THROMBOLYTIC THERAPY AND BETA-ADRENERGIC BLOCKADE IN ACUTE MYOCARDIAL INFARCTION: A PROSPECTIVE EVALUATION AT GROOTE SCHUUR HOSPITAL 1988-1990

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CONTENTS

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SUMMARY

The advent of intravenous thrombolytic agents has revolutionized the management of patients with acute myocardial infarction and has dramatically altered the morbidity and mortality associated with this condition.

The aims of this study in patients presenting with acute myocardial infarction and treated with thrombolytic agents are:

1. To evaluate the efficacy of thrombolytic agents used at Groote Schuur Hospital in terms of (a) patency of the infarct related artery; (b) short and long-term mortality.

2. To assess the feasibility and safety of combining intravenous beta-adrenergic blockade with intravenous thrombolytic therapy in patients presenting with acute myocardial infarction.

3. To assess the need for coronary angiography in all patients treated with thrombolytic agents for acute myocardial infarction.

4. To assess the effect on mortality of offering coronary angioplasty or coronary artery bypass grafting only to those patients manifesting spontaneous or inducible ischaemia post infarction.

SECTION 1

INTRODUCTION

In 1912 Herrick became the first physician to extensively describe the syndrome of sudden occlusion of the coronary arteries leading to acute myocardial infarction.[1] At that time acute myocardial infarction was a relatively rarely recognised condition, however as the century has progressed it has become increasingly prevalent, as has the broader category of ischaemic heart disease, of which acute myocardial infarction is a major component. Many studies have been performed over the last 50 years showing a wide variation in the incidence of ischaemic heart disease in various geographical locations and amongst different social groups, however, there has undoubtedly been a steady rise in incidence and prevalence since 1930 so that by 1960 ischaemic heart disease was, and still remains, the major cause of death in most industrialised societies.[2,3,4]

Most deaths (50%) from acute myocardial infarction occur prior to hospital admission.[5] This has remained a major problem despite the introduction of highly trained paramedical staff and fully equipped ambulance services, with the ability to administer intravenous drugs in the home environment. In-hospital mortality, however, has improved dramatically over the last three decades.

In the 1940's and 1950's treatment of this condition in hospital was almost entirely passive with the emphasis on maintaining the patient (and therefore his myocardium) at rest, for a prolonged period. In his book on cardiology in the 1950's Paul Wood recommended bedrest for

a minimum of six weeks with an eight hundred calorie diet.[6] In-hospital mortality was high despite these measures, approximately 30%.

However, towards the end of the 1940's treatment with anticoagulation was introduced in an effort to reduce deaths from thromboembolic complications. An immediate dose of intravenous heparin was given on arrival, and this was followed by regular subcutaneous or intramuscular doses. This treatment reduced deaths from thromboembolic complications by as much as 30% and the overall in-hospital mortality by 5% to an overall in-hospital mortality of 25%, and this remained the picture as the early 1960's approached.[7]

A watershed advance came in the 1960's with the introduction of Coronary Care Units. Now it was possible to closely monitor cardiac rhythms for life-threatening arrhythmias and to treat them promptly with defibrillators, new anti-arrhythmic drugs and pacemakers. Coronary Care Units and the therapeutic modalities they made possible had an immediate effect on in-hospital mortality, cutting this by almost half from 25% to 12-15%.

The status quo was maintained throughout the next two decades until the 1980's, when two therapeutic strategies were introduced that reduced in-hospital mortality even further. The first of these was the introduction of beta-adrenergic blockade. Clinical trials conducted in the early 1980's showed that intravenous beta-blockers given early in the course of acute myocardial infarction, and given chronically orally thereafter, reduced mortality by 30% in the first 24-hours and overall by 15% in the first week. In addition to this,

the number of cardiac events in the first week were reduced significantly in comparison to placebo.(8) It was also shown that continued administration of oral beta-blockers post-discharge reduced late (1 month) mortality by 15%.

The second major addition to the therapeutic armamentarium came with the introduction of agents designed to dissolve intracoronary thrombi i.e. thrombolytic therapy. These agents completely revolutionised the treatment of acute myocardial infarction and in doing so introduced a new set of problems in management.

They had first been recommended for use in the treatment of proximal deep vein thrombosis and serious pulmonary embolism in the late 1950's and early 1960's.(9) Towards the end of the 1970's and in the early 1980's several clinical trials took place using intracoronary streptokinase in an attempt to reperfuse the myocardium of patients with acute myocardial infarction. The results of these studies were encouraging but because of the small number of patients in the studies statistical significance was not achieved, and larger trials involving several thousand patients were needed to establish the efficacy of these agents beyond doubt.

The intracoronary administration was also cumbersome and led to delay in treatment of patients so several large studies were set up in the 1980's using intravenous thrombolytic agents and involving over 25 000 patients in total. These trials demonstrated a very significant effect of the use of thrombolytic agents on the morbidity and mortality of patients presenting with acute myocardial infarction.

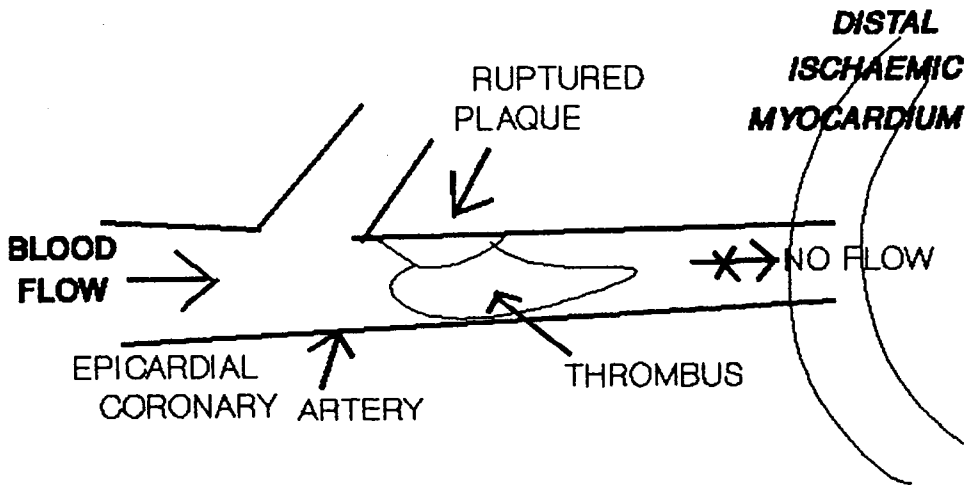
PATHOGENESIS OF ACUTE MYOCARDIAL INFARCTION

Ever since the first descriptions of acute myocardial infarction in 1912 controversy has raged over the pathogenesis, in particular over the occurrence of occlusive intracoronary arterial thrombosis as a primary or secondary event. Many scientists believed that intracoronary thrombosis was caused by acute infarction and indeed some evidence did point to this, especially post mortem studies that demonstrated acute myocardial infarction without coronary thrombosis and intracoronary thrombosis occurring without demonstrable myocardial infarction.(10,11,12,13,)

Introduced as a new postulate was the concept of coronary artery spasm,(14) this added further confusion to the matter and it was not until the latter half of the 1970's and early 1980's that it became generally accepted that intracoronary occlusive thrombosis was germane to the pathogenesis of acute myocardial infarction.(15) Fig 1.

Elegant post mortem studies have demonstrated occlusive intracoronary thrombi occurring at the site of atherosclerotic plaques in patients dying from acute myocardial infarction.(16) It has also been demonstrated that in many patients with fatal ischaemic heart disease at least 2 of the 3 major coronary arteries have severe (>75%) narrowings in their lumens caused by atherosclerotic plaques.(17)

FIG.1



REPRESENTATION OF OCCLUSIVE THROMBUS IN A MAJOR CORONARY ARTERY.

An angiographic study done by De Wood on patients with recent onset acute infarction (within 4 hours) demonstrated that the coronary artery supplying the infarcted area was totally occluded in the majority of cases (80%) and that retrieval of thrombus was possible using a Fogarty catheter.(15) Since that time many further studies have confirmed these findings, and in addition fresh thrombi have been recovered from the coronary arteries of patients undergoing emergency coronary artery bypass grafting for acute myocardial infarction. It has also become apparent that there is a natural process of fibrinolysis occurring and that up to 20% of occluded coronary arteries will be spontaneously recanalised within the first 24-hours. This phenomenon may account for some of the cases of acute infarction

occurring apparently in the absence of intracoronary thrombus, as the thrombus may have already undergone spontaneous lysis.

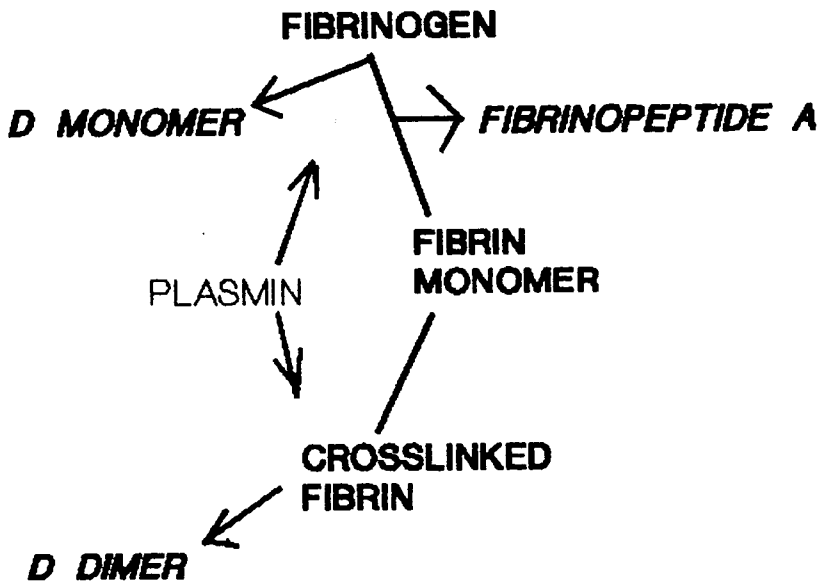
More recently angioscopy has been introduced as a diagnostic tool and using this technology intracoronary thrombi have been visualised in the coronary arteries of patients with unstable angina and myocardial infarction.

A growing quantity of biochemical evidence for intravascular thrombosis and thrombolysis, in patients with acute myocardial infarction, also lends considerable weight to the theory that intracoronary thrombosis is a primary event. Products of fibrin formation and degradation have been found to be markedly elevated when measured in patients with acute myocardial infarction.

Fibrinopeptide A is a small peptide released from the chain of fibrinogen by the action of thrombi. In normal controls the blood levels of fibrinopeptide A are low but when measured soon after the onset of symptoms in patient with acute myocardial infarction, especially transmural infarction, the levels are markedly elevated.(18)

Fibrin and fibrinogen related antigens (FRA) are byproducts and degradation products of cross-linked fibrin. Their presence in the serum is a sensitive indicator of intravascular thrombosis and thrombolysis. (Fig 2).

FIG.2 **FIBRIN AND FIBRINOGEN RELATED ANTIGENS.**



Kruskal et al [19] demonstrated that total serum FRA, fibrin monomer, D-dimer and D-monomer were elevated in the serum of patients with unstable angina and acute myocardial infarction when measured within 1 hour of the onset of symptoms. Patients with stable effort related chest pain and ill and healthy controls had normal levels of these substances.

These results all lend support to the theory that intracoronary thrombus formation is a primary event in the precipitation of acute myocardial infarction.

It is now generally accepted that the majority of acute myocardial infarctions are caused by an occlusive coronary thrombus occurring at the site of an atherosclerotic plaque often in association with

rupture of that plaque and subsequent intramural haemorrhage. The contribution of coronary arterial spasm is yet to be clearly elucidated as is the role of abnormal platelet function which has been more recently described in patients with unstable angina, a condition often progressing to acute myocardial infarction.[20]

Nevertheless, it would appear that the principal events culminating in acute thrombotic occlusion and subsequent acute myocardial infarction are coronary atherosclerosis, intimal injury and dynamic coronary artery changes.

Many recent studies have focused on intimal injury as the initiating event in a chain reaction that culminates in thrombus formation. The endothelium of the coronary arterial tree modulates smooth muscle tone through a number of potent substances that control local constriction and relaxation.[21] Haemodynamic alterations in coronary blood flow, and chemical substances, have been shown to cause the release of endothelium derived relaxing factor (EDRF).[22,23] This substance is a powerful vasodilator with inhibitory effects on platelet aggregation. EDRF is however synthesized and released locally and once liberated into the circulation is rapidly neutralised by free haemoglobin. Intact endothelium is therefore vital to the continued production of effective quantities of EDRF.

Endothelial damage can result not only from the physical presence of atherosclerotic plaques but also from more subtle alterations in vascular smooth muscle tone. Experimental evidence in rabbits has shown that the application of calcium chloride to the adventitia of

arteries produces profound endothelial damage with platelet aggregation.(24) High shear stress caused by non-flow limiting stenoses has also been shown to damage the vascular endothelium causing platelet activation.(25)

Platelet aggregation is not only enhanced by intimal damage and loss of EDRF but also promoted by exposure of the platelets to collagen, a powerful stimulator of platelet aggregation.

Increases in vascular tone and platelet aggregation lead to a volatile situation of vasoconstriction and further platelet activation. Activated platelets release several compounds including thromboxane A2, adenosine diphosphate and serotonin, which activate adjacent platelets and promote thrombus formation. Furthermore platelets provide a surface for the interaction of clotting factors. Platelet aggregation is enhanced by the haemostatic system through the generation of thrombin, a powerful platelet activator, and fibrin, which stabilizes the growing platelet mass and prevents its dislodgment by the blood flow.

Ultimately, thrombus forms at the site of intimal damage and occludes the lumen of the coronary artery. Obviously the myocardium distal to the occlusion is now deprived of its blood supply, and myocardial ischaemia and subsequent myocardial necrosis ensue, unless either sufficient collateral flow develops or spontaneous lysis of the thrombus occurs.

THE RATIONALE FOR THROMBOLYTIC THERAPY

Post mortem studies and animal experimental models have provided valuable information about the time required for necrosis to occur in the ischaemic myocardium and it would seem that after approximately six hours myocardial necrosis is complete.[26,27] It appears logical therefore, to assume that if the blood supply can be restored within this time frame then some myocardium may be preserved.

Mortality in myocardial infarction has been shown to be proportional to infarct size and residual left ventricular function, and a reduction in infarct size has been associated with improved survival.[28,29,30,31,32] Obviously infarct size is not the only factor influencing mortality but it is a major determinant.[33,34] Preservation of myocardial tissue therefore becomes of utmost importance in attempting to reduce mortality and morbidity associated with acute myocardial infarction.

Myocardial viability is critically dependent on blood supply, therefore in acute myocardial infarction with a fresh thrombus occluding a major epicardial artery, reperfusion of ischaemic myocardium is dependent on removal of the occluding thrombus, or on the development of sufficient collateral flow. Much of the data on patients with acute myocardial infarction indicates that in most study populations the majority of patients are young men presenting with a first myocardial infarction. Angiographic studies have demonstrated that most of these patients have single vessel disease with poor, or no collateral circulation.

Thrombus dissolution can be achieved either mechanically using angioplasty techniques, or pharmacologically using thrombolytic drugs. It has been conclusively shown that reperfusion in a select population can significantly reduce both mortality and morbidity associated with acute myocardial infarction, whether performed mechanically or pharmacologically.(35,36,37,38,39)

Both mechanical and pharmacological reperfusion techniques have disadvantages. Mechanical revascularisation demands the ready availability of a cardiac catheterization laboratory, skilled operators and back-up surgical facilities. It, however, has an impressive success rate given the above circumstances and has the added advantage of ameliorating the precipitating lesion. Despite the excellent success rate, however, no statistically superior effect on mortality has been demonstrated when compared with the effect of thrombolytic agents.(39)

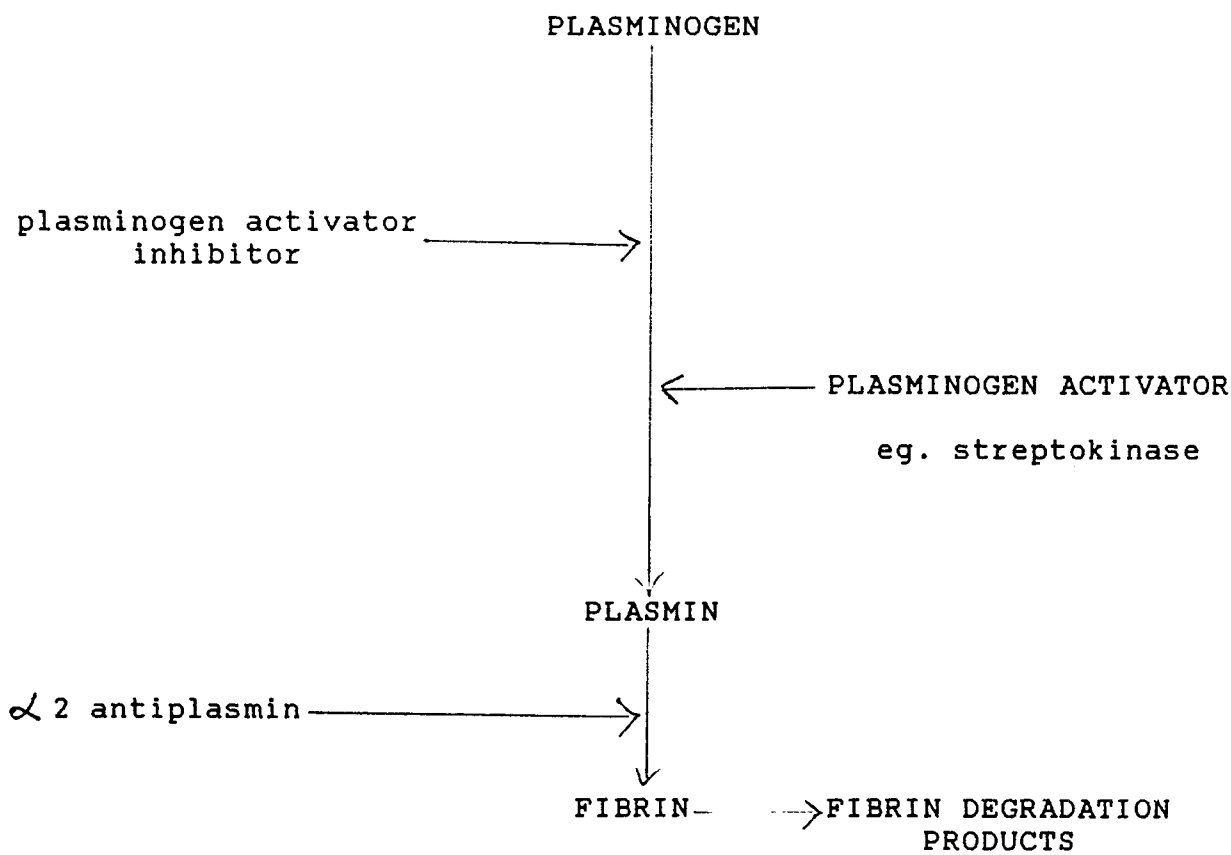
Thrombolytic agents themselves have many drawbacks and side-effects. They fail to recanalise the occluded artery in 20% or more of all cases, and a major disadvantage is that at the moment there is no reliable method of identifying those patients. The drugs also have a number of side-effects that will be discussed and are associated with a significant number of haemorrhagic complications. Nevertheless, their benefit on mortality has been clearly documented and they have a major advantage in that they can be given in peripheral hospitals lacking the facilities for angioplasty.

PHARMACOLOGY OF THROMBOLYSIS

THE FIBRINOLYTIC SYSTEM

The fibrinolytic system illustrated in Figure 3 contains a proenzyme, plasminogen, which can be converted to the active enzyme plasmin by the action of plasminogen activators. Plasmin is a serine protease which digests fibrin to degradation products. Natural inhibition of the system occurs at both the level of plasminogen activator and at the level of plasmin. (Fig 3)

FIGURE 3



Plasminogen is a 790 amino acid single chain glycoprotein. The molecule contains lysine binding sites which mediate its binding to fibrin and accelerates the interaction between plasmin and its

physiological inhibitor, α 2 antiplasmin. The lysine binding sites thus play a crucial role in the regulation of fibrinolysis. Naturally occurring plasminogen activators are serine proteases that have a high specificity for plasminogen, hydrolysing a peptide bond to yield the active enzyme plasmin.

Several plasminogen activators are available for clinical use including streptokinase, anistreplase (APSAC), tissue plasminogen activator and urokinase. The three most commonly used thrombolytic agents are discussed briefly below.

STREPTOKINASE

Streptokinase is a non-enzyme protein with a molecular weight of 47000. It is produced by beta-haemolytic streptococci and activates the fibrinolytic system indirectly. It forms a 1:1 stoichiometric complex with plasminogen which then undergoes a transition exposing an active site on the plasminogen moiety and transforms the complex into a potent plasminogen activator. The half life of streptokinase is estimated at 25 minutes. Because streptokinase is a foreign protein it is antigenic, and antibodies to streptococci are universally present in at least low titres. Streptokinase is therefore complexed on administration to the extent of the antibody present. The recommended dosage is usually greatly in excess of the amounts required to neutralise circulating antibodies.

Plasmin, the active enzyme produced by the streptokinase-plasminogen activator complex, is a non-specific proteolytic agent that can digest fibrin, fibrinogen, prothrombin and clotting factors V and V111.

Administration of streptokinase thus produces a generalised "lytic" state, which may cause haemorrhagic complications.

ACYLATED PLASMINOGEN-STREPTOKINASE ACTIVATOR COMPLEX (APSAC)

APSAC is an inactive derivative of the streptokinase-plasminogen activator complex obtained by acylation of active site serine. It reactivates at physiological pH following spontaneous deacylation. Both the deacylation and plasma half life are about 90-105 minutes. These pharmacological properties result in more sustained fibrinolytic activity than streptokinase, 4-6 hours as opposed to 1 hour. In addition the fibrin binding sites on fibrinogen in the APSAC complex are not affected by acylation and so are active on injection allowing circulating APSAC to bind rapidly to fibrin clot. This property confers semi-selective clot fibrinolytic activity on APSAC.

TISSUE TYPE PLASMINOGEN ACTIVATOR (tPA)

tPA is a trypsin-like serine protease, composed of 572 aminoacids. It occurs either as a single chain glycoprotein or as a two chain proteolytic derivative, but both forms have comparable enzymatic properties. tPA is a weak plasminogen activator in the absence of fibrin but binds specifically to fibrin and activates plasminogen at the fibin surface several hundredfold more efficiently than in the circulation. The half life of tPA in the circulation is only a few minutes. Because of the high clot specificy of tPA it does not create a generalised "lytic" state. tPA is now manufactured commercially using DNA recombinant techniques and is called r-tPA.

SIDE-EFFECTS AND COMPLICATIONS OF THROMBOLYTIC AGENTS

HAEMORRHAGIC COMPLICATIONS

Haemorrhage is the major complication of thrombolytic therapy. Bleeding may be secondary to venous or arterial punctures or may be spontaneous related to dissolution of previously formed haemostatic thrombus or related to fibrinogen/clotting factor depletion.

1. Cerebral haemorrhage

   Cerebral haemorrhage following thrombolytic therapy may be due to dissolution of an old haemostatic plug. The reported incidence is very low in most major trials <0.5%, and in the case of tPA is clearly dose related. With tPA a dose of >1.5 mg/kg is associated with a markedly increased incidence of cerebral haemorrhage. In ISIS 2 however the increased incidence of cerebral bleeding with streptokinase was more than offset against the reduction in non-haemorrhagic stroke.

2. Gastrointestinal bleeding

   Gastrointestinal bleeding occurring shortly after initiating thrombolytic therapy is almost certainly due to pre-existing unrecognised peptic ulceration. Reversal of the "lytic state" is usually although not always required. " Coffee ground" vomiting is common after myocardial infarction and is not necessarily related to thrombolytic therapy, indeed the gastric erosions seen at endoscopy may be secondary to aspirin therapy. Reversal of the lytic state is usually not necessary. Late massive gastrointestinal bleeding is often a manifestation of stress ulceration compounded by continued anticoagulation. It often

occurs in the sicker patient and may precipitate infarct extension or reinfarction.

3. Other sites

Intraperitoneal or urinary tract bleeding are very uncommon but microscopic haematuria is often seen for up to 48-hours post-treatment. The most common side-effect is iatrogenic bleeding from vascular access sites. Intramuscular injections and repeated venepunctures should be avoided. Placement of central lines or pacing electrodes should be avoided whenever possible. Decisions as to whether pacing or Swan Ganz catheterization will be needed should be made before the decision to institute thrombolytic therapy. When obligatory the insertion of central lines should be via the basilic vein in the antecubital fossa or via the femoral vein, as both of these sites may be compressed in the event of haemorrhage as opposed to the subclavian puncture sites. Arterial bleeding is another major complication and any arterial puncture should be sutured or a sheath must be left in situ until thrombolysis is complete.

IMMUNOLOGICAL

1. Immediate and anaphylactic

The presence of pre-existing antibodies can result in anaphylactic reactions. Fortunately these are rare occurring in less than 1% of the patients in the ISIS 2 trial.[36] Recombinant tPA does not appear to be associated with these type of reactions. Hypotension also occurs and would appear to be related to the speed of the infusion.[40] This may not be an

allergic reaction and may be related to histamine release or to the production of kinins. Transient skin rashes are seen in 5% of patients treated with streptokinase, but rarely seen in those receiving tPA.

2. Vasculitic reactions

A serum sickness type of reaction occurs with the formation of antigen/antibody complexes. This can result in a Henoch-Schoenlein reaction 6-21 days after treatment, presenting with a fever, arthralgia, abdominal pain, purpuric rash and in some instances microscopic haematuria. This reaction is rare and self limiting and has not been seen with tPA or urokinase.(41)

3. Glomerulonephritis

Acute renal failure is a rare but recognised complication of streptokinase therapy (for pulmonary embolism). A single case of crescentic glomerulonephritis has been reported in a patient after streptokinase was given for acute myocardial infarction.(42)

4. Antibody mediated platelet aggregation

This has been suggested as a cause of streptokinase enhanced thrombosis in patients with previous streptococcal exposure.(43)

UNRESOLVED PROBLEMS

Thrombolytic therapy is now used widely (depending on availability) and has had enormous effects not only on morbidity and mortality but on health care costs. Despite the acceptance of these agents there are still unanswered questions many of which are fundamental to their use.

Streptokinase is perhaps one of the best understood agents available and it is one of the cheapest. It is usually given in a dose of 1.5 million units over 30 minutes. Nevertheless, one of the unresolved problems concerns the most efficacious dose to use offset against the side-effect profile at that dose. This is also true of tPA. Many of the trials comparing the various agents have used differing doses of streptokinase and tPA for example and have used differing methods of administration, some using bolus doses whilst others have used continuous infusions.

Another problem has been the use of adjunctive therapy. The ISIS 2 trial published in 1986 clearly demonstrated that the administration of oral aspirin reduced mortality in acute myocardial infarction and that when given in conjunction with streptokinase the effects of the two on mortality at 7 days were additive. The dose of aspirin given in subsequent trials has again not been uniform with dosages varying from 50 mgs daily to 600 mgs daily.

Heparin is also given in most centres in order to try and prevent reocclusion of the culprit vessel once opened with thrombolytic agents. Unfortunately because of the systemic anticoagulant effects cerebral haemorrhage may be promoted.

Major controversy still exists over which agent to use. Tissue plasminogen activator is clearly superior to streptokinase in opening coronary arteries with a 90 minute patency rate of approximately 80% versus 55% for streptokinase. However there is a catch-up phenomenon with streptokinase so that by 24-36 hours the patency rates are similar. Whether this early reperfusion supremacy is translated into improved mortality has not been demonstrated. The GISSI II trial looked at this problem comparing streptokinase with tPA with or without heparin. The results have shown that there is no difference in mortality at 2 weeks. Unfortunately, this has sparked off a whole new debate as there is some evidence to suggest that tPA is more efficacious when heparin is given early intravenously as opposed to subcutaneously and late, starting at 12 hours, as given in GISSI II.[44]

Beta-adrenergic blockade has been another controversial subject with some institutions giving beta-blockers intravenously, some orally and some not at all. Despite the evidence in favour of beta-adrenergic blockade in acute infarction[45,46] many have expressed doubts about the safety of combining intravenous thrombolytic therapy and intravenous beta-blockers.[47] Beta-blockers given intravenously without thrombolytic therapy has been shown to be safe in the clinical setting of acute myocardial infarction provided contraindications to their use are carefully excluded and patients carefully monitored. However, no clinical trials have been done to date specifically looking at the question of the safety and efficacy of combining beta-

blockers with thrombolytic therapy in the setting of acute myocardial infarction.

Apart from the difficulties examining and comparing the major trials looking at different thrombolytic agents, their most efficacious methods of administration, the timing of administration, the effects on infarct related artery patency, left ventricular function, morbidity and mortality, and the types and timing of adjunctive therapy, yet another important question remains to be satisfactorily answered; should all patients undergo mechanical revascularisation if they have residual coronary artery disease?

Angiographic studies performed on patients receiving thrombolytic therapy have demonstrated that the majority of them will have a residual high grade stenosis at the site of occlusion in the infarct related artery. It has been the practice until very recently to be very aggressive with these lesions subjecting them to coronary angioplasty in an effort to remove or ameliorate the precipitating cause for the initial thrombus formation. It has been demonstrated that the patients with these lesions are at high risk for the development of recurrent infarction or angina. Many clinicians recommend percutaneous transluminal coronary angioplasty (PTCA) at a variable length of time after infarction provided there are no contraindications. The TAMI I[48] trial looked at the effects of immediate versus delayed PTCA and found that the patients who underwent immediate PTCA had a higher rate of abrupt closure of the artery or recurrence of a high grade stenosis than those who underwent delayed PTCA. In addition to this, those undergoing immediate PTCA

had a higher rate of access site complications namely bleeding, and a higher rate of transfusion requirements than their counterparts who underwent delayed PTCA.

Despite all the controversy over immediate versus delayed PTCA no-one addressed the question as to whether all of these patients required PTCA and if not, who should have PTCA and what were the indications for the procedure?

In order to answer these questions the TIMI II trial was undertaken and published in 1989 [49]. This trial randomised patients into two groups, one to receive PTCA after thrombolytic therapy, and one to undergo conservative therapy only being offered PTCA if they manifest recurrent spontaneous or inducible ischaemia i.e. those with positive effort stress tests at follow-up or those developing post-infarction angina. As a side issue they also selected a group of patients suitable to receive beta-blockers and randomised half to receive intravenous followed by oral therapy and half to receive oral therapy only. The results of TIMI II showed no difference in mortality at 6 weeks between the conservatively treated group and the group undergoing PTCA, indicating that it is probably not necessary to intervene in these patients post thrombolysis unless ischaemia is clearly demonstrated.

SECTION 2

REASONS FOR THE STUDY

In 1988 thrombolytic therapy began to be widely used in the Coronary Care Unit of the Cardiac Clinic at Groote Schuur Hospital.

At this time many of the trials quoted above were as yet unfinished or unpublished. Streptokinase was and still is, the most frequently used of the thrombolytic agents mainly because of its relatively low cost in comparison to the more widely acclaimed tissue plasminogen activator (tPA). The Cardiac Clinic was also involved in an international multicentre trial evaluating a newer thrombolytic agent acylated plasminogen activator complex or APSAC. The patients who received thrombolytic therapy for their infarcts either received streptokinase or APSAC, and four patients received tPA, of which a very limited supply was available.

1. The initial part of the study was therefore designed to assess the efficacy of the thrombolytic drugs we were using, in terms of infarct related artery patency, morbidity and mortality.

2. Strong evidence is available that indicates a substantial benefit to be derived from the use of intravenous beta-blockers in acute myocardial infarction. In order to determine the feasibility of combining beta-blockers with thrombolytic therapy, at the finish of the infusion of the thrombolytic agent all patients were assessed for eligibility to receive intravenous beta-blockers.

3/4. The second part of the study was concerned with the management of the patients post-infarction. The prevailing opinion in the

Cardiac Clinic was that these patients did not require further intervention in terms of mechanical revascularisation unless they exhibited recurrent spontaneous ischaemia or inducible ischaemia, in other words unless they had post infarct angina or a strongly positive stress test on review one month after discharge. This type of conservative approach was in contradistinction to the interventionalists approach throughout most of Europe and the USA, where the policy was to perform PTCA on the infarct related artery as soon as possible. As this was a controversial approach to the management of these patients we thought that angiography should be performed if at all possible in order to determine the range of coronary artery disease, the patency of the infarct related artery, and to determine whether or not the patients with critical anatomy could be detected non-invasively. This last aspect of the study was important as it would mean angiography for all patients as opposed to only those with symptoms or a positive stress test.

Ultimately the final decision as to whether intervention or angiography was indicated, was at the discretion of the attending physician coupled with the wishes of the patient.

Patients were managed according to the protocol outlined overleaf, enrollment commenced on the 1st of January 1988 and ended on 31st of December 1989.

MANAGEMENT PROTOCOL (see flow chart).

ELIGIBILITY FOR THERAPY

All patients presenting to Groote Schuur Hospital Emergency Unit with a diagnosis of acute myocardial infarction were considered to be eligible for treatment with thrombolytic agents provided they fulfilled the entry criteria listed below.

1. Presentation within six hours of onset of symptoms.

2. Age under 70 years.

3. Evidence of acute myocardial infarction on electrocardiogram (ECG) - at least 2 mm of ST segment elevation in two contiguous praecordial leads or in two out of three limb leads.

4. No contraindications to the administration of thrombolytic agents. Contraindications were:

   a) A history suggestive of active peptic ulceration or past history of gastrointestinal bleeding.

   b) Previous cerebrovascular accident.

   c) Surgery within the past month, or catheterization of a major vein or artery within the preceding two weeks.

   d) Any bleeding diathesis.

   e) A history of severe atopy.

   f) Previous administration of streptokinase.

g) Evidence of dissecting aortic aneurysm.

h)a. Uncontrolled hypertension defined as a diastolic pressure >110 mmHg with evidence of end organ damage. If no evidence of end organ damage was present and the diastolic pressure responded to 5-10mg of sublingual nifedipine, thrombolytic therapy was administered.

b. Systolic hypotension (<90 mmHg).

i) Pregnancy.

All patients fulfilling the entry criteria were then given a thrombolytic agent (1.5-1.8 million units of intravenous streptokinase, 30 units of APSAC or 100mgs of tPA). Premedication with 100 mgms of intravenous hydrocortisone was given if possible.

150 mgs of oral acetyl salicylic acid (aspirin) were then given to each patient as soon as possible and continued thereafter in a dose of 150 mgs daily.

When the infusion of the thrombolytic agent had finished each patient was considered a candidate to receive intravenous beta-blockers. Contraindications to this were considered to be:

a) Clinical evidence of left ventricular dysfunction including moist crepitations heard half way up the posterior lung fields, the presence of a gallop rhythm, or radiographic evidence of pulmonary oedema.

b) Extreme sinus bradycardia with a ventricular rate of less than 50 beats per minute, or first, second or third degree atrioventricular block.

c) Systolic blood pressure less than 90 mmHg.

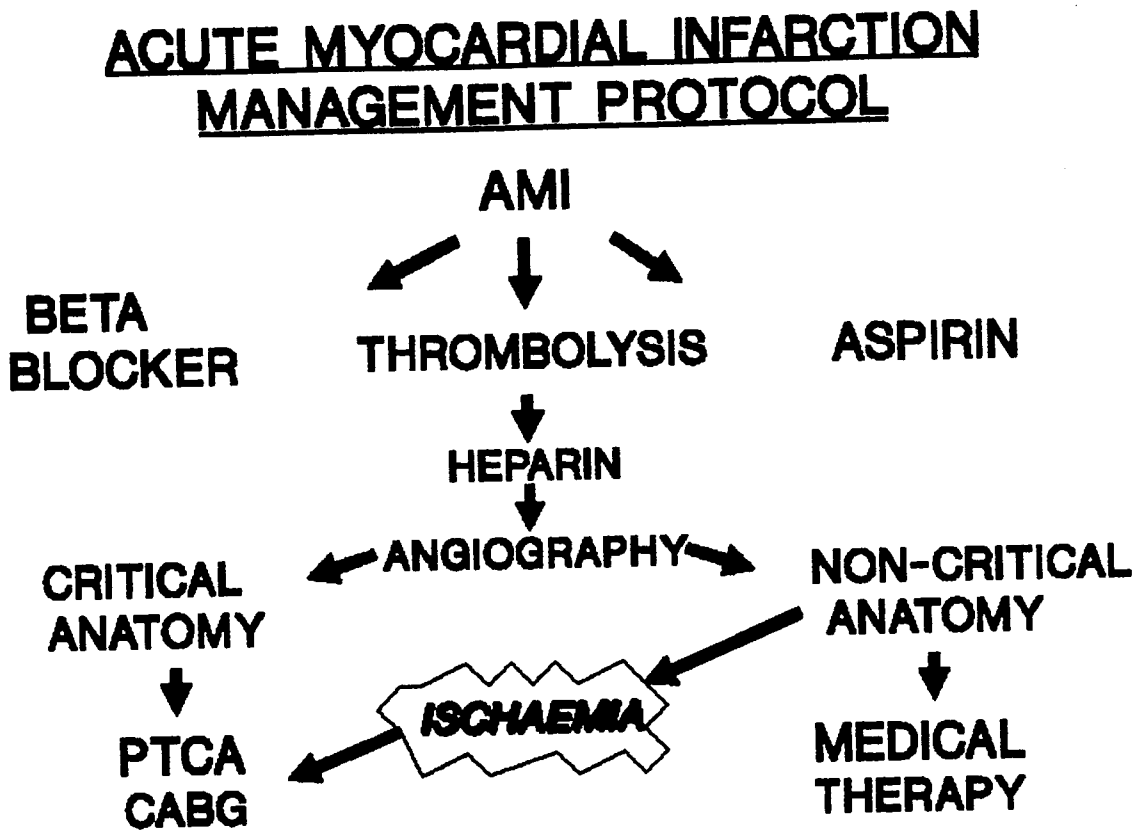
d) A past history of asthma or severe atopy.

e) Oral administration of a beta-blocker within the previous 12 hours.

Provided there were no contraindications each patient was then given either 15 mgs of intravenous metoprolol or 5 mgs of intravenous atenolol slowly over a five minute period with careful monitoring of vital signs. Three hours after the intravenous dose an oral dose of either 50 mgs of metoprolol or atenolol was given and then a daily dosage commenced.

In the case of patients who were entered into the APSAC study each patient was given 30 units of intravenous APSAC over a 15 minute period and then were considered eligible to receive beta-blockers.

In addition to the APSAC study tPA was available for use in 4 patients. These patients received tPA in a dose of 10 mg immediately followed by 90 mg as an infusion over 3 hours.



At this point in the study protocol the management of the patients receiving APSAC and tPA differed from those receiving streptokinase.

The APSAC study was designed to assess the safety profile and the efficacy of the drug in terms of the patency of the infarct related artery at 90 minutes post infusion and at 24-hours. Therefore those patients who received APSAC underwent angiography at 90 minutes and again at 24-hours. The patients who received streptokinase underwent routine angiography at approximately 72 hours or earlier if the clinical condition of the patient indicated that intervention was

necessary. The 4 patients who were treated with tPA also underwent angiography at 90 minutes.

At the time of angiography if the patient was found to have either left mainstem disease or triple vessel coronary artery disease with impaired left ventricular function, they were considered to have a life-threatening condition and as such offered immediate coronary artery bypass grafting if the vessels were considered suitable.

Two hours post infusion of thrombolytic drug a heparin infusion was commenced. Twenty-five thousand units of heparin were given over a 24-hour period without monitoring the activated thromboplastin time. The infusion was continued until angiography was performed or until the patient was mobilized.

All other drugs administered were given at the discretion of the attending physician with routine nursing care and close monitoring of vital signs.

Once the patients were considered to be stable they were transferred for mobilisation and further management to a general medical ward. Prior to discharge, or at follow-up at one month, all the patients underwent a submaximal exercise stress test.

The exercise stress test was performed in the Cardiac Clinic Stress Test Room under the supervision of one of the medical staff. The test was performed with the patients on therapy and conducted according to the Bruce protocol. The test was continued until 70% of the patient's maximal heart rate was achieved or until symptoms of ischaemia

developed. A positive stress test was defined as the development of at least 2 mm of planar ST segment depression in at least two contiguous praecordial leads or in two out of three limb leads, with or without the development of ischaemic symptoms.

If the stress test was positive or if the patient had recurrent angina then the angiographic anatomy was reviewed and revascularisation, (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty), was offered to the patient if considered suitable.

All the patients were followed routinely in the Cardiac Clinic at Groote Schuur Hospital until they were considered to be stable.

Informed consent was obtained from all the patients and they were kept informed of the results of their tests. The implications and complications of all intervention were fully explained. The study was approved by the Ethics Committee of the University of Cape Town.

SECTION 3

RESULTS

During the two year period of enrollment between January 1988 and December 1989, 131 patients presenting with acute myocardial infarction were considered to be suitable for thrombolytic therapy. This number represents approximately 25% of all patients presenting with acute myocardial infarction.

The mean age of the patients was 52.9 (± 9.6) years. One hundred and four of them were men. The average time from onset of symptoms to treatment with thrombolytic therapy was 3 (±1.5) hours. There were 72 anterior infarcts and 59 inferior infarcts.

Ninety-four patients received streptokinase, 33 patients received APSAC and 4 patients received tPA.

All 131 patients received 150 mg of oral aspirin as soon as possible. One hundred and eleven patients (84.7%) also received intravenous followed by oral beta-blockers. The reasons for withholding beta-blockers, the side-effects, the necessity for additional therapy, and the long-term follow-up of these patients will be extensively discussed in a later section.

ANGIOGRAPHY

One hundred and seventeen patients in total underwent angiography. The patients treated with APSAC underwent angiography at 90 minutes post infusion and again at 24-hours. In terms of reperfusion and patency rates the result of angiography at 24-hours are used, and in the case of the patients treated with tPA, the patency at 90 minutes

is used. All other patients underwent angiography at approximately 72 hours unless there were clinical indications to intervene earlier.

The reasons for not performing angiography are shown in Table 1. Table 2 shows the number of patients found to have mainstem disease, triple, double, and single vessel disease.

TABLE 1

NO ANGIOGRAPHY

INDICATION	NUMBER
CEREBROVASCULAR ACCIDENT	1
GIT BLEED	1
SEVERE PVD	1
REFUSED	3
NON INFARCT	1
DEATH	6
KNOWN TVD (INOPERABLE)	1
TOTAL	14

TABLE 2

ANGIOGRAPHIC ANATOMY

	MAINSTEM	TRIPLE VESSEL	DOUBLE VESSEL	SINGLE	NO CAD
GOOD LV FUNCTION	5	13	21	43	6
POOR LV FUNCTION	0	17	4	8	0
TOTAL	5	30	25	51	6
PERCENT	3.8	22.9	19	38.9	4.5

PATENCY AND REPERFUSION

All patency rates were assessed according to the TIMI criteria. Definitions of perfusion according to the TIMI Trial.

Grade 0 (no perfusion): there is no antegrade flow beyond the point of occlusion.

Grade 1 (penetration without perfusion): the contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.

Grade 2 (partial perfusion): the contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel - e.g.

the opposite coronary artery or the coronary bed proximal to the obstruction.

Grade 3 (complete perfusion): antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same territory.

In the 117 patients who underwent angiography the infarct related artery was identified in all (100%). This artery was considered to be patent (TIMI grade 2 and 3) in 95 (81.2%).

SUBGROUP ANALYSIS

Patency rate with streptokinase - 81 patients who received streptokinase underwent angiography. The infarct related artery was considered to be patent in 65 (80%).

Patency rate with APSAC - 32 of the patients who received APSAC underwent angiography. The infarct related artery was considered to be patent in 27 (84%).

Patency rate with tPA - 4 patients received tPA and all underwent angiography. The infarct related artery was considered to be patent in 3 (75%).

As the numbers are very small it is not possible to compare the patency rates with any degree of statistical significance. (Nor was this an aim of this evaluation).

REVASCULARISATION PROCEDURES

Mechanical revascularisation was considered necessary in two different groups of patients.

A. Those with life-threatening anatomy i.e. mainstem disease of the left coronary artery or triple vessel disease with impaired left ventricular function.

B. Those with severe symptomatic or inducible ischaemia.

Patients who underwent revascularisation procedures during their in-hospital stay were considered to have undergone an urgent procedure whilst those who were readmitted electively were considered to have undergone an elective procedure.

Table 3 indicates the number of cases requiring mechanical revascularisation both as an emergency and as an elective procedure.

TABLE 3

REVASCULARISATION PROCEDURES

	PTCA	CABG	TOTAL
URGENT	13	9	22
ELECTIVE	7	11	18
TOTAL	20	20	40

SUBGROUP ANALYSIS

Table 4 illustrates the number of patients requiring revascularisation and the corresponding coronary anatomy for the urgent and for the elective procedures.

In total 39 (29.7%) patients underwent 40 procedures, indicating that approximately 30% of patients treated for acute myocardial infarction with thrombolytic therapy, aspirin, heparin and intravenous beta-blockade will require mechanical revascularisation on the above criteria.

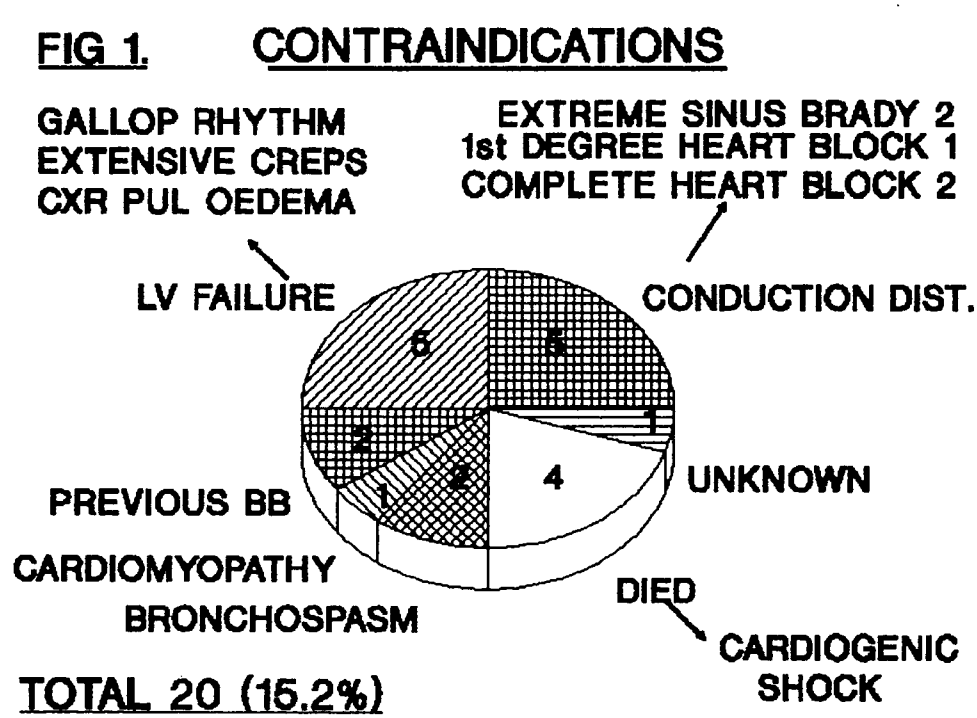
TABLE 4

REVASCULARISATION PROCEDURES AND CORONARY ANATOMY

PROCEDURES		MAINSTEM	TVD	DVD	SVD
PTCA	URGENT	0	0	4	9
	ELECTIVE	0	2	0	5
CABG	URGENT	5	2	1	1 (FAILED PTCA)
	ELECTIVE	0	7	4	0

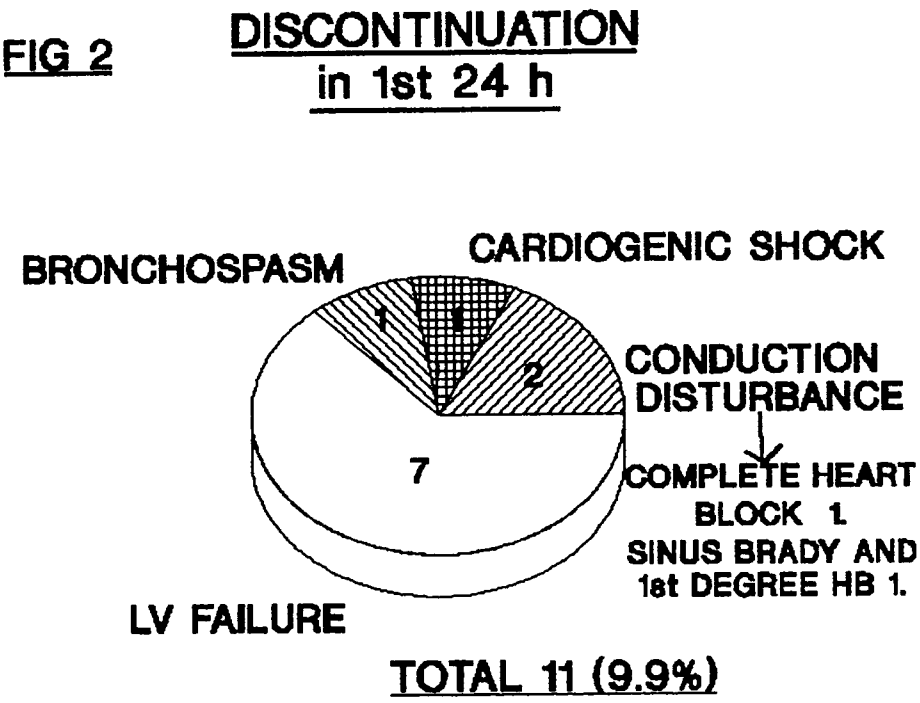
THE SIDE-EFFECTS AND COMPLICATIONS OF INTRAVENOUS BETA-ADRENERGIC BLOCKADE

Of the original 131 patients presenting with acute myocardial infarction and treated with thrombolytic therapy 111 (84.7%) also received intravenous followed by oral beta-blockers. The reasons for withholding the drug are shown in Figure 4.



Eleven (9.9%) had the beta-blocker discontinued in the following 24-hour period as indicated in Figure 5.

FIG 2



A further 8 (7.2%) had the drug discontinued prior to their discharge and additional therapy was required in 5 (4.5%). During the follow-up period of 2 years, mean follow-up period 13.3 (± 6) months 9 patients had their beta-blocker discontinued either because of side-effects or after complete mechanical revascularisation (Table 5).

TABLE 5

REASON FOR DISCONTINUATION	1ST 24-HOURS	DAY 1-D/C	AFTER D/C	TOTAL
Left ventricular failure	7	6	4	17
Conduction* disturbance	2	-	-	2
Cardiogenic shock	1	-	-	1
Bronchospasm	1	-	-	1
After mechanical revascularization	-	2	4	6
Non-compliance	-	-	1	1
				27

* 1 Patient with complete heart block
1 Patient with 1^{o} AV block and sinus bradycardia

INFARCT EXTENSION, REINFARCTION AND MORTALITY

INFARCT EXTENSION

Infarct extension was arbitrarily defined as occurring after the initial 24-hour period and prior to hospital discharge. The diagnosis was made on clinical symptoms, new ECG changes and a fresh CPK rise (MB fraction positive). Three patients had evidence of infarct extension, one of which occurred after a gastrointestinal bleed caused profound hypotension.

REINFARCTION

There were 3 reinfarctions in the follow-up period. One patient had a 95% proximal left anterior descending artery lesion and reinfarcted one month later after a negative stress test, on treatment with a beta-blocker and aspirin. A second patient received APSAC for an acute anterior infarct. Angiography showed a patent infarct related vessel with a 95% proximal lesion and a well contracting left ventricle. He was then lost to follow-up and presented again 13 months later with a further anterior infarct treated on this occasion with streptokinase. The third patient had an inferior infarct. Angiography showed a 95% mid right coronary artery lesion with preserved left ventricular function. He was discharged on atenolol and aspirin after a negative stress test and reinfarcted in the same territory two weeks later.

MORTALITY

There were 4 deaths due to cardiogenic shock in the immediate 24-hour period following admission. None of the patients had received intravenous beta-blockers. A further 2 patients died suddenly during the hospital admission and a further patient during coronary artery bypass grafting (CABG) performed urgently for symptomatic mainstem disease. The early mortality rate was thus 5.3%.

During the follow-up period one further patient died at CABG for symptomatic triple vessel disease and impaired left ventricular function and 5 patients died suddenly at home. One patient was awaiting cardiac transplantation for inoperable coronary artery disease, 1 patient had a poorly contracting left ventricle and inoperable triple vessel disease and was not considered suitable for transplant. One patient had double vessel disease and an occluded culprit vessel and a poorly contracting left ventricle and 2 patients had single vessel disease with patent vessels but a poorly contracting left ventricle. Thus the late mortality was 9.9% at 2 years with a mean follow-up time of 13.3 months. (Fig 6)

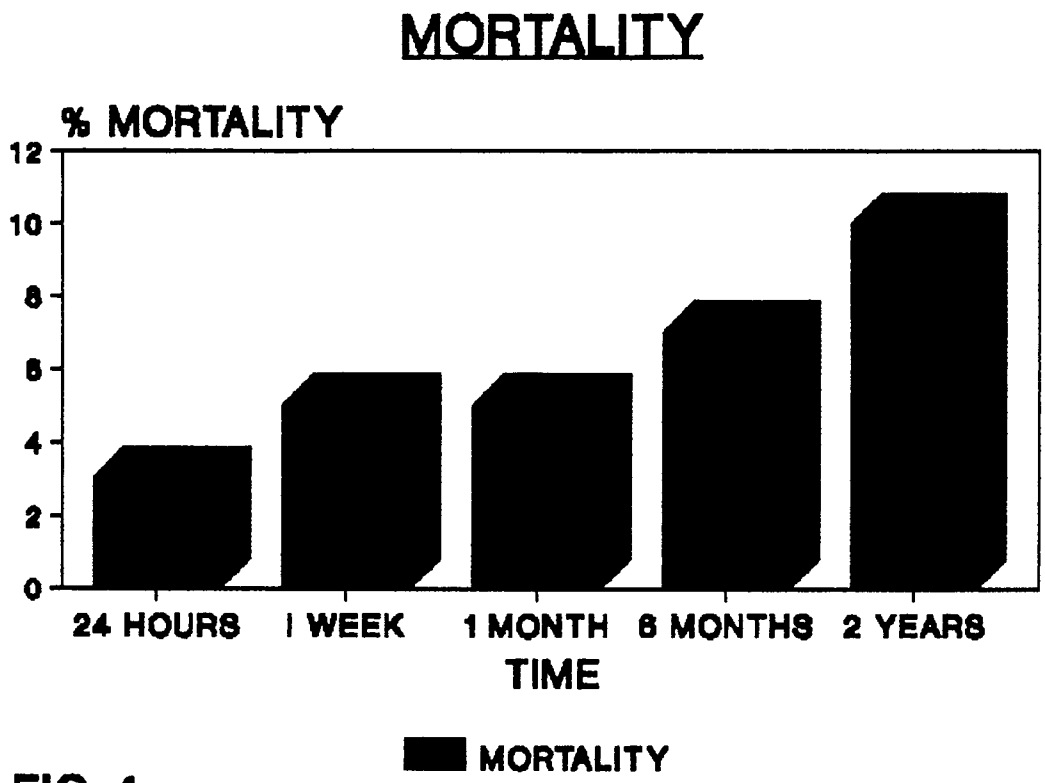


FIG 4

COMPLICATIONS

Cerebrovascular accident (CVA)

Two patients developed symptoms and signs of cerebrovascular accidents. CT scans were performed on both and evidence of infarction rather than haemorrhage was found. It is therefore likely that the CVA's were due to arterial thromboembolism rather then intracerebral haemorrhage.

Gastrointestinal bleeding

Four patients had GIT bleeding. One had a frank haematemesis several hours after admission, became hypotensive and extended his infarct. He was successfully resuscitated without the need for surgery. Two

patients had coffee ground vomitus which responded to antacids and a fourth patient developed melaena for which no other cause could be found.

Local access sites and other

Four patients developed spontaneous intramuscular haematomas and a further two had haematomas of the arterial access sites; all resolved without further problems.

Allergic reactions

Three cases of hypotension were documented all responding rapidly to fluids. Two patients who received APSAC developed a serum sickness type illness some 10 days after the drug was given.

SECTION 4

DISCUSSION

MORTALITY

Thrombolytic therapy, whether streptokinase, tPA or APSAC, has been conclusively shown to reduce infarct size, salvage myocardium and substantially reduce mortality in acute myocardial infarction. One hundred and thirty one consecutive patients were treated at our institution with thrombolytic therapy over a 2 year period, the majority of these received streptokinase. Angiography was performed in almost 90% of the patients in order to delineate coronary anatomy. The infarct related artery was found to be patent in 81.2% of the cases undergoing angiography. This figure is comparable with that noted in several studies.

It would appear logical that the earlier the artery becomes patent and the myocardium reperfused, the more myocardium will remain viable and so systolic left ventricular function as measured by the ejection fraction should be preserved to a greater extent. tPA certainly opens more arteries earlier than streptokinase; 80% reperfusion at 90 mins versus 55% for streptokinase. However in controlled trials the left ventricular ejection fraction in the tPA treated patients was no different from that of the streptokinase group.[50,51] In our cohort of patients the ejection fraction was only measured in those with large infarcts clinically. Nevertheless, the results of other trials in part justify the continued use of streptokinase in our institution, streptokinase being ten times cheaper than tPA.

The more recently completed and just published GISSI II trial* compared tPA with streptokinase looking at mortality and left ventricular function as the primary end points. The results have confirmed no difference between the two groups on comparing ejection fraction or mortality, again affirming that our continued use of streptokinase is not only economical but ethical.

Mortality has been one of the primary end points of most of the major clinical trials. When comparing streptokinase against placebo all clinical trials have demonstrated a significant reduction in in-hospital mortality which has been maintained at one year.(36,37,52,53) Table 6 shows the mortality rates for the major trials of streptokinase and the GSH experience although we do not have a control group for comparison.

TABLE 6

MORTALITY IN AMI WITH THROMBOLYTIC THERAPY

TRIAL	DRUG	MORTALITY		FOLLOW-UP
		Rx%	Cont%	
GISSI 1 [37] 1986	SK	10.7	13	IN HOSPITAL
ISAM [53] 1986	SK	6.3	7.1	21 DAYS
W.W. [72] 1988	SK	6.3	9.6	14 DAYS
AIMS [74] 1988	APSAC	6.4	12.2	30 DAYS
ISIS 2 [36] 1988	SK	8.9	11.7	5 WEEKS
ASSET [73] 1988	rtPA	7.2	9.8	4 WEEKS
GSH	SK	5.2	--	2 WEEKS

Rx% = Percentage of treatment group.

Cont% = Percentage of control group.

Figure 7 shows the survival rates for GSH versus two of the larger trials that quote one year survival. The results show a favorable comparison between the GSH treatment protocol and the two other major trials.

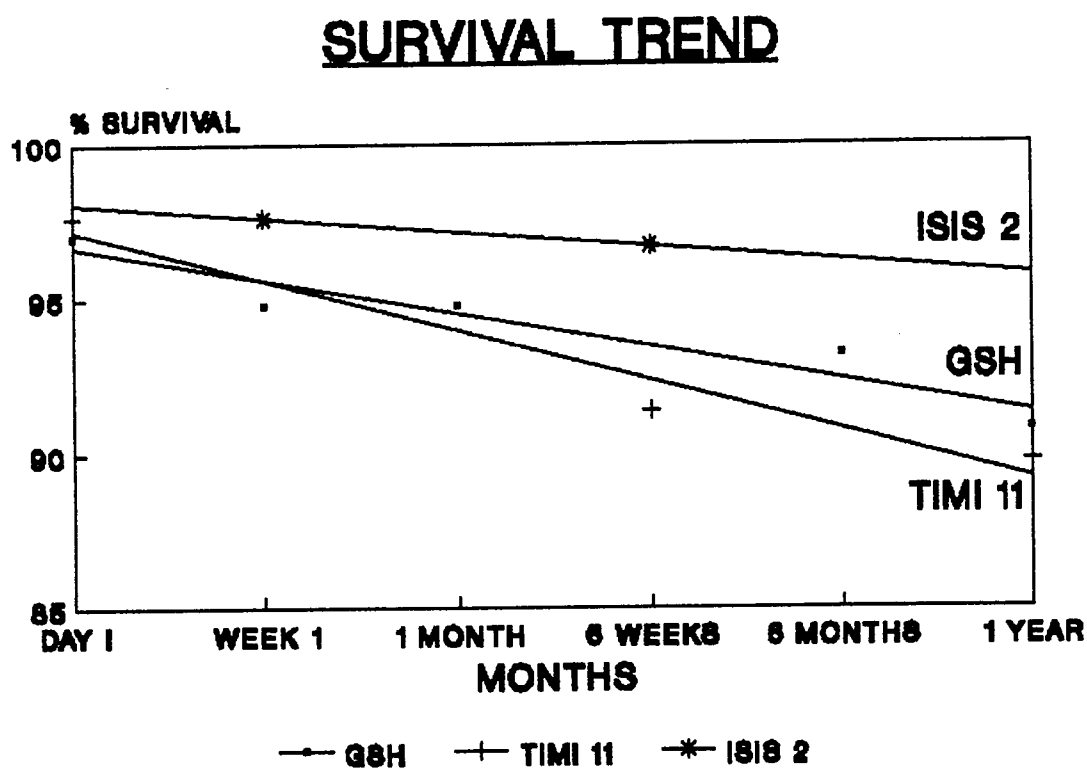


FIG.7

The ISIS 1 trial of intravenous beta-blockade in acute myocardial infarction showed a significant reduction in mortality especially on the first day of admission, that was maintained at 1 year. Subgroup analysis of some of those patients who died during the first day indicated that the most reduction in mortality was in the group of patients who died of acute cardiac rupture.(54) This finding was

confirmed in the MIAMI trial of early intravenous beta-blockade in acute myocardial infarction.(55) It is not known whether the incidence of cardiac rupture is proportional to infarct size but it is proportional to the degree of hypertension. Beta-adrenergic blockade reduces the stress on acutely ischaemic myocardium by reducing the rate and force of contraction, and thus secondarily reducing the rate of rupture. Subgroup analysis of the GISSI 1 trial in which beta-blockers were not given routinely indicates that most of the mortality reduction occurred after the first 24-hours. A large number of deaths, 50%, in the first 24-hours, were attributed to cardiac rupture and it may be that if this is the case the effects of thrombolytic therapy and intravenous beta-blockers may be additive. Subgroup analysis of the in-hospital mortality in our study shows that although there were 4 deaths in the first 24-hours, all of these were in the first hour of admission and none of the patients received intravenous beta-adrenergic blockade, although one was on an oral beta-blocker. In other words none of the patients who were treated with intravenous thrombolytic therapy and then intravenous beta-blockers died in the first 24-hours.

INFARCT EXTENSION, REINFARCTION AND RECURRENT EVENTS

The TIMI IIB trial(49) showed that there was a reduction in recurrent ischaemic events at 6 days in the immediate (intravenous) versus delayed (oral) beta-blocker treated groups, (15.4% v 21.2% i). In our group of patients who received intravenous beta-blockers 17 (15.3%) had recurrent ischaemic events in the first 6 days which according to our protocol, required intervention in the form of mechanical

revascularisation. The incidence of infarct extension and reinfarction at 42 days in the TIMI II trial was 7.3%, and our long-term infarct extension and reinfarction rates are 4.5% (6 patients).

MORBIDITY ASSOCIATED WITH INTRAVENOUS BETA-BLOCKADE

Early clinical trials and latterly experimental canine models combined with thrombolytic therapy,[56,57,58] have provided evidence in favour of the use of intravenous beta-blockers in acute myocardial infarction. Despite this their use has been limited in patients receiving thrombolytic therapy mainly due to doubts that have arisen about their safety. Beta-blockers are of course both negatively inotropic and chronotropic and have effects not only on sinus node function but also on atrio-ventricular node function. During the course of acute myocardial infarction death from acute "pump" failure or heart block is of considerable concern and may be aggravated or precipitated by beta-blockers. The incidence of these side-effects is not well documented in many of the early clinical trials.

Yusuf et al in an overview of randomised beta-blocker trials[59] found that most series reported an increase in the incidence of sinus bradycardia and hypotension. Few however reported the need for atropine and no documented excess of atrio-ventricular block was noted. In our study only 2 patients developed atrio-ventricular node conduction problems both of whom had acute inferior infarctions, a condition well known to predispose to sinus bradycardia and atrio-ventricular block. Neither of the patients required anything further than discontinuation of the beta-blocker. Again Yusuf et al found that some trials reported an excess of left ventricular failure that was not statistically significant in short-term trials (17.5% in treatment groups v. 16.8% in controls). Beta-blockers were discontinued in 7(6.3%) of our 111 patients treated in the first 24-hours due to left ventricular failure. A further 6 (5.4%) had their

beta-blocker stopped because of persistent left ventricular failure during their hospital admission, whilst a further 4 (3.6%) had their beta-blocker stopped because of left ventricular failure in the follow-up period, at a variable length of time post discharge. In total therefore 17 (15.3%) of all patients receiving intravenous then oral beta-blockers had the drug discontinued because of persistent left ventricular failure. Additionally 3 patients required further therapy, in order to continue with the beta-blocker, in the form of diuretics or angiotensin converting enzyme inhibitors; 2 more patients were commenced on these drugs in the follow up period. In total therefore almost 20% of the treated patients either had to have the beta-blocker stopped because of left ventricular failure or required additional anti-failure therapy.

The development of cardiogenic shock is of major concern in acute myocardial infarction because it still carries a distressingly high mortality rate of approximately 80%. As mentioned before beta-blockers are negatively inotropic and may have a tendency to precipitate cardiogenic shock. This possibility has not however been reported in clinical trials, and indeed in support of this data only one of our patients developed cardiogenic shock post-administration of the beta-blocker. He was subsequently shown to have severe coronary artery disease and markedly impaired left ventricular function and died 13 months later awaiting heart transplantation.

In our hands it would seem that the addition of intravenous beta-blockers to the treatment regime of thrombolytic therapy and aspirin is feasible in approximately 80% of the patients eligible to receive

thrombolytic therapy for acute myocardial infarction. Furthermore, only 20% of the treated patients may need to either have the drug discontinued because of side-effects, the most common of these being left ventricular dysfunction, or may need additional anti-failure therapy. Importantly, there were no major catastrophic consequences of beta-blocker in these patients. There are also encouraging signs that infarct extension, reinfarction and recurrent ischaemic event rates may be reduced by the use of beta-blockers, and large scale clinical trials seem to be indicated to evaluate the effects of combined intravenous beta-blockers and thrombolytic therapy on 24-hour mortality.

ROUTINE CORONARY ANGIOGRAPHY FOR ALL?

Concern has arisen with the use of thrombolytic agents as to whether or not non-invasive tests are sensitive enough to identify those patients who are at high risk of reinfarction both non-fatal and fatal. Mainstem disease of the left coronary artery and triple vessel disease with impaired left ventricular function have been associated with a poor prognosis and improved survival has been demonstrated after coronary artery bypass grafting in these particular patients.[60] Early post-infarction exercise stress testing has been shown to be safe and several studies have indicated that the patients at highest risk post-infarction may be identified but that the test is more sensitive in identifying the patients at very low risk.[61,62]

The prognostic information to be gained from early post-infarction stress testing may thus however have its greatest value in predicting which patients are at least risk of subsequent events.[63,64]

Left ventricular dysfunction and myocardial ischaemia are the primary pathophysiological processes underlying functional capacity and prognosis post-infarction. Resting left ventricular dysfunction is relatively easy to detect post-infarction, both clinically and with use of non-invasive tests such as echocardiography and radionuclide ventriculography. In the absence of resting left ventricular dysfunction a low effort stress test exercise capacity may reflect exercise induced or ischaemic left ventricular dysfunction. In these instances the workload capacity is inversely related to the extent and depth of exercise induced ischaemic ST segment depression. Exercise induced ischaemic ST segment depression in leads outside the infarct

zone is associated with up to a 20 fold increase in the risk of subsequent cardiac events. The magnitude of the ST segment depression and the heart rate and workload at the time of its appearance are important in determining the prognostic significance. In several recent studies performed on patients without clinically evident left ventricular failure only ST segment depression of more than 2 mm occurring at a heart rate of less than 135 had prognostic significance.(65,66,67)

Coronary artery obstructive anatomy and left ventricular dysfunction are the major determinants in prognosis post-infarction. In several angiographic studies performed post-infarction, coronary anatomy was predictive of recurrent events with the worst prognosis in those patients with triple vessel coronary artery disease. However within the anatomically defined subsets of single, double, and triple vessel coronary artery disease mortality was best predicted by evidence of left ventricular dysfunction during the in-hospital stay.(68,69,70)

Obstructive coronary artery anatomy in our cohort of patients is very similar in distribution to other studies, performed on unselected patients. Five patients had lesions of the mainstem of the left coronary artery and all 5 of them were symptomatic early post-infarction with recurrent ischaemia. The overwhelming majority of patients had single vessel disease. In the group of patients with triple vessel disease with or without impaired left ventricular function, identified angiographically, 28 of the 30 patients either had clinically evident left ventricular dysfunction, recurrent angina or a positive effort stress test. A single patient with triple vessel

coronary disease and a well contracting ventricle was discharged after a negative stress test and reinfarcted one month later in the same territory; one further patient with triple vessel disease moved to another city and has been lost to follow-up.

It would therefore appear that the patients whose prognoses could be improved significantly by revascularisation declare themselves early on either by clinically evident left ventricular failure or by severe recurrent symptomatic or inducible ischaemia. This in effect means that coronary angiography could be reserved for those patients with clear indications for mechanical revascularisation.

MECHANICAL REVASCULARISATION PROCEDURES: CONSERVATIVE VERSUS AGGRESSIVE APPROACH

The pro's and con's of intervention on all residual intracoronary arterial lesions as opposed to intervention in only those responsible for demonstrable ischaemia, have been discussed in an earlier section. It would appear from the results of our study that intervention, only indicated where ischaemia is demonstrable or manifest as angina, becomes necessary on these criteria in only 30% of all patients treated with thrombolytic therapy and aspirin. The in-hospital mortality rate is comparable to those of the major institutions overseas and supports the view based on the currently available data, that conservative management is as good as aggressive intervention. Long-term mortality rates are equally impressive, following the expected natural attrition rate found in most population groups, again supporting the conservative approach and helping to allay fears that the conservatively treated patients would have a higher incidence of reinfarction and sudden death.

What effect will this conservative approach have on the cost of treatment of myocardial infarction? Certainly, not being obliged to intervene on all patients will mean an enormous saving both in terms of money and time and will be appreciated mostly by centres outside the USA, the majority of which do not have the operator expertise in angioplasty, either urgent or elective, that the major centres in the USA have.

However, another aspect of the study that is somewhat disquieting is to analyse the cost effect of intervening in 30% of the patients. An analysis performed by Clinical Epidemiologists in Canada based on

CONCLUSIONS

The study was designed to assess the efficacy of the regime for the treatment of acute myocardial infarction in use at the Cardiac Clinic at Groote Schuur Hospital. The relatively small numbers of patients presenting to the Cardiac Clinic with acute infarctions meant that a controlled trial reaching statistically significant figures was precluded and therefore we performed an observational study. The morbidity and mortality figures are very comparable to those of the major institutions overseas indicating that our conservative approach to these patients post-infarction is acceptable.

However, although results of our evaluation are in keeping with other studies and show that there is no compelling need to perform angiography on all patients and angioplasty on those with significant lesions because there is no major overall benefit, the 3 patients who re-infarcted leave persistent doubts about the management of individual patients.

Additionally we have seen that the concomitant administration of intravenous beta-blockers is both feasible and safe, with some suggestion that 24-hour mortality may be reduced together with the recurrent event rate, and it would appear that future controlled trials of beta-blockers and thrombolytic therapy in combination, are indicated.

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