Recent Trends In Managing Acute Myocardial Infarction

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As the clinical research moves on at a ferocious pace it is perhaps wise to detach ourselves for a while and analyse as to what we have learnt so far about managing acute myocardial infarction (AMI).

The overall management of coronary artery disease is now looked upon in the context of:

* Primary prevention: Control of diabetes, Hyperlipidaemia and hypertension and advice about stopping smoking, regular exercise and weight reduction.

* Managing AMI in the hospital.

* Secondary prophylaxis with aspirin, B-Blockers and modification of risk factors. Advice against smoking is the most cost effective measure of all.

* Stratification of patients for consideration of bypass surgery and angioplasty if required. The subject of primary and secondary prophylaxis is beyond the scope of this article.

The aims of treating AMI are as follows:

* To alleviate patients symptoms.

* To prevent and treat the immediate complications.

* To salvage as much of the myocardium as possible by achieving and maintaining maximum coronary patency thus preserving the myocardial function. This ensures reduced long term morbidity and mortality.

Extensive research is now going on to achieve the two main objectives of treating AMI in the hospital, i.e., successful dissolution of the thrombus by thrombolytics and maintaining the coronary patency by antiplatelets and anticoagulants. The recent trends in treating AMI in a hospital setting are briefly discussed below.

PAIN RELIEF

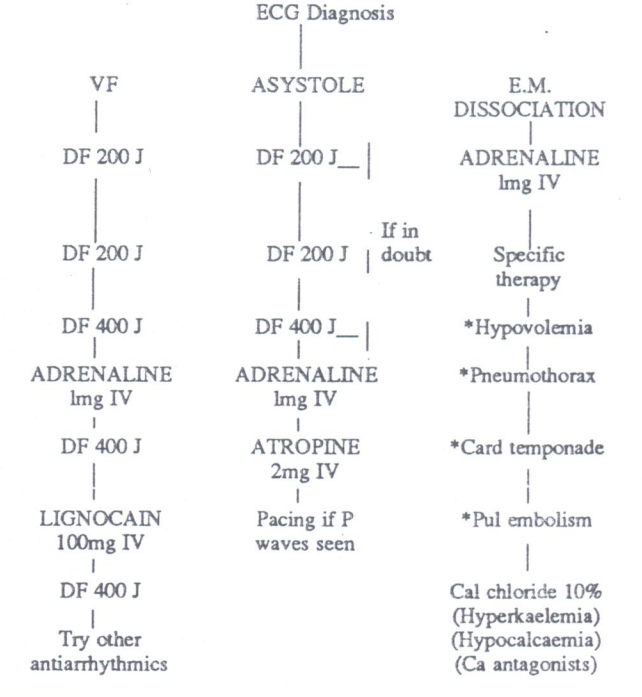
From the patients point of view the relief of pain is the most rewarding intervention by the physician. It must be borne in mind that though morphine by reducing the preload helps favourably to some extent to alter the balance of myocardial oxygen demand and supply, the underlying potentially serious pathology needs further immediate intervention. Hypotension and obstructive airways disease would favour the use of pethidine instead of morphine as it can induce an acute attack of asthma. 28-40% oxygen with a few words of assurance go a long way in relieving the patients apprehensions.

MANAGING IMMEDIATE COMPLICATIONS

It is now widely recommended that in cases of refractory malignant ventricular tachyarrythmias intravenous adrenaline should be given if electrical cardioversion is not successful (Table 1). The dose of 1 mg

TABLE 1

RECOMMENDATIONS FOR RESUSCITATION



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should be repeated after 5 minutes of further resuscitation followed by an attempt of cardioversion at 400 J. Next intravenous Lignocain and other antiarrhythmics should be used prior to further attempts of cardioversion.

In cases of asystole external percutaneous or transesophageal pace makers can be lifesaving.

Cardiogenic shock and pulmonary oedema have been treated conventionally by morphine, diuretics, vasodilators and ionotropes. Dobutamine is often combined with low dose Dopamine to maintain the renal perfusion. Their role in cardiogenic shock is questionable as intrinsic adrenaline already occupies all the B receptors in the myocardium. Further prolonged use beyond 3 days causes downregulation of the receptors with loss of potency. The unwanted increase in heart rate can increase the myocardial demand and can extend the infarct. Despite these shortcomings they can still be tried for short periods of time in patients who do not have significant tachycardia indicating poor adrenergic drive. Newer agents like Dopexamine have more selective renal vasodialatory effects[18]. The new breed of ionotropes include Enoximone and Milrinone. They act as phosphodiesterase inhibitors and apart from ionotropy also have a peripheral vasodialatory effect. Unlike the B-1 agonists they do not cause a significant increase in heart rate. The mean blood pressure is well maintained and the myocardial oxygen consumption is not increased[31]. Only Enoximone is so far licensed to be used in the setting of AMI and can be used alone or in combination with B-1 agonists. A recent study using long term oral Enoximone in patients with heart failure has shown increased mortality as compared to placebo therefore these agents are not recommended for oral use[14].

THROMBOLYSIS

The value of thrombolytics in achieving coronary patency and improving long term survival with good quality of life has been proven beyond doubt by many well designed studies like TIMI (thrombolysis in myocardial infarction) ISIS and GISSI etc. Contraindications to thrombolysis are given in (Table 2).

The benefit of giving thrombolytics after more than 8 hours of onset of the pain are limited and are perhaps justified in cases of younger patients with extensive Q wave infarcts. Uptill recently most hospitals limited the age for thrombolysis to 70 years.

TABLE 2

CONTRAINDICATIONS TO THROMBOLYSIS

Common to all agents.

*Recent surgery or trauma.
*History of cerebrovascular disease.
*Active peptic ulcer.
*Bleeding diathesis.
*Uncontrolled hypertension.
*Acute pancreatitis.
*Bacterial endocarditis.
*Esophageal varices.
*Severe liver disease.
*Recent abortion or delivery.
*Evidence of systemic bleeding like from genitourinary system.
*Pulmonary disease with cavitation.

For streptokinase only.

*Recent strept ococcal infection with high ASO titres.
*History of previous allergic reactions to streptokinase.
*Streptokinase therapy given more than 5 days and less than 3 months previously.

Contrary to earlier belief retrospective analysis of major studies have shown that for patients over 70 years thrombolysis confers a significant benefit. This view was supported in a recently reported TTOPP study (Thrombolytic therapy in older patient population).

Recent studies have focused attention on the question of choice between the three main contenders, Streptokinase, t-PA (Tissue plasminogen activator complex) and APSAC (Anisolyted plasminogen Streptokinase activator complex). The ECSG (European co-operative study group) and the TIMI group of studies (Thrombolysis in myocardial infarction) have directly compared streptokinase with t-PA. The 90-minute patency rates for the two studies are given in (Table 3). It is clear that t-PA achieves higher patency

TABLE 3

STUDY	t-PA	STREPTOKINASE
E.S.G-1	70	56
T.I.M.I-1	70	42
COMBINED	70	46

*Evidence indicating higher patency rates with t-PA.

rates but do they mean a reduced long term mortality remains uncertain. Three recent studies aimed to address this question. GISSI-2 (Gruppo Italiano per lo Studio della Sofravvivenza nell Infarto Miocardico)[12] and the allied International t-PA streptokinase study[13] reported in September 90 failed to show any difference in mortality between the two agents (Table 4). It is worth remembering that in these studies s/c heparin was given after 12 hours of thrombolysis. It was argued that the time delay in instituting heparin made the results unreliable as t-PA being a selective and a short acting drug needs heparinisation for maximum benefit. Results of ISIS 3 were presented in March 91 and they reinforce and support the findings of GISSI 2 and the International t-PA Streptokinase trial. ISIS-3 compared streptokinase, t-PA and APSAC and heparin was given at 4 hours subcutaneousely (Table 5). Though the overall mortality was slightly lower with t-PA the difference did not reach statistical significance (Table 6&7). It is still argued that t-PA did not get a fair trial as immediate intravenous heparin could have altered the results in favour of t-PA. The AIMS study (Anistreplase in myocardial infarction) compared APSAC to placebo and showed an odds reduction of 43% at 1 year follow up which is comparable to other thrombolytics[1].

As the three agents are so far equally efficacious the choice between them depends on the side effects and the cost. Though Streptokinase has a marginally higher incidence (statistically insignificant) of systemic anaphylaxis, hypotension and haemorrhage the cost of one dose of streptokinase is about £75 as compared to £750-900 for a single dose of t-PA. Streptokinase can be repeated within 5 days before the antibodies develop or after 90 days once the agglutinin titre has fallen. Therefore t-PA should be used only in cases where there is either a history of anaphylaxis to Streptokinase or the patient needs a repeat thrombolysis within 3 months of previously given streptokinase.

TABLE 4

RESULTS OF GISSI-2

	t-PA	Streptokinase
*Mortality	3.4	3.2
*Reinfarction	3.1	2.8
*Angina	17	18.5
*LV failure	5.6	6.3
*Stroke	0.3	0.4
*V. Tachycardia	0.3	0.3

Results at 6 months follow up of GISSI-2 presented as (%) incidence.

TABLE 5

SUMMARY PROTOCOL FOR ISIS-3 (ALL PATIENTS RECEIVED IMMEDIATE ASPIRIN (160 MG) AND THEN 160 MG DAILY)

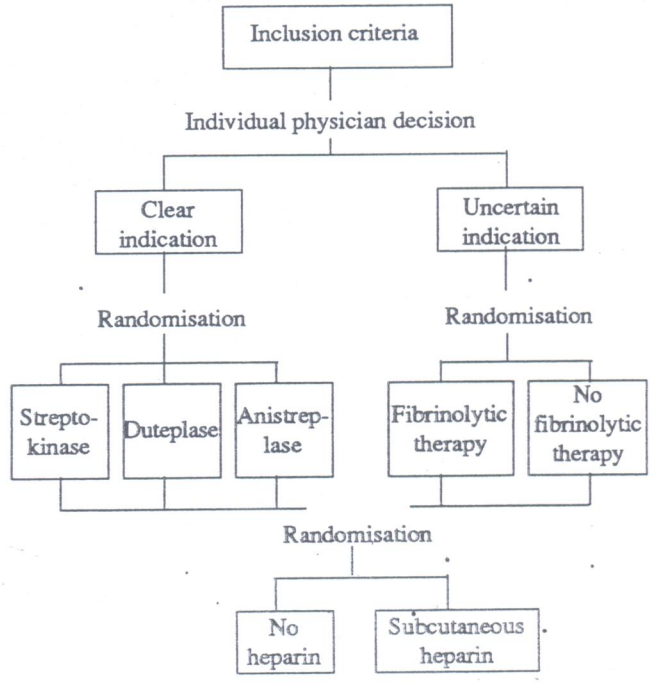


TABLE 6

RESULTS OF ISIS-3

	Heparin	No Heparin
Streptokinase	10.4	10.7
t-PA	9.9	10.7
APSAC	10.4	10.7

*Mortality rates (%) from 0-35 days after randomisation in ISIS-3

TABLE 7

MORTALITY AND CLINICAL EVENTS 0-35 DAYS

ISIS-3 RESULTS

	SK %	rt-PA %	Absolute difference per 1000 treated	Trend in favour of
Death	10.5	10.3	2	rt-PA
Cardiac rupture	1.4	1.3	1	rt-PA
Cardiogenic shock	7.1	6.9	2	rt-PA
Reinfarction*	3.6	3.1	5	rt-PA
V.F.	5.6	5.5	1	rt-PA
Cardiac arrest	5.5	5.2	3	rt-PA
Major bleed	0.9	0.9	-	-
Stroke*	1.1	1.5	4	S.K.
Heart failure	17.3	16.8	5	rt-PA
Allergic reactions* (causing shock)	0.3	0.1	2	rt-PA
Hypotension* (profound)	6.8	4.3	25	rt-PA

APSAC despite being expensive can be given as an intravenous injection over 5 minutes in contrast to the other two who need to be given as an infusion. As the mortality and morbidity of AMI rises in proportion to the time interval between the onset of symptoms and institution of thrombolytics (Table 8&9) therefore it is foreseen that APSAC will have a greater role in the future when general practitioners and the paramedical staff will be able to give the injection at the time of their first encounter with the patient. This will prevent the delay due to the time taken by the ambulance to come, the transfer to the hospital, time spent in the casualty before being transferred to coronary care and the start of an infusion. A recent study has shown that the average time between the arrival at the hospital and

TABLE 8

RELATION BETWEEN THE TIME DELAY TO ONSET OF THROMBOLYSIS AND LEFT VENTRICULAR FUNCTION

Time to thrombolysis after pain	:	Mean global ejection fraction
1 HOUR	:	54%
2 HOURS	:	50% (p=0.002)
3 HOURS	:	45%

TABLE 9

RELATION BETWEEN TIME TO TREATMENT AND REDUCTION IN MORTALITY. MODIFIED FROM GISSI-1.

Time from onset of pain to treatment	:	Reduction in mortality
0-1 HOUR	:	46%
< 3 HOURS	:	20%
3-6 HOURS	:	15%

start of thrombolytics (door to needle time) is 68 minutes in the UK. In the currently undergoing EMIP study (European myocardial infarction project) patients will be randomised to receive Eminase (APSAC) or placebo injection in the ambulance or at home compared with the administration of the same agent in hospital.

Evidence is accumulating that there may be greater benefit from combining a selective agent (t-PA) with a systemic one like streptokinase. Various TAMI and KAMIT [30] studies have combined t-PA with either streptokinase or urokinase. In the largest of these trials, TAMI-5,[28] the reocclusion rate for t-PA monotherapy was 12%, High dose urokinase monotherapy 7% and combination therapy only 2%. GUSTO (Global utilisation of streptokinase and t-PA in occluded coronaries) is about to start recruiting. Patients eligible to receive thrombolytics within 6 hours of pain will be randomised to receive either of the one, Streptokinase, t-PA or a combination of both. The results of this interesting study will be keenly awaited by the physicians but not by the hospital managers whose cost of treatment per patient will rise astronomically. Till then streptokinase remains the first choice with t-PA preferred for repeat thrombolysis.

ROLE OF ANTIPLATELETS

Aspirin is the most cost effective treatment for ischemic heart disease. ISIS 2 (International study of infarct survival) confirmed the benefit of aspirin in secondary prophylaxis after AMI [29]. It is however not certain if a similar reduction in mortality will be achieved when aspirin is combined with t-PA or APSAC. A dose of 75-150 mg is usually given and it is generally acceptable to use aspirin in every patient with angina even without prior infarct. There is no convincing evidence to suggest that aspirin confers any protection to apparently healthy people. In dyspeptics the enteric coated preparation is often tolerated and should be given a trial. Aspirin can be safely used in combination with anticoagulants and patients who bleed invariably always have an underlying cause. In patients allergic or intolerant to aspirin other antiplatelet agents like dipyridamol should be considered. In the usual 100 mg t.i.d. dose dipyridamol does not cause any significant reflex tachycardia or coronary steel due to vasodilatation.

ROLE OF ANTICOAGULANTS

The benefit of low dose s/c heparin for prophylaxis of D.V.T in high risk patients and of intravenous infusion in unstable angina is clear. The use of heparin in AMI followed by long term anticoagulation has been the subject of much controversy in recent years. Previous studies have shown conflicting results. GISSI 2 addressed this question by giving heparin subcutaneously to all the randomised patients after 12 hours of thrombolysis. The results failed to show any benefit of heparin. It was argued that a delay of 12 hours was sufficient to reform the clot after thrombolysis. Therapeutic efficacy of subcutaneous heparin was also questioned. In ISIS 3 heparin was given subcutaneously within 4 hours of thrombolysis in a dose of 12500 IU twice a day for 7 days but the results do not show any distinctive benefit. However from subanalysis it appears that there is a little further reduction of mortality when heparin is given after thrombolysis with t-PA but not with the other two agents. The explanation can be found in the fact that as streptokinase acts systemically it depletes the plasma fibrinogen so that the chances of further clot formation are lessened. As t-PA acts only locally without altering the serum fibrinogen it needs further support from anticoagulants to prevent recurrence of thrombosis. However most of the future studies have incorporated heparin within 4 hours of thrombolysis as a standard regime. HART (Heparin aspirin reperfusion trial) compares the benefit of oral aspirin or intravenous heparin when given with t-PA. Early results show a 52% patency at 18 hours with aspirin as compared to 82% with heparin [8]. In the ECSG-6 study (European co-operative study group trial) all patients were randomised to receive t-PA, aspirin and heparin or no heparin. Patients treated with heparin showed 83% patency at a mean of 81 hours as compared to 75% without heparin. The results of future studies will clarify this situation further but so far it appears that immediate intravenous heparin should be given after t-PA. In keeping with the general trends patients with enlarged poorly functioning left ventricles should also be anticoagulated.

ROLE OF B-BLOCKERS

Previous studies showed that B-Blockers reduced the mortality when given intravenously within 4 hours of AMI. Most of the reduction in mortality was due to

the prevention of cardiac rupture. ISIS 4 which is described below recommends the use of iv B-Blockers on preferential basis within 4 hours of onset of pain. The role of B-Blockers in secondary prophylaxis is fairly well established. In uncomplicated infarcts oral B-Blockers should be started by the third day.

ROLE OF CALCIUM ANTAGONISTS

Unlike B-Blockers there is no convincing evidence that cardioinhibitory calcium antagonists like Verapamil improve long term mortality. In the DAVIT-II trial (Danish verapamil infarction trial) patients were randomised to receive either 360 mg of verapamil or placebo after 1 week of AMI. The mortality rates were 11.1% in the active group as compared to 13.8% in the placebo group (not statistically significant). Despite no change in mortality however there was significant reduction in overall cardiovascular events [10].

The dominantly vasodilator calcium antagonists like Nifedipine, Nicardipine and Amlodipine can produce a detrimental effect if given without B-Blockers in the acute phase of MI. The reflex tachycardia can increase the myocardial demand and a fall in blood pressure can reduce the coronary flow thus extending the infarct. There is therefore no role of Nifedipine in the acute phase of AMI[15]. The interesting INTACT study (International Nifedipine trial on antiatherosclerotic therapy) showed that oral Nifedipine given in a dose of 80 mg daily over 3 years reduced the development of new atherosclerotic lesions by 28%[6]. The mechanism of action remains unclear but further studies are needed to confirm these findings.

There is no evidence that Diltiazem reduces mortality after a Q-wave myocardial infarct. A study of 576 patients with non Q-wave infarct who were given 90 mg of diltiazem 6 hourly showed a 50% reduction in the incidence of reinfarction and refractory angina after 2 weeks [16]. Another large study looked at the long term effects of diltiazem after AMI. There was no benefit overall but in a subgroup of patients with non Q-wave infarct without cardiac failure there was a reduction of 34% in cardiac events at the end of 4 years. Thus Diltiazem is recommended for routine prophylaxis in patients with non Q-wave infarcts.

ROLE OF ACE INHIBITORS (ACEI)

The tremendous benefit of ACEI in heart failure was confirmed by the CONSENSUS study[22]. Now CONSENSUS-2 (Cooperative north scandinavian enalapril survival study) is looking at the effects of ACEI given immediately after AMI. Activation of the renin angiotensin system in AMI increase the coronary and systemic vascular resistance which may lead to infarct extension. Initial small studies have shown that ACEI improve myocardial function and ventricular remodelling [23-26]. ISIS-4 has been set up where patient will be recruited within 24 hours of AMI. Routine thrombolytics, anticoagulants, aspirin, B-Blockers and vasodilators will be used as required. In addition each patient will be randomised to the following treatments for a period of 1 month.

* Active or placebo long acting oral nitrates once a day.

* Active or placebo captopril twice a day.

* Av intravenous infusion of magnesium or no infusion.

Magnesium reduces the coronary tone and inhibits calcium influx into the ischemic cells and thus stabilises them [27].

ROLE OF NITRATES

The use of oral and/or intravenous nitrates in a dose that does not produce hypotension has a beneficial effect on the infarcted myocardium. They act either as coronary vasodilators or reduce the myocardial workload [19-20]. There is evidence that even in cases of fixed coronary lesions there is some degree of overlying spasm of the vessel during an infarct. Early studies have shown upto 31% reduction of mortality. [21]. Nitrates may also directly effect the function of platelets as suggested by a study that showed that intravenous nitrates reduced the platelet aggregation response to ADP [9].

Results of ISIS-4 as explained above will be eagerly awaited.

In GISSI-3 all the patients will receive streptokinase, intravenous B-Blockers and aspirin. Patients

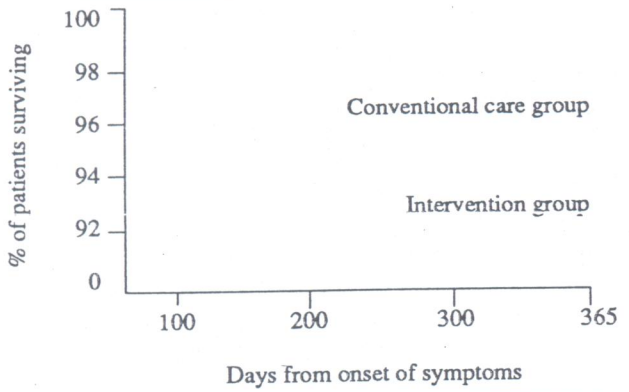
will then be randomised to receive either oral Lisinopril (ACE inhibitor) or intravenous nitrates which will be carried on after the acute phase as a nitrate patch. Results of GISSI-3 and ISIS-4 will clarify the value of nitrates.

EARLY OR LATE INTERVENTION

The idea of angiography and angioplasty if possible immediately after AMI sounded very appealing to start with. This early enthusiasm has now largely died as studies show that there is no benefit from early intervention mainly because the reocclusion rate after early angioplasty is in the order of 50%. Early angioplasty was done in the CRAFT (catheterisation/ rescue angioplasty following thrombolysis) study and failed to show any clear advantage in the actively treated group. All the patients received t-PA, aspirin and heparin. Recently published SWIFT (Shall we interfere after thrombolysis)[15] study compared patients who received early pre discharge angiography with a group who were treated conservatively. After a follow up of 365 days the mortality in the intervention group was higher than those treated conservatively (Table 10). There is also a higher incidence of reinfarction in the intervention group. Similar results were obtained from ECSG, TAMI (thrombolysis and angioplasty in myocardial infarction)[11] and TIMI-2 (thrombolysis in myocardial infarction) studies[7,9]. It therefore seems appropriate that patients after AMI should be stratified into various groups. Those with post MI unstable angina need early angiography preferably prior to discharge. Predischarge exercise test around 7-10 days should be done in high risk patients or in patients with large infarcts where a second infarct could be fatal. A high proportion of patients with subendocardial infarct have underlying partially occluded or reperfused vessels with a greater chance of Q wave infarct within 2 months. A predischarge exercise test therefore seems necessary. Rest of the patients should undergo exercise testing at 6 weeks after AMI. Only patients with poor effort capacity or significant ischemia at a low work load should be referred for angiography.

TABLE 10

ONE YEAR SURVIVAL CURVES FOR PATIENTS RANDOMISED TO CONVENTIONAL CARE OR INTERVENTION (THE SWIFT STUDY)



As a rule all patients should be discharged on a B-Blocker and aspirin if not contraindicated. The rôle of long term oral anticoagulants after AMI is not certain. Studies in the 1970s demonstrated a 20% reduction in overall mortality after AMI [2,3]. The Dutch sixty plus reinfarction study also demonstrated a 25% reduction in mortality after 2 years [4]. Recent WARIS (Norwegian warfarin reinfarction study) which randomised patients to receive warfarin or placebo after a month of AMI shows a 24% reduction of mortality [5]. It is however not clear if this degree of benefit is still conferred despite the early intervention of thrombolytics followed by aspirin and heparin with possibly B-Blockers as these interventions were not part of the routine management in most of the above trials. Large well designed randomised studies are needed in the future to evaluate the benefits of long term anticoagulation after the state of the art management.

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