Acute myocardial infarction: patent or die?

The treatment of acute myocardial infarction (AMI) has changed dramatically over the past 15 years. In this issue (p. 617), Dr Gershlick presents an excellent review of strategies available to promote coronary artery patency in AMI, highlighting the limitations of thrombolytic therapy. In particular, he criticizes the preoccupation with door to needle or pain to needle time. Is there really more to optimizing myocardial salvage than timely thrombolysis?

BENEFITS OF THROMBOLYSIS

There is compelling evidence that appropriate administration of aspirin and thrombolytic agents increases survival in myocardial infarction (MI) associated with ST elevation. The recognition that 'time is muscle' has rightly resulted in this now being regarded as a medical emergency. Widespread acceptance of thrombolysis has been associated with a significant improvement in the AMI survival rate. Furthermore, complications of AMI, e.g. need for temporary pacing, are also less frequent.

As Dr Gershlick correctly observes, the dramatic benefit of thrombolysis can lead to a blinkered view that there is little else to maximizing the probability of reperfusion in the early management of MI. This is reinforced by the fact that the administration of a thrombolytic agent is an easily documented therapy, and the diagnosis of AMI with ST elevation is relatively dichotomous. Thus, thrombolysis lends itself well to audit, where appropriateness of treatment and door to needle times can be evaluated retrospectively with relative ease. While such analyses, promoted in the National Service Framework, are beneficial, there is a danger that other aspects of early treatment can be overlooked in the quest to meet targets, since they encourage mechanisms that ensure rapid and appropriate treatment. The limitations of thrombolysis and its role in evolving treatments merit further consideration.

LIMITATIONS OF THROMBOLYSIS

While failure to satisfactorily recanalize the occluded artery is associated with a relatively poor prognosis, this relationship is complex. For example, when infarction is extensive, the resistance within the myocardial microvasculature becomes high, leading to low or no reflow despite a patent vessel. Even scoring quality of flow using the traditional or modified TIMI score, defined in Dr Gershlick's review, underestimates true tissue perfusion.

It is well known that most patients with a TIMI 3 flow post-AMI still have poor tissue perfusion when assessed by more sensitive techniques. These microvascular abnormalities lead to abnormal flow patterns in the epicardial vessel that are likely to make thrombolysis less efficient and increase the probability of reocclusion. Thus, reocclusion or the failure to achieve full reflow or patency may result from, rather than be the cause of, extensive MI. This may explain why patients treated with front-loaded tissue plasminogen activator (tPA) have a relatively modest improvement in survival compared with those treated with streptokinase, but the prevalence of a patent coronary artery after 90 minutes in this group is almost twice that of those treated with streptokinase.

Nonetheless, there is no doubt that early in the evolution of infarction, when myocardial salvage by reperfusion is likely, an open vessel must be better than a closed one. The question is can we improve on front-loaded tPA without the mortality benefits associated with myocardial salvage being negated by major haemorrhage and disabling stroke, particularly in the elderly?

In part this has been answered by the GUSTO V study, where front-loaded tPA was compared with a combination of half-dose tPA and full-dose abcximab (a platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor blocker) in 16 588 patients. This combination achieves patency at 90 minutes in 80% of patients compared with 55% when front-loaded tPA is given alone (Topol, 2001) — not too different to the patency expected 90 minutes after hospital admission in centres using primary percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice. Despite this higher prevalence of patency, 30-day mortality was identical (Topol, 2001). Again, the conclusion must be that there is more to myocardial salvage and mortality reduction than early patency.

However, even with the best available thrombolytic regimen, there will inevitably be patients with evolving infarction that fail to thrombolyse. Can they be recognized and treated?

Failure of resolution of ST segment elevation is an easily measured, relatively robust indication of continued myocardial ischaemia, which is often the result of 'failed thrombolysis'. However, evidence that informs management is lacking. A conservative approach has a high mortality. At present, there is insufficient evidence to assess the role of repeat thrombolysis. Data from the TIMI 4 trial (Gibson et al, 1997) suggest that percutaneous coronary intervention (PCI) as a 'rescue' is not associated with a survival benefit. However, newer catheter laboratory techniques, in particular the introduction of stents and GPIIb/IIIa inhibitors, may now have significantly improved the results of rescue PCI.

The lack of available evidence emphasizes the importance of trials such as REACT and MERLIN highlighted in Dr Gershlick's review. They are also the driving force behind trials involving half-dose thrombolysis before planned primary PTCA protected by full-dose GPIIb/IIIa inhibitor in the CADILLAC-2 and FINESSE trials.

As well as lifestyle changes, medical therapies are available to reduce the risk of plaque rupture. Beta-blockade can improve survival post-infarction and reduce re-infarction rates (Freemantle et

al, 1999). Statin therapy may reduce the risk of further plaque rupture (Schwartz et al, 2001). Angiotensin-converting enzyme inhibition is associated with improved survival and a reduction in subsequent events post-AMI (Yusuf et al, 2000). Despite this, a significant number of suitable patients do not receive these agents — Krumholz et al (1999) reported a low rate of β-blocker use post-AMI. More widespread use of available agents would probably improve survival post-infarction above and beyond the benefits of thrombolysis.

Improved antiplatelet therapies given post-infarction may help minimize the consequences of plaque rupture. There is some suggestion, albeit not yet conclusive, that GPIIb/IIIa inhibition can in itself reduce ST elevation MI in unstable angina, supporting the view that these agents may reduce post-thrombolytic re-occlusion rates. In clinical practice, the use of cheaper oral agents, e.g. clopidogrel, would be more acceptable. Preliminary reports of the CURE trial, although as yet unpublished, suggest a potential role for clopidogrel in combination with aspirin in unstable angina and, by extrapolative speculation, AMI.

THE ROLE OF ANGIOPLASTY

With these uncertainties surrounding thrombolysis why not just mechanically disrupt the thrombus and plaque with a balloon? Dr Gershlick gives a clear analysis of the role of primary PCI as an alternative to thrombolysis. The trials to date are incomplete — the elderly in particular are under-represented in published studies. The role of primary angioplasty in those 75 years and older is currently being addressed in the senior PAMI trial.

A case can be made for primary angioplasty in high-risk patients and those with AMI in whom thrombolysis is contraindicated. In skilled hands, PCI can achieve high rates of coronary artery patency with a significantly lower risk of serious haemorrhage than thrombolysis. Furthermore, there is a reduced risk of re-occlusion. By analogy with the treatment of unstable angina, there is clinical evidence that PCI can stabilize vulnerable plaques (Cannon et al, 2001). Although primary angioplasty studies to date are small, lacking the statistical power of the thrombolysis studies, they provide the only available evidence of a condition in which PCI may impact on mortality. In addition, in contrast to systemic lytic therapies, where improvements are likely to be limited by increased haemorrhagic risk, techniques in PCI have demonstrated significant and continued improvement. It is likely that PCI techniques will continue to improve, and their superiority over thrombolysis alone may become greater in magnitude and significance.

LOGISTIC ISSUES

Current management of AMI in a non-specialist unit, with early administration of appropriate thrombolytic and adjunctive therapies, remains an appropriate treatment. Survival is significantly improved compared with 15 years ago.

However, we believe that the optimal treatment of MI is likely to evolve into regimens where thrombolytics, GPIIb/IIIa inhibitors and primary PTCA are used in combination. Given this likely evolution, management of AMI requires the close involvement of a cardiologist with a good working knowledge of thrombolysis regimens and the role of PCI. Primary angioplasty should be made available now for those patients with AMI at high risk, e.g. those under the age of 75 years with cardiogenic shock and those in whom thrombolysis is contraindicated. In the authors' view, the proportion of patients treated by primary PTCA will need to increase in the same way as it has in the USA.

Post-appointment consultant training is likely to be required in many cases; the availability of appropriately skilled technical, radiography and nursing staff is already a problem at current levels of activity and the increased costs of a more invasive strategy are expected to be high. Whether primary PTCA plays a more dominant role in achieving and maintaining vessel patency in AMI in the UK is more likely to depend on political will than an improving evidence base. HM

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KEY POINTS

- Appropriate thrombolysis is associated with a clear survival benefit in acute myocardial infarction and represents the mainstay of treatment.
- Adjunctive therapies, platelet antagonists, β-blockers, statins and angiotensin-converting enzyme inhibitors are also important and are currently underused.
- Increasingly, evidence supports percutanous coronary intervention in acute myocardial infarction.
- Future optimal treatment is likely to include fibrinolytics given in combination with glycoprotein IIb/IIIa inhibitors, together with percutanous coronary intervention.
- The profound logistic implications of such a change in therapy will require considerable forward planning if clinical practice is not to lag far behind the evidence base.