

Thrombolysis or primary angioplasty? Reperfusion therapy for myocardial infarction in the UK

A T Ratcliffe,¹ C Pepper²

¹ University of Leeds Medical School, Leeds, UK; ² Department of Cardiology, Leeds General Infirmary, Leeds, UK

Correspondence to:
Dr C Pepper, Department of Cardiology, Leeds General Infirmary, Leeds LS1 3EX, UK;
Chris.pepper@leedsth.nhs.uk

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ABSTRACT

Intravenous thrombolysis and percutaneous coronary intervention (PCI) are alternative treatment options for coronary reperfusion in acute myocardial infarction. Recent trials and meta-analyses have produced increasing evidence that primary coronary intervention produces better long-term outcomes for the treatment of acute myocardial infarction. Most of these studies, however, were performed in US or European healthcare systems and may not be directly transferable to an NHS setting. The widespread introduction of primary PCI would have major implications for the organisation of healthcare provision within the UK. An alternative to PCI that may produce similar outcomes at a reduced cost might be early (pre-hospital) administration of thrombolysis. In an era of unprecedented financial attention, the importance of interventions that are simultaneously beneficial to the patient and economical to the NHS has never been more important. The evidence base for primary PCI and its possible use in the NHS are discussed.

Myocardial infarction (MI) is the most common cause of death in the Western world,¹ and the World Health Organisation predict that, by 2020, it will be the leading cause of death in the world as a whole.² Approximately 240 000 people in England and Wales experience an acute MI every year, nearly 50% of whom die within 30 days of the event.³ Effective early treatment of MI by restoring blood flow to the myocardium is crucial to the clinical outcome.

MI is generally the result of acute rupture or ulceration of an atherosclerotic plaque situated within a major epicardial coronary artery. Exposure of the intimal layer initiates a cascade of platelet activation and thrombosis resulting in occlusion of the vessel and infarction of the subjacent myocardium. Thus the principle aim of acute treatment of MI is restoration of myocardial perfusion by recanalisation of the occluded vessel. For the last 20 years, the principle means of achieving this was by hospital-based systemic administration of thrombolytic drugs which result in non-specific dissolution of the thrombus. Current developments have led to a reappraisal of the most efficient means of achieving myocardial reperfusion; these include direct recanalisation of the vessel by inflation of an angioplasty balloon at the site of vessel occlusion (so-called primary angioplasty) and, more recently, pre-hospital delivery of thrombolytic drugs administered by trained paramedical staff. Both methods have implications for optimal delivery within a resource-limited healthcare system.

Determining which treatment strategy provides the optimal patient benefit while simultaneously

maximising efficient use of resources within the NHS is fundamental in the modern medical climate. Although considerable research has been conducted to examine the differences between the percutaneous coronary intervention (PCI) and thrombolytic therapy, most have been undertaken in healthcare settings other than our own in the UK. We aim to discuss the current literature in the context of the UK setting.

METHODS

A Medline search of full-text articles in the English language published in 1980–2006 was performed. Papers comparing primary coronary angioplasty with thrombolytic therapy were identified by using the search terms acute myocardial infarction, angioplasty, PCI and thrombolytic therapy. Further articles were obtained through review of the bibliography of the relevant papers.

This review examines several randomised trials, registry studies and previous reviews. Case-control studies and case series were excluded. Studies were compared with regard to the intervention used and patient outcomes, including mortality, reinfarction, stroke and revascularisation. We also analysed the cost-efficacy of the two treatments and their relative success in comparison with pre-hospital thrombolysis.

EARLY THROMBOLYSIS STUDIES

The early 1980s saw huge advances in the treatment of acute MI. Cardiologists had recognised the importance of early reperfusion in limiting ischaemic damage to the myocardium, and, although some benefits of angioplasty were beginning to be proved, the treatment of choice at the time was still the use of thrombolytics. This was primarily due to two groundbreaking mega trials: the Second International Study of Infarct Survival Group (ISIS-2)⁴ and an Italian group (GISSI)⁵ both studied the effects of intravenous streptokinase given to patients with suspected acute MI. Data from ISIS-2 indicated that 5-week mortality was significantly reduced in patients given streptokinase, and, although the benefits of treatment are greatest when given to patients presenting <6 h after onset, there were favourable outcomes in patients treated up to 24 h after onset. The overall reduction in mortality in patients presenting in <6 h was 14%; this equates to the prevention of 15–20 deaths per 1000 patients.⁴

The evidence from this study, combined with very similar results from the GISSI trial, which found that early intravenous streptokinase given within 6 h of the onset of pain reduces in-hospital mortality by ~47%, confirmed that the most

Table 1 Results of trials examining post-procedural complications associated with percutaneous coronary intervention (PCI) and thrombolysis

Reference	PCI (% of patients)				Thrombolysis (% of patients)			
	Death	Reinfarction	Revascularisation	Stroke	Death	Reinfarction	Revascularisation	Stroke
Keeley <i>et al</i> ⁷	7	3	–	1	9	7	–	2
Zijlstra <i>et al</i> ⁶	13	6	25.8	–	24	22	51.7	–
Grines <i>et al</i> ⁹	2.6	2.6	–	0	6.5	6.5	–	2
Widimsky <i>et al</i> ¹⁰	40	12	34	–	53	19	51	–

suitable treatment for acute MI in terms of both prevented deaths and cost-effectiveness was thrombolytic therapy.⁵

The undoubted benefits of thrombolysis are offset by its non-specificity for the coronary circulation, resulting in a risk of bleeding complications and time-dependent uncertainty about the efficacy of reperfusion. In addition, there is limited evidence of the benefit of thrombolytic therapy in a number of high-risk groups including older patients, MI associated with ST depression rather than elevation, and in the context of cardiogenic shock.⁶ An invasive strategy (ie, PCI) has potential benefits of specific and confirmed recanalisation of the culprit vessel as well as knowledge of the detailed coronary anatomy, which can be used to guide later management. On the other hand, a whole medical infrastructure has been developed to facilitate the prompt administration of thrombolysis, and a wholesale move away from this will require further extensive logistical changes, including investment in staff, medical hardware and hospital protocols.

OUTCOMES OF PRIMARY PCI

Clinical trials comparing the efficacy of thrombolysis and primary angioplasty have concluded that superior outcomes can be obtained with an invasive approach.^{5–6} Not only has PCI been demonstrated to reduce short- and long-term major adverse events, but its clinical outcomes appear to be independent of time to treatment, with angioplasty consistently achieving greater outcomes when reperfusion was delayed because of transportation.

A meta-analysis by Keeley and colleagues⁷ demonstrated that patients treated by PCI had a significantly reduced likelihood of death, non-fatal reinfarction or stroke than those given thrombolytic therapy. Figures comparing outcomes after transfer for PCI and immediate on-site thrombolysis were also examined and produced similar conclusions, PCI still gaining better clinical outcomes. Consistent findings were also made for high-risk patient groups (older patients and those in cardiogenic

shock), leading to the suggestion that angioplasty is a more universally suitable treatment option.

Zijlstra *et al*⁶ examined the long-term outcomes in patients treated with PCI or thrombolysis and concluded that, at 5 years after the procedure, angioplasty offered greater success rates, with fewer deaths (13% vs 24%) and a reduction in reinfarction (6% vs 22%). These results are supported by Grines and colleagues,⁹ who compared intravenous administration of tissue plasminogen activator with primary angioplasty and found lower incidences of intracranial haemorrhage (0% vs 2%), reinfarction (2.6% vs 6.5%) and death (2.6% vs 6.5%) at 1 year in the angioplasty group.

A more recent evaluation of patients recruited into the PRAGUE-2 Study has found that, at 5 years after the procedure, the incidence of reinfarction, revascularisation and death from all causes was considerably reduced in those patients randomised to the PCI arm (table 1). These benefits were primarily due to the reduction in adverse events occurring within the first month after the initial MI. It was also found that PCI is associated with a greater success rate in opening occluded coronary vessels: 90% success rate in PCI group vs 50–60% for thrombolysis.¹⁰

There are, however, recognisable risks to such an invasive procedure. Prevention of thrombosis of an intracoronary stent requires aggressive inhibition of platelet aggregation, and, unsurprisingly therefore, bleeding is often reported after PCI. This is usually localised to access sites and has been shown to be reduced by use of smaller cannula sizes and lower doses of intravenous heparin.⁷ Other potential complications associated with primary PCI concern transportation (discussed below) and radiographic contrast-related acute renal failure.^{11–12}

HIGH-RISK GROUPS

There is evidence that both thrombolysis and primary PCI carry a greater chance of adverse outcome in recognised high-risk patient groups. Thrombolysis provides a rapid method of restoring coronary blood flow. However, because it acts

Table 2 Trials comparing percutaneous coronary intervention (PCI) with thrombolysis in relation to time-to-treat and post-procedural complications at 30 days

Study	Adverse events occurring within 30 days (% of patients)							
	Time to treatment (min)		PCI			Thrombolysis		
	PCI	Thrombolysis	Mortality	Reinfarction	Stroke	Mortality	Reinfarction	Stroke
GUSTO IIb ¹⁵	228	180	5.7	4.4	0.2	7.0	6.5	0.9
PRAGUE ²⁰	215	192	7.0	1.0	0.0	14.0	10.0	1.0
DANAMI-2* ²¹	188	160	6.7	0.9	0.0	5.9	6.4	2.3
Air PAMI ¹³	174	63	8.4	1.4	0.0	12.1	0.0	4.5
Zijlstra <i>et al</i> ²² (early group)	≤ 120	≤ 120	3.9	1.7	0.2	5.0	6.6	0.9
Zijlstra <i>et al</i> ²² (intermediate group)	120–240	120–240	4.1	4.1	0.4	6.3	6.3	1.6
Zijlstra <i>et al</i> ²² (late group)	≥ 240	≥ 240	4.7	2.4	0.6	12.1	6.0	1.3
de Boer <i>et al</i> ³³	59	31	7.0	–	–	22.0	–	–

Table 3 Comparison of costs of percutaneous coronary intervention (PCI) and thrombolysis

Study	Cost		
	PCI	Thrombolysis	PHT
Hammersmith ³²	£6 681	£8 248	–
de Boer <i>et al</i> ³³	17 316	16 681	–
PAMI ³⁴	23 468	26 904	–
CAPTIM ³⁵	23 610	–	26 103

Charges are given in US\$ unless otherwise stated. It should be noted that, when professional fees were taken into account in the PAMI study, although charges were still favourable towards PCI, there was no statistically significant difference between the two treatment options. PHT, pre-hospital thrombolysis.

systemically, many patients, notably the elderly, are at risk of haemorrhage and major bleeding. Similarly, PCI requires aggressive antiplatelet therapy, including aspirin, thienopyridines and often glycoprotein IIb and IIIa inhibitors, and consequently carries its own risk of haemorrhagic complications.

Whether primary PCI is beneficial for older patients has been addressed by several studies. An investigation by Berger *et al*¹⁴ analysed patients aged over 65 admitted with acute MI and treated with either thrombolysis or percutaneous transluminal coronary angioplasty (PTCA). They found that, at the 30-day and 1-year follow-up, patients treated with angioplasty had lower mortality (8.7% vs 11.9% and 14.4% vs 17.6%, respectively). In terms of post-procedural complications, the angioplasty group again had lower rates of occurrence of post-MI angina, reinfarction, cerebral haemorrhage and stroke (table 2).

These results suggest that angioplasty benefits older patients presenting with acute MI. This was, however, a retrospective non-randomised comparison with potential for confounding. Also the large number of thrombolytic procedures used in the analysis offset against a relatively small number in the PTCA group is not ideal for comparison. Despite these caveats, the report is in agreement with the GUSTO IIB¹⁵ and PAMI¹⁶ studies, which both found a reduced mortality associated with primary PTCA when given to patients ≥ 65 years of age.

IMPACT OF TRANSFER TIMES

The time between arrival in hospital and the administration of thrombolytic drugs (door-to-needle time) or inflation of a coronary catheter (door-to-balloon time) are key index measures of NHS hospital performance. Extensive efforts have been made to streamline treatment to minimise delays. A shift from thrombolytic therapy to primary angioplasty might be expected to invoke delays in the achievement of definitive reperfusion. The time dependency of PCI-delivered reperfusion has been the subject of considerable attention. Although early reports^{17–19} showed that overall benefits of primary PCI decline with increasing delay to reperfusion, it appears that this decline is slower than that of thrombolysis. Thus current European guidelines¹⁴ recommend PCI as the primary method of reperfusion for patients presenting to a facility with the appropriate skills and infrastructure.

Many centres receiving patients with acute ST elevation MI, however, cannot offer on-site PCI. A number of studies investigating outcomes following transfer of patients to an interventional centre have shown that PCI still affords benefit over locally delivered thrombolysis (table 2).

Patients randomised to the PCI arm of every study outlined in table 2 experienced greater delays to treatment than their

counterparts treated with thrombolysis. Despite this, the number of patients experiencing adverse effects within 30 days is consistently lower in those treated with angioplasty than those given thrombolytic therapy. This therefore suggests that transport to tertiary angioplasty centres is not only safe and practical but reduces risk of major complications. The studies help to reinforce the notion that moderate delays to reperfusion does not adversely affect outcome in patients treated with angioplasty.

However, the PRAGUE-2 and STOPAMI-2 investigators suggest that, within the first 3 h after MI, the relative benefits of primary PCI over thrombolysis are modest. Thus when on-site PCI is not available, local thrombolysis is a valid alternative to transfer when patients present very early in the course of the MI.²³ After 3 h, however, the benefits of PCI in improving reperfusion and reducing stroke risk support an interventional approach.²³

Thus the benefits of both treatments are dependent on the time from symptom onset to the initiation of treatment.²⁴ Studies agree that the benefits of both procedures decrease as occlusion time increases. Angioplasty results in lower rates of reinfarction and stroke,^{25,26} but thrombolysis is well established and most emergency departments are well set up to facilitate its prompt administration. Where PTCA is not available on-site, a decision needs to be made in accordance with both the condition of the patient and the hospital expertise.¹⁴ In general, despite the potential delay to treatment associated with angioplasty, its benefits in terms of reduced reinfarction and cerebral haemorrhage seem to outweigh those of thrombolysis.³

PRE-HOSPITAL FIBRINOLYSIS VERSUS PRIMARY ANGIOPLASTY

Optimum results in terms of myocardial salvage are obtained when reperfusion is achieved as early as possible. Although angioplasty can only be performed in hospital, thrombolysis can potentially be administered in the pre-hospital setting, allowing significant savings in time to reperfusion. This might be expected to enhance the therapeutic benefits of thrombolysis.²⁷

Pre-hospital fibrinolysis has been widely used to treat acute MI in France for the last decade. This system provides ambulances with an on-board doctor who is able to administer immediate pre-hospital thrombolysis or select PTCA. Danchin *et al*²⁸ investigated the benefits of this system and found that, although time from symptom onset to hospital admission was similar in all groups (ie, pre-thrombolysis, in-hospital thrombolysis or PTCA), time to reperfusion in the pre-hospital group was significantly lower and consequently 1-year survival was higher (94%, 89% and 89%, respectively).

Other investigations have found similar results. A subgroup of the CAPTIM study examined the outcome in patients presenting in under and over 2 h from symptom onset and randomised to either PCI or pre-hospital thrombolysis.²⁹ Patients treated in under 2 h with pre-hospital fibrinolysis were found to have lower mortality (2.2% vs 5.7%) and cardiogenic shock (1.3% vs 5.3%).²⁹ After 2 h, the effects reversed, PTCA achieving lower mortality. The reason for this is that time to treatment with pre-hospital thrombolytic therapy was reduced by ~ 1 h; consequently blood flow was restored faster and heart muscle was preserved. However, the study also found that pre-hospital thrombolysis was more expensive than PTCA³⁴ (discussed below).

Thus very early thrombolysis may offer benefits over primary PCI if administered within 2 h of symptom onset. After this, however, its benefits decline rapidly with increasing time.³⁰

A more recent registry study by Stenestrand and colleagues³¹ comparing pre-hospital thrombolysis (PHT), in-hospital thrombolysis (IHT) and primary PCI found that in-hospital reinfarction, readmission with acute MI and mortality were much reduced in the PCI groups compared with the IHT or PHT group. Time to treatment was, once more, fundamental to the outcome. Investigators concluded that, up to 2 h after MI, PHT produced comparable results to PCI in terms of mortality, but after this period PCI consistently produced lower morbidity and mortality; it was only with delays of more than 7 h that PCI produced poorer outcomes than thrombolysis. The authors concluded that, only if administered within 2 h of symptom onset and if transport time to a PCI centre was >4 h should PHT be considered over PCI.

Thus, if treatment with thrombolytics can be given within the “golden hour”, the benefits may be equivalent to or possibly greater than those of primary angioplasty. For patients with prolonged symptoms (>2 h), angioplasty still seems to offer superior results. As the availability of catheterisation laboratories is limited in many UK regions, a strategy to implement early thrombolysis is an option. The French protocol has been shown to be successful in reducing mortality, but, in the UK, the shortage of doctors would create difficulties in introducing an identical policy. Administration of thrombolysis by trained ambulance staff has, however, been shown to be feasible, and the efficacy of this approach is being tested in the UK in the ongoing REACT-2 study.

COST IMPLICATIONS OF PRIMARY ANGIOPLASTY OVER THROMBOLYSIS

For any procedure, the ideal treatment is one that will produce the optimal outcome for the patient while at the same time minimising costs for the health service. This is particularly important in a resource-limited healthcare system such as in the UK. The clinical merits of using angioplasty over thrombolysis with regard to clinical outcomes have been discussed, but the question remains whether the benefits of such a procedure are lost because of low cost-effectiveness.

Several investigations have examined the cost-effectiveness of the two treatments and found that, although initial costs of angioplasty often exceed those of thrombolysis, after 1 year, the costs were on average US\$2032 lower for those treated with PCI (table 3). The de Boer and PAMI studies also examined the charges incurred 12 months after the procedure by examining the efficacy of both treatments in terms of cost per event-free survivor and found that costs were still lower in the PCI cohorts.

The Hammersmith investigation, concordant with the other four studies, found that the primary determinant of cost was hospitalisation time and the occurrence of related ischaemic episodes. As angioplasty offers reduced rates of complications, patients are discharged earlier and are less likely to be readmitted with a related cardiac event.^{32–35} The main hospital charges are therefore considerably reduced in patients receiving PCI, accounting for the reduced cost after 1 year.

All the study groups in this report had some form of pre-existing infrastructure to deal with mass PTCA treatment. Hypothetical models for implementing a cost-effective primary PCI infrastructure in the NHS have been proposed by a number of studies. These suggest that there are four main criteria that should be adhered to in order to replicate the economical savings that other European and American studies have demonstrated.

1. The use of existing catheterisation laboratories
2. A throughput of at least 200 cases per annum

3. A view to providing the service for at least 6 years
4. Utilisation of existing nursing and technical staff^{36 37}

By following these guidelines the potentially considerable costs associated with the provision of additional staff, training and equipping the laboratories constantly over a 24 h period could be minimised.

FUTURE CONSIDERATIONS

Currently the Yorkshire Heart Centre is one of six sites across the UK taking part in the National Infarct Angioplasty Project (NIAP), a pilot research group set up by the British Cardiovascular Society and the Department of Health to determine the feasibility of establishing a nationwide angioplasty service to treat MI. The report, which examines different service models, patient and carer experiences, and the cost-effectiveness and logistical difficulties in establishing such a procedure, is due to be completed and its results released in 2007/8. The data produced will then be used to determine Government policy on the treatment of MI using PCI as the first-line treatment.

SUMMARY

- ▶ Prompt restoration of coronary blood flow in MI saves lives and improves clinical outcome.
- ▶ The current standard of care is hospital-delivered systemic thrombolytic therapy. This has limitations, including unpredictable reperfusion, limited benefit in a number of high-risk groups and haemorrhagic complications.
- ▶ Direct reperfusion by primary PCI has been shown to offer better clinical outcomes, but would require a major investment in infrastructure within the NHS.
- ▶ Very early reperfusion with pre-hospital thrombolysis may offer equivalent benefit in selected individuals presenting early in the course of their MI.
- ▶ The potential role of primary PCI in the NHS is currently being evaluated.

We have seen that both thrombolytic therapy and primary angioplasty are successful methods for the treatment of acute MI. They provide suitable means for restoring coronary blood flow and reperfusing cardiac tissue, thus achieving the principle aim of treatment. However, the long-term benefit to both the patient and their respective healthcare system varies with each treatment option.

Time to treatment and outcomes

As we have discussed, the time taken to restore blood flow to cardiac tissue is fundamental to outcome. Most hospitals in the UK are set up to administer thrombolytic therapy in the emergency setting. Although delays to treatment in some studies have been substantial, transportation to tertiary angioplasty centres has not been found to increase the risk of adverse events. PCI consistently produces better patient outcomes at 30 days and 1 year after the procedure with lower rates of death, reinfarction and stroke.

Pre-hospital thrombolysis

This treatment option, if given within 2 h of the onset of symptoms, has been shown to produce outcomes in line with those of PCI and could therefore be the alternative strategy in the UK. However, after this small time window, its benefits are once again inferior to those offered by angioplasty. Before such the decision is taken to adopt this protocol, further research needs to be carried out to determine the lag period between

patients experiencing pain and seeking medical assistance. If subjects are requesting such assistance and paramedics are able to arrive within this 2 h time frame, pre-hospital thrombolysis may be an acceptable alternative in the UK.

Cost-effectiveness

All studies reviewed in this paper have shown angioplasty to be the more cost-effective treatment in the long term. Although initial costs are higher, because of the need for specially trained staff, catheterisation laboratories and equipment, the reduction in mortality, reinfarction and stroke in this group means that hospitalisation time is considerably shorter and therefore long-term medical costs are significantly reduced.

LIMITATIONS

Our study has several limitations. Although we were able to review a large number of papers during our investigation, most of these studies were written in English and retrieved by searching only one database: Medline. By only searching in this library, other studies that match our inclusion criteria may have been overlooked. This may limit the strength of some of our conclusions.

CONCLUSION

Thrombolysis has been the mainstay reperfusion strategy for ST elevation MI for a number of years. Primary PCI has been shown to have superior acute and long-term clinical outcomes. Incorporating a primary PCI strategy within an NHS setting seems likely to offer superior clinical outcomes, but will require significant service reorganisation.

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