Trials of the European Working Party on Streptokinase and of the European Cooperative Study Group on Alteplase in Patients with Acute Myocardial Infarction

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The first trial of the European Working Party was commenced in 1962 at a time when no controlled, strictly randomized, large scale trials on the clinical use of thrombolytic drugs in patients with recent myocardial infarction (MI) were available.

At that time, the frequency with which a fresh thrombus complicates the coronary atheromatous lesion in acute MI was derived from autopsy studies and reported to vary from 13%–74%.[1] This disparity was doubtless due in part to the selection of the patient samples (sudden, early, late deaths), to types of infarctions (transmural, subendocardial), and to the methods of postmortem study (dissection or angiography). The prevailing hypothesis that a coronary thrombus was often *secondary* to a MI was based, among other things, on the fact that at autopsy a thrombus was found more frequently in the older infarcts, after cardiac shock, or after severe heart failure.[2] The finding that radioactive fibrinogen, given in the acute phase of MI, has been recovered in the coronary thrombus at autopsy was wrongly considered as an argument in favor of the thesis that the thrombus follows the MI. In fact, thrombi that are already old may still extend and continue to take up radioactive fibrinogen. New opportunities available 20 years later presented by coronary angiography and performed during the first hours after the initial symptoms of acute MI have brought this long debate to a halt; it is now clear that there is an 85% chance of finding in vivo an occlusion in the coronary artery near the infarcted zone in the first hours after acute MI.

The following considerations, although essentially speculative, appeared to provide in the early 1960s a rational basis for controlled trials with thrombolytic drugs in patients with acute MI. Associated with MI, fibrin had been observed not only in the occluded coronary artery, but also in the collateral circulation in the myocardium, in thrombi forming in the cavity of the ventricle—perhaps provoking peripheral emboli—and in peripheral veins, where deep venous thrombosis, possibly complicated by pulmonary embolism, can occur. At that time, one could question the wisdom to lyse intraventricular clots. It was indeed conceivable that lysis may be incomplete, and fragmentation with resultant arterial embolism might occur. Second, what would be the fate of thrombi which may form during the period of severe plasminogen depletion associated with the administration of high doses of urokinase or streptokinase?

Trials of the European Working Party on Streptokinase in MI

EWP-1: Single-Blind Randomized Trial Comparing Intravenous Streptokinase and Heparin

EWP steering committee: A. Amery; J. Vermylen; and M. Verstraete. ECSG steering committee: M. Verstraete (chairman); D.P. de Bono; R.J. Lennane; J. Lubsen; D. Mathey; P. Raynaud; W. Rutsch; W. Schmidt; P. Serruys; M.L. Simoons; R. Uebis; A. Vahanian; F. Van de Werf; and R. von Essen. The ECSG was founded in 1984 and has conducted six trials between 1984 and 1991.

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(72-Hour Infusion) in Patients with Recent MI (Less than 72 Hours). Patients diagnosed in different centers as having, according to the criteria of each center—a MI of < 72 hours' duration—were preselected for this first study, after exclusion of those patients where heparin or streptokinase treatment was considered contraindicated. All patients received the standard general treatment for recent MI appropriate to each center.[3]

Using a sealed envelope system, the candidates for the study were allocated at random in a heparin and streptokinase group. The patients of the heparin group received an initial dose of 10,000 IU heparin over a 30-minute period and 1,250 IU per hour during 72 hours thereafter. The patients belonging to the streptokinase group received an initial dose of 1,250,000 IU streptokinase within 30 minutes, and during the next 72 hours, 100,000 units streptokinase per hour. Twenty-five mg prednisolone was injected intravenously to all patients just before the initial dose of heparin or streptokinase, and daily during the first 3 days.

Of 167 patients, 84 patients were treated with heparin and 83 with streptokinase. On retrospective analysis, the two treatment groups were homogeneous at the time of admission into the study in parameters which might influence the course of a MI.

In an intention-to-treat analysis, no significant difference could be found between these two groups as a whole in the hospital mortality and serum transaminases at different intervals after the start of infusion.

In a secondary analysis, patients of both groups were divided into subgroups, according to several parameters: for example, age; the interval between the onset of the acute retrosternal pain; the start of the heparin respectively streptokinase infusion; and the presence of definite ECG signs of MI (central blind analysis). No significant difference in hospital mortality was found between the two treatment groups of these subgroups. This small trial can be criticized because the minimum criteria for MI were not defined in the protocol, and particularly because very late entry of patients was allowed.

EWP-2: Single-Blind Randomized Trial Comparing Intravenous Streptokinase and Heparin (24-Hour infusion) in Patients with Acute MI (Less than 24 Hours). Although no significant difference in outcome was obtained in the previous study, this does not exclude the possibility that a favorable result could be reached by streptokinase, administered using another dosage scheme in more selected patient groups. Therefore, a new trial was organized in patients suffering from MI of < 24 hours' duration. This time interval was selected because in the meantime the results of another study in patients with an evolving MI of < 12 hours' duration became available.[4] The overall mortality over the first 40 days in the latter study was 14.1% in the streptokinase-treated patients and 21% in the heparin-treated group ($P = 0.031$). Excluding the first 24 hours in hospital, the mortality was 8.7% and 16.1%, respectively ($P = 0.021$).

In the second multicenter trial of the European Working Party, a lower initial dose of streptokinase was used (250,000 compared to 1,250,000 IU in the first study) with the same maintenance dose (100,000 IU hourly), but for a shorter duration (24 hours instead of 72 hours). In the control group, the initial dose of heparin was 10,000 IU over a 20-minute period, followed by 30,000 IU over the next 24 hours. Coumarin was commenced in both at the start of thrombolytic treatment.[5] Both groups received oral anticoagulants, and special attention was paid to the transition period between the trial infusion and the effect of the coumarin treatment, which was covered with repeated heparin injections.

Out of 764 patients who entered in the study, 28 from one center were excluded from the analysis because they were not treated in accordance with the system of serially numbered envelopes. Six other patients also had to be excluded, as in 4 the charts were lost and in 2, the treatment code was not followed. Thus, 730 patients were included in the first analysis: 373 treated with streptokinase and 357 with heparin. Eight centers cooperated in the trial. In this study conducted at the end of the 1960s, only about one-third of the patients were treated in a coronary care unit.

The cases in the two groups did not differ appreciably in those factors which are considered to influence the risks associated with MI, nor in several other ways. The number of patients who had already suffered two or more MIs was only slightly higher in the heparin-treated group (44 out of 344) than in the streptokinase-treated group (35 out of 355). This difference is not significant ($P > 0.10$), nor is the higher incidence of arrhythmia on admission in patients treated with streptokinase ($P = 0.10$).

The mean duration of stay in hospital averaged 43 days. The total hospital mortality was 18.5% of 373 patients allotted to streptokinase treatment, and 26.3% of 357 given heparin ($P = 0.014$). The mortality after infusion (24 hours) was 10.6% of 340 patients treated with streptokinase, and 17.8% of 320 given heparin

(P = 0.011). Bleeding from puncture sites and pyrexia occurred more frequently during streptokinase treatment.

After exclusion of those patients whose diagnosis was unconfirmed on blinded retrospective assessment, the total hospital mortality rate was 19.0% of 357 patients treated with streptokinase and 27.4% of 339 treated with heparin (P = 0.011). These results indicate that in acute MI, streptokinase was superior to heparin in reducing hospital mortality and reinfarction rate during an average period of 6 weeks in hospital.

Death was taken as the main yardstick for assessing the effect of treatment, and that meant that only those patients who died contributed directly to the final analysis. No attempt was made to use figures for deaths from specific causes, since a small change in fatality from cardiovascular causes without an overall difference in deaths from all causes may indicate either a diagnostic shift or at most a trivial benefit. It is worth noting, however, that reinfarction while in hospital was less frequent in the streptokinase-treated (6 out of 340) than in the heparin-treated patients (16 out of 320), this difference being significant (P = 0.036).

EWP-3: Single-Blind Randomized Trial Comparing Streptokinase with Glucose (24-Hour Infusion) in Medium Risk Patients with Acute MI (Less than 12 Hours' Duration) Admitted in a Coronary Care Unit. In the second trial of the European Working Party, only one-third of the patients were admitted in a coronary care unit, but in the EWP-3 trial, all patients were. At that time, the value of heparinization in the acute phase of MI had been challenged, as heparin might increase ventricular irritability because of a rise in plasma-free fatty acid. For this reason the comparative arm of streptokinase was a glucose instead of a heparin infusion. The required ECG changes for inclusion of patients in the study were detailed in the protocol, as were the criteria for enzymes creatine kinase; in the previous two EWP trials the minimum criteria for infarction were not defined; however, the diagnosis based on the criteria in use in each participating hospital was retrospectively reviewed by an independent expert, blinded with regard to the treatment given. In EWP-3, patients were stratified according to clinical severity and only high and medium risk patients were randomized.

Five hundred fifteen patients entered the study; 307 were randomized in the medium risk group and the 8 in the high risk group. The 197 low risk patients were not randomized but followed for mortality.[6,7] Randomized patients received either a loading dose of streptokinase (250,000) to overwhelm circulating antistreptokinase antibodies or a placebo; these doses were followed by a 24-hour infusion of streptokinase (100,000 per hour) or glucose. All subjects subsequently received oral anticoagulants. The two treatment groups were roughly comparable, although more patients in the placebo group had frequent ventricular premature beats and more had a history of previous infarction. Various analyses of the role of this accident of randomization did not explain the outcome of the trial.

In contrast to the EWP-2 study, this trial did not reveal a significant difference in mortality rates before the twenty-first hospital day (28 deaths in the control group vs 18 in the streptokinase group), although there was a trend in favor of streptokinase. However, the difference in mortality after the third week was significant (P < 0.01). The death rate at 3 weeks of low risk patients (not randomized) was 6.1%. At 6 months, the mortality rate was 30.6% in the control group and 15.6% in the streptokinase-treated group (the survival curves are shown in Fig. 1) The difference in favor of streptokinase was statistically significant (P < 0.01). The frequency of sudden arrhythmia as a cause of death was 54% in the control group, but only 36% in the streptokinase group. Reinfarction was the cause in 10% of the patients who died in the streptokinase group, but none in the streptokinase group. As usual, fever, chills, and bleeding complications occurred more frequently in the patients who received streptokinase.[7]

Although the EWP-2 and EWP-3 trials revealed a reduction in total mortality in 40-day of 30% (EWP-2) and at 6-month of 49.3% (EWP-3), these results

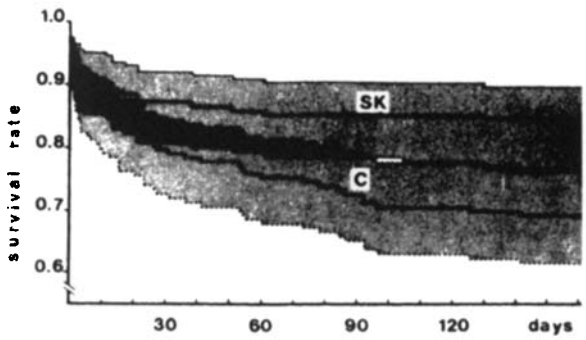

Figure 1. Survival curves with 95% confidence limits in the streptokinase-treated (solid lines) (SK) and the control group (dotted lines) (C).

did not impress cardiologists. As a consequence, in the early 1980s thrombolytic treatment was rarely used in patients with acute MI.

Trials of the European Cooperative Study Group for tPA in Acute MI (Table 1)

ECSG-1: Double-Blind Randomized Trial of Intravenous tPA Versus Placebo. In a double-blind randomized trial, 129 patients with first MI of < 6 hours' duration received a bolus of heparin (5,000 IU) intravenously and were allocated to treatment with human recombinant double-chain tissue type plasminogen activator (tPA) (0.75 mg/kg body weight) given intravenously over 90 minutes, or to placebo infusion.[8] Coronary angiography at the end of this infusion showed that the infarct related vessel was patent in 61% of 62 assessable coronary angiograms in the tPA-treated group, compared with 21% in the control group (2P = 0.0001). Treatment with tPA was not accompanied by major complications; minor bleeding was noted in 11 patients after tPA, and in 5 patients treated with placebo. In the tPA group, the circulating fibrinogen level at the end of drug infusion was 52% ± 29% (mean ± SD) of the starting value.

Table 1. Historical Review of the European Cooperative Study Group for rt-PA

1983	Genentech and the Center for Thrombosis and Vascular Research in Leuven, Belgium reported the cloning of human tPA in *Nature*.
1984	A first meeting was organized in Bad Söden (near Frankfurt), bringing together clinical investigators. The European Cooperative Study Group (ECSG) for Recombinant Tissue-type Plasminogen Activator was established. Prof. Dr. M. Verstraete, head of the Center for Thrombosis and Vascular Research in Leuven, Belgium, was appointed as chairman. The data center was established at the Thoraxcenter in Rotterdam headed by Prof. Dr. J. Lubsen.
1985	Within 1 year after the inaugural meeting, the first two ECSG trials were published in *Lancet*.
1987	ECSG-3, the "Reocclusion study," assessing coronary patency and reocclusion with and without a second tPA infusion of 6 hours in duration, was published in the *American Journal of Cardiology*.
1988	ECSG-4, the "rt-PA/placebo trial," was published in the *British Medical Journal*.
1988	ECSG-5, the "rt-PA/PTCA trial," was published in *Lancet*.
1990	ECSG-6, the "Heparin trial," assessing coronary patency after tPA and aspirin with and without intravenous heparin was presented at the European Congress of Cardiology in Stockholm. Publication occurred in 1992 in the *British Heart Journal*.

ECSG-2: Single-Blind Randomized Trial of Intravenous tPA Versus Intravenous Streptokinase. Patients with acute MI of < 6 hours in duration received a bolus injection of 10,000 IU heparin and were randomized to double-chain tPA or streptokinase only; the latter group also received aspirin (0.5 g) and methylprednisolone (0.25 g).[9] Sixty-four patients were assigned 0.75 mg tPA/kg over 90 minutes, and the infarct related coronary artery was patent in 70% of 61 assessable coronary angiograms taken 75–90 minutes after the start of infusion; 65 patients were allocated to 1,500,000 IU streptokinase over 60 minutes, and the infarct related vessel was patent in 55% of 62 assessable angiograms. The 95% confidence interval of the difference ranges from ± 30 to −2% (P = 0.054). Bleeding episodes and other complications were less common in the tPA patients than in the streptokinase group. Hospital mortality was identical in the two treatment groups. At the end of the tPA infusion, the circulating fibrinogen level was 61% ± 35% of the starting value, as measured by a coagulation rate assay, and 69% ± 25% as measured by sodium sulphite precipitation. After streptokinase infusion, corresponding fibrinogen levels were 12% ± 18% and 20% ± 11%. In the tPA group, only 4.5% of the fibrinogen was measured as incoagulable fibrinogen degradation products, compared with 30% in the streptokinase group. Activation of the systemic fibrinolytic system was thus far less pronounced with tPA than with streptokinase.

Quantitative analysis of the coronary stenosis both immediately after thrombolysis and at 3 weeks' follow-up was possible in 33 cases.[10] Residual stenosis (percentage narrowing of diameter) decreased from 74% ± 14% to 56% ± 17% (P < 0.05). No difference was observed between the groups of patients treated with streptokinase (74% ± 9% to 57% ± 12%, n = 17) and with tPA (74% ± 17% to 56% ± 21%, n = 16). Despite the significant regression, a coronary stenosis of > 50% of the diameter persisted in 82% of the patients 3 weeks after the infarction.

ECSG-3: Effect of Prolonged tPA Infusion on Early Reocclusion and Residual Stenosis. To be clinically relevant, thrombolysis requires not only early recanalization, but also long-term maintenance of patency of the infarct related artery. Different studies had shown that coronary reocclusion occurred in circa one-third of patients during the first hours or days

after thrombolysis as documented by repeat angiography.[11] The ECSG-3 trial was performed to determine early and late predischarge reocclusion, after patency of the infarct related artery had been shown by coronary angiography in patients with acute MI treated with intravenous tPA. Because reocclusion was reported to occur within 1 hour after cessation of the tPA infusion,[11] an early repeat catheterization was planned at the end of the second infusion: 6 hours after start of the second infusion; the latest after 24 hours (Fig. 2). A second aim was to assess whether a continued infusion with tPA over 6 hours could prevent early and late reocclusion and further reduce residual stenosis as measured by quantitative coronary angiography.

An intravenous infusion of 40 mg of recombinant double-chain tPA was given intravenously over 90 minutes to 123 patients with acute MI of < 4 hours' duration.[12] A coronary angiogram was recorded at the end of the infusion in 119 patients (Fig. 2). Central assessment of the angiograms revealed a patent infarct related artery in 78 patients (patency rate 66%, 95% confidence limits 57 to 74%). Patients with a patent infarct related artery at the first angiogram were randomized in a double-blind manner to receive a subsequent 6-hour infusion of either 30 mg of double-chain tPA or placebo. All patients had received an initial bolus of 5,000 IU of heparin and then 1,000 IU/hour until a second angiogram was recorded 6–24 hours after the start of the second perfusion. At central assessment of the second coronary angiogram, the reocclusion rate was 2 of 36 patients who received tPA at the second infusion, and 3 of 37 patients not receiving this drug (or the two groups combined: 7%, 95% confidence limits 2 to 15%). Three of 69 patients (5%, 95% confidence limits 1 to 14%) with patent arteries on both previous angiograms had a later occlusion as judged on the angiogram recorded at hospital discharge. No difference in late reocclusion rates between the two treatment groups was observed.

Quantitative angiography was performed with a computer-assisted cardiovascular angiography analysis system (CAAS).[13] A persistent trend of improvement in minimal lumen diameter was found from 90 minutes to 6–24 hours and predischarge. A reduction in "plaque area," the area between the detected and the reference contours of the infarct related segment,

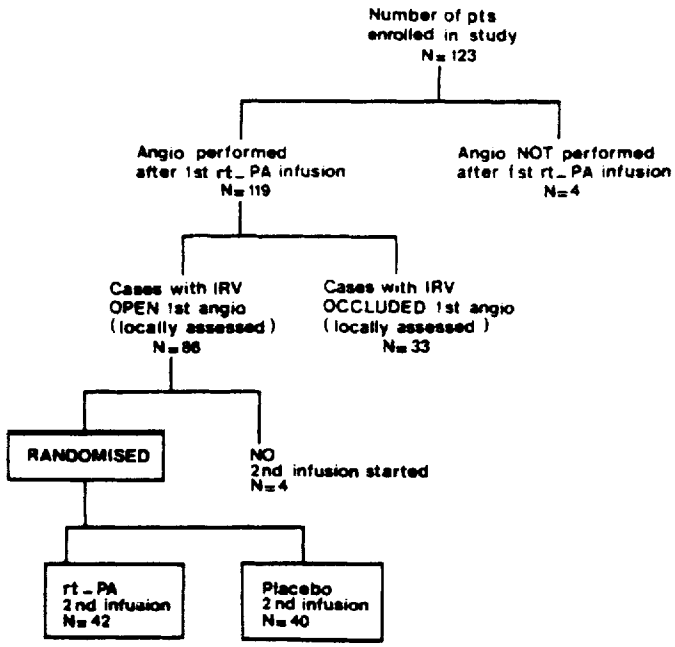

Figure 2. Flow diagram of patients in whom tPA infusion was given. Subsequent randomization based on local assessment of the patency of the infarct related artery at first angiogram. The second angiogram was read blindly by the care laboratory. IRV = infarct related vessel.

was more frequently seen in patients receiving a second infusion of tPA than in patients with no prolonged thrombolytic therapy (83% vs 57%, 2P < 0.025).

ECSG-4: Double-Blind Placebo-Controlled Randomized Trial on the Effect of Alteplase on Enzymatic Infarct Size, Left Ventricular (LV) Function, and Mortality. The aim of this trial was to assess the effect of intravenous alteplase (single-chain tPA) on size of infarct, LV function, and mortality in patients with MI of < 5 hours' duration.[14] Seven hundred and twenty-one patients were enrolled, and 355 patients were allocated to receive intravenous alteplase. Controls comprised 366 similar patients randomized to receive placebo. All patients were given aspirin 250 mg and bolus injection of 5,000 IU heparin immediately before the start of the trial. Patients in the treatment group were given 100 mg alteplase over 3 hours (10 mg intravenous bolus, 50 mg during 1 hour, and 40 mg during next 2 hours) by infusion. Controls were given placebo intravenously. Full anticoagulation treatment and aspirin were given to both groups until angiography (10–22 days after admission); β-blockers were given at discharge.

Compared to controls, mortality was reduced by 51% (95% confidence interval: −76 to 1) in treated patients at 14 days after start of treatment and by 36% (confidence interval [CI] −63 to 13) at 3 months. In patients who had treatment within 3 hours after MI, the mortality was reduced by 82% (CI −95 to −31) at 14 days, and by 59% (CI −83 to −2) at 3 months. During hospital stay (14 days) the incidence of cardiac complications was lower in treated patients than controls (cardiogenic shock, 2.5% vs 6.0%; ventricular fibrillation, 3.4% vs 6.3%; pericarditis, 6.2% vs 11.0%, respectively), but that of coronary angioplasty or artery bypass, or both, was higher (15.8% vs 9.6%) during the first 3 months. Bleeding complications were more common in treated than in untreated patients. Most bleeding was minor, but 1.4% of treated patients had intracranial hemorrhage within 3 days after the start of infusion.

Enzymatic size of infarct, determined by α-hydroxybutyrate dehydrogenase (HBDH) concentrations, was less (20%, 2P = 0.0018) in treated patients than in controls. Left ventricular ejection fraction (LVEF) was 2.2% higher (CI 0.3 to 0.4) and end-diastolic and end-systolic volumes smaller by 6.0 mL (CI −0.2 to −11.9) and 5.8 mL (CI −0.9 to −10.6), respectively, in treated patients.

One-year mortality was reduced from 9.3% to 5.6% (difference 8.7, 95% CI −0.2 to 7.5%) in patients treated with alteplase, aspirin, and intravenous heparin, in comparison with a strategy of aspirin and intravenous heparin alone.[15] Bleeding complications were more common in patients treated with alteplase, with intracranial bleeding in 1.4% of patients. The results of this trial indicate that survival after hospital discharge in patients with completed MI is determined by the remaining LV function, the extent of coronary artery disease, and by the degree of infarct related residual coronary artery narrowing.

ECSG-5: Randomized Trial Comparing the Combined Thrombolytic Treatment with Alteplase, Aspirin, and Intravenous Heparin Plus Percutaneous Transluminal Coronary Angioplasty (PTCA) Versus a Noninvasive Strategy with the Same Drugs but Without Immediate Angiography and PTCA. Three hundred and sixty-seven MI patients were randomly allocated to an invasive strategy of alteplase, aspirin, and intravenous heparin (bolus followed by maintenance infusion), combined with immediate coronary angiography and balloon dilatation of narrowings in the infarct related vessel or to a noninvasive strategy with alteplase, aspirin, and intravenous heparin.[16] Intravenous infusion of 100 mg alteplase was started within 5 hours after onset of symptoms (median 156 min). Angiography was performed 6–165 minutes later in 180 of 183 patients allocated to the invasive strategy, and immediate angioplasty was attempted in 168 patients (92%); 184 patients were allocated to the noninvasive strategy. Coronary angiography was done before discharge in all patients. 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 ischemia during the first 24 hours (17%). The clinical course was more favorable after noninvasive therapy, with a lower incidence of recurrent ischemia within 24 hours (30%), bleeding complications, hypotension, and ventricular fibrillation. Mortality at 14 days was lower in patients allocated to noninvasive 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 HBDH or in LVEF after 10–22 days. Thus, since immediate PTCA does not provide additional benefit, there seems to be no need for immediate angiography and PTCA in patients with acute MI treated with alteplase, aspirin, and heparin.

The failure of the invasive/intervention treatment strategy can be explained by more frequent coronary

reocclusion and reinfarction in the invasive treatment.[17] After exclusion of patients with these events, and after adjustment for other determinants of regional wall motion by multivariate regression analysis, a small benefit in parameters of regional wall motion was found similar to the benefit in the alteplase placebo trial. This suggests that an invasive strategy might be beneficial in selected patients, when additional treatment modalities to prevent reocclusion and reinfarction become available.

The high proportion of patients in whom angioplasty was attempted in the invasive strategy group must be viewed in the context of the underlying philosophy, based on laboratory studies, that maximal myocardial salvage would be achieved by the earliest and most complete myocardial reperfusion, even the initiation of nearly half (43%) of the immediate angioplasty procedures in a vessel not yet reperfused, as was done in this trial. It is important to appreciate that this is a totally different philosophy from that of the TAMI and TIMI-IIB trials, where the question was, having achieved coronary vessel patency, how best to maintain it.

ECSG-6: Double-Blind Randomized Trial of Intravenous Heparin Versus Placebo in Patients Treated with Alteplase and Aspirin. This trial was designed to determine whether concomitant treatment with intravenous heparin affects coronary patency and outcome in patients treated with alteplase for acute MI.[18] Patients aged 21–70 years with clinical and ECG features of infarcting myocardium in whom thrombolytic therapy could be started within 6 hours of the onset of major symptoms were selected. Six hundred and fifty-two patients were randomly allocated either to receive heparin (n = 328) or heparin placebo (n = 324). The treatment regimens were alteplase 100 mg (not weight adjusted) plus aspirin (250 mg intravenously followed by 75–125 mg on alternate days) plus heparin (5,000 units intravenously followed by 1,000 units hourly, without dose adjustment) compared with alteplase plus aspirin plus placebo for heparin. Coronary patency (TIMI grades 2 or 3) at 48–120 hours (mean 81 hours) was 83.4% in the heparin group and 74.7% in the group given placebo for heparin (Fig. 3). The relative risk of an occluded vessel in the heparin tested group was 0.66 (95% CI 0.47 to 0.93). Mortality was the same, with trends towards a smaller enzymatic infarct size and a higher incidence of bleeding complications in the group treated with heparin.

Plasma fibrinopeptide A levels, as a marker of ongoing in vivo fibrin formation, increased from 21 ng/ml (80%, range 2–390) at baseline to 30 ng/ml (3–390) at 36 hours in patients without intravenous heparin, but decreased in the heparin group from 18 ng/ml (2–210) at baseline to 10 ng/ml (1–170) (2P = 0.0001) (Table 2).[19] Thus, administration of intravenous heparin reduced ongoing fibrin formation. In 48 patients in the heparin group with adequate anticoagu-

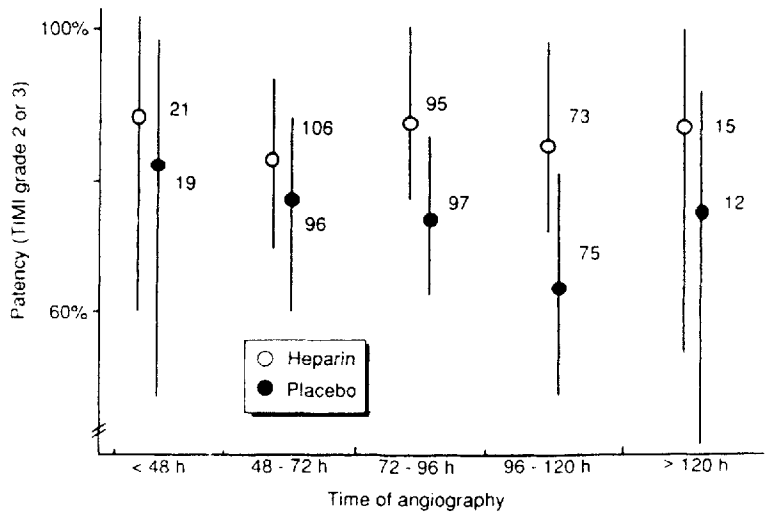

Figure 3. Means and 95% confidence intervals for TIMI grade 2 or 3 perfusion in angiograms performed at different times in heparin and placebo groups.

Table 2. Correlation Between FPA Levels at 24 Hours and Subsequent Coronary Artery Patency in Patients with FPA Data at 24 Hours

Patient Group	Patency	FPA Concentration > 50 ng/ml	FPA Concentration < 50 ng/ml	P
Heparin (n = 148)	Occluded	13	14	< 0.0001
	Patent	17	104	
Placebo (n = 139)	Occluded	14	26	0.99
	Patent	33	66	
Adequate Anticoagulation (n = 43)	Occluded	2	1	0.01
	Patent	1	39	

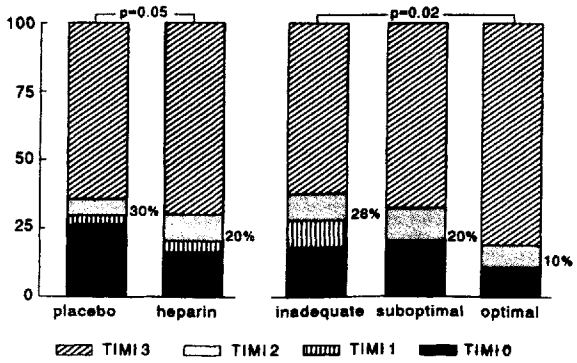

Figure 4. Coronary reperfusion status (TIMI grades 0–3) at angiography within 144 hours in both treatment groups (heparin [n = 149], placebo [n = 132]), and in the heparin subgroups classified on the basis of aPTT into those with optimal (n = 48), suboptimal (n = 40), and inadequate (n = 61) anticoagulation. The figures next to the bars present the percent of occluded vessels (TIMI grade 0 and 1). P values are for differences in TIMI grades 0 and 1 versus TIMI grades 2 and 3.

lation defined as no activated partial thromboplastin time (aPTT) below twice the baseline value, the plasma fibrinopeptide A levels remained normal (< 4 ng/ml), while in 102 patients allocated to intravenous heparin, but without adequate anticoagulation the plasma fibrinopeptide A levels at 12, 24, and 36 hours were 12 (2–80), 16 (2–240), and 15 (2–240) ng/ml (2P = 0.001). With these findings, the need for individual titration of intravenous heparinization is illustrated.

In a subgroup of patients pertaining to ECSG-6 trial, the relation between the level of anticoagulation and sustained coronary patency was studied.[20] This analysis comprises 149 of 324 patients allocated to heparin therapy and 132 of 320 patients allocated to placebo administration; in both groups an interpretable coronary angiogram was obtained within 6 days of treatment and there were sufficient plasma samples to assess the level of anticoagulation. aPTTs, fibrinogen and D-dimer levels were determined on plasma samples at baseline and at 45 minutes and 3, 12, 24 and 36 hours after the start of alteplase administration.

The coronary artery patency rate in this subgroup of patients who entered the ECSG-6 trial was higher in patients allocated to heparin therapy than in those allocated to placebo (80% and 71%, respectively, P = 0.05). Patients allocated to heparin were classified into three groups: 48 patients (32%) with all aPTTs prolonged to at least twice their own baseline value (optimal anticoagulation), 40 patients (27%) with the lowest aPPT at 3, 12, 24, or 36 hours between 130% and 200% of the baseline value (suboptimal anticoagulation), and 61 patients with at least one aPTT < 130% of baseline (inadequate anticoagulation). In the heparin group, coronary artery patency correlated with the level of anticoagulation: 90%, 80%, and 72%, respectively, in patients with optimal, suboptimal, and inadequate anticoagulation (P = 0.02, optimal vs inadequate anticoagulation) (Fig. 4). Heparin administration was associated with a smaller reduction in fibrinogen and a smaller increase in D-dimer level during and after alteplase administration. No correlation was found between fibrinogen or D-dimer levels and coronary artery patency. No intracerebral bleeding occurred in these patients; however, bleeding was more frequent in the subgroup with optimal anticoagulation (P = 0.05).

The conclusion of the ECSG-6 trial is that intravenous heparin improves coronary patency in patients with alteplase, provided the anticoagulation is intensive enough. Whether this can be translated into improved clinical benefit had to be tested in a much larger trial, as was later done in GUSTO-1.

Ancillary Studies in the ECSG Trials

Risk Stratification Before Hospital Discharge. The question whether coronary angiography before hospital discharge is needed for the identification of high risk patients after thrombolytic treatment was addressed in 1,043 hospital survivors studied in the ECSG-4 and ECSG-5 trials.[21] Coronary angiography was not useful in patients without symptoms of recurrent ischemia and without risk factors such as a previous infarction, use of diuretics and/or digitalis, or an

inadequate systolic blood pressure response to exercise (at least 30 mmHg). These patients (47% of the study population) have a very good prognosis (98.6% 1-year survival); prediction of mortality was not improved by knowledge of the coronary anatomy.

The ECG and Thrombolytic Therapy. The value of the Selvester and Cardiac Infarction Injury Scores was assessed in the 721 patients of the ECSG-4 trial with acute MI.[22] ECGs obtained at admission, 6 hours, and 10–22 days after the start of therapy were analyzed. Patients with prior MI or QRS duration $\geq$ 120 msec were excluded, leaving 322 in the alteplase group and 33 in the placebo group. Cumulative 72-hour release of HBDH and global EF derived from angiography and nuclear scintigraphy were used as independent measures of infarct size. Predischarge results demonstrated a net benefit of alteplase therapy, with the Selvester Score 11% lower ($P < 0.01$) and the Cardiac Infarction Injury Score 5.4% lower (P = NS) in the alteplase than the control group. Total enzyme release was reduced by 19.2% ($P < 0.001$) in the alteplase group. In patients with inferior infarction, neither enzyme release ($r = 0.30$ to 0.40) nor EF ($r = 0.22$ to 0.31) correlated well with the ECG indices of infarct size. In anterior infarction, the correlations were better, especially between the Selvester Score and enzyme release ($r = 0.40$ to 0.48), as well as EF ($r = -0.48$ to -0.67). It is concluded that ECG scoring systems, especially the Selvester Score, although imperfect, are useful to assess thrombolytic therapy in clinical trials. However, their value for the management and assessment of thrombolytic therapy in individual patients is still limited.

In 655 patients without previous infarction and with narrow QRS complexes from the ECSG-4 trial, the initial sum of ST segment elevation was related to infarct size, mortality, and the treatment effect of thrombolytic therapy with alteplase. Reciprocal ST segment depression was also related to infarct size and mortality, based on ST segment elevation, both in patients with anterior and inferior infarctions.[23]

Evaluation of the Effect of Thrombolytic Treatment on Infarct Size and LV function by Enzymatic, Scintigraphic, and Angiographic Methods. In a subset of 312 patients of the ECSG-4 trial, infarct size was assessed by the cumulative myocardial release of HBDH during the first 72 hours and by planar thallium scintigraphy (index of hypoperfusion) performed 10–22 days after the acute event.[24] LVEF was determined by contrast and nuclear angiography. The median values of HBDH during the first 72 hours were 20% lower, and the median values of thallium-201 28% smaller in the tPA group in comparison with controls. A significant but limited improvement of angiographic LVEF (2 absolute percentage points) was also shown in the patients treated with alteplase. A moderate but statistically significant linear association between both measurements of infarct size and LVEF was found.

Early and Late Effects of Thrombolysis on LV Function Measured by Nuclear Ventriculography. The aim of this study was the functional reevaluation of 296 patients pertaining to the ECSG-4 trial, 12–18 months after a double-blind trial evaluating the effect of alteplase versus placebo given within 5 hours of onset of symptoms caused by an acute MI.[25] All patients underwent rest-stress radionuclide angiography (Egna). For each exercise level, the global LVEF was calculated together with an estimate of regional wall motion abnormalities (RWMA). A clear difference of the total workload and the peak workload was found between both therapeutic groups. Discriminant analysis evaluating four parameters (LVEF at peak exercise and at the end point and the workload at those levels) revealed a beneficial therapeutic effect. The RWM at rest showed only a difference in the apicoinferior region. There were less wall motion abnormalities in the treated group. Radionuclide analysis demonstrated a larger functional capacity and a better coordination of myocardial contractility during stress radionuclide angiography 1 year after thrombolytic therapy. At rest, no major differences were found between the hospital stage and the follow-up in both therapeutic groups 1 year later.

Effect of Open Versus Closed Infarct Related Coronary Artery After Thrombolytic Therapy on Serum C-Reactive Protein and Infarct Size

Serum C-reactive protein rises in acute MI, correlating positively with infarct size if thrombolytic treatment is not given. This correlation disappears if thrombolytic treatment is given, although the serum C-reactive protein concentration is still associated with the clinical outcome of the patient. The effect of early coronary recanalization induced by thrombolytic treatment alone or combined with coronary angioplasty on the infarct related rise in serum C-reactive protein concentration was investigated.[26]

The C-reactive protein response caused by the myocardial infarct was lower in patients with an open infarct related coronary artery than in patients with a closed infarct related coronary artery, or in control patients who did not receive thrombolytic therapy. In control patients the expected strong positive correlation between infarct size and serum C-reactive protein ($r = 0.58$; $P < 0.001$, $n = 48$) was found, which was similar to that in patients with a closed infarct related coronary artery ($r = 0.58$; $P < 0.001$, $n = 17$), or in control patients who did not receive thrombolytic therapy. In patients with an open infarct related coronary artery, the correlation between infarct size and serum C-reactive protein was much weaker ($r = 30$; $P < 0.01$, $n = 91$). Consequently, infarct size explained approximately 35% of the variation in serum C-reactive protein values in the control patients and 36% in the patients with a closed infarct related coronary artery, but only 9% of the variation in patients with an open infarct related artery. EF correlated negatively with serum C-reactive protein in both control and recanalized patients. The association was again much stronger in the control patients. EF explained 27% (28% if only the first infarctions were considered) of the variation in serum C-reactive protein in the control patients and 8% (6%) in the recanalized patients.

The results of this analysis show that coronary recanalization variably reduces the infarct associated rise in serum C-reactive protein. This explains the weaker association between serum C-reactive protein and infarct size in the patients receiving thrombolytic treatment when compared to those treated without thrombolytic drugs, and may have clinical implications.

Long-Term (5 Years') Mortality is Related to TIMI Perfusion grade 3 Flow at Discharge. Long-term follow-up in patients treated with thrombolysis for acute MI thus far has been reported in a few studies only, and no long-term follow-up is available for patients who underwent additional PTCA. This report describes 5-year survival as collected in patients who received placebo, recombinant tissue plasminogen activator (alteplase), or alteplase with additional immediate PTCA in two European Study Group trials.[27-28] Determinants for long-term survival were assessed in 1,043 patients discharged alive. Five-year follow-up information on mortality was collected. Hospital mortality was lower after alteplase than placebo (2.5% vs 5.7%, $P = 0.04$) and higher after alteplase without additional intervention (6.0% vs 2.2%, $P = 0.07$). Of the 1,043 hospital survivors, data were available for 923 patients, of whom 109 died. In the placebo group, mortality after hospital discharge was 10.7% versus 11.0% in the comparative placebo group. The patients treated with alteplase and immediate PTCA had a mortality rate of 10.5% versus 8.9% in the alteplase group without PTCA (all P = NS). Significant determinants of mortality in multivariate proportional hazards analysis were enzymatic infarct size, indicators of residual LV function, number of diseased vessels, and TIMI perfusion grade at discharge. Patients with TIMI grade 2 flow had mortality rates similar to those with TIMI flow grades 0 and 1, while prognosis was better in patients with TIMI flow grade 3.

In conclusion, the initial in-hospital benefit of thrombolysis with intravenous tPA is maintained throughout 5 years, with no early or late beneficial effect of systematic immediate PTCA. Enzymatic infarct size, LV function, and extent of coronary artery disease are predictors for long-term survival. TIMI perfusion grade 2 at discharge should be considered as an inadequate result of therapy.

Conclusions

As was recently summarized[26] the ECSG trials provided evidence that treatment with tPA results in early patency of the infarct related coronary artery (ECSG-1 trial), reduces enzymatic infarct size, preserves LV function, and reduces mortality (ECSC-4 trial). Early (90 min) coronary patency after tPA was superior to patency after intravenous streptokinase (ECSG-2 trial). Reocclusion of the infarct related coronary artery was infrequent after tPA (ECSG-3 trial), provided that full intravenous heparinization was applied during the first days (ECSG-6 trial). The superiority of alteplase in comparison to intravenous streptokinase in terms of mortality was confirmed in the GUSTO-1 trial. An invasive strategy of alteplase followed by immediate angioplasty was not superior in terms of enzymatic infarct size reduction and preservation of LV function, probably due to early reocclusion and reinfarction (ECSG-5 trial).

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