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Immediate Coronary Angioplasty Versus Intravenous Streptokinase in Acute Myocardial Infarction: Left Ventricular Ejection Fraction, Hospital Mortality and Reinfarction

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Objectives. The purpose of the present study was to compare intravenous streptokinase therapy with immediate coronary angioplasty without antecedent thrombolytic therapy with regard to left ventricular function and hospital mortality and reinfarction.

Background. Despite the widespread use of intravenous thrombolytic therapy and immediate percutaneous transluminal coronary angioplasty, these two strategies to treat patients with an acute myocardial infarction have only recently been compared in randomized trials. Coronary angioplasty has been shown to result in a higher patency rate of the infarct-related coronary artery, with a less severe residual stenotic lesion, compared with streptokinase therapy, but whether this more favorable coronary anatomy results in clinical benefit remains to be established.

Methods. We studied 301 patients with acute myocardial infarction randomly assigned to undergo immediate coronary angioplasty without antecedent thrombolytic therapy or to receive intravenous streptokinase therapy. Before discharge left ventricular ejection fraction was measured by radionuclide scanning.

Results. The in-hospital mortality rate in the streptokinase group was 7% (11 of 149 patients) compared with 2% (3 of 152 patients) in the angioplasty group ($p = 0.024$). In the streptokinase group recurrent myocardial infarction occurred in 15 patients (10%) versus in 2 (1%) in the angioplasty group ($p < 0.001$). Either death or nonfatal reinfarction occurred in 23 patients (15%) in the streptokinase group and in 5 patients (3%) in the angioplasty group ($p = 0.001$). Left ventricular ejection fraction was 44 ± 11% (mean ± SD) in the streptokinase group versus 50 ± 11% in the angioplasty group ($p < 0.001$).

Conclusions. These findings indicate that immediate coronary angioplasty without antecedent thrombolytic therapy results in better left ventricular function and lower risk of death and recurrent myocardial infarction than treatment with intravenous streptokinase.

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During the past decade the efficacy of thrombolytic therapy and coronary angioplasty in restoring patency of the infarct-related coronary artery has been studied extensively (1–11). Currently, the combination of streptokinase, aspirin and heparin is one of the generally accepted treatment strategies in patients with acute myocardial infarction (8–10). Direct coronary angioplasty without antecedent thrombolytic therapy avoids the potentially adverse effects of myocardial and intraplaque hemorrhage that can be observed after thrombolytic therapy (12) and may be an appropriate alternative therapy (7,13–15). In a previous report we showed that direct coronary angioplasty is associated with a higher patency rate, a less severe residual stenotic lesion in the infarct-related vessel, better preserved left ventricular function as well as less recurrent ischemia before hospital discharge compared with intravenous streptokinase therapy (13). However, several important questions are still to be answered before direct angioplasty can be accepted as the therapy of choice in patients with acute myocardial infarction. In particular, does the superior coronary anatomy result in a more favorable clinical outcome? Although the results of the Primary Angioplasty in Myocardial Infarction trial (14) showed a strong trend toward survival benefit and lower rate of reinfarction with angioplasty versus intravenous tissue plasminogen activator, additional data are needed before definitive conclusions can be drawn. We therefore extended our trial to investigate differences in mortality, recurrent myocardial infarction and left ventricular ejection fraction before hospital discharge.

Methods

The research protocol was reviewed and approved by the institutional review board. The enrollment of patients began

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on August 20, 1990 and ended on April 26, 1993. Inclusion criteria were 1) symptoms of acute myocardial infarction persisting >30 min, accompanied by an electrocardiogram (ECG) with >1-mm (0.1 mV) ST segment elevation in two or more contiguous leads; 2) presentation within 6 h after symptom onset or between 6 and 24 h, if there was evidence of continuing ischemia; 3) age <76 years; 4) no contraindication to thrombolytic intervention. Before randomization the following variables were recorded: age, gender, Killip class on admission (16), ECG site of infarction, history of previous infarction, time of symptom onset and time of hospital admission.

Randomization and treatment. After informed consent was obtained, patients were randomly assigned to one of the two treatment modalities by means of a closed-envelope system. All patients received aspirin and heparin. Heparin was given intravenously and titrated to a dose that resulted in an activated partial thromboplastin time of two to three times the normal value. Patients assigned to streptokinase therapy received 1.5 million U intravenously in 1 h. Patients assigned to undergo coronary angioplasty were immediately transported to the catheterization laboratory for coronary angiography. If the coronary anatomy was suitable for angioplasty, this procedure was performed immediately using standard techniques.

End points. The study end points were the following: 1) death before hospital discharge. 2) Recurrent myocardial infarction before hospital discharge, defined as chest pain accompanied by changes in ST-T waves or new Q waves, and a second increase in creatine kinase of more than two times the upper limit of normal or an increase of this magnitude over the previous value if the level had not decreased below the upper limit of normal (13). 3) Left ventricular ejection fraction was measured with a radionuclide technique before hospital discharge. The technique used in our hospital has been described elsewhere (13).

Statistical analysis. Statistical analysis was performed with an SPSS personal computer, version 4.01, 1990. All end points were analyzed according to the principle of intention to treat. Differences between group means were tested by a two-tailed Student *t* test. A chi-square method was used to test differences between proportions, with calculation of relative risks and exact 95% confidence intervals (17). Patients randomized to undergo angioplasty were defined as the reference group. The Fisher exact test was used if there was an expected cell value <5. Statistical significance was defined as a p value < 0.05. Multivariate analysis was performed by fitting a logistic regression model, permitting calculation of odds ratios that could be interpreted as relative risk and their 95% confidence interval (CI). All baseline characteristics that could have had an effect on the occurrence of in-hospital death or recurrent infarction were incorporated into the model to estimate the proper treatment effect. In the multivariate analysis, adjustments were made for differences in age (continuous variable), gender, infarct location (anterior versus nonanterior), Killip class on admission, time from onset of symptoms to admission and previous myocardial infarction. In the presentation of the data, continuous variables are given as mean value ± SD, whereas discrete variables are given as absolute values and percents.

Results

The 301 patients in this study include the 142 patients evaluated previously (13). During the enrollment period, 301 patients were randomized to undergo either streptokinase therapy (149 patients) or coronary angioplasty (152 patients). All patients assigned to the angioplasty group underwent immediate coronary angiography, with one exception: One patient died of cardiogenic shock immediately after randomization. Five patients had an open infarct-related artery and were treated conservatively. Six patients with extensive coronary artery disease not suitable for angioplasty underwent primary coronary artery bypass grafting. Angioplasty was performed in 140 patients, and the procedure was successful in 136 (97%). In four patients angioplasty failed to reopen the infarct-related vessel. Three of them underwent emergency coronary artery bypass grafting, and one patient was treated conservatively. Of the 136 patients with successful angioplasty, 7 underwent elective coronary artery bypass grafting for left main coronary artery or extensive three-vessel coronary artery disease. All patients assigned to therapy with intravenous streptokinase were treated accordingly, with one exception: One patient died of cardiogenic shock immediately after randomization. Another 16 patients with hemodynamic compromise and signs of ongoing ischemia within 24 h after admission underwent rescue angioplasty, with procedural success in 15 patients. Emergency coronary artery bypass grafting was performed in one patient. Sixteen patients underwent emergency coronary angioplasty because of signs of recurrent ischemia, with emergency coronary artery bypass grafting in 1 patient and

Table 1. Baseline Characteristics of the Patients

	Streptokinase Group (n = 149)	Angioplasty Group (n = 152)	p Value
Age (yr)	61 ± 9	59 ± 10	0.06
Male gender	121 (81%)	127 (84%)	0.59
Anterior infarction	68 (46%)	79 (52%)	0.27
Previous infarction	21 (14%)	32 (21%)	0.11
Time from onset to admission (min)*	176 ± 172	195 ± 227	0.43
Killip class on admission			
I	122 (82%)	116 (76%)	0.22
II	15 (10%)	22 (14%)	0.36
III	9 (6%)	6 (4%)	0.41
IV	3 (2%)	8 (5%)	0.14
Multivessel disease	88 (59%)	95 (63%)	0.63

*From onset of symptoms of myocardial infarction to hospital admission (the moment the ambulance drives through the door). Values presented are mean value ± SD or number (%).

Table 2. Clinical Data

	Streptokinase Group (n = 149)	Angioplasty Group (n = 152)	p Value
Hospital stay	14.4 ± 6.8	12.3 ± 5.3	0.003
Stroke	3 (2%)	1 (1%)	0.37
Vascular repair	0 (0%)	1 (1%)	1.0
Mechanical ventilation	3 (2%)	2 (1%)	0.68
Heart failure	17 (11%)	7 (5%)	0.03
Bleeding	9 (6%)	8 (5%)	0.97
IABP	12 (8%)	19 (13%)	0.28
Peak CK	1,403 ± 1,376	1,268 ± 1,088	0.33

Values presented are mean value ± SD or number (%). Bleeding = bleeding requiring a blood transfusion or intracranial bleeding; CK = creatine kinase; Heart failure = signs of heart failure requiring therapy with diuretic agents and angiotensin-converting enzyme inhibitors <24 h after admission; IABP = intraaortic balloon pump; Vascular repair = surgical repair of the femoral artery.

procedural success in 15 patients. Nine patients underwent elective angioplasty, and 13 patients underwent elective coronary artery bypass grafting for exercise-induced signs of myocardial ischemia. The remaining 94 patients were treated conservatively. Coronary angiography was performed in 141 of the 149 patients assigned to receive streptokinase (95%). Baseline characteristics are shown in Table 1, and additional clinical data are shown in Table 2.

End points. *Death.* A total of 14 patients (5%) died, 11 (7%) in the streptokinase group and 3 (2%) in the angioplasty group (p = 0.024). The cause of death is shown in Table 3. If patients in cardiogenic shock were excluded, there was still a significantly lower mortality in the patients randomized to undergo angioplasty (2 of 144 versus 10 of 146, p = 0.03).

Recurrent myocardial infarction. A total of 17 patients (6%) had a recurrent myocardial infarction, 15 (10%) in the streptokinase group and 2 (1%) in the angioplasty group (p < 0.001). Death or a nonfatal recurrent infarction occurred in 23 patients (15%) in the streptokinase group and in 5 patients (3%) in the angioplasty group (p = 0.001). The results of the univariate analysis are shown in Table 3.

Age was associated with mortality. Nonsurvivors were 66 ± 9.8 years old, and survivors were 59 ± 5.5 years old (p = 0.01). After multivariate analysis, age, Killip class on admission, previous myocardial infarction and treatment with streptokinase were associated with the end points of death and recurrent myocardial infarction, as well as the combination of death and nonfatal recurrent infarction. Patients with a previous myocardial infarction had an increased risk of recurrent infarction (relative risk 4.5, 95% CI 1.4 to 14.5). Killip class on admission was associated with an increased risk of death (relative risk 3.6 per step, 95% CI 2.0 to 6.6). After adjustments were made for differences in age, gender, previous myocardial infarction, time from onset of symptoms to admission, location of the infarction and Killip class on admission, the relative risk of reinfarction in the streptokinase group was 9.7 (95% CI 2.1 to 45.1) compared with the angioplasty group, and the relative risk of death was 8.5 (95% CI 1.7 to 41.7) in the streptokinase group compared with the angioplasty group.

Left ventricular ejection fraction. Left ventricular ejection fraction was measured in 140 patients (94%) in the streptokinase group and in 149 patients (98%) in the angioplasty group. Patients in the streptokinase group had an ejection fraction of 44 ± 11%, and those in the angioplasty group had an ejection fraction of 50 ± 11% (p < 0.001). A previous myocardial infarction, the location of the infarction and the time from symptom onset to admission were related to ejection fraction, as shown in Table 4. Before discharge 260 (86%) of the 301 patients performed a symptom-limited exercise stress test. The results are shown in Table 5.

Discussion

Although thrombolytic therapy is one of the major advances in the care of patients with an acute myocardial infarction (1–4,6,9,10), reperfusion of the occluded infarct-related artery is not obtained in 20% to 32% of patients (8,11,13). Recent trials have shown that immediate coronary angioplasty without antecedent thrombolytic therapy results in a reperfusion rate >90% (7,13,14). Furthermore, signs of recurrent myocardial ischemia that occur often in patients

Table 3. Comparison of Outcome Between 149 Patients Assigned to Streptokinase Therapy and 152 Patients Assigned to Undergo Coronary Angioplasty (univariate analysis)

	Streptokinase Group (no. of pts)	Angioplasty Group (no. of pts)	p Value	RR	95% CI
Death	11	3	0.024	3.96	1.01–22.5
Cardiogenic shock	5	2			
Cardiac rupture	2	0			
Sudden death	3	1			
Stroke	1	0			
Recurrent infarction	15	2	0.001	8.40	1.89–76.58
Death or recurrent infarction	23	5	0.0003	5.40	1.91–18.51

CI = confidence interval; pts = patients; RR = relative risk of outcome of streptokinase-treated patients compared with angioplasty-treated patients.

Table 4. Left Ventricular Ejection Fraction

	Streptokinase Group (n = 149)		Angioplasty Group (n = 152)			Difference	
	% (mean ± SD)	No.	% (mean ± SD)	No.	p Value	Absolute (%)	Relative (%)
All pts	44 ± 11	140	50 ± 11	149	< 0.001	6	12
Anterior infarction	38 ± 12	61	47 ± 12	76	< 0.001	9	19
No anterior infarction	48 ± 9	79	52 ± 9	73	0.006	4	8
Previous infarction	37 ± 12	18	45 ± 14	31	0.136	6	14
No previous infarction	45 ± 11	122	51 ± 9	118	< 0.001	6	12
>120-min from onset to admission	44 ± 12	53	49 ± 9	48	0.01	5	10
<120-min from onset to admission	46 ± 10	59	53 ± 8	71	< 0.001	7	13
<180-min from onset to admission	44 ± 13	20	57 ± 6	15	0.002	13	23

pts = patients.

after thrombolytic therapy and result in reinfarction, as well as subsequent in-hospital interventions (5), seem to be reduced after immediate angioplasty (13,14). We therefore extended our previous trial (13) to investigate whether these differences in coronary patency and recurrent ischemia would result in differences in mortality and the incidence of recurrent myocardial infarction. Our data support this hypothesis.

Myocardial salvage and left ventricular ejection fraction. Left ventricular ejection fraction has been proposed (18), as well as rejected (19), as an end point in trials of acute myocardial infarction. Long-term survival is strongly related to left ventricular ejection fraction (6), but one of the main objections to the use of ejection fraction as an end point has been the problem of "missing values" and the consequent debate about imputing data because studies are unavailable or technically inadequate (19). We therefore chose a radionuclide technique that is easy to perform, requires only 10 to 15 min and is not cumbersome for the patient (13). We were thus able to measure ejection fraction in nearly all of our patients (289 [96%] of 301). Our results show (Table 4) that immediate angioplasty salvages more myocardium than thrombolytic therapy, especially in patients with an infarction of the anterior wall, and in patients with a short interval between symptom onset and hospital admission.

Impact of coronary angiography immediately after hospital admission. All but one patient randomized to undergo angioplasty had immediate coronary angiography. Therefore, in patients randomized to undergo angioplasty, coronary anatomy was known at an early stage as opposed to patients randomized to receive streptokinase. This knowledge of the coronary anatomy certainly played a role in the subsequent therapeutic strategy because it allowed emergency surgical intervention in patients with a high risk coronary anatomy. In patients randomized to receive streptokinase, revascularization procedures were performed only on clinical indication. "Rescue" angioplasty for failed thrombolysis was performed in 11% of patients, and angioplasty or bypass surgery for recurrent ischemia was performed in 26% of patients randomized to receive streptokinase. The difference in results between the two groups might therefore not only be due to differences in initial treatment but, possibly, to subsequent different management as well.

Which patients with acute myocardial infarction should have primary angioplasty? If immediate angioplasty were offered to all patients with an acute myocardial infarction, a tremendous logistic burden would result and be impossible to organize at the present time (15). However, this may not be necessary. A substantial number of patients fare very well with thrombolytic therapy. The most important task for the coming years will therefore be to identify on admission those patients that will do well with thrombolytic therapy and to apply immediate angioplasty without antecedent thrombolytic therapy in subgroups of patients who are likely to gain the most benefit from this procedure (15). This policy of "tailored" angioplasty and thrombolytic therapy in patients with a low risk of death or other complications should be based on easily obtainable clinical data available immediately after hospital admission.

Study limitations. Given the limited number of patients in our study it is impossible to conclude exactly which subgroups do benefit most from angioplasty, the only easy applicable criterion being Killip class ≥II on admission. Also the magnitude of the effect of angioplasty on the risks of reinfarction and death should be viewed with caution because of the wide confidence intervals.

Conclusions. Our results show that immediate coronary angioplasty without antecedent administration of a thrombolytic agent results in better left ventricular function and a

Table 5. Bicycle Exercise Test Before Discharge

	Streptokinase Group (n = 122)	Angioplasty Group (n = 138)	p Value
Angina	17 (14%)	9 (7%)	0.04
ST segment depression >1 mm	49 (40%)	30 (22%)	< 0.001
Maximal workload (W)	90 ± 30	98 ± 30	0.03

Values presented are mean value ± SD or number (%).

lower in-hospital incidence of recurrent infarction and death than treatment with intravenous streptokinase.

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