', were recorded as 'severe or life-threatening'

Using a similar methodology to those shown above, targeted on patients requiring transfusion, yields estimates of 12.25% streptokinase, 9.90% alteplase, 7.82% reteplase and 7.77% tenecteplase, based on GUSTO I, GUSTO-III and ASSENT-2.

However, clinical expert opinion argued that these incidence rates were not consistent with the notion of 'major bleed'. An alternative more restrictive definition is possible limiting attention only to the small number of episodes classed as severe or life-threatening: this uses a weighted average of seven trials comparing alteplase with streptokinase (Central Illinois, ECSG, GISSI-2/ISG, ISIS 3, NZ-White, Taiwan and TIMI 1) to provide severe bleeding referent event rates of 0.90% for alteplase and 1.11% for streptokinase. Then results from GUSTO-III can be rescaled to the referent rate for Alteplase to yield an estimate for reteplase (0.705%), with a similar rescaling of ASSENT-2 results to obtain a revised rate for tenecteplase (0.710%).

11. REFERENCES

11.1 Clinical: Included studies:

Study:	Reference(s)
	Alteplase/Streptokinase
Central Illinois	Taylor GJ, Moses HW, Koester D, Colliver JA, Katholi RE, Dove JT, et al. A difference between front-loaded streptokinase and standard-dose recombinant tissue-type plasminogen activator in preserving left ventricular function after acute myocardial infarction (the Central Illinois Thrombolytic Therapy Study). *American Journal of Cardiology* 1993;**72**:1010-4.
Cherng *et al*	Cherng WJ, Chiang CW, Kuo CT, Lee CP, Lee YS. A comparison between intravenous streptokinase and tissue plasminogen activator with early intravenous heparin in acute myocardial infarction. *American Heart Journal* 1992;**123**:841-846.
ECSG	Verstraete M, Bernard R, Bory M, Brower RW, Collen D, de Bono DP, et al. Randomised trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. Report from the European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator. *Lancet* 1985;**1**:842-7.
GISSI-2/ISG	*Feruglio GA, Lotto A, Rovelli F, Solinas P, Tavazzi L, Tognoni G, et al. GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990;**336**:65-71. *Van de Werf F, Wilcox RG, Barbash GI, Diaz R, Franzosi MG, Hampton JR, et al. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet* 1990;**336**:71-75. Feruglio GA, Lotto A, Rovelli F, Solinas P, Tavazzi L, Tognoni G, et al. Six-month survival in 20 891 patients with acute myocardial infarction randomized between alteplase and streptokinase with or without heparin. *European Heart Journal* 1992;**13**:1692-1697. Fresco C, Franzosi MG, Maggioni AP, Tognoni G. The GISSI-2 trial: Premises, results, epidemiological (and other) implications. *Clinical Cardiology* 1990;**13**(8 SUPPL.8):32-36. Glasziou PP, Bromwich S, Simes RJ. Quality of life six months after myocardial infarction treated with thrombolytic therapy. AUS-TASK Group. Australian arm of International tPA/SK Mortality Trial. *Medical Journal of Australia* 1994;**161**:532-6. Maggioni AP, Franzosi MG, Santoro E, White H, Van de Werf F, Tognoni G, et al. The risk of stroke in patients with acute myocardial infarction after thrombolytic and antithrombotic treatment. *New England Journal of Medicine* 1992**;327**:1-6. Volpi A, De Vita C, Franzosi MG, Geraci E, Maggioni AP, Mauri F, et al. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis. Results of the GISSI-2 data base. The Ad hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base. *Circulation* 1993;**88**:416-29. White HD, Barbash GI, Modan M, Simes J, Diaz R, Hampton JR, et al. After correcting for worse baseline characteristics, women treated with thrombolytic therapy for acute myocardial infarction have the same mortality and morbidity as men except for a higher incidence of hemorrhagic stroke. The Investigators of the International Tissue Plasminogen Activator/Streptokinase Mortality Study. *Circulation* 1993;**88**:2097-103.
GUSTO I (Acc t-PA)	*An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *New England Journal of Medicine* 1993;**329**:673-82. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators. *New England Journal of Medicine* 1993;**329**:1615-22. Aylward PE, Wilcox RG, Horgan JH, White HD, Granger CB, Califf RM, et al. Relation of increased arterial blood pressure to mortality and stroke in the context of contemporary thrombolytic therapy for acute myocardial infarction. A randomized trial. *Annals of Internal Medicine* 1996;**125**:891-900. Brieger DB, Mak KH, White HD, Kleiman NS, Miller DP, Vahanian A, et al. Benefit of early sustained reperfusion in patients with prior myocardial infarction (The GUSTO I Trial). American Journal of Cardiology 1998;**81**:282-287.

Study:	Reference(s)
	Califf RM, White HD, Van de Werf F, Sadowski Z, Armstrong PW, Vahanian A, et al. One-year results from the global utilization of streptokinase and TPA for occluded coronary arteries (GUSTO I) trial. *Circulation* 1996;**94**:1233-1238.
	Gore JM, Granger CB, Simoons ML, Sloan MA, Weaver WD, White HD, et al. Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO I trial. Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation* 1995;**92**:2811-8.
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	Kleiman NS, White HD, Ohman EM, Ross AM, Woodlief LH, Califf RM, et al. Mortality within 24 hours of thrombolysis for myocardial infarction. The importance of early reperfusion. The GUSTO Investigators, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *Circulation* 1994;**90**:2658-65.
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	Tsang TS, Califf RM, Stebbins AL, Lee KL, Cho S, Ross AM, et al. Incidence and impact on outcome of streptokinase allergy in the GUSTO I trial. Global Utilization of Streptokinase and t-PA in Occluded Coronary Arteries. *American Journal of Cardiology* 1997;**79**:1232-5.
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ISIS-3	Hunt D, Varigos J, Dienstl F, Lechleitner P, Mauel C, Dienstl A, et al. ISIS-3: A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;**339**:753-770.
KAMIT	Grines CL, Nissen SE, Booth DC, Gurley JC, Chelliah N, Wolf R, et al. A prospective, randomized trial comparing combination half-dose tissue-type plasminogen activator and streptokinase with full-dose tissue-type plasminogen activator. *Circulation* 1991;**84**:540-549.
White *et al*	*White HD, Rivers JT, Maslowski AH, Ormiston JA, Takayama M, Hart HH, et al. Effect of intravenous streptokinase as compared with that of tissue plasminogen activator on left ventricular function after first myocardial infarction. *New England Journal of Medicine* 1989;**320**:817-21.
	Cross DB, Ashton NG, Norris RM, White HD. Comparison of the effects of streptokinase and tissue plasminogen activator on regional wall motion after first myocardial infarction: Analysis by the centerline method with correction for area at risk. *Journal of the American College of Cardiology* 1991;**17**:1039-1046.
PAIMS	Magnani B. Plasminogen Activator Italian Multicenter Study (PAIMS): comparison of intravenous recombinant single-chain human tissue-type plasminogen activator (rt-PA) with intravenous streptokinase in acute myocardial infarction. *Journal of the American College of Cardiology* 1989;**13**:19-26.
TIMI 1	*Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;**76**:142-54.
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Study:	Reference(s)
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RAPID 1	

* Primary reports

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Barbagelata A, Califf RM, Sgarbossa EB, Goodman SG, Stebbins AL, Granger CB, et al. Thrombolysis and Q wave versus non-Q wave first acute myocardial infarction: a GUSTO I substudy. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries Investigators. *Journal of the American College of Cardiology* 1997;**29**:770-7.	Outcomes
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