

# Acute myocardial infarction: the case for pre-hospital thrombolysis with or without percutaneous coronary intervention

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The open artery hypothesis suggests that establishing reperfusion as soon as possible after the onset of symptoms of acute myocardial infarction should be a priority; this has been highlighted as an important objective in the National Service Framework document in the UK.<sup>1</sup> Currently, patients with acute myocardial infarction are treated with thrombolytic therapy or by percutaneous coronary intervention (PCI). The vast majority at the present time receive in-hospital thrombolysis. With thrombolytic treatment, the earlier that patients are treated, the better their outcome. As a result, there has been a move towards the administration of thrombolytic treatment before hospital admission.

## THROMBOLYTIC TREATMENT

There are many large randomised clinical trials which have shown benefit for thrombolytic treatment in acute myocardial infarction. These are summarised in the fibrinolytic therapy trialists collaborative group publication<sup>2</sup> which demonstrated an overall risk reduction in 35 day mortality of 18% with thrombolytic treatment.<sup>2</sup> The beneficial effect of thrombolysis includes patients presenting within 12 hours of the onset of symptoms, but it is clear that the earlier patients are treated the better their outcome. Thrombolytic treatment saves about 30 lives in 1000 patients presenting within six hours of symptom onset, but only 20 lives per 1000 when treatment is given between 6–12 hours. Beyond 12 hours, benefit is uncertain.

Fibrin specific lytics such as tissue plasminogen activator (t-PA) and reteplase should, in theory, be more effective at opening coronary arteries than streptokinase. Angiographic studies have shown a higher percentage of patients with patent arteries after t-PA treatment than with streptokinase (around 70% *v* around 35%).<sup>3</sup> In the GUSTO (global utilization of streptokinase and t-PA for occluded coronary arteries) trial, where a more aggressive regimen was compared to standard streptokinase, there was a small but significant mortality benefit favouring t-PA (6.3% *v* 7.3%).<sup>4</sup> Although there was an excess of strokes in the group treated with accelerated t-PA, this group still derived benefit when the end point was combined death and strokes. The “open artery” theory suggests that the short and longer term outcome after acute infarction is determined predominantly by the degree of patency obtained. The angiographic appearance at 90 minutes post-thrombolysis correlates with outcome. Patients with TIMI (thrombolysis in myocardial infarction) grade 0 flow (that is, complete occlusion) had a 30 day mortality of 8.4% whereas in those with TIMI grade 3 flow (that is, flow equivalent to that in unaffected arteries) it was only 4%.<sup>5</sup> A retrospective meta-analysis showed that mortality was 3.7% for patients with TIMI 3 flow, 6.6% for those with TIMI 2 flow, and 9.2% for those with TIMI 0/1

flow.<sup>6</sup> Five and 10 year follow up has indicated a continued benefit for those with initial TIMI 3 flow.

Unfortunately, thrombolytic treatment is unable to produce TIMI 3 flow in all patients. It occurs in 54% of patients treated with accelerated t-PA, 56% treated with reteplase, and only 30% treated with streptokinase.<sup>7</sup> The second limitation relates to vessel re-occlusion. Repeat angiographic study at three months of those patients who had a patent artery at 90 minutes has shown a re-occlusion rate of 30%.<sup>8</sup> Patients who re-occlude by three months have a lower one year event-free survival (63% *v* 83%) compared to those whose infarct related artery remained patent. Our goal in acute infarction management should be to achieve optimal TIMI flow initially and to reduce the incidence of re-occlusion.

## PRE-HOSPITAL THROMBOLYSIS

Reteplase (r-PA) is the first member of the third generation thrombolytics. It has an angiographic patency rate which is similar to t-PA, but it is easier to administer (as two boluses). Tenecteplase has been evaluated more recently<sup>9</sup> and can be given as a single bolus. Both of these agents are easier to administer than the earlier thrombolytics and therefore may be preferred when treatment is given before hospitalisation—that is, pre-hospital thrombolysis.

The early trials of thrombolysis introduced the concept that “time is muscle”, based on the fact that benefit from lytic therapy became less significant with time, even within the first six hours. The greatest reduction in mortality appears to occur when the thrombolytic is administered within the first 1–2 hours from the onset of pain. Studies have indicated that the time the patient takes to call for help (the “pain to call time”) accounts for about one hour<sup>10</sup>—patient education is required to reduce this delay. The MITI (myocardial infarction triage and intervention) trial demonstrated that initiating treatment before arrival in hospital reduced the period from onset of symptoms to thrombolysis treatment by 33 minutes.<sup>11</sup> Although there was no overall benefit in mortality, this was not the case in those patients who received treatment early (within 70 minutes) from the onset of pain. These “very early” patients had outcomes that were significantly better in terms of mortality (1.2% *v* 8.7%) and infarct size (4.9% *v* 11.2%). Such data confirm the importance of overall time (that is, onset of symptoms to administration of thrombolysis). The administration of thrombolysis pre-hospital should result in a shorter time than in-hospital treatment.

**Abbreviations:** EMIP, European myocardial infarction project; GUSTO, global utilization of streptokinase and t-PA for occluded coronary arteries; MITI, myocardial infarction triage and intervention; PCI, percutaneous coronary intervention; PRAGUE, primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction

The EMIP (European myocardial infarction project) group randomised over 5000 patients to either pre-hospital lysis or in-hospital treatment. The time to treatment saving was 55 minutes and there was a significant reduction in cardiac mortality (8.3% *v* 9.8%, a relative reduction of 17%).<sup>12</sup> In a meta-analysis of pre-hospital thrombolysis, it was shown that the overall time to thrombolysis was 104 minutes for pre-hospital treatment and 162 minutes for those treated in-hospital. All cause mortality was significantly reduced (odds ratio 0.83, 95% confidence interval (CI) 0.70 to 0.98) (fig 1). Despite such data, pre-hospital thrombolysis is currently being administered to only a minority of eligible patients. This is now being addressed and the infrastructure is being developed (for example, training of paramedics) to enable thrombolysis to be administered appropriately and safely before hospital admission. The introduction of the lytic agents which can be given as a bolus (for example, reteplase or tenecteplase) will facilitate this development.

### PRIMARY ANGIOPLASTY

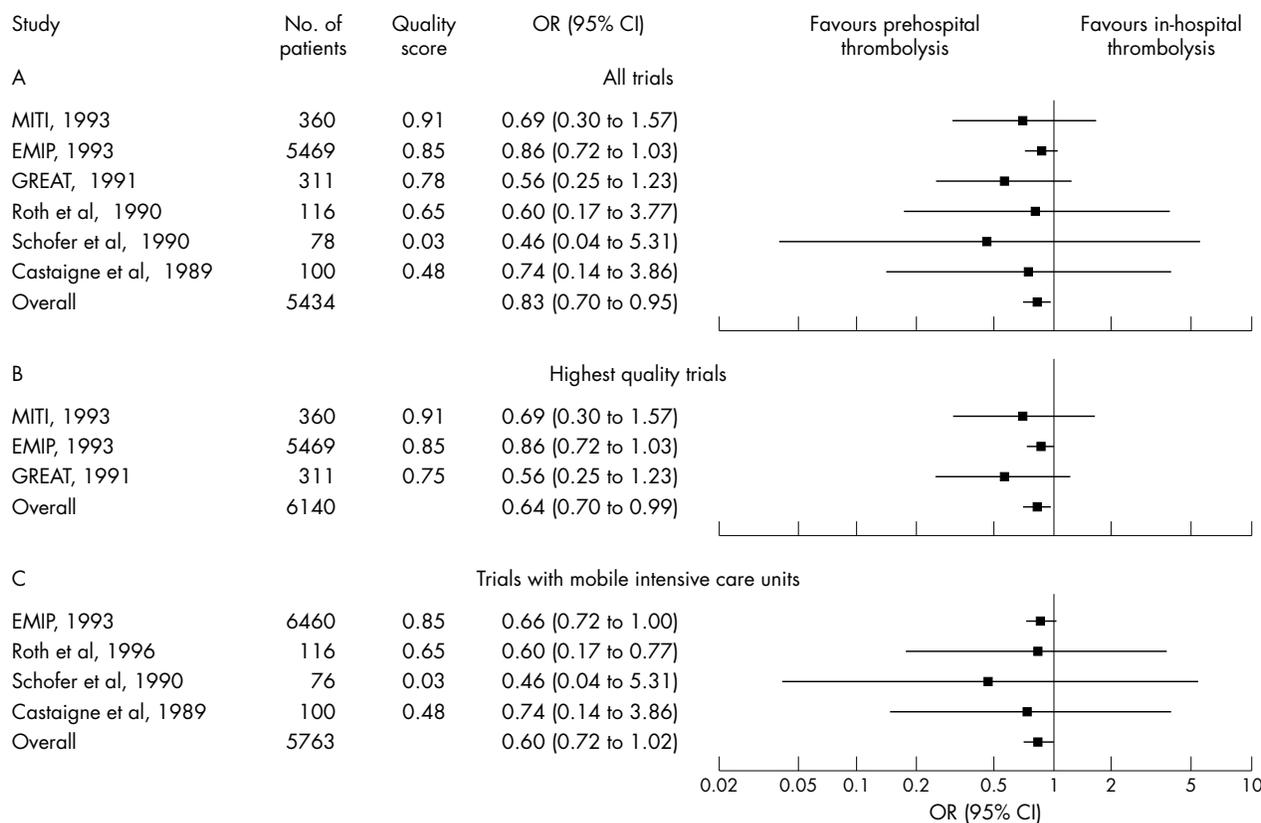
Currently, the only treatment shown to be better than thrombolysis is to open the infarct related artery at the time of presentation with coronary angioplasty/stenting. If the patient is taken to the catheter laboratory within 12 hours of the onset of pain (and within two hours of arrival in hospital) and the artery successfully opened and the stenosis dilated, then TIMI grade 3 flow can be obtained in 80–97% of cases.<sup>13</sup> While re-occlusion of the vessel remains a problem with thrombolysis, this is not the case with PCI. The three month vessel patency after PCI is between 87–91%.<sup>14</sup>

The pooled data from trials comparing PCI with thrombolysis suggest an improved outcome for angioplasty in terms of mortality (2.5% *v* 6.4%), re-infarction (2.0% *v* 7.9%), and

stroke (0.3% *v* 2.5%)<sup>13</sup> (table 1, fig 2). Recurrent ischaemia occurs in between 9–15% of patients undergoing PCI and 27–36% of those receiving thrombolysis. The two year follow up data demonstrate that this early separation of the outcome curves is maintained. Treating the underlying stenosis as well as “rescuing” any patients who have not reperfused are the likely mechanisms of benefit from PCI.

The trials of PCI, however, have included a smaller number of patients than the trials of thrombolysis. When the data are pooled, it appears that the high risk patients (older age, larger infarcts, and anterior infarcts) benefit from PCI both in terms of mortality and re-infarction, whereas the low risk group benefit only in terms of re-infarction. With PCI for acute myocardial infarction, time is also important—the “door to balloon” time should be less than 120 minutes. In a large study of patients treated by angioplasty, the door to balloon time was a significant factor in predicting outcome (adjusted odds of mortality 1.41 (95% CI 1.08 to 1.84) for times > 2 hours, and 1.61 (95% CI 1.25 to 2.08) for times > 3 hours).<sup>15</sup> The more recent trials in which stenting has been employed have shown significant improvement in immediate patency rates. One study demonstrated an event-free survival at six months of 81% in those stented as compared with 73% in those treated by balloon angioplasty alone.<sup>16</sup>

The case for treating patients with acute myocardial infarction by PCI is strong, particularly when patients are treated within 12 hours of the onset of symptoms, when the door to balloon time is short (that is, < 2 hours), and when optimal techniques are used (that is, stents).<sup>17</sup> It may be possible to improve the results of PCI further by using additional pharmacological treatment, such as the glycoprotein IIb/IIIa inhibitors or low dose thrombolysis. The biggest problem with the use of PCI for acute myocardial infarction is

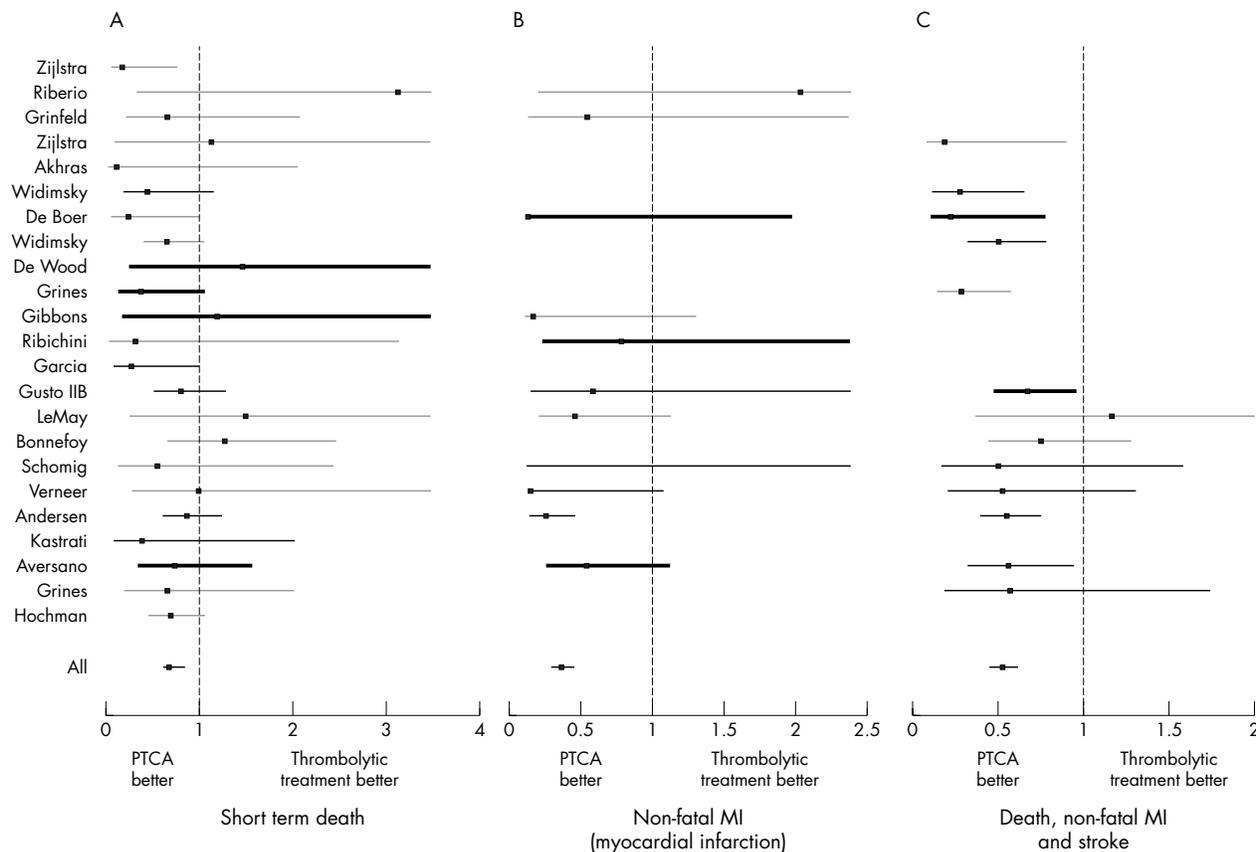


**Figure 1** Results of randomised trials of pre-hospital thrombolysis on hospital mortality. Panel A: z score = -2.14; p = 0.03. Panel B: z score = 2.06; p = 0.04. Panel C: z score = -1.73; p = 0.005. CI, confidence interval; EMIP, European myocardial infarction project; GREAT, Grampian region early anistreplase trial; MITI, myocardial infarction triage and intervention; OR, odds ratio.

**Table 1** Comparative trials (1): details of the trials comparing percutaneous coronary intervention with thrombolytic therapy

Patient characteristics	Symptom duration (h)	Number randomised to PTCA (n = 3872)	Number randomised to thrombolysis (n = 3867)	Stents used	Gp IIb/IIIa antagonists used	Thrombolytic agent used, administration time	Time to treatment (mins)	
							PTCA	Thrombolysis
<i>Streptokinase trials (n = 1837)</i>								
Zijlstra 1993	6	152	149	No	No	1.5 million USK, 1 h	62	30
Riberio 2001	6	50	50	No	No	1.2 million USK, 1 h	238	179
Grinfield 2000	12	54	58	No	No	1.5 million USK, 1 h	63	18
Zijlstra 1996	6	47	53	No	No	1.5 million USK, 1 h	68	30
Akhras	12	42	45	No	No	1.5 million USK, 1 h	NA	NA
Widimsky 1997	6	101	99	Yes	No	1.5 million USK, 1 h	80	70
De Boer	6	46	41	Yes	No	1.5 million USK, 1 h	59	31
Widimsky 2000	12	429	421	Yes	Yes	1.5 million USK, 1 h	277	245
<i>Fibrin specific trial (n = 5902)</i>								
DeWood 2000	12	46	44	No	No	Duteplase, 4 h	126	84
Grines 1997	12	195	200	No	No	t-PA, 3 h	60	32
Gibbons 1999	12	47	56	No	No	Duteplase, 4 h	45	30
Ribichini 2002	6	55	55	No	No	Accelerated t-PA	40	33
<i>Other trials</i>								
Garcia 2001	5	95	94	No	No	Accelerated t-PA	84	69
GUSTO IIB 2001	12	565	573	No	No	Accelerated t-PA	114	72
Le May 2002	12	62	61	Yes	Yes	Accelerated t-PA	77	15
Bonnafant 2002	12	421	419	Yes	Yes	Accelerated t-PA	190	130
Schomig 2000	12	71	69	Yes	Yes	Accelerated t-PA	65	30
Vemer 2001	6	75	75	Yes	No	Accelerated t-PA	100	85
Andersen 1997	12	790	782	Yes	NA	Accelerated t-PA	NA	NA
Kastrati 1995	12	81	81	Yes	Yes	Accelerated t-PA	75	35
Aversano 1997	12	225	226	Yes	Yes	Accelerated t-PA	102	46
Grines 2000	12	71	66	Yes	Yes	Accelerated t-PA	155	51
Hochman 1998	36	52	150	Yes	Yes	Accelerated t-PA	75	168

GP, glycoprotein; LBBB, left bundle branch block; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; t-PA, tissue plasminogen activator; USK, units of streptokinase



**Figure 2** Comparative trials (2): results of the pooled data on mortality, non-fatal myocardial infarction, and stroke.

the mismatch between the availability of interventional facilities and where patients normally present—that is, to non-interventional centres.

### FACILITATED PCI

Thrombolytic treatment is easy to administer and restores patency in a substantial proportion of patients. While PCI is more effective at achieving vessel patency and dealing with the underlying stenosis, it requires specialist facilities and cannot be provided as rapidly as lytic therapy. It has been suggested that a combination of thrombolysis followed by PCI may be optimal.<sup>18</sup>

A recent study demonstrated no significant benefit of PCI compared to pre-hospital lysis.<sup>19</sup> There was an 8.2% incidence of the primary end point in the pre-hospital lysis group and 6.2% in those undergoing PCI. One of the problems with this study is that neither pre-hospital lysis nor PCI were optimally time mandated. Secondly, since stents and the adjunctive use of glycoprotein IIb/IIIa inhibitors are standard treatment options during PCI, the treatment in the PCI arm may not have been optimal.

The PRAGUE (primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction) study<sup>20</sup> compared the outcome in patients randomised to immediate thrombolysis (group 1), thrombolytic treatment during transfer for PCI (group 2), or immediate transfer for PCI (group 3) in patients presenting to a district general hospital. Therefore, patients had to be transferred to a specialist centre for PCI, and some of these (group 2) received thrombolysis on route. Interestingly the need for transport did not seem to impact significantly on the admission to reperfusion times. The combined end point of

death, re-infarction, or stroke was reached in 23%, 15%, and 8% of patients, respectively. Others have demonstrated that adjunctive lysis before PCI increased the initial patency rate (61% compared to 34% in those receiving placebo), with PCI then restoring TIMI grade 3 flow in 77% and 78% of patients, respectively.<sup>18</sup>

There are, in addition, some observational studies that support the concept of combination therapy. One group<sup>21</sup> reported patients treated with pre-hospital lysis administered 150 minutes after the onset of chest pain. Angiography at 90 minutes post-lysis revealed a TIMI grade 3 flow of 64% and TIMI 0/1 in 29%. PCI was undertaken successfully in 49 out of 50 patients in this latter group to give an overall TIMI grade 3 flow of 91%. The overall in-hospital mortality was 4.1% and was similar to a “matched cohort” of patients receiving primary angioplasty. The study suggests that patients receiving pre-hospital thrombolysis may need angiography and possibly PCI to achieve optimal patency rates. In another observational study, 49% of patients receiving pre-hospital lysis had TIMI grade 3 flow which increased to 92% with PCI.<sup>22</sup>

The ADMIRAL trial<sup>23</sup> showed a reduction in primary end point (death, reinfarction, and need for urgent revascularisation) in those patients treated with glycoprotein IIb/IIIa inhibitors (7.4%) as compared to placebo (15.9%) before PCI for acute myocardial infarction. The benefit at six months was only seen in those receiving the agent from a “mobile intensive care team” who went to the patient. To administer this drug in this way routinely would be difficult logistically, with complex training issues. It is therefore unlikely to happen routinely in the foreseeable future. There are, however, ongoing studies of facilitated PCI, including the FINESSE and ASSENT 4 trials.

## SUMMARY

Thrombolytic treatment is effective for the treatment of patients with acute myocardial infarction. The earlier treatment is administered, the better is the outcome and we should move towards the routine use of pre-hospital thrombolysis for most patients. Investment should be made to establish the infrastructure (including training, etc) for this treatment to be available.

Percutaneous coronary angioplasty offers additional benefit since it enables TIMI grade 3 flow to be established in the vast majority of patients, including those who did not reperfuse following thrombolysis, as well as treating the underlying stenosis.<sup>24</sup> Most patients should therefore receive pre-hospital thrombolysis (although some will be ineligible for lytic therapy), with a view to immediate angiographic evaluation and PCI where indicated. Again investment will be required to establish such a service in the UK. Studies have shown that patients can be transferred safely and rapidly between hospitals to enable optimal therapy to be administered.

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