REVIEW

Non-invasive treatment of ST elevation myocardial infarction

J B Jones, A Docherty

Postgrad Med J 2007;**83**:725–730. doi: 10.1136/pgmj.2007.059071

There is good evidence that timely restoration of coronary blood flow in obstructed infarct related arteries is a significant determinant of both short and long term mortality and morbidity. This is irrespective of whether it is achieved using fibrinolytic therapy or percutaneous coronary intervention (PCI). Despite the clear advantages of primary PCI, it is thrombolysis that remains the main reperfusion strategy in the UK. Recent data have highlighted mortality benefits when antiplatelet treatment and anticoagulation are used as adjuncts to thrombolysis. Moreover, of those who receive thrombolysis, 60% proceed to coronary arteriography within 6 months of their index event. Recent studies have been published clarifying the timing of coronary arteriography in patients who receive thrombolysis as reperfusion therapy.

In certain quarters, significant confusion remains surrounding the current recommendations for drug treatment when thrombolysis is used as reperfusion therapy. This article aims to give practical advice to non-cardiologist physician specialists on the modern non-invasive treatment of ST elevation myocardial infarction (STEMI). It reviews several recent large randomised controlled trials on the use of both clopidogrel and the low molecular weight heparin (LMWH) enoxaparin (table 1) and addresses the benefits of systematic invasive strategies following thrombolysis.

THROMBOLYSIS

Restoration of coronary blood flow is the ultimate aim of any reperfusion strategy and, where effective, a determinant on outcome.[1–3] There is agreement that, when compared with thrombolysis, primary percutaneous coronary intervention (PCI) is associated with a reduced incidence of stroke and in many patients an improvement in survival.[4–6]

Over a decade has passed since accelerated tissue plasminogen activator (tPA) was shown to offer mortality benefits over streptokinase.[7 8] Numerous attempts have been made to improve vessel patency rates and survival, but these have not improved mortality and many have been associated with an increase in bleeding complications.

Use of the fibrin-specific lytic tPA necessitated the inconvenience of an intravenous infusion and this prompted the search for agents that could be administered more easily. Tenecteplase is a variant of the tPA molecule that has a 14-fold greater fibrin specificity, a longer half life, slower plasma clearance and greater resistance to inhibition.[9] Its long half life allows single bolus administration and, in comparative trials, tenecteplase was shown to have non-inferior efficacy when compared with recombinant tPA (alteplase).[10 11] The rate of intracranial haemorrhage with tenecteplase was similar to that with alteplase, but the use of tenecteplase was associated with fewer non-cerebral complications and a reduced requirement for blood transfusion. However, where tenecteplase was co-administered with high dose LMWH among an older population (over 75 years of age), there was an increased risk of intracranial haemorrhage.[12]

Improving thrombolysis

The ''open artery'' theory suggests that outcome following an acute MI is determined by the time taken to achieve a patent infarct related artery and the degree of flow within it.[13] Large randomised trials have tested the effects of dual antiplatelet treatment and the effects of LMWH, and have demonstrated the first advances in medical reperfusion therapy in over 12 years.

CLARITY

CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy)[14] was a double blind randomised control study of over 3000 patients aged 18–75 years, presenting within 12 h of onset of STEMI and eligible to receive thrombolysis. Patients were randomised to either clopidogrel or placebo (fig 1). In the active treatment group, patients received a 300 mg loading dose of clopidogrel at the time of thrombolysis and, thereafter, received clopidogrel 75 mg daily until coronary arteriography was undertaken. This was in addition to standard treatment with aspirin and heparin, where appropriate. The patients were scheduled to undergo coronary arteriography between day 2 and day 5 following randomisation.

This was a mechanistic study to test the hypothesis that clopidogrel treatment would be associated with an increase in infarct related coronary artery patency at the time of coronary

See end of article for authors' affiliations

Correspondence to: Dr J B Jones, Department of Medicine, Wishaw General Hospital, Wishaw ML2 0DP, UK; jeremy@jonesonthe.net

Received 24 February 2007
Accepted 14 August 2007

Abbreviations: ARR, absolute risk reduction; ASSENT-4, Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction; CI, confidence interval; CLARITY, Clopidogrel as Adjunctive Reperfusion Therapy; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction Trial; ECG, electrocardiogram; EXTRACT, Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-Elevation Myocardial Infarction; GRACIA-1, Grupo de Analisis de la Cardiopatia Isquemica Aguda-1; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; REACT, REscue Angioplasty versus Conservative treatment or repeat Thrombolysis; RRR, relative risk reduction; sc, subcutaneously; STEMI, ST elevation myocardial infarction; tPA, tissue plasminogen activator

Table 1 Overview of important studies

Strategy	Trial	Outcomes
PCI	PCI vs thrombolysis.[4] *Lancet* 2003;**361**:13–20	Primary PCI is more effective than thrombolytic therapy for the treatment of STEMI
r-tPA	TIMI I.[7] *Circulation* 1987;**76**:142–54	r-tPA is more effective at opening occluded coronary arteries than streptokinase
Tenecteplase	TIMI 10B.[11] *Circulation* 1998;**98**:2805–14	Tenecteplase-tPA has similar efficacy and safety to r-tPA
Clopidogrel	CLARITY.[14] *N Engl J Med* 2005;352:1179–89 COMMIT.[15] *Lancet* 2005;**366**:1607–21	Dual antiplatelet therapy improves vessel patency in infarct related arteries Clopidogrel use reduces death, non-fatal MI and stroke without increasing major bleeding
LMHW	EXTRACT TIMI–25.[17] *N Engl J Med* 2006;**354**:1477–88	LMWH use reduces mortality and re-infarction when compared to unfractionated heparin
Rescue angioplasty	REACT.[19] *N Engl J Med* 2005;**353**:2758–68	Rescue angioplasty reduces death and reinfarction compared to repeat thrombolysis
Systematic PCI	GRACIA-1.[21] *Lancet* 2004;**364**:1045–53	Early PCI reduces length of stay and readmission but does not significantly affect mortality
Facilitated PCI	ASSENT-4.[25] *Lancet* 2006;**367**:569–78	PCI immediately following thrombolysis should only be performed as rescue PCI

ASSENT-4, Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction; CLARITY, Clopidogrel as Adjunctive Reperfusion Therapy; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction Trial; EXTRACT, Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-Elevation Myocardial Infarction; GRACIA-1, Grupo de Analisis de la Cardiopatia Isquemica Aguda-1; LMWH, low molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; REACT, REscue Angioplasty versus Conservative treatment or repeat Thrombolysis; r-tPA, recombinant tissue plasminogen activator; STEMI, ST elevation myocardial infarction; tPA, tissue plasminogen activator.

arteriography. The primary end point was a composite of patency at coronary arteriography, death before coronary arteriography, and re-infarction before coronary arteriography. Importantly, there was a pre-specified safety end point of major bleeding. The results indicate that the use of dual antiplatelet treatment after acute STEMI, when compared with aspirin alone, is associated with improved rates of vessel patency, with an absolute risk reduction of 6.7% in the rate of death, re-infarction or re-occlusion and a 36% reduction in odds ratio in the clopidogrel group (95% confidence interval (CI) 24% to 47%; p<0.001). By 30 days, clopidogrel treatment reduced the odds of the composite end point of death by 2.5%—that is, from cardiovascular causes, recurrent myocardial infarction, or recurrent ischaemia leading to the need for urgent revascularisation (relative risk reduction (RRR) from 14.1% to 11.6%; p = 0.03). The rates of major bleeding and intracranial haemorrhage were similar in the two groups. The CLARITY study was not powered to demonstrate mortality benefits of dual antiplatelet treatment. To investigate such a mortality benefit adequately we need to look to the results of the larger COMMIT study.

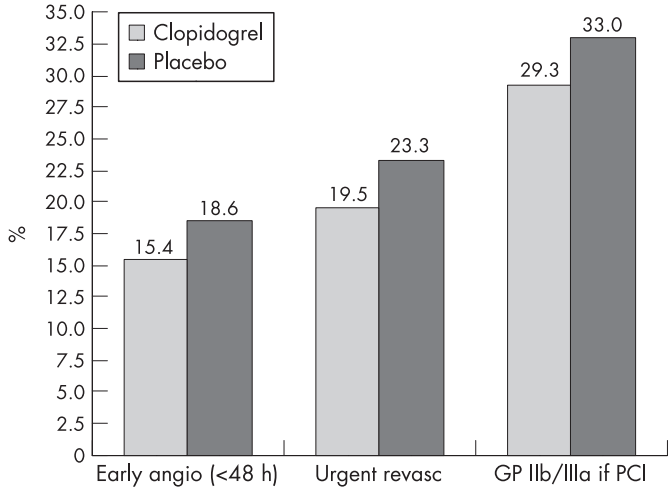

Figure 1 CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy): need for urgent or additional treatment.

COMMIT

COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial)[15] was a randomised double blind controlled trial designed to evaluate the use of dual antiplatelet treatment in patients presenting within 24 h of onset of an acute STEMI. The study was a collaboration between Oxford University and Beijing University and enrolled over 45 000 patients in China. Eligible patients presenting within 12 h of onset of acute STEMI received thrombolytic treatment. While CLARITY used a loading dose of 300 mg clopidogrel and a 75 year upper age limit, in COMMIT the first dose of clopidogrel was 75 mg and no upper age limit was imposed. The study was adequately powered for the composite end point of death, non-fatal reinfarction or stroke, and the pre-specified secondary end point of all cause mortality.

The results showed a relative risk reduction of 9% in the composite end point of death, non-fatal re-infarction or stroke. An absolute risk reduction (ARR) of 0.6% in all cause mortality was also noted (RRR of 7%, 95% CI 1% to 13%; p = 0.03). In the investigation period nine fewer events were recorded per 1000 patients in the clopidogrel group. The mean duration of treatment in COMMIT was only 16 days and, remarkably, the reduction in mortality and morbidity was achieved with no increase in major bleeding rates: the overall bleeding rate for the clopidogrel group was 134 (0.58%) as compared with the placebo group where there were 125 (0.55%) patient events (p = 0.59).

The time lapse between onset of pain and commencement of treatment had a predicable course: reduction in the composite end point of 17% was achieved for those receiving clopidogrel within 6 h, compared to 10% for those treated between 6–12 h after their index event, while there was no significant benefit in those treated between 12–24 h. These data are consistent with dual antiplatelet treatment reducing the risk of vessel re-occlusion in patients who respond to lytic therapy.

When there is complete inhibition of platelet function at the time of maximum lytic potential, we see significant increases in the risk of major haemorrhage as demonstrated in the ASSENT-3 study where lytic and abciximab were co-administered.[16] The safety of clopidogrel in the COMMIT trial, and the absence of major bleeding complications, may be explained by the maximal antiplatelet effect of clopidogrel not occurring until the maximal lytic effect of thrombolysis had waned. On this basis, it is recommended that clopidogrel is given at the time of thrombolysis and not before.

Despite successful thrombolysis, re-occlusion of the infarct related artery may occur secondary to platelet aggregation or fibrin clot. Treatment with aspirin and clopidogrel inhibits platelet function and reduces the risk of re-occlusion secondary to platelet aggregation. Unfractionated heparin has been used to inhibit re-occlusion secondary to fibrin thrombus: to assess the potential use of LMWH as a replacement for unfractionated heparin, we need to turn to EXTRACT TIMI-25.

EXTRACT TIMI-25

EXTRACT (Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-Elevation Myocardial Infarction)[17] was a double blinded randomised control study that was designed to compare the use of LMWH and unfractionated heparin as an adjunct to thrombolysis. Patients were eligible for randomisation if they presented with STEMI within 6 h of initial chest pain and importantly included patients who were aged over 75 years. In total, 20 479 patients from 674 sites in 48 countries were randomised. Patients who received standard treatment with aspirin and thrombolysis were randomised to receive either unfractionated heparin or LMWH, irrespective of the thrombolytic used.

The unfractionated heparin group was given a standard regimen of heparin bolus and a carefully adjusted heparin infusion for 48 h. The study was a double dummy, double blinded design with unfractionated heparin dose adjusted using a near-patient encrypted coagulation monitor. LMWH has a predictable and consistent anticoagulant effect but this effect can accumulate over time in patients with renal dysfunction. It was for this reason that those under 75 years were given an intravenous enoxaparin bolus of 30 mg and subsequent 1.0 mg/kg subcutaneously (sc) twice daily, and those over 75 were given no bolus and 0.75 mg/kg sc twice daily. Where creatinine clearance was <30 ml/min, the enoxaparin dose was halved to 1.0 mg/kg sc once daily.

The primary end point was a composite of death and non-fatal myocardial infarction and was measured at 30 days. A secondary safety end point of major haemorrhage was also studied. At 30 days, there was a 17% relative risk reduction in the primary end point in those who received enoxaparin (absolute risk of 12.0% in the unfractionated heparin group and 9.9% in the LMWH group). These improvements in mortality and morbidity were accompanied by a significant increase in both fatal and non-fatal major bleeding complications without an increase in intracranial bleeding. The net clinical benefit remained in favour of treatment with enoxaparin.

The benefit and convenience of LMWH will be particularly important in patients receiving out-of-hospital thrombolysis by paramedics. At present, patients are given unfractionated heparin as a bolus and commencement of heparin infusion is delayed until arrival in hospital; both the intravenous bolus of enoxaparin and subcutaneous injection of enoxaparin could be give by a paramedic at the time of thrombolysis.

PERCUTANEOUS INTERVENTION

Currently, there are three strategies for PCI following thrombolysis. The first relates to PCI attempted when thrombolysis fails. The second consists of PCI following successful thrombolysis and may be early and systematic or delayed and ischaemia driven. The third strategy uses thrombolysis as a bridge to emergent PCI and is termed ''facilitated PCI''.

Rescue angioplasty

Where thrombolysis is used as reperfusion therapy in acute myocardial infarction, failure to reperfuse the infarct related artery occurs in up to one third of patients and, despite best medical treatment, there remains a risk of vessel re-occlusion in those who do reperfuse. All patients receiving thrombolysis should have an electrocardiogram (ECG) carried out 90 min following the commencement of thrombolytic treatment. Where the degree of ST elevation has come down by $<50\%$ at 90 min there is a high probability that the infarct related artery has failed to reperfuse. In most centres, standard protocols will stipulate that coronary care nursing staff will perform these post-thrombolytic ECGs, but it important that these are reviewed and acted upon quickly.[18]

REACT

Where patients do not reperfuse following thrombolysis, it is important to determine who should be considered for rescue angioplasty. REACT (REscue Angioplasty versus Conservative treatment or repeat Thrombolysis)[19] was a study that randomised 427 acute STEMI patients who failed to reperfuse 90 min after initial thrombolytic therapy to either conservative treatment, repeat thrombolysis or rescue PCI. The primary end point was a composite of death, reinfarction, cerebrovascular events and severe heart failure within 6 and 12 months follow up. Secondary end points were a composite of death, reinfarction, cerebrovascular events, bleeding events and heart failure; severe bleeding complications; 1 month mortality and exercise test at 1 month. Based on power calculations, 150 patients were enrolled into each arm of the study.

A total of 427 patients were enrolled in the study. The average door-to-needle time was 27 min and pain-to-needle time was 140 min. The average time between admission and second lytic was 330 min with an average time between the two lytic treatments being 190 min. Time between initial pain and rescue PCI was 274 min equating to a difference of 84 min difference in timing between those receiving second lytic and rescue PCI. The composite end point of death, reinfarction, cerebrovascular events and severe heart failure was significantly lower in patients receiving rescue PCI. At 6 month follow up, the primary end point had been reached in 31.0% of the repeat thrombolysis arm, 29.8% of the conservative arm, and only 15.3% of the rescue PCI arm which represents an absolute risk reduction of 15.7% (RRR of 49% between the repeat thrombolysis and rescue PCI arms). The rate of major overt bleeding complications was significantly greater in the rescue PCI arm, but all of them were related to vascular access. The rates of minor bleeding complications were similar in all three arms of the study.

The trial was not powered to highlight a difference between the individual end points; however, despite being terminated early, it did highlight the benefit of rescue PCI over repeat thrombolysis in patients who fail to reperfuse at 90 min following attempted thrombolysis.

Meta-analysis

More recently, a meta-analysis of treatment after failed thrombolysis[20] reviewed eight trials and confirmed that rescue PCI is associated with improved outcomes. Where reperfusion did not occur after 90 min, repeat thrombolysis was associated with no improvement in all cause mortality (RR 0.68, 95% CI 0.41 to 1.14) or reinfarction (RR 1.79, 95% CI 0.92 to 3.48) and was associated with an increased risk of minor bleeding (RR 1.84, 95% CI 1.06 to 3.18).

Where failure to reperfuse led to a mechanistic reperfusion strategy via PCI, a significant reduction in all cause mortality was not seen (RR 0.69, 95% CI 0.46 to 1.05). Significant reductions in the risk of heart failure and reinfarction were noted as were an increased risk of stroke (RR 4.98, 95% CI 1.10 to 22.5) and minor bleeding (RR 4.58, 95% CI 2.46 to 8.55). While rescue PCI is associated with an improvement in clinical outcomes among patients who fail to reperfuse, these must be interpreted in the context of the potential risks that exist. Repeat thrombolysis is not associated with a significant clinical improvement.

Systematic PCI

Where fibrinolytic reperfusion therapy is successful in providing restoration of blood flow to the occluded artery and ST segment resolution is witnessed, traditional thoughts regarding the timing of PCI would be conservative and either delayed or driven by ischaemia.

GRACIA-1

GRACIA-1 (Grupo de Analisis de la Cardiopatia Isquemica Aguda-1)[21] explored the use of coronary arteriography following thrombolysis. In this study, 23 centres in Spain and Portugal randomised 500 patients who received thrombolysis following a STEMI to undergo either coronary arteriography within 24 h of admission or an ischaemia guided approach to coronary arteriography. Baseline characteristics were similar in both groups; 79.6% of patients in the interventional arm received coronary arteriography with stent placement, and in the conservative group 70% of patients were managed conservatively.

At 30 days, the primary composite end point of death, non-fatal reinfarction, or ischaemia guided revascularisation was not significantly different in either group and the 30 day mortality rate was also similar. Despite receiving PCI at an average of 16.7 h following thrombolytic therapy, the incidence of bleeding complications was similar to the conservative arm of the study. There was also a significantly shorter length of stay where patients received PCI.

The frequency of death, non-fatal reinfarction or ischaemia guided revascularisation at or before 1 year was significantly lower in the invasive group. When comparing the invasive and conservative groups, there was a relative decrease of 66% and an absolute decrease of 11% in the primary end point among the invasive group.

GRACIA-1 highlights the possibility of providing pharmacological treatments that facilitate reopening of an occluded artery until a more definitive and mechanical treatment can be administered. Data from other trials[22 23] highlight that performing coronary arteriography on the day following thrombolysis is safe and allows a reduction in length of stay and a reduction in re-admissions.

Meta-analysis

In a meta-analysis of PCI strategies after fibrinolysis,[24] the authors assessed six randomised controlled trials that compared systematic and early PCI with delayed or ischaemia guided PCI. Where intervention was ''balloon-only'', early PCI resulted in a non-significant trend towards higher mortality and reinfarction. It is of note that these studies were performed in the early days of mechanical intervention when the immediate use of aspirin was not common and at a time when thienopyridines were not available. The later and more contemporary studies tended towards intervention that involved stent deployment, and while the pooled data did not show significance, a trend towards reduced reinfarction and death was noted in the early PCI group (RRR 7.5% vs 13.2%; $p = 0.0067$). This benefit was obtained without a significant increase in major bleeding complications (odds ratio 1.18, 95% CI 0.60 to 2.30; $p = 0.64$).

When combined, the data from both balloon and stent PCI studies showed a non-significant trend towards a benefit for systematic and early PCI when compared with a more conservative strategy. These findings draw attention to the need for improvements in transport arrangements to ensure that all patients treated with fibrinolytics can be transported to a local catheterisation laboratory in a timely fashion, be it for rescue angioplasty or systematic PCI the day following successful medical treatment.

Learning points

- Fibrin specific thrombolytic should be used over streptokinase.
- Clopidogrel use: load with 300 mg clopidogrel and give 75 mg daily thereafter. Reduce the loading dose to 75 mg in patients over 75 years.
- Independent of the thrombolytic used, LMWH should be commenced with dose reduction in the elderly and those with renal impairment.
- Post-thrombolysis ECG should be performed at 90 min and where 50% resolution of ST segment elevation has not occurred, rescue angioplasty should be considered.
- Evidence suggests that PCI immediately following full dose thrombolysis is harmful except when considering rescue angioplasty.
- Where thrombolytic therapy is used to treat STEMI, systematic coronary arteriography on the day following thrombolysis offers reduced length of stay and a reduction in readmissions.

Facilitated PCI

Primary PCI is a highly effective treatment, but due to a number of geographic and other constraints, availability is limited to 20% of patients who present with STEMI within Europe. An even smaller percentage of patients are treated within 2 h of pain, which is recognised as the optimum therapeutic window. These limitations require a need for alternative treatment options which have been explored in various trials.

Facilitated PCI is defined as the immediate use of pharmacological treatment to establish early reperfusion followed by transport to a centre where emergent mechanical reperfusion in the form of percutaneous intervention can be performed to stabilise the ruptured plaque and maximise TIMI 3 flow.

ASSENT-4

ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction)[25] was designed to determine whether immediate thrombolysis before delayed PCI would mitigate the negative impact of potentially delayed primary PCI. Patients were randomised to either full

dose tenecteplase plus PCI or to primary PCI and treatment with unfractionated heparin. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the investigators in either arm. Inclusion criteria for randomisation were symptoms for less than 6 h before randomisation, intention to perform primary PCI, and ST segment elevation summation of more than 6 mm. The primary end point was a composite of death, cardiogenic shock or congestive heart failure within 90 days.

A total of 1667 patients were randomised in 24 countries between November 2003 and April 2005, with 829 patients receiving facilitated PCI and 838 receiving primary PCI. The study was terminated early due to a significant disadvantage in patients randomised to receive facilitated PCI. The time between onset of symptoms and randomisation was similar in both groups, as was time to first balloon. There was a significant difference between the two groups with regard to the use of glycoprotein IIb/IIIa inhibitors (50.4% vs 9.5%, respectively; $p<0.0001$).

The primary end point of death, cardiogenic shock or congestive heart failure within 90 days was significantly lower in the primary PCI group (13.7% vs 18.8% for the facilitated PCI group; $p = 0.0055$). Major inpatient bleeding complications were similar in the primary and facilitated PCI groups (5.7% vs 4.3%; $p = 0.22$), but minor bleeding complications were greater in the facilitated group (25.2% vs 18.9%; $p = 0.002$). There was a significant increase in the risk of stroke in the facilitated PCI group (1.81% vs 0%; $p<0.001$).

The concept of initiating lytic treatment before percutaneous arteriography among a population who cannot undergo immediate PCI for whatever reason is appealing. Unfortunately, the hypothesis does not hold and patients who were pre-treated with a thrombolytic had worse outcomes, increased rates of stroke and increased mortality. Among the facilitated PCI group, there was a significantly increased risk of reinfarction due to early stent occlusion. One explanation for such an observation is that the fibrinolytic causes a deleterious prothrombotic effect when administered immediately before PCI, and hence the rate of stent occlusion increases. A strategy of routine and immediate PCI following full dose lytic, as used in this study population, cannot be recommended as standard practice.

Outstanding controversies

- **Mandatory PCI:** Will a strategy of early thrombolysis and mandatory rescue or systematic PCI prove to be better than primary PCI?
- **Modifiable risk:** High risk and high modifiable risk are not the same thing. Research is ongoing and identifying patients with high modifiable risk may prove achievable using cardiac magnetic resonance, magnetic resonance imaging perfusion scanning, or brain (B-type) natriuretic peptides.
- **Anticoagulants:** What will the future position of fondaparinux be? In studies, low rates of bleeding complication have been reported but at the expense of increased incidence of catheter thrombosis at the time of coronary arteriography.
- **Clopidogrel loading:** In older patients receiving thrombolytic therapy, a loading dose of only 75 mg clopidogrel has not been studied. It is not clear if this is the most effective dose (loading dose of 300 mg given to those <75 years).
- **LMWH in renal failure:** Currently, a dose reduction is suggested in renal failure, but it has not been thoroughly investigated. What is the optimal dose reduction in patients with renal disease? Currently, a dose reduction is suggested in renal failure, but it has not been thoroughly investigated. What is the optimal dose reduction in patients throughout the spectrum of renal disease?

CONCLUSION

Primary angioplasty of the culprit vessel is the gold standard treatment for acute STEMI. Unfortunately, it is not possible for all patients with acute STEMI to have primary intervention and thrombolysis is an adequate alternative. While novel agents such as tenecteplase do not offer mortality benefits when compared to traditional agents such as tPA, their pharmacokinetics allow bolus administration rather than a thrombolytic infusion, making them easier to administer.

From recent data, we have seen that the use of dual antiplatelet treatment and supplementary anticoagulation can improve mortality and reduce morbidity, while not increasing the risk of major haemorrhage. Subsequent additional data suggest that, where thrombolysis is not successful and resolution of ECG changes does not occur by 90 min, rescue angioplasty should be considered. This strategy offers a significant benefit over repeat thrombolysis or conservative management.

Facilitated PCI with thrombolytic use before emergent coronary arteriography should not be undertaken. While major bleeding complications are similar when considering facilitated PCI and primary PCI, clinical outcomes are worse and mortality is higher.[26] Where thrombolysis is successful, systematic PCI within 24 h of thrombolysis is of clinical benefit. While there is no improvement in mortality at 30 days, there is a significant reduction in length of stay and readmission rates.

Authors' affiliations
J B Jones, A Docherty, Department of Medicine, Wishaw General Hospital, Wishaw, UK

Competing interests: AD was a co-investigator for EXTRACT TIMI-25 study and has held consultancy agreements with Sanofi and BMS.

REFERENCES

1 **De Luca G**, Suryapranata H, Zijlstra F, *et al*. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol* 2003;**42**:991–7.
2 **Boersm E**, Mercado N, Poldermans D, *et al*. Acute myocardial infarction. *Lancet* 2005;**361**:847–58.
3 **De Luca G**, Suryapranata H, Ottervanger JP, *et al*. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 2004;**109**:1223–5.
4 **Keeley EC**, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20.
5 **Keely E**, Hillis D. Primary PCI for myocardial infarction with ST-segment elevation. *N Engl J Med* 2007;**356**:47–54.
6 **Silber S**, Albertsson P, Aviles F, *et al*. Guidelines for percutaneous coronary interventions. *Eur Heart J* 2005;**26**:804–47.
7 **Chesebro JH**, Knatterud G, Roberts R, *et al*. Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;**76**:142–54.
8 **The GUSTO Angiographic Investigators**. The effects of tissue plasminogen activator streptokinase or both on coronary-artery patency ventricular function and survival after acute myocardial infarction. *N Engl J Med* 1993;**329**:1615–22.
9 **Davydov L**, Cheng JWM. Tenecteplace: a review. *Clin Ther* 2001;**23**:982–97.
10 **Cannon CP**, McCabe CH, Gibson CM, *et al*. TNK-tissue plasminogen activator in acute myocardial infarction. Results of the Thrombosis in Myocardial Infarction (TIMI) 10A dose-ranging trial. *Circulation* 1998;**95**:351–6.
11 **Cannon CP**, McCabe CH, Gibson CM, *et al*. TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction. Results of the TIMI 10B trial. *Circulation* 1998;**98**:2805–14.
12 **ASSENT-3 and ASSENT-3 PLUS Investigators**. Age, outcomes, and treatment effects of fibrinolytic and antithrombotic combinations: findings from Assessment

of the Safety and Efficacy of a New Thrombolytic (ASSENT)-3 and ASSENT-3 PLUS. *Am Heart J* 2006;**152**:684.e1–9.
13 **Antman EM**, Anbe DT, Armstrong PW, *et al.* ACC/AHA guidelines for the management of patients with st-elevation myocardial infarction. *Circulation* 2004;**110**:588–636.
14 **Sabatine MS**, Cannon CP, Gibson CM, *et al.* Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;**352**:1179–89.
15 **Chen ZM**, Jiang LX, Chen YP, *et al.* Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;**366**:1607–21.
16 **Van de Werf F**, Armstrong PW, Granger C, *et al.* Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001;**358**:605–13.
17 **Antman EM**, Morrow DA, McCabe CH, *et al.* Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006;**354**:1477–88.
18 **Gemmill JD**, Hogg KJ, MacIntyre PD, *et al.* A pilot study of the efficacy and safety of bolus administration of alteplase in acute myocardial infarction. *Br Heart J* 1991;**66**:134–8.
19 **Gershlick AH**, Stephens-Lloyd A, Hughes S, *et al.* Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 2005;**353**:2758–68.
20 **Wijesundera HC**, Vijayaraghavan R, Nallamothu BK, *et al.* Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2007;**49**:422–30.
21 **Fernandez-Avilés F**, Alonso JJ, Castro-Beiras A, *et al.* Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004;**364**:1045–53.
22 **Ross AM**, Coyne KS, Reiner JS, *et al.* A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT trial. PACT investigators. Plasminogen-activator Angioplasty Compatibility Trial. *J Am Coll Cardiol* 1999;**34**:1954–62.
23 **Topol EJ**, Ohman EM. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. *Circulation* 2000;**101**:2788–94.
24 **Collet JP**, Montalescot G, Gershlick A. Percutaneous coronary intervention after fibrinolysis. *J Am Coll Cardiol* 2006;**48**:1326–35.
25 **Van de Werf F**, Ross A, Armstrong P, *et al.* Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;**367**:569–78.
26 **Keely EC**, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 2006;**367**:579–88.