Repeated full dose thrombolysis in patients hospitalised with myocardial infarction: safety and efficacy.

David Ian Kettles
(KTTDAV002)
University of Cape Town

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Supervisor: Professor P Commerford

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SUMMARY

The treatment and outcome of myocardial infarction has been revolutionised by the demonstration that thrombolytic drugs can open the infarct-related artery, salvage ischaemic myocardium, preserve left ventricular function and save lives. However, thrombolytic drugs are not uniformly effective in securing or maintaining patency of the infarct-related artery.

There are two groups of infarct patients whose clinical situation demands consideration of additional reperfusion therapies. In some the infarct-related artery has not opened (reperfused) after an initial dose of thrombolytic (failed thrombolysis). In others, early reocclusion of the infarct-related artery (reinfarction) threatens the gains obtained by initial sucessful reperfusion. Despite little evidence that readministration of thrombolysis is either safe or effective, both these groups of patients have frequently been treated by a second dose of thrombolytic drug.

The paucity of data available to guide therapy in these common clinical situations and a clinical concern that there may frequently be little to gain with readministration of thrombolysis prompted this study. A retrospective review of all patients treated with more than one dose of thrombolytic therapy in a large United Kingdom District General Hospital over a period of eleven years was performed. Fifty-two patients were identified, of whom 49 had received relysis for early reinfarction. Notwithstanding the limitations of this retrospective study, interesting data emerged. No excess of haemorrhage or stroke could be documented for second thrombolysis. However, there was an apparent excess of mechanical infarct complications,

particularly cardiac rupture. Possible explanations for this excess, and the implications for clinical practice are discussed.

CHAPTER ONE: BACKGROUND

Introduction

" A man aged 55, supposedly in good health, was seized an hour after a moderately full meal with severe pain in the lower precordial region. He was nauseated and, believing that something he had just eaten had disagreed with him, he induced vomiting by tickling his throat. The pain continued, however, and his physician was called, who found him cold, nauseated, with small rapid pulse, and suffering extreme pain."

" The seizure is described by patients who have had previous experience with angina as of unusual severity, and the pain persists much longer. In some instances there has been no definite radiation of the pain, as to the neck or left arm, though this may have been a feature of other anginal attacks and the pain....may be referred to the lower sternal region or definitely to the upper abdomen. Cases with little or no pain have been described.... Nausea and vomiting, with belching of gas, are common.... Ashy countenance, cold sweat and feeble pulse complete the picture of collapse."

The above classical descriptions from "Clinical features of sudden obstruction of the coronary arteries"[1], a landmark 1912 article written by James B Herrick, mark the beginnings of decades of investigation into the entity of acute myocardial infarction (AMI). What follows in the same article gives cause to reflect on what has been accomplished: "Death is the result in nearly all of these cases.... yet there is no intrinsic reason why some patients with obstruction of even large branches of the coronary artery may not recover. Experimental animals sometimes do."

Herrick concluded his discussion and speculations with a prophetic statement: "The hope for the damaged myocardium lies in the direction of securing a supply of

blood…so as to restore so far as possible its functional integrity." Although he was referring to collateral vessels, he could not have known that his insights predicted an area of research that would be pursued into a new millennium.

Early myocardial infarction research

In 1941 Blumgart et al.[2] demonstrated (in dogs) that single coronary artery occlusion for less than 25 minutes resulted in no gross changes of infarction in the myocardium. However, there was macroscopic and histological evidence of infarction in the hearts of most dogs whose coronaries had been occluded for between 25 and 45 minutes. The extent of this infarction was in direct proportion to the duration of the arterial occlusion. Years later, Maroko and Braunwald [3], reviewing their own and others work in this field could state that reperfusing a coronary artery after three hours caused an abrupt fall in ST-segment elevation, and histological appearances showed preservation of extensive portions of myocardium otherwise expected to have lost viability. They concluded that myocardial tissue perfused by a vessel that becomes occluded does not necessarily have to become irreversibly damaged.

The relevance of these and many similar animal studies to human myocardial infarction was not entirely clear until the pathophysiological basis of the condition was unequivocally demonstrated. De Wood and colleagues outlined the problem: post-mortem studies had reported the incidence of thrombosis in infarct-related coronary arteries at anything between 21 and 93% [4]. Thrombus could frequently be found in coronary arteries post mortem: was this a pointer to the origin of the fatal myocardial infarct, or a post mortem artefact? These authors overcame traditional reluctance to perform coronary angiography during the first hours of acute myocardial infarction. They demonstrated total coronary occlusion in 110 of 126 patients studied within four hours of symptom onset. The prevalence of occlusion decreased as time

from onset of symptoms increased. Overall, 69.8% of 322 patients had angiographic evidence of thrombus related to their acute infarct.

Most patients who presented with ST elevation infarction thus had thrombotic occlusion of the infarct-related artery. Although speculation about the role of spasm continued, the unequivocal importance of thrombosis was established.

The foundations had been laid for modern management of myocardial infarction. The critical importance of a patent as opposed to an occluded infarct-related artery became accepted, and ultimately the 'open artery hypothesis'[5] could be formulated. This theory holds that early reperfusion of the infarct-related artery results in myocardial salvage. When an artery is opened, muscle is reperfused and thus salvaged. Consequently left ventricular function is preserved, and improved survival results.

The evolution of infarct management: thrombolysis

Before 1980 hospital management of acute myocardial infarction was centred on drug therapy directed at managing arrhythmias, and attempting to limit the size of the evolving infarct [6]. Morbidity and mortality from AMI was high.

Remarkably, the means to change forever the management of myocardial infarction had long been within our grasp! The use of intravenous thrombolysis in acute myocardial infarction had been described in 1958 [7]. Numerous small studies had followed this initial publication. In 1992 Lau et al [8] demonstrated by meta-analysis that a consistent, statistically significant reduction in total mortality in patients treated with thrombolysis was potentially demonstrable in 1973! Only in the late seventies however, was there a reawakening of interest in thrombolysis - initially an intra-coronary therapy, and subsequently administered intravenously [9]. Since that time thrombolysis for acute myocardial infarction has become one of the most extensively

investigated areas of clinical medicine, with more than 200 000 patients randomised in clinical trials by 1998 [10].

We have witnessed a management evolution: "from passive acceptance of the presence of coronary occlusion and merely managing its consequences to a strategy of actively attempting to secure reperfusion"[11].

Results of thrombolysis trials

In 1994 the Fibrinolytic Therapy Trialists Collaborative group reviewed nine trials randomising a total of 58 600 patients to fibrinolytic therapy or control [12]. Overall mortality at 35 days in fibrinolytic allocated patients was 9.6%, compared to 11.5% in controls, representing a highly significant 18% proportional reduction in mortality. There was very clear overall benefit in patients presenting with ST elevation or bundle branch block up to at least 12 hours after symptom onset. Twenty to thirty deaths were avoided per 1000 patients treated, with the hazard of an extra 4 strokes per 1000 treated patients. After the publication of multiple confirmatory 'mega-trials' thrombolysis was now clearly established as first-line treatment for many AMI patients.

The focus of research switched to finding new and better thrombolytic agents that opened arteries quickly and then kept them open. White and Van de Werf [10] have described the characteristics of an "ideal" thrombolytic agent. It would result in rapid reperfusion with close to 100% efficacy, could be given as a rapid intravenous bolus (rather than a prolonged infusion), would result in a low rate of intracranial and systemic bleeding, and would be specific for recently formed thrombi. After treatment there would be a low rate of early reocclusion of the infarct-related artery, with sustained long-term patency. The wonder drug would not be antigenic, nor react

with other adjunctive treatments. It would have no other significant side effects, and finally, it would not cost too much.

In a rapidly moving field the search for the ideal thrombolytic evolved into a search for the best combination of drugs to ensure rapid and reliable infarct artery patency. Novel and powerful antiplatelet agents, glycoprotein IIb/IIIa inhibitors, have shown remarkable early promise when used as part of a thrombolytic cocktail. Stand-alone thrombolytic agents restore TIMI 3 flow (normal angiographic perfusion) in approximately 60% of patients treated. Early results from trials of adjunct glycoprotein IIb/IIIa inhibitors combined with full dose or reduced dose thrombolytic therapy (trials include TAMI-8, IMPACT-AMI, TIMI-14, SPEED, GUSTO-IV pilot) have shown improvements in the rate of TIMI 3 flow to a range of 57-79% [13]. Multiple large studies currently in progress will yield further data on this latest development in intravenous thrombolytic regimens.

During the last one hundred years, the clinical entity of myocardial infarction has been described and its pathophysiological mechanisms have been extensively elucidated. Rational effective therapies, including thrombolysis, have been widely applied in its management, with associated dramatic improvements in outcome.

CHAPTER TWO:

LIMITATIONS OF THROMBOLYSIS: MANAGEMENT OPTIONS.

Limitations of thrombolysis

Early and complete restoration of infarct artery flow is the essential goal of myocardial reperfusion therapies [14]. This should ideally be achieved without serious treatment-related complications. However, the limitations of thrombolytic therapy are not limited to potential side effects of systemic administration of the necessary drug. Clot lysis is not uniformly effective: the drug may work partially, or not at all. Flow in the infarct-related artery flow is not always restored to normal. The ruptured atheromatous plaque underlying the acute thrombotic episode in an epicardial artery persists even after dissolution of occlusive coronary thrombus. Even when thrombolysis has been effective in restoring flow, and perhaps particularly in this circumstance, patients remain at substantial risk for future ischaemic events [15].

Failure of initial lysis

In the GUSTO-1 angiographic substudy, TIMI 3 flow (normal angiographic flow) in the infarct-related artery at 90 minutes was achieved in only 31% of patients with streptokinase and 54% of patients with tissue plasminogen activator [14]. A substantial number of treated patients are thus left with a suboptimal result, or perhaps derive no benefit whatsoever from thrombolytic therapy. Since the potential benefits of thrombolysis are related to the restoration of flow [14], these patients have been exposed to the risks of the treatment without significant gain accruing.

In clinical practice, ineffective initial thrombolysis may manifest as persistent chest pain and ST-segment elevation [11], inviting the attending physician to make an immediate decision regarding further reperfusion strategies.

Reocclusion of the infarct-related artery

Once thrombolytic therapy has successfully opened an infarct-related artery, the artery may stay open, or thrombotic occlusion may recur. We would expect the potential benefits of thrombolysis to be reduced in this context. One drawback of thrombolytic therapy for acute myocardial infarction has been an increase in the incidence of recurrent ischaemia after the infarct [16]. Given that with thrombolytic therapy many patients will have their acute infarct 'aborted' by the restoration of flow in the infarct artery, and that more patients will be left with an open artery in the early post-infarct days, this recurrent ischaemia is perhaps not surprising. Only an open artery would be a potential substrate for reocclusion and any associated clinical sequelae.

What perhaps is surprising is that it has been very difficult to correlate symptomatic recurrent ischaemia with the presence of angiographic reocclusion. A coronary angiogram represents flow at a single 'snapshot' in time. By contrast the flow in the infarct related artery might be part of a dynamic process with the vessel opening and closing over time. It is impossible to know whether a vessel has transiently occluded then recanalised [17].

Most likely is that the recurrence of chest pain and ST-segment elevation and reinfarction are frequently indicators of reocclusion [16]. Reocclusion may also be associated with recurrence of anginal symptoms, haemodynamic instability, or death[16, 18]. But many reocclusions – 42% in one study - are asymptomatic [18]. Twenty-eight angiographic studies have shown an incidence of reocclusion of 16 +/- 10%, after successful initial thrombolysis [16]. This incidence varies to some extent depending on the thrombolytic agent studied.

Patients with reocclusion of the infarct related artery fall into a poor prognostic group. They may have more than twice the in-hospital mortality rate of patients whose infarct-related artery remains patent [18]. Reocclusion prevents left ventricular recovery in the infarcted region of the ventricle, and is deleterious for long term ventricular function [16,18,19].

Reocclusion occurs most frequently in the first week after treatment with thrombolytic therapy [16]. Of the subgroup of patients with reocclusion who do manifest with symptoms, some will present during this time period with symptoms suggesting recurrent myocardial ischaemia, associated with repeat elevation of ST-segments on the ECG. This will be the group, similar in this respect to those patients with initially ineffective lysis, who invite a clinical decision regarding further reperfusion therapy. Becker suggested that 3-4% of patients will present with chest pain and recurrent ST elevation within the first 48 hours post lysis, and an additional 1-2% will develop findings of impending infarction between 48 and 72 hours after thrombolytic therapy[15]. In several large thrombolytic trials, clinical reinfarction has occurred in 2.8-4.1% of patients treated with thrombolysis [20-22].

Treatment options: failure of lysis and early reinfarction

Both drug therapies and percutaneous coronary interventions have been used to treat patients with failure of initial lysis or early clinical reinfarction.

Readministration of thrombolysis

Although pharmacological thrombolysis is established as an effective reperfusion strategy for acute myocardial infarction presenting with ST elevation or new bundle branch block, few data are available suggesting that the safety and efficacy of first-dose lysis can be duplicated when patients are re-lysed in these settings. However,

despite the acknowledged paucity of data, rethrombolysis has been recommended in various contexts in the British [11], American [15] and South African literature [23]. The existence of such guidelines reinforces the prevalence of these clinical scenarios.

Percutaneous coronary interventions

Interventional therapies – percutaneous transluminal coronary angioplasty (PTCA) and coronary stenting – have evolved rapidly over the last fifteen years. In the early 1980's percutaneous coronary angioplasty was not technically suited to securing reperfusion in the context of acute myocardial infarction. However, advances in instrumentation, increased operator experience and technical facility and the development of new and safer anti-platelet drug regimens have allowed primary angioplasty with coronary stent implantation to become a first-line treatment for acute myocardial infarction. Although 'rescue' angioplasty and stenting for failure of initial lysis is widely practised there is, as with re-lysis, surprisingly little data supporting what seems to be an inherently logical approach.

The 1994 'RESCUE' study [24] randomised 151 patients with first anterior myocardial infarction and failed thrombolysis to rescue angioplasty or conservative treatment within eight hours of onset of pain. Angioplasty appeared to be useful in preventing death or severe heart failure, and treated patients had an improvement in exercise but not resting ejection fraction. However these results did not achieve statistical significance. In the TIMI 4 trial [25] patients with an occluded infarct-related artery at 90 minutes were treated with rescue- or no rescue PTCA in a non-randomised fashion. Adverse outcomes occurred in 29% of successful rescue PTCA patients, and in 83% of failed rescue PTCA patients. Among all patients who had rescue PTCA, 35% experienced an adverse outcome, compared to a similar 35% in patients not assigned to receive PTCA. Outcomes were clearly better in the patients who had an open

artery at 90 minutes post thrombolysis. The authors concluded that although successful rescue PTCA could restore normal flow, the incidence of adverse events for the strategy of rescue PTCA as a whole was similar to that obtained when no PTCA was undertaken.

In 1998 rescue angioplasty experience from GUSTO-1 was published [26]. 68% of patients receiving an attempted rescue angioplasty attained TIMI 3 flow (normal angiographic flow) in the infarct artery. Again successful PTCA improved outcomes compared to patients managed without PTCA, but the mortality rate after a failed rescue attempt was 30.4%. Crucial to interpreting this data was the fact that five of the seven patients who died after attempted rescue PTCA were in cardiogenic shock before the procedure. The authors concluded that although rescue PTCA is often successful in restoring vessel patency, the patients selected for this procedure are a very high risk group, often in extremis before arriving in the lab!

Recently a French group published a matched comparison of pre-hospital thrombolysis and standby rescue angioplasty with primary angioplasty – in a 'real-life' rather than trial setting [27]. They showed no significant difference in hospital outcomes between these two groups. With the strategy of thrombolysis followed by angiography, with rescue angioplasty if necessary, 91% of patients achieved TIMI-3 flow at an average 113 minutes after thrombolysis, compared to an identical 91% TIMI-3 flow in matched patients treated with primary angioplasty. Rescue angioplasty was successful in 47 of 50 attempts (94%), and the mortality in this cohort of patients with failed initial thrombolysis was only 4%.

The little data available regarding the practice of rescue angioplasty may reflect in part the reluctance of practitioners to randomise patients to any trial where what is considered routine appropriate management may potentially be withheld. I am not

aware of any trial that specifically addresses the role of percutaneous coronary interventions in patients with early in-hospital reinfarction.

Dilemmas for the clinician

Cardiologists have at times tended to adopt new treatment strategies before clear evidence has emerged regarding clinical benefit and long term outcome, particularly with respect to mortality data [28]. There is intrinsic common-sense appeal apparent in choosing to open a closed artery and some data available regarding the efficacy of primary angioplasty and rescue angioplasty. It thus seems unlikely that any possible lack of clear evidence for benefit will curb the use of interventional procedures in treating failures of thrombolysis or early reinfarction. Rather, the lack of widespread 24-hour access to interventional cardiac facilities dictates that medical therapies must continue to be widely used in this group of patients. In both South Africa and the United Kingdom by far the majority of patients with myocardial infarction are treated in hospitals without interventional facilities.

The open artery hypothesis, discussed previously, is widely accepted and understood. The simplistic management corollary is that when heart muscle is infarcting, flow down the infarct-related artery must be restored, and when achieved this will confer substantial prognostic benefit. Doctors involved in the day-to-day management of post infarction patients are acquainted with the efficacy of thrombolysis. In the absence of a strong message to the contrary, it is not surprising to find that safety and efficacy data pertaining to initial infarction with standard dose thrombolysis are assumed to apply equally to scenarios of repeat thrombolysis.

A postal survey of members of the British Cardiac Society actively involved in the management of acute myocardial infarction corroborates this view [29]. Of 290

respondents, 149 (55%) regularly searched for evidence of reperfusion when treating AMI with thrombolysis. Amongst the practitioners who searched for evidence of reperfusion, the management of 'failed thrombolysis' varied. Fifty (34%) would proceed to urgent angioplasty. However, a greater proportion, 55 (37%), would administer a further dose of thrombolytic and 44 (29%) would employ a combination of these two strategies. Interestingly, even among those who had access to on-site cardiac catheterisation facilities, only the minority (46%) would select urgent angiography/angioplasty as treatment of choice.

For the foreseeable future, most eligible AMI patients in the United Kingdom and South Africa will continue to receive thrombolytic drugs as primary therapy for their infarct. Both failures of initial lysis, and presumed early reinfarctions will at times be treated with readministration of thrombolysis. This research project aims to explore this neglected area of clinical practice, with particular attention being paid to the safety and efficacy of readministering thrombolysis during a single hospital admission.

CHAPTER THREE: RESEARCH SETTING, MOTIVATION AND METHODS

The Royal Sussex County Hospital

This United Kingdom District General Hospital is situated in Brighton on the south coast of England. It serves as a local secondary level hospital to a population of some 350 000 people, and offers tertiary services in selected disciplines. It was upgraded to regional Cardiology centre in June 1999. Since that time it has offered full cardiology referral services with the exception of transplantation to a much wider population. Currently five full-time consultants, three specialist registrars, a research registrar, three staff grade cardiologists and numerous specialist technical staff provide tertiary services, assisted by senior house officer and house officer level junior staff, and a research nurse team.

The cardiac department has had on-site diagnostic angiography facilities since 1993 and on-site coronary interventional capability since June 1999. On average 240 patients per annum are thrombolysed for acute myocardial infarction.

Rethrombolysis: little data and a valid concern

In the course of routine practice as clinical and research registrar in this department two observations prompted this project. My attention was drawn to how recurrent chest pain after myocardial infarction was managed differently from how I, with my South African teaching hospital background, would have expected. Thrombolysis was readministered more frequently than I anticipated; angiography with angioplasty as necessary was favoured less often. This practice may have reflected previous status as a non-interventional hospital and the difficulty in that context of gaining access to interventional facilities. Additionally, I reviewed unpublished departmental research pertaining to mechanical complications of myocardial infarction. A local

researcher raised concerns that patients who had been rethrombolysed may be over-represented in a small series of patients with mechanical complications after acute myocardial infarction. A review of the cardiac literature, discussed in detail later, confirmed that there was little evidence to guide clinical practice in this area of readministration of thrombolysis.

I thus proceeded to review local experience with second administration of thrombolytic agents and compare our experience with the literature available addressing this topic. I hoped to address the local concerns, guide our future practice, and add meaningfully to the small body of published data available.

Methods

A retrospective folder review was conducted.

Inclusion criteria

Patients were included in this study if they received two or more doses of thrombolytic therapy as treatment for presumed acute myocardial infarction during a single hospital admission to the Royal Sussex County Hospital between January 1989 and March 2000. The interval between doses of lysis during the admission was not considered in deciding enrolment.

Identification of patients and data collection

The County Hospital coronary care unit (CCU) keeps a detailed patient register of each admission to the unit. Local protocols dictate that all thrombolysed AMI patients are admitted to the CCU subject to bed availability. Each admission record in the CCU register from 1989 onwards was checked for information suggesting in-hospital reinfarction or administration of more than one dose of thrombolysis. This process was assisted by the local custom of detailing in bold red letters the name of

any thrombolytic administered next to patients' names! The full hospital record of all potentially eligible patients was screened. Hospital records of patients who fulfilled the entry criteria were reviewed. A defined and detailed data-set of clinical information (from doctors and nurses records), drug chart information, and records of all cardiac procedures and blood investigation results was extracted from each hospital record into a computerised database. Where records were incomplete, particularly with respect to details of diagnostic or interventional cardiac procedures or long-term follow-up, such data were obtained from the regional referral centre or the patients' general practitioner. Where applicable, post-mortem reports were obtained from the coroner or hospital pathology department. All records were scrutinised and supplemental information collected by a single researcher, the author.

Ethical approval and local supervision

Local ethical approval was formally sought. The chair of the local committee responded that this investigation primarily constituted an audit activity, with retrospective data collection and observation of routine practice. Formal Ethics Committee approval was thus not required. Professor Richard Vincent of the County Hospital Cardiac Department and the Sussex University supervised the project locally (in Brighton).

Coronary Care Unit management

All patients received initial thrombolysis for ischaemic chest pain less than six hours from onset with an electrocardiogram (ECG) showing ST-segment elevation in 2 adjacent leads greater than or equal to 0.1 mV in the limb leads or greater than or equal to 0.2 mV in the chest leads. Before receiving a second dose of lytic drug all patients presented with ongoing chest pain or a recurrence of pain as well as persistence or recurrence of ST elevation. The specific thrombolytic agent used was

chosen at the discretion of the attending physician, according to current local practice. Drug selection on occasion reflected participation in multi-centre trials. Patients who received tenecteplase as part of the ASSENT 1 [30] or ASSENT 2 [22] protocols were considered as having received tissue plasminogen activator (tPA) for the purposes of this analysis.

Patients were managed according to established hospital protocols with an ECG on admission, after lysis, on arrival in CCU and daily thereafter, or as prompted by episodes of chest pain. All patients received additional routine medical therapy at the discretion of the attending cardiologist. Angiography was likewise at the clinicians' discretion: performed either during the initial admission or deferred until after hospital discharge pending results of non-invasive investigations (usually an exercise stress ECG). Blood was drawn at least daily for estimation of cardiac enzymes.

Definitions

Clinical notes were scrutinised for evidence regarding severity, duration, and cessation of chest pain in relation to thrombolytic therapy. Pain was defined as 'resolved' if a clear statement in the hospital record, not later than three hours after initiation of thrombolytic therapy, documented the absence or marked reduction of chest pain.

Electrocardiograms were analysed for territory of ST-segment elevation, and divided into anterior (leads V1-V6) or inferior groups (leads II, III, aVF). Where leads I and aVL showed ST-segment elevation, this was classified anterior if associated with changes in the chest leads, or inferior if associated with inferior changes.

Pre- and post-lysis ECG's were compared and ST-segment changes were considered to have 'resolved' if elevation in the single most elevated lead was reduced by at least 50% on an ECG no later than three hours after the onset of thrombolytic therapy.

Where data was available for both clinical and ECG resolution, patients were labelled as 'likely reperfusion' if both pain and ST-segments had resolved. In isolated patients appropriately timed ECG's were not available for assessment of reperfusion. If only later ECG's were available these were analysed for information regarding ECG outcome (Q wave infarction, Non-Q wave myocardial infarction, infarct territory). Details of any complications potentially related to thrombolytic administration were recorded. Major bleeding resulted in a drop of more than 1 gram of haemoglobin, or the need for blood transfusion. All other bleeds were considered 'minor', and details of each were documented.

All angiography reports were reviewed, and where not specified in the report flow in the infarct-related artery was classified according to the TIMI (thrombolysis in myocardial infarction) criteria [31]:

TIMI-0: Absent antegrade flow.

TIMI-1: Partial contrast penetration: incomplete distal filling.

TIMI-2: Opacification of the entire distal artery; delayed filling or washout.

TIMI-3: Normal flow.

Data capture and statistical analysis

All data was captured in a custom designed spreadsheet on Microsoft Excel ® software. Graphic and statistical analyses were performed within this package. The Chi squared test was used to compare the occurrence of reperfusion criteria after first and second thrombolysis episodes.

CHAPTER FOUR: RESULTS

Patient characteristics

Eighty-nine patients were identified from the CCU register for screening. The hospital records were available for scrutiny in 84 of these patients. Thirty-two patients did not meet entrance criteria – having examined their folders it was apparent that either they received thrombolysis for a non-MI indication (eg DVT, pulmonary embolus), or they only received a single dose. Fifty-two patients were thus included in the study. Their baseline characteristics are shown in Table 1.

Table 1: Baseline characteristics

Age: mean(SD)	68(9)	Range 42-83
Males	36	69%
Females	16	31%
Male age: mean(SD)	66(10)	
Female age: mean(SD)	73(6)	
Previous angina	17	33%
Previous MI	8	15%
Previous revascularisation	1	2%
Hypertension	17	33%
Diabetes	6	12%
Current smokers	13	25%
Ever smoked	32	64%

Thrombolysis

Forty-six patients received two- and six received three doses of thrombolysis. For the initial lysis episode ST elevation was anterior only in 25(48%) and inferior only in

25(48%). Two patients (4%) had ST elevation in anterior and inferior territories.

Median pain to needle time for first thrombolysis was 120 minutes (2.0 hours); mean pain to needle time was 167 minutes (2.8 hours).

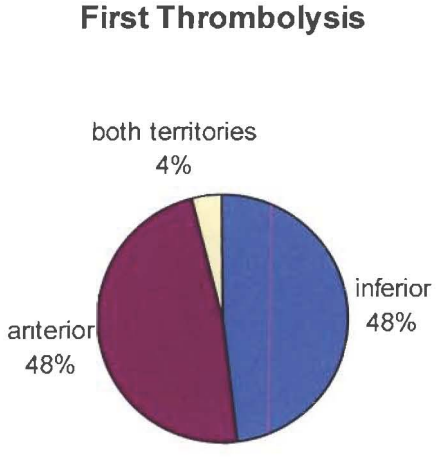
Second thrombolysis was administered at a median of 2.2 days (range 0.1-10.0) after the first dose. Three patients with non-resolving chest pain and ST elevation were rethrombolysed within three hours, for presumed failure of initial lysis. In 2 of these patients chest pain settled and ECG ST-segment elevation resolved.

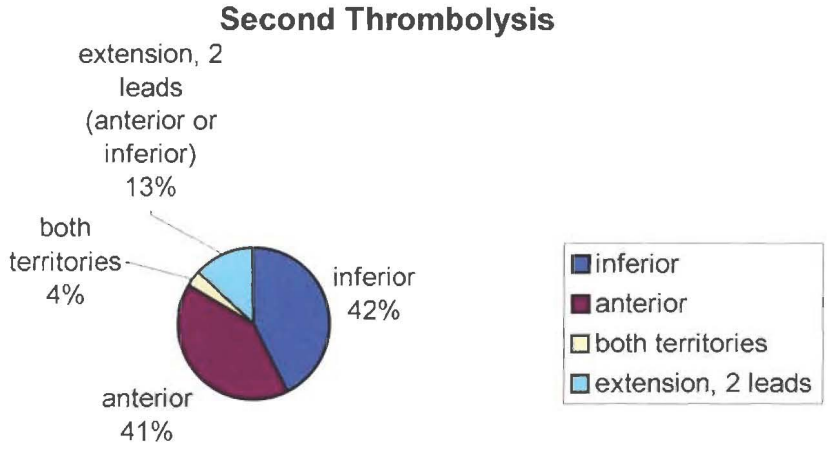
Forty-nine patients were rethrombolysed for clinical reinfarction with recurrence of chest pain and ST-segment elevation. In 45(87%), ST-segment elevation territory was identical to the first infarct. In 7(13%) patients ST elevation, anterior or inferior initially, had extended to 2 or more additional ECG leads.

The median pain to needle time for second thrombolysis was 83 minutes (1.4 hours); mean pain to needle time was 108 minutes (1.8 hours).

Ischaemic territories for first and second lysis are shown in figure 1.

Figure 1: Ischaemic territory on ECG: first and second lysis episodes

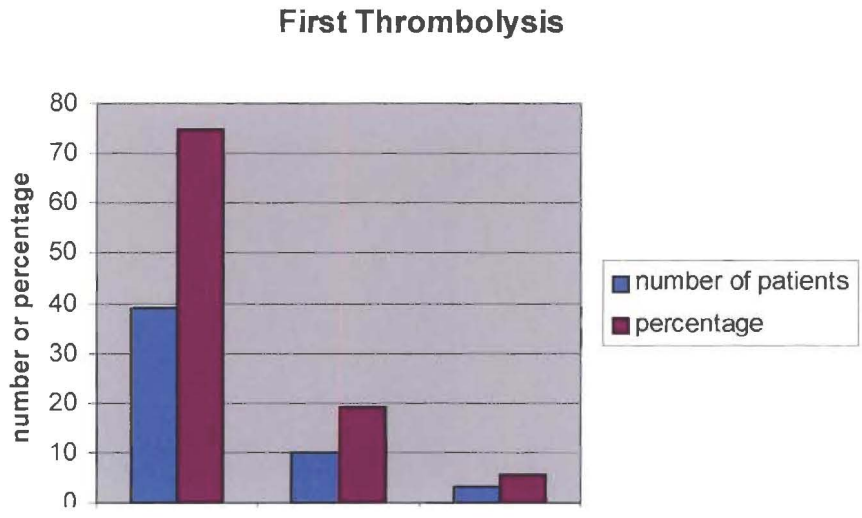




Thrombolytic drugs

Streptokinase (SK) was the most commonly used agent for first lysis (39 patients, 75%) and second lysis (35 patients, 67%). The commonest lytic combination (SK/SK) was used in 24 patients (46%), with maximally 5 days between doses. Other agents used included tPA, urokinase (Uro) and anisoylated plasminogen streptokinase activator complex (APSAC), alternatively known as anistreplase. Full details of thrombolytic agents for first and second lytic episodes individually are illustrated in figure two. Figure three illustrates the frequency of use of various lytic combinations

Figure 2: Thrombolytic agents for first and second lysis episodes



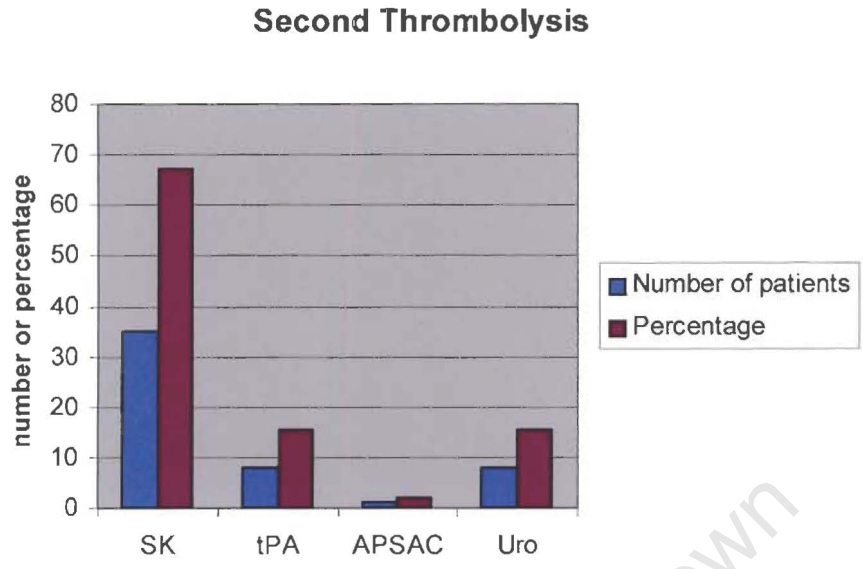
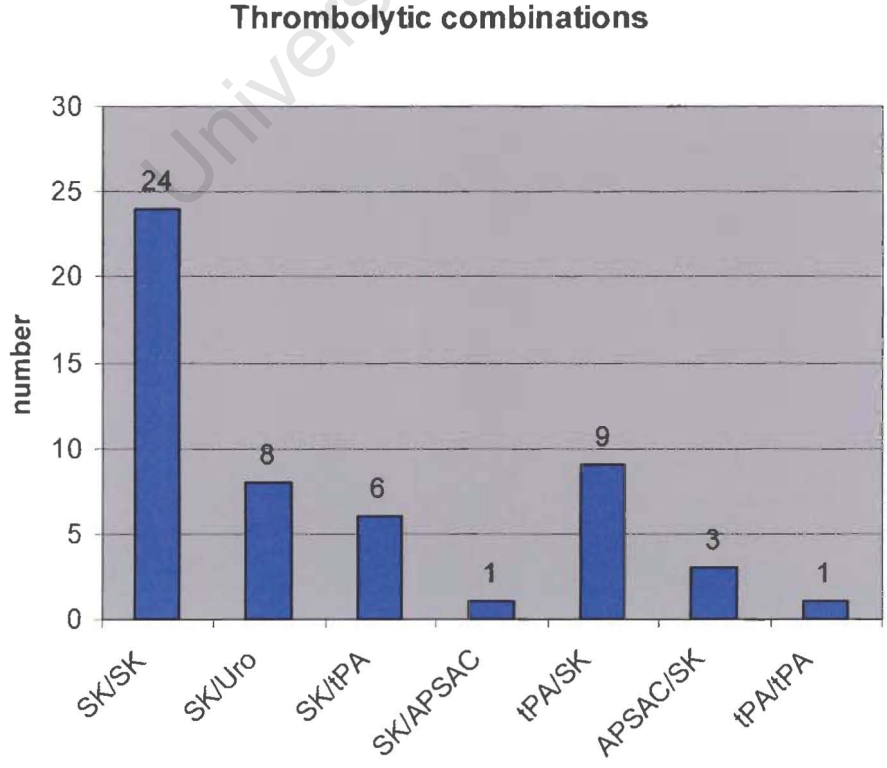


Figure 3: Thrombolytic drug combinations



Clinical assessment prior to rethrombolysis

Doctors notes made immediately prior to rethrombolysis were examined. These notes contained documentation of the jugular venous pressure in 23/52 cases (44%). In a single patients record there was evidence that the possibility of cardiac rupture had been considered. In this patient, and in no other, an echocardiogram was obtained to exclude mechanical complications prior to the administration of a repeat dose of thrombolysis.

When ECG's recorded prior to rethrombolysis were analysed all except one were felt to be compatible with infarction or reinfarction, in agreement with the initial interpretation by attending doctors. In all these cases ST elevation fulfilled usual criteria for thrombolysis. In a single patients ECG prior to relysis the changes that the attending doctor had interpreted as infarct extension were felt to represent classical changes of pericarditis.

Concomitant drug therapy

All patients received soluble aspirin at the time of the first infarct and lytic therapy, and were still receiving regular aspirin therapy when they were retreated with thrombolysis. On the day of first thrombolysis beta-blockers were administered to 33/52 patients (63%). Angiotensin converting enzyme inhibitors (ACEI) had been administered to 9/52 patients (17%) before the second episode of chest pain and ST elevation occurred. After rethrombolysis, one additional patient was treated with beta-blockade, and ACEI's were more frequently prescribed – to 20/52 patients (38%).

Indices of reperfusion

Resolution of chest pain

For first lysis, hospital records (doctors and nurses notes) were adequate to assess resolution of chest pain in 48 of the 52 patients (92%). In 34/48 (71%) patients pain resolved after first lysis, and in 14/48 (29%) pain continued. For second lysis, pain resolution could be ascertained for 44 patients (85%). Pain resolved in 35/44 (80%) patients and continued in 9/44 (20%) patients. Comparing first and second thrombolysis there was no significant difference in resolution of chest pain ($p = 0.33$).

Resolution of ST-segment elevation on the post thrombolysis ECG

After first thrombolysis an appropriately timed ECG was available for analysis for 38 patients (73%). A similar appropriate ECG was available for 40 patients after second lysis (77%). After first lysis the ECG demonstrated resolution in 26/38 (68%) and failure of resolution in 12/38 (32%). After second lysis resolution was found in 25/40 (62.5%) of ECG's, and failure to resolve in 15/40 (37.5%) of ECG's. Comparing first and second thrombolysis there was no significant difference in resolution of ST segments ($p = 0.58$)

Non-invasive assessment of reperfusion: ECG and pain resolution

For first lysis, both ECG and clinical parameters of reperfusion were available for 35 of 52 patients (67%). For second lysis this figure was 34/52 (65%). For first lysis both parameters suggested reperfusion in 23/35 (66%) of patients. For second lysis this figure was lower at 20/34 (59%). However, comparing first and second lysis, there was no significant difference in attainment of reperfusion by non-invasive criteria ($p = 0.55$)

Laboratory results: creatine kinase and fibrinogen

In all patients available measurements of CK and fibrinogen were recorded. However, the retrospective nature of this analysis made accurate timing of these measurements impossible. CK measurements were available after first and second lysis for 40/52 patients. In 30 of these patients only a single CK peak could be demonstrated, with no clear rise related to the second episode of thrombolysis. Fibrinogen results were collected. Like CK results, these values could not be accurately timed in relation to administration of thrombolysis. This data was thus not analysed further.

ECG outcome

After second thrombolysis new Q waves were present on the 12 lead ECG in 47/52 patients (90%), compared to the admission ECG. 5 patients did not develop Q waves on the 12 lead ECG (10%). In 10 patients (19%) the ECG after second lysis was substantially different from that after first lysis: 4 patients had developed Q waves after second lysis, having had an initial Non-Q-wave infarct, and in 6 patients additional Q waves had developed in at least 2 leads, compared to the ECG after first lysis.

Complications

First lysis administration was complicated by seven minor bleeding episodes (13% of patients): 3 cases of minor haemoptysis, 1 nosebleed, and 3 documented cases of superficial bruising. In 6 patients receiving SK the infusion was transiently stopped - in 5 for hypotension and in 1 for transient flushing and nausea. In all patients

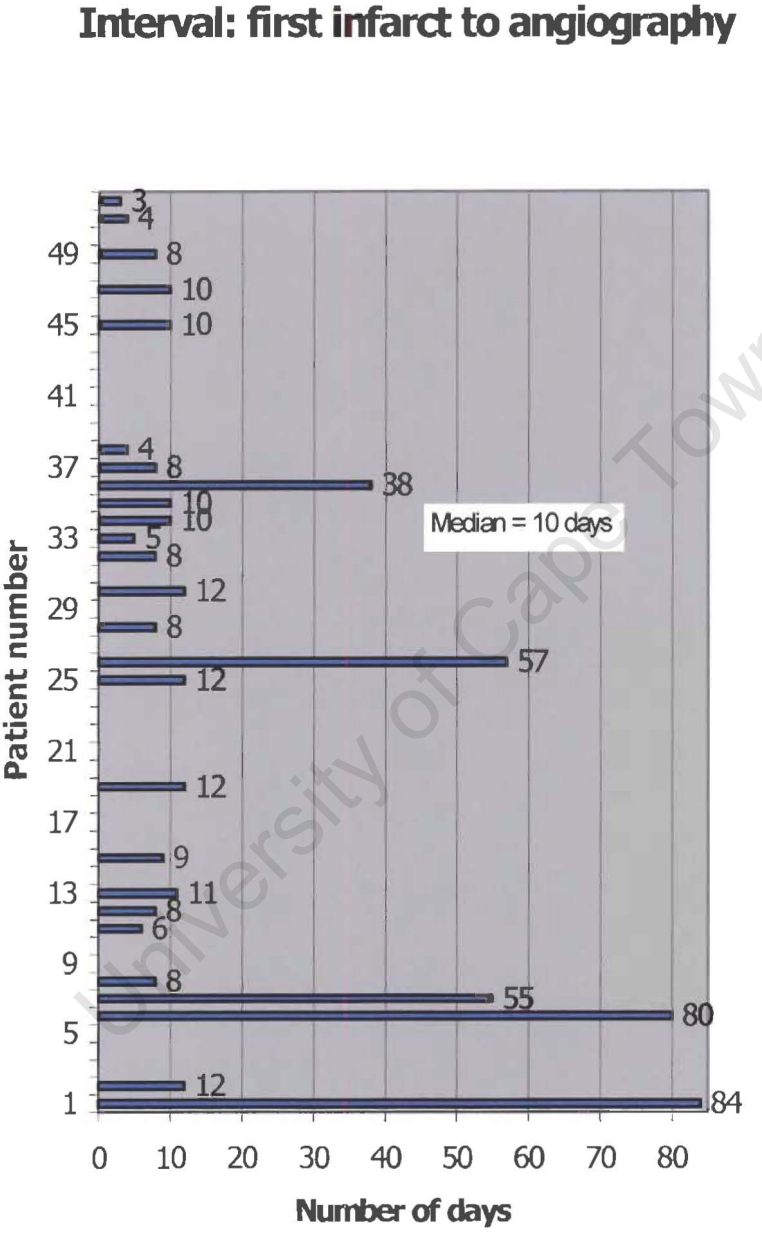
symptoms resolved and the infusion was completed. There were no major bleeds or strokes related to first lysis.

Second lysis administration was complicated by 1 haemorrhagic stroke (intraventricular cerebral bleed confirmed by CT scan) and 1 major bleed from a central venous puncture site (transfused 2 units of blood). Seven patients had minor bleeding episodes (13%): 3 developed large soft-tissue haematomas, 2 had extensive oozing from puncture sites, 1 had extensive superficial bruising and 1 patient had minor bleeding from his gums. Compared to first lysis, a similar number of patients, six, had their infusion stopped or slowed because of hypotension . In 5 of these patients the lytic drug was streptokinase, in one case it was urokinase. Only one allergic reaction (skin rash) was documented amongst the 24 patients who received SK twice. In this patient the interval between SK doses was 48 hours.

Angiography

Angiography was performed in 26 patients (50%). Twenty-one patients underwent angiography during the index admission at a median 8.5 days (range 3-12) after their first infarct. Five patients underwent angiography after hospital discharge at a median of 57 days from first infarct (range 38-84). Figure 4 indicates timing of angiography for each patient in whom it was performed, and demonstrates clearly the clustering into two groups: early angiograms, or studies performed after a longer interval.

Figure 4: Timing of angiography



Angiographic findings are summarised in table 2.

Table 2: Angiographic findings in 26 patients

1 vessel disease	10	38%
2 vessel disease	7	27%
3 vessel disease	9	35%
Infarct-related artery		
Left anterior descending	13	50%
Right coronary artery	11	42%
Circumflex artery	2	8%
Infarct-related artery flow		
TIMI 0	13	50%
TIMI 1 or 2	3	12%
TIMI 3	10	38%
Angioplasty performed	19	73%

In patients undergoing angiography, 38% of infarct-related arteries demonstrated normal flow after second lysis, and half were occluded.

Revascularisation: percutaneous coronary interventions

Twenty percutaneous interventions (11 balloon angioplasty only and 9 angioplasty with coronary stents) were performed in 19 of the 26 patients who underwent angiography. One death occurred in the catheterisation laboratory after acute vessel closure. In this patient with a chronically occluded right coronary artery and a critical proximal left anterior descending stenosis, the left anterior descending artery closed during attempted post-infarct angioplasty. One additional patient had a successful

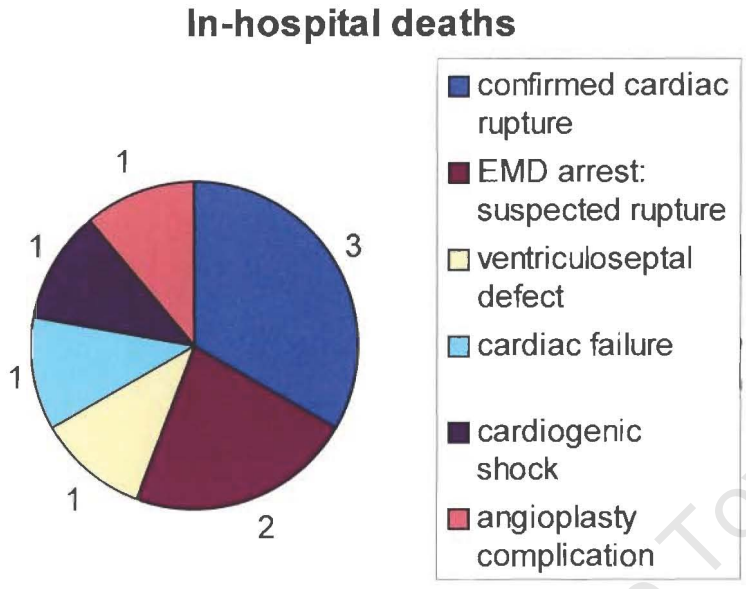
angioplasty to an occluded right coronary artery complicated by a stroke. No other interventional complications were recorded. The procedural operator rated angiographic results as 'excellent' in 10 cases, 'good' in 3, 'adequate' or 'reasonable' in 6, and the procedure failed in the single above-mentioned acute vessel closure. Angiograms were not independently reviewed – the formal report from the treating laboratory provided the necessary data.

In 2 patients, coronary vessels were considered unsuitable for any form of revascularisation. In an additional single patient further revascularisation was adjudged to be extremely high risk and declined. Delayed coronary artery bypass surgery was planned for one patient, and medical therapy was advised as most appropriate for 3 patients.

Outcome and cause of death

There were 9 early in-hospital deaths. Five patients sustained external cardiac rupture: two cases were confirmed by post-mortem examination and one was confirmed by echocardiography and pericardial aspiration. Two cases were diagnosed on clinical grounds: in both cases chest pain, hypotension and electro-mechanical dissociation arrest occurred on the third post infarct day and the attending staff concluded that death was likely due to cardiac rupture. A sixth patient died after developing a large ventricular septal defect (echocardiographically confirmed). The remaining early deaths were due to severe heart failure (2 deaths), and after acute vessel closure during angioplasty (1 death). In-hospital mortality was 17% and 30-day mortality was 20%. One-year follow up data was available for 48 of 52 patients and showed one-year mortality of 28%. Figure 5 indicates the causes of deaths in the nine patients who died before hospital discharge.

Figure 5: Cause of death – all in-hospital deaths



CHAPTER FIVE: DISCUSSION

Data collection

This study enrolled 52 patients treated with two or three doses of thrombolysis (49 treated for reinfarction), over a period in which the treating hospital would expect to thrombolyse 2900 patients for acute myocardial infarction. If we assume that 50-60% of post lysis reinfarction cases were rethrombolysed, this would imply a reinfarction rate of 3%, in keeping with the 2.8-4.1% reinfarction rate from the large trials discussed in chapter 2 [20-22]. This suggests successful retrospective identification of most patients fitting the study criteria. The figures above suggest that between 40 and 71 patients may have fallen in to the category of reinfarction treated with thrombolysis during the time period studied. Our results show that we do not actively identify patients with failure of lysis, as discussed below.

The relatively small number of patients collected in a busy hospital over a period exceeding ten years highlights how unlikely it is that a single centre randomised trial would have sufficient power to investigate prospectively the issues addressed in this study, particularly the treatment of early reinfarction. Since failure of lysis is commoner than reinfarction, numbers would be much higher if this entity were actively sought and treated. A multi-centre trial, necessary to include sufficient patients, would likely suffer poor recruitment due to a different set of problems. Many practitioners with access to interventional facilities may resist rethrombolysis, and certainly randomisation to a placebo treatment could only be contemplated in hospitals without such access. Retrospective case series thus become an important tool in evaluating the role of rethrombolysis.

Although in this study a very small proportion of potential relysis candidates may have been missed due to the unavailability of records, this potential omission is

unlikely to have significantly biased results. Misplaced hospital records probably resulted from filing errors related to the transfer of older case notes from the hospital to an outside company responsible for microfilming. Of course this study does suffer from the substantial limitations common to any cohort identified respectively, particularly where outcomes are not compared with a control group of patients treated differently.

Failure of lysis versus reinfarction

In this study only three patients were rethrombolysed for failure of initial lysis. This may reflect a failure to retrospectively identify this group of patients. More likely is that prospectively, in clinical practice, our practitioners did not identify or seek to treat this group of patients. In the light of the survey of members of the British Cardiac Society discussed in Chapter 2 [29], where 45% of 290 respondents rarely searched for evidence of reperfusion after administering initial thrombolysis for AMI, this is not a surprising finding. This failure to routinely assess the efficacy of thrombolytic would be duplicated in many other UK district general hospitals. Doctors' failure to monitor patients for clinical evidence of reperfusion probably has many origins. Contributing factors could include a failure of education, a perception that non-invasive indices of reperfusion are unreliable, a culture of unavailability of coronary interventional facilities, or a perception that further treatment is risky or futile. At the County Hospital thrombolysis is administered in the Accident and Emergency department by the admitting general medicine Senior House Officers. Local consultants find many benefits in this system, particularly a very short door to needle time. It is conceivable that the administration of lysis by relatively junior staff

outside of a CCU environment further contributes to the failure to identify cases of failed thrombolysis at this Hospital.

In the survey mentioned above 37% of United Kingdom (UK) respondents who looked for evidence of reperfusion when administering thrombolytic would choose to treat failure of initial lysis with a repeat dose of thrombolytic. Clinical experience and published data confirm that in the UK certain centres do regularly administer second dose thrombolysis for this indication [32]. Clinical trials performed to assess other thrombolysis-related issues further support the notion that 'rescue relysis' is commonly administered. Gaylani et al. examined the systemic lytic state attained after streptokinase therapy as a potential predictor of coronary reperfusion [33]. Their study group included 26 patients who were assessed as having 'unsuccessful reperfusion'. Seven of these patients had further intervention, and a total of eight further thrombolytic treatments were administered in this group of patients. Full details are not given in this paper. However, since two patients had successful angioplasty without relysis, and in one patient the infarct-related artery opened after injection of angiographic contrast, the data suggest that some patients had at least three doses of lysis related to their initial infarct.

This study de facto represents outcomes in patients re-thrombolysed for early reinfarction, rather than for failure of initial lysis.

Clinical or echocardiographic assessment prior to re-lysis

In the majority of patients jugular venous pressure was not documented in the clinical record prior to re-thrombolysis. The assumption that this represents a failure to consider the diagnosis of cardiac rupture is difficult to test, but this clinical sign was chosen because of its critical importance in the diagnosis of cardiac tamponade or

pericardial effusion. A failure of record keeping could account for such an omission, but all patients had substantial documentation made prior to re-administration of thrombolytic drugs. The solitary echocardiogram performed in 52 patients confirms the impression that cardiac rupture was not usually considered as part of the differential diagnosis.

Echocardiographic detection of cardiac rupture

Two-dimensional echocardiography is the most sensitive diagnostic modality for the diagnosis of sub-acute free wall rupture [34]. In a prospective study all patients with cardiac rupture had pericardial effusion at echocardiography [35]. However, pericardial effusion is a frequent finding after myocardial infarction occurring in 6-37% of patients, and was present in 29% of the patients without rupture in this series. The authors commented that the absence of pericardial effusion excludes cardiac rupture, but its presence (even when >15mm) does not reliably diagnose rupture. These authors also examined the use of other echo criteria. Intrapericardial echoes were, like the presence of effusion, very sensitive, but resulted in an unacceptable false positive rate. The presence of tamponade using echocardiographic criteria of right atrial and ventricular collapse was useful. If this was present together with effusion and clinical hypotension this triad had a diagnostic sensitivity of 88% with 9.4% false positive diagnoses. Other authors have found complete agreement between echocardiographic findings and necropsy or surgical findings in patients with mechanical infarct complications including free wall rupture [36].

Rupture presents with quite typical findings: relatively echodense circumferential intrapericardial haematoma which sometimes has a layered appearance, pericardial effusion measuring around 2 cm or more from the subcostal window, and possibly

right ventricular collapse in keeping with tamponade [37]. Usually the actual site of rupture cannot be easily identified [35,37].

When there is any diagnostic confusion in a post infarct patient with chest pain and ECG changes, an echocardiogram is thus an extremely useful investigation. Not only would the initial infarct frequently be demonstrable, but mechanical complications could also be identified or excluded with acceptable diagnostic accuracy. Ancillary evidence regarding left ventricular function would also assist further management.

The significance of ST-segment elevation and a diagnosis of reinfarction

All patients re-thrombolysed had ECG changes considered by the attending doctor to be indicative of infarction, and sufficient to warrant administration of thrombolytic drug.

However, even when considering the treatment of initial AMI, most physicians will recall patients who were inappropriately treated with thrombolytic - patients presenting with chest pain and ECG changes, thrombolysed, and subsequently found to have normal coronary arteries, or at least no evidence for current infarction.

The ECG ST-segment changes considered typical of the systolic 'injury current' of acute myocardial infarction are not pathognomonic for this diagnosis. Infarction can be mimicked by a delay in subendocardial repolarisation or premature subepicardial repolarisation. Even when due to subepicardial injury, ST elevation may be caused by infarction, ischaemia, pericarditis or tumour [38].

Pericarditis may occur overlying a transmural infarct during the time that patients are most vulnerable to reinfarction. This particular diagnostic pitfall is illustrated in this series in the one patient where re-thrombolysis was administered for chest pain and ECG changes most likely attributable to pericarditis.

After recent myocardial infarction there may be further potential causes of ST-segment changes that could be mistakenly attributed to reinfarction. Cardiac rupture, discussed below, is accompanied by ECG changes that may include ST-segment elevation. Katori and colleagues, investigating the mechanisms responsible for exercise induced ST elevation in the infarct zone after transmural infarction, administered various stimuli to dogs, 1 and 4 weeks after induced anterior myocardial infarction. They found that administration of noradrenaline produced marked ST-segment elevation in the infarct zone [39]. The presence of ST elevation at rest in leads with Q waves has further been related to large infarcts, severe left ventricular dysfunction and regional wall motion abnormalities, and predicts a higher likelihood of occlusion in the infarct-related artery [40].

Interpretation of any post infarction electrocardiogram must take into account a wide differential diagnosis for ST-segment elevation. When one considers further the multiple possible causes of chest pain after myocardial infarction, the potential for misdiagnosis of reinfarction is clear.

Non-invasive assessment of reperfusion

A simple and practical, yet accurate, non-invasive method for detecting myocardial reperfusion in patients treated with thrombolysis remains elusive. Various clinical and laboratory parameters have been tested for their utility in this regard – including changes in chest discomfort, reduction in elevation of the ST segments, the presence of various 'reperfusion' arrhythmias, and various changes in cardiac enzymes over time. These variables have been quantitated in various ways, and at various times in relation to the administration of thrombolysis [41-44]. Although non-invasive assessment of reperfusion is not the main focus of this study, clinical reperfusion data was sought

as a potential discriminator of efficacy between initial and subsequent doses of thrombolysis.

Resolution of chest pain

A reduction in chest pain is difficult to quantify, and may be influenced by opiate therapy. Some authors have utilised a 1 to 10 chest pain scale, looking for a 2 point reduction, others have stressed the importance of a sudden reduction in symptoms as a marker of reperfusion [41,43]. In these studies the sensitivity of pain reduction has been 65-81%, with specificity 73-96%.

Chest pain resolution assessed retrospectively from the admission record is subject to many potential inaccuracies, in addition to the pitfalls applicable to any analysis of pain. I could not accurately estimate from records the abruptness of pain relief, the nature of any ongoing pain, or any relation to opiate therapy. In many case notes a clear statement was made in the nursing process regarding freedom from pain at the time of arrival of a patient from the Accident and Emergency department in the Coronary Care Unit. However, this may have reflected a decision regarding administration of further pain relief rather than an accurate and sensitive description of reperfusion or its absence. Analysis of the chest pain data from this study must be interpreted in the light of significant potential inaccuracies.

Resolution of ST-segment elevation

ST segments after AMI have been analysed by various techniques and at times ranging from 60 minutes to 4 hours after onset of thrombolytic treatment. Average ST-segment elevation in all involved leads, or the 2 leads with maximal elevation, and total ST-segment deviation are amongst the measurements that have been used [41-43,45,46]. However, ST-segment resolution measured in only the one lead with initially highest ST-segment elevation closely correlates with the sum of ST-segment

32% and 95% respectively in one study [43]. Different authors have recorded positive predictive values of 84-100% when both parameters suggest reperfusion [41].

'Reperfusion' results in this study

Given the potential inaccuracy of this reperfusion data, particularly with respect to chest pain, it is not surprising that no significant differences could be detected in resolution of chest pain, resolution of ST-segment elevation, or both of these parameters considered together, when first thrombolysis was compared with second thrombolysis. Data for the combined 'reperfusion' endpoint were only available for 66% of lysis episodes.

Would one expect rethrombolysis to be less 'successful', by non-invasive criteria, if compared with initial lysis? Perhaps, if the relysed patients included some whose infarct artery had not opened after the first lysis episode, and thrombolytic efficacy falls off over time from initial vessel occlusion. Multiple complex variables make simplistic assumptions difficult. With the progression of myocardial necrosis, pain tends to disappear spontaneously. Since many re-occlusions are asymptomatic [18], the pattern of pain for a second ischaemic episode in an already infarcted territory clearly may differ from that experienced in the initial infarct [18]. For all 'reperfusion' variables studied one trial demonstrated greater positive predictive value for reperfusion in patients up to 3 hours into acute infarct evolution in comparison with those whose evolution time was between 3 and 6 hours. This was statistically significant for the ST-segment [41]. If the value of the data used to assess reperfusion status non-invasively decrease over time from the initial infarct, then commenting on the success of re-lysis on the strength of such data must be extremely unreliable. Previous trials of rethrombolysis, discussed below confirm this view.

Fibrinogen levels

Fibrinogen measurements have not been presented for similar reasons as discussed for CK. The marked variations in fibrinogen over time after thrombolysis mean that random specimen results cannot be interpreted. The achievement of a systemic lytic state (fibrinogen < 1gram/litre) is not necessarily a predictor of coronary reperfusion after thrombolysis [33]. However, when Mounsey and colleagues randomised patients with failed reperfusion after streptokinase to additional tPA or placebo in the only randomised trial of re-thrombolysis against placebo, they demonstrated significant benefits only in patients who failed to achieve fibrinogen < 1 g/l after streptokinase [47]. The usefulness of this measurement may thus be as a predictor of potential responders to second lysis, when this is administered for failure of initial therapy, but this has not been confirmed in any larger studies.

Haemorrhage and stroke

Our results are in keeping with previous small studies, showing no excess major bleeding or stroke risk when multiple doses of thrombolysis are administered with an intervening delay [48-50]. Barbash and colleagues [48] did demonstrate an increase in minor bleeding complications. In the current series the median delay between thrombolysis episodes was 2.3 days – and most patients were being treated for reinfarction rather than failed initial lysis. These patients were selected for re-lysis having tolerated the first thrombolytic agent without major bleeds or stroke.

The apparent safety with respect to bleeding and stroke may not apply when thrombolysis is repeated earlier, for failed initial lysis. Although small studies have shown no excess risk with 'rescue' relysis [43,51], in GUSTO the combination of SK and accelerated tPA resulted in a significant excess of haemorrhagic strokes [52].

Angiographic findings

Patients undergoing angiography in this study where chosen at the attending consultants discretion, and studied at varying times after the initial or repeat infarction episdode. The 50% angiography rate in this patient group, and the fact that 21 of 26 patients had angiography before hospital discharge confirms that they were assessed as a high-risk group. Routine angiography rates post-infarction at the County Hospital have been much lower, particularly when interventional cases required referral to a tertiary centre.

The selection criteria of patients for angiography and the timing of this procedure would substantially influence the observed infarct related artery patency rate. Normal flow was demonstrated in only 38% of infarct related arteries in this cohort of patients. Although there can be no certainty in ascribing this low rate to inefficacy of second thrombolysis, it is a substantially lower number than would be expected with angiography acutely post thrombolysis, or when delayed for 5 – 7 days. In the GUSTO angiographic substudy [53], complete reperfusion (TIMI grade 3 flow) was present in 46% and 54% respectively of patients having angiography at 24 hours and 5 to 7 days after intravenous streptokinase. The corresponding figures for patients treated with accelerated tPA were 45% and 58%.

Cardiac rupture

The major finding in this study is the demonstration of fatal mechanical infarct complications after relysis in six patients (12%), comprising two thirds of nine early deaths. Rupture would be expected to account for 8-20% of in-hospital deaths [34, 54, 55] and ventricular septal rupture usually complicates around 2% of infarcts [55].

Various explanations can be invoked for this apparent excess of mechanical complications. The diagnosis is unlikely to be incorrect in any of these cases. Four cases were unequivocally confirmed with imaging or post-mortem studies. The other two cases both had a clinical presentation and context that is highly suggestive of cardiac rupture, with little to include in a differential diagnosis. We cannot exclude that this apparent excess is due to chance alone. In this small series of patients, only nine deaths are recorded. There is no control group of patients who died after AMI without being administered a second dose of thrombolysis, and so statistical significance cannot be calculated. However, no other series of acute myocardial infarction fatalities has recorded a comparative number of mechanical complications, and concerns have been raised previously (see below) regarding an association between thrombolysis administration and rupture. It is useful to explore potential mechanisms of the association as noted in this study.

Rupture misdiagnosed as reinfarction

Though often apparently unheralded, cardiac rupture may be associated with a prodrome of pericarditis with chest pain, repetitive, unprovoked emesis >24 hours after infarction or restlessness and agitation [56]. Figueras et al. [57] confirmed that pericarditic chest pain was common, and demonstrated that intense anginal chest pain may precede rupture. A 1965 case-control autopsy study compared 47 cases of cardiac rupture with 200 control patients with AMI not complicated by rupture. Prolonged severe chest pain was present in 55% of rupture cases compared with only 10% of controls [58].

Characteristic ECG changes, including changes in the ST-segment, may precede rupture. Persistent, progressive or recurrent ST-segment elevation during the first 48-

72 hours is a recurring pattern, and lateral infarction on the initial ECG, especially with associated inferior or posterior infarction identifies patients at increased risk [56]. Rupture usually occurs between 1 and 4 days following infarction [34, 59]. Our patients 'reinfarcted' at a median of day 2.3. Given the similarity in clinical presentation, ECG appearances and timing of rupture and reinfarction, it is possible that some patients may have been re-thrombolysed inappropriately with incipient cardiac rupture masquerading as reinfarction. Other authors have previously noted that rupture, when it takes a sub-acute course, may be mistaken for infarct extension [60]. The accurate diagnosis of sub-acute rupture is imperative and a fatalistic approach to management is inappropriate. One small series of patients with sub-acute rupture and a 70% survival rate after surgery has been reported [61].

Reinfarction may cause cardiac rupture

Reinfarction may cause rupture. Figueras et al. [57] have speculated that recurrence of myocardial ischaemia may damage the formerly preserved outer layer of an infarcted area of myocardium. This delayed further damage may be particularly relevant when the initial infarct was ameliorated by successful thrombolysis. With reocclusion of the infarct-related artery the remaining viable myocardium is necrosed and rupture is promoted.

Thrombolytic drugs may promote rupture

The agents used to treat infarction may themselves promote cardiac rupture. In a meta-analysis of four thrombolytic trials, Honan et al. [62] concluded that early thrombolytic treatment decreases the risk of cardiac rupture, but late treatment promotes it. The odds ratio for cardiac rupture was >1.0 for thrombolytic therapy given after 11 hours from symptom onset, but the odds ratio for mortality only reached >1.0 after 21 hours – there was thus still some overall advantage in receiving

lysis up to 21 hours, even though rupture became more likely. Patients relysed for reinfarction will usually receive thrombolysis very late in relation to their initial infarct, if not in relation to the event prompting the readministration of thrombolytic. In GISSI-1 [63] and ISIS-2 [20] mortality on the first day of treatment with thrombolysis was higher than in patients not treated, despite the dramatic reduction in overall in-hospital mortality [64]. Becker et al. [65] analysed LATE trial data and concluded that tPA between 6 and 24 hours accelerated but did not increase the incidence of cardiac rupture.

The above data suggest that the 53 hours (2.2 days) median delay from first thrombolysis (original infarct) to second thrombolysis in this study could certainly have placed patients at increased risk from rupture.

Cardiac rupture is a stuttering process involving progressive dissection of blood through tears in haemorrhagic regions of transmural infarction [56, 62]. The effects of re-fibrinolysis on this process are likely to differ over time as the initial infarct evolves. Certainly the risk to benefit ratio of thrombolytic therapy must change once an initial transmural infarct is fully established and the potential benefits related to myocardial salvage are reduced.

Previous rethrombolysis studies

Barbash et al. [48] studied 52 re-thrombolysed patients, 35 of whom received re-lysis within an hour of the first dose. Forty-four of 52 patients (85%) responded to a repeat tPA infusion with significant resolution of chest pain and ST elevation. However, in 29 (56%), chest pain and ST elevation recurred after the repeat lysis prompting angiography. An occluded infarct related artery was present in 38%. Although only 17 patients received second lysis more than an hour after the first dose, no excess

hazard was noted apart from an increase in minor bleeding complications. These authors concluded that in some patients with early reinfarction any excess risk of bleeding with re-thrombolysis is outweighed by the risk of further progression of myocardial infarction. However it is clear that a substantial number of patients achieved some temporary relief from ischaemia, whereafter their symptoms recurred prompting catheterisation.

Simoons et al. [49] studied 26 patients who received repeat doses of tPA. In 14 of these patients re-lysis was administered within 5 hours of the initial dose. All patients had resolution of chest pain and ECG changes. Forty-six percent however, had an occluded infarct-related artery at angiography, despite the clinical and ECG response. Again, no excess adverse events were recorded. They concluded that early reocclusion could be treated with reasonable safety with a second infusion of alteplase, although like in the previous study there was an increase over expected bleeding complications. They conceded however that more data were needed to assess the risk/benefit ratio of repeated doses of thrombolytic.

White et al. [50] contribute a further 31 patients re-thrombolysed a median of five days after first lysis to this literature. However, 8 subjects included in his study had more than a two-week delay – in some almost two years - between doses of lysis (range 19-716 days in this subgroup). The inclusion of patients with prolonged delays between doses of thrombolytic may contribute data about allergy to thrombolytic drugs, but issues governing risk and benefit in such patients would be very different from patients retreated during a single hospital admission. Angiography was performed in 22 patients: 73% had TIMI 2 or 3 flow in the infarct related artery. The number of patients who had normal (TIMI 3) flow is not stated. In this study allergic reactions, specifically transient fever and rigors, were noted in four of eight patients who were

administered Streptokinase twice, on days 3, 3, 5 and 7. These authors concluded that re-thrombolysis is appropriate in patients with threatened reinfarction and is likely to be as safe and effective as the initial therapy. They recommended avoiding streptokinase re-administration within one year given the possibility of antibodies being present.

Bragadeesh and colleagues [32] recently reported in abstract form that of 529 patients treated with thrombolytic for AMI over three years in a UK District General Hospital, 149 patients failed to reperfuse by 90 minutes, as judged by failure of 50% resolution of the most elevated ST-segment. Seventy-two patients were retreated with thrombolytic – 39 for primary reperfusion failure, and 33 for reocclusion or reinfarction. By resolution of ST-segment elevation, re-thrombolysis was judged to be successful in 41% and 48% of these groups respectively, with an overall success rate of 44%. However, no angiographic data is available. Selection criteria for re-thrombolysis are not indicated. There is also no information published regarding the management or outcomes of the 110 patients who failed to reperfuse but did not receive re-lysis. There was no increased bleeding with the second thrombolytic, but no outcome or mortality data are supplied, and there is no information regarding any complications other than haemorrhage.

The small number of patients discussed above represent the total number of patients described in the cardiology literature that I was able to identify as having been treated for reinfarction with repeated doses of thrombolysis, despite this practice being fairly widespread. All these studies, and the current one, suffer from substantial limitations: small numbers, retrospective data collection and analysis and the potential for significant bias in treatment allocation, since no randomisation took place. No untreated control group with a similar presentation exists for purposes of comparison.

Re-thrombolysis has been further documented in small studies of "rescue" re-lysis that are not strictly comparable to this series of patients. The limitations of these studies are similar to those discussed above, but one prospective randomised trial stands out.

Mounsey and colleagues randomised patients with failed lysis after streptokinase (assessed by resolution of ST segments) to 'rescue re-thrombolysis' with tPA or placebo [47]. They demonstrated significant benefit in patients who did not achieve a systemic lytic state after the initial treatment. After failed initial fibrinolysis (with streptokinase), re-thrombolysed patients (tPA treatment) had smaller infarcts by ECG criteria, and improved left ventricular function, compared to those who were not re-thrombolysed. This study was not set up to examine safety issues. However, there was no demonstrable excess risk, and the authors concluded that the absence of serious treatment related complications suggested that haemorrhage rates in excess of those seen in GUSTO [53] were unlikely. In this small study, only 19 patients received tPA and 18 received placebo. No mortality benefit could be demonstrated.

White and colleagues have also published their experience with rescue re-lysis [51]. Patients presenting with AMI within 6 hours from onset received streptokinase and had a diagnostic angiogram at 2.5 hours after the onset of therapy. If flow in the infarct related artery was not normal, intra-coronary tPA was administered. Twenty-three patients received intra-coronary tPA. Reperfusion was achieved in 48% who were treated. The authors state that intra-coronary tPA could be used as an alternative to angioplasty, but state that there is only a success rate of 80% in this context. It seems unlikely that a hospital would be able to provide emergency catheterisation at 2.5 hours after lysis, and not provide a trained operator to perform coronary angioplasty with stenting. There is thus very little relevance to current clinical

practice, apart from the demonstration that no haemorrhagic strokes were recorded. One patient developed a very large groin haematoma, and two others required transfusion for an inapparent source of bleeding.

One other group [66] has proposed the use of rescue thrombolysis when primary lysis has failed. They published a letter with their results of administration of 'rescue' tPA to selected patients whose ST-segments had not returned to normal 90 minutes after treatment with anistreplase (APSAC). There was no excess major bleeding. Six of 39 patients had died by 21 days. The authors estimated that the extent of myocardial infarction was smaller with rescue thrombolysis when compared to rescue angioplasty. However, they made this conclusion on the basis of lower peak CK release in the thrombolysis group. The lower CK levels are more likely explained by lower early patency rates in this group. An open artery in the angioplasty group would allow early washout of high levels of CK. This study has been eloquently challenged by a subsequent letter to the publishing journal [67].

The scarcity of data available on re-thrombolysis may seem surprising when one considers the proliferation of studies on thrombolytic treatment. However, the difficulties in enrolling patients in a re-thrombolysis trial have been discussed. Funding for a multi-centre study is unlikely to be forthcoming from the pharmaceutical industry. No undue cynicism is required to conclude that once a drug is established as a first line thrombolytic, further study aimed at second thrombolysis would add very little to its overall marketability, and risks producing unnecessary adverse publicity for the drug.

Choosing a drug for second thrombolysis

In the current study a single allergic reaction was documented in the 23 patients who received two doses of streptokinase, but previous authors [50] have found such reactions more commonly. Allergy to streptokinase occurs even when this drug is administered for the first time [20,63]. Furthermore, neutralising antibodies sufficient to inhibit conventional doses of streptokinase develop as early as four days after lysis [50]. After streptokinase administration these IgG antibodies rise to a peak at two weeks and slowly fall over the next 12 months, but 50% of patients still have antibody levels sufficient to neutralise a standard dose of streptokinase up to four years after initial administration [68]. Recent in-vitro studies [69] demonstrated greatly enhanced platelet reactivity to shear stress in patients who had previously received streptokinase. In this study a fourfold increased in-vitro efficacy of streptokinase in patients who had not previously been exposed to this drug was also demonstrated. These authors concluded that the chances of achieving patency with second administration of streptokinase are poor.

The occurrence of allergic reactions, the presence of antibodies, and the reduced efficacy of streptokinase when readministered, as well as the inferior patency rates achievable compared to tPA [53] all suggest that tPA is the preferred agent for re-thrombolysis. Where this drug cannot be used because of its significant cost premium, this study and other authors have found streptokinase safe when reused within five days of the initial dose.

CHAPTER SIX: CONCLUSIONS

The cardiology unit in Brighton has not systematically identified thrombolysed AMI patients with failure of reperfusion. As only three patients in this study were retreated for failure of initial lysis, no conclusions can be drawn regarding safety or efficacy of this treatment approach. Previous studies suggest that this practice carries an increased bleeding risk that needs to be weighed against any potential benefit that may be achieved.

It is clear from the literature that where evidence for failure of reperfusion is sought, even using non-invasive criteria, there will be a cohort of patients who have apparently failed to open the infarct-related artery with a first dose of thrombolytic. Undoubtedly some patients in that group will benefit from re-lysis. If serum fibrinogen could be measured timeously, then failure to achieve a systemic lytic state after the first dose of thrombolysis may assist in predicting potential benefit. Readministration of thrombolysis has never been compared in a controlled fashion with rescue angioplasty. However, percutaneous intervention is likely to be superior to further drug therapy because of superior reperfusion rates, more sustained patency of the infarct-related artery and a lower rate of cerebral haemorrhage. Additionally, the use of coronary angiography as diagnostic modality before further intervention means that the diagnostic uncertainty inherent in non-invasive detection of failed thrombolysis falls away.

In my own opinion, the literature available suggests that whenever rescue angioplasty is available, this strategy should be preferred over re-thrombolysis.

This study adds a larger cohort of patients to those who have been re-thrombolysed for reinfarction than any previously published study. A high mortality from

mechanical infarct complications has been recorded, a finding probably explained by misdiagnosis of cardiac rupture as reinfarction, or by a significant hazard attached to what amounts to very late thrombolysis.

Simple recommendations regarding the readministration of thrombolytic drugs for in-hospital reinfarction can be formulated.

1. Cardiac rupture or other mechanical complications should always be considered and excluded when a diagnosis of reinfarction is made.
2. Echocardiography, if available, should be mandatory before thrombolytic is readministered. This test is fast and accurate in identifying complications of infarction. These complications are frequently overlooked clinically and can exactly mimic reinfarction.
3. If the facility for percutaneous coronary intervention is available, the strategy of emergency angiography and intervention as appropriate must be preferred. Angiography and coronary intervention carries known defined risks, has diagnostic and interventional potential, and high success rates in opening acutely occluded arteries.
4. Tissue plasminogen activator is the preferred thrombolytic in this context. If streptokinase has been previously administered, it should not be used again once four days have lapsed since the first dose.

Re-thrombolysis can and should be used on occasion as treatment for early reinfarction, but this decision requires the insights and discretion of an experienced practitioner, and must be made on a case-by-case basis, not according to a set protocol. This is a heterogeneous group of patients. The clinical context, various

aspects of a patient's in-hospital course and results of investigations become crucial in making what often will be a complex decision.

A thirty-five-year-old man presents to hospital within half an hour of chest pain onset and receives streptokinase for an evolving extensive anterior infarct. He is pain free by thirty minutes, and within sixty minutes has complete resolution of his ST-segment elevation. His CK becomes marginally elevated and his surface ECG normalises completely by day two. Chest pain and ST-segment elevation recur on day 5, and an urgent echo shows a preserved anterior wall and no evidence of pericardial effusion. The treating hospital has no interventional catheterisation facility. He needs reperfusion therapy immediately, and lysis is available. He must be retreated with tPA.

An eighty year old, 40kg lady with hypertension presents five hours after onset of chest pain and is found to have an evolving inferior infarct. She is treated with streptokinase but requires multiple doses of opiates for prolonged chest pain. Despite therapy her ST- segments remain elevated, only settling partially over the next 48 hours as she evolves the classical changes of a Q-wave inferior myocardial infarct. She has neither 'reperfusion' arrhythmias, nor any haemodynamic compromise from her infarct. Her initial thrombolysis is complicated by extensive deep soft tissue haematoma formation, and she has a history of a remote cerebrovascular event, with full recovery of function. An echocardiogram shows an extensive area of inferior dyskinesia and wall thinning on day two. On day three she has a recurrence of chest pain with some re-elevation of her ST segments in the same leads as previously. This elderly lady stands to gain little and potentially lose a lot if she is retreated with thrombolysis. Rupture must be excluded immediately by re-echocardiography.

Repeat thrombolysis is definitely inappropriate, even if there is no evidence of cardiac rupture or other mechanical complication on her repeat echocardiogram.

These are extreme cases, but indicate the importance of the clinical context and the individualisation of therapies.

Simoons and Arnold [70] have called for a 'tailored' approach to initial thrombolysis. This takes into account individual benefits and risks of proposed therapy. They suggest that the benefits of thrombolysis should be assessed from patient characteristics, the estimated myocardial area at risk, and treatment delay. Then the risk of intracranial haemorrhage should be estimated – risks are increased in advanced age, hypertension and various other categories. They then recommend the selection of an appropriate thrombolytic regimen for the particular patient.

When re-thrombolysis is administered for 'reinfarction', potential benefits are usually reduced. There is the substantial possibility of diagnostic inaccuracy. Treatment is directed at a vessel supplying a recent infarct, with reduced potential for myocardial salvage, even if the infarct artery is successfully opened. Initial lysis may have been unsuccessful despite clinical and ECG resolution. In routine practice less than 40% of re-thrombolysed patients achieve normal flow in the infarct-related artery.

Potential risks are enhanced, and range from the possibility of allergic reactions, through the possibility of promoting cardiac rupture or an increased bleeding risk.

In the absence of a large randomised prospective study demonstrating safety and net clinical benefit, re-thrombolysis should not be considered routine management of post infarction chest pain with re-elevation of ST segments in the infarct territory. It is inappropriate to expand the routine clinical indications for thrombolysis to include these patients with presumed in-hospital re-infarction, and potentially dangerous to

assume that the risks and benefits of thrombolytic therapy as established in routine practice apply in this setting.

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