

REVIEW

Transfer for primary angioplasty: who and how?

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Randomised trials have led to the conclusion that percutaneous coronary intervention (PCI) is the best reperfusion strategy for most patients with acute myocardial infarction (AMI). However, these trials have limited application to routine practice. Modern trials of mechanical reperfusion strategies need to take account of logistics, transfer times, and adjunctive drug treatment during transfer (facilitated PCI). Such PCI protocols need to be judged against very early thrombolysis with modern agents. This has been the thrust behind a series of recent studies addressing these “real world” issues in early AMI management

thrombolytic group, 15% of the thrombolysis during transfer group, and 8% of the transfer without thrombolysis group ($p < 0.02$). Reinfarction was greatly reduced in the latter group (1%) compared with the local thrombolytic group (10%) and the thrombolysis during transfer group (7%) ($p < 0.03$).² This study supports the superiority of PCI over thrombolysis in real world scenarios. It furthermore suggests that streptokinase is not an effective facilitating agent.

The results of the DANAMI-2 (Danish multi-centre randomized trial on thrombolytic treatment versus acute coronary angioplasty in acute myocardial infarction) trial have recently been presented. In this trial patients with ST elevation AMI were randomly assigned to local hospital thrombolytic treatment with tissue-type plasminogen activator (tPA) or transfer (of up to three hours) to a specialist centre for primary PCI with no thrombolysis. The trial was stopped prematurely, 1572 patients having been recruited, when a significant 40% reduction in the combined end point of death/reinfarction/disabling stroke at 30 days was observed with PCI (8.0%) compared with thrombolysis (13.7%) ($p = 0.0003$). Furthermore, the revascularisation rate in the first 30 days was 5.9% with PCI and 16.6% with thrombolysis ($p < 0.001$).³

The results of the C-PORT (Atlantic cardiovascular patient outcomes research team) trial have also been recently published. In this trial, which was prematurely halted because of a lack of funds (and therefore underpowered), 454 patients from 11 centres with ST elevation AMI < 12 hours were enrolled and randomly assigned to receive tPA ($n = 226$) or to undergo primary PCI ($n = 225$). The primary end point of death/myocardial infarction/stroke at six weeks was reached by 17.7% of thrombolysis patients and 10.7% of PCI patients ($p = 0.03$). At six months the rates were 19.9% and 12.4%, respectively ($p = 0.03$). The median length of hospital stay was also reduced in the PCI group (4.5 v 6.0 days, $p = 0.02$).⁴ The PRAGUE and DANAMI-2 trials further support the superiority of PCI over thrombolysis observed in the meta-analysis from Weaver and colleagues,¹ even if significant transfer times are involved. The C-PORT trial indicates that PCI does not have to be exclusively at major surgical centres, which may require prohibitive transfer times, to realise this benefit.

On the other hand, the findings of the CAPTIM (comparison of primary angioplasty and prehospital thrombolysis in the acute phase of myocardial infarction) trial were somewhat different.

At present, for most patients with acute myocardial infarction (AMI), percutaneous coronary intervention (PCI) is the best reperfusion strategy.¹ The randomised trials reaching this conclusion were conducted at experienced interventional centres, without long transfer times. However, even in the best resourced health care systems, only a minority of patients with AMI present initially to such centres. Furthermore, in these early trials patients were randomly assigned to PCI or thrombolysis at the interventional centres, thus precluding early domiciliary or ambulance thrombolysis and potentially therefore underestimating the benefit of expeditious pharmacological reperfusion. These factors limit the degree to which the trial conclusions can be applied in routine practice. Modern trials of mechanical reperfusion strategies need to take account of logistics, transfer times, and adjunctive drug treatment during transfer (facilitated PCI). Such PCI protocols need to be judged against very early thrombolysis with modern agents. This has been the thrust behind a series of recent studies addressing these “real world” issues in early AMI management (table 1).

TRANSFER FOR PRIMARY PCI OR LOCAL THROMBOLYSIS?

The PRAGUE (primary angioplasty in patients transferred from general community hospitals to specialised PTCA units with or without emergency thrombolysis) trial compared three reperfusion strategies for patients within six hours of myocardial infarction presenting at hospitals without PCI facilities: local thrombolytic treatment with streptokinase ($n = 99$), thrombolytic treatment during transfer for PCI ($n = 100$), and transfer for PCI without thrombolysis ($n = 101$). The combined end point of death/reinfarction/stroke at 30 days was reached by 23% of the local

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Table 1 Studies discussed in this paper

Study acronym	Study name
ADMIRAL	Abciximab before direct angioplasty and stenting in myocardial infarction regarding acute and long term follow-up
ADVANCE-MI	Addressing the value of facilitated angioplasty after combination treatment or eptifibatid monotherapy in acute myocardial infarction
ASSENT-4 C-PORT	Fourth assessment of the safety and efficacy of a new thrombolytic Atlantic cardiovascular patient outcomes research team
CADILLAC	Controlled abciximab and device investigation to lower late angioplasty complications
CAPTIM	Comparison of primary angioplasty and prehospital thrombolysis in the acute phase of myocardial infarction
DANAMI-2	Danish multicentre randomized trial on thrombolytic treatment versus acute coronary angioplasty in acute myocardial infarction
FINESSE PCI-CURE	Facilitated intervention with enhanced reperfusion speed to stop events Percutaneous coronary intervention in the clopidogrel in unstable angina to prevent recurrent events
PRAGUE	Primary angioplasty in patients transferred from general community hospitals to specialized PTCA units with or without emergency thrombolysis
TIMI	Thrombolysis in myocardial infarction

Patients with ST elevation AMI within six hours were randomly assigned to prehospital thrombolysis with tPA (n = 419) or PCI (n = 421). The median time from symptom onset was 60 minutes longer for PCI than for thrombolysis. There was a non-significant trend towards a reduction in the combined end point of death/reinfarction/disabling stroke for PCI (6.2%) compared with prehospital thrombolysis (8.2%), driven by a reduction in reinfarction for PCI (p = 0.29). However, a non-significant trend towards increased mortality was seen in the PCI group (4.8% v 3.8% p = 0.6). The differences were not significant, however, and there was a high rate of crossover from the thrombolytic to the invasive group.⁵

Overall, these trials indicate that transfer for primary PCI is probably the best option even if significant distances are involved. In most countries, however, this is not always achievable, and strategies need to be developed to identify patients likely to gain most from transfer, such as the elderly, those with extensive infarcts or haemodynamic compromise, and those with contraindications to thrombolytics. Although PCI is superior at all time points, thrombolytics are extremely effective in early myocardial infarction—the “golden hour”—but are largely ineffective after six hours.⁶ Therefore, in early myocardial infarction it is particularly important to decide quickly on the revascularisation strategy, since if PCI is delayed too much, its (late) efficacy may well be inferior to very early thrombolysis. Thus, availability and quality of transfer become key determinants in the revascularisation strategy.

QUALITY OF TRANSFER

The primary aspects of transfer are speed, care during the transfer, and the ability to deliver the patient directly to a well trained cardiac catheterisation laboratory. “Quick and dirty” systems are fast but have only basic equipment and do not use adjunctive drugs. “Slow and clean” systems use fully equipped ambulances but lack the infrastructure to be rapidly deployed or to deliver patients directly to the catheterisation laboratory. A “fast and clean” service uses a modern mobile intensive care ambulance with ECG monitoring, defibrillator, physician, and nurse on board. It delivers the patient directly to the cardiac catheterisation laboratory without time consuming stops in emergency departments or coronary care units. Conventional drugs and facilitating agents are given during transfer.

There is an increasing number of evidenced based treatments suitable for use during transfer. Clearly, aspirin should be administered as early as possible, although it remains alarmingly underused in some reports.⁷ There is no evidence for or against early use of clopidogrel in primary PCI

for AMI since the PCI-CURE (percutaneous coronary intervention in the clopidogrel in unstable angina to prevent recurrent events) study excluded ST elevation myocardial infarction.⁸ However, the recently published CADILLAC (controlled abciximab and device investigation to lower late angioplasty complications) trial indicated a much better outcome after primary PCI with stenting than balloon angioplasty (allaying to a large extent the concerns from previous reports of a trend towards lower TIMI (thrombolysis in myocardial infarction) III flow rates and increased mortality with stenting).⁹ Therefore, if a primary PCI strategy is anticipated it seems reasonable to give an early clopidogrel loading dose, since near steady state platelet inhibition can be achieved in two hours.¹⁰

FACILITATED PCI AND GLYCOPROTEIN IIB/IIIA INHIBITORS

Abciximab has been proposed not only as a periprocedural PCI adjunct but also as a facilitating agent, particularly in view of its beneficial effects on coronary flow seen in TIMI 14.¹¹ Furthermore, it appears to reduce stent induced platelet aggregation and distal embolisation and to improve coronary flow following primary PCI.¹² Surprisingly the CADILLAC study found no benefit with abciximab in primary stenting for AMI; however, the relevant end points were not prespecified, the study was open label, and high risk patients were excluded (for example, those with shock or coronary artery bypass graft). Randomisation was done *after* coronary angiograms had been performed; thus, the trial conclusions do not apply to early “facilitation” use of abciximab, nor can they be generalised to unselected AMI patients.

In the ADMIRAL (abciximab before direct angioplasty and stenting in myocardial infarction regarding acute and long term follow-up) study, 300 patients with AMI within 12 hours were randomly assigned to stent with placebo or stent plus abciximab. Patients were recruited and assigned to treatment as early as possible, always before coronary angiography and in 25% before getting to the catheterisation laboratory, so that abciximab treatment could be started as soon as possible.¹³ As a result there was no angiographic selection bias. The primary end point of death/reinfarction/urgent target vessel revascularisation at 30 days was reached by 6.0% the abciximab group and 14.6% of the placebo group (p = 0.02). This benefit was maintained at six months with combined end point rates of 7.4% for abciximab and 15.9% for placebo (p = 0.02). TIMI III flow was seen in 16.8% of the patients taking abciximab at the time of catheterisation compared with 5.4% of those taking placebo (p = 0.01). The best flow rates were seen with the

earliest abciximab administration. Diabetic patients appeared to gain most from glycoprotein IIb/IIIa blockade, with a significantly reduced six month mortality rate of 0% compared with 16.7% with placebo ($p = 0.02$). This study supports the use of glycoprotein IIb/IIIa blockade either early as a facilitating agent or at the time of catheterisation, with the former strategy offering greater gains. This beneficial effect of IIb/IIIa blockade as a facilitating agent was supported by two subsequent small studies, using tirofiban (D Lee, personal communication) and eptifibatide,¹⁴ respectively. In both studies, early drug administration in the emergency room resulted in significantly improved baseline TIMI-3 flow rates compared with periprocedural use in the catheter laboratory. IIb/IIIa blockers are currently therefore the facilitating agents of choice, with clinical outcome data favouring abciximab.

Some questions remain, however, including the role of early low molecular weight heparins and alternative facilitation strategies. In the ASSENT-4 (fourth assessment of the safety and efficacy of a new thrombolytic) trial design, full dose thrombolytics will be used. In the FINESSE (facilitated intervention with enhanced reperfusion speed to stop events) and the ADVANCE-MI (addressing the value of facilitated angioplasty after combination treatment or eptifibatide monotherapy in acute myocardial infarction) trials, reduced dose thrombolytics with IIb/IIIa blockade will be investigated.

CONCLUSIONS

A number of key questions remain regarding real world primary PCI. Is there a cut off time? What type of centre should be doing it? What adjunctive treatment should be used? "Cut off time" for benefit from primary PCI is not well defined; however, late presenting patients do better with PCI than thrombolysis, and many AMI patients will ultimately undergo angiography with or without revascularisation in any case. Regarding the centre, although this remains controversial, the findings of the C-PORT trial suggest that primary PCI may not need to be restricted to surgical centres. Early, preferably prehospital adjunctive treatment with abciximab, appears to be the optimal adjunctive facilitation strategy.

In summary, contemporary management of AMI should ideally include fast and clean transfer direct to the catheterisation laboratory followed by immediate PCI. The question for modern trials in this situation is therefore not whether to transfer but how to transfer and what facilitation strategy to use. If resources are limited, however, protocols need to be in place to stratify patients immediately into those who should be prioritised for transfer and those who should receive rapid local thrombolysis. The next phase of real world management of myocardial infarction will focus on integrating early

prehospital management planning, modern thrombolytics, facilitating agents, high quality transfer logistics, and PCI to provide the best care for specific patients in any location given the available resources.

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