Recent advances

Treatment of myocardial infarction

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Coronary artery occlusion is responsible for 180 000 admissions to hospital each year in the United Kingdom. Vessel obstruction is commonly caused by the formation of a thrombus, and timely treatment with thrombolytic drugs such as streptokinase has improved the immediate and longer term outlook after acute myocardial infarction.[1–5] Mortality in patients given thrombolytic drugs sufficiently early is 10% to 12%—a third less than mortality in untreated patients. The benefits of thrombolytic treatment have been shown clearly in clinical trials, but there are limitations. We review current practice and the research that is currently under way to improve outcome in patients who have had acute myocardial infarction.

Recent advances

Thrombolytic drugs have reduced mortality in patients with acute myocardial infarction, but current treatments have limited success in achieving immediate vessel patency and in maintaining this in the longer term

The best current thrombolytic treatment—accelerated tissue plasminogen activator—restores complete perfusion in only 54% of patients, while streptokinase achieves this in 30% only

Thrombolytic drugs such as recombinant plasminogen activator and prourokinase are being developed, but must be tested in large clinical trials

The future of recently developed antithrombin drugs to reduce arterial reocclusion is uncertain

New platelet receptor blocking drugs seem to have most potential to improve rates of immediate and longer term vessel patency

The greater benefits of primary angioplasty compared with thrombolysis have not been established definitively

Current practice

Current clinical practice is based on considerable research and debate over the past 10 years. Thrombolytic drugs should be given as soon as possible, although benefit may occur for up to 12 hours after onset of symptoms.[6] Use of audit review to ensure that thrombolysis is given early is a priority. An electrocardiogram should be done within 15 minutes and thrombolysis started within 30 minutes of the patient's arrival in hospital.

The global utilisation of streptokinase and tPA for occluded arteries (GUSTO-I) trial showed that tissue plasminogen activator may be better than streptokinase in those patients who are younger, present earlier, have anterior infarction, and who have been given streptokinase for a previous myocardial infarction.[5] Aspirin seems to be as beneficial as thrombolytic drugs, although its action is unclear and may not be entirely related to its anticoagulant effects.[3] Lifelong treatment with aspirin after myocardial infarction seems to be generally accepted.[7] Early treatment with angiotensin converting enzyme inhibitor drugs in people with impaired ventricular function, and β blocking drugs in those whose ventricular function is not severely impaired, improve the outcome in the longer term.[8] Nitrates and prophylactic antiarrythmic drugs do not have any benefit.[8 9] Consensus opinion is also against giving magnesium, although some doctors favour its use, especially in patients who are not receiving thrombolytic treatment.[8 10]

Keeping arteries open

The "open artery" principle is considered a vital one in improving the outcome after myocardial infarction. The obstructed vessel should be unblocked as soon as possible, and patency should be maintained to improve the patient's prognosis and reduce morbidity. Reimer et al showed that early restoration of blood flow improved the subsequent function of the left ventricle.[11] A more recent trial using graded outcomes determined by the thrombolysis in myocardial infarction trial (TIMI) showed that the higher the grade achieved (see box), the lower the mortality at 30 days.[12] Patients with TIMI grade 0 (complete occlusion) at 90 minutes had a 30 day mortality of 8.4%, whereas mortality was 4% in patients with TIMI grade 3.[12]

TIMI grade

Grades determined in the thrombolysis in myocardial infarction trial (TIMI) measure blood flow and luminal narrowing.[12]

- Grade 0: no flow of contrast beyond the point of occlusion
- Grade 1: penetration with minimal perfusion (contrast fails to opacify the entire coronary bed distal to the stenosis for the duration of investigation)
- Grade 2: partial perfusion (contrast opacifies the entire distal coronary artery, but the rate of entry or clearance, or both, is slower in the previously blocked artery than in nearby normally perfused vessels)
- Grade 3: Complete perfusion (contrast filling and clearance are as rapid in the previously blocked vessel as in normally perfused vessels)

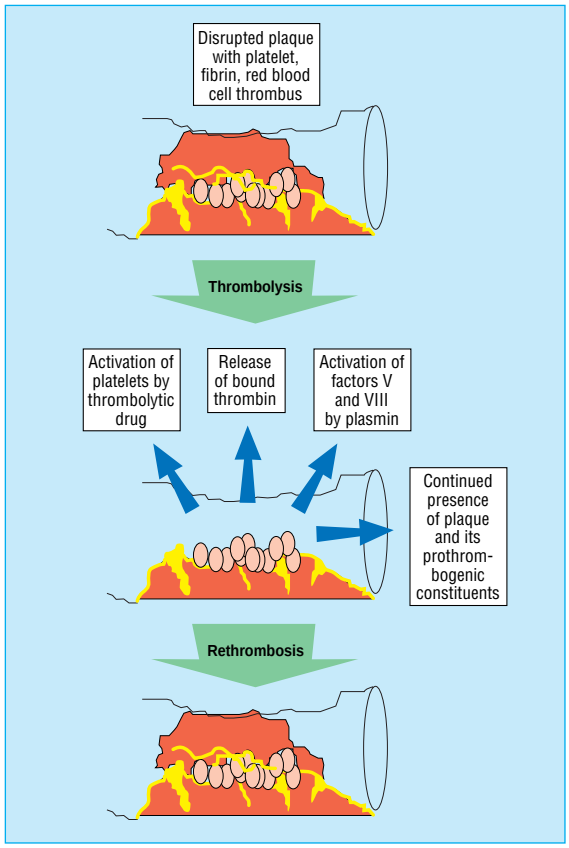
How successful is current treatment?

Current thrombolytic treatments are not wholly successful in clearing the vessel immediately, and perhaps more importantly, they are not particularly good at maintaining patency. Lowest mortality is associated with TIMI grade 3—restoration of complete perfusion in the obstructed coronary artery. The best thrombolytic treatment currently available—accelerated tissue plasminogen activator—achieves grade 3 patency in only 54% of patients. Although this is better than streptokinase (30% of patients treated had TIMI grade 3), there is clearly still room for improvement. The differences in vessel patency achieved by tissue plasminogen activator and streptokinase treatment have not resulted in a significant difference in mortality in most trials (table).[13] Though the GUSTO-I trial showed reduced mortality with tissue plasminogen activator treatment, this benefit was partly offset by an excess of strokes in this treatment group.[5]

Arterial reocclusion

Tissue plasminogen activator may fail to show a clear benefit because the artery may become blocked again in the first few hours after initial opening. This is a particular problem with drugs such as tissue plasminogen activator that have a short half life. Reocclusion is time dependant—up to 30% of previously open arteries are obstructed after 3 months. This is important since the event free survival after 3 years is significantly less in patients with a subsequently occluded artery (68% *v* 92%).[14]

Increased understanding of the central role of platelets and thrombus after the disruption of plaque in coronary occlusion has led to research directed at increasing and maintaining vessel patency early with newly developed drugs. Rethrombosis depends on a favourable local environment. Generated plasmin can activate coagulation factors V and VIII, and plaque contents, thrombin release, and platelet activation by the thrombolytic drug may all contribute to reocclusion (figure).[15 16] The effectiveness of heparin and aspirin, which are widely used as adjunctive antithrombotic drugs, may be limited in an environment that is so favourable to thrombus formation, and newer and more powerful drugs have become available.



Reactivation of the pathways of coagulation, and the persistence of stimuli that led to the thrombotic occlusion in the first place, cause rethrombosis

Which drug, which regimen?

Thrombolytic drugs that are currently available include streptokinase, tissue plasminogen activator, and recombinant single chain urokinase. In the United Kingdom, streptokinase is generally used first because it is cheapest, but this practice has been changed slightly by the results of the GUSTO-I trial (table).[12] Tissue plasminogen activator is now given to patients previously treated with streptokinase because the development of antistreptokinase antibodies puts them at risk of allergic reactions and reduces the effectiveness of thrombolysis.

Changing the treatment regimen for tissue plasminogen activator seems to increase the success rate. In the GUSTO-I trial, 100 mg of tissue plasminogen activator given over 90 minutes rather than 3

Overview of mortality in large trials comparing streptokinase and tissue plasminogen activator or tissue plasminogen activator mutant drugs

Trial	No of patients	Mortality (%)	
		Tissue plasminogen activator	Streptokinase
Gruppo Italiano per lo studio della sopravivenza nell'infarcto miocardico-2 (GISI-2)	12 490	9.0	8.6
Third international study of infarct survival (ISIS-3)	41 299	10.3	10.6
Global utilisation of streptokinase and tPA for occluded arteries (GUSTO)	41 021	6.3*	7.3
International joint efficacy comparison of thrombolytics (INJECT)	6 000	8.9†	9.4

*Accelerated tissue plasminogen activator.
†Recombinant tissue plasminogen activator (reteplase).

hours increased the proportion of patients with a TIMI grade of 2 or 3 from 70% to 81%. Preliminary data suggest that a regimen of two bolus doses of 50 mg of tissue plasminogen activator, given 30 minutes apart, may result in 91% of patients achieving TIMI grade 2 or 3 perfusion, but this needs to be confirmed in larger clinical trials. The short half life of tissue plasminogen activator and the fact that its early success in clearing blocked vessels has not been translated into an obvious clinical advantage has led investigators to look for better thrombolytic drugs. Reteplase was recently shown to be as effective as tPA.[17]

New thrombolytic drugs

New thrombolytic drugs, including tissue plasminogen activator mutants or variants of tissue plasminogen activator, are currently in development or undergoing clinical trials. These drugs may have altered resistance to inhibitors such as plasminogen activator inhibitor-1 or require binding to fibrin to become active.[18] Other approaches have involved altering thrombolytic molecules (for example, changing the kringle 2 region of tissue plasminogen activator) to reduce their plasma clearance, although these modifications may lessen the drugs' thrombolytic effectiveness. The results of early clinical trials of tissue plasminogen activator mutants are promising.[19]

Recombinant plasminogen activator and prourokinase drugs

New plasminogen activator drugs such as recombinant plasminogen activator and prourokinase are currently undergoing clinical studies. Reteplase, a recombinant plasminogen activator, is a non-glycosylated deletion mutant of wild type tissue plasminogen activator. It differs from tissue plasminogen activator at two molecular points, and deletion of these molecular domains contributes to its longer half life.[20] Initial studies (the RAPID 1 and RAPID 2 trials [21]) were open, randomised studies to determine dosage. Results of recombinant plasma activator treatment studies are encouraging; they show vessel patency rates similar to those achieved with accelerated tissue plasminogen activator. Reteplase was compared with streptokinase in the international joint efficiency comparison of thrombolytics trial (INJECT) and is being compared with tissue plasminogen activator in the GUSTO-III trial. The former trial, in 6000 patients, showed that reteplase was as effective as streptokinase in reducing mortality, and was even better in some ways.[22] Patients in the reteplase group had significantly fewer side effects such as atrial fibrillation and cardiogenic shock. Complete resolution of the ST segment (an indirect measure of vessel patency and a predictor of mortality) occurred in a significantly higher proportion of patients treated with reteplase. Unpublished data from studies indicate no significant difference in mortality in patients treated with reteplase and tissue plasminogen activator. Ease of administration may favour reteplase. Other drugs such as TNK-tPA and lanoteplase (which is entering the phase III trial stage) are also likely to challenge tissue plasminogen activator in the future.

Other investigators are evaluating "combination" thrombolytic drugs (for example, chimeric molecules of tissue plasminogen activator and urokinase-type plasminogen activator), and pilot studies are under way.[23] Thrombolytic substances that occur naturally, such as the vampire bat plasminogen activator, have also attracted attention. This agent is similar to human tissue plasminogen activator, but does not have a processing site which is sensitive to plasmin. It thus seems to be resistant to plasminogen activator inhibitor-1 and has greater fibrin selectivity than tissue plasminogen activator. Experimental data have shown that bat tissue plasminogen activator is effective without activating systemic plasminogen, and it may have a lower rate of bleeding complications. Clinical trials are planned.

Staphylokinase

Staphylokinase, a protein produced by *Staphylococcus aureus,* has profibrinolytic properties. In experimental studies, a recombinant form was less immunogenic and more active against arterial clots rich in platelets than streptokinase.[23] Recombinant staphylokinase has now been evaluated in small published clinical trials. A dose of 10-20 mg given over 30 minutes resulted in rates of coronary artery patency similar to those after treatment with accelerated tissue plasminogen activator, but without any fibrinogen breakdown (staphylokynase was therefore more specific to fibrin than was tissue plasminogen activator).[23] Unfortunately, all the patients developed neutralising antibodies to recombinant staphylokinase from the second week after treatment, which suggests that this drug is not as hypoallergenic as was hoped. Further clinical trials are planned.

Monoclonal antibody against fibrin

Researchers have worked on localising the thrombolytic agent and increasing its specificity and potency by conjugating it to targeting molecules directed at the site of fibrin deposition. Bode and colleagues used a monoclonal antibody against the β chain of fibrin as a targeting agent. In an experimental model of thrombolysis, the conjugate of tissue plasminogen activator and monoclonal antibody against fibrin was up to 10 times more potent than tissue plasminogen activator alone, and at "equivalent" thrombolytic concentrations it degraded less fibrinogen and consumed less α antiplasmin.

Future thrombolytic drugs

Any new strategy, regimen, or drug will have to be tested against its current counterpart, which means that clinical trials will need to be large to show a difference in mortality. Clinical practice in the future will probably incorporate some of the ideas and concepts outlined above. The current contender for the primary position held by accelerated tissue plasminogen activator seems to be reteplase, and the results of the GUSTO-III trial are eagerly awaited. Bat tissue plasminogen activator and some of the chimeric conjugates are also likely to progress to clinical trials.

Antithrombin drugs

Even after successful thrombolysis, reocclusion remains a problem. Heparin (followed by warfarin) and aspirin have been used to reduce rethrombosis, but in the aspirin versus coumadin (APRICOT) study

these drugs did not have a significant impact on the reocclusion rate at 3 months (25% *v* 32% for placebo).[14] Heparin, while relatively safe, has disadvantages: it requires endogenous cofactors for activity (principally antithrombin III and heparin cofactor II); it is inactive against thrombin bound to fibrin and is unable to displace thrombin bound to platelets; and its action can be neutralised by products released by activated platelets (for example, platelet factor 4).

Direct acting antithrombin drugs

These disadvantages have led to an interest in newer antithrombin drugs which act directly. Preclinical and clinical research programmes are currently investigating several drugs—in particular, hirudin, argatroban, and efegatran. All are independent of antithrombin III, but their precise mechanism of inhibition varies, and the last two are reversible inhibitors. Hirudin was developed first, and much of what we know about this group comes from studies with it. Hirudin binds to both the active catalytic site and the substrate recognition site of thrombin, and inhibits both thrombin catalysed activation of factors V, VIII, and XIII and thrombin induced platelet activation. In animal models it prevented rethrombosis after tissue plasminogen activator treatment.[24]

Hirudin

Originally isolated from the leech *Hirudo medicinalis*, hirudin is now produced through recombinant DNA technology, and it is the desulfatohirudin form that has been evaluated in clinical trials. Early results from the TIMI-5 trial suggested that, after accelerated tissue plasminogen activator, hirudin was better than heparin 18-36 hours after treatment in initiating patency (vessel patency 98% with hirudin *v* 89% with heparin).[25] Clinical outcomes (death or recurrent myocardial infarction) also favoured hirudin. Additional encouraging results were obtained when hirudin was compared with heparin in conjunction with streptokinase (TIMI-6 trial).[26] Three large clinical trials were started and reported early in 1994: the GUSTO-II study, the TIMI-9 trial, and the third trial of hirudin for the improvement of thrombolysis (HIT-III). The trials were stopped because there was a high rate of intracerebral bleeding. They were restarted at lower drug doses, but unfortunately preliminary results from the GUSTO-IIb study also suggested no increase in clinical benefit with hirudin at this lower dose.[27]

The narrow therapeutic window of these new antithrombin drugs make it difficult at present to define their exact role. Delivering these drugs to the site of the damaged vessel wall or targeting after systemic injection may be ways forward.[28]

Antiplatelet treatments

Platelets are central to the development of a thrombus after arterial injury. We know that aspirin affects only one pathway in platelet activation—the arachidonic acid pathway. Work by Collen et al in the early 1980s revolutionised our understanding of effective antiplatelet treatment. It became clear that the fibrinogen (glycoprotein IIb/IIIa) receptor on platelets was central to aggregation of platelets and to the development of a fibrin-platelet mesh into a mature thrombus. Aspirin alone cannot, for example, block the stimulatory effects of high doses of collagen and thrombin on platelets. Inhibition of the final common pathway that usually leads to glycoprotein IIb/IIIa activation would be more effective.

Monoclonal antibody 7E3

A humanised monoclonal antibody against the receptor (monoclonal antibody7E3) is now available. Animal work has shown that a number of drugs (such as the monoclonal antibody and others such as integrelin) are valuable in animal models of coronary occlusion.[29 30] Given alone, 7E3 improves vessel patency. Small clinical studies have reported profound platelet inhibition, low bleeding rates, and a low incidence of recurrent ischaemia when 7E3 was used after tissue plasminogen activator.[31]

Synthetic glycoprotein IIb/IIIa antagonists

Synthetic glycoprotein IIb/IIIa antagonists such as the peptide integrelin and the non-peptide compounds tirofiban and lamifiban seem promising replacements for, or supplements to, aspirin in clinical trials. The early results of a pilot study using 7E3 and integrelin in patients with acute myocardial infarction suggest that this regimen may improve coronary artery patency and reduce recurrent ischaemic events. Complications of bleeding will need to be assessed, but these powerful platelet receptor blockers seem the most promising of the potential adjuncts to thrombolysis.

Primary angioplasty

Although new thrombolytic drugs are becoming available, it is unlikely that TIMI grade 3 patency rates will ever be greater than 70-80% nor that the high reocclusion rates will improve. Since vessel patency is generally held to be paramount, ways of increasing patency rates and reducing reocclusion have been evaluated.

One alternative to thrombolysis is coronary angioplasty: a wire and balloon is used to mechanically compress the thrombus and at the same time deal with the underlying stenotic atheromatous plaque. The patient must be taken to the catheter laboratory for this intervention. Angioplasty undertaken within 12 hours of onset of chest pain has been shown to improve clinical outcome in comparison to thrombolysis.[32] Intervention should be as expeditious as possible to reduce muscle death. In addition, with angioplasty, stroke is uncommon.

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An alternative to thrombolysis is coronary angioplasty

Angioplasty used instead of thrombolysis in acute infarction results in over 95% patency (with over 90% TIMI grade 3)[33] compared with current best overall patency rates of 80% (54% TIMI 3 flow) with thrombolysis. Studies have shown lower early mortality and better outcome in the longer term with angioplasty than with thrombolysis.[34] Angioplasty was associated with a lower enzyme rise, better left ventricular function, less reinfarction (7% *v* 30%), and lower 31 month mortality (5% *v* 1%, P = 0.03). Although vessel reocclusion is a problem with thrombolysis (30-40% by 3-6 months), long term patency after direct angioplasty is reported to be much higher at 87-91%.[35] Pooling of data shows that high risk patients (those with older age, larger infarcts, and anterior infarcts) benefit in particular, both in terms of mortality and reinfarction. Despite trials indicating that the early promise of angioplasty for acute infarction may not be so great when applied to all comers, studies still show an overall benefit in comparison to thrombolysis.[36]

Although it clearly improves the outcome after infarction, primary angioplasty is unlikely to become widely available because most patients with myocardial infarction are admitted to hospitals without interventional facilities. Angioplasty should be considered in patients who have a recognised contraindication to thrombolysis (even if this means transferring the patient) or who are considered high risk and present with their infarction to a hospital where angioplasty can be performed.

Patients who have received thrombolysis and who seem on clinical grounds (reduction in maximal ST segment elevation by 50% and resolution of chest pain) not to have reperfused at 90 minute review should seriously be considered for rescue angioplasty, again even if this means transferring the patient.

In conclusion

Further major breakthroughs in the management of acute myocardial infarction are unlikely within the next year or two. Thereafter the desire to open the occluded artery quickly and reliably, and to sustain patency, may mean there is a need to develop some of the new strategies we have outlined.

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