Keeping the coronary arteries open: current opportunities

AH Gershlick

Thrombolysis has reduced mortality from myocardial infarction, but effective opening of the artery with normal flow continues to be an important goal. Thrombolysis is not always as successful as it should be; alternatives include adjunctive therapy and mechanical opening of the arteries. In patients with acute coronary occlusion opening the artery should continue to be the primary aim.

Acute myocardial infarction (AMI) accounts for up to 250 000 deaths with 150 000 admissions to hospital each year in the UK. While many deaths occur before help arrives, there is no doubt that it was the increased understanding of the pathology of coronary occlusion that led to the trials of lytic agents. It was the results of these studies together with the subsequent development of clinical standards for their implementation that resulted in the reduced mortality associated with AMI. However, strategies designed to keep the coronary arteries open once lysis has taken place have received less attention.

Important pathological studies by Davies and Thomas (1985) helped explain clinical progression or regression in patients with coronary disease and identified targets for therapy. In essence these authors described the coronary arteries from patients with acute coronary syndromes who had died. It became clear that the important primary event was plaque disruption, the consequences of which depended on the patient's response to it.

The development of such a concept, which placed the thrombus central to the clinical problem, was important for a number of reasons. First, it became clear that the cornerstone of treatment should become dissolution of the thrombus, which formed after a plaque event. Second, the potential of combining lytic plus adjunctive therapy needed to be explored if all components of developing thrombus were to be addressed. In addition, an understanding of the pathology has implications for not only optimizing coronary patency but also for keeping the coronary arteries open.

In order to influence mortality and morbidity after AMI the aim of all therapies should be the early, complete and maintained patency of the infarct-related artery.

FACTORS INFLUENCING MAINTAINED PATENCY

A coronary artery cannot be kept open if it has not been opened in the first place. Thus the first aim of anyone concerned with the maintenance of patency is to optimally open the artery as soon as possible. The success of the thrombolytic trials and the ease with which non-specialized junior doctors in non-specialized hospitals can administer this therapy, has led to the misconception that once administered, the battle is over. Success is perceived as the giving of the agent after which there should be no more concerns (Predergast et al, 1997). While there clearly are recognized goals to be achieved in the optimal administration of lytic therapy (patent education, door to needle time), unfortunately it is generally held that once these have been reached then everything possible has been done for the patient in terms of mortality and morbidity.

While there is indeed evidence of true benefit from the efficient delivery of thrombolytic treatment, mortality unfortunately is still high and the problem of reocclusion has not been fully addressed. The overall relative risk reduction in 35-day mortality with treatment in the various thrombolytic trials was a significant 18%, from about 13% in controls to about 8–9% with treatment. However, in real life where the population is older the true mortality may be higher in treated patients with figures reaching 18–20%. After 12 hours there appears to be only a small and statistically uncertain benefit. The LATE Trial, for example, clearly showed a lack of benefit 12 hours after onset of symptoms (LATE Study Group, 1993).

Thus while the cornerstone of managing AMI remains the efficient institution of lytic treat-

Dr AH Gershlick is Consultant Cardiologist, Academic Department Cardiology, Clinical Sciences Building, University Hospitals Leicester, Leicester LE3 9QP

ment this neither optimally opens arteries, leading to a residual high mortality, nor prevents them re-occluding.

OPENING THE ARTERY: THE FIRST ABSOLUTE GOAL

The earlier the dissolution of a clot occurs, the more likely the vessel will be opened. In addition, there may be a greater likelihood that it will remain patent, because of the increased reduction in thrombus load. Lytic efficacy is therefore important.

The evidence for the benefit of having an open artery is generally accepted. The 'open artery' hypothesis suggests that the short- and longer-term outcome after AMI is determined by the degree of patency obtained with treatment, and that when optimal patency is achieved, it is also maintained. In other words benefit is lost if the vessel re-occludes.

Degree of patency is conventionally graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification, where TIMI grade 0 flow = total closure and TIMI grade 3 flow = flow equivalent to that in unaffected arteries. A number of studies have clearly shown that the longer-term outcome correlates with angiographic TIMI flow, especially at 90-minute angiogram (Ross et al, 1998). Thus data from the angiographic study arm of the GUSTO trial (GUSTO Angiographic Investigators, 1993) clearly demonstrate that patients with TIMI grade 0 flow (i.e. complete occlusion) at 90-minute angiogram had a 30-day mortality of 8.4%, whereas this was only 4% in those with TIMI grade 3.

Other non-randomized data are available to support the belief that the better the patency the better the long-term outcome. Thus in a retrospective meta-analysis of 4607 patients mortality was 3.7% for TIMI grade 3 flow, but 6.6% ($P<0.0003$) for TIMI grade 2 and 9.2% ($P<0.0001$) for TIMI 0/1 flow (Fath-Ordoubadi et al, 1997. Five- and 10-year follow-up suggests a continued and statistically significant benefit in those patients in whom grade 3 flow can be achieved.

Unfortunately best current thrombolytic therapy results in TIMI grade 3 flow in only 54% of patients treated with front-loaded tissue plasminogen activator (tPA) and in only 30% with streptokinase. Thus thrombolysis with currently available agents appears to have a therapeutic plateau. This may be the result of a number of factors, including atheromatous bulk, degree of intimal disruption, platelet hyperactivity or lytic resistance.

KEEPING THE ARTERY OPEN: THE SECOND ABSOLUTE GOAL

The second problem with current thrombolytic regimens is that they are inadequate to prevent vessel reocclusion. A number of studies have compared early patency (usually at 90 minutes) with late patency to determine the reocclusion rate (Hsia et al, 1990; French et al, 1998). Reocclusion is a time-related phenomenon, and reaches an astonishingly high, albeit plateaued, rate of 30% by 3 months (Meijer et al, 1993). The reasons for this include re-release of thrombin, the presence of residual prothrombogenic plaque and/or activation of coagulation factors V and VIII by plasmin. In addition, the original stimuli are still present (exposed collagen, disrupted atheroma, damaged endothelium and potentially residual flow limiting obstruction). Activation of platelets by lytic agent itself may also be important.

Clearly if there is significant residual plaque then blood flow will be reduced and thrombotic reocclusion more likely. Angiographic predictors of reocclusion include poor flow (TIMI 0 or 1 flow) (TAMI trial; Khalif et al, 1988). Residual stenosis severity is an intuitive factor and is supported by data from the TIMI 4 study among others (Gibson et al, 1995). Theoretically the adverse consequences of residual flow restriction may be attenuated to some degree by maximally inhibiting the primary factors leading to the formation of the platelet-rich thrombus. In individual patients the various different causes of reocclusion may have different importance. Whatever the mechanism the consequences and importance of reocclusion have been under-emphasized.

Consequence of reocclusion

Reocclusion may be associated with recurrent angina, recurrent infarction, pump failure and death. However, it may also occur without any symptoms. Data from the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT) trial (Meijer et al, 1994) demonstrate that reocclusion, whether symptomatic or not, has an adverse outcome. Those subjects who had a patent artery 48 hours after thrombolysis but had re-occluded by the 3-month follow-up angiogram developed progressive left ventricular dilatation and had higher cardiac mortality at 1 year compared to those whose infarct-related artery remained patent (83% *vs* 63% survival, $P<0.001$). Reocclusion affecting the anterior wall has been shown to be particularly pernicious.

These data are supported by follow-up data from the thrombolysis arm of the TAMI 5 studies

which clearly showed that mortality was increased in the reocclusion group (12.8% *vs* 4% mortality, in reocclusion group *vs* patent artery group).

The current data thus suggest two crucial points. First, the combination of thrombolytic and currently used antiplatelet therapy (aspirin) does not open occluded arteries optimally, and second, in those that do become patent, reocclusion is not uncommon and is associated with an adverse outcome. Current goals should be aimed at dealing with these two problems — optimal TIMI flow and preventing reocclusion. Strategies include the development of new thrombolytics, altering adjunctive therapy or by treating the occluded artery mechanically with balloon angioplasty and stenting.

New thrombolytics: Various investigators have studied tPA mutants or variants of tPA. These agents may possess altered resistance to inhibitors such as plasminogen activator inhibitor-1 (PAI-1) or require binding to fibrin to become active. Other approaches have involved altering thrombolytic molecules to reduce their plasma clearance, although such modifications may lessen their thrombolytic effectiveness. One mutant produced by an alteration at the kringle 2 region of the tPA molecule appears to have a prolonged half life, which may prove to be of value (Rydzewski and Castellino, 1993).

The only new lytic to come to the market to date is Reteplase (Roche Products Ltd, Welwyn Garden City) or rPA. It is a non-glycosylated deletion mutant of wild type tPA and was the first member of the third generation thrombolytics. Unfortunately patency rates have been shown to be no greater with Reteplase than with tPA and choice between these agents is frequently a commercial one. No evidence has been produced concerning the benefits of the newer agents on reocclusion.

Adjunctive therapy: ***Antithrombins:*** Heparin has limitations as an antithrombin. Newer antithrombins such as hirudin have been tested in a number of studies of initial patency. These suggest that the therapeutic window for such agents is very narrow, with bleeding at effective doses. The value of longer-term subcutaneous heparin on post thrombolytic coronary patency has not been tested.

Glycoprotein IIb/IIIa antagonists: Regardless of the mechanism of activation, the final common pathway for platelet aggregation is the cross-linking of platelets through fibrinogen bound to the glycoprotein (GP) IIb/IIIa receptor. Early animal studies with monoclonal antibodies to GPIIb/IIIa demonstrated the potent antiplatelet effects accruing from blocking the binding of fibrinogen to activated GPIIb/IIIa. This has lead to a number of fibrinogen receptor antagonists being developed. Their value in interventional cardiology and in the management of acute coronary syndromes has been demonstrated in various well controlled trials (Brown et al, 2001).

Since the overall aim is to attempt to reduce thrombotic occlusion and since thrombus in the arterial system is both platelet initiated and platelet propagated, these agents have come under some scrutiny as to their value in the setting of acute infarction. Thus phase I studies and early safety pilot studies have shown an increase in TIMI grade 3 patency at 60 and 90 minutes when a half-dose thrombolytic agent was given in combination with a GPIIb/IIIa receptor blocker. Improved patency especially with the use of such platelet inhibitors may well lead to less reocclusion through prolonged effective platelet inhibition in the early critical post-lytic phase.

These studies have led to the initiation and now published GUSTO V trial (Topol, 2001). This trial showed that there was no difference between thrombolytic therapy and the combination of half-dose thrombolytic therapy with full dose Reteplase. The therapeutic window was narrow since there were more intracranial bleeding complications in the combination group.

Other antiplatelet options include adenosine diphosphate (ADP) receptor inhibitors. The recent CURE trial data suggest that such agents may have a role in improving outcome in acute coronary syndromes of which myocardial infarction is the extreme end (Mehta et al, 2001). The oral nature of drugs such as clopidogrel may have an impact on reducing reocclusion. However, to date there is only one study ongoing to assess the value of ADP receptor antagonism in acute myocardial infarction (Second Chinese Cardiac Study Collaborative Group, 2000). This study investigated conventional therapy plus or minus ticlopidine 250 mg twice daily. At this time aspirin therapy was not in routine use, however, monotherapy with ticlopidine produced a 46% reduction in the primary combined end-point of vascular death and non-fatal myocardial infarction (7.3% compared with 13.6%; P=0.009).

Potent pharmacotherapy to produce maximal patency and low reocclusion rates may still have limited potential, however. There will always be patients who fail thrombolytic therapy for mechanical reasons such as excess atheroma bulk or large spontaneous intimal disruption. Coronary occlusion comprises both haematological and mechanical factors. Both may need to be treated to best improve long-term patient outcome.

PRIMARY ANGIOPLASTY: PRODUCING MAXIMAL PATENCY AND REDUCED REOCCLUSION

Grade 3 TIMI flow can only be achieved in 54% of patients with thrombolysis — perhaps it will be shown to be more with lytic therapy plus powerful antiplatelet agent. Currently, however, the only treatment shown to be better than thrombolysis is to open the artery at the time of presentation with balloon angioplasty (plus stent).

A number of studies, albeit with small numbers, have shown that if a patient can be taken to the catheter laboratory within 12 hours and the artery successfully opened and dilated, TIMI grade 3 flow can be obtained in 80–97% of cases (Grines et al, 1993). Short- and long-term survival and morbidity have been improved compared to thrombolysis. Reocclusion of the vessel remains a real problem with thrombolytic therapy (reaching 30–40% by 3–6 months, and remaining at 25% at 1 year). The comparable 3–6-month vessel patency after primary angioplasty is much higher (87% to 91%) (Kastrati et al, 2000) not least because the treatment deals with the underlying stenosis.

Pooled data from the various thrombolytic trials not surprisingly suggest a worse long-term outcome compared to direct angioplasty (death 6.4% *vs* 2.5%; reinfarction 7.9% *vs* 2.0%; stroke 2.5% *vs* 0.3%; death and/or reinfarction 13.1% *vs* 4.3%, respectively). Recurrent ischaemia in the three comparative trials (MAYO clinic, PAMI and Zwolle) varied between 27% and 36% for thrombolytic treated patients and between 9% and 15% for direct angioplasty patients. The 2-year event-free survival (i.e. no myocardial infarction, cardiac death or need for reintervention) for the PAMI I trial patients is reported to be 85% (Nunn et al, 1999), indicating that the early separation of the outcome curves for thrombolytic-treated and angioplasty-treated patients is maintained.

However, there are difficulties with these trials. The small numbers of centres and patients involved randomized results in wide confidence intervals. The data therefore have been pooled and evaluated on the basis of 'high' and 'low' risk patients. It would appear that the high-risk patients (older age, larger infarcts and anterior infarcts) benefit both in terms of mortality and reinfarction from direct angioplasty, whereas the low-risk group benefit only in terms of reinfarction. The GUSTO IIb study (GUSTO IIb Angioplasty Sub-study Investigators, 1997) failed to demonstrate long-term benefit. This was undoubtedly in part the result of inadequate angioplasty (failure to achieve TIMI grade 3 flow in greater than 80% patients). More recent trials in which stenting has been employed have shown significant improvement in optimal patency rates, which may be the critical factor.

The same factors that influence benefit in thrombolytic treatment also need to be considered in primary angioplasty. Thus Cannon et al (2000) found that in 27 080 patients treated with primary angioplasty the door-to-balloon time was a significant factor in mortality outcome (adjusted odds of mortality odds ratio (OR) = 1.41, 95% confidence interval (CI) = 1.08–1.84, P=0.01 for door-to-balloon time >2 hours; OR = 1.61, 95% CI = 1.25–2.08, P<0.001 for >3 hours). Others have asserted that even late after the event primary percutaneous coronary intervention (PCI) may beneficially influence left ventricular remodelling (Ottervanger et al, 2001). This is not current practice in the absence of recurrent symptoms or electrocardiographic (ECG) changes, however.

The most important factor determining an improved outcome in patients undergoing intervention for AMI appears to be the use of stents. In a small study, Maillard et al (2000) found the 6-month event-free survival rates were 81.2% in those stented *vs* 72.7% in those who were not stented. The major study, however, was published by the Beaumont Hospital group (Grines et al, 1999). They studied patients who only received PCI for the primary treatment of their infarct. The acute result was significantly better in the stented group. The 6-month event-free survival rate was also higher in the stented group (12.6% (n= 452) *vs* percutaneous transluminal coronary angioplasty (PTCA) 20.1% (n= 448), P<0.01) (Grines et al, 1998).

What are the advantages of primary angioplasty?

Although still a matter for debate, the case for direct angioplasty for AMI appears compelling, particularly for selected high-risk cases presenting within 12 hours to a hospital equipped with a catheter laboratory. It appears as effective or more effective than thrombolysis, with significantly lower risk of stroke and lower risk of the high mortality associated with cerebral bleeding (stroke PTCA = 0.7% *vs* lytic = 2.0% (OR = 0.35, 95% CI = 0.14–0.77, P=0.007); intracerebral haemorrhage PTCA = 0.1% *vs* lytic = 1.1% (OR = 0.07, 95% CI = 0.0–0.42, P<0.001)) (Yusuf et al, 1997). These figures do not, of course, take account of current strategies that incorporate GPIIb/IIIa receptor blocker use. Importantly, intervention deals with the stenosis which lytic agents cannot do.

There are data to support the concept that the greater the residual stenosis the more likely the artery will reocclude (Wilkes et al, 1991).

Failure of reperfusion is more likely with lytic therapy when there is significant atheroma bulk or severe disruption of the plaque. Knowing the state of the coronary arteries allows for better triage of patients post infarct. Thus the normal 5–7-day inpatient stay may be reduced if the infarct-related artery is open and the rest of the arteries are known to be normal.

What are the problems with primary angioplasty?

Primary and rescue angioplasty may be being undertaken in patients who are unwell and the best outcomes may require the most experienced operators. In a retrospective study Magid et al (2000) showed the benefits of primary angioplasty outweighed those of thrombolysis in high and intermediate volume centres but not in low volume centres (mortality 3.4% PTCA *vs* 5.4% thrombolysis in high volume centres, $P<0.001$; 6.2% *vs* 5.9%, $P=0.58$ in low volume centres). Outcomes for patients with cardiogenic shock remain high no matter what treatment is instigated. Cost effectiveness data are less available for the current interventional strategy of using stents and GPIIb/IIIa receptor blocker, than for just balloon angioplasty.

While better early patency rates can be achieved with primary PTCA which translates into improved clinical outcome, both in the short and medium term in patients, this treatment is not widely available. The problem is that most patients are admitted to hospitals without interventional facilities. There are neither the personnel nor financial resources to place such facilities in all hospitals receiving AMI patients.

THROMBOLYSIS *VS* ANGIOPLASTY FOR AMI

There are a number of options. Some have advocated a policy of thrombolysis followed by angiography in all patients with angioplasty when indicated (occlusion or significant residual stenosis in the infarct-related artery). Others believe that in the current resource-limited climate primary angioplasty for acute infarction cannot be delivered and that angiography and angioplasty where indicated should be reserved for those who demonstrate failure of lytic therapy.

There are two UK trials ongoing investigating such a policy. The first, the MERLIN trial run by de Belder, has reported preliminary data (Grech et al, 2000). In 179 patients undergoing emergency angiography for failed thrombolysis 156 were deemed to need angioplasty. Providing at least TIMI grade 2 flow was attained (124/135 patients) they showed the mortality was low (5.9%). In the 11 patients in whom TIMI grade 2 flow was not successful the mortality was very high at 48%. Interestingly reinfarction or need for revascularization was 37% in the 41 patients deemed not to need intervention following their angiogram. In the second trial, the UK-based British Heart Foundation-funded ongoing REACT trial, patients shown on 90-minute ECG to have failed thrombolysis (failure of resolution ST to > 50%) are randomized to conservative therapy, second thrombolytic or intervention.

Whether high-risk patients will do better receiving thrombolysis at their admission hospital or primary angioplasty after transfer to another hospital is also currently being tested, both in the UK and in Europe. Yet others are developing strategies for early out of hospital triage. Thus on arrival at a patient suffering chest pain the paramedic would record an ECG and electronically transmit it to a dedicated coordinator in a dedicated catheter laboratory. The patient would then be received by this laboratory and undergo angiography and intervention if necessary. Such concepts will need serious resource examination.

The most important action, taking account of what has been stated about the importance of having an open artery, is that if a patient fails to settle after thrombolysis (ongoing pain or recurrent ECG changes) intervention (with transfer if necessary, for so-called rescue angioplasty) remains an important option.

CONCLUSIONS

Effective opening of the infarct-related artery is of paramount importance. It saves lives in the short, medium and long term and reduces complications. Reocclusion and its importance has, however, been understated. While lytic therapy is cheap and relatively safe, it neither optimally opens arteries nor prevents the high (30%) reocclusion rate. New thrombolytic agents are becoming available, which may improve patency. Testing of the new antithrombins for reducing vessel reocclusion in such a setting have indicated that these agents have a relatively narrow therapeutic window. The assessment of half dose thrombolytics with full dose GPIIb/IIIa receptor blockers is awaited.

Primary angioplasty may prove the definitive treatment for AMI in selected cases such as young or elderly patients with anterior infarction, provided the procedure can be undertaken early enough to be of benefit. Reocclusion is less because the stenosis itself is dealt with. Limited resources may be the inhibiting factor in widespread use of this treatment modality. However, ways to provide primary angioplasty to

appropriate patients and importantly in a cost-effective manner should be the strategic aim over the next few years. Early assessment of the thrombolysed patients or triage at the prehospital stage is the way forward. HM

Conflict of interest: none.

Brown DL, Fann CS, Chang CJ (2001) Meta-analysis for the effectiveness and safety of abciximab versus eptifibatide or tirofiban in percutaneous coronary intervention. *Am J Cardiol* **87:** 537–41

Cannon CP, Gibson CM, Lambrew CT et al (2000) Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* **283:** 2941–7

Davies MJ, Thomas AC (1985) Plaque fissuring — the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J* **53:** 363–73

Fath-Ordoubadi F, Huehns T, Al-Mohammad A et al (1997) Significance of the thrombolysis in myocardial infarction scoring system in assessing infarct-related artery reperfusion and mortality rates after acute myocardial infarction. *Am Heart J* **134:** 62–8

French JK, Ellis CJ, Webber BJ et al (1998) Abnormal Coronary Flow in infarct after one year after myocardial infarction is predicted at 4 weeks by corrected Thrombolysis in Myocardial Infarction (TIMI) frame count in stenosis severity. *Am J Cardiol* **81:** 665–71

Gibson CM, Cannon CP, Piana RN et al (1995) Angiographic predictors of re-occlusion after thrombolysis: results from the Thrombolysis in Myocardial Infarction (TIMI 4 trial). *J Am Coll Cardiol* **25:** 582–9

Grech ED, Sutton AG, Campbell PG et al (2000) Reappraising the role of immediate re-intervention following thrombolytic re-canalisation in acute myocardial infarction. *Am J Cardiol* **86:** 400–5

Grines CL, Browne KF, Marco J (1993) A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* **328:** 673–9

Grines CL, Marsalese DL, Brodie B et al (1998) Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction. PAMI-ll Investigators. Primary Angioplasty in Myocardial Infarction. *J Am Coll Cardiol* **31:** 967–72

Grines CL, Cox DA, Stone GW et al (1999) Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* **341:** 1949–56

GUSTO IIb Angioplasty Sub-study Investigators (1997) A clinical trial comparing primary angioplasty with tissue plasminogen activator with acute myocardial infarction. *N Engl J Med* **336:** 1621–8

GUSTO Angiographic Investigators (1993) The effects of tissue plasminogen activator, streptokinase, or both on coronary patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* **329:** 1615–22

Hsia J, Hamilton WP, Kleiman N et al (1990) Comparison between heparin and low dose aspirin as a junctive therapy with tissue plasminogen activator for acute myocardial infarction. Heparin-Aspirin Reperfusion Trial (HART) investigators. *N Engl J Med* **323:** 1433–7

Kastrati A, Pache J, Dirschinger J et al (2000) Primary intracoronary stenting in acute myocardial infarction: long term clinical and Angiographic follow-up and risk factor analysis. *Am Heart J* **139:** 208–16

Khalif RM, Topol EJ, George BS et al (1988) Characteristics and outcome of patients in reperfusion with intravenous tissue type plasminogen activator fails: results of Thrombolysis and Angioplasty Myocardial Infarction (TAMI) 1 trial. *Circulation* **75:** 1090–9

LATE Study Group (1993) Late Assessment of Thrombolytic Efficiency (LATE) study with Alteplase 6-24 hours after onset of acute myocardial infarction. *Lancet* **342:** 759–66

Magid DJ, Calonge BN, Rumsfeld JS et al (2000) Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA* **284:** 3131–8

Maillard L, Hamon M, Khalife K et al (2000) A comparison of systematic stenting and conventional balloon angioplasty during primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. STENTIM-2 Investigators. *J Am Coll Cardiol* **35**(7): 1729–36

Mark DB, O'Neill WW, Brodie BR (1995) Baseline and six-month costs of primary angioplasty therapy for acute myocardial infarction: results from the Primary Angioplasty Registry. *J Am Coll Cardiol* **26**(3): 688–95

Mehta SR, Yusuf S, Peters RJ et al (2001) Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI/CURE study. *Lancet* **358**: 527–33

Meijer A, Verheugt FW, Werter CJ, Lie KI, van der Pol JM, van Eenige MJ (1993) Aspirin *vs* coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study. Results of the APRICOT Study. *Circulation* **87**(5): 1524–30

Meijer A, Verheught FW, van Eenige MJ et al (1994) Left ventricular function at three months after successful thrombolysis. Impact of re-occlusion without re-infarction on injection fraction, regional function and remodelling. *Circulation* **90:** 1706–14

Ohman EM, Califf RM, Topol EJ et al (1990) Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. TAMI Study Group. *Circulation* **82:** 781–91

Ottervanger JP, van'Hof AW, Reiffers S et al (2001) Long-term recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *Eur Heart J* **22:** 2785–90

Predergast BD, Shandal A, Buchalter MB (1997) What do we do when thrombolysis fails? A United Kingdom Survey. *Int J Cardiol* **61:** 39–42

Ross AM, Coyne KS, Moreyra E et al (1998) Extended mortality benefit of early post-infarction reperfusion. GUSTO-1 Angiographic Investigators. Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial. *Circulation* **97:** 1549–56

Rydzewski A, Castellino FJ (1993) The effector role of kringle 1 and kringle 2 in the enzymatical properties of recombinant tissue type plasminogen activator as revealed by generation of recombinant molecules containing each cringle linked to the protease domain. *Arch Biochem Biophys* **300:** 472–82

Second Chinese Cardiac Study Collaborative Group (2000) Rationale, design and organization of the Second Chinese Cardiac Study (CCS-2): a randomized trial of clopidogrel plus aspirin, and of metoprolol, among patients with suspected acute myocardial infarction. *J Cardiovasc Risk* **7(6):** 435–41

Topol EJ (2001) Reperfusion therapy for acute myocardial infarction with fibrinolyse therapy of combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition; the GUSTO V randomised trial. *Lancet* **357:** 1904–14

Wilkes MP, Jones MP, O'Rourke MF, Nelson GI (1991) Determinates of a current ischaemia and revascularisation procedures after thrombolysis without recombinant tissue plasminogen activator and primary coronary occlusion. *Int J Cardiol* **30:** 69–76

Yusuf S, Pogue J (1997) Primary angioplasty compared with thrombolytical therapy for acute myocardial infarction. *JAMA* **278:** 2093–8

KEY POINTS

- Achieving an open artery following coronary occlusion is critical for reducing mortality.
- Reocclusion has not been adequately addressed in clinical trials.
- Reocclusion carries a high risk of poor late outcome.
- Lytic therapy currently remains the cornerstone of therapy, but is neither maximally effective at opening arteries nor at keeping them open.
- Adjunctive therapy (such as antiplatelet) agents may improve both early patency and reocclusion.
- Coronary intervention appropriately targeted may be the optimal treatment.