

THROMBOLYSIS WITH TISSUE PLASMINOGEN ACTIVATOR IN ACUTE MYOCARDIAL INFARCTION: NO ADDITIONAL BENEFIT FROM IMMEDIATE PERCUTANEOUS CORONARY ANGIOPLASTY

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(rTPA) *

Summary A randomised trial of 367 patients with acute myocardial infarction was performed to determine whether an invasive strategy combining thrombolysis with recombinant tissue-type plasminogen activator (rTPA), heparin, and acetylsalicylic acid, and immediate percutaneous transluminal coronary angioplasty (PTCA) would be superior to a noninvasive strategy with the same medical treatment but without immediate

angiography and PTCA. Intravenous infusion of 100 mg rTPA was started within 5 h after onset of symptoms (median 156 min). Angiography was performed 6–165 min later in 180 out of 183 patients allocated to the invasive strategy; 184 patients were allocated to the non-invasive strategy. Immediate PTCA reduced the percentage stenosis of the infarct-related segment, but this was offset by a high rate of transient (16%) and sustained (7%) reocclusion during the procedure and recurrent ischaemia during the first 24 h (17%). The clinical course was more favourable after non-invasive therapy, with a lower incidence of recurrent ischaemia within 24 h (3%), bleeding complications, hypotension, and ventricular fibrillation. Mortality at 14 days was lower in patients allocated to non-invasive treatment (3%) than in the group allocated to invasive treatment (7%). No difference between the treatment groups was observed in infarct size estimated from myocardial release of alpha-hydroxybutyrate dehydrogenase or in left ventricular ejection fraction after 10–22 days. Since immediate PTCA does not provide additional benefit there seems to be no need for immediate angiography and PTCA in patients with acute myocardial infarction treated with rTPA.

Introduction

RANDOMISED trials of thrombolytic therapy with intracoronary streptokinase¹ or intravenous streptokinase² have demonstrated improved survival as well as limitation of infarct size³ and preservation of left ventricular function⁴ in patients treated within 4–6 h after onset of symptoms of acute myocardial infarction. Several groups have proposed

*Participating clinics are listed at the end of the article.

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immediate percutaneous transluminal coronary angioplasty (PTCA) for reperfusion of the ischaemic myocardium in addition to⁵ or without⁶ thrombolytic therapy. Immediate PTCA may open vessels that remain occluded despite thrombolytic therapy and reduce the residual coronary stenosis after thrombolytic therapy. The improved bloodflow might further reduce infarct size and preserve left ventricular function.⁷ Finally, PTCA might reduce the incidence of post-infarction angina, reocclusion, and reinfarction after thrombolytic therapy.^{8,9}

The European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator (rTPA) has conducted a randomised trial to determine whether an invasive strategy, combining thrombolysis with rTPA, heparin, acetylsalicylic acid, and immediate PTCA, would be superior to a non-invasive strategy of treatment with intravenous rTPA, heparin, and acetylsalicylic acid alone. The end-points were enzymatic infarct size, global left ventricular function, and findings on clinical follow-up. Patient enrolment started in May, 1986. The trial was prematurely terminated in June, 1987, on the advice of the data monitoring and ethical committee. This report presents the main results of the trial.

Patients and Methods

Ten hospitals with extensive PTCA experience in six European countries participated in the trial. Patients were admitted with a diagnosis of suspected myocardial infarction, characterised by chest pain of at least 30 min duration and typical changes in the electrocardiogram: ST-segment elevation of 0.3 mV or greater in two or more chest leads (V_1 - V_4) and/or greater than 0.2 mV in leads I, II, III, aVL, aVF, V_5 , or V_6 . In addition, patients were included with at least 0.1 mV ST-segment elevation in two leads (II, III, aVF, V_5 , V_6) and at least 0.2 mV ST-segment depression in two chest leads V_1 - V_4 .

Patients younger than 71 years in whom treatment could be started within 5 h after the onset of symptoms were included. The usual contraindications for thrombolytic therapy were applied.¹⁰ In addition, patients with a previous myocardial infarction at the same site or with previous coronary artery bypass surgery were excluded. Patients with heart failure or shock were not excluded.

When informed consent had been obtained, intravenous administration of rTPA was started without delay. After a 10 mg bolus injection, 50 mg was given in the first hour, followed by 40 mg in the next 2 h. Thus, in total 100 mg was administered in 3 h. Single-chain rTPA (Genentech Inc, G-11044) was supplied by Boehringer Ingelheim International GmbH. In addition to rTPA, 250 mg acetylsalicylic acid was given intravenously, plus heparin 5000 IU followed by a continuous infusion of 1000 IU/h. Patients were allocated by telephone to either the non-invasive strategy of treatment with intravenous rTPA, acetylsalicylic acid, and heparin or to the invasive strategy with the same medical treatment combined with immediate PTCA. At first a lower dose of 75-125 mg acetylsalicylic acid was given as initial treatment. As the PTCA procedure was complicated by reocclusion in about 5 out of 7 patients allocated to invasive strategy, the initial dose of acetylsalicylic acid was increased to 250 mg.

The protocol specified that coronary angiography was to be performed as soon as the catheterisation laboratory was available. Mechanical recanalisation should be attempted if the infarct-related segment of the coronary artery appeared occluded. PTCA should be attempted in all patients, unless the diameter stenosis of the lesion was judged to be less than 60%. Until hospital discharge all patients were anticoagulated with heparin, which could be replaced by warfarin after 3 days, provided that full anticoagulation was maintained. In addition, 75-125 mg acetylsalicylic acid was given every other day. Beta-blockers, calcium antagonists, and nitrates could be prescribed when indicated but were to be withdrawn the night before late angiography.

TABLE I—BASELINE CHARACTERISTICS

	Non-invasive strategy	Invasive strategy
No of patients	184	183
Age (yr)	54 (37-67)	58 (38-68)
Male	164 (89)	161 (88)
History of angina	133 (72)	136 (74)
Previous infarction	12 (7)	13 (7)
Anterior infarction	82 (45)	83 (45)
Heart rate (/min)	76 (52-100)	76 (55-100)
Systolic blood pressure (mm Hg)	130 (100-160)	130 (95-160)
Diastolic blood pressure (mm Hg)	80 (60-100)	80 (60-100)
Mild heart failure	46 (25)	36 (20)
Overt heart failure/shock	1 (1)	7 (4)
Immediate angiography	—	180 (98)
Infarct-related vessel		
Left main stem	—	1
Anterior descending artery	—	80
Left circumflex artery	—	28
Right coronary artery	—	69
Normal coronary arteries	—	2

Actual number of patients are shown. Continuous variables are presented as median and 90% range. Percentages of patients in each treatment group or ranges are shown in parentheses.

Infarct size was estimated from serial alpha-hydroxybutyrate dehydrogenase (HBDH) determinations by the core laboratory for enzyme determination.^{11,12} Blood samples were taken at admission and at 12, 24, 36, 48, 72, and 96 h. Enzymatic infarct size was estimated by the cumulative quantity of HBDH released by the heart per litre plasma in 72 h (Q72).

Coronary arteriography and ventriculography were performed before hospital discharge. To ensure comparability, each hospital chose a time window in which late angiography was scheduled: 10-14, 12-16, 14-18, 16-20, or 18-22 days after admission. Left ventricular ejection fraction was computed by the core laboratory for quantitative angiography. In addition to local assessment of the coronary angiograms, both acute and late angiograms were centrally assessed by members of the angiography assessment group. In patients who underwent immediate PTCA, all intracoronary manipulations, including further dilatations with a larger size balloon in case of reocclusion, were considered to be part of the same PTCA procedure until the guiding catheter was withdrawn. Further procedures that were performed after withdrawal of the guiding catheter are reported as new interventions (re-PTCA). Two methods of grading of coronary angiograms were applied—the grades of diameter stenosis as previously used by the European Cooperative Study Group¹⁰ and the TIMI perfusion score:¹³

Grades of Stenosis

- 5 = 100% diameter stenosis
- 4 = 91-99% diameter stenosis, no complete filling within 3 cycles
- 3 = 91-99% diameter stenosis, complete filling within 3 cycles
- 2 = 50-90% diameter stenosis
- 1 = less than 50% diameter stenosis
- 0 = normal

Grades of Perfusion

- 0 = non-perfusion
- 1 = penetration with minimal perfusion (contrast fails to opacify entire coronary bed distal to the stenosis for the duration of the cine run)
- 2 = partial perfusion (contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in coronary bed distal to the obstruction than in comparable areas not perfused by the infarct related vessel)
- 3 = complete perfusion (filling and clearance of contrast as rapid in coronary bed distal to stenosis as in other coronary beds)

Both the core laboratory for enzyme determination and the core laboratory for quantitative angiography were unaware of the treatment allocation.

Results

367 patients were evaluated. The median number of patients per hospital was 34, ranging from 13 to 78 patients. 184 patients were allocated to non-invasive treatment and 183 to rTPA followed by immediate angiography and PTCA. 1 additional patient had been allocated to non-invasive therapy but has been excluded from analysis because treatment allocation as given by telephone was not correctly interpreted by the local investigator and immediate PTCA was performed. This patient had an uneventful follow-up. Baseline characteristics were similar in the two treatment groups, except that the non-invasive group had 1 patient with severe cardiac failure on admission and the invasive group 7 patients, and mild heart failure on admission was more frequent in the non-invasive group (table 1). Immediate angiography was performed in 180 patients (fig 1). Angiography was not performed in 1 patient who died from shock, in 1 patient because of withdrawal of consent, and in 1 patient for technical reasons. The delay between onset of symptoms and rTPA infusion ranged from 30 to 294 min, median 156 min, and the delay between infusion and angiography ranged from 6 to 165 min, median 42 min.

TABLE II—CLINICAL COURSE AND FOLLOW UP

	Non-invasive strategy (n = 184)	Invasive strategy (n = 183)
Recurrent ischaemia within 24 h	6 (3)	31 (17)
Hypotension (less than 90 mm Hg)	17 (9)	57 (31)
Shock	6 (3)	11 (6)
Pulmonary oedema	8 (4)	9 (5)
3rd degree A-V block	7 (4)	11 (6)
Ventricular fibrillation	6 (3)	21 (11)
Ventricular tachycardia	51 (28)	54 (30)
Pericarditis	12 (7)	11 (6)
Bleeding complications:	43 (23)	75 (41)
Local haematoma	30	55
Prolonged bleeding	11	22
Intracranial bleeding/CVA	1*	1
Haemoptysis	1	1
Epistaxis	1	1
Gingival bleeding	3	9
Haematemesis	—	5
Melaena	1	1
Rectal bleeding	2	—
Macroscopic haematuria	4	5
Retroperitoneal haematoma	1	3
Haemopericardium	1	2
Blood transfusion	7 (4)	18 (10)
Surgical correction at bleeding site	1 (1)	2 (1)
Status at 14 days		
Mortality	5 (3)	12 (7)
Recurrent ischaemia after 24 h	21 (11)	23 (13)
Reinfarction (re-)PTCA	12 (7)	8 (4)
CABG	11 (6)	8 (3)
(re-)PTCA + CABG	—	3 (2)
(re-)PTCA + CABG	1 (1)	—
Status at 3-month follow-up:		
Mortality	6 (3)	15 (8)
Recurrent ischaemia after 24 h	55 (30)	52 (28)
Reinfarction (re-)PTCA	18 (10)	12 (7)
CABG	23 (13)	11 (6)
(re-)PTCA + CABG	7 (4)	9 (5)
(re-)PTCA + CABG	3 (2)	—

Actual number of patients with an event after allocation are presented; percentages of patients in each treatment group are shown in parentheses. Recurrent ischaemia after 24 h represents patients without reinfarction. Numbers given for status at 3-month follow-up are cumulative. *CT scan: no bleeding.

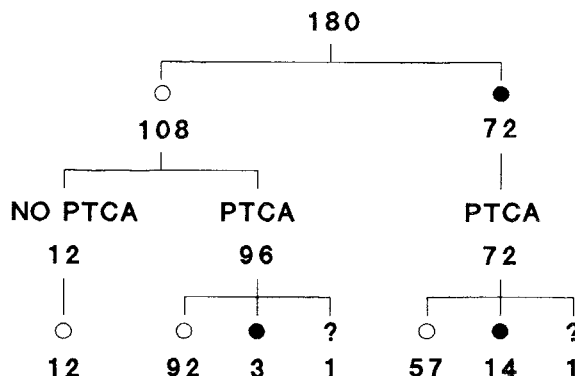


Fig 1—Results of angiography and PTCA in 180 patients allocated to invasive treatment who underwent immediate angiography.

Vessels were classified as patent (○ = stenosis grades 0–3) or occluded (● = stenosis grades 4–5). In 2 patients no angiogram was available after attempted PTCA.

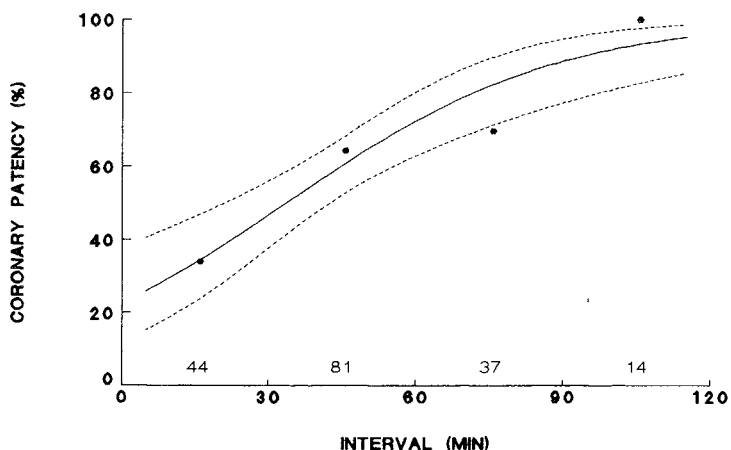


Fig 2—Patency of infarct related vessel (stenosis grades 0–3) in relation to interval between start of rTPA infusion and angiography.

The four large dots indicate percentage of patients with a patent vessel when angiography was performed within 30, 30–60, 60–90, and later than 90 min after start of infusion. A logistic regression model was used to estimate the relation between the duration of rTPA infusion and patency. The result of this analysis is presented by the closed line, and its 95% confidence intervals by the dotted lines. Estimated patency at 90 min was 89%. In 4 patients the exact delay was uncertain. In the four groups patency was 15/44, 51/81, 25/37, and 14/14.

Immediate Angiography

In patients allocated to invasive therapy, patency (defined as stenosis grades 0–3) was related to the delay between onset of rTPA infusion and angiography as shown in fig 2. Complete occlusion (grade 5) was observed in 42 patients and subtotal occlusion without complete filling of the distal vessel (grade 4) in 30 patients (fig 3a). PTCA was attempted in 168 patients. No immediate PTCA was done in 8 patients who did not have significant lumen narrowing, in 3 patients in whom the anatomy was judged unsuitable for PTCA (1 left main equivalent, 1 severe 3-vessel disease, and 1 old occlusion in the anterior descending artery with retrograde filling by the right coronary artery), and in 1 patient in whom the infarct-related vessel could not be identified (fig 1).

Immediate PTCA in this study appeared to be more troublesome than elective PTCA. The number of balloon inflations ranged from 1 to 15, median 4, with a total inflation time between 30 and 885 s, median 180. In 5 patients the lesion could not be crossed with guidewire or balloon. In 32 patients more than one stenosis was dilated. At the end of intervention, central angiographic assessment revealed an occluded vessel (grades 4 and 5) in 17 patients and less than 50% stenosis (grades 0 and 1) of the infarct-related segment in 103 patients (fig 3). Before the initial acetylsalicylic acid dose was increased to 250 mg

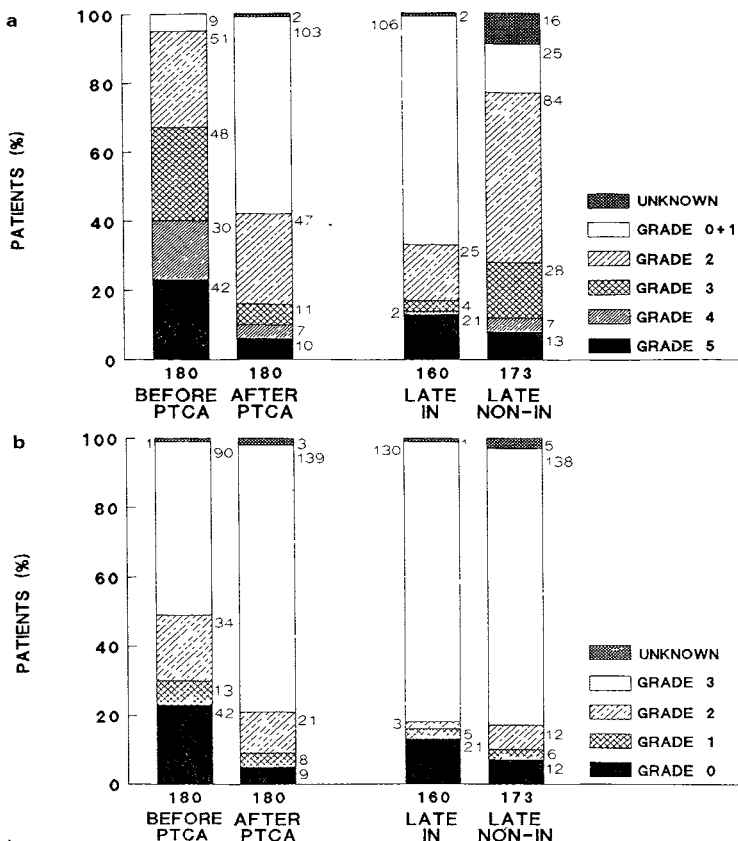


Fig 3—Grades of stenosis (a) and perfusion (b) of infarct-related vessel before and after PTCA and after 10–22 days in patients allocated to invasive (IN) and non-invasive (non-IN) therapy.

Unknown = patients in whom the infarct-related segment (a) or artery (b) could not be identified in the angiogram. The number of patients with angiography is given under each bar; numbers next to the bars represent the number of patients in that particular subgroup.

intravenously, transient reocclusion during intervention occurred in 4 out of 7 patients and permanent reocclusion in 1. After increasing the acetylsalicylic acid dose, transient reocclusion during intervention occurred in 22 and permanent reocclusion in 12 patients in whom PTCA was attempted. Additional intracoronary streptokinase was given in 2 patients with transient reocclusion and in 1 patient because of recurrent stenosis. In 2 patients an initially patent infarct-related segment was found to be occluded after completion of the PTCA procedure. In 1 other patient reocclusion occurred during coronary angiography before PTCA. Subsequent PTCA was not successful.

Clinical Course

The clinical course is summarised in table II. Overall, the outcome was more favourable in patients with non-invasive therapy. Differences between the treatment groups were equally distributed over the participating clinics, and not dependent on infarct location at admission. Mortality at 14 days and at three months was low (3%) in patients allocated to non-invasive strategy. 1 patient in this group was resuscitated during rTPA infusion (table III). He had intraperitoneal bleeding from a liver haematoma on day 2 and died on day 3 after reinfarction and shock. In patients allocated to invasive therapy, 14 day mortality was 7%. 4 of the 7 patients in this group admitted with severe heart failure or shock died. Two deaths after immediate PTCA were associated with bleeding complications, one of them in a patient who died from intraperitoneal bleeding, probably caused by trauma before hospital admission.

Recurrent ischaemia within 24 h was observed in 17% of patients with immediate PTCA and in 3% of patients allocated to non-invasive therapy. In the latter group exacerbation or recurrence of chest pain was recorded in 1 patient, chest pain with ST-segment elevation in 4 patients, and ST-elevation without chest pain in 1 patient. After PTCA these figures were 4, 19, and 8, respectively. Episodes of hypotension and ventricular fibrillation were more frequent after PTCA.

Bleeding complications were more prominent after immediate PTCA, mostly as a result of arterial puncture and the catheterisation procedure. 1 patient in the PTCA group underwent surgery for a retroperitoneal haematoma after angiography, and 2 patients survived after pericardiocentesis for cardiac tamponade. In 1 patient this was related to perforation by a pacemaker electrode, in the other there was no apparent trauma. In the group allocated to non-invasive treatment, 1 patient survived after pericardiocentesis for cardiac tamponade. The greater incidence of bleeding complications after attempted PTCA is also apparent from the greater drop in haematocrit in these patients (44 SD 4% at admission and 37 SD 5% after 72 h) in comparison with those treated non-invasively (44 SD 4% and 40 SD 5%, respectively), and from the greater need for blood transfusions.

Enzymatic Infarct Size

Complete blood sample series for determination of enzymatic infarct size by the core laboratory were obtained in 309 patients (84%). HBDH-Q72 could be estimated from series of HBDH measurements obtained up to 36 or 48 h in 18 patients, and from a single HBDH plasma level between 24 and 96 h after onset of symptoms in 25 patients. Local determinations of aspartate aminotransferase (ASAT) or HBDH could be employed to estimate HBDH-Q72 in 7 patients. Thus, enzymatic infarct size could be assessed in 359 patients (98%). In 7 patients HBDH data were not available because of early death and in 1 patient because of early bypass surgery. Enzymatic infarct size did not differ between the non-invasive group (median 665 U/l, 90% range 32–2022 U/l) and the invasive group (median 706 U/l, 90% range 115–1914 U/l). Similar results were obtained when only complete sample series from 309 patients were used.

Late Angiography

The effect of immediate PTCA on the status of the infarct-related segment after 10–22 days is best described by the grade of residual stenosis (fig 3a). An occluded vessel (grades 4 and 5) was observed in 20 patients without PTCA and in 23 patients with immediate PTCA. On the other hand, stenoses of less than 50% diameter were observed more frequently in patients allocated to invasive therapy (n = 106) than in the other group (n = 25). These differences were not apparent if the TIMI perfusion score was applied as shown in fig 3b. Complete perfusion (TIMI grade 3) was observed in 138 patients after non-invasive initial therapy and in 130 patients after immediate PTCA.

Left ventricular angiography was performed in 33 patients between days 10 and 22. Missing angiograms were due to patient death (n = 17), patient refusal (n = 6) coronary bypass surgery (n = 3), very poor ventricular function (n = 2), ventricular tachycardia (n = 1), and reinfarction (n = 1), and in 4 cases to clinical, non-cardiac reasons. Quantitative analysis was performed in 29

TABLE III—EARLY AND LATE MORTALITY

Sex	Age	Site	IRV	Stenosis grades/ intervention	Time	Cause of death and details of intervention
<i>Non-invasive strategy</i>						
M	59	I	—	—	8 h	Shock, cardiac arrest
M	55	I	—	—	3 d	Intraperitoneal bleeding after resuscitation, reinfarction
M	58	A	—	—	3 d	Shock
M	59	A	LAD	—	7 d	Shock after reinfarction PTCA not successful
M	62	A	—	—	13 d	At LV-angio possibly dissection aorta, shock
M	67	A	—	—	22 d	Low output after aneurysmectomy
<i>Invasive strategy</i>						
M	64	I	RCA	2-PTCA-2	2 h	Shock after PTCA, VF
M	58	I*	—	—	2 h	Shock, no angiography
F	64	I	RCA	5-PTCA-5	4 h	Cardiac arrest, VF
M	62	A	LAD	2-PTCA-1	15 h	Cerebral bleeding
F	67	I	RCA	4-PTCA-1	15 h	Intraperitoneal bleeding
M	61	A*	LAD	5-PTCA-1	17 h	Mainstem lesion, shock, death during CABG
M	45	I	LCX	3-5	2 d	Occlusion during angio, PTCA attempt failed, shock
F	69	I	RCA	3-PTCA-3	3 d	Reinfarction
F	62	I	LCX	2	3 d	No PTCA (3 vessel), asystole after delayed PTCA for angina
M	53	A	LAD	5-PTCA-2	3 d	Reinfarction, shock
F	66	A*	LAD	3-PTCA-2	7 d	Reocclusion, shock
M	67	A*	LAD	3-PTCA-2	14 d	Shock
M	56	I	RCA	3-PTCA-1	47 d	Late VF, coma
M	60	I	RCA	3-3	48 d	Failure to cross lesion, old anterior MI, sudden death
M	47	A	LAD	3-PTCA-4	66 d	Sudden death

Baseline data, results of angiography and PTCA, when performed, as well as time and cause of death are given. Stenosis grades before and after PTCA as centrally assessed are presented. IRV = infarct-related vessel; A = anterior, I = inferior; * = shock at admission; LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery; VF = ventricular fibrillation; CABG = coronary artery bypass grafting; h = hours after allocation; d = days after allocation.

angiograms of adequate quality. There were no differences in left ventricular ejection fraction between patients allocated to non-invasive therapy and those allocated to invasive therapy (median 51%, 90% range 29–65%, versus median 51%, 90% range 31–66%).

Discussion

Contrary to what was expected when the study was designed, thrombolytic therapy combined with immediate PTCA did not appear to be superior to early non-invasive treatment with intravenous rTPA, heparin, and acetylsalicylic acid in acute myocardial infarction. Immediate PTCA was effective in increasing the number of patients with a patent infarct-related vessel and improved perfusion as visualised during angiography (fig 3). However, in the setting in which it was studied, PTCA was associated with a high rate of early reocclusion and/or early recurrent ischaemia. Also, immediate PTCA did not further reduce enzymatic infarct size or improve global left ventricular function when compared with non-invasive treatment. Finally, a complicated clinical course occurred more frequently after PTCA and 3-month mortality was higher than after non-invasive therapy.

The present study was planned to include a total of 400 patients. However, when the data monitoring and ethical committee reviewed the data in June 1987, it became apparent that immediate PTCA in this setting was not beneficial and might even be detrimental in some cases. At that time mortality was 6 out of 171 patients allocated to non-invasive therapy and 11 out of 173 patients allocated to invasive therapy, while cardiovascular and bleeding complications were also more frequent in the latter group.

Enzymatic infarct size had been determined in 165 patients and left ventricular ejection fraction in 110 patients. Median values in the non-invasive and invasive group were 730 U/l versus 911 U/l for HBDH-Q72 and 53% versus 47% for left ventricular ejection fraction. Therefore, patient intake was terminated by the steering committee as of June 27, 1987.

In patients allocated to invasive strategy who underwent angiography 42 min after the start of rTPA infusion (median), the infarct-related segment was patent (stenosis grades 0–3) in 59%. It should be appreciated that in most other studies^{8,10,13,14} patency rates were reported after 90 minutes' infusion of rTPA. Fig 2 shows that patency is achieved gradually during rTPA administration and ranges from 34% in patients studied within 30 min to 100% in patients studied between 90 and 165 min from the start of infusion. Patency at 90 min, estimated by a logistic regression model, was 89%.

Recurrent ischaemia and/or reinfarction within 14 days was observed in 15% of patients after non-invasive therapy. Similar results were obtained in the TAMI Study, where recurrent ischaemia and/or reinfarction was observed in 17% of patients with a patent vessel without immediate PTCA.¹⁴ It should be appreciated that the clinical observation of recurrent ischaemia or reinfarction does not necessarily coincide with angiographic reocclusion. For example, in the TAMI study reocclusion was observed in only 6 out of 17 patients who underwent angiography for recurrent ischaemia.¹⁴ These observations confirm the results from an earlier study by the European Cooperative Study Group in which reocclusion occurred in 7% of 73 patients 6–24 h after double-chain rTPA.¹⁵ Thus reocclusion after thrombolysis with rTPA occurs less frequently than indicated by earlier

studies in a small number of patients treated with a relatively low dose of double-chain rTPA.¹⁶

Immediate PTCA in patients with acute myocardial infarction was introduced as an extension of intracoronary thrombolytic therapy with streptokinase.⁵ In selected patients, PTCA after intracoronary streptokinase has been reported to reduce the risk of reocclusion and mortality.^{5,6} In a randomised trial, Erbel et al¹⁷ compared treatment with intracoronary streptokinase with and without immediate PTCA in 162 patients. These workers report that PTCA reduced the reocclusion rate at 4 weeks from 14 out of 71 patients with a patent vessel without PTCA (20%) to 10 out of 71 patients (14%) after PTCA, while a trend towards lower mortality in patients with immediate PTCA was also observed.¹⁷⁻¹⁹ Thus, the question arises whether the response to angioplasty in patients treated with streptokinase differs from that in patients treated with rTPA. The higher tendency to reocclude in the latter group might be related in part to the "thrombus specificity" of rTPA. Remnants of thrombus material, together with the endothelial trauma caused by PTCA and subintimal bleeding,^{20,21} can then be held responsible for the tendency to thrombosis in patients treated with rTPA, despite concomitant treatment with acetylsalicylic acid and heparin, while early rethrombosis after PTCA in patients treated with streptokinase may be prevented by the depletion of fibrinogen and other coagulation factors due to streptokinase. On the other hand, it is possible that differences between studies of PTCA in combination with streptokinase or rTPA are merely due to patient selection and small sample sizes.

The clinical course in the present study was less favourable in patients allocated to immediate PTCA. The higher mortality in the invasive group may be due in part to the greater number of patients with severe heart failure or shock at admission, of whom 4 died, and to the high incidence of reocclusion during or after immediate PTCA. The latter factor can also explain the higher incidence of hypotension and ventricular fibrillation. The higher incidence of bleeding complications was related to arterial puncture for angiography and PTCA. The observations in the present trial are similar to those reported from the TAMI¹⁴ trial which likewise showed a trend towards higher mortality without improvement in global or regional ejection fraction. It should be noted, however, that the design of these two studies was different. In TAMI all patients underwent acute angiography and only those with a patent vessel, suitable for PTCA, were randomised (197 out of 386 patients). In the present study acute angiography was performed only in patients randomised to invasive strategy and PTCA was attempted in 92% of these. TAMI answered the question whether PTCA would be beneficial in a selected subgroup of patients who underwent angiography during thrombolytic therapy with intravenous rTPA. The European Cooperative Study Group investigated whether an invasive strategy, including angiography and immediate PTCA, would be superior to non-invasive intravenous thrombolytic therapy with rTPA. These differences notwithstanding, both studies indicate that immediate PTCA after intravenous rTPA in combination with acetylsalicylic acid and heparin should be avoided.

The present study was not designed to demonstrate the effect of thrombolysis with intravenous rTPA per se. The value of thrombolytic therapy in selected patients with acute myocardial infarction has been shown by randomised trials with intracoronary and/or intravenous streptokinase.¹⁻⁴ Patient selection criteria in the present trial were similar to

those of the trial conducted by the Interuniversity Cardiology Institute in the Netherlands.¹ Hospital mortality in conventionally treated patients in that study was 10%, and 6% in patients allocated to intracoronary streptokinase. In the present trial 14-day mortality in patients treated non-invasively was even lower—3%. Were these findings to be confirmed by ongoing trials comparing the effect of intravenous rTPA and placebo on enzymatic infarct size, left ventricular function, and mortality, treatment with rTPA should certainly be recommended in selected patients. An invasive strategy of treatment with rTPA, acetylsalicylic acid, and heparin, in combination with immediate angiography and PTCA has no additional benefit. Delayed angiography, PTCA, or bypass surgery might be offered to patients with new episodes of myocardial ischaemia.

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CORONARY THROMBOLYSIS AND MYOCARDIAL SALVAGE BY TISSUE PLASMINOGEN ACTIVATOR GIVEN UP TO 4 HOURS AFTER ONSET OF MYOCARDIAL INFARCTION

NATIONAL HEART FOUNDATION OF AUSTRALIA
CORONARY THROMBOLYSIS GROUP *

Summary 144 patients presenting within 4 h of onset of myocardial infarction were randomised to receive either 100 mg of single-strand recombinant tissue plasminogen activator (rTPA) in 3 h (n=73) or placebo infused at the same rate (n=71). All patients were given heparin 5000 units before the infusion and heparin was continued, initially at 1000 units per hour, after the infusion. Minor bleeding was more frequent in the rTPA recipients, and during subsequent anticoagulant therapy there were three clinically significant bleeding episodes in this group. Patency of the infarct-related coronary artery was determined by coronary angiography about one week post-infarction, 125 angiograms being assessable. The infarct-related artery was patent in 70% of patients who received rTPA and in 41% of those who did not (p=0.0015). In the 103 patients who had assessable contrast ventriculograms, the global ejection fractions were 57.7% and 51.7%, respectively (p=0.04). The difference in ventricular function was largest in patients with anterior infarction (52.7% versus 40.0%, p=0.02). The magnitude of these changes suggests an improvement in ejection fraction of 12% overall and about 30% in patients with anterior infarction.

Introduction

CORONARY thrombolysis with an intravenous fibrinolytic agent has been shown to be a feasible and effective therapy for patients presenting early after acute myocardial infarction.¹⁻⁵ Recombinant tissue plasminogen activator (rTPA) has properties of clot selectivity and lack of antigenicity which render it suitable for use in these circumstances.^{6,7} Initial clinical experience in Europe and the United States showed that it is a highly effective thrombolytic agent achieving coronary recanalisation in up

to 70% of cases.⁸⁻¹¹ To date there is no certainty that the reperfusion so achieved will improve left ventricular function and it is not clear whether the coronary artery will remain patent for long enough to allow elective management of the residual stenosis. To answer these questions we designed a trial to assess the effect of rTPA on ventricular function and coronary patency one week after intravenous administration. The timing of cardiac catheterisation was chosen to avoid the phase of early ventricular dysfunction that persists after coronary perfusion¹² while allowing examination of the results before the patient left hospital (so that coronary revascularisation, if indicated, could be planned).

The trial was a randomised double-blind, placebo-controlled, multicentre study in five Australian teaching hospitals, conducted between May, 1986, and August, 1987.

Patients and Methods

Patient Selection

Patients aged 75 years or less, with suspected new or recurrent myocardial infarction, were considered for the trial if they presented to hospital within 4 h of symptoms, if they had cardiac pain of typical character and location, and if the electrocardiogram showed ST segment elevation in two or more leads (>2 mm in suspected anterior infarction or >1 mm in suspected inferior infarction). Patients were excluded if there was a contraindication to thrombolytic therapy. After informed consent patients were randomised to active or placebo groups with separate strata for patients <2 h from onset of pain and recurrent infarction.

rTPA and Heparin Infusion

The active drug was recombinant tissue plasminogen activator produced by a cell suspension culture process that generates predominantly the single-chain product (manufactured by Genetech and supplied by Boehringer Ingelheim Pty Ltd). All patients received intravenous heparin, 5000 units, immediately before the rTPA/placebo infusion. Patients in the active group received a bolus injection of 10 mg of rTPA followed by 50 mg over the next hour and 40 mg over the subsequent 2 h. Patients in the placebo group received an inactive infusion of normal saline at the same rate. After completion of the infusion, heparin was begun at a rate of 1000 units per hour and monitored regularly to achieve therapeutic heparin activity.

*Participating centres are listed at the end of the article.

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