REVIEW

Thrombolysis: past, present, and future

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Management of myocardial infarction evolved because of understanding of underlying disease processes and clinical trials of “chemical” and “mechanical” clot dissolution that reduced in-hospital mortality. Meta-analysis comparing these treatment strategies marginally favours angioplasty. Current European Society of Cardiology guidelines propose primary angioplasty as the preferred therapeutic option but few units in the UK can offer angioplasty on demand as a designated “heart attack centre”. Thrombolysis will continue as it is widely available and training needs and costs less than angioplasty. Community thrombolysis should be made available for those patients who do not wish for such aggressive intervention or as a prelude to transfer time to a heart attack centre distant from a triage hospital.

A series of multicentre, international mega-trials investigated the clinical relevance of thrombolysis-SK^{8,9} and APSAC, a variant of SK¹⁰ reduced early mortality by 23%–50% with minimal risk of bleeding and stroke if given within six hours or so of the acute event, the so called thrombolytic window. Aspirin reduced mortality at least as well as SK but the combination proved even more effective.⁹ These clinical trials changed medical practice as thrombolysis was rapidly adopted as the gold standard (table 1).

Genetic engineering produced a crop of new agents. First came tissue plasminogen activator or t-PA that improved coronary patency more than SK¹¹ and a larger first dose (or front loading) of t-PA produced more rapid re-perfusion,¹² followed by Reteplase¹³ and Tenecteplase,¹⁴ both at least as effective as existing agents, but with simpler dosing regimens.

POTENTIAL PROBLEMS WITH THROMBOLYTIC DRUGS

Thrombolytic drugs are remarkably well tolerated, with nausea, vomiting, and bleeding from injection sites the most common problems. Allergic reactions may occur with SK but all agents can cause hypotension, reperfusion arrhythmias, and intracerebral haemorrhage.

Contraindications generally relate to risk of bleeding and in the case of streptokinase, allergy, or lack of efficacy due to persistent antistreptococcal antibodies.

CONVERTING TRIAL SUCCESS INTO ROUTINE CLINICAL PRACTICE

Thrombolysis was introduced fairly quickly into routine hospital practice soon after the publication of clinical trials in 1988, with most CCUs adopting a treatment time window of up to six hours after the onset of symptoms, based on ISIS-2, and later up to 14 hours in line with ASSET findings.

At this time, all patients tended to be examined and diagnosed either in the CCU or in the emergency department by a junior doctor, who prescribed a thrombolytic for administration by a nurse. Systems were not efficient and a door to needle time in excess of an hour was not unusual.

After a meta-analysis of published studies,¹⁶ it became clear that the sooner thrombolysis was given after the onset of chest pain, the greater the survival benefit—the golden hour (later lengthened to about three hours¹⁷) identified the period in which greatest benefit derived. The concept of fairly leisurely treatment on the basis of the thrombolytic window had to be abandoned.

Acute myocardial infarction remains one of the most common causes of death in the western world. Mortality and morbidity are the result of ischaemia, causing pump failure, ventricular arrhythmia, and cardiac rupture. Mortality was reduced after the opening of coronary care units (CCUs) in the late 1960s to monitor for and treat cardiac arrhythmia, particularly ventricular fibrillation, and training of ambulance crew in first basic, and later advanced, cardiopulmonary resuscitation. Pharmacological intervention was hindered by imperfect understanding of the pathophysiology of coronary disease as at that time thrombotic occlusion of a coronary artery at a site of atherosclerotic plaque was considered to be a consequence rather than a cause of infarction¹ until pioneering work by Falk² and by Davies and Thomas³ in the 1980s. Improved knowledge of the coagulation and fibrinolytic systems and their contribution to the acute coronary occlusive process heralded the era of thrombolysis.

A BRIEF HISTORY OF THROMBOLYSIS

That some strains of streptococci could induce fibrinolysis in human plasma clots had been known for decades.⁴ The results of early trials in acute myocardial infarction showing a significant reduction in mortality were ignored for over 30 years because of uncertainty about the aetiology of the infarction process until both intra-arterial⁵ and intravenous streptokinase (SK)⁶ induced rapid recanalisation of occluded vessels, preserved left ventricular function,⁷ and decreased mortality.

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Table 1 Selected landmark clinical trials in thrombolysis

Clinical trial	Thrombolytic	Trial design and treatment regimen	Main findings
GISSI-1	SK ⁸	Randomised, un-blinded. Conventional treatment +/- SK 1.5M units IV. Concomitant therapy according to normal practice.	21 day mortality SK 10.7% v controls 13%. At one year, mortality SK 17.2% v 19% controls.
AIMS	APSAC ¹⁰	Randomised, double blind, placebo controlled. APSAC 300units IV bolus over 5 minutes within 6 hours of symptom onset; or placebo. Concomitant therapy heparin IV and other medication according to normal practice. β blocker on hospital discharge.	Premature termination of trial as 47% reduction in 30 day mortality with anistreplase.
ASSET	t-PA ¹²	Randomised, double blind, placebo controlled. t-PA 10 mg bolus within 5 hours of symptom onset, followed by infusion of 50 mg/h for first hour and 20 mg/h for next 2 hours; or placebo. Concomitant therapy heparin bolus and infusion for 21 hours. Anticoagulation, aspirin, and other antiplatelet drugs not permitted. β blockers permitted on hospital discharge.	30 day mortality t-PA 7.2% v 9.8% placebo. 6 month mortality t-PA 10.4% v 13.1% placebo.
ISIS-2	SK + ASA ⁹	Randomised, double blind, placebo controlled. Streptokinase 1.5M units over 1 hour, and/or aspirin 162.5 mg/day orally for 1 month; or placebo. Concomitant therapy according to normal practice.	35 day vascular mortality SK 9.2% v 12% placebo; Aspirin 9.4% v 11.8% placebo; SK plus aspirin 8% v 13.2% placebo.
GUSTO-1	SK +/- Tpa ¹¹	Randomised. SK 1.5M units over 1 hour plus SC heparin 12500 units twice daily; or SK 1.5M units over 1 hour plus IV heparin bolus 5000 units followed by 1000–1200 units/hr adjusted to APTT of 60–85 seconds; or accelerated t-PA as 15 mg bolus then 0.75 mg/kg up to 50 mg over 30 minutes and 0.5 mg/kg up to 35 mg over next 60 minutes with IV heparin as above; or t-PA 1 mg/kg over 1 hour up to 90 mg plus SK 1.5M units over 1 hour given simultaneously and IV heparin as above. Concomitant therapy aspirin 160–325 mg daily, Atenolol 5 mg IV then oral 50–100 mg daily. Other treatment according to normal practice.	30 day mortality SK plus SC heparin 7.2% v 7.4% SK plus IV heparin; t-PA plus IV heparin 6.3% v 7% t-PA plus SK plus IV heparin.
INJECT	r-PA v SK ¹³	Randomised, double blind. SK 1.5M units over 1 hour, or r-PA 10 mg double bolus 30 minutes apart. Concomitant aspirin and heparin.	35 day mortality r-PA 9% v 9.5% SK.
ASSENT-2	n-PA vs t-PA ¹⁴	Randomised, double blind. n-PA 30–50 mg according to bodyweight over 5–10 seconds, or t-PA 15 mg bolus followed by 0.75 mg/kg up to 50 mg infused over 30 minutes then 0.5 mg/kg up to 35 mg infused over 1 hour; or placebo. Concomitant aspirin and heparin.	30 day mortality n-PA 6.18% v 6.15% t-PA.
GREAT	Anistreplase ¹⁵	Randomised, double blind. Anistreplase 30 units IV over 5 minutes at home or on arrival in hospital. Patients receiving placebo at home given anistreplase in hospital. Concomitant therapy according to normal practice.	1 year mortality 10.4% community treated v 21.6% thrombolysed in hospital. Average "time to thrombolysis" reduced from 240 minutes in hospital to 101 minutes in community, accompanied by significant reduction in hospital and one year mortality.

SK, streptokinase (non-proprietary and Streptase); t-PA, alteplase (Actilyse); r-PA, reteplase (Rapilysin); n-PA, tenecteplase (Metalyse); APSAC (anisoylated plasminogen streptokinase activator complex), anistreplase—no longer available in the UK. GISSI-1, Gruppo Italiano per lo Studio della Streptichinasi nell'Infarto miocardico. AIMS, APSAC intervention mortality study. ASSET, Anglo-Scandinavian study of early thrombolysis. ISIS-2, second international study of infarct survival. GUSTO-1, global utilisation of streptokinase and t-PA for occluded coronary arteries-1. INJECT, international joint efficacy comparison of thrombolytics. ASSENT-2, assessment of the safety and efficacy of a new thrombolytic-2. GREAT, Grampian Region early anistreplase trial.

done in favour of rapid appraisal, speedier diagnosis, and prompt delivery of thrombolysis.

SYSTEMS RE-DESIGN

The National Service Framework for Coronary Heart Disease¹⁸ provided a stimulus to rapid diagnosis and management of acute infarction, setting a target door to needle time of 30 minutes and later 20 minutes. Re-thinking of clinical roles because of pressure on junior doctors' time and workload encouraged many hospitals to expand the role of the experienced CCU nurse and nurse initiated, protocol driven thrombolysis was introduced. Nationally, 76% of units meet the 30 minutes criterion.¹⁹

ADVANTAGES AND DISADVANTAGES OF INDIVIDUAL THROMBOLYTICS

All thrombolytic agents are of proved efficacy, but convenience and simplicity of administration are important, especially when considering speedy delivery.

Four agents are licensed in the UK: SK (non-proprietary and Streptase), alteplase (Actilyse), reteplase (Rapilysin), and tenecteplase (Metalyse).

Each must be reconstituted before use. SK must be infused over an hour, making it more suitable for hospital than community use. Two drugs are bodyweight dependent—Metalyse, which is injected in a single bolus and alteplase, which must be infused, working best with an accelerated infusion rate. Reteplase is independent of weight and is injected as a double bolus, 30 minutes apart.

Only SK does not require heparin as adjunctive therapy for at least 24 hours to prevent re-thrombosis.

TRENDS IN HOSPITAL BASED THROMBOLYSIS THERAPY

SK the cheapest thrombolytic, has been the UK's drug of choice in a first infarction for many years. For a second infarct, however, most clinicians recommend an alternative agent as antibodies to streptokinase develop in almost half of all patients; these persist for years, rendering further administration of SK useless. European and American doctors favour Alteplase, which produces marginally better outcomes in younger patients and those with an anterior infarct.

With many units adopting protocol driven thrombolysis, the greater convenience, simple dosing regimen, ease, and

speed of administration and time and cost saving of bolus thrombolytics become more apparent, especially when considering emergency treatment in the community.

THROMBOLYSIS IN THE PREHOSPITAL ENVIRONMENT

Even modest delays in treatment may be detrimental as myocardial cell death starts within minutes of symptom onset so the finding in the GREAT trial¹⁵ that prehospital thrombolysis saved lives was not surprising. This ought to become routine clinical practice, with the goal of minimising pain to needle time.

Rural patients with prolonged ambulance transport times are likely to benefit from early thrombolytic treatment in the community but even urban patients should be considered for community thrombolysis if traffic congestion is likely to delay treatment.

KEY FACTORS IN PROVIDING EFFECTIVE PREHOSPITAL THROMBOLYSIS

Usually drugs are prescribed on an individual basis to an individual patient by a doctor. Legislative changes to allow non-medical health professionals to prescribe drugs may be necessary, including a detailed written instruction relating to the supply and administration of specific drugs in specific clinical settings—a Patient Group Directive.

Training, experience, and confidence are essential key components of any successful clinical intervention. UK paramedics already have a variety of clinical skills relevant to the management of acute coronary disease in the community; inevitably, some will need training in ECG recognition and others in drug administration but all will need to become confident in the decision making process of who should, and should not, be thrombolysed. Pending the provision of a round the clock service of paramedics able to manage infarct patients independently, access to advice from a nearby CCU, or some other remote source will be invaluable. Development of a robust protocol designed in conjunction with and shared by secondary care would be clinically invaluable.

DELIVERING PREHOSPITAL THROMBOLYSIS THROUGHOUT UK

Community thrombolysis is already available in some parts of the UK. Patient Group Direction, growing awareness of and interest in thrombolysis will facilitate an expansion of the number of crews able to provide prehospital treatment.

PRIMARY ANGIOPLASTY: ALTERNATIVE OR ADJUNCT TO THROMBOLYSIS?

Percutaneous coronary angioplasty, well established in chronic stable angina, opens the occluded artery mechanically, first restoring coronary patency by disrupting the acute thrombosis with a high degree of certainty (unlike chemical lysis in which reperfusion is assumed if the ST segments of the ECG resolve soon after thrombolysis); and second obliterating the underlying coronary plaque.

Angioplasty may be offered as a primary procedure in preference to thrombolysis or as an adjunct when thrombolysis has failed to restore the ST segments to baseline within 90 minutes, so called rescue angioplasty. Both strategies require an important commitment in terms of laboratory access and trained staff but in-hospital mortality can be as low as 2%.²⁰

A meta-analysis of 23 trials reported that angioplasty may have the edge, reducing re-infarctions, strokes, and mortality over in-hospital lysis²¹ but not prehospital lysis.²²

A VIEW OF THE FUTURE FOR ACUTE MYOCARDIAL INFARCTION IN THE UK

Coronary angioplasty has become widely available in many centres in Europe and the USA, either as primary treatment or as rescue for failed reperfusion. Guidelines from the European Society of Cardiology²³ now recommend angioplasty rather than thrombolysis, provided that it can be delivered within 90 minutes of first medical contact.

At present, most NHS patients will be given a thrombolytic agent, as few units are able to provide a round the clock angioplasty service. The Hammersmith Hospital, London runs the UK's first round the clock primary angioplasty service and their 30 day mortality is reported as 3% with angioplasty compared with 12% for thrombolysis.²⁴ Hospitals able to fund a similar service may soon receive patients with an acute infarction diverted from a local hospital to a designated heart attack centre for mechanical clot dissolution rather than chemical lysis.

POTENTIAL IMPLICATIONS FOR THE UK

Undoubtedly, setting up heart attack centres would demand considerable investment in equipment, training, and staffing levels; existing services would have to be reconfigured; more out of hours work might warrant shift working of key cardiac catheter lab staff; greater journey times from remote country areas would place greater strain on ambulance services already struggling to meet response time targets; delayed treatment because of travelling might precipitate potentially fatal arrhythmia; and patients and their relatives might be inconvenienced. Routine angiography after thrombolysis has been proposed,²⁵ so with lab staff and equipment on continual alert, there may well be an adverse (albeit unintended) impact on elective angiography and angioplasty rates.

The financial, staffing, and training implications are considerable. Commissioning new catheter lab facilities might be prohibitively expensive so it is probable that existing units will face unprecedented and potentially overwhelming demand.

CONCLUSION

In acute myocardial infarction, medical practice has changed considerably over the past 40 years, rapidly incorporating clinical trial findings into clinical practice.

Time remains an important factor in acute myocardial infarction. Thrombolysis and primary angioplasty can do little to reduce the 50% of all deaths that occur in the community²⁶ unless medical (or paramedical) help is sought more quickly than at present. Campaigns to raise public awareness have met with limited success.²⁷ For some patients, their local hospital will provide rapid access to primary angioplasty. For others, the heart attack centre may be relatively remote.

Despite the lack of conclusive data,²⁸ thrombolysis given by paramedic crews en route to the heart attack centre may restore coronary patency sufficiently to salvage myocardium. Ambulance crew may observe an increase in cardiac arrhythmia solely because of prolonged contact time. A decision regarding angioplasty can be made on arrival at the centre, either as a rescue procedure or delayed 24 hours.

There are clear differences in cost and cost effectiveness of the various thrombolytics. "Given the similarity in outcome, cost-effectiveness becomes largely determined by the acquisition costs of the drug".²⁹ An economic evaluation of the cost effectiveness of primary angioplasty compared with thrombolysis is awaited, but if primary angioplasty emerges as a feasible strategy and displaces thrombolysis as the treatment of choice in acute myocardial infarction in the UK, as it has done in Europe and the USA, clinicians must ensure that it

does not take the 25 years it took, from first clinical trial reports to routine, optimal provision of lysis on demand, to achieve the same with angioplasty.

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