RAPID REVIEWS FOR THE HTA PROGRAMME

Early thrombolysis for the treatment of Acute Myocardial Infarction (AMI)

This protocol is provisional and subject to change

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B. Full title of research question

A rapid and systematic review of the comparative clinical and cost effectiveness of available drugs for early thrombolysis in Acute Myocardial Infarction (AMI) in two settings: i) pre-hospital, and ii) hospital.

C. Clarification of research question and scope

The review will examine the comparative clinical and cost effectiveness of drugs used for early thrombolysis in AMI. The review will be handled in two distinct sections. The first will address the use of thrombolytic drugs within the hospital setting (all settings e.g. accident and emergency, coronary care unit). The second will examine the use of early thrombolysis in the pre-hospital setting provided by appropriate health care workers (e.g. general practitioners, paramedics) in all settings (e.g. home/community, GP surgery, ambulance, community hospital or minor injury units).

Clinically, the review will compare the effectiveness and practicality of four currently available agents (alteplase (tPA), reteplase, streptokinase and tenecteplase) in the two previously defined settings. Background data for two additional drugs (anistreplase and urokinase) which are not currently utilised in the UK will be discussed in the review as appropriate but will not be included as part of data synthesis. Relevant clinical outcomes will include: survival (short and long term), further coronary events, time from on-set of symptoms to thrombolysis, call to thrombolysis time, admission to thrombolysis time, clinical estimates of perfusion (e.g. TIMI flow, ejection fraction, time to reperfusion), quality of life and major adverse events.

The evaluation of economic evidence will include quality assessment of existing cost effectiveness analyses, cost-utility analyses and cost-benefit analyses. An economic model will be developed to estimate the cost effectiveness of the treatment alternatives over the short and medium term. A key focus of this evaluation will be the incremental cost effectiveness of decreasing time to thrombolysis including implications for logistics, staffing and safety in relation to the pre-hospital and hospital setting.

D. Report Methods

Search strategy
The following databases will be searched for relevant published literature (details of the search strategy are given in Appendix 1):

- CCTR (Cochrane Controlled Trials Register)
- CDSR (Cochrane Database of Systematic Reviews)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment (HTA) database
- ISTP (Index to Scientific & Technical Proceedings)
- MEDLINE
- NHS EED (NHS Economic Evaluation Database)
- Science Citation Index

Research groups identified through searches of the registers listed below will be contacted for information about ongoing trials:

- National Research Register
- Cochrane Library CD-ROM
- UKCCCR Register (http://www.cto.mrc.ac.uk/ukcccr/text_only/search.html)
- National Institute of Health (http://clinicaltrials.gov/ct/gui/c/r)

- CenterWatch Clinical Trials Listing Service (http://www.centerwatch.com/main.htm)
- Current Controlled Trials (CCT) (http://www.controlled-trials.com/)

Bibliographies of previous reviews, retrieved articles and industry submissions made to the National Institute for Clinical Excellence (NICE) will be searched for further studies.

Inclusion and exclusion criteria

Identified titles and abstracts will be independently examined by two reviewers. Studies deemed to be relevant will be obtained and assessed for inclusion using criteria described below. Studies which initially appear to meet criteria, but on examination do not, will be excluded and their bibliographic details provided in an appendix of the review. Discrepancies will be resolved by consensus and where necessary a third reviewer will be consulted.

1. Study design

Clinical effectiveness (pre-hospital and hospital)
Randomised controlled trials (RCTs) that include comparison of included drug regimes and any or all of the listed outcomes

Economic evaluation
Full economic evaluations that compare two or more options and consider both costs and consequences: including cost-effectiveness, cost-utility and /or cost-benefit analyses. Full economic evaluations that include a decision analytic model.

2. Interventions

Administration of thrombolytic therapy (alteplase(tPA), reteplase, streptokinase and tenecteplase) in the early stages of AMI delivered in the pre-hospital or hospital setting. Studies that examine the use of anistreplase (not currently available) or urokinase (not currently licensed for use in thrombolysis in the UK) will be identified and used to inform the background of the review but not included in the analysis.

3. Participants

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

4. Outcomes

Data on the following outcome measures will be included:

- Overall survival (short term and long term)
- Other coronary events
- Time from onset of symptoms to thrombolysis
- Time from call to thrombolysis
- Time from hospital admission to thrombolysis
- Clinical evaluation of effectiveness (e.g. TIMI flow rates, ejection fraction, time to reperfusion)
- Quality of life
- Major adverse events

Data extraction strategy

Data relating to study design, findings and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted on pre-tested data extraction forms. Time permitting, attempts will be made to contact authors for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all relevant other publications listed. Only data from English language studies will be included in the report.

Quality assessment strategy

All included studies will be assessed for methodological quality. The quality of clinical effectiveness studies will be assessed using criteria based on CRD Report No. 4 [1](see Appendix 3A). Study quality will be evaluated independently by two reviewers. Disagreements will be resolved through consensus and if necessary a third reviewer will be consulted.

The quality of the cost-effectiveness studies will be assessed using a checklist updated from that developed by Drummond et. al. 1997 [2] (see Appendix 3B). This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Clinical Excellence.[3] This information will be presented in table form and summarised within the text of the report. Where economic evaluations include a decision analytic model the model will be assessed using the check list by Sculpher et al.[4]

Methods of analysis/synthesis of clinical studies

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed.

Analysis of data for pre-hospital and hospital data will be carried out independently. Where sufficient data is available, treatment effects will be presented in the form of relative risks (RR), mean differences (for continuous data) or ratios as appropriate. Relative risk data will be pooled only if this makes sense clinically and statistically. Heterogeneity between studies will be assessed by considering differences in the (a) study population, (b) intervention, (c) outcome measures and (d) study quality. Where appropriate, study results will be subgrouped and analysed according to previously identified risk factors (e.g. age, sex, time to treatment, Killip class, location of infarction).

Methods of analysis for economic studies

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed.

A model will be developed to estimate the comparative cost-effectiveness of early thrombolysis for the treatment of AMI, comparing the alternative treatment strategies. The results will be presented in terms of cost/life year gained. This model will combine data on clinical and cost-effectiveness available from the systematic review and expert clinical opinion (e.g. review panel members, clinicians implementing early thrombolysis) with cost data relevant to the UK NHS. Further details of the modelling and data requirements are summarised below.

Cost data

The primary perspective for the costing will be the NHS. Cost data will therefore focus on the direct health service costs associated with the treatment options (e.g. drugs, equipment for GP, training etc).

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (eg PSSRU cost database) or obtained from other relevant sources (drug price lists, NHS reference costs). All cost data will be converted to a single year (2001) in pounds sterling.

The following data will be needed to estimate costs incurred by the NHS for particular procedures.

- Staff time costs, consumables, overheads and capital charges associated with the treatment alternatives
- Length of stay and treatment intensity during initial hospitalisation
- Post-treatment secondary care treatment during the period of hospitalisation and convalescence

Where appropriate costs will be discounted at 6%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions.

Development of a model will also require data on the following:

- Incidence and prevalence of AMI in the UK by age group, nature of AMI and other appropriate sub-groups
- Time to needle for each of the alternatives
- Outcome data (years of life gained)
- Mortality rates

Assessment of benefits

A balance sheet will be constructed to list benefits and costs arising from alternative treatment strategies. We anticipate that the main measures of benefit will be reduced mortality and improved quality of life post AMI.

Where appropriate, effectiveness and other measures of benefit will be discounted at 1.5%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions. [3]

Modelling

To estimate costs and effectiveness over the lifetime of cohorts of patients who initially receive the different treatment strategies a Markov model will be used. The precise nature of the model will be constrained by the data available. The results in terms of costs and effectiveness will be presented in terms of a balance sheet. A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified in the different treatment options.

Ideally, the results would be presented as incremental cost per QALY ratios for early thrombolysis compared to the alternatives considered. However, it is unlikely that sufficient data will be available to construct these measures with substantial precision. Therefore, in order to inform decision-makers, incremental cost effectiveness analysis will be undertaken.

Detailed sub-group analysis is essential. Individual cost-effectiveness ratios will be identified for each distinct sub-group of the patient population (e.g. type of infarct, setting). As we do not expect to have any data for long follow-up periods (e.g. five years or more), the model may be most suitable for estimating the cost-effectiveness of the treatment alternatives over the short to medium term. Modelling techniques will be used to obtain long-term estimates, though any such projections must be viewed as indicative rather than definitive.

In addition to developing our own economic model, we will undertake a detailed analysis of the industry model(s), (if submitted), which will include an assessment of strengths and weaknesses and a discussion of the implications of different assumptions.

Sensitivity Analysis

Sensitivity analysis will be applied to the model in order to assess the robustness of the results to realistic variations in the levels of the underlying data (e.g. acquisition price of drugs). Where the overall results are sensitive to a particular variable, the sensitivity analysis will analyse the exact nature of the impact of variations.

The results of the evaluation will be used to estimate comparative cost-effectiveness ratios under different treatment scenarios based upon appropriate sub-groups of patients.

E. Handling the company submission(s)

Industry submissions received by January 30, 2002 will be assessed using the review protocol. Data arriving later than this date will be considered only if time and resources allow. Confidential information submitted will be identified and handled as per previously established NICE guidance.[3]

F. Project Management

Timetable/milestones - submission of:

Draft protocol: Due October 15, 2001
Submission of final protocol: November 05, 2001
Receipt of company submission: January 30, 2002
Progress report: February 6, 2002
Submission of draft final report: April 11, 2002

Competing Interests

None of the research team has any competing interests to declare. Any competing interests relating to the external reviewers will be declared in the final report.

External reviewers:

B. The rapid review will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, however, if the rapid review encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will receive a complete and near final draft of the rapid review and will understand that part of their role is to undertake external quality assurance. Where the review contains data that is regarded as 'commercial in confidence' we will require peer reviewers to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will return peer reviewers' signed copies to NCCHTA. Comments from external reviewers and our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

Appendix 1. Details of search strategy

The review team has decided to limit the literature search to randomised controlled trials and cost effectiveness/utility/benefit studies. The following search strategy will be used in MEDLINE, and subsequently translated and adapted for use in the other databases.

1. randomized controlled trial in pt
2. explode "randomized controlled trials"/all subheadings
3. "random allocation"/all subheadings
4. "double blind method"/ all subheadings
5. "single blind method"/ all subheadings
6. clinical trial in pt
7. explode "clinical trials"/all subheadings
8. "controlled clinical trials"/ all subheadings
9. (clin* near3 trial*) in ti, ab
10. ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*))in ti,ab
11. placebo* in ti,ab
12. "placebos"/all subheadings
13. random* in ti,ab
14. explode "research design"/all subheadings
15. explode "Evaluation-Studies"/ all subheadings
16. "Follow-Up-Studies"/ all subheadings
17. "Prospective-Studies" / all subheadings
18. (control* or prospectiv* or volunteer*) in ti,ab
19. #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 or #17 or #18
20. tg=animal
21. tg=human
22. #20 not (#20 and #21)
23. #19 not #22
24. alteplase in ti,ab
25. tPA in ti,ab
26. reteplase in ti,ab
27. streptokinase in ti,ab
28. tenecteplase in ti,ab
29. anistreplase in ti,ab
30. urokinase in ti,ab
31. #24 or #25 or #26 or #27 or #28 or #29 or #30
32. “acute myocardial infarction”/all sub headings
33. (myocard* near4(infarct* or acute)) in ti,ab
34. #32 or #33
35. #23 and #31 and #34

Full details of the searching process will be recorded.

Appendix 2. Details about data extraction

A. Clinical effectiveness data to be extracted will include but not be limited to

Study Details

- Study bibliographic data
- Type of report (abstract, full manuscript, interim report)
- Type of study
- Comparison drugs
- Concomitant drug therapy

Participants

- Age
- Sex
- Killip class
- Site of infarction (ECG results)
- Previous cardiac history
- Number recruited or accrued
- Length of follow-up

Results (data for all outcomes specified in the protocol will be extracted as available)

- Mortality (short term and long term)
- Other coronary events
- Time from onset of symptoms to thrombolysis
- Time from call to thrombolysis
- Time from admission to thrombolysis
- Clinical evaluation of effectiveness (e.g. TIMI flow rates, time to reperfusion)
- Quality of life
- Major adverse events

Appendix 3. Details about quality assessment

A. Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No. 4 [1]

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 will be graded in terms of ✔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.

B. Studies of cost effectiveness will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond:[2]

1. Study question
2. Selection of alternatives
3. Form of evaluation
4. Effectiveness data
5. Costs
6. Benefit measurement and valuation
7. Decision modelling
8. Discounting
9. Allowance for uncertainty
10. Presentation of results

All items will be graded as either ✔yes (item adequately addressed), ✕ no (item not adequately addressed), **?** unclear or not enough information, NA not applicable or NS not stated.

Appendix 4. Background information

Coronary heart disease is a major cause of morbidity and mortality in England and Wales.[5] Within the broad category of heart disease Acute Myocardial Infarction (AMI) affects an estimated 270,000 people each year. Of these approximately 50% die within 30 days of infarct and over half of these die prior to reaching hospital.[5]

Description of the technology

Standards for early treatment of symptoms of AMI are based on a goal of pharmacological dissolution of thrombotic coronary artery occlusion. This is achieved through intravenous infusion of plasminogen activators designed to activate the fibrinolytic system.

Research over the past 30 years has evaluated a number of thrombolytic agents. Initial research provided evidence of effectivness of streptokinase versus placebo. A cumulative meta-analysis by Lau et al in 1992[6] indicated that by 1977 the results of trials of early thrombolysis showed decreases in mortality. Evaluation of large trials conducted by the Fibrinolytic Therapy Trialists (FTT) Collaborative Group[7] indicated that fibrinolytic therapy decreases mortality and that the its use was beneficial in a wider range of patients then were currently receiving treatment. Analysis of pooled data also identified the benefits of early versus late thrombolysis.

However, the formation of antibodies precludes repeated use of streptokinase and its delivery as an intravenous solution over time makes its delivery cumbersome. Subsequent research has focused on the equivalence of new agents such as reteplase and tenecteplase that have the advantage of bolus administration but the disadvantage of higher per dose costs.

Thrombolysis is not without its drawbacks. Side effects, primarily bleeding, can be catastrophic. Assessment of any new agent requires analysis of the risk of major adverse events such as stroke or haemorrhage.

Current indications for thrombolysis

Treatment is aimed at patients in the early stages of AMI. However, diagnosis of myocardial infarction is not always simple. Patients may present with typical chest pain that is severe and lasts more than 15 minutes. However pain may not be severe and manifestations of dyspnoea or syncope are common. Pain may radiate to the neck jaw or arm. ECG readings may indicate changes consistent with myocardial damage (e.g. ST elevation, new Q waves or bundle branch block). However, newly evolving infarctions may not yet manifest these changes and repeat readings may be necessary.

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.[8]

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

Current available agents

Generic Name	Proprietary name	Supplier	Dosage	Method of adminstration	Approximate cost [9]
Streptokinase(SK)	*Kabikinase*® No longer produced *Streptase* ®	Aventis	1.5 million units	IV infusion	£80-85
Alteplase Tissue plasminogen activator t-PA rtPA	*Actilyse* ®	Boehringer Ingleheim	Accelerated: 15 mg bolus 50 mg over 30 minutes 35 mg over 60 minutes	IV bolus/infusion	£600
Tenecteplase	*Metalyse* ® TKN-tPA *TKNase* ®	Boehringer Ingleheim	40-50 mg	IV bolus	£700-800
Reteplase	*Rapilysin* ®	Roche	10 U followed by 2nd 10 U in 30 minutes	IV bolus	£720
Urokinase	N/A	N/A	2.0 million units	IV bolus	£460
Anistreplase APSAC	N/A	N/A	30 units	IV bolus	£495

Current service provision

The National Service Framework for Coronary Heart Disease and the NHS Plan for England include standards for reduction in 'call to needle time' to 60 minutes, 'door to needle' time of 20 minutes and provision of pre-hospital thrombolysis when 'call to hospital' time is greater than 30 minutes.[10] The National Service Framework for Wales includes similar response times but does not currently include pre-hospital thrombolysis.[11] The recommendations within these framework are consistent in concept with recommendations previously made by the British Heart Foundation[12] although recommended time to treatment is somewhat shorter in the National Framework.

Delivery of early thrombolysis is complex and delays in treatment are a result of both patient and service factors.[13 14] Service delivery varies across the country as shown through examination of treatment of patients with AMI in 39 UK hospitals.[15] In addition, a report of research conducted in Scotland to assess call to needle times[16] prompted multiple responses from practitioners in the UK describing extensive variations in practice.[17 18]

A recent survey of Ambulance Trusts (personal communication Prof Chamberlain) indicates that only a small number of Trusts administer thrombolysis in the pre-hospital setting and in only one of these do the paramedics act autonomously.

Current options in thrombolysis for AMI include streptokinase, alteplase, reteplase and tenecteplase. In addition to variation in costs, there are differences in the ease of administration, monitoring and

associated treatments. Differences in favourable and unfavourable outcomes will be included in the current review.

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