Heart Online First, published on May 27, 2005 as 10.1136/hrt.2004.059485

Should primary angioplasty be available for all patients with an ST elevation myocardial infarction?

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A patient with cardiac chest pain calls for the emergency services.

Scenario 1

Within minutes a trained paramedic crew has established the diagnosis of AMI, and transmits an ECG electronically to a Myocardial Infarction Centre, where a co-ordinator mobilises the catheter laboratory staff to prepare for angioplasty. On instruction from the cardiologist co-ordinator, the trained staff administer drugs (aspirin, clopidogrel, perhaps thrombolysis or abciximab or bivalirudin) and consents the patient for coronary intervention. The patient does not go to the A and E. of the nearest hospital.

Scenario 2

An ambulance arrives and the patient is taken to the nearest hospital, where an ECG establishes the diagnosis of an AMI. Intravenous streptokinase is given, but after 90 minutes chest pain continues and the ST segments have not shifted. A decision is made to transfer the patient to a PCI centre. Due to a heavy workload the ambulance facility cannot give the patient urgent priority, but is eventually taken to another hospital where 9 hours after the onset of chest pain an angioplasty is performed.

What would you want?

Many papers of animal and human AMI have shown that the duration of a coronary occlusion is the main determinant of final infarct size. The matters are biologically complex involving endothelial oedema, oxidative stress, reperfusion injury, embolisation of thromboresistant clots , and formation of leucocyte aggregates within the microcirculation, but what is important is to establish normal flow in the infarct related vessel, as soon as is feasible.
The 2 strategies available to achieve this aim , thrombolysis and primary angioplasty, have been pitched against each other vying for ascendancy as to which is best treatment. An evaluation of the 23 randomised trials comparing primary PCI with IV thrombolytic therapy have shown that the PCI strategy

- saves lives in the short and long term
- leads to better TIMI III flow in the infarct related artery
- has less reinfarction
- leads to a shorter hospital stay
- has less hospital readmission
- causes less heart failure
- leads to less angina
- causes less strokes

The overall combined endpoint (death, re-infarction and Stroke) was 8% for primary PCI vs 14% for thrombolysis ($p<0.0001$).[1]

But what happens to patients over the long term?

The pioneering Zwolle group whose randomised trial between PCI and thrombolysis in non-cardiogenic shock STEMI patients reported 5-year mortality rates of 13% vs 24%, respectively ($p<0.01$), with a reduction in non-fatal MI (6% vs 22%), recurrent ischaemia and heart failure

with no differences in overall costs. These Kaplan-Meier curves were divergent showing an increased benefit with time.[2]
In this month's Heart, Parodi et al publish their 5 year outcome data for patients undergoing primary coronary intervention for acute ST elevation MI (all ages and including cardiogenic shock) in a single centre.[3] The door-to-balloon time was a remarkable 22±15 minutes, which shows what can be achieved with good organisation and communication. The 5 year mortality of 20% after 5 years is all the more extraordinary when a comparison is made with a thrombolysis driven service giving comparable mortality at 30 days. [4]

Why has there been such reluctance to implement what seems to be a superior treatment for a common life threatening condition? A cursory glance of the medical literature will find many examples whereby evidence is ignored in favour of accepted, though flawed, dogma.

PCI vs. early thrombolysis.

Prehospital thrombolysis delays the time of onset of symptoms by 33[5] to 55[6] minutes, and the mortality benefits for patients treated within 60 minutes of onset of chest pain was significant. The CAPTIM investigators compared a strategy of prehospital thrombolysis with transfer to an interventional facility for primary PCI. Patients randomised <2 hours from symptom onset showed a trend toward lower 30 day mortality in the pre-hospital thrombolysis group (2.2% vs 5.7%)(p=0.05), and the mortality for patients treated after 2 hours was similar (5,9% vs 3.7%)(p=0.47).[7] It's fair to conclude that PCI does not confer any mortality benefit over thrombolysis that is given within 2 hours of chest pain onset.

It's okay for those places that have the facilities, but what about the real world where scarce resources make this option an impossibility?

The DANAMI-2 study examined whether transfer of patients to a PCI centre would still offer patient benefit – 1572 patients were randomised to PCI (n=790) or intravenous alteplase given on admission (n=782). All transfers were made within 3 hours. The primary endpoint (mortality, reinfarction, disabling stroke at 30 days) was14.2% in the thrombolysis group vs 8.5% in the primary PCI group (p=0.002), the majority of the benefit being from prevention of reinfarction.[8]

The Czech Republic have harnessed their resources and now provide a 24 hour PCI service for AMI throughout the country, and yet they only have 22 catheter laboratories. Their management strategy is based on the PRAGUE 2 trial – a RCT comparing long distance travel for PCI versus thrombolysis in the nearest available hospital (n=850). The study was stopped prematurely because of 2.5-fold excess mortality in the thrombolysis group among patients treated more than 3 hours after the onset of symptoms (15.3% - thrombolysis vs. 6% PCI), but there was no significant difference between the strategies if the patient was treated less than 3 hours from symptom onset.[9]

Why should thrombolysis be mutually exclusive of a PCI service?

The PRAGUE study examined 3 strategies for PCI for patients presenting with STEMI to a district hospital without on-site catheterisation facilities – immediated thrombolysis, thrombolytic therapy during transfer for PCI and transfer for primary angioplasty. The combined endpoint of death, reinfarction or stroke was reached in 23%,15% and 8% patients respectively. [10]

The timing and delivery of glycoprotein IIbIIIa inhibitors prior to PCI for STEMI has improved results [11,12,13], but the delivery of these agents is not straightforward in the prehospital setting.

Perhaps, this so-called facilitated angioplasty with thrombolysis±/IIbIIIa inhibitors may have a role, particularly for patients who may have to travel long distances for their PCI. The outcome of trials such as FINESSE and ASSENT IV will provide the answer, but I would be surprised if these strategies will provide such striking differences that the investment of expensive drugs combined with intervention will become routine.

What about a strategy of thrombolysis with backup PCI for those patients in whom chest pain or ECG changes persist.

This is the default position of many units, which dramatically reduces the number of patients requiring PCI in the short term. The randomised trials are not fully clear on the best course of action – there is a suggestion that late PCI may have some benefit, but only if the intervention is successful.[14]

Most patients that survive a STEMI subsequently undergo angiography and revascularisation at later date – why not do it at the time the data strongly shows is the best time for PCI to occur - as soon after the acute occlusion as possible.

Primary PCI – moving forwards

Indeed for those involved in primary PCI, the debate has moved on. Previous studies have established the benefit of stenting over POBA, mainly for the benefit of recurrent angina. Parodi and his colleagues have analysed their data to discuss the role of IIb/IIIa inhibitors, appropriateness and timing of non-culprit coronary lesion treatment, and the provision of a risk stratification score based on simple clinical criteria. In most catheter laboratories patients are undergoing PCI for lesions causing stable angina – a procedure that confers little or no prognostic benefit, yet the patients with STEMI for whom this procedure has proven prognostic benefit, are denied it. Our priorities need to refocus.

Are there enough interventional cardiologists to provide such a service?

To reproduce Parodi's results, primary PCI should be performed at facilities that do sufficient volume to develop and maintain skills.[15] The ACC/AHA guidelines suggest that institutions performing PCI should be doing at least 400 cases/year with a 24 hour capability.[16] To my mind, if a patient can reach such a PCI facility within 2 hours of arrival of the emergency services, reorganisation of regional strategies should take place to facilitate this. For those areas where this is currently an impossibility, regional discussions should take place to decide where such a centre could be developed.
Many centres are embracing this challenge, but there remain manpower issues which need to be grasped, understood and dealt with, if PCI is to become a routine procedure.

"We can't do an angioplasty – it will affect our door-to-needle times"

Most units are highly efficient in the delivery of thrombolysis to patients coming through the hospital door, yet paradoxically, protocols such as this can become barriers to change - the measurement of door-to-needle times has some bearing on the patient's outcome, but unless the crucial time measurement of onset of symptoms becomes the yardstick, the patient may well end up with the wrong treatment– all decisions should be based on the onset of the infarct, and not the time medical care starts.

So what is there to do?

- The most significant delay contributing to delays in treatment for STEMI is the time it takes for the emergency services to be called by the patient and their family. The average time for pain-to-call time is 1 hour. Media campaigns have made little difference in reducing this, but the message that chest pains require immediate contact with the emergency services needs to be hammered home.
- Establish a local high volume PCI centre if one is not available.
- Once contact is made with the patient, the main purpose is to establish an ECG diagnosis and make an immediate strategy for treatment by contacting the local AMI co-ordinator.
- Data from the various travelling trials for STEMI PCI have shown that the visit to the local hospital engenders a 30-50 minute delay. Therefore, it is no longer acceptable for patients with STEMI to be transferred to the most local hospital, but to one that delivers the best treatment.

References

1. 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.

2. Zijlstra F, Hoorntje JCA, de Boer M et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. New Engl J Med 1999;341:1413-9

3. Parodi G, Memisha G, Valenti R et al. Five year outcome after primary coronary intervention for acute ST-elevation myocardial infarction: results from a single centre experience Heart 2005

4. Mahon NG, O'Rorke C, Codd MB et al. Hospital mortality of acute myocardial infarction in the thrombolytic era. Heart 1999;81:478-482

5. Weaver WD, Cerqueira M, Hallstrom AP et al. Prehospital-initiated vs hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. JAMA 1993;270(10):1211-6

6. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. The European Myocardial Infarction Project Group. New Engl J Med 1993;329:383-9

7. Steg PG, Bonnefoy E, Chabaud S, *et al*. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation* 2003;108:2851-6.

8. Andersen HR, Nielsen TT, Rasmussen K, *et al*. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;349:733-42.

9. Widimsky P, Budesinsky T, Vorac D, *et al*. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction: final results of the randomized national multicentre trial - PRAGUE-2. *Eur Heart J* 2003;24:94-104.

10. Widimský P, Groch L, Zelízko M, *et al*. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolyis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. *Eur Heart J* 2000;21:823-31.

11. Montalescot G, Barragan P, Wittenberg O, *et al*. Platelet Glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;344:1895-903.

12. Stone GW, Grines CL, Cox DA, *et al*. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;346:957-66.

13. Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2004;292:362-6.

14. Sutton AG, Campbell PG, Graham R et al. A randomized trial of rescue angioplasty versus a conservative approach for failed thrombolysis in ST-segment elevation myocardial infarction: the Middlesborough Early Revascularisation to Limit INfarction (MERLIN) trial. J Am Coll Cardiol 2004;44(2):287-296.

15. Canto JG, Every NR, Magid DJ, *et al*. The volume of primary angioplasty procedures and survival after acute myocardial infarction. *N Engl J Med* 2000;342:1573-80.

16. Smith SC, Jr., Dove JT, Jacobs AK, *et al*. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines) - executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). *J Am Coll Cardiol* 2001;37:2215-39.