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**Guidance on
the use of
drugs for early
thrombolysis in
the treatment
of acute
myocardial
infarction**

Technology Appraisal No. 52

Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction

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Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction

1. Guidance

This guidance provides recommendations on the selection of thrombolytic drugs in patients with acute myocardial infarction (AMI). Recommendations are made in relation to the use of the drugs in hospital and pre-hospital settings. The guidance does not compare hospital and pre-hospital models of delivering thrombolysis.

1.1 It is recommended that, in hospital, the choice of thrombolytic drug (alteplase, reteplase, streptokinase or tenecteplase) should take account of:

- the likely balance of benefit and harm (for example, stroke) to which each of the thrombolytic agents would expose the individual patient
- current UK clinical practice, in which it is accepted that patients who have previously received streptokinase should not be treated with it again
- the hospital's arrangements for reducing delays in the administration of thrombolysis.

1.2 Where pre-hospital delivery of thrombolytic drugs is considered a beneficial approach as part of an emergency-care pathway for AMI (for example, because of population geography or the accessibility of acute hospital facilities), the practicalities of administering thrombolytic drugs in pre-hospital settings mean that the bolus drugs (reteplase or tenecteplase) are recommended as the preferred option.

This section (Section 1) constitutes the Institute's guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. The remainder of the document is structured in the following way:

2 Clinical need and practice	7 Implementation and audit
3 The technology	8 Related guidance
4 Evidence and interpretation	9 Review of guidance
5 Recommendations for further research	Appendix A: Appraisal Committee
6 Resource impact for the NHS	Appendix B: Sources of evidence
	Appendix C: Patient information

A bi-lingual summary is available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number N0157.

Mae crynodeb ar gael yn Gymraeg ac yn Saesneg ar ein gwefan yn www.nice.org.uk neu drwy ffonio 0870 1555 455 gan ddyfynnu cyfeirnod N0157 .

- 2.1 Acute myocardial infarction (AMI) is caused by blockage of a coronary artery by a thrombus or clot. This is usually the result of rupture of an atherosclerotic plaque within the artery. The heart muscle supplied by that artery is damaged or dies because of lack of oxygen (ischaemia). Patients with AMI may develop heart failure or potentially fatal cardiac arrhythmias as a result of damage to the heart muscle. These and other complications may occur early, within the first few hours of the event, or may develop over the subsequent months or years.
- 2.2 Around 240,000 people experience AMI in England and Wales each year. Up to 50% of people who have an AMI die within 30 days of the event, and over half of these deaths occur before medical assistance arrives or the patient reaches hospital.
- 2.3 Onset of AMI symptoms is usually rapid and the highest risk of death (usually as the result of an acute fatal arrhythmia) is within the first hour of experiencing symptoms – around one-third of all AMI deaths occur within the first hour.
- 2.4 Thrombolytic drugs break down the thrombus so that the blood flow to the heart muscle can be restored to prevent further damage and assist healing. The sooner the blood flow can be restored, the better the chances of avoiding the death of the heart muscle. Along with clinical symptoms (typically but not exclusively chest pain), characteristic changes in the 12-lead electrocardiogram (ST segment elevation) provide the most immediate indication of the diagnosis of AMI for patients requiring thrombolysis for AMI.
- 2.5 Intravenous thrombolytic therapy is an established standard treatment for AMI. It is estimated that around 50,000 patients currently receive thrombolysis in England and Wales each year. However, evidence suggests that thrombolysis continues to be under-used.
- 2.6 Thrombolytic drugs are routinely given in hospital as soon as possible after a confirmed diagnosis of AMI. Additionally, their administration in pre-hospital settings, principally by ambulance paramedics, is becoming more common.
- 2.7 Early primary percutaneous coronary intervention (PCI) may be an alternative to thrombolysis. Despite research evidence of the potential value of early PCI, currently few hospital trusts have the capacity to provide it. Treatment delivering thrombolytics in combination with glycoprotein IIb/IIIa inhibitors is also the subject of research studies. However, these interventions are beyond the scope of this appraisal.

3.1 Thrombolytic drugs

- 3.1.1 In the UK, four thrombolytic agents are licensed and available to treat AMI. All act by promoting the activity of circulating plasminogen. There is a long history of use of one, streptokinase, whereas the other three, alteplase, reteplase and tenecteplase, are newer options. Streptokinase is derived from streptococcal bacteria. Streptokinase is given by intravenous (IV) infusion. Alteplase was introduced in the late 1980s. It is essentially the same as the naturally occurring activator of plasminogen in the human body, and is produced by recombinant DNA technology. It is given by IV infusion. Reteplase and tenecteplase have been introduced more recently (1997 and 2001, respectively). They are new modified forms of plasminogen activator and can be given by rapid IV bolus injection, rather than infusion.
- 3.1.2 The timing of administration is a crucial factor determining the extent of benefit achieved by thrombolysis, and treatment should ideally be given as soon as possible (normally up to 12 hours) after the onset of AMI symptoms.
- 3.1.3 Bleeding complications are the main risks associated with thrombolysis. The most important bleeding complication is haemorrhagic stroke, which occurs in 0.5–1.0% of patients and is associated with high mortality and long-term disability in survivors. Bleeding may occur at the injection site, in the gastrointestinal tract or elsewhere. Hypotension may also occur. The risks and benefits of giving thrombolysis need to be considered in individual patients and settings. The risk of haemorrhagic stroke following thrombolysis increases with age and blood pressure. Thrombolysis is contraindicated in individuals with bleeding disorders or a history of recent haemorrhage, trauma, surgery or acute cerebrovascular event. For full details of side effects and contraindications, see the Summary of Product Characteristics for the individual agents.
- 3.1.4 Heparin (an anticoagulant) is given with all of the thrombolytic drugs except streptokinase. It is usually administered as an IV bolus injection before thrombolysis, followed by an IV infusion. When given with tenecteplase the heparin dose is weight adjusted. Aspirin (an antiplatelet agent) is also usually given with any thrombolytic drug, because it delivers a mortality benefit in its own right.

- 3.1.5 **Streptokinase** (Streptase) is indicated up to 12 hours after onset of symptoms. It is administered as an IV infusion over 1 hour. It has been extensively studied and remains widely used. Streptokinase is associated with hypotension, infrequent allergic reactions and, rarely, anaphylaxis. Patients treated with streptokinase develop anti-streptococcal antibodies, which can inactivate the drug if subsequent treatment is needed. Consequently in current UK practice, patients are usually treated with streptokinase only once. It is estimated that around one-third of people with AMI have contraindications to streptokinase. A recent survey found that 82% of hospitals in England use streptokinase for eligible patients experiencing their first AMI; other data suggest that streptokinase represents between 53% and 65% of thrombolytic drug use. Streptokinase costs £80 to £90 per patient (excluding VAT) (*British National Formulary* 43, March 2002).
- 3.1.6 **Alteplase** (Actilyse, recombinant human tissue plasminogen activator, rtPA) can be delivered in a standard or accelerated regimen. The accelerated regimen, which is much more commonly used, is indicated up to 6 hours after symptom onset and is delivered by an initial IV bolus injection, followed by two IV infusions, the first given over 30 minutes and the second over 60 minutes. The standard regimen is indicated between 6 and 12 hours after symptom onset and requires a bolus injection followed by five infusions over 3 hours. Like the other newer drugs, alteplase does not stimulate the production of antibodies, so it can be used repeatedly. It is estimated that alteplase represents between 23% and 32% of thrombolytic drug use in the UK. Alteplase costs £600 per patient (excluding VAT) (*British National Formulary* 43, March 2002).
- 3.1.7 **Reteplase** (Rapilysin) is indicated up to 12 hours after symptom onset. It is given as two IV bolus injections 30 minutes apart. It is estimated that reteplase represents between 12% and 15% of thrombolytic drug use in the UK. Reteplase costs £716 per patient (excluding VAT) (*British National Formulary* 43, March 2002).
- 3.1.8 **Tenecteplase** (Metalyse) is indicated up to 6 hours after symptom onset. It is administered as a single (weight-adjusted) IV bolus injection. It is estimated that tenecteplase currently accounts for around 1% of thrombolytic drug use in the UK, the manufacturer indicates that the proportion is increasing. Tenecteplase costs £700 to £770 per patient (excluding VAT) (*British National Formulary* 43, March 2002).

3.2 Delivering thrombolytic drugs

- 3.2.1 The National Service Framework (NSF) for coronary heart disease (CHD) in England and *Tackling CHD in Wales* specify that eligible patients with AMI should be given thrombolysis within 60 minutes of calling for professional help ('call-to-needle' time) and should receive thrombolysis within 20 minutes of arriving at hospital ('door-to-needle' time). It is also suggested that it may be appropriate to provide pre-hospital thrombolysis where local 'call-to-hospital' times are likely to be over 30 minutes. The NHS Plan in England gave a commitment to train and equip ambulance paramedics to provide thrombolysis.
- 3.2.2 Direct admission to a coronary care unit (CCU) is often not possible, and accident and emergency (A&E) departments are being encouraged to administer thrombolysis to reduce delays in door-to-needle times. The potential for specialist nursing input in the delivery of thrombolysis is being developed.
- 3.2.3 Given the benefits of early administration of thrombolysis on reducing damage to heart muscle and consequently on long-term outcomes, pre-hospital administration of thrombolysis by ambulance paramedics is being gradually implemented in the NHS.
- 3.2.4 Currently, pre-hospital thrombolysis is administered by fewer than five ambulance services and a small number of remote community hospitals in England and Wales. Ongoing changes in infrastructure and training will be required to implement the requirements of the NSF for CHD, *Tackling CHD in Wales* and the NHS Plan to allow more widespread delivery in pre-hospital settings.
- 3.2.5 Currently, streptokinase is the only thrombolytic that paramedics are authorised to administer under the Prescription Only Medicines (Human Use) Order 1997. However, paramedics can administer other thrombolytic drugs under local Patient Group Directions, and guidelines on their use by paramedics have been developed by the Joint Royal Colleges Ambulance Liaison Committee (JRCALC).
- 3.2.6 There are practical difficulties in giving controlled-rate infusions in pre-hospital settings, including drug preparation requirements, the practicalities of giving an infusion in an ambulance and, for streptokinase, concerns about higher rates of allergic reactions and hypotension, which are more difficult to manage away from hospital.

3.2.7 Although they are not within the scope of this appraisal, a number of organisational models of service delivery are relevant when considering the feasibility of administering different thrombolytic agents and their effectiveness in particular settings. These involve organisational, practical and operator issues. In-hospital thrombolysis models include:

- assessment and treatment in A&E
- rapid assessment in A&E and transfer to CCU
- direct admission to CCU.

Pre-hospital models include:

- community hospital administration (nurse or general practitioner)
- general practitioner administration (at the point of contact)
- telemetry-supported paramedic administration
- autonomous paramedic administration.

The Appraisal Committee considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

4.1.1 *In-hospital thrombolysis*

4.1.1.1 Fourteen randomised controlled trials (RCTs) comparing thrombolytic drugs were included in the review. Overall the studies were considered to be of excellent quality. In total, the trials involved over 142,000 patients, and five of the trials included over 10,000 patients each. The trials had similar inclusion criteria in terms of age (usually <70 or <75 years), ECG changes, duration of symptoms, and presentation within 6 hours of symptom onset. Five of the trials included between 12% and 26% of patients aged over 70–75 years. Women were under-represented in all of the studies. Primary endpoints included 30-day mortality, 90-minute artery patency/flow rates and left ventricular function. Secondary endpoints included bleeding, stroke, congestive heart failure, reinfarction, allergy and anaphylaxis. The results of the trials were also pooled in a meta-analysis.

- 4.1.1.2 No direct trial comparisons between tenecteplase and streptokinase or between tenecteplase and reteplase have been undertaken, and only cautious conclusions can be drawn from the indirect comparisons that can be deduced from other studies.

Streptokinase

- 4.1.1.3 Two placebo-controlled trials were instrumental in establishing the efficacy of streptokinase in reducing mortality. The GISSI trial (published in 1986) included 11,712 patients, and the ISIS-2 trial (published in 1988) included 17,187 patients. In the GISSI study, 21-day mortality was 10.7% in patients treated with streptokinase and 13% in those treated with placebo. This represents a statistically significant absolute reduction of 2.3% (risk ratio 0.81; 95% confidence ratio [CI] 0.72 to 0.9). In the ISIS-2 study, vascular mortality at 5 weeks was 9.2% in patients treated with streptokinase and 12% in those treated with placebo. This represents a statistically significant absolute reduction of 2.8%. These benefits were independent of those of early aspirin treatment.

Alteplase

- 4.1.1.4 A meta-analysis of eight comparisons of standard alteplase with streptokinase found no significant difference between the two drugs in terms of mortality up to 35 days (odds ratio 1.0; 95% CI 0.94 to 1.06). A statistically significant difference in reinfarction rates in favour of alteplase was found (odds ratio 0.86; 95% CI 0.77 to 0.95). However, alteplase was associated with a statistically significant higher risk of stroke (odds ratio 1.37; 95% CI 1.16 to 1.62), due to a doubling in the risk of haemorrhagic stroke (odds ratio 2.13; 95% CI 1.04 to 4.36). However, streptokinase was associated with a statistically significant higher risk of major bleeds (other than stroke) than alteplase (odds ratio 0.81; 95% CI 0.68 to 0.97). The categorisation and reporting of major bleeding varied between the trials and so it is difficult to judge the clinical significance of these findings.
- 4.1.1.5 The studies included in this meta-analysis used the standard alteplase administration regimen, whereas the GUSTO-I trial used the accelerated regimen and is the only trial to have demonstrated superiority between different thrombolytic agents. The GUSTO-I trial included over 40,000 patients. It found an odds ratio of 0.85 (95% CI 0.78 to 0.94) for 30-day mortality for accelerated alteplase compared with streptokinase, and an absolute reduction in mortality at 30 days of 1.0% (6.3% versus 7.3%; 95% CI 0.4% to 1.6%) in favour

of accelerated alteplase. However, this benefit was balanced by a statistically significantly higher incidence of haemorrhagic stroke (odds ratio 1.42; 95% CI 1.05 to 1.91). Using a combined outcome measure of mortality and disabling stroke, the absolute advantage of accelerated alteplase over streptokinase was lower (0.9%; $p = 0.006$). Rates of bleeds (moderate or worse), allergic reaction, anaphylaxis, congestive heart failure, and sustained hypotension were statistically significantly lower in the group treated with accelerated alteplase. A further meta-analysis of nine comparisons of alteplase with streptokinase, including the findings of GUSTO-I (i.e. accelerated alteplase), found no significant difference between the two drugs in terms of mortality up to 35 days (odds ratio 0.94; 95% CI 0.85 to 1.04).

Reteplase

- 4.1.1.6 Reteplase has also been compared with streptokinase in a study involving 5986 patients (the INJECT study). This study found an absolute difference of 0.5% (95% CI -1.98% to 0.96%) in 35-day mortality in favour of reteplase (not statistically significant). If it is accepted that a 1% difference in mortality is the limit of equivalence in thrombolytic therapy, this suggests that it is unlikely that reteplase is inferior to streptokinase. An alternative interpretation is that in terms of overall effects on mortality and disabling stroke reteplase may be inferior to streptokinase, as the trial also found a statistically significantly lower risk of haemorrhagic stroke (odds ratio 2.1; 95% CI 1.02 to 4.31) in the streptokinase group. However, the trial also found that the rates of heart failure (23.6% vs 26.3%, $p < 0.05$) and allergic reactions (1.1% vs 1.8%, $p < 0.05$) were statistically significantly lower in the reteplase group.
- 4.1.1.7 Reteplase has also been compared with accelerated alteplase in one relatively small ($n = 324$) study that examined intermediate angiographic endpoints of coronary vessel patency (RAPID-2), and one larger study that examined patient-focused endpoints (GUSTO-III, $n = 15,059$). GUSTO-III was designed to test the clinical superiority of reteplase over accelerated alteplase, following the findings in RAPID-2 of better coronary artery patency with reteplase. However, GUSTO-III found no statistically significant difference between the two drugs, in terms of survival or adverse effects. The mortality rate at 30 days was 7.5% in the reteplase group and 7.2% in the accelerated alteplase group: an absolute risk reduction of 0.23% in favour of accelerated alteplase (95% CI -1.10% to 0.66%). Given the confidence limits, reteplase cannot be considered as equivalent to accelerated alteplase.

Tenecteplase

4.1.1.8 ASSENT-2, an equivalence trial of over 16,000 patients compared tenecteplase and accelerated alteplase. The study found that 30-day mortality was almost the same in the tenecteplase group (6.2%) and the accelerated alteplase (6.2%) group. The absolute difference of 0.03% in favour of accelerated alteplase was not statistically significant (95% CI -0.55% to 0.61%). Given the confidence limits, tenecteplase and accelerated alteplase can be considered equivalent in terms of mortality. However, there was a small but statistically significant reduction in the incidence of bleeding with tenecteplase (26.4% compared with 28.9% in the accelerated alteplase group), resulting in fewer blood transfusions in the tenecteplase group (4.3% of patients compared with 5.5% in the accelerated alteplase group). Also, the rate of heart failure was statistically significantly lower in the tenecteplase group than in the accelerated alteplase group (6.1% vs 7.0%, $p = 0.026$).

Subgroups

4.1.1.9 None of the trials discussed was designed to investigate clinical subgroups, such as by age or site of infarct (anterior, inferior). It was concluded that there was no convincing evidence of relative differences in the effectiveness of the available drugs in subgroups. The greater absolute benefit found in patients with anterior infarcts in GUSTO-I may simply be a reflection of the higher baseline risk in this group. The greater relative benefit in patients aged under 75 years was not reflected in their level of absolute risk reduction. None of the differences between the subgroups appeared to be statistically significant by interaction.

Summary

4.1.1.10 In summary, given the evidence on clinical effectiveness, it can be concluded that, in the hospital setting, in terms of mortality:

- standard alteplase is as effective as streptokinase
- reteplase is at least as effective as streptokinase, and
- tenecteplase is as effective as accelerated alteplase.

4.1.1.11 If accelerated alteplase is believed to be superior to streptokinase, then indirectly tenecteplase would also be considered to be superior to streptokinase.

- 4.1.1.12 Conclusions regarding the equivalence of reteplase compared with accelerated alteplase depend on the interpretation of GUSTO-III.
- 4.1.1.13 Furthermore, if reteplase is considered to be equivalent to accelerated alteplase, then this indirectly implies that reteplase is as effective as tenecteplase.
- 4.1.1.14 Important differences in major adverse events between the thrombolytic agents are also apparent. The newer drugs are associated with a higher risk of haemorrhagic stroke compared with streptokinase, but there are no apparent differences in the frequency of haemorrhagic stroke between accelerated alteplase and reteplase (GUSTO-III), or between accelerated alteplase and tenecteplase (ASSENT-2). However, compared with streptokinase, the newer drugs may also be associated with a lower incidence of congestive heart failure. In addition, allergic reactions are more common with streptokinase than with the other drugs, and major bleeds (leading to transfusions) may also be more common with streptokinase, although the evidence on this is not consistent across the trials. There is also some evidence that tenecteplase may be associated with lower rates of major bleeds and heart failure than accelerated alteplase.

4.1.2 Pre-hospital thrombolysis

- 4.1.2.1 No RCTs were found comparing the different thrombolytic drugs in pre-hospital settings.
- 4.1.2.2 However, nine RCTs and a systematic review investigating the feasibility, safety and efficacy of pre-hospital administration of thrombolysis compared with hospital administration were considered in the context of the appraisal. A number of other papers reporting non-randomised studies and audits of pre-hospital thrombolysis were also considered in relation to practical and implementation issues.
- 4.1.2.3 The RCTs were small, except for one that included over 5000 patients (EMIP). They were undertaken in a mixture of urban and/or rural settings in Israel, continental Europe, Canada, the USA, Northern Ireland, and Scotland. A variety of thrombolytic drugs were studied – four studies used alteplase, four used streptokinase-type drugs, and one used urokinase (which is not available in the UK). Only the USA study (MITI) involved paramedics administering the thrombolytic (after remote consultation with a physician). In all but one of the other studies, a hospital physician attended the patient and

administered the drug. In the rural Scottish trial (GREAT) a general practitioner undertook assessment and treatment.

4.1.2.4 The RCTs found that, on average, pre-hospital thrombolysis was administered 58 minutes earlier than hospital thrombolysis; the differences ranged from 33 minutes in the MITI study to 130 minutes in the GREAT study. Individually, the trials failed to show statistically significant reductions in in-hospital mortality, although findings in all of the studies favoured pre-hospital administration. However, a meta-analysis of six of the trials found a statistically significant absolute reduction in mortality of 1.6% (95% CI 0.2% to 3%), and a relative risk reduction of 17% (95% CI 2% to 30%, $p = 0.03$) favouring pre-hospital administration of thrombolysis. This analysis is heavily influenced by the results of the GREAT study (in which thrombolysis was administered by general practitioners in rural Scotland) and therefore does not directly relate to the potential for paramedic based pre-hospital thrombolysis.

4.1.2.5 A number of observational studies examining pre-hospital thrombolysis were considered, although these generally only provide further insight into feasibility and safety. They include studies of administration of anistreplase (a streptokinase-like drug that is no longer available in the UK) by paramedics or general practitioners in a Dutch city, reteplase administered by ambulance-based nurses in Sweden, reteplase administered by paramedics in the USA, anistreplase administered in a rural Italian emergency room, and two reports of a small number of cases of reteplase administered by paramedics with hospital telemetry support in England.

4.2 Cost effectiveness

4.2.1 In-hospital thrombolysis

4.2.1.1 The Assessment Group's literature review found eight published articles on the cost-effectiveness of thrombolytic agents that met the inclusion criteria for the review of cost effectiveness. All compared streptokinase and alteplase (standard and accelerated) in a hospital setting. Three of the articles reported different aspects of the same cost-effectiveness model. Most studies reported incremental costs per life-year gained, and three also reported incremental cost per quality-adjusted life year (QALY). Most of the studies were based on the effectiveness results of GUSTO-I, in which data on resource use were collected only for USA centres. Consequently the analyses undertaken in Canada, Ireland and France had to attempt to translate these to settings in other countries.

- 4.2.1.2 In general, the studies had the following limitations: costs and benefits were not measured in the same populations; comparator treatments were often inadequately described; and the derivation of utility values was inadequately explained. None of the studies undertook costing at a patient level and, while in general similar cost categories were included, only some of the studies included the longer-term costs of stroke and heart failure. Some of the studies included consideration of adverse events, including stroke, reinfarction, major bleeds, anaphylaxis, and congestive heart failure.
- 4.2.1.3 The analyses undertaken following GUSTO-I, which found a survival advantage for accelerated alteplase at 30 days, showed the drug to be cost effective compared with streptokinase within the context of the clinical trial in the US healthcare system. In all of the studies, sensitivity analyses found that assumptions regarding mortality differences and costs were important, and so any conclusions drawn are heavily dependent on the interpretation of the effectiveness findings of GUSTO-I.
- 4.2.1.4 In particular, the economic analysis undertaken in the USA alongside GUSTO-I modelled lifetime costs and benefits, and reported an incremental cost per life-year gained of \$32,678 and an incremental cost per QALY of \$36,402 for accelerated alteplase compared with streptokinase. The subgroup analyses found that accelerated alteplase became more cost effective in patients with higher absolute mortality risk – for example, \$13,410 per life-year gained in patients older than 75 years with anterior myocardial infarction. However, the analysis requires extremely cautious interpretation given a number of issues, including uncertainties over the interpretation of GUSTO-I (in general and in subgroups), application of US data on resource use, and the assumption that costs did not differ significantly between treatment groups.
- 4.2.1.5 Overall, there is little relevant published evidence on the economics of thrombolytics in a UK setting, and none examining the currently available bolus drugs. However, two cost-effectiveness models were submitted by manufacturers.
- 4.2.1.6 It is logical to assume that the earlier the administration the greater the reduction in damage to the heart. However, while precise assumptions about the survival/time-to-treatment curve affect the benefit results in any modelling, it is unlikely that any one drug has a large advantage over any other with regard to timing of administration.

- 4.2.1.7 The two manufacturers' models are similar in structure and scope, although they differ in terms of method and level of detail. Roche's model examines costs up to 30 days, assumes all four drugs have equivalent efficacy, and has less detailed costing. In contrast the Boehringer Ingelheim model includes costing up to 10 years, includes long-term costing for individual complications (such as congestive heart failure and stroke), and incorporates differential survival and complication outcomes for the drugs and more detailed estimation of utilities. Both models incorporate a range of different assumptions regarding adverse events. The models also incorporate adjustment for the timing of administration, including time-savings in pre-hospital settings in which only bolus drugs are compared.
- 4.2.1.8 The Roche model essentially represents a cost-minimisation analysis, and finds reteplase slightly less costly than accelerated alteplase or tenecteplase in hospital. The Boehringer Ingelheim model assumes better survival and a lower incidence of post-infarct congestive heart failure (streptokinase 15.4%, accelerated alteplase 13.5%, reteplase 13.5%, tenecteplase 11.8%) for tenecteplase. These assumptions, together with 10-year discounted costs, lead to a finding that tenecteplase dominates accelerated alteplase and reteplase in hospital (that is, it is of lower cost and greater effectiveness).
- 4.2.1.9 The Assessment Group adjusted key parameters, tested sensitivities and presented revised results using the manufacturers' models. The sensitivity analysis examined the parameter values submitted by the manufacturers for the following: 30-day mortality, strokes, major bleeds, reinfarctions and congestive heart failure.
- 4.2.1.10 The Assessment Group used the adjusted models to compare the three newer drugs with streptokinase. For each comparison, the additional benefit (using QALYs) of the newer thrombolytic was small, while the additional cost was substantial. The cost differences between the newer drugs are relatively small. The most reliable finding is that streptokinase is by far the cheapest drug and although it is a little less effective (in terms of discounted QALYs), it is the most cost effective.
- 4.2.1.11 Using the adjusted manufacturers' models, the incremental costs per QALY reported for the three drugs compared with streptokinase were: accelerated alteplase, £7219 (adjusted Boehringer Ingelheim model) and £7878 (adjusted Roche model); reteplase, £7893 and £10,247; and tenecteplase, £8321 and

£9509. However, these cost–utility rankings of the three drugs relative to streptokinase are sensitive to changes in assumptions in the models, and so are not conclusive.

4.2.1 Pre-hospital thrombolysis

- 4.2.2.1 No published articles examining the cost effectiveness of different thrombolytic drugs in pre-hospital settings were found.
- 4.2.2.2 There is a published economic analysis of the GREAT study comparing cost effectiveness of pre-hospital and in-hospital thrombolysis (that is, the cost effectiveness of the different drugs), which found that pre-hospital delivery had an incremental cost per life saved of £3890. The sensitivity analysis found that the cost per life saved could increase to £88,000. It should also be borne in mind that the benefits found in the GREAT trial were larger than those found in other studies, the economic analysis was not undertaken alongside the trial, the interventions were not described in detail, and the model of rural Scottish general practitioner care is unlikely to be applicable throughout the NHS in England and Wales.
- 4.2.2.3 In the pre-hospital setting, Roche’s model assumes that reteplase and tenecteplase have equivalent efficacy and that reteplase is slightly cheaper. The Boehringer Ingelheim model finds that tenecteplase dominates reteplase in pre-hospital settings (that is, it has a lower cost and greater effectiveness).
- 4.2.2.4 Building on the conclusions about in-hospital cost effectiveness, and since the general pre-hospital delivery costs for the two suitable bolus drugs (reteplase and tenecteplase) would be the same, the relative cost effectiveness of the drugs in pre-hospital settings is likely to be similar to that in hospital (assuming equal effectiveness of both drugs in each setting). On this basis it was concluded that it was not possible to distinguish between reteplase and tenecteplase on grounds of cost effectiveness in pre-hospital settings.

4.3 Consideration of the evidence

4.3.1 In-hospital thrombolysis

- 4.3.1.1 The Committee noted the debate over the applicability of the findings of GUSTO-I beyond the North American centres (where most of the benefit of alteplase over streptokinase was found). The Committee considered that the efficacy of accelerated alteplase should not be determined solely from the results of the GUSTO-I trial.

- 4.3.1.2 Despite concerns over the interpretation of GUSTO-I, the Committee concluded that it was likely that the newer thrombolytic agents are more effective than streptokinase in terms of 30-day mortality.
- 4.3.1.3 The Committee was aware of the documented higher rates of stroke associated with the newer agents and carefully considered the views of clinical experts on this issue.
- 4.3.1.4 The Committee considered that differences in the benefit of one thrombolytic agent over another are less clear if the combination of mortality and stroke endpoints are taken into account, particularly for subgroups at higher risk of haemorrhagic stroke. Furthermore, when considering the combination of mortality and stroke endpoints, it could be argued that the differences in overall benefit are less clear, particularly for subgroups at higher risk of developing haemorrhagic stroke.
- 4.3.1.5 In taking the view that the use of streptokinase is cost effective, the Committee concluded that, although the acquisition cost of each of the newer drugs is substantially higher than that of streptokinase, the available economic evidence demonstrates that the newer drugs have an acceptable incremental cost-effectiveness ratio when compared with streptokinase.
- 4.3.1.6 Given that streptokinase is associated with a lower risk of stroke and is a cost-effective drug, the Committee also considered it appropriate that all of the available thrombolytic drugs should be considered as options for use in care pathways for AMI. Local organisational and clinical policy considerations, such as proximity of CCU facilities and A&E staffing, will also have an impact on decisions regarding the appropriate use of each of the drugs in hospital.
- 4.3.1.7 Because the drugs will have different risk–benefit profiles for individual patients, the Committee concluded that the decision about which of the available drugs to use should be made after balancing the likelihood of the benefits and risks (for example, stroke) to which the different drugs would expose the individual.
- 4.3.1.8 The Committee took into account the potential importance of the methods of administration of the different thrombolytics and their effect on door-to-needle times. However, the impact of this factor on reducing myocardial damage and important clinical outcomes was very dependent on the overall pain-to-needle time. Thus, a saving of a few minutes in the

door-to-needle time was likely to have a much greater impact on these endpoints where the pain-to-needle time was 1 hour compared with the situation where the pain-to-needle time was 6 hours.

4.3.2 Pre-hospital thrombolysis

4.3.2.1 The Committee noted that while there is observational evidence to support pre-hospital thrombolysis, applying the results to the current NHS context is difficult, in that a minority used currently available bolus drugs, most are not paramedic based, and none was reliably generalisable to England and Wales.

4.3.2.2 In the absence of comparative evidence on thrombolytics in pre-hospital settings, the Committee considered that the findings of trials comparing different thrombolytic drugs in hospital could still reasonably be applied to pre-hospital settings, with consideration of the additional relevant factors including safety and applicability examined in the pre-hospital studies outlined above.

4.3.2.3 On the basis of advice from experts that only the bolus drugs were appropriate for pre-hospital administration given the practical difficulties explained in section 3.2.6, and given that no high-quality evidence was available to differentiate reteplase and tenecteplase in terms of clinical effectiveness or cost effectiveness in pre-hospital settings, the Committee considered that either reteplase or tenecteplase could be used in these settings, provided that the necessary infrastructure and training is provided to fully establish an appropriate model of pre-hospital thrombolytic administration.

4.3.2.4 Given the risks associated with thrombolytic drugs and the fact that pre-hospital administration is an emerging practice in England and Wales, the Committee considered it important to ensure high-quality training and supervision of staff involved in the administration of thrombolysis. It was also considered important that clinicians and organisations delivering pre-hospital thrombolysis should develop clear clinical protocols for the use of thrombolytic drugs, such as those developed by the JRCALC, and adopt robust clinical governance arrangements to monitor the use of and outcomes associated with these drugs.

5

Proposed recommendations for further research

5.1 In light of the on-going introduction of pre-hospital thrombolysis, it is recommended that opportunities for the evaluation of the administration of thrombolytic drugs in pre-hospital settings are explored.

6

Resource impact for the NHS

- 6.1 Using estimates of the total number of people receiving thrombolysis and the mixture of thrombolytic drugs used, current annual spending on thrombolytic drugs in England and Wales is estimated to be between £13 million and £26 million (i.e. drug costs alone, excluding VAT).
- 6.2 If, as is believed, the current need for thrombolysis is only partly met, and more clinically eligible patients were to receive thrombolytic drugs, cost estimates would be markedly higher.
- 6.3 It is difficult to predict the local impact of the guidance on the hospital prescribing patterns of available thrombolytic drugs. Consequently only approximate estimates of the likely NHS resource impact of this guidance can be made, based on possible patterns of hospital prescribing of the alternative available drugs.
- 6.4 Assuming that the current overall level of thrombolytic therapy remains unchanged, if streptokinase represented 20% of thrombolytic drugs prescribed, alteplase 10%, and reteplase and tenecteplase each accounted for 35%, then the total annual spending on thrombolytic drugs in England and Wales would be between £27 million and £45 million. If these levels were assumed to be 35%, 20% and 22.5% respectively, then the total would be between £22 million and £36 million.
- 6.5 In addition, substantial costs are associated with the introduction of pre-hospital thrombolysis. These include the costs of additional equipment, training, and potentially longer ambulance time spent treating patients with AMI. Also, any expansion of pre-hospital thrombolysis would result in a shift of drug costs from acute hospital trusts to other services such as ambulance trusts or primary care trusts and, potentially, result in an increase in total local spending on thrombolytic drugs where bolus drugs were not widely used in hospital. Such costs are difficult to estimate usefully on the basis of the information available to the Institute at the time of this appraisal.

7

Implementation and audit

- 7.1 NHS organisations that currently offer or plan to offer treatment for patients with AMI, including ambulance paramedic services, general practitioners and all clinicians involved in the care of these patients, should review policies and practices regarding drugs for early thrombolysis in the treatment of patients with AMI to take account of the guidance set out in Section 1.
- 7.2 Clinical teams involved in the care of patients with AMI should review and revise, if appropriate, any local guidelines or care pathways on early thrombolysis in the treatment of patients with AMI to incorporate the guidance in Section 1.

7.3 The CHD Collaborative of the NHS Modernisation Agency is developing approaches to increase the timeliness of care to people with AMI. For more information, see www.modernnhs.nhs.uk/serviceimprovement/1338/4668/ThrombolysisBulletin2.pdf.

7.4 The Myocardial Infarction National Audit Project (MINAP) collects data that enable clinicians to examine the management of patients with AMI within their hospitals in comparison to the standards in the NSF for CHD. This national audit includes collection of the following data that are relevant to this guidance:

- thrombolytic drug used
- reasons for non-administration of thrombolytic treatment
- reasons for delay in the administration of thrombolytic treatment
- location for the administration of treatment
- who made the initial decision for treatment.

For more information on MINAP, see:

Birkhead JS, Norris R, Quinn T, Pearson M on behalf of the NSFCHD Steering Group (1999) *Acute Myocardial Infarction Core Data Set for Monitoring Standards of Care*. London: Royal College of Physicians, or www.rcplondon.ac.uk/college/ceeu/ceeu_ami_home.htm

The current core dataset appears on the website; the newly revised dataset appears on www.ccad.org.uk

7.5 The JRCALC and the Ambulance Service Association (ASA) are carrying out a national clinical audit to assess the quality of care by ambulance services for people with AMI. The audit relates to the standards set for ambulance services in the NSF for CHD, including pre-hospital thrombolysis. This national audit includes collection of the following data that are relevant to this guidance:

- thrombolytic drug used
- who made the decision to administer thrombolysis
- location of the administration of treatment
- reasons for non-administration of thrombolytic treatment.

For more information on the national clinical audit of AMI, including pre-hospital thrombolysis, contact the ASA National Clinical Effectiveness Programme or see www.asancep.org.uk.

- 7.6 Local clinical audits on the care of patients with AMI also could include criteria for the management of AMI based on the national standards, including standards in the NSF. However, given existing national audit programmes no further audit suggestions are made.

8

Related guidance

- 8.1 In April 2001, NICE issued an inherited clinical guideline on prophylaxis for patients who have experienced a myocardial infarction:

National Institute for Clinical Excellence (2001), Prophylaxis for patients who have experienced a myocardial infarction. NICE Inherited Clinical Guideline A. London: National Institute for Clinical Excellence. Available from www.nice.org.uk

9

Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

The guidance on this technology will be reviewed in October 2005.

Andrew Dillon
Chief Executive

October 2002

Appendix A

Appraisal Committee members

Note The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members appears below. The Appraisal Committee meets twice a month other than in December, when there are no meetings. The Committee membership is split into two branches, with the Chairman, Vice-chairman and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declaration of interests, are posted on the NICE website.

Dr Jane Adam

Radiologist, St. George's Hospital,
London

Professor RL Akehurst

Dean, School of Health Related
Research, Sheffield University

Dr Sunil Angris

General Practitioner, Waterhouses
Medical Practice

**Professor David Barnett
(Chairman)**

Professor of Clinical Pharmacology,
University of Leicester

Dr Sheila Bird

MRC Biostatistics Unit, Cambridge

Professor Carol Black

Consultant Physician, Royal Free
Hospital & UCL, London

Professor John Brazier

Health Economist, University of
Sheffield

Professor Martin Buxton

Director of Health Economics
Research Group, Brunel University

Professor Mike Campbell

Statistician, Institute of General
Practice & Primary Care, Sheffield

Dr Karl Claxton

Health Economist, University of York

Professor Sarah Cowley

Professor of Community Practice
Development, Kings College, London

Professor Jack Dowie

Health Economist, London School of
Hygiene & Tropical Medicine, London

Mr Chris Evennett

Chief Executive, Mid-Hampshire
Primary Care Group

Dr Paul Ewings

Statistician, Taunton & Somerset NHS
Trust

Professor Terry Feest

Clinical Director and Consultant
Nephrologist, Richard Bright Renal
Unit, and Chairman of the UK Renal
Registry

Professor Gary A Ford

Professor of Pharmacology of Old Age/
Consultant Physician, Newcastle upon
Tyne Hospitals NHS Trust

Mrs Sue Gallagher

Chief Executive, Merton, Sutton and
Wandsworth Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety &
Pharmacovigilance, GlaxoSmithKline

Sally Gooch
Director of Nursing, Mid-Essex
Hospital Services Trust

Mr John Goulston
Director of Finance, The Royal Free
Hampstead NHS Trust

Professor Trisha Greenhalgh
Professor of Primary Health Care,
University College London

Miss Linda Hands
Consultant Vascular Surgeon, John
Radcliffe Hospital, Oxford

Professor Philip Home
Professor of Diabetes Medicine,
University of Newcastle

Dr Terry John
General Practitioner, The Firs, London

Dr Diane Ketley
Research into Practice Programme
Leader, NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate
Surgery, Leicester, and Lecturer,
University of Leicester

Ruth Lesirge
Lay Representative; Director, Mental
Health Foundation

Dr George Levvy
Lay Representative; Chief Executive,
Motor Neurone Disease Association

Dr Gill Morgan
CEO, North & East Devon Health
Authority

Professor Miranda Mugford
Health Economist, University of East
Anglia

Mr M Mughal
Consultant Surgeon, Chorley and
South Ribble NHS Trust

Mr James Partridge
Lay Representative; Chief Executive,
Changing Faces

Siân Richards
General Manager, Cardiff Local Health
Group

Professor Philip Routledge
Professor of Clinical Pharmacology,
University of Wales College of
Medicine

Dr Rhiannon Rowsell
Pharmaceutical Physician,
AstraZeneca UK Ltd

Dr Stephen Saltissi
Consultant Cardiologist, Royal
Liverpool University Hospital

**Professor Andrew Stevens
(Vice-chairman)**
Professor of Public Health, University
of Birmingham

Professor Ray Tallis
Consultant Physician, Hope Hospital,
Salford

Dr Cathryn Thomas
General Practitioner, and Senior
Lecturer, Department of Primary Care
and General Practice, University of
Birmingham

Professor Mary Watkins
Head of Institute of Health Studies,
University of Plymouth

Dr Norman Waugh
Public Health Consultant, University of
Southampton

Appendix B

Sources of evidence considered by the Committee

The following documentation and opinion were made available to the Committee

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| <p>A. Assessment report prepared by the Liverpool Reviews and Implementation Group, Department of Pharmacology and Therapeutics, University of Liverpool: <i>Early Thrombolysis for the Treatment of Acute Myocardial Infarction</i>, April 2002</p> <p>B. Manufacturer/sponsor submissions:</p> <ul style="list-style-type: none">• Aventis Behring• Boehringer Ingelheim• Roche <p>C. Professional/specialist and patient/carer group submissions:</p> <ul style="list-style-type: none">• British Association for Immediate Care• British Association for Nursing in Cardiac Care• British Heart Foundation• Faculty of Accident & Emergency Medicine and British Association of Accident and Emergency Medicine• Faculty of Pre-Hospital Care, Royal College of Surgeons, Edinburgh• Joint Royal Colleges Ambulance Liaison Committee and Ambulance Service Association• Primary Care Cardiovascular Society• Royal College of Physicians and British Cardiac Society• Warwickshire Health Authority• Welsh Ambulance Services NHS Trust | <p>D. Expert perspectives:</p> <ul style="list-style-type: none">• Professor Douglas Chamberlain, Chairman, Joint Royal Colleges Ambulance Liaison Committee• Mr Andrew Marsden, Consultant Medical Director, Scottish Ambulance Service• Professor Richard Vincent, Consultant Cardiologist and Professor of Medicine, Trafford Centre for Medical Research |
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Appendix C

Information for patients

Drugs for early thrombolysis in the treatment of acute myocardial infarction

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference number N0172 for the English patient leaflet and N0173 for the bi-lingual patient leaflet.

What is NICE guidance?

The National Institute for Clinical Excellence (NICE) is part of the NHS. It produces guidance for both the NHS and patients on the use of medicines, medical equipment, diagnostic tests and clinical and surgical procedures and under what circumstances they should be used.

To produce this guidance, NICE looks at how well the medicine, equipment or procedure works and also how well it works in relation to how much it costs. This process is called an appraisal. The appraisal process involves the manufacturer of the medicine or equipment for which guidance is being produced and the organisations that represent the healthcare professionals, patients and carers who will be affected by the guidance. Each appraisal takes about 12 months to complete.

NICE was asked to look at the available evidence on the early treatment of heart attacks with drugs that aim to restore the flow of blood to the heart muscle, and provide guidance that would help the NHS in England and Wales decide when they should be used.

What is acute myocardial infarction?

An acute myocardial infarction is a heart attack. A heart attack happens when a blood clot blocks one of the large blood vessels that carry oxygen-rich blood to the heart (known as the coronary arteries). The blockage stops blood reaching part of the heart muscle and the part of the heart affected is so seriously starved of oxygen that it becomes permanently damaged.

A blood clot that forms inside a blood vessel is called a thrombus. In the coronary arteries the blood clot usually forms where the artery is already narrowed by a build-up of fatty substances on its inside wall.

Around 240,000 people experience a heart attack in England and Wales each year. The symptoms develop very quickly and the highest risk of death is within the first hour of experiencing symptoms.

What is early thrombolysis?

A thrombolytic drug is one that breaks down the blood clot so that the blood flow to the heart muscle can be restored and further damage can be prevented. The sooner the blood flow can be restored, the better the chances of limiting the damage to the heart. 'Early thrombolysis' means giving a thrombolytic drug as soon as possible after the heart attack starts.

The usual symptom of a heart attack is a persistent crushing pain in the chest which doesn't disappear with rest. A test called an electrocardiogram, which measures the activity of the heart, is used to confirm that someone has had a heart attack and needs treatment with a thrombolytic drug.

Thrombolytic drugs are given by injection into a vein (called intravenous injection) or by infusion into a vein (called intravenous infusion). ('Intravenous infusion' – often called a 'drip' – means that the liquid drug is slowly delivered to the body through a tube inserted into a vein.) Thrombolytic drugs are routinely given in hospital as soon as possible after it has been confirmed that a patient has had a heart attack. Increasingly, thrombolytic drugs are being given by ambulance paramedics before the patient reaches hospital.

Four thrombolytic drugs are currently available in the UK: alteplase, reteplase, streptokinase and tenecteplase. Alteplase and streptokinase are given by intravenous infusion. Reteplase and tenecteplase are given by intravenous injection.

With thrombolytic drugs there is a risk of bleeding problems, and particularly of bleeding in the brain causing a stroke. People treated with streptokinase develop substances in their blood called antibodies that can prevent streptokinase working if they are treated with it again.

What has NICE recommended?

This guidance from NICE makes recommendations about which thrombolytic drugs should be used for patients who have had a heart attack.

For treatment with thrombolytic drugs in hospital, NICE recommends that doctors should take the following factors into account when deciding which thrombolytic drug (alteplase, reteplase, streptokinase or tenecteplase) to use for an individual patient.

- The benefits and risks, such as stroke, that the thrombolytic drugs are likely to have for the individual patient.
- It is normal practice in the UK that patients who have been treated with streptokinase before should not be treated with it again.
- How the hospital arrangements are set up to ensure that thrombolysis is given as soon as possible after the patient has been admitted.

NICE has also made recommendations about which drugs to use where emergency care arrangements for people having a heart attack include giving thrombolytic drugs before the patient reaches hospital – for example, this might be the set up for communities a long way from a hospital with emergency facilities. Because of the difficulties of setting up an intravenous infusion of a thrombolytic drug somewhere other than in hospital, NICE recommends that in these circumstances a thrombolytic drug given by intravenous injection (reteplase or tenecteplase) should be used.

What should I do?

In a non-emergency situation you may wish to discuss the guidance in this leaflet with your doctor if you have heart problems, have had a heart attack in the past, or think you are at risk of having a heart attack.

Will NICE review its guidance?

Yes. The guidance will be reviewed in August 2005.

Further information

The NICE website (www.nice.org.uk) has further information on NICE and the full guidance on the use of early thrombolysis that has been issued to the NHS. The guidance can also be requested from the NHS Response Line by phoning 0870 1555 455 and quoting reference N0170.

If you have access to the Internet, you can find more information about heart attack, including information about treatment with thrombolytic drugs, on the NHS Direct website (www.nhsdirect.nhs.uk). You can also phone NHS Direct on 08 45 46 47.

