# Thrombolytic therapy for acute coronary thrombosis

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## THE NEED FOR MYOCARDIAL SALVAGE

Pump failure is presently the leading cause of death in the coronary care unit in patient with acute myocardial infarction. Furthermore follow-up studies have shown that left ventricular function after myocardial infarction is the major determinant of prognosis[1–4]. Thus further improvement in the clinical course after myocardial infarction and survival must be sought through salvage of myocardial tissue in order to preserve left ventricular function.

Experimental limitation of infarct size through reduction of myocardial oxygen consumption by beta blockers, calcium antagonists and nitrates seemed promising. However, clinical rials with early intravenous administration of beta blockers, nitroprusside, nitroglycerine, and calcium antagonists showed no major effect on infarct size or mortality[5–14]. More recently methods have been developed for restoration of myocardial oxygen supply in acute myocardial infarction through thrombolytic therapy[15–25], percutaneous transluminal coronary angioplasty[26–28] or bypass surgery[29,30]. Careful analysis of studies on thrombolytic therapy, as presented in this review, now indicates that this approach does indeed lead to a substantial reduction of infarct size and improves prognosis in a specific subset of patients with extensive myocardial ischaemia who can be treated within a few hours after the onset of symptoms of myocardial infarction[31]. Accordingly strategies aimed at early reperfusion in myocardial infarction should now be adopted in clinical practice. The design of such strategies will be discussed.

## THE DEVELOPMENT OF IRREVERSIBLE MYOCARDIAL DAMAGE AFTER CORONARY OCCLUSION

The causal role of thrombosis in acute myocardial infarction has been a matter of long debate. Only in recent years has coronary arteriography during the first few hours after the onset of myocardial infarction demonstrated complete occlusion in 80% to 90% of patients[15,32], which could be resolved in the majority of patients by intracoronary administration of a thrombolytic agent such as streptokinase[15,33]. Thus in most patients, myocardial infarction is indeed caused by sudden or gradual thrombotic coronary occlusion at the site of an ulcerating atherosclerotic plaque. Sudden rupture of a 'dormant' plaque is most likely the luxating factor, although the cause of plaque rupture at a given moment remains uncertain. The release of lipids as well as the ragged edges of the plaque in addition to the increased stenosis from the swollen plaque lead to thrombus formation and further narrowing or complete obstruction of the vessel[34,36].

The time course of development of irreversible myocardial damage after coronary occlusion was studied by Schaper *et al.*[37] in various animal species (Fig. 1). In rats and rabbits the infarct appeared to be completed after approximately one hour occlusion, such that subsequent reperfusion in these species did not salvage any myocardial tissue. On the other hand, reperfusion of the ischaemic myocardium in cats and dogs after 1–3 hours of occlusion resulted in salvage of approximately half of the myocardium at risk, while in guinea pigs coronary occlusion did not result in myocardial necrosis at all. Recently we computed a similar graph for the time course of development of myocardial infarction from enzyme release in patients treated with intracoronary administration of streptokinase versus those in the control group of a large randomized trial conducted in the Netherlands[38]. From these data it is evident that reperfusion within two hours after the onset of symptoms will salvage approximately 50% of the myocardium at risk, thus halving the ultimate infarct size. Other data indicate that early reperfusion can achieve a return to normal myocardial metabolism[39], while several other studies have demonstrated preservation of left ventricular function after early reperfusion[25,40]. It is evident that the amount of irreversible damage rapidly pro gresses in the first hours after coronary occlusion. The delay between occlusion (or onset of sympt-oms) and thrombolytic therapy is the crucial factor to achieve optimal results.

From other studies it is evident that measures aimed at reduction of myocardial oxygen consumption can delay the development of myocardial infarction after coronary occlusion. However, such

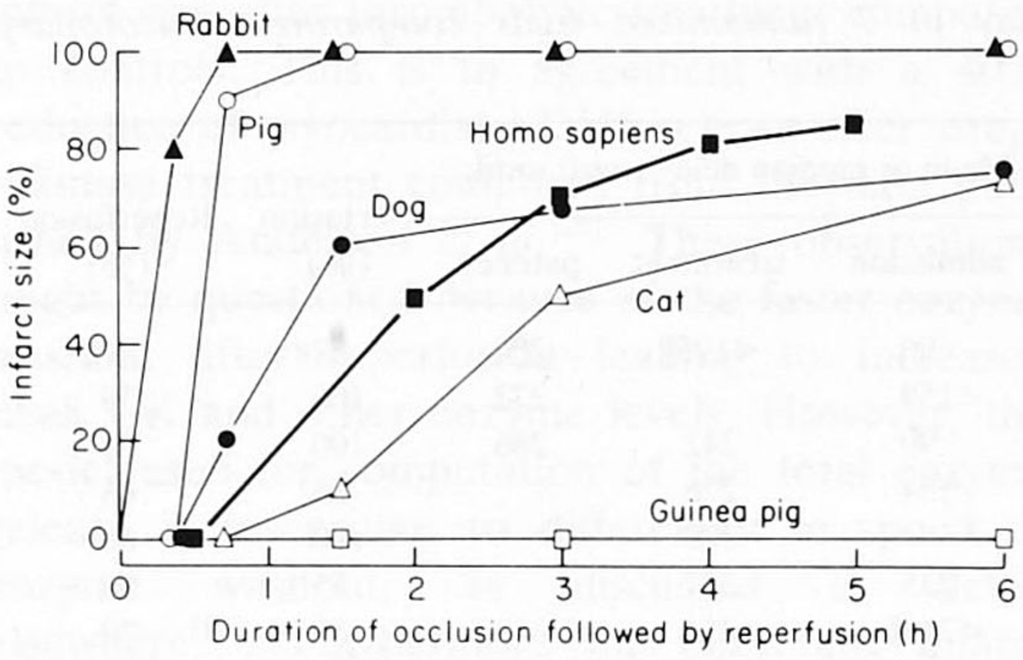


*Figure 1* Development of irreversible myocardial damage (infarct size) in various animal species in relation to the duration of complete coronary occlusion. Data published by Schaper[37]. Data in humans have been derived from enzymatic determination of infarct size in the trial conducted by the Netherlands Interuniversity Cardiology Institute[38].

measures have little influence on the ultimate infarct size unless subsequent reperfusion is achieved[41]. The optimal treatment of patients with myocardial infarction may therefore be a combination of measures aimed at delay of the development of irreversible cell damage (beta blockers and nitrates, early reperfusion of the ischaemic myocardium via thrombolysis or PTCA) and drugs which might prevent reperfusion damage (scavengers of free radicals). Since it is unrealistic, and probably unnecessary to give such a mixture of therapy to all patients, it is a major challenge to define the optimal mode of therapy for each individual patient.

## METHODS FOR REPERFUSION OF THE INFARCTED MYOCARDIUM

Reperfusion of the ischaemic and infarcted myocardium can be achieved by intravenous or intracoronary infusion of thrombolytic substances such as streptokinase, urokinase, their derivatives, tissue plasminogen activator (tPA) or prourokinase. Recent angiographic studies in acute myocardial infarction have demonstrated that without any intervention the infarct related coronary artery will be patent in 15–20% of patients studied within 4 hours after the onset of symptoms[15,23,32]. After intravenous administration of streptokinase approximately 50% of patients have a patent infarct related vessel[23]. The first trials with tissue plasminogen activator indicated that reperfusion can be obtained in 70% of patients[42–44]. Early intracoronary administration of streptokinase results in 85% patency[15,23], while 90–95% patency has been reported after combined administration of thrombolytic agents and mechanical perforation followed by PTCA[28], or by the latter alone[45,46]. A few centres have proposed to perform immediate bypass surgery in order to reperfuse the infarcted myocardium. Reports indicate that surgery can indeed be performed at low risk in selected patients with acute myocardial infarction. However, the reported beneficial effect have not been verified in large randomized trials[29,30].

## RANDOMIZED TRIALS WITH INTRACORONARY STREPTOKINASE

A number of studies have provided evidence for the beneficial effect of thrombolytic treatment through comparison of data from treated patients with historical controls[47] and comparison of groups of patients in whom reperfusion was achieved with those in whom the occlusion persisted in spite of thrombolytic treatment[48–50]. More recently, data have become available from 7 studies in which intracoronary thrombolytic therapy was compared with conventional treatment in a prospective randomized manner. In Table 1 the design of these trials is summarized. In four studies randomization was performed after initial angiography in all patients. In the trials by the Netherlands Interuniversity Cardiology Institute[15] and by Anderson *et al.*[17], angiography was not performed in patients allocated to conventional treatment. Rentrop *et al.*[21] compared four modes of treatment. One group of 30 patients received intracoronary nitroglycerin after acute angiography and 31 other patients without acute angiography. In the analysis these two groups are combined and compared with 31 patients who received either intracoronary streptokinase alone and 32 patients after intracoronary streptokinase plus intracoronary nitroglycerin. Similarly Raizner *et al.*[20] compared intracoronary streptokinase, intracoronary nitroglycerin and CCU treatment without angiography. The outstanding difference between the 7 trials on intracoronary streptokinase treatment is the mean delay between onset of symptoms of infarction and actual treatment. This time-interval varied between approximately 3 hours in the trial conducted by the Netherlands Interuniversity Cardiology Institute[15] and 6 hours in Rentrop's trial[21]. Since it has become evident that time is the crucial factor which determines the potential beneficial effects of thrombolytic treatment, the results

*Table 1 Summary of patient allocation and treatment delay in 7 randomized trials comparing intracoronary streptokinase with other treatment modalities*

| First author | Number of patients | Treatment allocation | | | | Mean or median delay (min) until: | | | Occlusion (%) | Reperfusion (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CCU | IC–SK | IC–NTG | Angio | admission | treatment | patency | | |
| Simoons[15] | 533 | 264 | 269* | | | 90 | <195¶ | 200 | 82‖ | 79‖ |
| Anderson[16] | 50 | 25 | 25 | | | <159 | | 272 | 100 | 79 |
| Leiboff[17] | 40 | | 20 | | 20 | 90 | 242 | 286 | 100 | 68 |
| Kennedy[18] | 250 | | — | | — | 134 | 276 | | 86 | 68 |
| Khaja[19] | 40 | | 20 | | 20† | | 300 | | 100 | 60 |
| Raizner[20] | 64 | 16 | 29 | 19 | | 225 | 337 | | 55 | 50 |
| Rentrop[21] | 124 | 31 | 63 | 30 | | <246§ | 354 | | 67 | 70 |

CCU = coronary care unit treatment without acute angiography, IC–SK = acute angiography followed by intracoronary streptokinase treatment, IC–NTG = acute angiography followed by intracoronary treatment with nitroglycerin, Angio = acute angiography without intracoronary drug treatment.

* Including 35 patients allocated to thrombolytic treatment who did not undergo the intervention (see text), 136 patients who received IC–SK and 98 patients who received both IV–SK and IC–SK.

† Placebo infusion IC.

‡ 31 patients IC–SK only, 32 patients IC–SK and IC–NTG.

§ Delay until randomization, which must be later than hospital admission.

¶ Delay until intracoronary treatment. In 98 patients this was preceded by treatment with 500 000 U streptokinase intravenously.

‖ Data from patients without pre treatment with intravenous streptokinase.

of the 7 intracoronary trials have been arranged in Tables 1 and 2 according to the mean time interval between the onset of symptoms and treatment. Three studies[16,17,19] were restricted to patients with angiographically proven complete occlusion of the infarct related coronary vessel. In the other studies the prevalence of total occlusion varied between 55 and 86%. Reperfusion was achieved more frequently in patients treated after a short delay (79% reperfusion)[15,16] when compared with 50 to 70% reperfusion in the studies in which treatment delay was on average longer than 5 hours. The earliest and thus most effective reperfusion was achieved in the trial from the Interuniversity Cardiology Institute in the subset in whom intravenous streptokinase was given immediately after randomization, followed by angiography and subsequent treatment with intracoronary streptokinase[15,37].

Estimation of infarct size from serial HBDH enzyme analysis in the Netherlands Interuniversity Cardiology Institute[38,51] showed a 30% smaller

*Table 2 Summary of the major findings in 7 randomized trials comparing thrombolytic treatment with intracoronary streptokinase with a control group without thrombolytic therapy.*

| First author | *N* | Treatment delay (h) | Infarct | | Hospital mortality | | 6–12 months mortality | | Survival Difference |
|---|---|---|---|---|---|---|---|---|---|
| | | | Size | LVEF | C | T | C | T | |
| Simoons | 533 | 3·2 | −30% | +6% | 26 | 14 | 42 | 23 | +7% |
| Anderson | 50 | 4 | −40% | +8% | 4 | 1 | 5 | 2 | NS |
| Leiboff | 40 | 4 | | NS | 1 | 2 | 2 | 4 | NS |
| Kennedy | 250 | 4·5 | NS | NS | 13 | 5 | 17 | 11 | +7% |
| Khaja | 40 | 5 | | NS | 2 | 1 | 4 | 1 | NS |
| Raizner | 64 | 5·5 | | NS | 2 | 4 | | | |
| Rentrop | 124 | 6 | | NS | 4 | 10 | 6 | 13 | NS |

Percent limitation of infarct size, determined by determination of enzyme release in the first two studies and by thallium tomography in the fourth study; effect of thrombolytic treatment on global left ventricular ejection fraction (treated group minus control group); C = conventional therapy, T = streptokinase. The two largest studies[14,17] both observed a significant reduction of hospital mortality and one-year mortality by thrombolytic therapy.

infarct size after thrombolytic treatment compared to controls. This is in agreement with a 40% reduction of myocardial LDH1 release after streptokinase treatment computed from the data published by Anderson *et al.*[16]. These observations might be questioned because of the faster enzyme washout after reperfusion leading to increased peak CK and other enzyme levels. However, the model used for computation of the total enzyme release is insensitive to differences in speed of enzyme washout, as discussed in detail elsewhere[51]. Furthermore the enzymatic infarct size data were fully consistent with the scintigraphic estimation of infarct size in part of the patients[52] and with preservation of global and regional left ventricular function[38,40].

In all trials left ventricular function was measured by radionuclide angiography or contrast angiography before hospital discharge (Table 2). Significant improvement of left ventricular function was observed only in the two trials with shortest treatment delay. No effect on global left ventricular function was observed in the Western Washington Trial[53], which is not easily understood since a small but statistically significant improvement in survival was reported in patients treated with intracoronary streptokinase[18,54].

Five studies had insufficient numbers of patients to document the effect of thrombolytic therapy on survival. In three studies the trend was towards improved survival after thrombolytic treatment, while in two others the reverse applied (Table 2). Survival data were virtually identical with one year survival rates of 92% and 91% in treated patients in the Western Washington Trial and the Netherlands Interuniversity Cardiology Institute Trial versus 85% and 84% in conventionally treated patients. The combined data indicate a 30% reduction of hospital mortality and one year mortality after treatment with intracoronary streptokinase which is both statistically significant and clinically relevant (Fig. 2). These observations are supported by the presented but as yet unpublished data from Rentrop's larger trial: In 193 patients receiving intracoronary streptokinase or streptokinase with nitroglycerine on average 6 hours after the onset of symptoms, 6 month mortality was 11% compared with 15% in 200 patients without streptokinase treatment. Furthermore global left ventricular ejection fraction in the former group improved slightly (2·5%) while no change was observed between admission and hospital discharge in the latter group[22].

## RANDOMIZED TRIALS WITH INTRAVENOUS STREPTOKINASE

A review of the pooled data from 24 randomized trials of highly different design with intravenous

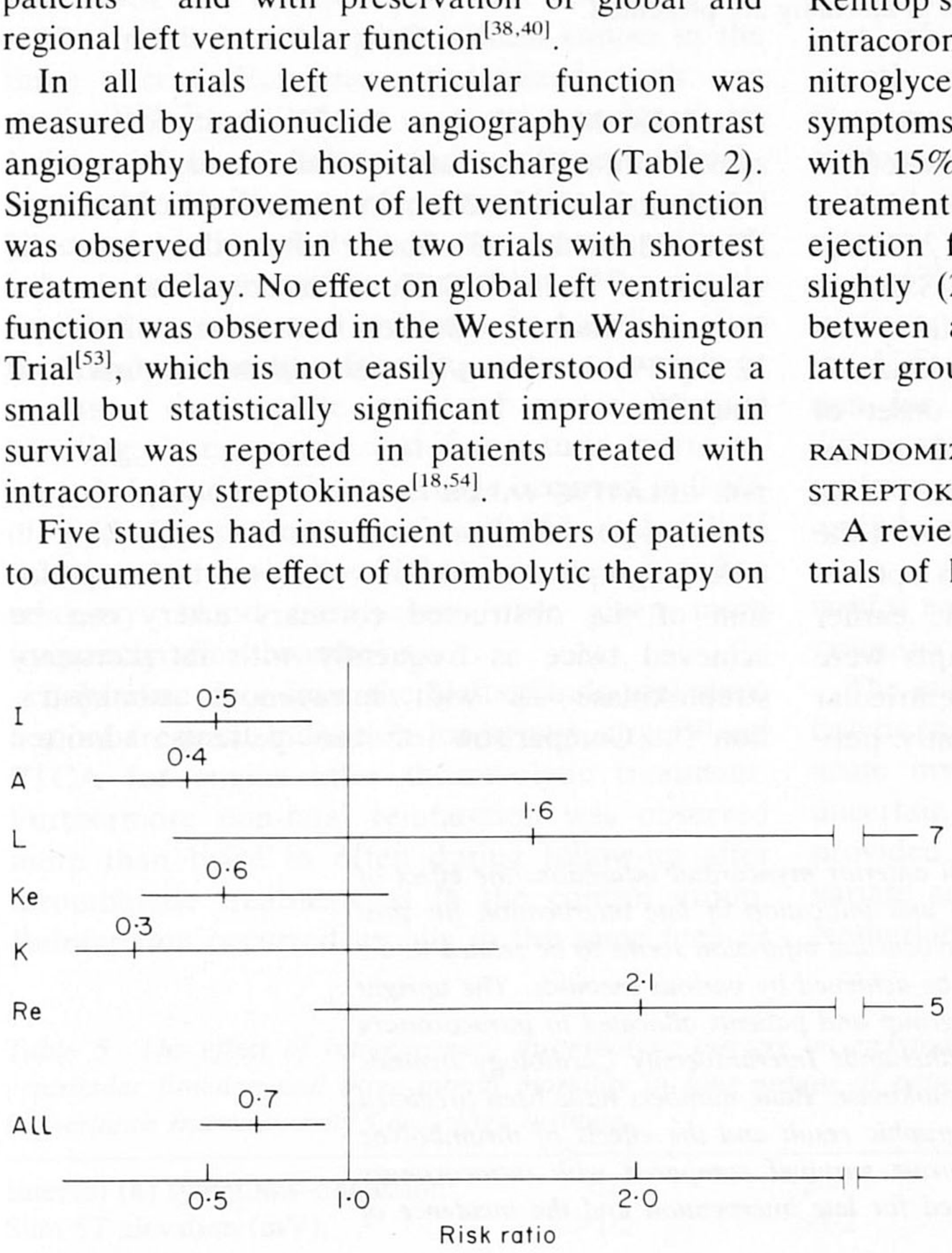


*Figure 2* The effect of thrombolytic therapy on one-year survival. Data from 6 randomized trials comparing thrombolytic therapy with conventional treatment: I = Interuniversity Cardiology Institute[15]; A = Anderson *et al.*[16]; L = Leiboff *et al.*[17]; Ke = Kennedy *et al.*[18]; K = Khaja *et al.*[19]; Re = Rentrop *et al.*[21]. The risk ratios of mortality in patients allocated to thrombolytic therapy *vs* conventional treatment are presented, with their 95% confidence intervals. On average mortality after thrombolysis is 0·7, or 30% lower, compared with conventional treatment.

*Table 3 GISSI in-hospital mortality*

| Time to randomisation | *N* | | Mortality | | Risk difference (95% interval) |
|---|---|---|---|---|---|
| | C | T | C | T | |
| <3 h | 3078 | 3016 | 12% | 9% | −3% (−4%, −1%) |
| 3–6 h | 1800 | 1849 | 14% | 12% | −2% (−5%, 0%) |
| 6–9 h | 659 | 693 | 14% | 13% | −1% (−5%, 0%) |
| 9–12 h | 302 | 292 | 14% | 16% | +2% (−4%, 8%) |
| All | 5852 | 5860 | 13% | 11% | −2% (−3%, −1%) |

Note a 3% reduction of mortality in patients admitted within 3 hours, a smaller reduction in patients admitted up to 9 hours, and a 3% increase mortality in patients admitted between 9 and 12 hours after the onset of symptoms. The confidence limits of the changes in mortality are presented.

streptokinase showed a mortality reduction of 22%[55]. Although in that review the beneficial effect of streptokinase seemed similar when it was given within 12 hours and between 12 and 24 hours after the onset of symptoms, the recent GISSI data confirm that a reduction of hospital mortality can be achieved only when intravenous streptokinase is administered within 6 hours after the onset of symptoms[24]. In patients admitted after 9 hours an adverse increase in mortality was apparent (Table 3). Thus it is now evident that most patients in the early trials were treated too late to obtain optimal myocardial salvage. Unfortunately in the earlier trials, and in the GISSI trial no attempts were made to measure infarct size or left ventricular function. Such observations in the recently published ISAM trial show a 15% limitation in enzymatic infarct size and a small increase in global left ventricular function in the subset of patients admitted within 3 hours after the onset of symptoms[25]. In ISIS II, an interim analysis also showed a marked reduction in early mortality from 12 to 8% in those treated within the first four hours[57].

## THE RELATIVE VALUE OF INTRAVENOUS- AND INTRACORONARY STREPTOKINASE

Angiographic studies have shown that reperfusion of the obstructed coronary artery can be achieved twice as frequently with intracoronary streptokinase as with intravenous administration[23]. Comparison of the patients admitted

*Table 4 Thrombolysis cost–benefit analysis in anterior myocardial infarction: the effect of thrombolytic therapy on infarct size, survival and indication of late intervention for post infarction angina. The incidence of recurrent myocardial infarction seems to be related to the patency of the infarct related vessel which can be achieved by various methods. The upright numbers have been derived from the control group and patients allocated to intracoronary streptokinase in the trial conducted by the Netherlands Interuniversity Cardiology Institute and from the ISAM trial with intravenous streptokinase. Italic numbers have been predicted assuming a linear relation between the angiographic result and the effects of thrombolytic therapy. Immediate PTCA may slightly improve survival compared with intracoronary streptokinase therapy, and may reduce the need for late intervention and the incidence of recurrent infarction[57].*

| | C | SK–IV | rtPA–IV | SK–IC | PTCA |
|---|---|---|---|---|---|
| Patency | 20% | 50% | 70% | 85% | 90% |
| Infarct size limitation | — | 15% | *22%* | 30% | 30% |
| Survival 1 year | 78% | 83% | *87%* | 98% | 90% |
| PTCA/CABG | 15% | *22%* | *26%* | 30% | 20% |
| Recurrent MI | 4% | *6%* | *8%* | 9% | 5% |

within three hours in the two recent intravenous trials, with those in the Netherlands trial with intracoronary streptokinase, suggests that intracoronary treatment is also twice as effective in limitation in infarct size (30% versus 15%), preservation of left ventricular function (6% versus 3%) and in reduction of mortality (6% versus 2% for ISAM and 3% for GISSI). Since intracoronary treatment is both more effective and more expensive the ultimate choice between the two treatment modalities must be based on a cost–benefit analysis such as presented in Table 4.

### CLINICAL FINDINGS AND COMPLICATIONS AFTER THROMBOLYTIC THERAPY AND THE ROLE OF PTCA

The trends in subsequent clinical course in the three recent European randomized trials are similar[14,24,25]. All three suggest a reduced incidence of heart failure and cardiogenic shock, ventricular fibrillation and pericarditis in patients allocated to thrombolytic therapy compared with conventionally treated patients. Also all three trials reported an increased incidence of bleeding after thrombolytic therapy. Bleeding occurred mainly at puncture sites, while non-fatal gastro-intestinal bleeding, haemoptysis and haematuria were reported. Intracranial haemorrhage occurred in 0·5% of (elderly) patients in the ISAM and GISSI studies. As a result of the increased bleeding tendency, blood transfusions were given more frequently after thrombolysis.

Follow-up data from the Netherlands trial show a more frequent indication for bypass surgery and PTCA for angina after thrombolytic treatment. Furthermore non-fatal reinfarction was observed more than twice as often during follow-up after thrombolytic treatment as in the control group. Reinfarction occurred usually in the same area as the first infarct. It was somewhat surprising that nonfatal reinfarction after thrombolysis occurred predominantly in patients with an inferior wall infarction and right coronary disease[56]. Several authors have suggested that reocclusion and reinfarction may be prevented in part by early PTCA or bypass surgery. This is supported by a 'matched pair' comparison of patients in whom immediate PTCA was performed after thrombolytic therapy with patients with similar coronary anatomy without PTCA[58]. During one year follow up of two matched groups of 36 patients, reinfarction occurred in 6 patients with immediate PTCA versus 11 patients with thrombolytic therapy only ($P = 0{\cdot}04$). Similarly late PTCA or bypass surgery for post infarction angina was performed less frequently in patients treated with immediate PTCA (8 versus 14). Also follow up data from the larger randomized trial of thrombolytic therapy with or without immediate PTCA indicate a reduced incidence of reinfarction and post infarction angina[28]. Again prospective larger randomized studies, presently on their way in both Europe and the U.S.A., should determine the proper indication for PTCA after thrombolytic therapy and define whether such additional treatment should be performed immediately or may be deferred for 24 or 48 hours.

### WHICH PATIENTS BENEFIT FROM THROMBOLYTIC THERAPY?

The evidence presented shows that early thrombolytic therapy is an effective mode of treatment in acute myocardial infarction. However, it is yet uncertain to which patients such therapy should be provided. In order to answer this question, multivariate analysis was applied to the data from the Netherlands Interuniversity Cardiology Institute. It

*Table 5 The effect of intracoronary thrombolytic therapy on enzymatic infarct size, global left ventricular function and three month mortality in four groups of patients from the study by the Netherlands Interuniversity Cardiology Institute.*

| Interval (h) symptoms–admission: | <2 | | 2–4 | | <2 | | 2–4 | |
|---|---|---|---|---|---|---|---|---|
| Sum ST elevation (mV): | >1·2 | | >1·2 | | <1·2 | | <1·2 | |
| | C | SK | C | SK | C | SK | C | SK |
| Number of patients | 112 | 92 | 35 | 372 | 72 | 81 | 24 | 35 |
| HBDH release (U $1^{-1}$) | 1440† | 820 | 1640* | 1180 | 800* | 500 | 680 | 660 |
| LVEF (%) | 40† | 48 | 44 | 46 | 44† | 57 | 52 | 47 |
| Mortality (%) | 16* | 7 | 17 | 8 | 10 | 4 | 8 | 9 |

* $P < 0{\cdot}05$; † $P < 0{\cdot}0005$; C *vs* SK C = conventional treatment, SK = intracoronary streptokinase

*Table 6 Indication for thromboyltic therapy: extensive anterior wall ischaemia: the effect of thrombolytic therapy is related to the delay of onset of symptoms and treatment, and the extent of myocardial ischaemia as expressed by the sum of ST-segment elevations in the 12-lead electrocardiogram. Intracoronary or intravenous thrombolytic therapy should only be initiated in patients with certain delay since the onset of symptoms, if the sum of ST-segment elevation exceeds the given threshold as indicated in the table*

| | Sum ST-segment elevation (mV) | |
|---|---|---|
| Delay (hours) | IC–SK | IV–SK |
| 0–1 | >0·4 | >0·8 |
| 1–2 | >0·8 | >1·2 |
| 2–3 | >1·2 | >1·6 |
| 3–4 | >1·6 | >2·0 |
| 4–? | ? | ? |

appeared that both the reduction in enzymatic infarct size, and the improvement in global left ventricular function as well as the reduction of three month mortality by intracoronary thrombolytic therapy were related to two baseline factors: the delay between onset of symptoms and hospital admission and the extent of myocardial ischaemia as assessed from the sum of ST-segment elevation in the 12-lead electrocardiogram upon admission[31,59]. The greatest benefit of thrombolytic therapy in terms of infarct size limitation, left ventricular function and survival was found in patients with extensive myocardial ischaemia admitted within 2 hours after the onset of symptoms (Table 5). In contrast, no benefit was found in patients with less than 1·2 mV ST-segment elevation, admitted between 2 and 4 hours. This analysis is supported by data by the GISSI and ISAM trials indicating that time is the crucial factor which determines the efficacy of thrombolytic therapy (Table 3). In addition to treatment delay and the extent of ischaemia at admission, the long-term efficacy of thrombolytic therapy was related to the site of infarction. In patients with right coronary disease and inferior wall infarction, the modest short term beneficial effects were negated by a high incidence of reocclusion and reinfarction. On the other hand, thrombolytic therapy improved both survival and quality of life at one year follow-up in patients with anterior or antero-septal infarction[56].

On the basis of these observations, thrombolytic therapy may now be recommended in patients with extensive anterior wall ischaemia admitted early after the onset of symptoms. Based on the multivariate analysis we have developed criteria for the amount of ST-segment elevation required for thrombolytic therapy to be effective in patients with a given delay after the onset of symptoms as shown in Table 6. Since intravenous administration of streptokinase appears to be half as effective as intracoronary infusion, while the risks of bleeding and cerebro-vascular accidents might even be greater, indications for intravenous streptokinase therapy should even be more strict. Although it can be given easily, intravenous thrombolytic therapy should not be given to patients with small inferior infarcts nor in those admitted beyond the fourth hour.

## FURTHER DEVELOPMENTS OF THROMBOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION

Recent studies with tissue plasminogen activator (rtPA) indicate that intravenous administration resulted in approximately 70% patency of the infarct related coronary arteries. Thus rtPA seems to be more effective than intravenous streptokinase, but less effective than intracoronary thrombolytic treatment. Accordingly it may be expected that its clinical effects will also be intermediate (Table 4). The same may be true for the acylated streptokinase/plasminogen complex (APSAC) which is presently under clinical investigation[60,61]. However, the true clinical value of these newer drugs can only be defined after completion of the presently ongoing trials in Europe and the U.S.A.

Since the yield of thrombolytic therapy in patients with extensive anterior infarction is higher when treatment is started early after the onset of symptoms, initiation of therapy in the pre-hospital phase should be considered[62]. However, the risk of such therapy, particularly the risk of cerebrovascular accidents is not negligible. Thus initiation of thrombolytic therapy by the ambulance-service will require ECG confirmation of extensive anterior ischaemia. Contra-indications such as age greater than 70 years, coma, trauma or traumatic resuscitation and history of bleeding or cerebrovascular accidents should be respected. We believe that if proper precautions are taken, and paramedic personnel are appropriately trained, initiation of thrombolytic therapy outside the hospital can reduce the damage to the myocardium even further.

The optimal therapy of patients with acute extensive anterior myocardial ischaemia will prob-

ably include immediate initiation of intravenous therapy by streptokinase, rtPA or other drugs, followed by transfer to a hospital with full catheterization facilities where intracoronary treatment can be followed by PTCA when appropriate. The development of such new referral systems requires optimal cooperation between the cardiology staff in the referral centre, their colleagues in the referring hospitals without catheterisation laboratory facilities, general practitioners and ambulance service. The development of such integrated systems with guidelines for additional therapy and methods for prevention of reocclusion after initially successful reperfusion remain the challenge for the immediate future.

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