Primary PCI for acute myocardial infarction

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Long-term Results of the Zwolle Trial

CHAPTER 2.1

Prognostic Importance of Left Ventricular Function After Angioplasty or Thrombolysis for Acute Myocardial Infarction: Long-term Results of the Zwolle Trial

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Abstract

Objectives. To compare long-term clinical outcome after acute myocardial infarction treated with primary coronary angioplasty or thrombolytic therapy, and to study the determinants of survival.

Background. Primary coronary angioplasty results in a higher patency rate and a better short-term survival when compared with thrombolytic therapy, but so far limited information has been available regarding long-term clinical outcome.

Methods. Patients with acute myocardial infarction (n=395) were randomised to treatment with either intravenous streptokinase or primary angioplasty, and were followed for up to eight years.

Results. A total of 105 patients died, 42 patients in the primary coronary angioplasty group compared with 63 patients in the streptokinase group (p=0.03). Death and nonfatal reinfarction occurred in 53 patients in the angioplasty group, compared with 94 patients in the streptokinase group (p<0.001). The major cause of long-term mortality is sudden death. Multivariate analysis showed that left ventricular function was the most important predictor for both total mortality and sudden death.

Conclusion. The benefits of primary coronary angioplasty compared with streptokinase are well sustained during long-term follow-up.

Introduction

The prognosis of acute myocardial infarction has improved the last two decades, but sudden death before and after admission is still a major concern. In hospital survival has improved due to several factors, most importantly due to the use of reperfusion therapy. Thrombolytic therapy has reduced mortality by 20-30 % (1-3). Primary coronary angioplasty, when performed by experienced interventional cardiologists, restores normal blood flow in 80-95 percent of the patients (4-8), compared to 50-70 % of the patients treated with thrombolytic therapy (3,5,9). Restoration of blood flow is the most important factor in preserving myocardial function. Short-term analyses have been in favor of primary coronary angioplasty (10), although some doubt has risen about the difference between these two treatment modalities (11,12). Recently we were able to demonstrate a better long term survival in patient with acute myocardial infarction treated with primary coronary angioplasty compared to streptokinase (13), and in this report we extended the follow-up period up to 8 years to see whether this improved outcome is maintained over the following years.

Material and methods

The patients have been described before (5,13). Base-line characteristics, clinical data, angiographic data and outcomes were recorded in a dedicated database. Patients were enrolled if they had no contraindications for thrombolytic therapy; had symptoms of acute myocardial infarction lasting longer than 30 minutes, accompanied by an electrocardiogram with ST-segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads; and presented within 6 hours, or between 6 to 24 hours if there was evidence for continuing ischaemia. After informed consent had been obtained, patients were randomly assigned to undergo primary coronary angioplasty or to receive streptokinase. All patients received heparin and aspirin. Patients assigned to the streptokinase group received 1.5 million units intravenously over one hour. Patients assigned to the angioplasty

group were immediately transported to the catherization laboratory: if the coronary anatomy was suitable for angioplasty, the procedure was performed with standard techniques. Global left ventricular ejection fraction was measured by equilibrium radionuclide ventriculography between days 4 and 10 after treatment (5). Coronary angiography was performed during follow-up in all patients to assess the extent to which the patency of the infarct-related artery was maintained, as previously described (7,8). For purposes of this study, patency in the angioplasty group was defined as grade 3 blood flow (according to the TIMI classification) after the angioplasty procedure and on follow-up angiograms. In the streptokinase group, patency was also defined as TIMI grade 3 blood flow as assessed by coronary angiography (8). In the latter group, an initial, conservative approach of watchful waiting after treatment was followed by elective coronary angiography. For all patients, additional revascularization procedures were performed if indicated for symptoms or signs of myocardial ischaemia (15,16). Follow-up information was obtained in September 2000. All outpatients' reports were reviewed, and general practitioners were contacted by telephone. For patients who had sustained clinical events during follow-up, hospital records were reviewed. All subsequent hospital admissions (for angina, recurrent infarction, additional intervention, or heart failure) and medications used during follow-up were recorded. Nonfatal recurrent myocardial infarction was defined as the combination of chest pain, changes in the ST-T segment, and a second increase in the serum creatine kinase level to more than two times the upper limit of normal. If the creatine kinase level had not decreased to normal levels, a second increase of more than 200 U per liter over the previous value was regarded as indicating a recurrent infarction (5).

Statistical Analysis

The primary endpoints were death and the combined incidence of death and nonfatal reinfarction. In univariate analyses we investigated the association between these study outcomes and the following risk factors; left ventricular ejection fraction (in quartiles and as a continuous variable), patency of the infarct-related artery, diabetes, age (as a continuous variable), multivessel disease,

treatment assignment (angioplasty vs. streptokinase), infarct location (anterior vs. other), presence or absence of previous myocardial infarction, time from onset of symptoms to admission and sex. Multivariate analyses included infarct location, left ventricular ejection fraction, age, sex, treatment regimen and patency. All outcomes were analyzed according to the intention to treat principle. Differences between group means were assessed with two-tailed Student's t-test. Chi-square analysis or Fisher 's exact test was used to test differences between proportions. Survival was calculated by the Kaplan-Meier product -limit method (18). The Mantel -Cox (or log-rank) test was used to evaluate differences in survival between the two treatment groups. Cox proportional-hazards regression model was used for multivariate analysis (19). Left ventricular ejection fraction was included as a dichotomous variable greater than 40% compared with lower than or equal to 40%. Statistical significance was considered to be indicated by a two-tailed P value of less than 0.05. Relative risks were calculated with 95 percent confidence intervals.

Results

Of the 395 patients enrolled, 194 were randomized to undergo primary angioplasty and 201 to receive streptokinase. The groups were similar in age, sex, infarct location, presence of previous myocardial infarction multivessel coronary artery and diabetes mellitus (Table 1). Survivors underwent follow-up coronary angiography to analyze patency of the infarct-related vessel. The infarct-related artery was more often patent in the angioplasty group (90%), compared to the streptokinase group (65%, $P<0.001$). The ejection fraction of the left ventricle was measured in 189 patients of the angioplasty group and in 188 patients of the streptokinase group.

Table 1. BASELINE CHARACTERISTICS OF PATIENTS

		PCI	SK	P
Age	(yr)	59 ± 11	60 ± 10	0.63
Male	no. (%)	160 (82)	158 (79)	0.37
Anterior infarction	no. (%)	77 (40)	74 (34)	0.60
Previous infarction	no. (%)	38 (20)	31 (31)	0.29
Diabetes Mellitus	no. (%)	16 (8)	16 (8)	1.00
Patent IRA†	no. (%)	171 (90)	127 (65)	<0.001
LVEF ≤ 40% ‡	no. (%)	27 (14)	48 (26)	0.006
LVEF ‡	no. (%)	49.8 ± 10.3	44.9 ± 11.3	<0.001

PCI: primary coronary angioplasty, SK: streptokinase, IRA: infarct related artery, † Patency of the infarct-related artery was analyzed in 191 patients in the angioplasty group and 196 patients in the streptokinase group
‡ Left ventricular function was analyzed in 189 patients in the angioplasty group and 188 patients in the streptokinase group

The mean ejection fraction of the left ventricle was higher in the angioplasty group compared to streptokinase group (50% versus 45%, P<0.0001). The proportion of the patients with an ejection fraction of the left ventricle equal to or less than 40 percent was lower in the angioplasty group, compared to the streptokinase group (14% versus 26%, P=0.006). Patients were followed for mean of 8±2 years. One patient was lost to follow-up. A total of 105 patients died, 37 from documented noncardiac causes. Mortality and causes of death are summarized in Table 2. In the angioplasty group 42 (22%) patients died, compared to 63 (31%) patients in the streptokinase group (relative risk of death for patients in the streptokinase group, 1.65; 95 percent confidence interval, 1.05 to 2.60). Nonfatal recurrent myocardial infarction occurred in 58 patients. Fatal recurrent myocardial infarction occurred 8 patients, all these patients were in the streptokinase group.

Table 2. MORTALITY AND CAUSES OF EARLY AND LATE DEATH

	<30 Days after MI			>30 Days after MI			Total Follow-up		
	PCI (N=194)	SK (N=201)	P	PCI (N=194)	SK (N=201)	P	PCI (N=194)	SK (N=201)	P
Cardiac	2	13	<0.01	18	35	0.018	20	48	<0.001
Heart failure	1	11	<0.01	6	11	0.244	7	22	0.005
Sudden death	0	1	1.0	12	23	0.07	12	24	0.047
Rupture	1	1	1.0	0	1	0.49	1	2	1.0
Noncardiac	0	1	1.0	22	14	0.198	22	15	0.19
Lungcancer	0	0	1.0	5	5	1.0	5	5	1.0
Other cancer	0	0	1.0	9	5	0.25	9	5	0.25
Stroke	0	1	1.0	1	1	1.0	2	3	0.68
All other	0	0	1.0	6	2	0.14	6	2	0.14
All causes	2	14	0.01	40	49	0.371	42	63	0.029

PCI: primary coronary angioplasty, SK : streptokinase

Nonfatal reinfarction, occurred in 13 patients in the angioplasty group (7%) and 45 patients in the streptokinase group (22%, relative risk, 0.25; 95 percent confidence interval, 0.13 to 0.48). In the first 30 days after enrollment, only 1 patient of the angioplasty group (0.5%) suffered nonfatal myocardial infarction, compared to 19 patients in the streptokinase group (9%, relative risk, 0.06;95 percent confidence interval, 0.01 to 0.40). Of the 38 nonfatal reinfarctions after 30 days, 12 patients were in the angioplasty group (6%) and 26 patients were in the streptokinase group (13%, relative risk, 0.48;95 percent confidence interval, 0.25 to 0.92). All reinfarctions that occurred within the first 30 days affected the region of the index infarction. Of the 38 reinfarctions after day 30, (15 during the first year of follow-up

and 23 afterwards), 20 involved the original infarct related artery. Of the 18 reinfarctions, not related to the index artery, there was an almost equal distribution in both groups (8 patients in the primary coronary angioplasty group compared to 9 patients in the streptokinase group). The difference in reinfarction rate was thus entirely due to events in the original infarct related artery. The combined incidence of death and nonfatal reinfarction was lower in the angioplasty group than in the streptokinase group within the first 30 days (relative risk, 0.13;95 percent confidence interval, 0.05 to0.37) and after 30 days (relative risk,0.62;95 percent confidence interval, 0.43 to 0.91). Kaplan-Meier curves for overall survival and for survival, free of reinfarction, are shown in Figure 1 and 2. Univariate and multivariate analyses of risk factors for total mortality are shown in Table 3. There was a strong relation between ejection fraction of the left ventricle and total mortality.

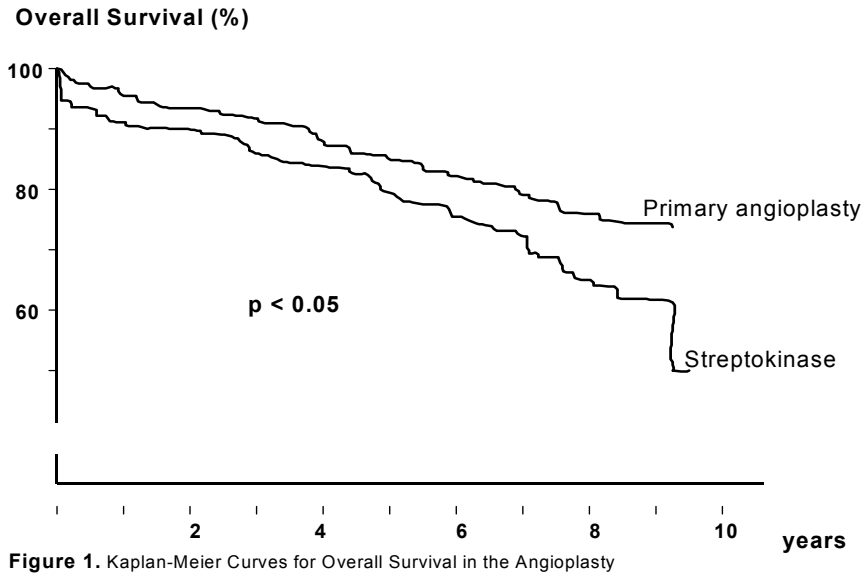

Figure 1. Kaplan-Meier Curves for Overall Survival in the Angioplasty and Streptokinase Groups during 8 years Follow-up

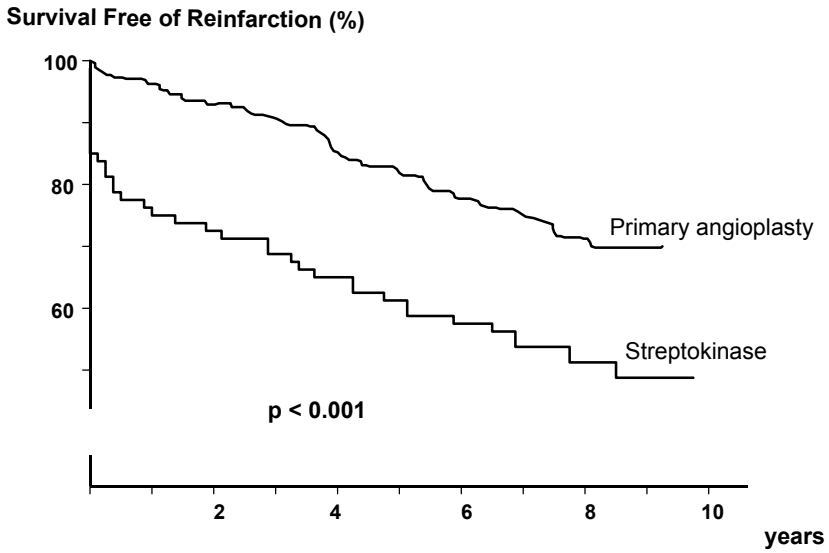

Figure 2. Kaplan-Meier Curves for Survival Free of Reinfarction in the Angioplasty and Streptokinase Groups during 8 years Follow-up

Table 3. UNIVARIATE AND MULTIVARIATE ANALYSES OF RISK FACTORS TOTAL MORTALITY*

Variables	Univariate		Multivariate	
	RR	(95%CI)	RR	(95%CI)
Age	1.05	1.03 – 1.08	1.05	1.02 - 1.08
Sex (Male vs Female)	0.76	0.48 – 1.19	0.92	0.56 - 1.52
SK vs. PCI	1.53	1.04 – 2.26	1.18	0.77 - 1.80
Infarct Location (Anterior vs Non-Anterior)	1.72	1.17 – 2.53	1.25	0.80 - 1.95
LVEF ≤ 40 %	2.88	1.88 – 4.42	2.39	1.52 - 3.76

PCI: percutaneous coronary intervention, SK: streptokinase, LVEF: left ventricular ejection fraction, *RR : Relative Risk; CI : Confidence Interval

Sudden death occurred in 36 patients, 24 patients in the streptokinase group and 12 patients in the primary coronary angioplasty group (relative risk, 2.06;95 percent confidence interval, 1.03 to 4.12). Kaplan-Meier curves for the difference in survival due to sudden death are shown in Figure 3. In the sudden death patients, more patients had anterior location of the myocardial infarction (n=24) than nonanterior location (n=12, relative risk, 2.29: 95 percent confidence interval, 1.18 to 4.45). Mean left ventricular ejection fraction in the sudden death patients was 36.9±13.9 and in the survivors 49.2±9.2 ($p<0.001$). Univariate and multivariate analyses of risk factors for sudden death are shown in Table 4. Multivariate analysis revealed that age and left ventricular ejection fraction $\leq$ 40 % were predictors for sudden death.

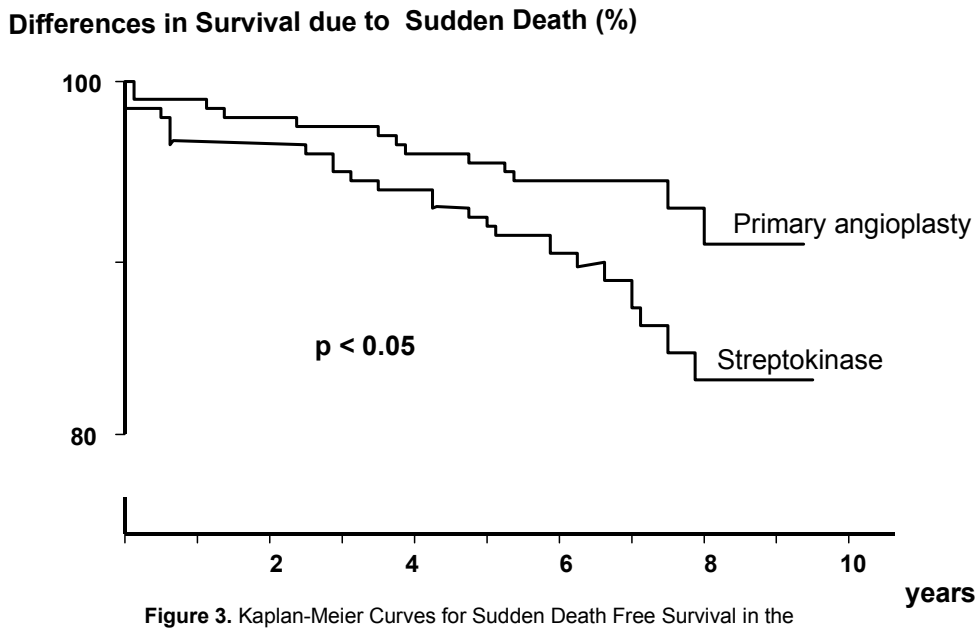

Figure 3. Kaplan-Meier Curves for Sudden Death Free Survival in the Angioplasty and Streptokinase Groups during 8 years Follow-up

Table 4. UNIVARIATE AND MULTIVARIATE ANALYSES OF RISK FACTORS FOR SUDDEN DEATH*

Variables	Univariate		Multivariate	
	RR	(95%CI)	RR	(95%CI)
Age	1.08	1.04 – 1.12	1.08	1.03 - 1.12
Sex (Male vs Female)	1.10	0.46 – 2.66	1.63	0.66 - 4.00
SK vs. PCI	2.06	1.03 - 4.12	1.75	0.86 - 3.56
Infarc Location (Anterior vs Non-Anterior)	2.29	1.18 - 4.45	1.87	0.91 - 3.83
LVEF $\leq$ 40 %	5.01	2.58 - 9.72	3.43	1.70 - 6.94

PCI: percutaneous coronary intervention, SK: streptokinase, LVEF: left ventricular ejection fraction LVEF: left ventricular ejection fraction,*RR : Relative Risk;
CI : Confidence Interval

Discussion

This study confirms that patients treated with primary coronary angioplasty for acute myocardial infarction have better overall and cardiac survival and a lower reinfarction rate both short-term and long-term when compared to treatment with streptokinase. In the present study the follow-up period was extended to 8 years, confirming that the benefits of primary coronary angioplasty are maintained over a very long follow-up period. Reocclusion of the infarct related artery in acute myocardial infarction treated with thrombolytic therapy occurs up to 30 percent, while after angioplasty this is only 10 percent (8,20). This difference is possibly due to the placque sealing effect (21). Our study confirms these findings; a significantly lower reinfarcion rate in patients treated with angioplasty compared to thrombolytic therapy.

Several authors report that early reperfusion limits infarct size (9), thereby improving long-term survival (24,25). Today, ejection fraction of the left ventricle is considered to be one of the major endpoints after treatment for myocardial infarction and is strongly related to long-term survival (22,23). In this study the

importance relevance of the left ventricular ejection fraction is clearly demonstrated as it is related to total mortality as well as sudden death. The improvement in short-term survival is mainly caused by a lower rate of heart failure. Late mortality is lower in the angioplasty group mainly due to a lower rate of sudden death. Further analysis demonstrates that randomization to streptokinase, anterior infarct location and left ventricular ejection fraction $\leq$ 40% are related to sudden death. However when multivariate analysis was performed only age and in particular left ventricular ejection fraction $\leq$ 40% were predictors for sudden death.

Limitations of the study

While multicenter thrombolysis trials have included many thousands of acute myocardial infarction patients, undergoing reperfusion, our study included 395 only patients from a single center. During the study period intracoronary stenting and the use of GP 2B-3A receptor antagonists was not used. These two new therapy modes may well have a profound effect on clinical outcome (24,25).

Conclusions

These data show that primary coronary angioplasty is superior to streptokinase in patients with acute myocardial infarction, in terms of both short-and long-term survival. The reinfarction rate is lower after primary coronary angioplasty compared to streptokinase and reinfarction free survival is better. Death within 30 days after myocardial infarction is predominantly caused by heart failure. Late death is mainly caused by sudden death. There was a significant difference in sudden death when both treatment modalities were compared, with less sudden death in the primary coronary angioplasty group. Left ventricular ejection fraction was a strong predictor for both total mortality as well as sudden death.

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Appendix

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CHAPTER 2.2

Additional Benefits of Primary PCI Compared to Thrombolytic Therapy in Acute Anterior STEMI Patients During Long-term Follow-up; The Importance of Left Ventricular Function

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Submitted

ABSTRACT

Background. The clinical significance of infarct location during long-term follow up in trials comparing thrombolysis and primary angioplasty (PCI) has not been studied.

Methods and results. We studied survival in the Zwolle trial patients according to infarct location. 395 acute STEMI patients were randomized to intravenous streptokinase (SK) or PCI and mean follow up was 8±2 years.

105 patients died; 63 patients in the SK group and 42 patients in the primary PCI group (RR 1.6 95%CI: 1.0-2.6, p=0.03). In anterior STEMI patients, mortality was higher in the SK group compared with the PCI group (RR 2.7, 95%CI:1.4-5.5, p=0.004). The number needed to treat to prevent 1 death is 5. Kaplan-Meier analysis confirms the benefits of primary angioplasty in the first year and demonstrates additional benefit of PCI compared to SK between 1 and 8 years after the acute event. During long-term follow up, age and left ventricular function independently determine survival in patients after anterior myocardial infarction.

Conclusions. Patients with anterior STEMI have better long-term survival when treated with PCI, compared with SK treatment. In patients alive 1 year after the acute event, PCI confers a significant additional survival benefit, due to better preserved residual left ventricular function.

Introduction

Reperfusion treatment in acute myocardial infarction aims at early and sustained reperfusion of the myocardium at risk (1). Reperfusion can be obtained by thrombolysis or primary coronary intervention (PCI). Several studies have demonstrated a better survival in patients with acute STEMI treated with primary PCI, when compared with treatment with thrombolysis (2-3). A previous pooled analysis of all randomized studies showed that clinical outcome was better with primary PCI when compared to thrombolysis (4). Therefore, nowadays more patients with acute ST segment elevation myocardial infarction (STEMI) are being treated with primary PCI. Recent studies have demonstrated a better survival in acute STEMI patients treated with primary PCI, even when patients need to be transported for this treatment (5-8). A recent pooled analysis (9) and a separate quantitative review of 23 randomized trials of all randomized trials between both reperfusion therapy modalities (10) confirmed and demonstrated an improved survival in patients with acute STEMI, when treated with primary PCI compared with thrombolytic therapy on site even when transportation to a PCI center is needed. However, in daily clinical practice, there are still patients who are being treated with thrombolyis due to logistical and non-medical reasons, such as reimbursement.

Patients with anterior STEMI, have worse clinical outcome compared to non-anterior STEMI (11,12). This worse clinical outcome is related to a larger final infarct size and a subsequent lower residual left ventricular ejection fraction, which is a powerful predictor for outcome (13,14). The clinical significance of infarct location during long-term follow up in trials comparing thrombolysis and primary angioplasty has not been studied. We studied survival in the Zwolle trial patients according to infarct location, with a mean long-term follow up of 8 years.

Methods

The patients have been described before (15). Briefly, 395 patients with acute STEMI were randomized to primary PCI or thrombolytic therapy. Base-line

characteristics, clinical data, including infarct location and outcomes were recorded in a dedicated database. Patients were enrolled if they had no contraindications for thrombolytic therapy; had symptoms of acute myocardial infarction lasting longer than 30 minutes, accompanied by an electrocardiogram with ST-segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads; and presented within 6 hours, or between 6 to 24 hours if there was evidence for continuing ischaemia. After informed consent had been obtained, patients were randomly assigned to undergo primary PCI or to receive streptokinase (SK). All patients received heparin and aspirin. Patients assigned to SK treatment received 1.5 million units intravenously over one hour. Patients assigned to primary PCI were immediately transported to the catheterization laboratory: if the coronary anatomy was suitable for PCI, the procedure was performed with standard techniques. Global left ventricular ejection fraction was measured by equilibrium radionuclide ventriculography between days 4 and 10 after treatment (16). Enzymatic infarct size was measured by cumulative enzyme release from five to seven serial measurements up to 72 hours after symptom onset was calculated (16). For all patients, additional revascularization procedures were performed if indicated for symptoms or signs of myocardial ischaemia (17,18). Follow-up information was obtained in September 2000. All outpatients' reports were reviewed, and general practitioners were contacted by telephone. For patients who had sustained clinical events during follow-up, hospital records were reviewed. Nonfatal recurrent myocardial infarction was defined as the combination of chest pain, changes in the ST-T segment, and a second increase in the serum creatine kinase level to more than two times the upper limit of normal. If the creatine kinase level had not decreased to normal levels, a second increase of more than 200 U per liter over the previous value was regarded as indicating a recurrent infarction (16).

Statistical Analysis

The primary endpoints were death and the combined incidence of death and nonfatal reinfarction (MACE). All outcomes were analyzed according to the intention to treat principle. Statistical analysis was performed using SPSS 10.0.

Differences between group means were tested by two-tailed Student's t-test; A chi-square statistic was calculated to test differences between proportions, with calculation of relative risks and exact 95% confidence intervals. The Fisher exact test was used when the expected value of cells was smaller than 5. Statistical significance was defined as a p-value of less than 0.05. Cumulative survival (and mortality) curves were constructed according to the Kaplan–Meier method (19), and differences between the curves were tested for significance by the log-rank statistic (20). Cox proportional-hazards regression models (21) were used to estimate hazard ratios of variables that were significantly different in univariate analysis. Age (>60) and left ventricular function (LVEF<40 %) were dichotomized for the purpose of the multivariate analysis.

Results

Of the 395 patients enrolled, 194 were randomized to undergo primary PCI and 201 to receive SK. The groups were similar in age, sex, infarct location, previous myocardial infarction and a history of diabetes mellitus (Table 1).

Table 1. Clinical variables and infarct size in the Zwolle trial patients.

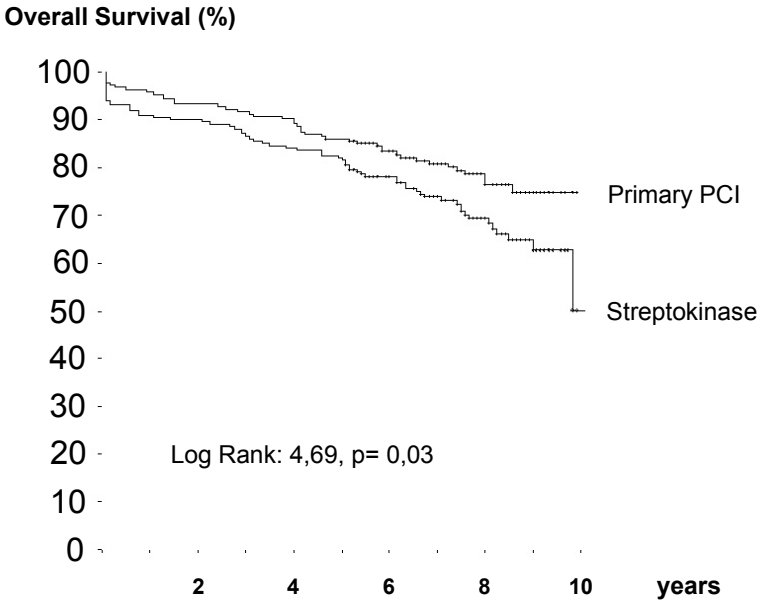
		PCI (n=194)	SK (n=201)	P
Age >60	(%)	94 (48)	109 (54)	0.25
Male	(%)	160 (82)	158 (79)	0.37
Hypertension	(%)	36 (19)	40 (20)	0.73
Anterior MI	(%)	77 (40)	74 (34)	0.60
Previous MI	(%)	38 (20)	31 (15)	0.29
Diabetes	(%)	16 (8)	16 (8)	1.00
Infarct size				
LVEF	(%)	49.8 ± 10.3	44.9 ± 11.3	<0.001
LDH_{Q72}		939 ± 738	1289 ± 1144	<0.001

PCI = primary coronary intervention, SK = streptokinase
LVEF = left ventricular ejection fraction, LDH_{Q72} = enzymatic infarct size

The residual ejection fraction of the left ventricle was measured in 189 patients of the PCI group and in 188 patients of the SK group. The mean ejection fraction of the left ventricle was higher in the PCI group compared to the SK group (50% versus 45%, P<0.001). Enzymatic infarct size was measured in 367 patients (93%). Mean follow up was 8 ± 2 years. One patient was lost to follow-up. At follow up a total of 105 patients had died. In the SK group 63 (31%) patients died, compared to 42 (22%) patients in the PCI group (RR 1.65; 95%CI: 1.05 - 2.60). Nonfatal recurrent myocardial infarction occurred in 58 patients. Nonfatal reinfarctions, occurred in 13 (7%) patients in the PCI group and 45 (22%) patients in the SK group (RR 0.25; 95%CI 0.13 - 0.48). All reinfarctions that occurred within the first 30 days affected the region of the index infarction. Of the 38 reinfarctions after day 30, (15 during the first year of follow-up and 23 afterwards), 20 involved the original infarct related artery. The difference in the reinfarction rate was thus entirely due to events in the original infarct related artery. Kaplan-Meier curves for overall survival between patient treated with SK or PCI are shown in Figure 1.

Figure 1. Kaplan-Meier Curves for Overall Survival of all Zwolle trial patients.

Figure 1



Non-Anterior STEMI patients in the Zwolle Trial

Table 2 shows the baseline characteristics of the Zwolle trial patients according to the infarct location, either anterior or non-anterior. In the non-anterior STEMI patients there were no significant differences in baseline characteristics between the patients who underwent primary PCI or those who received SK, see Table 2. Enzymatic infarct size was larger in patients treated with SK primary PCI, compared with patients treated with primary PCI (1099 ± 1027 vs. 822 ± 566, p=0.01). Residual left ventricular ejection fraction was lower in patients treated with SK, when compared with patients treated with primary PCI (48 ± 9 vs. 52 ± 9, p=0.005). At follow up, 23 (20%) patients with non-anterior STEMI died in the group treated with PCI compared to 28 (22%) patients treated with SK (RR 1.1, 95%CI 0.6-2.1, p=0.68). Kaplan-Meier curves for overall survival between non-anterior STEMI patients treated with SK or PCI are shown in Figure 2. The combined endpoint of MACE was significantly higher in the SK group when compared to the PCI group; 39 (50%) patients in the SK group and 28 (24%) patients in the PCI group (RR 2.1 95%CI: 1.2-3.6). Number needed to treat to prevent 1 MACE was 4.

Table 2. Clinical variables and infarct size in the Zwolle trial patients according to infarct location.

	Anterior (n=151)			Non-anterior (n=244)		
	PCI (n=77)	SK (n=74)	P	PCI (n=117)	SK (n=127)	P
Clinical variables						
Age >60 (%)	31 (40)	43 (58)	0.03	63 (54)	66 (52)	0.78
Male (%)	61 (79)	54 (73)	0.37	99 (85)	104 (82)	0.57
Hypert (%)	18 (24)	16 (22)	0.80	18 (15)	24 (19)	0.47
Prev.MI (%)	20 (26)	9 (12)	0.03	18 (15)	22 (17)	0.68
DM (%)	6 (8)	9 (12)	0.37	10 (8)	7 (5)	0.35
Infarct size						
LVEF (%)	47±12	38±12	<0.001	52± 9	48±9	0.005
LDH_{Q72}	1117±917	1592±1261	0.01	822±566	1099±1027	0.01

MI = myocardial infarction, PCI = primary coronary intervention, SK = streptokinase
LVEF = left ventricular ejection fraction, LDH_{Q72} = enzymatic infarct size

Figure 2. Kaplan-Meier Curves for Overall Survival for **Non-Anterior STEMI** in the PCI and SK Groups during 8 years Follow-up.

Figure 2

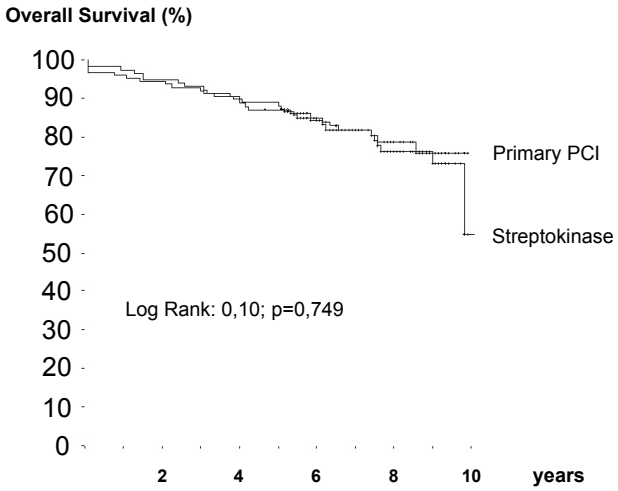
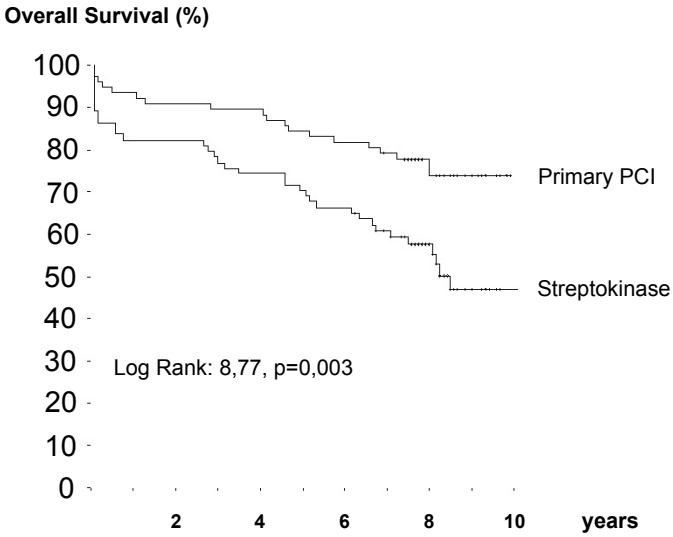


Figure 3. Kaplan-Meier Curves for Overall Survival for **Anterior STEMI** in the PCI and SK Groups during 8 years Follow-up.

Figure 3



Anterior STEMI patients in the Zwolle Trial

In the anterior STEMI patient group, there were no significant differences in the two treatment arms in sex and a history of diabetes mellitus. In the anterior STEMI patients, more patients with previous myocardial infarction were treated with PCI (26% vs. 12%, p=0.03). The anterior STEMI patient group that received SK was older than the patient group treated with PCI (Age >60 years: 58% vs. 40%, p=0.03). Enzymatic infarct size was larger in patients treated with SK, compared with patients treated with primary PCI (1592 ± 1261 vs. 1117 ± 917, p=0.001). Residual left ventricular ejection fraction was lower in patients treated with SK, when compared with patients treated with primary PCI (38 ± 12 vs. 47 ± 12, p<0.001). At follow up, in patients with anterior STEMI, 35 (47%) patients in the SK treated group died compared with 19 (25%) patients in the PCI treated group (RR 2.7, 95%CI:1.4-5.5, p=0.004). The number needed to treat to prevent 1 death was 5. Kaplan-Meier curves for overall survival in anterior STEMI patients according to treatment with SK or PCI are shown in Figure 3.

Table 3. Predictors of long-term mortality in anterior STEMI patients in the Zwolle trial.

	OR*	(95% CI)	p-value
Age	2.2	1.2-3.8	0.01
SK vs. PCI	2.2	1.2-3.8	0.01
Previous MI	1.3	0.7-2.6	0.40

Age = Age>60 vs. Age <60 years, SK = streptokinase, PCI = primary coronary intervention, MI = myocardial infarction, *Odds Ratios taken from the Cox Regression Analysis

Table 4. Predictors of long-term mortality in anterior STEMI patients in the Zwolle trial.

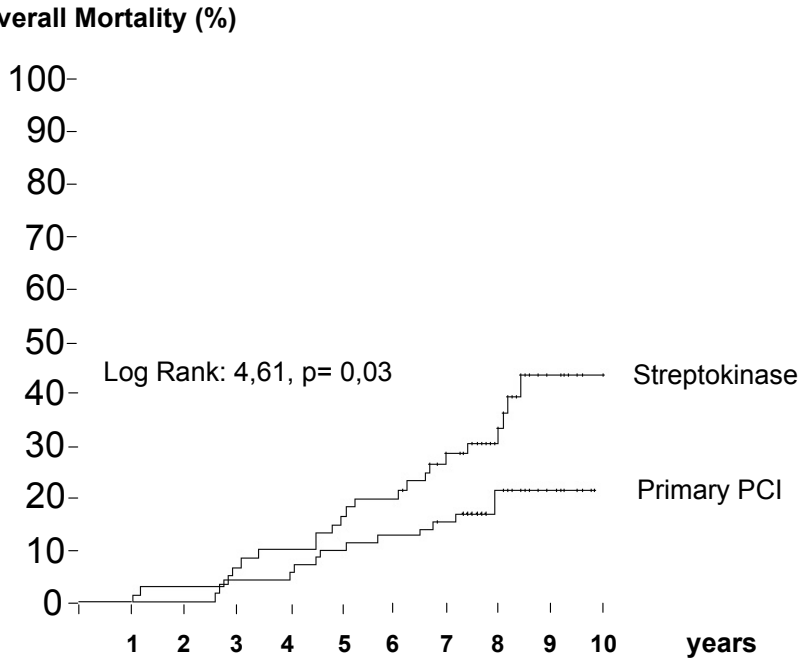
	OR*	(95% CI)	p-value
LVEF	3.5	1.8-6.7	<0.001
Age	2.2	1.2-4.3	0.01
Previous MI	1.2	0.5-2.4	0.69
SK vs. PCI	1.2	0.6-2.4	0.54

LVEF = left ventricular ejection fraction <40% vs. >40%, Age = Age>60 vs. Age <60 years, SK = streptokinase, PCI = primary coronary intervention, MI = myocardial infarction, *Odds Ratios taken from the Cox Regression Analysis

In univariate analysis of anterior STEMI patients, there were some differences in baseline characteristics and in residual left ventricular function between the PCI group and the SK group. We included these variables (age>60, previous MI, randomization and left ventricular function) in a multivariate model to study their independent value of long-term mortality. Multivariate analysis revealed that age > 60 and randomization to PCI treatment were equally strong predictors of long-term mortality (Table 3). When LVEF was included in the same model, the only two predictors of long-term mortality were age > 60 and LVEF <40% (Table 4). The combined endpoint of MACE was significantly higher in the SK group when compared to the PCI group; 44 (59%) patients in the SK group and 25 (32%) patients in the PCI group (RR 3.0 95%CI: 1.7-5.9). The number needed to treat to prevent 1 MACE was 4. We additionally analyzed mortality in anterior STEMI patients excluding the deaths in the first year after the index myocardial infarction. From the total of 395 patients, 25 died in the first year. After the first year, 14 (19%) patients from the PCI treatment group died and 21 (36%) patients from the SK treatment group (RR 2.3, 95%CI 1.1-5.1). Figure 4 shows a significantly better survival in anterior STEMI patients treated with PCI, compared with SK treatment, even when first year deaths are excluded from analysis.

Figure 4: Kaplan-Meier Curves for Overall Mortality for **Anterior STEMI**, Without Deaths in First Year of 8 Years Follow up in the PCI and SK Groups.

Figure 4



Discussion

This study strongly supports our principal goal: all anterior STEMI patients should be treated with primary PCI. In the western world where PCI has demonstrated its superiority over thrombolysis in randomized trials, some patients are still being treated with thrombolytic regimens due to several reasons. Although these reasons may be valid in some cases, it is essential that we treat patients, who have proven long-term benefit, with primary PCI.

Non-Anterior STEMI – Primary PCI vs. Streptokinase

In our study we could not find a better long-term survival in patients treated with PCI over those treated with SK. To show differences in outcome between treatment arms in non-anterior STEMI patients it is necessary to have large sample sizes, as are used in thrombolysis studies to demonstrate benefit of one regimen over another. Although we did not demonstrate a better long-term survival, it is clear that patients treated with PCI had a significantly smaller infarct size, as measured by residual left ventricular ejection fraction (52 ± 9 vs. 48 ± 9, p=0.005) and by enzymatic infarct size during 72 hours (822 ± 566 vs. 1099 ± 1027, p=0.01). Residual left ventricular ejection fraction is a known important endpoint of reperfusion therapy and a strong predictor of long-term outcome (13,14). Additionally, patients with non-anterior STEMI, treated with SK had more often recurrent myocardial infarction needing additional admissions and therapy as evidenced by a significantly higher incidence of MACE in patients treated with SK. Therefore, although long-term survival was not significantly different in both treatment modalities, we conclude that also in non-anterior STEMI, primary PCI offers clinical benefits over treatment with SK. In addition, patients with uncomplicated non-anterior STEMI can be discharged 2 to 3 days after primary PCI (22).

Anterior STEMI – Primary PCI vs. Streptokinase

Our study clearly confirms that primary PCI is the treatment of choice in anterior STEMI. Patients treated with primary PCI had higher residual left ventricular ejection fraction (47± 12 vs. 38± 12, p<0.001) and smaller enzymatic infarct size (1117 ± 917 vs. 1592 ± 1261, p=0.01). The absolute difference of residual left ventricular ejection fraction was 9% in anterior STEMI when both treatment arms were compared, whereas this absolute difference was only 4% in the patients with non-anterior STEMI in both treatment arms. These differences have been described before, but their importance comes clearly to expression during long-term outcome (12).

Furthermore, residual left ventricular ejection fraction after primary PCI improves over time, especially in anterior STEMI patients. Therefore, not only is there an immediate better residual left ventricular ejection fraction after the index acute STEMI, but the long-term recovery after STEMI, when treated with PCI, may importantly contribute to the better survival (12,13). Patients with anterior STEMI had an markedly better survival when treated with primary PCI, compared to patients treated with SK. Long-term mortality was 25% in the PCI group and 47% in the SK group. Therefore, there was a 22% absolute risk reduction for long-term mortality; the number needed to treat to save 1 life is only 5 patients. Since there were some differences in the baseline characteristics between patients treated either with primary PCI or SK, we performed multivariate regression analysis to study the independent predictors of long-term mortality. This analysis revealed that age (>60 years) and randomization to PCI were the two predictors for long-term survival in anterior STEMI patients. However, when residual left ventricular ejection fraction (< 40%) was included in this model, the two predictors for long-term survival in anterior STEMI patients were age (>60 years) and residual left ventricular ejection fraction (< 40%). This analysis demonstrates that the long-term improved survival in anterior STEMI patients treated with PCI is the result of better preserved left ventricular ejection fraction, when compared to treatment with SK. Treatment with thrombolysis, as in our study with SK, results in more recurrent myocardial infarction when compared with primary PCI. It is therefore conceivable, that the better survival in patients treated with primary PCI would in part be due to the recurrent (fatal) reinfarctions, that occur mainly within one year after the acute event. We therefore analyzed long-term mortality, after excluding all deaths in the first year after the index acute STEMI. Figure 4 clearly demonstrates the difference in mortality of anterior STEMI patients when the two treatment modalities are compared.

Limitations

While multicenter thrombolysis trials have included many thousands of acute myocardial infarction patients, undergoing reperfusion therapy, our study included

only 395 patients from a single center. During the study period intracoronary stenting and the use of GP 2B-3A receptor antagonists was not used. These two new therapies may well have a profound effect on clinical outcome (23-25).

Conclusion

In all acute STEMI patients, left ventricular function is better preserved, when treated with primary PCI compared to treatment with SK. In acute anterior STEMI patients treated with primary PCI, the additional mortality benefit during long-term follow is due to better preserved residual left ventricular function. The number needed to treat to prevent 1 death is 5 and the number needed to treat to prevent 1 MACE is 4. In non-anterior STEMI patients treated with primary PCI, the principle benefit is the reduction in MACE; the number needed to treat to prevent 1 MACE is 4. Independent predictors of long-term mortality after acute anterior STEMI are age and residual left ventricular function.

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