

The New England Journal of Medicine

© Copyright, 1999, by the Massachusetts Medical Society

VOLUME 341

NOVEMBER 4, 1999

NUMBER 19



LONG-TERM BENEFIT OF PRIMARY ANGIOPLASTY AS COMPARED WITH THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION

FELIX ZIJLSTRA, PH.D., JAN C.A. HOORNTJE, PH.D., MENKO-JAN DE BOER, PH.D., STOFFER REIFFERS, PH.D.,
KOR MIEDEMA, PH.D., JAN PAUL OTTERVANGER, PH.D., ARNOUD W.J. VAN 'T HOF, PH.D.,
AND HARRY SURYAPRANATA, PH.D.

ABSTRACT

Background As compared with thrombolytic therapy, primary coronary angioplasty results in a higher rate of patency of the infarct-related coronary artery, lower rates of stroke and reinfarction, and higher in-hospital or 30-day survival rates. However, the comparative long-term efficacy of these two approaches has not been carefully studied.

Methods We randomly assigned a total of 395 patients with acute myocardial infarction to treatment with angioplasty or intravenous streptokinase. Clinical information was collected for a mean (\pm SD) of 5 ± 2 years, and medical charges associated with the two treatments were compared.

Results A total of 194 patients were assigned to undergo primary angioplasty, and 201 to receive streptokinase. Mortality was 13 percent in the angioplasty group, as compared with 24 percent in the streptokinase group (relative risk, 0.54; 95 percent confidence interval, 0.36 to 0.87). Nonfatal reinfarction occurred in 6 percent and 22 percent of the two groups, respectively (relative risk, 0.27; 95 percent confidence interval, 0.15 to 0.52). The combined incidence of death and nonfatal reinfarction was also lower among patients assigned to angioplasty than among those assigned to streptokinase, with a relative risk of 0.13 (95 percent confidence interval, 0.05 to 0.37) for early events (within the first 30 days) and a relative risk of 0.62 (95 percent confidence interval, 0.43 to 0.91) for late events (after 30 days). The rates of readmission for heart failure and ischemia were also lower among patients in the angioplasty group than among patients in the streptokinase group. Total medical charges per patient were lower in the angioplasty group (\$16,090) than in the streptokinase group (\$16,813, $P=0.05$).

Conclusions As compared with thrombolytic therapy with streptokinase, primary coronary angioplasty is associated with better clinical outcomes over five years. (N Engl J Med 1999;341:1413-9.)

©1999, Massachusetts Medical Society.

IN recent years, the prognosis for patients with acute myocardial infarction has been improved mainly by timely restoration of blood flow in the infarct-related coronary artery. Intravenous thrombolytic therapy lowers the early mortality rate by an estimated 20 to 30 percent.¹⁻³ Primary angioplasty, when performed by experienced clinicians, restores normal blood flow (grade 3 flow, according to the Thrombolysis in Myocardial Infarction [TIMI] classification) in 80 to 95 percent of patients.⁴⁻⁸ This result compares favorably with the 50 to 70 percent of patients in whom normal flow is restored after thrombolytic therapy.^{3,5,9} Publication of the results of three randomized trials⁴⁻⁶ prompted a debate about the benefits and limitations of these two treatments,^{10,11} but the discussion has been hampered by a lack of data on long-term follow-up. A recent analysis of data pooled from 10 randomized trials confirmed that during the first weeks after an acute myocardial infarction, the rates of death, nonfatal reinfarction, and stroke are lower after primary angioplasty than after thrombolytic therapy.¹²

Therefore, three questions about primary angioplasty should be resolved before it can be considered the most efficacious therapy for patients with evolving myocardial infarction. Does the higher rate of patency of the infarct-related coronary artery result in a more favorable clinical outcome during long-term follow-up? Is the survival benefit sustained? What is the rate of morbidity due to coronary artery disease during long-term follow-up? We addressed these questions in a study of 395 patients randomly assigned to treatment with primary angioplasty or intravenous streptokinase and followed for a mean (\pm SD) of 5 ± 2 years.

From the Departments of Cardiology (F.Z., J.C.A.H., M.-J.B., J.P.O., A.W.J.H., H.S.), Nuclear Medicine (S.R.), and Clinical Chemistry (K.M.), Hospital De Weezenlanden, Zwolle, the Netherlands. Address reprint requests to Dr. Zijlstra at the Department of Cardiology, Hospital De Weezenlanden, Groot Weezenland 20, 8011 JW Zwolle, the Netherlands, or at v.derks@diagram-zwolle.nl.

METHODS

The research protocol was reviewed and approved by our institutional review board. Patients were enrolled if they had no contraindications to thrombolytic intervention; 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 after the onset of symptoms, or within 6 to 24 hours after the onset of symptoms if there was evidence of continuing ischemia.⁵ The clinical description of these patients and the short-term results of the study have been reported previously.^{5,7,13} With rare exceptions, the study population consisted of a consecutive series of patients, since the majority of patients who presented to our hospital with acute myocardial infarction accompanied by ST-segment elevation agreed to participate.¹⁴ From August 1990 through April 1993, all presenting patients were asked to participate,^{5,7,14} and thereafter patients with marked hemodynamic instability or electrocardiographic signs of extensive infarction were excluded, as previously described in detail.¹³ Enrollment ended in April 1995. Base-line characteristics, clinical data, angiographic data, and outcomes were recorded in a dedicated data base.

Randomization and Treatment

After informed consent had been obtained, patients were randomly assigned to undergo primary coronary angioplasty or to receive streptokinase. All the patients received aspirin and heparin. Patients randomly assigned to the streptokinase group received 1.5 million units intravenously over a one-hour period. Patients randomly assigned to the angioplasty group were immediately transported to the catheterization laboratory; if the coronary anatomy was suitable for angioplasty, the procedure was performed immediately, 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 the patients, additional revascularization procedures were performed if indicated for symptoms or signs of myocardial ischemia.^{15,16}

Follow-up information was obtained in September 1998. All outpatient reports were reviewed, and general practitioners were contacted by telephone. For patients who had died or who had had 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 values, a second increase of more than 200 U per liter over the previous value was regarded as indicating a recurrent infarction.⁵ All electrocardiograms and laboratory results were reviewed for evidence of recurrent ischemia by two cardiologists who were unaware of the treatment assignments.⁵

Medical Charges

Medical charges were calculated on the basis of estimated unit charges for all aspects of medical care — namely, days spent in the hospital (for standard care, coronary care, or postoperative intensive care), diagnostic and therapeutic procedures, and medications (including thrombolytic drugs given as the study treatment). Data

were collected for the initial admission, readmissions, and visits to the outpatient clinic. Unit charges for procedures and hospital days were calculated on the basis of hospital records for 1992. These included professional charges and were adjusted for increased charges on nights or weekends. Charges per patient for diagnostic catheterization were \$716; for angioplasty, \$3,818; and for bypass surgery, \$8,591. Charges for one day on a general ward were \$238; for one day in the coronary care unit, \$740; and for one day in the postoperative intensive care unit, \$1,074. The charge for streptokinase was \$191. Charges for additional pharmacologic treatment were based on the average charges in 1992 for the various drugs, including pharmacy charges. Charges per patient per month were estimated as follows: for aspirin, \$5; for nitrates, \$9; for diuretics, \$15; for warfarin, \$16 (including coagulation tests); for antiarrhythmic drugs, \$17; for beta-blockers, \$28; for calcium-channel blockers, \$34; for angiotensin-converting-enzyme inhibitors, \$50; and for cholesterol-lowering drugs, \$64. This method has been described previously.¹⁷

Statistical Analysis

The outcomes assessed 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), 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, and sex.

All outcomes were analyzed according to the intention-to-treat principle. Differences between group means were assessed with the 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. The Cox proportional-hazards regression model was used for multivariate analysis.¹⁹ Left ventricular ejection fraction was included as a categorized variable (in quartiles). 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 randomly assigned to undergo primary angioplasty and 201 to receive streptokinase. According to the results of angiography at base line, 9 patients in the angioplasty group were treated conservatively, and 7 were referred for urgent coronary-artery bypass grafting; the other 178 patients underwent angioplasty. One patient in the streptokinase group died before the infusion could be started; the other 200 patients received streptokinase. The clinical characteristics of the two groups are shown in Table 1. The groups were similar with regard to age, sex, infarct location, and the presence or absence of a previous myocardial infarction, multivessel coronary artery disease, and diabetes mellitus. Patency of the infarct-related vessel was analyzed in all patients who survived to the time of follow-up angiography: 191 patients in the angioplasty group and 196 in the streptokinase group. The infarct-related coronary artery was patent in a greater proportion of patients in the angioplasty group (90

TABLE 1. BASE-LINE CHARACTERISTICS OF PATIENTS ASSIGNED TO ANGIOPLASTY OR STREPTOKINASE FOR ACUTE MYOCARDIAL INFARCTION.*

CHARACTERISTIC	ANGIOPLASTY GROUP (N=194)	STREPTOKINASE GROUP (N=201)	P VALUE
Age — yr	59 ± 11	60 ± 10	0.63
Male sex — no. (%)	160 (82)	158 (79)	0.37
Anterior infarction — no. (%)	77 (40)	74 (37)	0.60
Previous infarction — no. (%)	38 (20)	31 (15)	0.29
Diabetes — no. (%)	16 (8)	16 (8)	1.00
Patent infarct-related vessel — no. (%)†	171 (90)	127 (65)	<0.001
Left ventricular ejection fraction <40% — no. (%)‡	27 (14)	48 (26)	0.006

*Plus-minus values are means ±SD.

†Patency of the infarct-related vessel was analyzed in 191 patients in the angioplasty group and 196 patients in the streptokinase group.

‡Left ventricular ejection fraction was analyzed in 189 patients in the angioplasty group and 188 patients in the streptokinase group.

percent) than in the streptokinase group (65 percent, P<0.001). The left ventricular ejection fraction was measured before discharge by radionuclide imaging in 189 patients in the angioplasty group and 188 patients in the streptokinase group. The proportion of patients with a left ventricular ejection fraction of less than 40 percent was higher in the streptokinase group (26 percent) than in the angioplasty group (14 percent, P=0.006).

Patients were followed for a mean of 5 ± 2 years, and only one patient was lost to follow-up (after 1.5 years).

A total of 74 patients died, 21 from a proven noncardiac cause. Mortality and causes of death are shown in Table 2. There were 26 deaths in the angioplasty group (13 percent) and 48 in the streptokinase group (24 percent) (relative risk of death for patients in the angioplasty group, 0.54; 95 percent confidence interval, 0.36 to 0.87). There was a very strong relation between the left ventricular ejection fraction (in quartiles) and the incidence of death due to cardiac causes. The rate of death from cardiac causes was 23 percent for patients with a left ventricular ejection fraction of less than 43 percent, 10 percent for those with an ejection fraction of 43 to 49 percent, 6 percent for those with an ejection fraction of 50 to 55 percent, and 4 percent for those with an ejection fraction greater than 55 percent.

Nonfatal reinfarction occurred in 56 patients: 12 in the angioplasty group (6 percent) and 44 in the streptokinase group (22 percent) (relative risk, 0.27; 95 percent confidence interval, 0.15 to 0.52). In the first 30 days after enrollment, there was 1 nonfatal reinfarction (0.5 percent) in the angioplasty group as compared with 19 (9 percent) in the streptokinase group (relative risk, 0.06; 95 percent confidence interval, 0.01 to 0.40). After 30 days, there were 11 reinfarctions (6 percent) in the angioplasty group as compared with 25 (12 percent) in the streptokinase group (relative risk, 0.05; 95 percent confidence interval, 0.02 to 0.85). All 20 reinfarctions that occurred within the first 30 days affected the same region of myocardium as the index infarction. Of the 36 reinfarctions that occurred after day 30 (15 during the first year of follow-up and 21 thereafter), 20 involved the original infarct-related coronary artery, and 16 in-

TABLE 2. MORTALITY AND CAUSES OF EARLY AND LATE DEATH.

CAUSE OF DEATH	≤30 DAYS AFTER STUDY TREATMENT			>30 DAYS AFTER STUDY TREATMENT			TOTAL FOLLOW-UP PERIOD		
	ANGIO-PLASTY (N=194)	STREPTOKINASE (N=201)	P VALUE	ANGIO-PLASTY (N=194)	STREPTOKINASE (N=201)	P VALUE	ANGIO-PLASTY (N=194)	STREPTOKINASE (N=201)	P VALUE
	no. (%)			no. (%)			no. (%)		
Cardiac	2 (1.0)	13 (6.5)	<0.01	11 (5.7)	27 (13.4)	<0.01	13 (6.7)	40 (19.9)	<0.001
Myocardial rupture	1 (0.5)	1 (0.5)	1.0	0	1 (0.5)	0.49	1 (0.5)	2 (1.0)	1.0
Heart failure	1 (0.5)	11 (5.5)	<0.01	5 (2.6)	9 (4.5)	0.25	6 (3.1)	20 (10.0)	<0.01
Sudden death	0	1 (0.5)	1.0	6 (3.1)	17 (8.5)	0.02	6 (3.1)	18 (9.0)	0.02
Noncardiac	0	1 (0.5)	1.0	13 (6.7)	7 (3.5)	0.19	13 (6.7)	8 (4.0)	0.23
Stroke	0	1 (0.5)	1.0	2 (1.0)	0	0.50	2 (1.0)	1 (0.5)	0.62
Lung cancer	0	0	1.0	4 (2.1)	3 (1.5)	1.0	4 (2.1)	3 (1.5)	0.72
Other cancer*	0	0	1.0	5 (2.6)	3 (1.5)	0.72	5 (2.6)	3 (1.5)	0.50
Other†	0	0	1.0	2 (1.0)	1 (0.5)	1.0	2 (1.0)	1 (0.5)	0.62
All causes	2 (1.0)	14 (7.0)	0.01	24 (12.4)	34 (16.9)	0.12	26 (13.4)	48 (23.9)	0.01

*Other cancers included colon cancer (in two patients), metastatic carcinoma with unknown primary tumor (in two), pancreatic cancer (in one), sarcoma (in one), breast cancer (in one), and esophageal cancer (in one).

†Other noncardiac causes included renal failure (in one patient), pulmonary embolism (in one), and an automobile accident (in one).

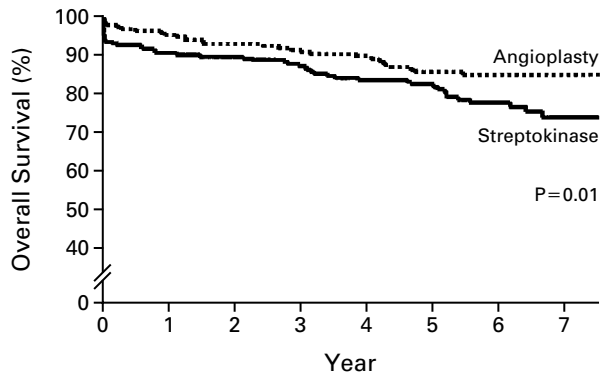


Figure 1. Kaplan–Meier Curves for Overall Survival in the Angioplasty and Streptokinase Groups during Follow-up. The rate of survival was higher in the group of 194 patients assigned to undergo angioplasty than in the group of 201 assigned to receive streptokinase.

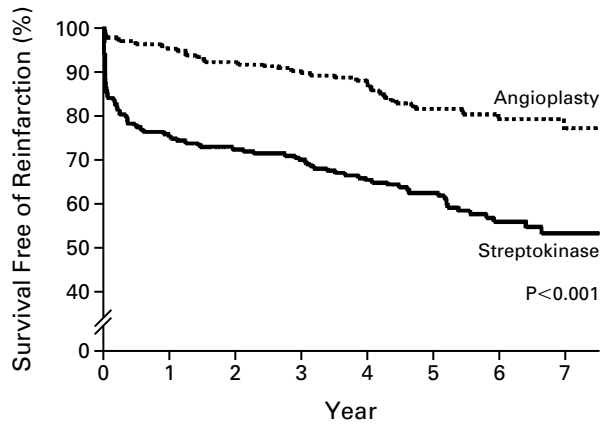


Figure 2. Kaplan–Meier Curves for Survival Free of Reinfarction in the Angioplasty and Streptokinase Groups during Follow-up. The rate of survival free of reinfarction was higher in the group of 194 patients assigned to undergo angioplasty than in the group of 201 assigned to receive streptokinase.

involved another coronary artery. The 16 events that involved another artery were equally distributed between the two groups (8 in each). The difference in the rate of reinfarction was therefore due entirely to events that affected the index infarct-related coronary artery.

The combined incidence of death and nonfatal reinfarction was lower in the angioplasty group than in the streptokinase group during the first 30 days (relative risk, 0.13; 95 percent confidence interval, 0.05 to 0.37) 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 Figures 1 and 2.

The results of multivariate analysis of various char-

TABLE 3. MULTIVARIATE ANALYSES OF RISK FACTORS FOR DEATH FROM CARDIAC CAUSES AND FOR THE END POINT OF DEATH OR NONFATAL REINFARCTION.*

RISK FACTOR	DEATH		DEATH OR NONFATAL REINFARCTION	
	RELATIVE RISK	95% CI	RELATIVE RISK	95% CI
Treatment assignment (streptokinase vs. angioplasty)	2.28	1.10–4.73	2.31	1.51–3.54
Location of myocardial infarction (anterior vs. other)	2.21	1.07–4.54	1.24	0.81–1.90
Left ventricular ejection fraction (per lower quartile)	1.52	1.04–2.22	1.17	0.96–1.43
Age (per additional yr)	1.05	1.01–1.09	1.01	0.99–1.03
Sex (male vs. female)	1.23	0.55–2.73	1.13	0.68–1.86

*CI denotes confidence interval.

TABLE 4. NEED FOR ADDITIONAL REVASCULARIZATION PROCEDURES.

TIME	ANGIOPLASTY GROUP (N=194)	STREPTOKINASE GROUP (N=201)	P VALUE
	no. (%)		
Early (≤30 days)			
Angioplasty	7 (3.6)	70 (34.8)	<0.001
Coronary-artery bypass grafting	17 (8.8)	16 (8.0)	0.77
Late (>30 days)			
Angioplasty	43 (22.2)	34 (16.9)	0.31
Coronary-artery bypass grafting	23 (11.9)	23 (11.4)	0.92
Total follow-up period			
Angioplasty	50 (25.8)	104 (51.7)	<0.001
Coronary-artery bypass grafting	40 (20.6)	39 (19.4)	0.76

acteristics in relation to death and to the combined incidence of death and nonfatal reinfarction are shown in Table 3.

Data on additional revascularization procedures are shown in Table 4. Within the first 30 days, angioplasty was performed more often in the streptokinase group than was a second angioplasty in the angioplasty group. After 30 days, the need for angioplasty was similar in the two groups. There were no significant differences between the groups in the need for early coronary-artery bypass grafting (within 30 days) or late grafting (after 30 days).

The use of medication at the end of the follow-up period is shown in Table 5. Warfarin, nitrates, and diuretics were used significantly more frequently by

TABLE 5. USE OF MEDICATIONS AT THE END OF FOLLOW-UP.

MEDICATION	ANGIOPLASTY GROUP	STREPTOKINASE GROUP	P VALUE
	(N=167)	(N=154)	
	no. (%)		
Aspirin	149 (89)	132 (86)	0.40
Warfarin	16 (10)	30 (19)	0.02
Statins	72 (43)	65 (42)	0.91
Beta-blockers	66 (40)	68 (44)	0.40
Calcium-channel blockers	36 (22)	27 (18)	0.40
Nitrates	23 (14)	39 (25)	0.01
Digitalis	9 (5)	13 (8)	0.38
Diuretics	25 (15)	38 (25)	0.03
Angiotensin-converting-enzyme inhibitors	52 (31)	57 (37)	0.29
Antiarrhythmic drugs	3 (2)	4 (3)	0.71

patients assigned to streptokinase. The use of aspirin, statins, beta-blockers, angiotensin-converting-enzyme inhibitors, and other cardiac medications was similar in the two groups of patients. During the follow-up period, 74 patients in the angioplasty group were readmitted to the hospital, with a total of 115 readmissions, as compared with 104 patients and a total of 221 readmissions in the streptokinase group ($P < 0.001$). There were 101 readmissions for ischemia in the angioplasty group, as compared with 180 in the streptokinase group ($P < 0.001$). There were 14 readmissions for heart failure in the angioplasty group, as compared with 41 in the streptokinase group ($P < 0.001$). The New York Heart Association class was determined on the basis of information obtained from the patients' general practitioners. Of the patients in the angioplasty group who were alive at the end of follow-up, 149 were in class I, 17 in class II, and 1 in class III, as compared with 113, 33, and 8, respectively, in the streptokinase group (P for trend < 0.001).

The total medical charges per patient at the end of the follow-up period, including the initial hospital stay, readmissions, procedures, physicians' charges, and medications, were \$16,090 for patients assigned to angioplasty and \$16,813 for patients assigned to streptokinase ($P = 0.05$). The total charges per patient for those who were alive at the end of follow-up were \$18,664 in the angioplasty group and \$21,772 in the streptokinase group ($P = 0.008$).

DISCUSSION

This study shows that primary angioplasty, as compared with intravenous streptokinase therapy, results in lower mortality and reinfarction rates both within the first 30 days and during long-term follow-up. The risk of death from cardiac causes is strongly associ-

ated with the left ventricular ejection fraction as well as with whether there is early and sustained patency of the infarct-related coronary artery. Readmission for heart failure, the use of medications associated with poor left ventricular function, and New York Heart Association class as assessed by the patients' general practitioners also suggest that left ventricular function is better preserved with primary angioplasty than with streptokinase. Although angioplasty is initially more expensive than thrombolytic therapy, long-term follow-up shows that angioplasty results in comparatively lower charges, mainly because of a marked decrease in hospital readmissions for ischemia after angioplasty.

The primary goal of all reperfusion therapies is rapid and complete reopening of occluded coronary arteries. This concept has been confirmed by the results of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial.⁹ Coronary patency, defined as the restoration of normal blood flow in the infarct-related vessel, preserves myocardial tissue and results in improved survival. Patency rates achieved with primary angioplasty cannot currently be obtained with thrombolytic agents.^{4-6,8,9} Indeed, our data indicate that the higher patency rate among patients assigned to angioplasty, as compared with those assigned to streptokinase, resulted in a higher left ventricular ejection fraction, a lower incidence of reinfarction, and improved survival. These findings suggest that thrombolytic agents or adjunctive therapies that would result in a higher rate of early and sustained TIMI grade 3 flow might offer a similar benefit.

Successful primary angioplasty may also improve the long-term clinical outcome by reducing the incidence of reocclusion of the infarct-related artery to less than 10 percent,⁸ as compared with reocclusion rates of up to 30 percent after successful reperfusion by thrombolytic agents.²⁰ With regard to this difference in the rate of reocclusion, it should be realized that, especially during the first year after the acute coronary event, reinfarctions are generally related to the artery that was initially occluded and associated with infarction. This is in accordance with the concept that coronary angioplasty has a plaque-sealing effect.²¹

The use of the left ventricular ejection fraction as an end point in trials of acute myocardial infarction has been controversial.^{22,23} Some investigators have reported that early reperfusion limits infarct size and results in superior left ventricular function,⁹ thereby improving long-term survival.^{24,25} Our data confirm that higher rates of early and sustained patency of the infarct-related vessel are associated with superior left ventricular function. This association is probably due in part to the influence of successful reperfusion on left ventricular remodeling.²⁶

Heart failure is a common cause of hospitalization and death, and the rates of admission and death due

to heart failure, unlike those due to ischemic heart disease, are increasing and are predicted to continue to increase.^{27,28} A recent survey of general-practice settings shows that myocardial infarction is an important risk factor for the subsequent development of left ventricular dysfunction and clinical signs of heart failure.²⁹ In this regard, our finding that the rate of admission for heart failure was lower among patients assigned to undergo angioplasty than among those assigned to receive streptokinase is of clinical importance. Together with the differences in the use of medication and in functional status at the end of follow-up, which favored the angioplasty group, this finding suggests that the higher left ventricular ejection fraction in the angioplasty group before the initial hospital discharge helped preserve long-term ventricular function. The greater use of warfarin and diuretics by patients in the streptokinase group is probably related to the poorer left ventricular function in this group, since diuretics are used for heart failure and warfarin for severely depressed ventricular function or aneurysms. The use of nitrates is related to the occurrence of angina in daily life. If we take into consideration the large number of patients who were hospitalized for treatment of heart failure or ischemic events or for additional revascularization procedures, the number of patients who received beta-blockers and angiotensin-converting-enzyme inhibitors is probably too low for optimal secondary prevention in both groups.³⁰ Optimal prevention of a second myocardial infarction seems to be difficult to accomplish in general practice,³¹ and although use of these drugs is becoming more widespread, there are still many missed opportunities for prevention of reinfarction after an initial infarction.³²

Some limitations of our study should be noted. A trial comparing angioplasty with pharmacologic reperfusion therapy cannot be blinded. Furthermore, in contrast to multicenter trials that have included thousands of patients undergoing reperfusion therapy for acute myocardial infarction,^{1,2,9} our study included only 395 patients from a single institution. During enrollment of the patients in our study, intracoronary stents and abciximab were not used. Both additional therapeutic options may have a considerable effect on the clinical outcome in patients with ischemic syndromes.^{33,34} Finally, our cost analysis is based on estimated charges rather than actual charges.

Supported by a grant (92.321) from the Netherlands Heart Foundation.

We are indebted to the many general practitioners in our region for their speedy referral of patients with acute myocardial infarction and for their superb assistance in obtaining follow-up information, and to Vera Derks for expert secretarial assistance.

REFERENCES

- ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both,
- or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-60.
- Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1:397-402.
- Granger CB, Califf RM, Topol EJ. Thrombolytic therapy for acute myocardial infarction: a review. *Drugs* 1992;44:293-325. [Erratum, *Drugs* 1993;45:894.]
- Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1993;328:673-9.
- Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;328:680-4.
- Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. *N Engl J Med* 1993;328:685-91.
- de Boer MJ, Suryapranata H, Hoorntje JCA, et al. Limitation of infarct size and preservation of left ventricular function after primary coronary angioplasty compared with intravenous streptokinase in acute myocardial infarction. *Circulation* 1994;90:753-61.
- de Boer MJ, Reiber JHC, Suryapranata H, van den Brand MJB, Hoorntje JCA, Zijlstra F. Angiographic findings and catheterization laboratory events in patients with primary coronary angioplasty or streptokinase therapy for acute myocardial infarction. *Eur Heart J* 1995;16:1347-55.
- The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615-22. [Erratum, *N Engl J Med* 1994;330:516.]
- Every NR, Parsons LS, Hlatky M, Martin JS, Weaver WD. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. *N Engl J Med* 1996;335:1253-60.
- Lange RA, Hillis LD, Grines CL. Should thrombolysis or primary angioplasty be the treatment of choice for acute myocardial infarction? *N Engl J Med* 1996;335:1311-7.
- Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA* 1997;278:2093-8. [Erratum, *JAMA* 1998;279:1876.]
- Zijlstra F, Beukema WP, van't Hof AWJ, et al. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. *J Am Coll Cardiol* 1997;29:908-12.
- Zijlstra F, de Boer MJ, Suryapranata H. Treatment of acute myocardial infarction. *N Engl J Med* 1993;329:432.
- The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Acute myocardial infarction: pre-hospital and in-hospital management. *Eur Heart J* 1996;17:43-63.
- Madsen JK, Grande P, Saunamäki K, et al. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). *Circulation* 1997;96:748-55.
- de Boer MJ, van Hout BA, Liem AL, Suryapranata H, Hoorntje JCA, Zijlstra F. A cost-effective analysis of primary coronary angioplasty versus thrombolysis for acute myocardial infarction. *Am J Cardiol* 1995;76:830-3.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
- Meijer A, Verheugt FWA, Werter CJPS, Lie KI, van der Pol JMJ, van Eenige MJ. Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study: results of the APRICOT Study. *Circulation* 1993;87:1524-30.
- Meier B, Ramamurthy S. Plaque sealing by coronary angioplasty. *Cathet Cardiovasc Diagn* 1995;36:295-7.
- Califf RM, Harrelson-Woodlief L, Topol EJ. Left ventricular ejection fraction may not be useful as an end point of thrombolytic therapy comparative trials. *Circulation* 1990;82:1847-53.
- Norris RM, White HD. Therapeutic trials in coronary thrombosis should measure left ventricular function as primary end-point of treatment. *Lancet* 1988;1:104-6.
- Simoons ML, Serruys PW, van den Brand M, et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. *J Am Coll Cardiol* 1986;7:717-28.
- Simoons ML, Vos J, Tijssen JGP, et al. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the interuniversity Cardiology Institute of the Netherlands. *J Am Coll Cardiol* 1989;14:1609-15.

26. Kloner RA. Coronary angioplasty: a treatment option for left ventricular remodeling after myocardial infarction? *J Am Coll Cardiol* 1992;20:314-6.
27. Goldberg RJ. Assessing the population burden from heart failure: need for sentinel population-based surveillance systems. *Arch Intern Med* 1999;159:15-7.
28. Bonneux L, Barendregt JJ, Meeter K, Bonsel GJ, van der Maas PJ. Estimating clinical morbidity due to ischemic heart disease and congestive heart failure: the future rise of heart failure. *Am J Public Health* 1994;84:20-8.
29. Morgan S, Smith H, Simpson I, et al. Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. *BMJ* 1999;318:368-72.
30. Mehta RH, Eagle KA. Secondary prevention in acute myocardial infarction. *BMJ* 1998;316:838-42. [Erratum, *BMJ* 1998;317:1516.]
31. Campbell NC, Thain J, Deans HG, Ritchie LD, Rawles JM. Secondary prevention in coronary heart disease: baseline survey of provision in general practice. *BMJ* 1998;316:1430-4.
32. McCormick D, Gurwitz JH, Lessard D, Yarzebski J, Gore JM, Goldberg RJ. Use of aspirin, β -blockers, and lipid-lowering medications before recurrent acute myocardial infarction: missed opportunities for prevention? *Arch Intern Med* 1999;159:561-7.
33. Suryapranata H, van't Hof AWJ, Hoorntje JCA, de Boer MJ, Zijlstra F. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. *Circulation* 1998;97:2502-5.
34. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. *Circulation* 1998;98:2695-701.