Revascularisation and beyond

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Abstract

Thrombolytic therapy has revolutionised the management of acute myocardial infarction (MI) and saved many thousands of lives. Since these agents first became available nearly 20 years ago, many new pharmacological therapies have been developed to try and improve both short-term and long-term outcome following MI. Surgical interventions too are being considered as a serious option during the immediate post-MI period to avoid the adverse effects of thrombolysis and improve long-term outcome. At the same time, research is focusing on what therapy should follow acute MI treatment to improve the long-term outlook for patients. Both old and new therapeutic options need to be considered to offer patients the best chance of a full recovery and long-term survival after MI.

Key words: myocardial infarction (MI), thrombolysis, antiplatelet and anticoagulation therapy, angioplasty, beta blockers, calcium channel blockers.

Br J Cardiol 2002;**9**:539–45

Introduction

Thrombolytic therapy has transformed the management of acute myocardial infarction (MI) since it first became available in the 1980s. This treatment modality has been shown to reduce mortality, promote myocardial salvage, and enhance left ventricular function in selected patients with evolving acute MI.[1-3] The net effect of thrombolysis is a reduced myocardial necrosis in those patients whose acute MI was destined to be more extensive in the absence of early coronary reperfusion.[4]

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Before thrombolytic therapy became available, a non-transmural or non-Q wave MI was considered to be a 'naturally occurring' early spontaneous coronary reperfusion. This natural form of revascularisation is favourable in the short term yet results in a high cardiac event rate (re-infarction, and post-infarction angina) in the long term.[4] The so-called 'prognostic paradox' is related presumably to the residually ischaemic myocardium, which renders such patients at increased risk for ischaemic sequelae.

This 'naturally occurring' non-Q wave MI can be compared with the 'incomplete' infarction that results from thrombolytic therapy or primary percutaneous transluminal coronary angioplasty (PTCA). Early thrombolysis produces partial recanalisation of a total, or subtotal, thrombotic coronary artery occlusion that then culminates, presumably, in an aborted, interrupted, or 'incomplete' infarction.

The concept of an 'incomplete' infarction following thrombolytic therapy or primary PTCA is important when we consider what treatment should follow the initial interventions used in the management of acute MI. For example, it seems plausible that there may be a role for adjunctive anti-ischaemic therapy.[5]

In this article we review the pharmacological approaches in the management of acute MI and consider the best options to date. We also examine what alternatives are emerging to thrombolysis and what adjuvant therapy, if any, may improve the outcome following early acute intervention.

Thrombolysis

The aim of thrombolytic therapy for acute MI is to restore coronary flow as quickly and as fully as possible. The two major thrombolytic agents, the inexpensive streptokinase and expensive rt-PA (tissue plasminogen activator), are similarly effective in opening occluded coronary arteries. However, rt-PA opens coronary arteries faster, but with more reocclusions, than streptokinase. As the main objective of thrombolytic therapy is to re-open coronary arteries as soon as possible, rt-PA would appear to be the best agent.

Three major trials have compared the relative efficacy of the thrombolytic agents on the survival after acute MI: the International trial[6] (i.e. the extended GISSI-2 trial), ISIS-3[7] and GUSTO-1.[8] The differences in the rt-PA strategies in the three trials are: front-loading in GUSTO, where about two-thirds of the drug is given in the first 30 minutes (intravenous heparin therapy was also used in GUSTO); and the subcutaneous administration of heparin in GISSI-2 (started 12 hours after thrombolysis) and ISIS-3 (started after four hours).

The GUSTO angiographic substudy showed that the front-

Table 1. Efficacy and safety of heparin as adjunct to rt-PA in the randomised trials

Study	Heparin administration	Efficacy as number of hospital deaths/ number of patients (%)			
		Heparin	*No heparin*	*RR(95% CI)*	*p*
GISSI-2 International study[6]	sc 12h after Tx	476/5,170 (9.2%)	453/5,202 (8.7%)	1.05 (0.93–1.20)	ns
ISIS-3[7]	sc 4h after Tx	684/6,870 (10%)*	734/6,876 (10.7%)*	0.93 (0.84–1.02)	ns
ECSG[10]	iv immediately after Tx	9/324 (2.8%)	11/320 (3.4%)	0.81 (0.34–1.92)	ns
Bleich[11]	iv immediately after Tx	6/46 (13%)	5/49 (10.2%)	1.28 (0.26–2.37)	ns
HART-1[12]	iv immediately after Tx	2/106 (1.9%)	4/99 (4.0%)	0.47 (0.09–2.50)	ns
Total		1,177/12,516 (9.4%)	1,207/12,546 (9.6%)	0.98 (0.91–1.06)	ns
Study		**Safety as events of cerebral bleeding/ number of patients (%)**			
		Heparin	*No heparin*	*RR(95% CI)*	*p*
GISSI-2 /International study[6]		24/5,170 (0.4%)	20/5,202 (0.4%)	1.21 (0.67–2.17)	ns
ISIS-3[7]		49/6,870 (0.7%)	40/6,876 (0.6%)	1.23 (0.81–1.87)	ns
ECSG[10]		2/324 (0.6%)	0/320 (0.0%)	Infinity	
Bleich[11]		0/46 (0.0%)	0/49 (0.0%)	0	
HART-1[12]		0/106 (0.0%)	1/99 (1.0%)	Infinity	
Total		76/12,516 (0.6%)	61/12,546 (0.5%)	1.25 (0.90–1.75)	ns

Key: sc = subcutaneous; h = hours; Tx = thrombolytic therapy; iv = intravenous; *35 days mortality

loaded rt-PA regimen combined with early full heparinisation leads to the fastest reperfusion.[9] The most serious side effect of thrombolysis, intracerebral bleeding, was more common with rt-PA than with streptokinase. In all three trials rt-PA increased the number of intracerebral haemorrhages suggesting that the fibrin specificity of rt-PA does not protect at all against major bleeding.

The other major drawbacks of thrombolytic therapy are recurrent ischaemia and reocclusion. In the early years of thrombolysis it was suggested that rt-PA leads to more reocclusion than streptokinase. This is unproven.[9] It was shown, however, that rt-PA needs the addition of heparin to achieve better early and late patency.[10-12] The time window in which heparin should be given is more difficult to establish. Heparin can probably be discontinued 24 hours after treatment with rt-PA.[13] The role of heparin as adjunctive therapy to streptokinase is less well studied. In the GUSTO study there were no clinical or angiographic advantages of intravenous over subcutaneous heparin during and after streptokinase therapy. Subcutaneous heparin after streptokinase offered no clinical benefit in GISSI-2 and ISIS-3 over placebo, but increased the incidence of cerebral bleeding by 20 to 25% (table 1).

Bolus thrombolytic agents may improve early coronary patency and are easier to administer, which has advantages in pre-hospital thrombolysis and in primary care centres. However, large clinical trials (INJECT,[14] GUSTO-III,[15] COBALT[16] and ASSENT-2[17]) did not show significant net clinical benefit over standard thrombolytic regimens.

Reocclusion can occur early or late after thrombolytic therapy.[18] Early reocclusion is probably more deleterious than late reocclusion of the infarct related vessel because of lack of sufficient collateral circulation. Reocclusion impedes improvement of left ventricular function[19] and probably of survival[20] after thrombolysis for acute MI. How to keep reperfused coronary arteries open is the subject of intense research.

Antiplatelet and anticoagulation therapy

Antiplatelet therapy in the form of aspirin is the standard treatment in all cases of acute MI, whether or not thrombolytic therapy has been administered. It should be given as soon as MI is suspected and continued indefinitely.[4] In addition to aspirin, there seems to be a role for clopidogrel, started at a dose of 300 mg and continued at a dose of 75 mg/day.[21]

Anticoagulation therapy in the form of intravenous unfractionated heparin or subcutaneous low molecular weight heparin (LMWH) should be added to antiplatelet therapy as part of the standard therapeutic regime for all patients presenting with acute MI.[4] Whether to opt for unfractionated heparin or LMWH is probably down to individual doctors' preference and experience. Although there have been four direct comparative trials of the two regimens, the results are still inconclusive about the best treatment option in the immediate post-MI phase.[4] There is little doubt, however, that LMWH is more convenient to use than unfractionated heparin and evidence is emerging that it may also be superior to unfractionated heparin in preventing re-occlusion.[22]

Triple therapy using a combination of aspirin, heparin and a platelet GP IIb/IIIa receptor antagonist may be necessary in patients whose symptoms continue and in whom a PTCA is planned.[4]

Another intriguing option to keep reperfused coronary arteries open is the newer antithrombotic drug hirudin, a highly specific antithrombin agent. Hirudin is expensive and is, in conjunction with thrombolytic therapy, disappointing with regard to efficacy and safety.[23] The Organisation to Assess Strategies for Ischemic Syndromes (OASIS) 2 study failed to show a reduction in mortality or further cardiovascular events.[24] Until further trials are conducted in patients with MI, the use of hirudin should be restricted to patients with thrombocytopenia following treatment with heparin and to prevent deep vein thrombosis in patients undergoing hip replacement surgery.[4]

In the long term, the role of anticoagulation therapy remains

unclear.[4] Four pilot studies initially raised hopes that warfarin may help reduce deaths and further cardiovascular episodes after patients were discharged from hospital after treatment for acute MI.[25-28] Other studies have failed to reproduce these findings, suggesting there may be no place for long-term anticoagulation therapy following acute MI.[29] For the time being only antiplatelet therapy should be given after acute intervention; post-MI warfarin should be reserved for patients with a mural thrombus, a large area of dyskinesia, low left ventricular ejection fraction, heart failure, atrial fibrillation or mechanical prosthetic heart valves.[4,30]

Coronary angioplasty

Mechanical preservation of infarct related vessel patency after successful thrombolysis has been studied extensively but has not been proven to improve clinical outcome. In some studies coronary angioplasty tends to predispose to reocclusion and recurrent myocardial ischaemia – for this reason routine angioplasty after coronary thrombolysis is not advisable.[31] The role of bypass surgery after thrombolysis is restricted to patients with left main coronary artery disease or triple vessel disease with involvement of the proximal left anterior descending coronary artery, in accordance with guidelines of the American College of Cardiology/American Heart Association.[4]

Primary angioplasty

Although thrombolytic therapy for acute MI is widely applicable, it is only successful in restoring full early patency in about 50% of patients and has a low, but significant, risk of severe side effects. Acute PTCA carried out as an alternative to thrombolysis circumvents the cost and risk of thrombolytic therapy and might restore patency in nearly 90% of cases.

Angioplasty for acute MI was first described as a rescue therapy in the case of failed intracoronary thrombolysis. It was studied extensively as adjunctive therapy and performed immediately (within hours), early (within one to two days), late (after two days), or electively for angina or inducible ischaemia after intravenous thrombolytic therapy. Primary angioplasty, without the use of thrombolytic therapy, was described in 1983.[32] It can be applied as an alternative reperfusion therapy in candidates for thrombolytic therapy and is the only reperfusion option in the many patients with acute MI ineligible for thrombolytic therapy.[31]

An overview of the short-term results from 10 comparisons[33] of the two approaches has shown that, compared to thrombolysis, primary angioplasty results in a lower mortality (4.4% versus 6.5%, relative risk 0.66, 95% CI 0.46–0.94), translating into an absolute benefit of two lives saved per 100 patients treated with angioplasty rather than thrombolysis. There were also fewer non-fatal re-infarctions in the angioplasty-treated group compared with the group of patients treated with thrombolysis. With respect to safety, stroke was reduced from 2.0% with thrombolysis to 0.7% with angioplasty (relative risk 0.35, 95% CI 0.14–0.77).

Recently, long-term follow-up data were published of 395 patients randomly assigned to treatment with angioplasty or intravenous streptokinase.[34] Clinical information was collected for a mean (±SD) of 5±2 years, and medical charges were compared. A total of 194 patients were assigned to undergo angioplasty and 201 to receive streptokinase. Mortality was 13% in the angioplasty group, compared with 24% in the streptokinase group (relative risk 0.54, 95% CI 0.36–0.87). Non-fatal re-infarction occurred in 6% and 22% of the two groups respectively (relative risk 0.27, 95% CI 0.15–0.52). The combined incidence of death and non-fatal re-infarction was lower in the angioplasty group, when compared to the streptokinase group, for early events, within the first 30 days, with a relative risk of 0.13 (95% CI 0.05–0.37), as well as for late events, after 30 days, with a relative risk of 0.62 (95% CI 0.43–0.91). The rates of readmission for heart failure and ischaemia were lower in patients in the angioplasty group than in patients in the streptokinase group. Total medical charges per patient were similar in the angioplasty (US$ 16.090) and the streptokinase group (US$ 16.813). In several settings the cost of primary angioplasty has been shown to be lower than that for thrombolysis.[35]

Results from the meta-analysis, together with those of a more recent trial,[36] are shown in table 2.

Given the superior safety and efficacy of primary angioplasty, this treatment is now preferred when logistics allow. The results of primary angioplasty are dependent, in part, on the setting in which it is performed; results from various hospitals may differ considerably. This is a consequence of the fundamental difference between a procedure and pharmacotherapy;[37] it has also been shown with angioplasty in stable and unstable angina. Quality control, outcome monitoring and adherence to guidelines and recommendations of task forces, such as those of the European Society of Cardiology[31] and the American College of Cardiology/American Heart Association,[4] are of crucial importance.

Table 2. Efficacy and safety of primary angioplasty versus thrombolysis

Study	Follow-up	Efficacy as number of hospital deaths/ number of patients (%)			
		Angioplasty	*Thrombolysis*	*RR (95% CI)*	*p*
Meta-analysis[33]	Discharge-30 days	57/1,290 (4.4%)	86/1,316 (6.5%)	0.67 (0.48–0.95)	0.022
Schömig[36]	30 days	3/71 (4.2%)	5/69 (7.2%)	0.58 (0.15–2.36)	ns
Total	(4.4%)	60/1,361 (6.7%)	93/1,385 (0.48–0.90)	0.66	0.011
Study		**Safety as events of cerebral bleeding/ number of patients (%)**			
		Angioplasty	*Thrombolysis*	*RR (95% CI)*	*p*
Meta-analysis[33]		1/1,290 (0.1%)	15/1,316 (1.1%)	0.07 (0.01–0.52)	0.001
Schömig[36]		0/71 (0.0%)	0/69 (0.0%)	1.00	
Total		1/1,361 (0.1%)	15/1,385 (1.1%)	0.07 (0.01–0.50)	0.001

Table 3. Early intervention: total mortality in days 0–7 from all available randomised trials of early beta blockade (starting with iv dose) in acute myocardial infarction (adapted from reference 38)

Early intervention trials	Beta blocker death/ no. of patients	Control death/no. of patients	Approx. % change on odds of death	p
26 small trials	117/2,901	126/2,830	-9+/-13	ns
MIAMI trial[39]	79/2,877	93/2,901	-15+/-14	ns
Subtotal: all intervention trials other than ISIS-1	196/5,778	219/5,731	-12+/-9	ns
ISIS-1 trial[40]	317/8,037	367/7,990	-15+/-7	<0.05
Total mortality available	513/13,815 (3.7%)	586/13,721 (4.3%)	-14+/-6	<0.02

Beta blockers

The beneficial use of beta-blockade in non-revascularised MI was well established in the 1970s and 1980s[38] (table 3). The benefit of beta blocker administration after reperfusion therapy has not been thoroughly investigated.

The TIMI-II B results of early intravenous followed by oral metoprolol after tissue plasminogen activator (tPA) therapy for evolving acute MI showed no effect on 42-day mortality.[41] In addition, vascular morbidity (non-fatal infarction and post-MI angina) was favourably influenced only by early (0–2 hours) intravenous metoprolol.[42] Van de Werf and coworkers reported a short-term study in which beta blockade did not reduce cardiac events.[42] To date, the role of beta blockers – although convincingly established as safe and effective therapy for secondary prevention following non-reperfused MI – has not been adequately studied in prospective trials for it to be recommended as adjunctive therapy during or after thrombolytic therapy or PTCA.[21] Some centres however, still include beta blockers in their management protocols.

Calcium channel blockers

The role of calcium channel blockers in the management of cardiovascular disease has been controversial.[43,44] The situation is complicated by the fact that this group of compounds is not homogenous in its pharmacological mode of action. The dihydropyridines have been shown to have no additional benefit after an MI (which has not been treated with thrombolysis or primary PTCA.[43-47] Studies involving nifedipine show that it increases mortality in patients with coronary heart disease[43] (table 4).

Experimental and clinical data from small scale trials have suggested that diltiazem and verapamil may have a useful role when administered as adjuvant therapy for 'thrombolysed' infarction.[62-65]

The Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Infarct (INTERCEPT) trial has shown that although mortality is low in patients receiving thrombolysis, the incidence of ischaemic events is relatively high.[66] These ischaemic events were consistently lowered by approximately 25% during treatment with diltiazem 300 mg once daily. In addition, the need for revascularisation was reduced by over 40%, indicating a cost-effective benefit of secondary prevention after thrombolytic therapy with diltiazem.[66]

Similarly, the DAVIT II study showed that the administration of verapamil 120 mg once daily from the second week after acute MI led to a significant reduction in mortality and major cardiac events.[64]

Table 4. Mortality in trials of nifedipine in myocardial infarction and unstable angina (adapted from reference 41)

Dose and study	Calcium antagonist (deaths per no. of patients)	Control (deaths per no. of patients)	Risk ratio	95% CI	p
30 mg/d					
SPRINT I[47,48]	85/1,130	65/1,148	1.01	0.73–1.42	NA
40 mg/d					
Gordon *et al.*[49]	0/13	0/13			
Branagan *et al.*[50]	7/60	5/68			
Wilcox *et al.*[45]	150/2,240	141/2,251			
Subtotal	157/2,313	146/2,332	1.00	0.67–1.35	0.40
50 mg/d					
Sirnes *et al.*[51]	10/112	10/115	1.03	0.44–2.37	NA
60 mg/d					
Walker *et al.*[52]	7/106	7/120			
Erbel *et al.*[53]	10/74	6/75			
SPRINT II[54]	105/880	90/878			
MHINT[46]	1/341	2/327			
Subtotal	123/1,201	105/1,200	1.08	0.93–1.50	1.15
80 mg/d					
Muller *et al.*[55]	7/93	2/88			
Eisenberg *et al.*[56]	0/28	0/25			
Gerstenbith *et al.*[57]	7/88	5/70			
Lichtien *et al.*[58]	72/214	2/211			
Subtotal	26/400	9/394	2.83	1.35–5.93	2.53
> 100 mg/d					
Gottlieb *et al.*[59]	4/64	4/68			
Jaffe *et al.*[60]	1/13	0/9			
Muller *et al.*[61]	4/60	0/65			
Subtotal	9/145	4/142	2.20	0.69–6.55	NA
Total	**335/4,171**	**274/4,183**	**1.16**	**1.01–1.33**	**12.83**

Future antithrombotic strategies

Many doctors feel that the maximum patency effect of the current thrombolytic agents has now been achieved. Bolus agents like TNK-tPA, lanoteplase and staphylokinase are easier to administer but are not 'superior' thrombolytic drugs; they are very suitable for pre-hospital thrombolysis. Primary angioplasty is currently being compared to pre-hospital thrombolytic therapy in the French CAPTIM trial.

Pharmacological innovation has been achieved by the introduction of drugs interfering with the platelet glycoprotein IIb/IIIa receptor (or fibrinogen receptor) as adjunct to thrombolysis. Results of the ASSENT-3 trial suggest that the combination of TNK-tPA and a glycoprotein IIb/IIIa antagonist provide a useful

Key messages

- The best thrombolytic option currently remains streptokinase with heparin for hospital treatment, while bolus TNK-tPA, lanoteplase and staphylokinase are suitable for pre-hospital thrombolysis
- Aspirin plus heparin is the standard antiplatelet therapy; addition of a platelet glycoprotein IIb/IIIa receptor antagonist may be necessary for some patients
- Angioplasty after successful thrombolysis is not advisable
- Bypass surgery after thrombolysis is only indicated in patients with left main coronary artery disease or triple vessel disease with involvement of the proximal left anterior descending coronary artery
- Primary angioplasty (within at least two days of MI) is superior to thrombolysis and may be the preferred option where logistics allow
- Some centres still advocate the use of intravenous beta blockers in the acute treatment of MI, although the evidence to support its use is scant
- Diltiazem and verapamil are effective post-MI

and effective treatment option.[67] This and similar strategies need to undergo further rigorous scrutiny before they can be called 'superior thrombolytic regimens'. Results from the INTEGRITY, FASTER and ENTIRE studies (in which TNK-tPA serves as the thrombolytic) are eagerly awaited.

Conclusion

The optimal management of acute MI currently involves early restoration of coronary blood flow and prevention of reocclusion. To date, front-loaded rt-PA or bolus TNK-tPA with heparin offer the most effective pharmacological options. Striking results with primary angioplasty used as an alternative to thrombolysis mean that percutaneous coronary intervention is now challenging this traditional initial management of acute MI. What remains to be seen is whether it is better to wait for surgery or to go ahead with proven life-saving thrombolytic treatment in the community.

While the debate on the most appropriate initial intervention rumbles on, the question as to the best means of preventing reocclusion remains a vexing problem. We know that beta blockers save lives in the absence of thrombolysis, but their role after reperfusion is yet to be clarified. Similarly, the new class of platelet glycoprotein IIb/IIIa receptor antagonists used in conjunction with thrombolysis looks promising. More trials need to be performed to evaluate their role more fully. It will be interesting to see whether this new strategy can compete with modern primary angioplasty using stents.

One thing that has become clear in the last few years is the role of calcium channel blockers. After some years of uncertainty about the usefulness of this class of drugs, we can now say that the dihydropyridines present a hazard after MI, but the heart-rate lowering diltiazem and verapamil offer considerable benefits.

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