For and against

Primary angioplasty should be first line treatment for acute myocardial infarction

The UK government is considering establishing a national primary angioplasty service for patients with acute myocardial infarction. David Smith and Kevin Channer debate whether moving away from first line thrombolysis is appropriate or practical

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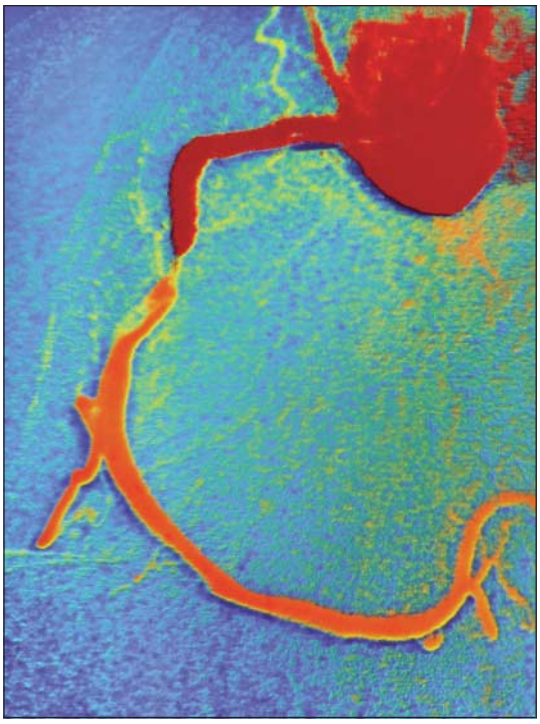
FOR There seems little doubt that acute ST elevation myocardial infarction is the result of coronary arterial occlusion and that myocardial necrosis can be limited by early restoration of normal antegrade blood flow. The relation between normal coronary artery blood flow and mortality after myocardial infarction is well documented. A meta-analysis of angiographic infarct trials showed normal flow was associated with a mortality of 3.7% compared with 6.6% (P = 0.0001) in patients with impaired flow and 9.2% (P = 0.0003) in patients with occluded or nearly occluded infarct related arteries.[1] This relation extends to microvascular reperfusion so that mortality after myocardial infarction can be reduced to less than 1% if normal epicardial blood flow and myocardial perfusion are restored.[2] The mortality benefits of restoring normal flow have been shown to extend up to 12 years.[3] Early restoration of normal myocardial blood flow must therefore be the therapeutic goal of the management of acute myocardial infarction.

Angioplasty is more widely applicable

For the past 20 years there have been two methods for restoring blood flow. Thrombolysis (the current first line treatment) is pharmacological, can be applied to only 60-80% of the presenting population, fails to make a definitive diagnosis, and leaves the treatment goal unconfirmed. Coronary angioplasty, on the other hand, is mechanical, can be applied to any patient, is guided by an accurate definitive diagnosis, and results in certainty about the therapeutic end point. Primary angioplasty carries no risk of inappropriate treatment and a low risk of serious complications whereas thrombolysis can be used inappropriately in up to 10% of presenting patients and has an appreciable risk of producing disabling stroke.

All trials comparing the two treatments support primary angioplasty as the better management. None of the trials show thrombolysis is superior, despite the favourable bias of restricting the studies to patients suitable for thrombolysis. Nevertheless, only a tiny proportion of patients with ST elevation myocardial infarction in Britain get primary angioplasty.

Let us consider the use of thrombolysis in 100 patients presenting with ST elevation myocardial infarction. About 25% of patients are ineligible because of late presentation, bleeding history, hypertension, etc, and some have treatment stopped prematurely because of reactions such as hypotension and allergy. Of the 75 patients who receive treatment 24 (32%) can expect to have normal coronary flow restored if streptokinase is used or 40.5 (54%) if alteplase is used.[4] Of these, about 10% would have had spontaneous reperfusion and will have therefore received thrombolysis unnecessarily. On this basis between a quarter (streptokinase) and a half (alteplase) of patients presenting achieve the therapeutic goal without undue risk.



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Coloured angiogram showing blocked right coronary artery

If primary angioplasty is used for the 100 patients, no patient is exempt and the diagnostic angiogram can usually identify the infarct related artery and assess the state of coronary perfusion. Treatment can then be given to those patients who have not reperfused spontaneously, and normal epicardial blood flow is likely to result in 90-97% of attempted angioplasties.[5] With this approach, the therapeutic goal is achieved and documented in more than 90% of patients with no unnecessary risk.

More effective and efficient

Twenty three randomised trials have compared primary angioplasty with thrombolysis. A meta-analysis of these trials concludes that primary angioplasty has a highly significant benefit over thrombolysis for mortality, non-fatal reinfarction, and haemorrhagic stroke.[6] None of these 23 trials suggests a trend in favour of thrombolysis, although only one trial individually shows a mortality benefit in favour of primary angioplasty.[7] A similar meta-analysis of trials of thrombolysis versus control[8] showed only an 18% risk reduction in mortality and, somewhat perversely, an increase risk of death in the first 24 hours.

The current strategy for management with thrombolytic drugs relies on electrocardiography as the prime diagnostic tool. It is used initially to diagnose ST elevation myocardial infarction, and resolution of the ST changes is used as a surrogate for reperfusion. Patients then wait for 3-7 days for a non-invasive test such as an exercise test or a myocardial perfusion scan to identify those at high risk; high risk patients are then either kept in hospital for angiography with a view to revascularisation or referred to another hospital where this can take place. This occupies a considerable number of bed days. If a strategy of primary angioplasty were used the angiographic diagnosis and the definitive treatment would be completed within the time taken for a streptokinase infusion to run through. Further non-invasive tests would not be required, and in many cases the patient could be discharged within 72 hours.[9]

Goal oriented treatment

The management suggested in the National Service Framework for Coronary Heart Disease is procedurally oriented and not goal oriented.[10] The procedure is the administration of a fibrinolytic drugs, and performance is audited through the myocardial infarction national audit project (MINAP) returns, which record the percentage of patients receiving the drug within certain time limits. No mention is made of the therapeutic goal. It seems more appropriate to have a goal oriented guideline such as "80% of patients presenting with ST elevation myocardial infarction should have normal coronary flow restored in the infarct related artery within 90 minutes of presentation." Primary angioplasty fulfils this role admirably. Not only does diagnostic angiography ensure appropriate and better guided treatment, but the therapeutic goal is easily audited and patients can be informed more accurately of their diagnosis and prognosis.

Primary angioplasty is not widely available in the United Kingdom, but it could be. On site cardiac surgery is not a requirement, and primary angioplasty can be performed safely and effectively in a district general hospital.[11] Many more cardiac catheter laboratories and interventional cardiologists with the appropriate skills would be needed. However, much could be achieved by reordering clinical priorities. Angioplasty is of greater benefit in patients with ST elevation myocardial infarction than in those with non-ST elevation myocardial infarction; such patients, in turn, receive greater benefit from angioplasty than those with chronic stable angina. It seems more appropriate to apply the relatively limited resources where the benefit is greatest pending the development of more facilities.—David Smith

Contributors and sources: DS has been interested in primary angioplasty since 1987 and has pressed for the development of the service since 1995. In 1996, with John Dean, he performed a three month pilot of a 24 hour, 7 day a week primary angioplasty service in Exeter.

Competing interests: None declared.

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AGAINST Thrombolysis is the established treatment for patients with an acute ST segment elevation myocardial infarction based on large trials in the past two decades.[1] Studies show that treatment within an hour after onset of symptoms results in a 6.5% absolute reduction in mortality compared with placebo; this benefit falls quickly with time to 3.7% at 1-2 hours, 2.6% at 2-3 hours, 2.9% at 3-6 hours, 1.8% at 6-12 hours, and 0.9% at 12-24 hours.[2] However, thrombolysis also causes an absolute increase in stroke of 0.4% (half of which are fatal), an absolute increase of 0.7% in major non- cerebral bleeds, and a 3% increase in early non-fatal reinfarction.[1]

Although thrombolysis saves lives in hospital, it has no later benefits; the survival curves of patients given placebo or thrombolysis exactly superimpose after 35

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days, or even after discharge from hospital.[3 4] The mechanism for the reduction in hospital mortality is unclear since all causes of death are reduced. It is not accounted for by a reduction in infarct size because this effect is small (6% at 4 days and only 2% at 10-28 days),[5] and a reduction in infarct size would confer a long term survival advantage, which is not seen.

Implementing policy

Hospital mortality from acute myocardial infarction has been falling,[6] but the contribution made by thrombolysis is difficult to ascertain.[7] The National Service Framework for Coronary Heart Disease focused on the need to give thrombolysis quickly. This led to targets for treatment of within 60 minutes of an emergency call and within 30 minutes of arrival in hospital by April 2002 (reducing to 20 minutes by April 2003).[8] Trusts have changed their models of care to achieve this target. Changes include prehospital thrombolysis by ambulance paramedics (which trials show give a 2% absolute reduction in mortality[9]), rapid triage of patients admitted with chest pain, and administration by nurses rather than doctors. For the first time in the United Kingdom, a national strategy for the implementation of data from randomised controlled trials is beginning to show results.[10]

Evidence for angioplasty is weak

Any fundamental change in management of ST elevation myocardial infarction must be driven by significant improvements in outcome. Patients with a patent, infarct related artery have a better prognosis than those with persistently occluded arteries. Large randomised trials comparing different thrombolytic drugs with differing early patency rates showed no mortality benefit from patency.[11 12] If a difference in patency were important, then a difference in long term prognosis would have been expected, but this has not been seen.[3 4] The move to primary angioplasty is driven by the holy grail of infarct related artery patency but the evidence that it affects hospital mortality is limited.

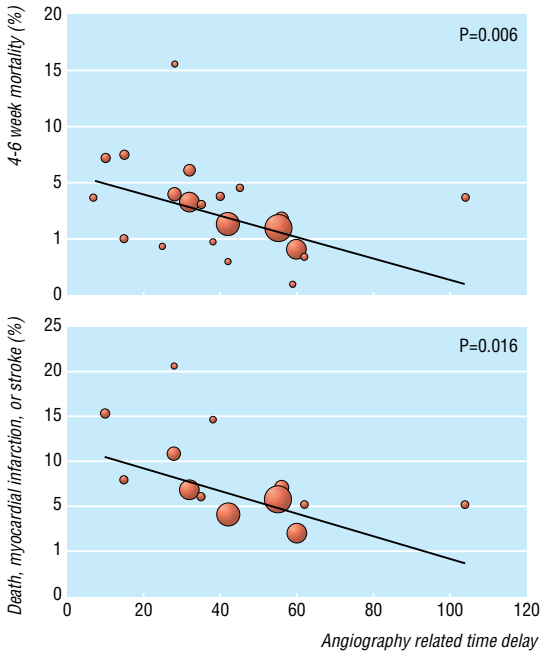
Comparative trials between primary angioplasty and thrombolysis have recruited only patients eligible for thrombolysis. All have been selective and have typically recruited only a minority of eligible, usually younger, patients. A recent meta-analysis of over 7000 patients showed an absolute 2% improvement in mortality for patients having angioplasty[13]; fewer patients had early non-fatal reinfarction, recurrent ischaemia, and strokes.

The earlier studies were mainly done in centres of excellence, but a large Danish study could be used as a model for implementation in the United Kingdom.[14] In this study, patients were transferred from district general hospitals to regional centres for primary angioplasty; there was no significant mortality benefit compared with on-site thrombolysis, and the only benefits were in recurrent ischaemia requiring intervention and reinfarction. Although these events have been argued to affect survival, early placebo controlled thrombolysis trials showed that the increase in reinfarction after thrombolysis was not associated with increased early or late mortality. Moreover, the Danish study did not count reinfarction after angioplasty, further biasing against thrombolysis. Thus, the only relevant comparator for the two treatment strategies is all cause mortality, which was not reduced by angioplasty in the study.[14]

Of more importance for the United Kingdom, interventionalists in the United States have been unable to replicate the trial results, and registry data recording the results of primary angioplasty in practice show less benefit than expected from the trials. This is explained by the delays incumbent in this approach, which requires clinical evaluation in the emergency room and then transfer to a cardiac catheterisation laboratory, coronary angiography, and angioplasty. The average time delay in 661 centres was 1 hour 56 minutes, with more than half of patients waiting over two hours before balloon inflation, which was associated with an increase in mortality of 41-62%.[15] A meta-analysis of published randomised trials shows that when the time delay related to angiography (that is the door to balloon minus the door to needle time) exceeds 60 minutes, the mortality benefits of primary angioplasty over thrombolysis are lost (figure).[16] For every 10 minute delay, there is a 1% reduction in the composite end point of death, reinfarction, or stroke, so that by 90 minutes there is no measurable difference between primary angioplasty and immediate thrombolysis.

Practical issues

Thrombolysis took decades to become established as the standard, and in the United Kingdom structural changes to the way patients are managed have been driven by the results of the many randomised controlled trials showing the benefits of this treatment. To provide a national service for primary angioplasty for



Absolute risk reduction in 4-6 week mortality (top) and combined end point of death, reinfarction, or stroke after primary angioplasty as a function of angiography related time delay (door to balloon minus door to needle time).[13] Circle sizes reflect sample size of individual study; values >0 represent benefit; values <0 represent harm; solid line=weighted meta-regression. Adapted from Boersma et al[9]

patients with acute myocardial infarction demands a big increase in cardiac catheter facilities and staff. Treatment would need to be delivered by consultants because it requires a high level of training and experience, and consultants are in short supply. None of the regional centres has sufficient numbers to provide a 24 hour primary angioplasty service. The result will be patchy implementation and confusion among general physicians, who continue to supervise the management of most patients admitted with myocardial infarction. Thrombolysis will be delayed while negotiations with cardiologists about the most appropriate therapy take place.

The reality will be postcode primary angioplasty offered to those lucky patients who present to regional centres during the day. In other cases the benefits of early reperfusion by thrombolysis will be reduced.

Conclusion

The importance of time to reperfusion in reducing mortality cannot be overestimated. However, the absolute effect depends on when delays occur in the natural course of infarction. It is right to emphasise earlier thrombolysis because this has been shown to deliver larger mortality benefits. The benefits of angioplasty over thrombolysis are too small in patients presenting early not to be offset by the delays that occur with this approach. The same or bigger benefit would be achieved by prehospital thrombolysis.—Kevin S Channer

Contributors and sources: For 15 years I have supervised the care of patients on a coronary care unit and have overseen the rationalisation and standardisation of the treatment of acute myocardial infarction. We introduced the first chest pain specialist nurse in the region in my centre and have some of the best door to needle times. Part of my research has been in implementation strategies for evidence based medicine.

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Primary angioplasty or thrombolysis? a topical parable

Peter Bogaty, James M Brophy

Primary angioplasty is being touted as a revolutionary treatment that should supersede thrombolysis in modern management of acute myocardial infarction. Would our perspective be different if angioplasty had been developed first?

Myocardial infarction used to be a nasty scourge, with 15-25% mortality. Then came the breakthrough discoveries that thrombotic coronary occlusion caused myocardial infarction and that balloon catheters could cross the occlusion, squash the thrombus, and re-establish flow. Thus, it was possible to abort the progression of myocardial infarction and reduce mortality. Cardiologists became interventionists. Cardiac catheterisation laboratories grew like mushrooms. Balloons and hubris were inflated as many lives were saved. A gigantic industry sprang forth of catheters, sophisticated stents, and expensive adjunctive drugs. It seemed that all was now for the best "in the best of all possible worlds" and "that things in general were settled forever."

Creaking system

And yet there were downsides. In a substantial proportion of cases, myocardial perfusion was unsatisfactory, even when coronary artery flow seemed adequate.[1] It was speculated that this could be due to distal migration of thrombus secondary to mechanical intervention. This spurred an interest in lassoes, aspirators, and other devices designed to capture such debris during angioplasty. While increasing costs, these failed to satisfactorily resolve this vexing problem. Also, the (insatiable) demands of the mechanical approach were draining the healthcare system and exhausting cardiologists and support staff, who had to get up at

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