Isn't it time for primary angioplasty in the UK?

Introduction

Thrombolytic therapy remains the predominant reperfusion strategy for ST segment elevation myocardial infarction (STEMI) in the UK, with government policy directed towards optimising thrombolytic delivery. However, the publication of the first Myocardial Infarction National Audit Project (MINAP) report last year informed us that only 28% of hospitals supplying data treated the target 75% of eligible patients inside 30 minutes.[1] While there is consensus that we are not delivering therapy adequately, there is perhaps less agreement as to whether we are actually delivering an adequate therapy. The superiority of primary angioplasty over thrombolysis has been demonstrated in multiple randomised trials over the past 10 years.[2] In this article we consider the limitations of the current UK approach to reperfusion therapy and address the logistics of delivering primary angioplasty to the majority of STEMI patients in the UK. With the data now available from 'real world' trials employing contemporary interventional techniques, we question how much more evidence it will take before this strategy is included in our National Service Framework (NSF) directives.

Door to needle versus door to open artery time

Our persistence with thrombolysis as the primary reperfusion strategy for the majority of STEMI patients is flawed. The large multicentre randomised controlled trials of the 1980s and early 1990s demonstrated beyond doubt that thrombolysis saves lives, but this was only when compared to aspirin alone.[3-7] Newer preparations such as tenecteplase and reteplase that have been bioengineered to be more clot-specific are also easier to administer (in bolus form). However, while superior angiographic infarct-related artery (IRA) patency has been demonstrated, prognostic benefits have remained much the same.[8-10]

'Fibrin-platelet lysis' – the co-administration of glycoprotein IIb/IIIa receptor antagonists (GPRA) with reduced dose thrombolytic – appears to reduce recurrent ischaemia and ST segment elevation and to improve IRA patency, but again has not been shown to influence mortality.[11,12] With optimal therapy only 50–70% of patients achieve completely effective patency (TIMI-3 flow) in the infarct-related artery,[8,9,11] and even where thrombolysis is effective, the rate of early reocclusion remains unacceptably high (up to 30% by three months).[13,14]

Furthermore, a significant proportion of patients are ineligible for treatment and, perhaps more importantly, a significant number who are eligible are denied treatment. Analysis of the Myocardial Infarction Registry (MIR) and the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) registries (21,092 patients) demonstrated that 48% of STEMI patients did not receive reperfusion therapy: 29% were ineligible and 19% had no obvious contraindication.[15]

Improving delivery without improving the therapy itself does not guarantee a favourable outcome.

The problem we face is that in measuring only the speed with which we deliver treatment, the NSF stops short of assessing outcome. While door to needle time (DTN) is a measurable audit tool, it gives no indication of whether arterial patency is achieved. Furthermore, we have no NSF strategy to recognise and treat the 30–50% of patients who fail to reperfuse. Thus there is a danger that once DTN targets are satisfied, this will falsely reassure us that we are treating our STEMI patients effectively. Only when the emphasis moves from DTN to 'Door to Open Artery' will we appreciate that our approach to reperfusion therapy in the UK needs to change.

Thrombolysis versus early primary angioplasty

Primary angioplasty can achieve TIMI-3 flow in 90–95% of cases, and treats both the occlusive thrombus and the ruptured plaque. The therapy is not new: it is 10 years since the Primary Angioplasty in Myocardial Infarction (PAMI) trial and Zwolle groups first demonstrated a mortality benefit and reductions in recurrent ischaemia and reinfarction, respectively, in patients treated with primary angioplasty compared with thrombolysis.[16,17] Meta-analysis of the short-term results of 10 randomised controlled trials conducted prior to 1997 demonstrated a mortality of 4.4% with angioplasty versus 6.5% using thrombolysis (p=0.02), with the composite end point of death or non-fatal myocardial infarction (MI) of 7.2% *vs*. 11.9% respectively (p<0.001).[18] Stroke was also significantly reduced. Long-term follow-up data from the Zwolle group[19] demonstrated an absolute mortality reduction of 11% (13% angioplasty *vs*. 24% streptokinase) after a mean of five years. Patients presenting with cardiogenic shock fare better following primary angioplasty,[20] and it is the only reperfusion strategy for those ineligible for thrombolysis.

The evolution of primary angioplasty

Since the publication of these studies PCI has evolved. Stenting following primary angioplasty reduces six-month major adverse cardiac events (MACE) when compared with balloon angioplasty alone (POBA),[21] and there have been further improvements in outcome with the addition of GPRA therapy.[22]

Our understanding of PCI in the setting of STEMI has now moved beyond achieving patency of the epicardial artery, to appreciating the importance of a patent microcirculation. Among those patients who achieve TIMI-3 flow, left ventricular (LV) function and prognosis are further improved in those with evidence of microvascular reperfusion, such as complete ST segment resolution or improved angiographic tissue perfusion scores.[23-25] Adjuvant GPRA therapy has been demonstrated to preserve microvascular integrity and improve myocardial salvage in this setting.[26] Montalescot *et al*.[27] have further demonstrated that administration of abciximab prior to primary angioplasty with stenting improves TIMI flow pre- and post-procedure, with lower six-month MACE (7.4% abciximab *vs.* 15.9% placebo, p=0.02) and improved LV recovery. Therapy was always given before catheterisation in this study. Moreover, the 25% of patients in the abciximab arm who received the drug early (in a mobile intensive care unit or the emergency department) derived the greatest benefit (table 1).

As yet it is not clear whether there may also be a role for pre-procedural thrombolysis (either alone or in combination with GPRA therapy) to facilitate primary angioplasty. Results of ongoing trials such as the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) and the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT IV) will address this issue in due course. What is clear is that contemporary primary angioplasty is no longer a purely mechanical approach.

Table 1. Improved outcome after angioplasty following early administration of abciximab in the ADMIRAL study

Timing of abciximab		Death, reinfarction or early target vessel revascularisation: 6 months (%)	Relative risk
MICU/ER (early)	Stent + abciximab	2.5	0.11
	Stent + placebo	23.7	p<0.05
CCU/Cath lab	Stent + abciximab	9.2	0.69
	Stent + placebo	13.3	p=NS

Key: MICU = mobile intensive care unit; ER = emergency room; CCU = coronary care unit

Adapted from Montalescot G, Barragan P, Wittenberg O *et al*.[27]

Primary angioplasty for all patients?

While these data are convincing, they can only support primary angioplasty in regional cardiac centres with on-site angioplasty facilities, where large numbers of procedures are performed. Canto *et al.*[28] emphasised the importance of this issue, demonstrating an alarming difference in outcome between high- and low-volume primary angioplasty centres (in-hospital mortality was 28% lower in the high-volume group). Despite these results, we have not embraced primary angioplasty in the UK, even at the regional centre level. Therefore the logistics of providing such a reperfusion strategy for the majority of STEMI patients have until very recently been thought impossible.

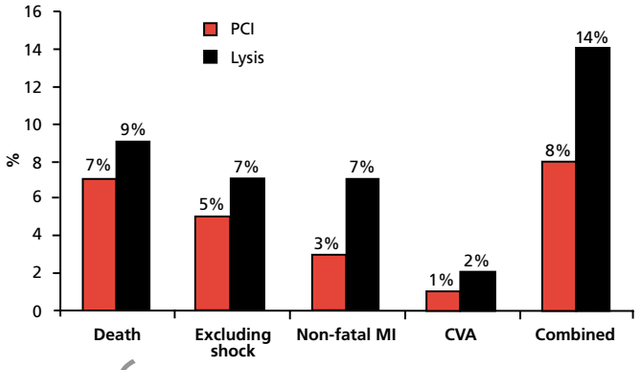
It has been largely through the vision of our European counterparts that the debate between primary angioplasty and thrombolysis has been put firmly back on the agenda, with a group of studies that have addressed 'real world' delivery of therapy. The Primary Angioplasty in patients transferred from General community hospitals to specialised PTCA Units with or without Emergency thrombolysis (PRAGUE) investigators[29] first showed that it was safe and feasible to transfer patients from a district general hospital (DGH) without PCI capabilities for primary angioplasty to a regional centre: for these patients outcome was improved compared to on-site thrombolysis. The Danish Multicentre Randomised Trial on Thrombolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2)[30] randomised both regional centre and DGH patients to on-site thrombolysis with tPA or primary angioplasty, with stenting in most cases (93%). This was a high-risk group of patients with > 4 mm ST elevation and with symptoms for up to 12 hours. The composite end point of death/reinfarction/stroke was significantly reduced in the PCI group (13.7% *vs.* 8.0%, p=0.0003). Remarkably, this outcome was observed even with transfer times (time from first presentation to arrival at the cardiac centre) of up to three hours. The results are all the more striking as primary angioplasty was not available in two of the five participating centres prior to the study, and operators were trained during a pilot period.

PRAGUE-2,[31] has now provided further support for a primary PCI transfer strategy. It randomised DGH patients to on-site thrombolysis with streptokinase or to transfer for PCI. Although the mortality reduction (10% thrombolysis [TL] *vs.* 6.8% PCI) was not significant across all patients, it became significant in patients who presented more than three hours after onset of symptoms (15.3% TL *vs.* 6% PCI, p<0.02). This is in keeping with the exponential deterioration in efficacy of thrombolysis with increasing duration of symptoms that we might expect, which appears significantly attenuated with PCI.[32] It also underlines the need to define outcome in relation to time of symptom onset rather than from the time of arrival at hospital.

In addition to evidence on long-distance transfer for STEMI patients, there is also evidence to support a district-based primary angioplasty strategy without on-site cardiac surgical backup. The Cardiovascular Patient Outcomes Research Team (C-PORT) investigators[33] demonstrated a significantly reduced composite of death/MI/stroke at six months in primary PCI patients in this setting when compared with thrombolysis (12.4% PCI *vs*. 19.9% TL, p=0.03). Hospital stay was also reduced in the PCI group.

Whether patients are transferred or PCI is performed on site, primary angioplasty is the strategy of choice. A recent meta-analysis of 23 trials comparing primary angioplasty and thrombolysis[3] included all these transfer studies and other trials employing current interventional techniques (12 using stents and eight using GPRA therapy). Mortality following PCI was significantly reduced (whether or not cardiogenic shock patients were included), as was stroke and non-fatal MI (figure 1). This is contemporary primary angioplasty in a wider group of patients than previously described.

Figure 1. Meta-analysis of 23 randomised trials of primary angioplasty versus thrombolysis – short term clinical outcome



Key: PCI = percutaneous coronary intervention; MI = myocardial infarction; CVA = cerebrovascular accident

Adapted from Keeley EC, Boura JA, Grines CL[2]

Pre-hospital thrombolysis and rescue angioplasty

Despite this now overwhelming body of evidence, our NSF remains committed to thrombolysis. In the hope of deriving the maximum benefit that this therapy can deliver, there has been renewed interest in pre-hospital thrombolytic administration. Significant funds have been invested in 12-lead ECG machines, communication/fax equipment and thrombolytic agents for ambulance crews, with paramedic training in ECG recognition and drug delivery. However, although early trials demonstrated that significant time savings can be achieved (median 30–130 minutes),[34-36] none translated the time saved into a mortality benefit.

Furthermore, the problem of failure to reperfuse persists. The conclusions of the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study[37] underline this issue. In 840 patients randomised to either pre-hospital thrombolysis or primary angioplasty the two strategies appeared to be equally effective. However, in CAPTIM randomised patients were taken by physician-manned mobile intensive care units directly to a cardiac centre with PCI facilities where a large proportion of the thrombolysis group went on to receive an unscheduled PCI (33% immediately and 70% by 30 days). Thus the pre-hospital lysis group was backed by an aggressive rescue angioplasty strategy.

Meanwhile, the rescue strategy (i.e. angioplasty following thrombolysis performed for failure to reperfuse) has already been adopted to varying degrees by centres around the UK, despite the fact that as yet the data supporting this strategy are far weaker than those supporting primary angioplasty. Of nine randomised rescue PCI trials only four were prospective comparisons with conservative therapy, and these included only 368 patients.[38] There are still no specific non-invasive criteria that identify those having greatest benefit. Ongoing studies such as Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT) may address this issue in due course.

In the meantime we are left with a piecemeal approach to reperfusion failure that is all too often characterised by poor recognition, late referral and wide variations in the willingness or ability to accept such patients when offered (both within and between centres). If we were to offer an explicit rescue angioplasty service nationally, we would need 24-hour facilities to treat at least a third of all patients treated with thrombolysis.[39-41] The infrastructure required to achieve this would come close to that required for a primary angioplasty strategy from the start.

A model for primary angioplasty in the UK

The exact mode of delivery of primary angioplasty will need to vary for particular UK populations, according to local geography, ambulance services and the existing PCI services in that region. For example, existing cardiac centres may serve as regional Heart Attack Centres (HAC) for all their local referring hospitals. Alternatively, secondary cardiac centres already performing PCI without surgical backup may join forces with interventionists at other DGHs to provide a more local HAC service according to the C-PORT model. More remote populations could be targeted for pre-hospital thrombolysis, but backed by a rescue strategy.

Our own interpretation is that, irrespective of the type of HAC, the key to providing the earliest possible reperfusion is

pre-hospital diagnosis and delivery of patients directly to a dedicated team in the catheter lab, bypassing delays in Accident and Emergency (A&E). In DANAMI-2 the door to balloon times for transfer patients were comparable to, and in some cases shorter than, those presenting to a cardiac centre. While at first glance this seems a positive result demonstrating rapid patient transfer, it also suggests significant delays in the A&E departments of regional centres. Such a 'direct access' strategy would take full advantage of the resources that are already being channelled into pre-hospital thrombolysis. Furthermore, ambulance crews could administer pre-hospital clopidogrel and GPRA therapy. If forthcoming studies are supportive, optimal combination therapy with thrombolysis could be administered before the procedure.

UK application; how realistic?

We accept that resources in UK cardiac centres are already stretched. High-risk acute coronary syndrome patients without ST elevation (NSTE-ACS) can wait more than two weeks for transfer from district hospitals around the country. There are fears that even a limited primary angioplasty strategy solely for regional centre STEMI patients would be performed at the expense of these NSTE-ACS patients. Meanwhile other areas within cardiology, including prescription of statins, clopidogrel and ACE inhibitors, implantable defibrillators and drug-eluting stents, are also competing for funding. However, these must be weighed against the consequences of persisting with a reperfusion strategy that fails to treat nearly half those targeted. Our own experience suggests that we are already dealing with a significant proportion of the STEMI cohort invasively, including not only those patients with failure to reperfuse, but also those with post-infarct angina and recurrent infarction. Taking such patients for immediate intervention should at least partially relieve in-patient transfer lists.

However, providing primary angioplasty will also require reorganisation. Interventionists will need to change their current working practices by collaborating in 24-hour on-site on-call rotas at HACs. Ambulances carrying STEMI patients will need clearance to bypass local hospital A&E departments on the way there. And in the short term at least it will necessitate investment. Whether improved outcomes and reduced complications may save money in the long term will require prospective audit. We cannot wait any longer. Primary PCI must be included in national guidelines for STEMI treatment as the preferred strategy in all but the most remote populations, and we need to change our fixation from door to needle time, to door to open artery time. While we wait for these objectives to be adopted, we will still need to improve door to needle times and get the best we can out of thrombolysis. If forthcoming trials prove a role for thrombolysis within a strategy of facilitated primary angioplasty, door to needle times may yet have relevance. If not, our currently inadequate delivery of thrombolytic therapy should be the stimulus to stop delivering it at all.

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Elliot J Smith
Research Registrar
Martin T Rothman
Professor of Interventional Cardiology and
Director of Cardiac Research & Development
London Chest Hospital, Bonner Road,
London, E2 9JX.
Correspondence to: Dr EJ Smith
(email: elliot.smith@bartsandthelondon.nhs.uk)

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