# CORONARY THROMBOLYSIS

## Which patients benefit most from early thrombolytic therapy with intracoronary streptokinase?

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ABSTRACT The effect of thrombolysis in acute myocardial infarction on enzymatic infarct size, left ventricular function, and early mortality was studied in subsets of patients in a randomized trial. Early thrombolytic therapy with intracoronary streptokinase (152 patients) or with intracoronary streptokinase preceded by intravenous streptokinase (117 patients) was compared with conventional treatment (264 patients). All 533 patients were admitted to the coronary care unit within 4 hr after onset of symptoms indicative of acute myocardial infarction. Four hundred eighty-eight patients were eligible for this detailed analysis, and 245 of these were allocated to thrombolytic therapy and 243 to conventional treatment. Early angiographic examinations were performed in 212 patients allocated to thrombolytic therapy. Patency of the infarct-related artery was achieved in 181 patients (85%). Enzymatic infarct size, as measured from cumulative $\alpha$-hydroxybutyrate dehydrogenase release, was smaller in patients allocated to thrombolytic therapy (median 760 vs 1170 U/liter in control patients, $p = .0001$). Left ventricular ejection fraction measured by radionuclide angiography before discharge from the hospital was higher after thrombolytic therapy (median 50% vs 43% in control patients, $p = .0001$). Three month mortality was lower in patients allocated to thrombolytic therapy (6% vs 14% in the control group, $p = .006$). With the use of multivariate regression analysis, infarct size limitation, improvement in left ventricular ejection fraction, and three month mortality were predicted by sum of the ST segment elevation, time from onset of symptoms to admission, and Killip class at admission. Thrombolysis was most effective in patients admitted within 2 hr after onset of symptoms and in patients with a sum of ST segment elevation of 1.2 mV or more. On the other hand, no beneficial effects of streptokinase on enzymatic infarct size, left ventricular function, or mortality were observed in the subset of patients with a sum of ST segment elevation of less than 1.2 mV who were admitted between 2 and 4 hr after onset of symptoms.

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IN APPROXIMATELY 80% to 90% of patients with acute myocardial infarction, intracoronary infusion of streptokinase given in the first hours after onset of chest pain leads to thrombolysis and recanalization of the occluded coronary artery.[1–3] angiographically proven obstruction, without major complications. The high patency rate after thrombolysis was associated with limitation of infarct size, higher left ventricular ejection fraction (LVEF), and improved survival in comparison with these variables in conventionally treated patients. The design of this study, clinical course in the hospital, complications of early catheterization, limitation of enzymatic infarct size, and improvement in left ventricular function and survival during the follow-up period have been described elsewhere.[4–7]

The aim of the present analysis was to define subsets of patients that benefitted most from early recanalization. Special attention was paid to patient characteristics available early after hospital admission, such as

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history, the delay between onset of symptoms and admission, the extent of myocardial ischemia as reflected by the sum of ST segment elevation (ΣST) on the electrocardiogram (ECG), and the hemodynamic state of each patient.

## Patient selection and methods

Patients were eligible for the trial if they were admitted to one of the participating coronary care units within 4 hr after the onset of chest pain and with electrocardiographic signs typical of acute myocardial infarction: ST segment elevation of at least 0.1 mV in one or more extremity leads or that of at least 0.2 mV in one or more precordial leads, or ST segment depression of at least 0.2 mV in one or more precordial leads, compatible with posterior wall infarction.[4] Exclusion criteria were age over 70 years, previous treatment with streptokinase, recent trauma (including prolonged resuscitation), enhanced risk of bleeding, pregnancy, bypass surgery of a vessel corresponding to the infarct location, and mental confusion that precluded the patient from giving informed consent. Patients who met the inclusion criteria were registered by a central telephone answering service and were allocated either to thrombolytic therapy or to conventional treatment. Informed consent was obtained from patients allocated to thrombolytic therapy only. Patients who refused consent or patients in whom thrombolytic therapy was withheld for other reasons received conventional treatment, but were included in the analysis according to original treatment allocation.[8]

Early coronary angiographic examinations were performed only in patients allocated to thrombolytic therapy, after informed consent had been obtained (figure 1). If the infarct-related coronary artery appeared to be occluded, intracoronary streptokinase was given at a rate of 4000 U/min, until all visible clots had disappeared or the total of 250,000 U of streptokinase had been given. In the second part of the study cardiac catheterization was preceded by infusion of 500,000 U of streptokinase over 20 min, administered intravenously to reduce treatment delay. After catheterization patients allocated to thrombolytic therapy were treated according to the same treatment protocol as the control group.

Serum α-hydroxybutyrate dehydrogenase (HBDH) levels were determined upon admission, every 12 hr for 2 days, and then daily up to the fifth day. Cumulative HBDH release was calculated from these data as described before.[9, 10] Radionuclide angiography was performed 1 to 3 days after admission, before discharge, and again after 3 months. Cardiac catheterization was offered to all patients before discharge. All patients were followed at the outpatient clinic for at least 1 year after admission.

For identification of subgroups the following data, available at the moment of randomization, were considered: (1) history (age, gender, previous myocardial infarction, history of angina pectoris, time from onset of symptoms to admission), (2) results of physical examination (heart rate, blood pressure, Killip class), (3) electrocardiographic findings (location of the infarct, extent of ST segment elevation and depression).

All ECGs were reviewed independently by two experienced cardiologists. Consensus about the interpretation was always reached. The location of the infarct was defined as anterior if there was ST segment elevation in leads $V_1$ to $V_4$, and as inferior if there was ST segment elevation in leads II, III, and aVF. In the case of ST segment elevation in leads I, aVL, $V_5$, and $V_6$, the location of the infarct was defined as anterior, unless ST segment elevation was also present in leads II, III, and aVF, or ST segment depression was present in leads $V_1$ to $V_4$. In the latter case the location of the infarct was defined as inferior. The ΣST on the ECG was defined for anterior infarcts as the sum of ST segment elevation in leads I, aVL, and $V_1$ to $V_6$ and that for inferior infarcts was defined as the sum of ST segment elevation in leads I, II, III, aVL, aVF, $V_5$, and $V_6$ and ST segment depression in leads $V_1$ to $V_4$.

**Statistical analysis.** Missing data for cumulative HBDH release and LVEF were supplemented by various means, as described in the results. Because arbitrarily chosen values for cumulative HBDH release and LVEF were used for some of the patients, nonparametric statistical tests were used. Differences between groups were tested with the Fisher exact test or the Mann-Whitney rank-sum test when appropriate. Two-sided p values are reported. Linear regression analysis was used to select the significant and clinically relevant predictors of enzymatic infarct size, LVEF, and 3 month mortality. A BMDP statistical software package was used. Baseline variables shown by univariate analysis to be related to cumulative HBDH release were entered stepwise into the regression model. Factors that modified the effects of thrombolytic therapy were included as interaction factors.[11] The same procedure was used to predict LVEF and 3 month mortality.

## Results

Five hundred thirty-three patients were admitted to the trial between June 1981 and March 1985. Two

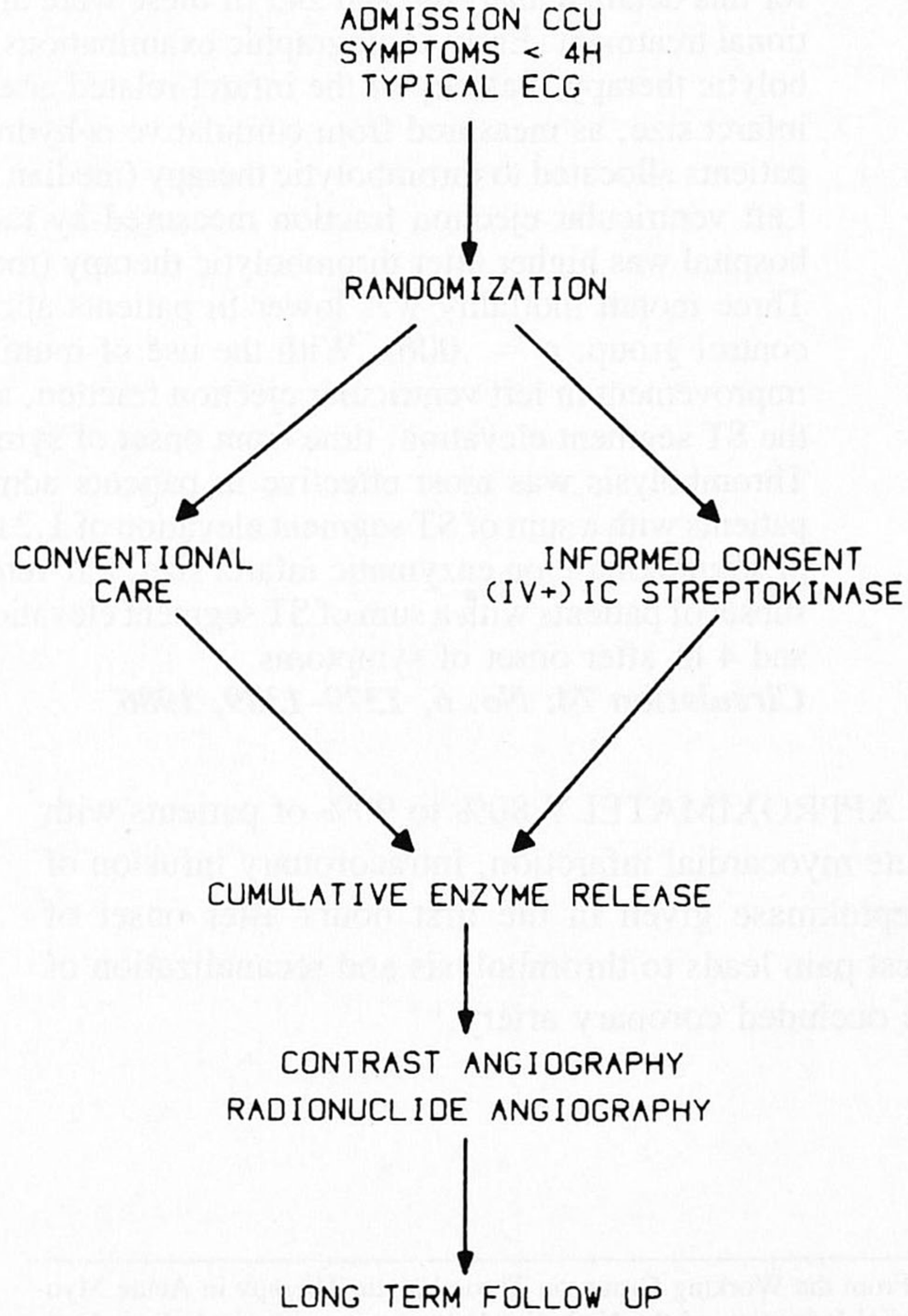


**FIGURE 1.** Flow chart of the study protocol. Informed consent was obtained from patients allocated to thrombolytic therapy only. Patients who refused consent received conventional treatment, but were included in the analysis according to original treatment allocation. CCU = coronary care unit; H = hours.

hundred sixty-four patients were allocated to conventional treatment and 269 to thrombolytic therapy; 152 of these were allocated to treatment with intracoronary streptokinase and 117 to intracoronary streptokinase preceded by intravenous streptokinase.

Forty-five patients were excluded from the present analysis because the ECG obtained at admission to the trial could not be interpreted in accordance with the definitions presented above. These patients were evenly distributed between the two treatment groups. Nineteen patients were excluded because they did not have the required amount of ST segment elevation on the ECG and 17 were excluded because they had only ST segment depression. Two patients with third-degree atrioventricular block and ventricular escape rhythm, one patient with left bundle branch block, and one patient with preexcitation due to an abnormal atrioventricular conduction pathway were also excluded. The ECGs from five patients could not be retrieved for review.

Table 1 lists the baseline and follow-up data from the patients admitted to the trial, including 488 patients included in this analysis and 45 patients excluded. One year follow-up was complete in all patients. All baseline characteristics were equally distributed between the two treatment groups. Patients allocated to thrombolytic therapy had lower cumulative HBDH release, higher LVEFs as measured by radionuclide and contrast angiography, and improved survival compared with patients allocated to conventional treatment.[4–6] From here on results are presented for patients included in this analysis only.

Early angiographic examinations were performed in 212 patients allocated to thrombolytic therapy (figure 2). Among patients treated with intracoronary streptokinase only, the infarct-related vessel was patent on the first angiogram in 22 of 118 patients (19%) and patency was achieved in 100 patients (85%). In the group pretreated with intravenous streptokinase initial vessel patency was observed in 39 of 94 (41%), and final patency was achieved in 81 patients (86%).

**Effect of thrombolytic therapy on enzymatic infarct size.** Enzymatic infarct size was measured by cumulative HBDH release in the first 72 hr after onset of symptoms in 414 patients. To eliminate bias caused by missing data, infarct size was estimated in 74 patients. Twenty-seven patients who died within 72 hr all had extensive myocardial infarction and were assigned to the largest infarct category and 10 patients without significant enzyme elevation were assigned to the group with the smallest infarct size. In 29 patients infarct size was estimated from cumulative HBDH release in the first 48 hr, and in eight patients it was estimated from cumulative creatine kinase release.

**TABLE 1**
**Baseline and follow-up data**

| | Patients included in this analysis | | Patients excluded from this analysis | |
|---|---|---|---|---|
| | T | C | T | C |
| Baseline data | | | | |
| No. of patients | 245 | 243 | 24 | 21 |
| Males | 197 | 204 | 20 | 20 |
| Age (median) | 57 | 56 | 61 | 55 |
| Previous myocardial infarction | 45 | 54 | 11 | 6 |
| Anterior infarction | 116 | 105 | 13 | 11 |
| In hospital at onset of symptoms | 29 | 41 | 10 | 3 |
| Killip class III/IV on admission | 10 | 11 | 2 | — |
| ΣST (mV) | 1.2 | 1.3 | 0.2 | 0.1 |
| Median time since onset of symptoms (min) | 95 | 85 | 50 | 90 |
| Follow-up data | | | | |
| Median cumulative HBDH release (U/l) | 760 | 1170 | 720 | 560 |
| Median radionuclide angiographic LVEF on day 10–20 (%) | 50 | 44 | 42 | 45 |
| Median contrast angiographic LVEF on day 10–40 (%) | 56 | 48 | 50 | 42 |
| Total 3 month mortality | 15 (6%) | 33 (14%) | 4 (17%) | 1 (5%) |
| Total 1 year mortality | 22 (9%) | 41 (17%) | 4 (17%) | 2 (10%) |

All baseline characteristics were distributed evenly among groups. Patients allocated to thrombolytic therapy had smaller enzymatic infarct size, higher LVEF, and improved survival compared with control patients.

T = allocated to thrombolysis group; C = control group.

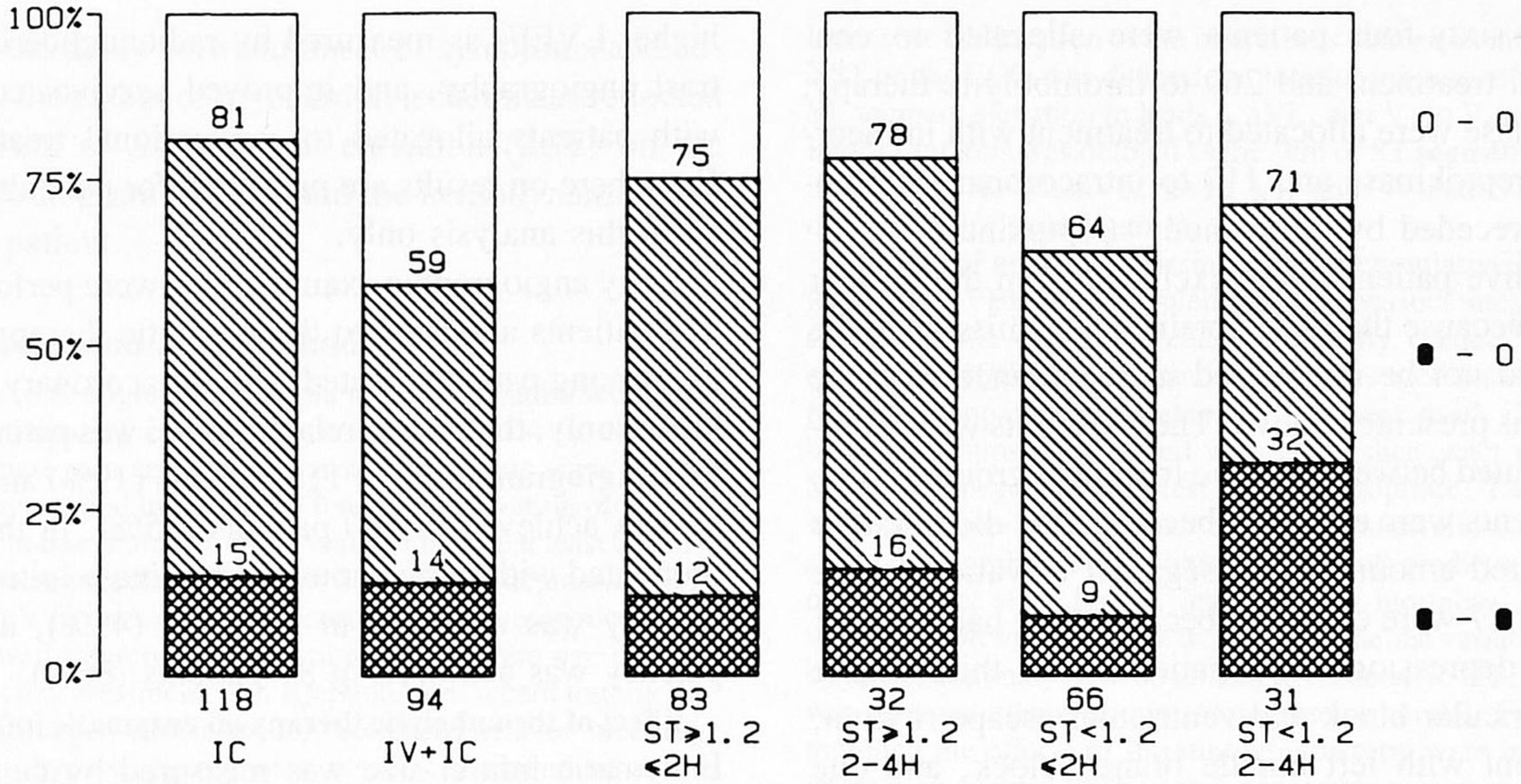


**FIGURE 2.** Results of early angiography in subsets of patients. Early catheterization was offered to patients allocated to thrombolytic therapy only. Final patency rate was lower in patients admitted 2 to 4 hr after onset of symptoms than in patients admitted within 2 hr after onset of symptoms. ST = sum of ST segment elevation on the ECG at admission (mV); H = hours; ○-○ = infarct-related vessel patent at first angiogram; ●-○ = infarct-related vessel opened during intracoronary infusion of streptokinase; ●-● = infarct related vessel remained occluded.

Median cumulative HBDH release was 1170 U/liter in patients allocated to conventional treatment, and 760 U/liter in patients allocated to thrombolytic therapy ($p = .0001$). The difference in cumulative HBDH release between the two treatment groups (410 U/liter) represents limitation of infarct size by thrombolytic therapy. The largest differences in enzymatic infarct size were found in patients with high ΣST (table 2). The relationship between time from onset of symptoms to hospital admission and enzymatic infarct size is also given in table 2. Patients admitted to the hospital before onset of symptoms were considered a special

**TABLE 2**
**Cumulative HBDH release, LVEF, and 3 month mortality in subsets of patients eligible for this analysis**

| | n | | HBDH (median, U/l) | | | LVEF (median, %) | | | Mortality (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | T | C | T | C | p value | T | C | p value | T | C | Risk difference |
| All | 245 | 243 | 760 | 1170 | 0.0001 | 50 | 43 | 0.0001 | 6 | 14 | −8 (−13, −2) |
| Streptokinase ic only | 133 | 134 | 760 | 1100 | 0.0001 | 50 | 41 | 0.0001 | 8 | 12 | −4 (−12, 3) |
| Streptokinase iv + ic | 112 | 109 | 770 | 1270 | 0.0001 | 50 | 44 | 0.006 | 4 | 15 | −11 (−20, −3) |
| Anterior infarct | 116 | 105 | 820 | 1300 | 0.0001 | 44 | 32 | 0.0001 | 8 | 18 | −10 (−20, −2) |
| Inferior infarct | 129 | 138 | 670 | 1000 | 0.0001 | 55 | 49 | 0.0001 | 5 | 10 | −6 (−12, 1) |
| In hospital at onset of symptoms | 29 | 41 | 400 | 970 | 0.004 | 56 | 44 | 0.004 | 3 | 12 | −9 (−23, 6) |
| Admitted within 60 min | 45 | 54 | 620 | 1310 | 0.0001 | 51 | 42 | 0.0006 | 4 | 18 | −14 (−27, −1) |
| Admitted 61–120 min | 99 | 90 | 760 | 1160 | 0.0003 | 50 | 41 | 0.002 | 6 | 11 | −5 (−14, 3) |
| Admitted 121–240 min | 72 | 58 | 970 | 1320 | 0.06 | 47 | 49 | 0.5 | 8 | 14 | −6 (−18, 6) |
| ΣST 0.1−0.6 mV | 36 | 38 | 500 | 780 | 0.005 | 57 | 50 | 0.03 | 0 | 5 | −5 (−17, 5) |
| ΣST 0.7–1.1 mV | 80 | 58 | 590 | 820 | 0.05 | 51 | 44 | 0.03 | 7 | 12 | −5 (−16, 6) |
| ΣST 1.2–1.7 mV | 61 | 68 | 800 | 1280 | 0.003 | 50 | 46 | 0.07 | 8 | 12 | −4 (−15, 8) |
| ΣST >1.7 mV | 68 | 79 | 1120 | 1770 | 0.0001 | 44 | 37 | 0.003 | 6 | 20 | −14 (−26, −4) |
| First MI | 200 | 189 | 780 | 1150 | 0.0001 | 52 | 46 | 0.0001 | 3 | 6 | −3 (−8, 1) |
| Previous MI | 45 | 54 | 710 | 1250 | 0.03 | 40 | 33 | 0.06 | 20 | 41 | −21 (−38, −2) |
| Killip class I or II | 235 | 232 | 760 | 1140 | 0.0001 | 50 | 43 | 0.0001 | 5 | 11 | −6 (−11, −1) |
| Killip class III or IV | 10 | 11 | 1440 | 3310 | 0.02 | 38 | 27 | 0.1 | 20 | 64 | −44 (−73, −1) |

Two-sided p values (Mann-Whitney rank-sum test) or risk differences with 95% confidence interval are reported. Thrombolytic therapy led to limitation of enzymatic infarct size, improvement in LVEF and reduction in 3 month mortality in all subsets of patients. Most prominent differences were in patients with high ΣST, in patients in Killip class III or IV at admission, and in patients with an anterior infarct.

MI = myocardial infarction; other abbreviations are as in table 1.

group. For patients admitted to the hospital after onset of symptoms there was no relationship between duration of symptoms and enzymatic infarct size in the control group, but limitation of infarct size by thrombolytic therapy decreased as the delay between onset of symptoms and admission lengthened. Limitation of infarct size was greater in patients with an anterior infarct (480 U/liter) than in patients with an inferior infarct (330 U/liter). Patients in Killip class III or IV at admission had extensive myocardial infarction and in these patients there was a substantial limitation of enzymatic infarct size by thrombolytic therapy.

**Effect of thrombolytic therapy on left ventricular function.** LVEF was measured by radionuclide angiography 1 to 3 days after admission, before discharge, and again after 3 months, and by contrast angiography 10 to 40 days after admission. Radionuclide angiographic LVEF before discharge was used to assess the improvement in left ventricular function induced by streptokinase (336 patients). If data on radionuclide angiographic LVEF before discharge were missing, measurements obtained after 3 months (56 patients), after 1 to 3 days (62 patients) or of contrast angiographic LVEF (six patients) were used. A LVEF of 0% was assigned to 24 patients who died within 10 days after admission without undergoing angiography. Median LVEF was 43% in the control group and 50% in the streptokinase group ($p = .0001$). The largest differences in median LVEF between the two treatment groups were found in patients with an anterior infarct, in patients admitted within 2 hr after onset of symptoms, and in patients in Killip class III or IV at admission (table 2).

**Effect of thrombolytic therapy on 3 month mortality.** Three month mortality was higher in patients allocated to conventional treatment (14%) than in patients allocated to thrombolytic therapy (6%, $p = .006$). This difference in mortality was expressed as a negative risk difference ($6\% - 14\% = -8\%$) produced by thrombolytic therapy. The largest reduction in 3 month mortality was observed in patients admitted within 1 hr after onset of symptoms, in patients with ΣST greater than 1.7 mV, in patients pretreated with intravenous streptokinase, in patients with previous myocardial infarction, and in patients in Killip class III or IV at admission (table 2).

**Multivariate analysis.** Multivariate regression analysis was used to define the relative contributions of baseline factors to the effect of thrombolytic therapy on enzymatic infarct size, LVEF, and mortality. In the 27 patients who died within 72 hr, a cumulative HBDH release of 3500 U/liter was used in the computations. In stepwise regression analysis the following baseline variables appeared to be relevant predictors of cumulative HBDH release, LVEF, and 3 month mortality: ΣST, allocation to thrombolytic therapy, location of the infarct, and Killip class at admission. The effect of thrombolytic therapy was modified by ΣST, delay in admission, and Killip class on admission. Other factors, including age, gender, history of angina, participating center, and allocation to intracoronary streptokinase or intravenous and intracoronary streptokinase did not contribute to the prediction of cumulative HBDH release, LVEF, or 3 month mortality when the above-mentioned variables were included in the regression model.

The results of the regression analysis are given in table 3. At the top, the coefficients for the baseline variables predicting cumulative HBDH release, LVEF, and 3 month mortality are given. The bottom of table 3 gives additional values for predictive variables for patients allocated to thrombolytic therapy, indicating the limitation of enzymatic infarct size, the improvement in LVEF, and the reduction in 3 month mortality as a result of thrombolytic therapy. From the coefficients for the variables used in the regression analysis, the predicted effect of thrombolytic therapy on enzymatic infarct size, LVEF, and mortality can be calculated. For example, a patient with an anterior infarction was admitted 1 hr after onset of symptoms

**TABLE 3**
**Regression coefficients for the multivariate regression models predicting enzymatic infarct size, LVEF, and mortality**

| | HBDH (U/l) | LVEF (%) | Mortality (%) |
|---|---|---|---|
| Intercept[A] | 450 | 57 | −4 |
| ΣST (each mV) | 600 (70) | −6 (1) | 9 (3) |
| Admission delay (each hour) | −10 (60) | 0 (1) | 0 (2) |
| In hospital | −300 (150) | 1 (3) | −1 (6) |
| Killip class III or IV | 1230 (230) | −13 (4) | 49 (9) |
| Previous MI | 200 (80) | −12 (2) | 8 (3) |
| Location Anterior | 240 (70) | −10 (1) | 5 (3) |
| Additional value of predictive variables for patients allocated to thrombolytic therapy | | | |
| Thrombolytic therapy | −300 (220) | 9 (4) | 3 (8) |
| ΣST (each mV) | −200 (100) | 2 (2) | −8 (4) |
| Admission delay (each hour) | 100 (80) | −3 (3) | 2 (3) |
| In hospital | 130 (240) | 1 (4) | −3 (9) |
| Killip class III or IV | −630 (340) | 2 (6) | −33 (13) |
| Standard error of the estimate | 740 | 13 | 28 |

Standard errors for the regression coefficients are given in parentheses.
MI = myocardial infarction.
[A](Hypothetic) Val outcome variable if all independent variables are 0.
See text.

with a ΣST of 1.5 mV. He was in Killip class II and had suffered a previous myocardial infarction. If he were not treated with streptokinase, predicted enzymatic infarct size would be 450 U/liter + 1.5 × 600 U/liter (ΣST) − 10 U/liter (admission delay) + 200 U/liter (previous myocardial infarction) + 240 U/liter (anterior location) = 1780 U/liter. If the same patient were treated with streptokinase, enzymatic infarct size would be 1780 U/liter − 300 U/liter (allocation to thrombolytic therapy) − 1.5 × 200 U/liter (ΣST) + 100 U/liter (admission delay) = 1280 U/liter. Predicted limitation of enzymatic infarct size by thrombolytic therapy would be 1780 U/liter − 1280 U/liter = 500 U/liter (95% confidence interval 360 to 640 U/liter). Similarly, predicted LVEF would be 26% and risk of mortality 22% if the patient were not treated with thrombolytic therapy, while predicted LVEF would increase to 35% and risk of mortality would be reduced to 15% after treatment with streptokinase. The expected improvement in LVEF induced by thrombolytic therapy would be 9% (95% confidence interval 7% to 11%), and the risk difference for mortality −7% (95% confidence interval −2% to −12%).

The expected limitation of infarct size, improvement in LVEF, and reduction in mortality can be expressed as a function of ΣST and time from onset of symptoms to admission. Corrections must be made for patients in hospital at the time of onset of symptoms and patients in Killip class III or IV at admission. The predicted effect of thrombolysis on enzymatic infarct size is a limitation with 300 U/liter + 200 U/liter for each millivolt of ΣST − 100 U/liter for each hour delay between onset of symptoms and admission (figure 3). The predicted improvement in LVEF as a result of thrombolysis is 9% + 2% for each millivolt of ΣST − 3% for each hour after onset of symptoms. The risk difference for mortality after thrombolytic therapy is 3% − 8% for each millivolt of ΣST + 2% for each hour between onset of symptoms and admission.

Since these computations are somewhat cumbersome, four subgroups of patients that can easily be recognized in clinical practice were defined: patients with ΣST less than 1.2 mV, those with ΣST of 1.2 mV or more, those with times from onset of symptoms to admission of less than 2 hr, and those with times from onset of between 2 and 4 hr. Patency rate at the end of the procedure was high in all these subsets of patients, although somewhat lower (68%) in patients with ΣST less than 1.2 mV who were admitted between 2 and 4 hr after onset of symptoms (figure 2). Limitation of infarct size by thrombolytic therapy was greatest in patients with ΣST of 1.2 mV or more and in patients admitted within 2 hr after onset of symptoms (figure 4). Improvement in LVEF was seen only in patients

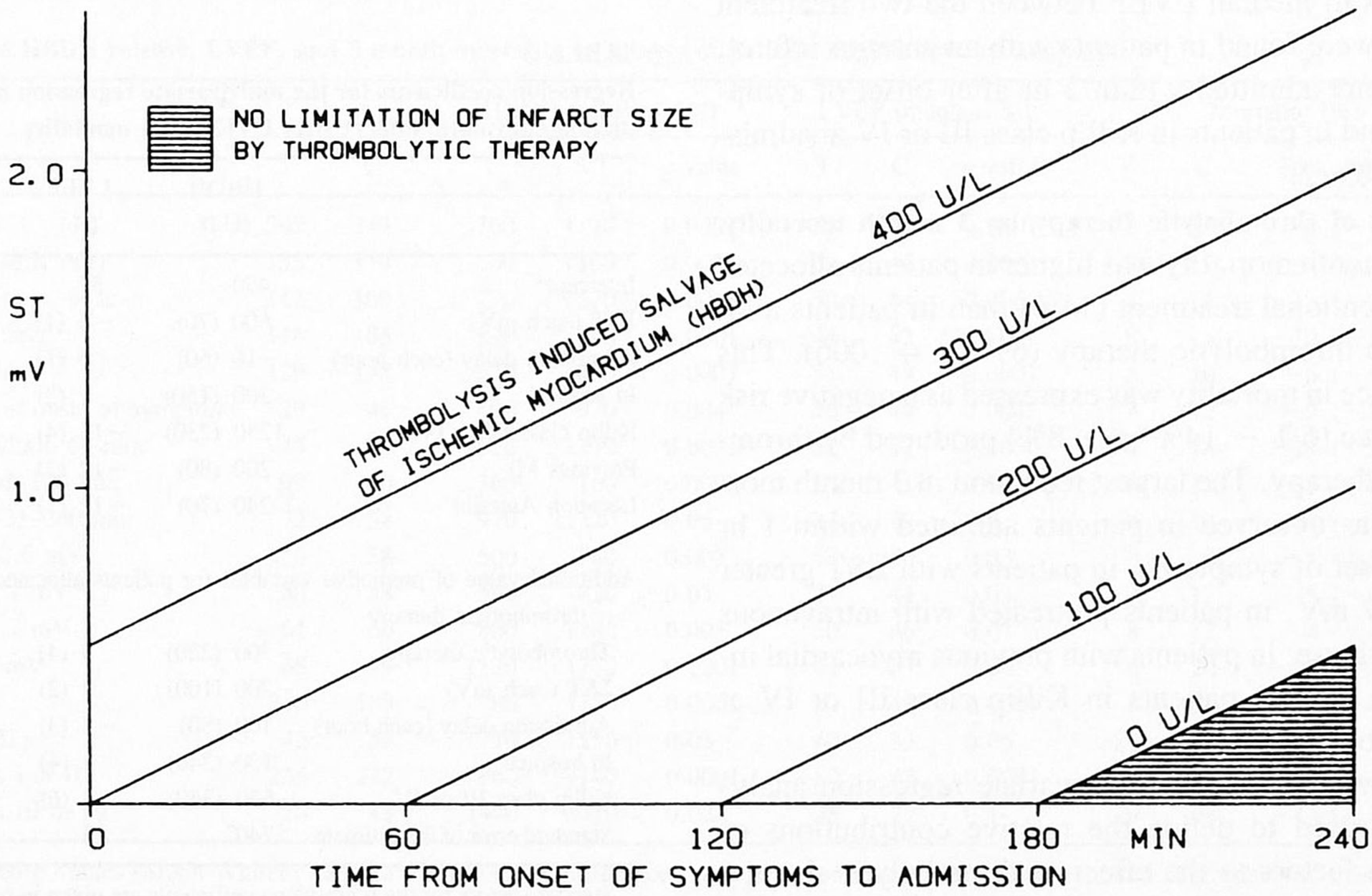


**FIGURE 3.** Limitation of infarct size by streptokinase. Results of the multivariate regression model. Predicted limitation of infarct size is a function of ΣST and time from onset of symptoms to admission. ST = sum of ST segment elevation on the ECG at admission (mV).

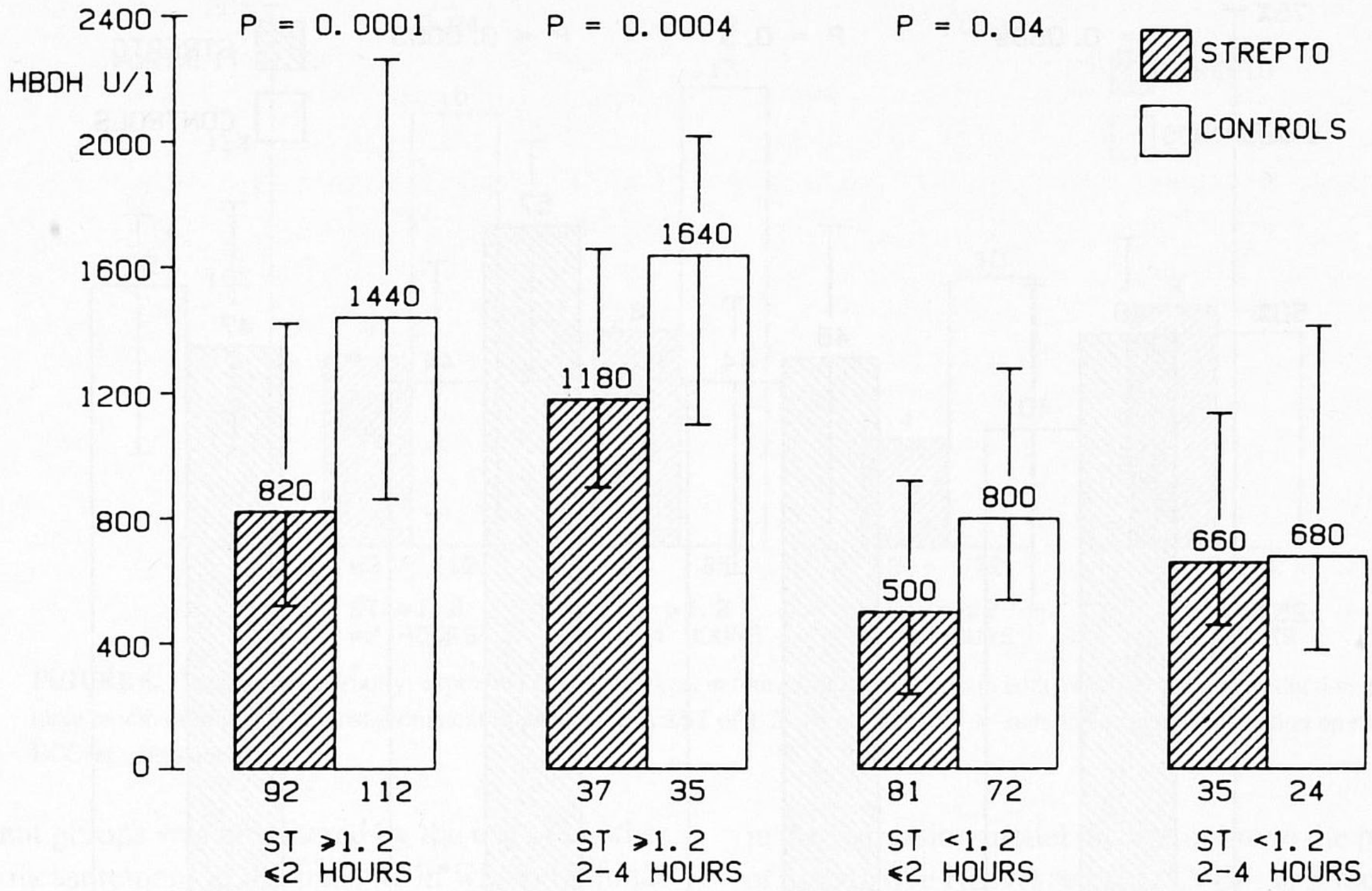


**FIGURE 4.** Median values and quartiles of enzymatic infarct size in four subsets of patients in both treatment groups. Limitation of infarct size is most prominent in patients with ΣST of 1.2 mV or more and in patients admitted within 2 hr after onset of symptoms. ST = sum of ST segment elevation on the ECG at admission (mV).

admitted within 2 hr after onset of symptoms (figure 5), while reduction in mortality predominated in patients with ΣST of 1.2 mV or more (figure 6).

No beneficial effect of streptokinase on enzymatic infarct size, left ventricular function, or mortality was observed in the subset of patients with a small ischemic area, as indicated by a ΣST less than 1.2 mV, who were admitted between 2 and 4 hr after onset of symptoms.

## Discussion

The randomized trial conducted by the Netherlands Interuniversity Cardiology Institute has shown that recanalization of an occluded coronary artery by early therapy with intracoronary streptokinase can lead to limitation of infarct size, improvement in left ventricular function, and a reduction in mortality. The present analysis indicates that the largest limitation of enzymatic infarct size by thrombolytic therapy was observed in patients with extensive myocardial ischemia, as reflected by a high ΣST, who were admitted within 2 hr after onset of symptoms, while no limitation was apparent in patients with a low ΣST who were admitted between 2 and 4 hr after onset of symptoms. Improvement in LVEF was related to the same factors as limitation of enzymatic infarct size. However, this improvement was of greater clinical value in patients with impaired left ventricular function than in patients with normal left ventricular function. The clinically most important improvement in LVEF induced by thrombolytic therapy was seen in the subsets of patients with anterior infarction (44% vs 32% in the control group, p = .0001), those with previous myocardial infarction (40% vs 33%, p = .06), and those in Killip class III or IV at admission (38% vs 27%, p = .1). Similarly, 3 month mortality was high and significantly reduced by thrombolytic therapy in the subsets of patients with high ΣST (20% vs 6% in the thrombolysis group), with previous myocardial infarction (41% vs 20%), with anterior infarction (18% vs 8%), and in Killip class III or IV at admission (64% vs 20%). In the other subgroups 3 month mortality was below 5% in the control patients.

**Calculation of enzymatic infarct size.** Enzymatic infarct size can be calculated from the cumulative release of enzymes into plasma.[5, 9, 10] The two-compartment model used in the present study has been verified for several cardiac enzymes,[12] and takes into account the fractional catabolic rate or clearance of the enzymes from the blood. After thrombolytic therapy peak serum enzyme levels are increased due to faster washout after reperfusion.[13, 14] However, the total amount of enzyme release does not change after reperfusion,[15, 16] so that the model used for computation of infarct size is not

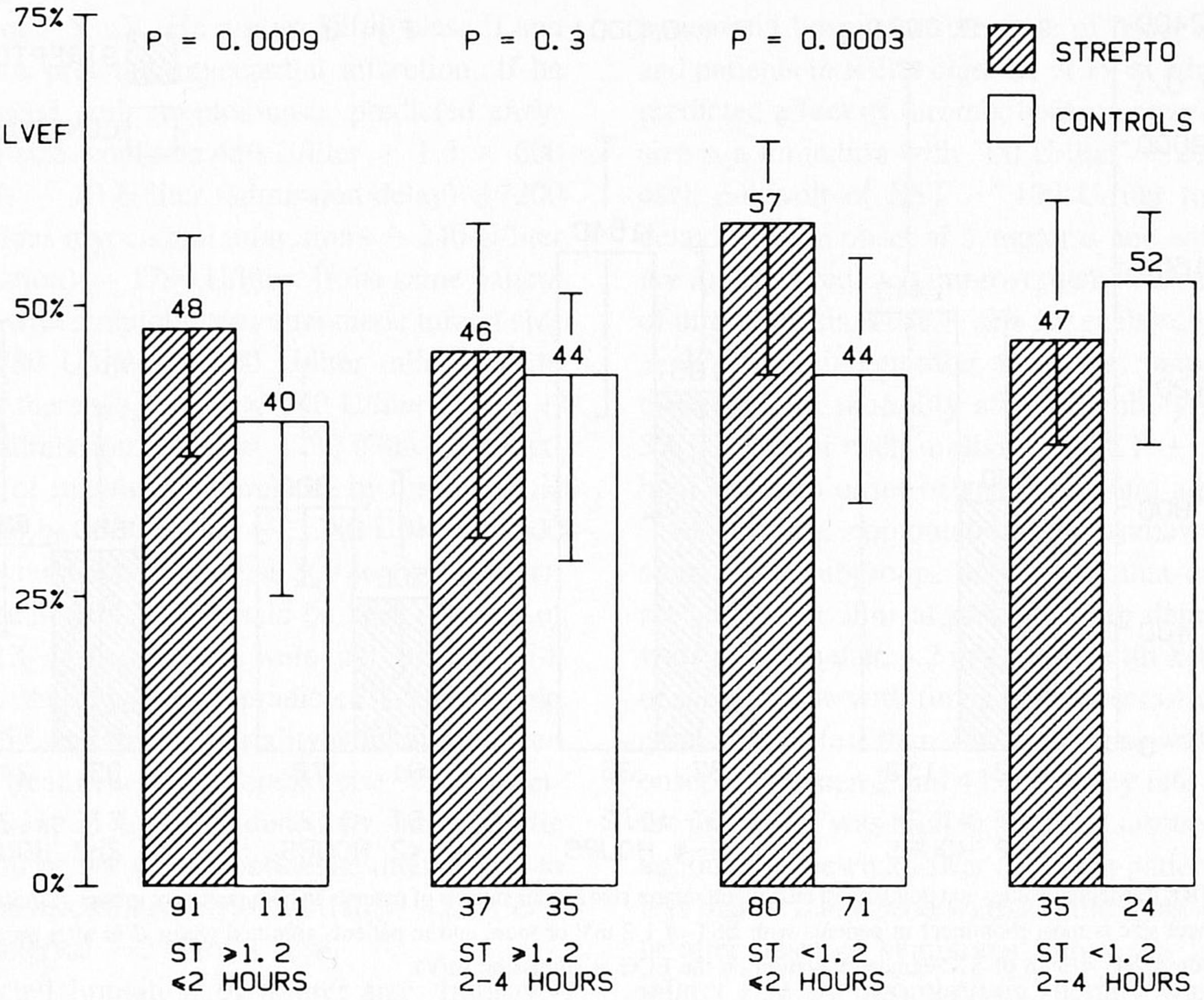


**FIGURE 5.** Median values and quartiles of LVEF measured by radionuclide angiography in four subsets of patients in both treatment groups. Improvement in LVEF is most prominent in patients admitted within 2 hr after onset of symptoms. ST = sum of ST segment elevation on the ECG at admission (mV).

invalidated by thrombolytic therapy.[5, 10] In the present study HBDH release was measured because it can be computed accurately from samples taken at 12 hr intervals, whereas creatine kinase should be sampled for more frequently. The method of calculation of cumulative HBDH release used in the present study has been described in detail by Van der Laarse et al.[10]

**Regression analysis.** In the regression analysis, linear models were used for the prediction of enzymatic infarct size, LVEF, and 3 month mortality. For the prediction of cumulative HBDH release and LVEF the use of linear regression analysis was indicated.[11] The relationship between ΣST, delay in admission, and treatment allocation vs cumulative HBDH release and LVEF was best described by a linear model. Various nonlinear relationships between these variables were tested, but the resulting models appeared not to provide a better description of the data than the linear model. An advantage of the linear model is that data are presented in such a way that absolute differences in cumulative HBDH release and LVEF can easily be calculated from the regression coefficients of the baseline variables (table 3), as presented in the example in Results. For the prediction of 3 month mortality logistic regression analysis was an alternative to linear regression. Similar results were obtained with the two regression techniques. Linear regression was chosen because the resulting regression coefficients are easier to interpret, and the same model could be applied to the three regression analyses. Predictors of the beneficial effects of thrombolytic therapy were not influenced by the models and the regression technique chosen.

**Missing data.** This analysis might be criticized with respect to the handling of the missing data for cumulative HBDH release and LVEF. Inclusion of the 27 patients who died within 72 hr as a group of those with the largest infarcts was necessary to eliminate bias, since more patients in the control group died than in the group of patients allocated to thrombolytic therapy. These patients all had large infarcts, as indicated by a rapid rise in creatine kinase.[4] For the regression analysis these patients were assigned a cumulative HBDH release of 3500 U/liter, this being the upper limit of the normal distribution for cumulative HBDH release in patients with acute myocardial infarction. Inclusion of the other patients with incomplete enzyme data did not alter the difference observed in cumulative HBDH release in the two treatment groups.[10]

LVEF was measured by radionuclide angiography. The difference observed between LVEF in the two

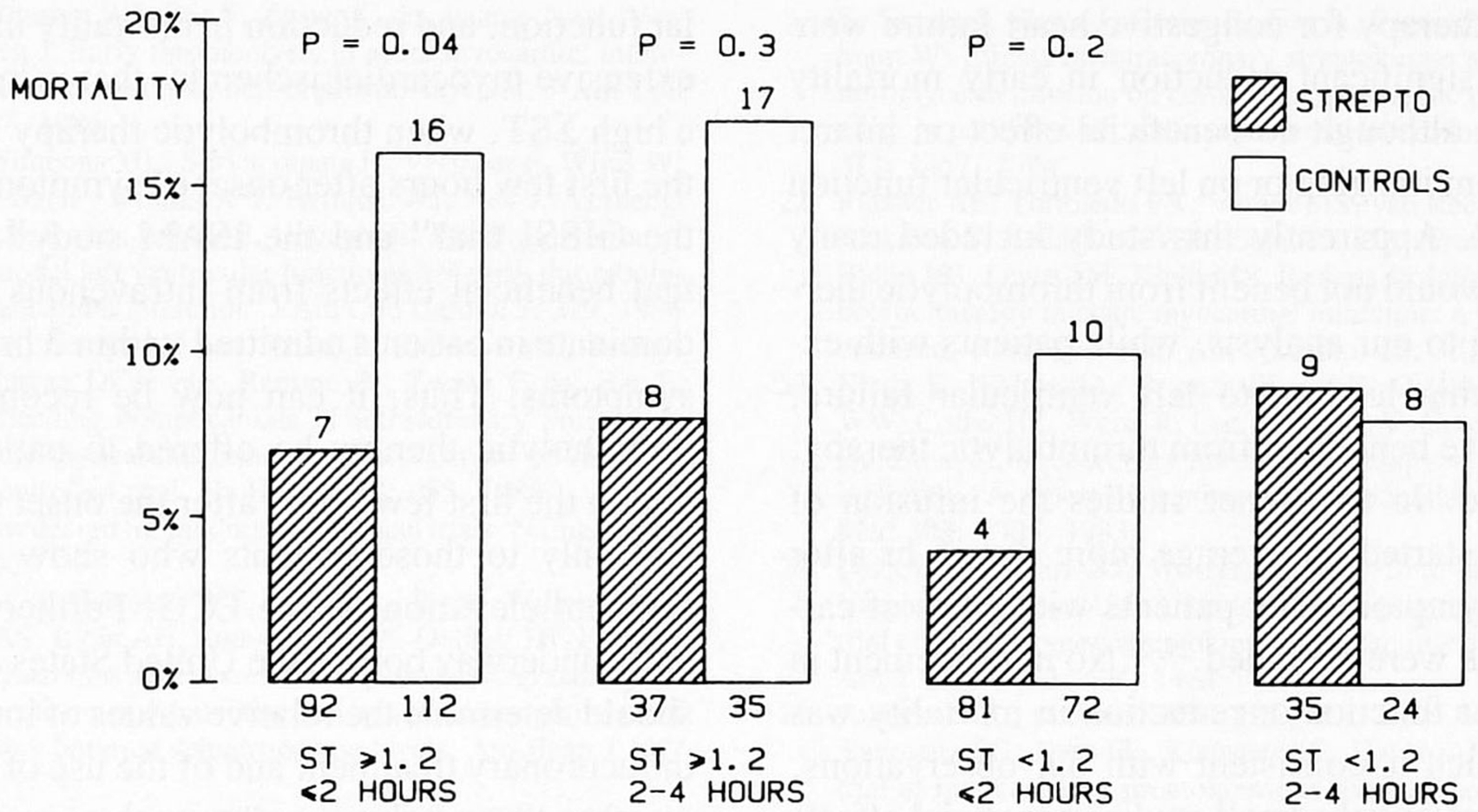


**FIGURE 6.** Three month mortality, expressed as a percentage, in four subsets of patients in both treatment groups. Reduction in three month mortality was most prominent in patients with ΣST of 1.2 mV or more. ST = sum of ST segment elevation on the ECG at admission (mV).

treatment groups was not altered by the use of another LVEF measurement in the patients in whom radionuclide angiography was not performed before discharge. The 24 patients who died within 10 days after admission without angiography (22 of them died within 72 hr after admission) were included to prevent the bias described above in the discussion of cumulative HBDH release. To these patients a LVEF of 0% was assigned; no apparent differences with respect to the prediction of LVEF were found in the regression analysis when LVEF values of 10% or 20% were assigned to these patients.

The effects of thrombolytic therapy on limitation of enzymatic infarct size, improvement in LVEF, and reduction in mortality were related to the same independent factors. No relevant changes in the value of these independent factors were found when the regression analyses were repeated without the inclusion of estimates for missing data on cumulative HBDH release and LVEF.

**Pretreatment with intravenous streptokinase.** During the course of this trial on early reperfusion by intravenous streptokinase other studies have been reported.[13] Since it was our aim to achieve reperfusion as quickly as possible, pretreatment with intravenous streptokinase was added to the protocol for patients allocated to thrombolytic therapy since January 1984. Earlier analysis suggested that, although intravenous pretreatment resulted in a larger fraction of patients with a patent infarct-related vessel at the first angiographic examination (figure 2), effects on infarct size and left ventricular function were similar with and without pretreatment.[6, 10] Accordingly, inclusion of pretreatment in the regression model did not improve the prediction of cumulative HBDH release, LVEF, or 3 month mortality when the other predictors were included in the model. Due to the low number of patients pretreated with intravenous streptokinase (n = 94), no conclusions can be drawn about the merits of this additional therapy from our data.

**Comparison with other trials.** Other randomized trials[17–26] of intracoronary streptokinase have not shown consistent limitation of infarct size, improvement in left ventricular function, or reduction in early mortality. This discrepancy with our data can now be explained by the delays in admission and the different inclusion criteria in those trials. Time is a crucial factor in thrombolytic therapy after acute myocardial infarction. In nonrandomized trials it has been reported that recanalization leads to limitation of infarct size provided therapy is started within 4 hr after onset of symptoms,[27, 28] although beneficial effects of intracoronary streptokinase have been reported in individual patients treated up to 18 hr after the onset of chest pain.[29] In the present study beneficial effects of streptokinase in patients admitted between 2 and 4 hr after onset of chest pain were observed only in those with extensive myocardial ischemia, as reflected by a high ΣST, and in patients in Killip class III or IV at admission. Although recanalization was also observed in a high percentage (68%) of patients with low ΣST, this did not lead to limitation of enzymatic infarct size, improvement in LVEF, or reduction in mortality.

In the Western Washington trial,[17–20] mean time to initiation of streptokinase infusion was 276 min, and patients with newly formed Q waves or receiving

maintenance therapy for congestive heart failure were excluded. A significant reduction in early mortality was reported, although no beneficial effect on infarct size by thallium imaging or on left ventricular function was observed. Apparently this study included many patients who would not benefit from thrombolytic therapy according to our analysis, while patients with extensive ischemia leading to left ventricular failure, who might have benefitted from thrombolytic therapy, were excluded. In two other studies the infusion of streptokinase started on average more than 5 hr after the onset of symptoms and patients with signs of cardiogenic shock were excluded.[21, 22] No improvement in left ventricular function or reduction in mortality was observed, which is consistent with our observations. Among three relatively small studies beneficial effects of thrombolytic therapy were observed in only one, in which the mean time between onset of symptoms and admission was 160 min.[23–26] In most of these studies patients with newly formed Q waves or signs of cardiogenic shock were excluded, and these groups of patients were shown to benefit greatly from thrombolytic therapy in the present trial.[30]

**ST segment elevation as predictor of the effects of thrombolytic therapy.** In the regression analysis enzymatic infarct size was strongly related to ΣST, although ST segment elevation may vary considerably over longer periods of time in patients with acute myocardial infarction.[31, 32] The highest ST segment elevation is usually found within 1 hr after the onset of symptoms. In a group of patients who are already in the hospital before the onset of symptoms infarct size may be overestimated by ΣST. This explains why "in hospital at the onset of symptoms" was included as an independent variable in the regression model. In patients admitted after the onset of symptoms no correction was necessary for the gradual decrease in ST segment elevation with time.

Contrary to other observations,[33] we noted that patients with inferior infarction and precordial ST segment depression generally had larger infarctions than patients without precordial ST segment depression. The regression coefficient for the total ST segment elevation was equal to the regression coefficient for the total precordial ST segment depression, so both were combined. Contralateral ST segment depression was not related to enzymatic infarct size in patients with anterior infarction, and therefore was not included in the regression model.

**Which patients benefit most from thrombolytic therapy by intracoronary streptokinase?** Thrombolytic therapy with intracoronary streptokinase led to significant limitation of infarct size, improvement in left ventricular function, and reduction in mortality in patients with extensive myocardial ischemia, that is in patients with a high ΣST, when thrombolytic therapy was started in the first few hours after onset of symptoms. Data from the GISSI trial[34] and the ISAM study[35] also indicate that beneficial effects from intravenous streptokinase dominate in patients admitted within 3 hr after onset of symptoms. Thus, it can now be recommended that thrombolytic therapy be offered to patients admitted within the first few hours after the onset of symptoms, and only to those patients who show extensive ST segment elevation on the ECG. Further studies presently underway both in the United States and in Europe should determine the relative values of intravenous and intracoronary treatment and of the use of streptokinase or other thrombolytic agents such as recombinant tissue-type plasminogen activator.

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