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A Comparison of Coronary Angioplasty with Fibrinolytic Therapy in Acute Myocardial Infarction

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ABSTRACT

BACKGROUND

For the treatment of myocardial infarction with ST-segment elevation, primary angioplasty is considered superior to fibrinolysis for patients who are admitted to hospitals with angioplasty facilities. Whether this benefit is maintained for patients who require transportation from a community hospital to a center where invasive treatment is available is uncertain.

METHODS

We randomly assigned 1572 patients with acute myocardial infarction to treatment with angioplasty or accelerated treatment with intravenous alteplase; 1129 patients were enrolled at 24 referral hospitals and 443 patients at 5 invasive-treatment centers. The primary study end point was a composite of death, clinical evidence of reinfarction, or disabling stroke at 30 days.

RESULTS

Among patients who underwent randomization at referral hospitals, the primary end point was reached in 8.5 percent of the patients in the angioplasty group, as compared with 14.2 percent of those in the fibrinolysis group (P=0.002). The results were similar among patients who were enrolled at invasive-treatment centers: 6.7 percent of the patients in the angioplasty group reached the primary end point, as compared with 12.3 percent in the fibrinolysis group (P=0.05). Among all patients, the better outcome after angioplasty was driven primarily by a reduction in the rate of reinfarction (1.6 percent in the angioplasty group vs. 6.3 percent in the fibrinolysis group, P<0.001); no significant differences were observed in the rate of death (6.6 percent vs. 7.8 percent, P=0.35) or the rate of stroke (1.1 percent vs. 2.0 percent, P=0.15). Ninety-six percent of patients were transferred from referral hospitals to an invasive-treatment center within two hours.

CONCLUSIONS

A strategy for reperfusion involving the transfer of patients to an invasive-treatment center for primary angioplasty is superior to on-site fibrinolysis, provided that the transfer takes two hours or less.

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Percutaneous coronary intervention has been shown to be superior to fibrinolysis in the treatment of acute myocardial infarction with ST-segment elevation in patients admitted to highly experienced angioplasty centers.[1-4] In Western countries, primary angioplasty is offered only to the limited number of patients admitted directly to hospitals with interventional services. Transportation from the local hospital to an angioplasty center has been considered to represent a major limitation on the widespread use of primary angioplasty. We conducted a community-wide trial to compare the transfer of patients for primary angioplasty with the use of on-site fibrinolysis.

METHODS

STUDY DESIGN

We randomly assigned patients who had myocardial infarction with ST-segment elevation to fibrinolysis or primary angioplasty. From December 1997 to October 2001, we enrolled patients from 24 referral hospitals without angioplasty facilities and 5 invasive-treatment hospitals with such facilities and on-site surgical backup. The participating hospitals served 62 percent of the Danish population. Patients admitted to a referral hospital underwent randomization while they lay on the ambulance stretcher with the crew waiting. Transfer to the nearest angioplasty center had to be completed within three hours. A physician accompanied the patient. All ambulances had resuscitation equipment. The patients were transported directly to the catheterization laboratory.

TREATMENT

Patients randomly assigned to fibrinolysis received 300 mg of aspirin orally, a beta-blocker intravenously (up to the equivalent of 20 mg of metoprolol), accelerated treatment with tissue plasminogen activator (alteplase, given as a 15-mg bolus and an infusion of 0.75 mg per kilogram of body weight administered over a period of 30 minutes, followed by an infusion of 0.5 mg per kilogram for a period of 60 minutes), and an intravenous bolus of unfractionated heparin (5000 U), followed by a 48-hour infusion of unfractionated heparin. The starting dose of unfractionated heparin was 1000 U per hour; the dose was adjusted to maintain an activated partial-thromboplastin time of 70 to 90 seconds.

Patients randomly assigned to angioplasty received 300 mg of aspirin intravenously, the same dose of a beta-blocker as patients in the fibrinolysis group, and 10,000 U of unfractionated heparin. Additional heparin was given to achieve an activated clotting time of 350 to 450 seconds during the invasive procedure. Platelet glycoprotein IIb/IIIa–receptor blockers were administered at the discretion of the physician. The infarct-related artery was treated if it was totally occluded, if there was a culprit lesion with stenosis of more than 30 percent of the luminal diameter, or if it had a flow grade of less than 3 according to the Thrombolysis in Myocardial Infarction (TIMI) classification.[5] Stenting of the culprit lesion was attempted in all patients, unless the vessel had a diameter of less than 2.0 mm. Angioplasty of non–infarct-related arteries was not performed. Patients were not considered for immediate coronary-artery bypass grafting unless they had severe hemodynamic instability. Ticlopidine (500 mg) or clopidogrel (75 mg) was given daily for one month after stenting. The angiograms obtained before and after angioplasty were evaluated by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands).

When failed reperfusion was suspected (i.e., when there was no resolution of ST-segment elevation) or when there was reinfarction or recurrent ischemia with ST-segment elevation after fibrinolysis, the protocol recommended repeated fibrinolysis before consideration of rescue angioplasty. An early or late reinfarction or recurrent ischemia in patients with an index infarction that had been treated by angioplasty was treated by repeated angioplasty.

The primary end point was a composite of death from any cause, clinical reinfarction, or disabling stroke at 30 days of follow-up. Procedure-related reinfarction was not included in the primary end point. A reinfarction was diagnosed if there was an increase in the total creatine kinase and MB isoenzyme activity and either a history of ischemic chest discomfort or electrocardiographic changes. Clinical reinfarction was diagnosed if the creatine kinase MB level increased to above a reference limit in a patient in whom the level had normalized after the index infarction or if there was an increase of at least 50 percent from the last non-normalized measurement. A procedure-related reinfarction was diagnosed after coronary-artery bypass surgery if the creatine kinase MB level increased to five times the upper limit of normal or five times the preceding level; a procedure-related reinfarction was diagnosed

after angioplasty if the level increased to twice the upper limit of normal or twice the last non-normalized measurement.

Disabling stroke was defined as a fatal stroke or a stroke causing a clinically significant mental or physical handicap at 30 days of follow-up. Clinically significant handicaps were defined as ranging from slight disability (i.e., the inability to engage in all previous activities in a patient who was still able to take care of himself or herself without assistance) to very severe disability (i.e., a bedridden state involving a requirement for constant nursing care and attention). Detailed definitions of these end points are available elsewhere.[6] End-point events were reviewed by an end-points committee that was unaware of the treatment-group assignments.

CRITERIA FOR ELIGIBILITY

The criteria for inclusion were an age of 18 years or more, the presence of symptoms for at least 30 minutes but less than 12 hours, and cumulative ST-segment elevation of at least 4 mm in at least two contiguous leads. The criteria for exclusion were a contraindication to fibrinolysis, left bundle-branch block, acute myocardial infarction and fibrinolytic treatment within the previous 30 days, pulseless femoral arteries, previous coronary-bypass surgery, renal failure (indicated by a serum creatinine concentration above 2.83 mg per deciliter [250 μmol per liter]), diabetes treated with metformin, nonischemic heart disease, and noncardiac disease associated with a life expectancy of less than 12 months. Patients who were judged to be at high risk during transportation because of cardiogenic shock or severe heart failure (a sustained systolic blood pressure ≤65 mm Hg), persistent life-threatening arrhythmias, or a need for mechanical ventilation were excluded. The study was approved by the National Ethics Committee of Denmark. All eligible patients provided written informed consent. The study was supervised and monitored by an international safety and ethics committee.

At the start of the study, only two centers offered primary angioplasty as routine treatment. Each of the five invasive-treatment centers had to establish a 24-hour service for angioplasty before it was allowed to join the study.

STATISTICAL ANALYSIS

The trial consisted of two simultaneously conducted substudies, one involving patients who underwent randomization at referral hospitals and the other involving patients who underwent randomization at invasive-treatment centers. The results were analyzed both separately for each substudy and for the two substudies combined. Each substudy was designed with two groups, interim analyses, and stopping rules, with an overall two-sided alpha of 5 percent and a power (1 – beta) of 80 percent.

The calculation of the sample size was based on the assumption that the combined primary end point would be reached by 30 days in 16 percent of the patients randomly assigned to fibrinolysis, in 10 percent of the patients randomly assigned to angioplasty at referral hospitals, and in 9 percent of the patients randomly assigned to angioplasty in invasive-treatment centers. Under these assumptions, enrollment of 1100 patients was needed at the referral hospitals, and enrollment of 800 patients was needed at the invasive-treatment centers. Three interim analyses were to be performed in the referral-hospital substudy (after the enrollment of 25 percent, 50 percent, and 75 percent of the patients), and two interim analyses were to be performed in the invasive-treatment–center substudy (after the enrollment of 33 percent and 66 percent of the patients). Thus, each interim analysis was performed after the enrollment of approximately the same number of patients in both substudies.

In case of a treatment difference in favor of fibrinolysis, an alpha level of 0.05 was to be used in all interim analyses. In case of a treatment difference in favor of angioplasty, the significance level at the first interim analysis in each substudy was conservatively set to an alpha level of 0.001, which, together with an overall alpha level of 0.05, led to significance levels at subsequent interim analyses of 0.009 and 0.022 in the referral-hospital substudy and 0.016 in the invasive-treatment–center substudy. The design was a hybrid of a Pocock design and an O'Brien–Fleming design, and analyses were performed with the use of the EaSt software package, version 2.0 (Cytel Software).

If, in any interim analysis in the referral-hospital substudy, angioplasty was shown to be superior to fibrinolysis, both substudies were to be stopped, since the superiority of angioplasty in the referral-hospital substudy would imply its superiority at the invasive-treatment centers as well. If, in any interim analysis in the referral-hospital substudy, angioplasty was shown to be inferior to fibrinolysis, only the referral-hospital substudy was to be stopped. If, in

Table 1. Base-Line Characteristics of the Patients.

Characteristic	Referral Hospitals			Invasive-Treatment Centers		
	Fibrinolysis Group (N=562)	Angioplasty Group (N=567)	P Value	Fibrinolysis Group (N=220)	Angioplasty Group (N=223)	P Value
Age (yr)						
Median	64	62	0.06	62	64	0.25
Interquartile range	54–74	53–72		54–73	56–74	
Range	28–94	23–94		36–96	32–89	
Male sex (%)	73.3	74.3	0.72	73.6	71.7	0.66
Hypertension (%)	20.4	20.4	0.99	20.9	18.8	0.58
Diabetes (%)*	7.5	7.5	0.97	5.9	7.2	0.64
Current smoking (%)	57.3	59.0	0.49	61.9	55.7	0.27
Previous myocardial infarction (%)	12.5	12.1	0.46	10.0	8.1	0.48
Previous angioplasty (%)	2.7	4.6	0.08	2.3	3.6	0.41
Previous stroke (%)	4.3	2.7	0.15	3.6	2.7	0.57
Heart rate (beats/min)						
Median	72	74	0.23	73	75	0.75
Interquartile range	61–84	62–88		60–87	60–86	
Systolic blood pressure (mm Hg)						
Median	135	135	0.15	140	140	0.68
Interquartile range	115–150	120–151		120–153	120–155	
Anterior index myocardial infarction (%)	52.0	53.4	0.62	53.6	52.5	0.81
Medical treatment (%)						
Aspirin	22.2	21.7	0.86	24.5	18.8	0.14
Beta-blockers	13.6	13.4	0.92	11.9	10.8	0.76
ACE inhibitors†	10.4	8.9	0.42	5.5	7.2	0.46
Calcium antagonists	12.0	9.3	0.15	10.5	11.7	0.69
Nitrate	7.3	6.4	0.54	4.1	4.5	0.84
Diuretics	16.8	15.3	0.50	10.9	13.0	0.50
Lipid-lowering drugs	7.0	7.1	0.92	2.3	3.6	0.41
Coumarins	1.8	1.2	0.46	0.5	2.2	0.10
Angiographic features (%)‡						
Nonstenotic vessels		6.1			4.1	
Single-vessel disease		53.7			50.9	
Double-vessel disease		24.1			25.9	
Triple-vessel disease		13.1			15.0	
Involvement of the left main coronary artery		3.6			2.3	

* Data are for patients who were being treated with insulin or an oral antidiabetic agent (those who were treated with metformin were excluded from the study).
† ACE denotes angiotensin-converting enzyme.
‡ Information about angiographic features was available for 557 patients enrolled at referral hospitals and 220 patients enrolled at invasive-treatment centers.

any interim analysis in the invasive-treatment–center substudy, angioplasty was shown to be superior to fibrinolysis, only the invasive-treatment–center substudy was to be stopped. If, in any interim analysis in the invasive-treatment–center substudy, angioplasty was shown to be inferior to fibrinolysis, both substudies were to be stopped, since this would imply the superiority of fibrinolysis at referral hospitals as well.

Results were analyzed according to the intention-to-treat principle. For the comparison of categorical variables, Pearson's chi-square test was used. Values for continuous variables are reported as medians and interquartile ranges. Groups were compared with the use of the Mann–Whitney rank-sum test.

RESULTS

PATIENT POPULATION AND BASE-LINE CHARACTERISTICS

A total of 4278 patients who had myocardial infarction with ST-segment elevation were screened for inclusion. Enrollment was stopped on October 1, 2001, after the third interim analysis had demonstrated that angioplasty was superior to fibrinolysis in the referral-hospital substudy. At that time, 1129 patients had undergone randomization at referral hospitals, and 443 patients had undergone randomization at invasive-treatment centers. Base-line characteristics of patients randomly assigned to fibrinolysis were similar to those of patients randomly assigned to angioplasty (Table 1). Four percent of the patients screened at referral hospitals were excluded because they were judged to be unable to tolerate being transported. Detailed information on screened and excluded patients is available elsewhere.[6]

TIME FROM SYMPTOMS TO TREATMENT

The time from the onset of symptoms to the start of treatment is shown in Table 2. Twenty-seven percent of patients underwent randomization within one hour after onset, 31 percent between one and two hours after onset, 24 percent between two and four hours after onset, 9 percent between four and six hours after onset, and 9 percent six hours or more after onset. The median time from the onset of symptoms to randomization was 135 minutes for the total population.

The median distance that patients had to be transported from a referral hospital to an invasive-treatment center was 50 km, with a range of 3 to 150 km. Thirty percent of patients who were transferred had to be transported 3 to 25 km, 34 percent 26 to 50 km, 18 percent 51 to 75 km, and 18 percent 76 to 150 km. The transfer time was defined as the time from randomization at the referral hospital to

Table 2. Time from Onset of Symptoms to Start of Fibrinolytic or Angioplastic Treatment.*

Variable	Fibrinolysis Group		Angioplasty Group	
	Referral Hospitals (N=562)	Invasive-Treatment Centers (N=220)	Referral Hospitals (N=567)	Invasive-Treatment Centers (N=223)
	minutes			
Interval from onset of symptoms to admission				
Median	105	104	107	105
Interquartile range	60–202	54–189	60–205	61–185
Interval from admission to randomization				
Median	25	30	22	28
Interquartile range	18–40	20–45	15–35	20–43
Interval from randomization to start of treatment				
Median	20	20	90	63
Interquartile range	15–30	13–30	74–108	49–77
Interval from arrival to start of interhospital transportation by ambulance				
Median	—	—	50	—
Interquartile range			39–65	
Duration of interhospital transportation by ambulance				
Median	—	—	32	—
Interquartile range			20–45	
Interval from arrival at invasive-treatment center to first balloon inflation				
Median	—	—	26	93
Interquartile range			20–38	77–113
Total interval from onset of symptoms to start of treatment†				
Median	169	160	224	188
Interquartile range	110–270	110–255	171–317	145–273

* The start of treatment was defined as the start of fibrinolysis or the first balloon inflation.

† P<0.001 for the comparison between referral hospitals and invasive-treatment centers in terms of the interval from the onset of symptoms to the first balloon inflation in the angioplasty group; the difference between referral hospitals and invasive-treatment centers with respect to the start of fibrinolysis was nonsignificant.

arrival in the catheterization laboratory. The median transfer time was 67 minutes (interquartile range, 50 to 85). Forty-three percent of patients who were transferred had a transfer time of less than one hour, 53 percent a transfer time of one to two hours, and 4 percent a transfer time of two to three hours.

ADVERSE EVENTS DURING TRANSPORTATION

A total of 559 of the 567 patients randomly assigned to angioplasty at referral hospitals (99 percent) were transferred. Atrial fibrillation developed in 14 patients, intermittent advanced atrioventricular block in 13 patients, and ventricular fibrillation in 8 patients. There were no deaths during transportation. One patient had refractory ventricular fibrillation on arrival at the invasive-treatment center and died one hour later after an unsuccessful attempt at resuscitation.

IMMEDIATE TREATMENT AND ANGIOPLASTY RESULTS

Among the 782 patients randomly assigned to fibrinolysis, 775 patients (99 percent) received the assigned treatment. Of the 790 patients randomly assigned to angioplasty, 777 patients (98 percent) underwent immediate angiography. Angioplasty was attempted in 706 patients, and balloon inflation was performed in 686 patients (87 percent of the 790 who were randomly assigned to angioplasty). Stents were implanted in 638 of these patients (93 percent), and 310 patients were treated with platelet glycoprotein IIb/IIIa–receptor blockers during catheterization. The infarct-related vessel was the left anterior descending artery in 46 percent of the patients who underwent angiographic examination, the right coronary artery in 35 percent, and the left circumflex artery in 12 percent. The remaining infarct-related vessels were minor side branches.

The flow of the presumed infarct-related artery was of TIMI grade 0 or 1 on initial angiography in 68 percent of patients, grade 2 in 14 percent of patients, and grade 3 in 18 percent of patients. The postprocedural flow was of TIMI grade 0 or 1 in 3 percent of patients, grade 2 in 15 percent, and grade 3 in 83 percent (usable angiograms were available for 699 patients). Among the patients who underwent angioplasty, a postprocedural flow of TIMI grade 0 or 1 was achieved in 2 percent, grade 2 in 16 percent, and grade 3 in 82 percent.

Of the 91 patients who underwent immediate angiography but did not undergo balloon inflation, 31 had normal coronary arteries. Among the remaining 60 patients, medical treatment was considered to be the best initial strategy for 36 patients, balloon inflation was not possible for technical reasons in 17 patients, 3 patients had chronic occlusions without a culprit lesion, and 4 patients died before angioplasty could be performed. Only one patient underwent coronary surgery immediately after the angiographic examination.

CLINICAL OUTCOME

The clinical outcomes at 30 days are shown in Table 3, Figure 1, and Figure 2. The relative reduction in the rate of the composite outcome was 40 percent among patients enrolled at referral hospitals and 45 percent among those enrolled at invasive-treatment centers. The superiority of angioplasty over fibrinolysis was driven by a 75 percent reduction in the relative risk of clinical reinfarction, whereas the reduction in the risks of death and stroke did not reach statistical significance. The number of patients who

Table 3. Clinical Outcome at 30 Days.

Outcome	Referral Hospitals			Invasive-Treatment Centers			All Hospitals		
	Fibrinolysis Group (N=562)	Angioplasty Group (N=567)	P Value	Fibrinolysis Group (N=220)	Angioplasty Group (N=223)	P Value	Fibrinolysis Group (N=782)	Angioplasty Group (N=790)	P Value
	no. (%)			*no. (%)*			*no. (%)*		
Death	48 (8.5)	37 (6.5)	0.20	13 (5.9)	15 (6.7)	0.72	61 (7.8)	52 (6.6)	0.35
Reinfarction	35 (6.2)	11 (1.9)	<0.001	14 (6.4)	2 (0.9)	0.002	49 (6.3)	13 (1.6)	<0.001
Disabling stroke	11 (2.0)	9 (1.6)	0.64	5 (2.3)	0	0.02	16 (2.0)	9 (1.1)	0.15
Composite end point	80 (14.2)	48 (8.5)	0.002	27 (12.3)	15 (6.7)	0.05	107 (13.7)	63 (8.0)	<0.001

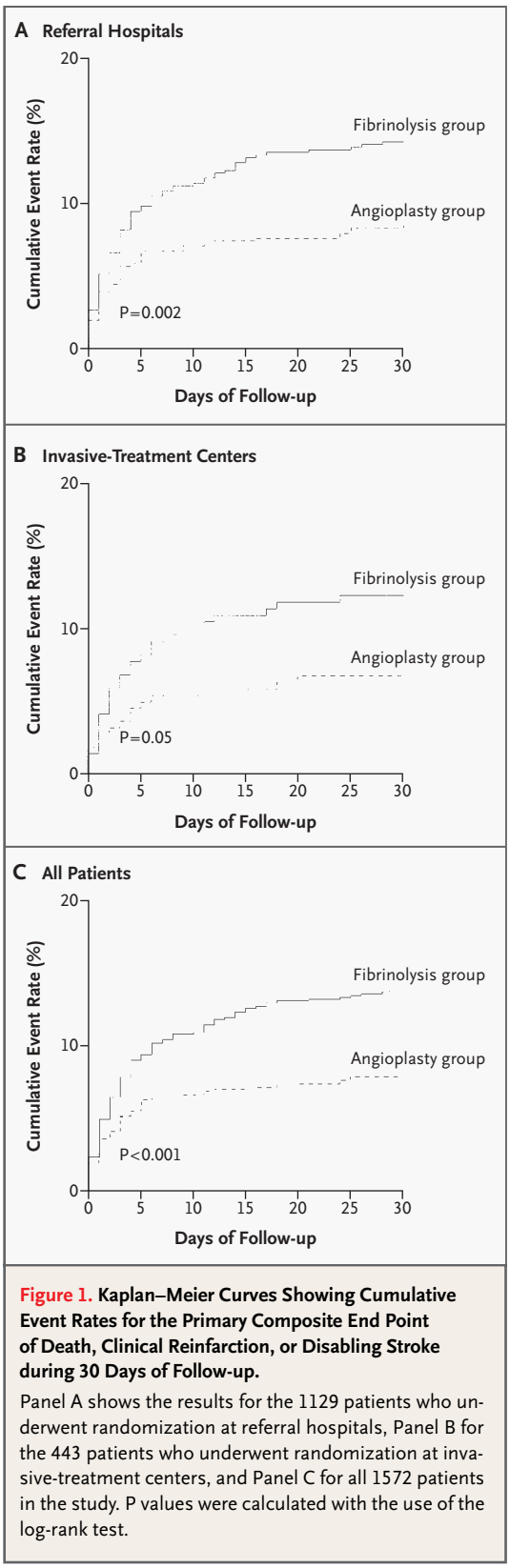

Figure 1. Kaplan–Meier Curves Showing Cumulative Event Rates for the Primary Composite End Point of Death, Clinical Reinfarction, or Disabling Stroke during 30 Days of Follow-up.

Panel A shows the results for the 1129 patients who underwent randomization at referral hospitals, Panel B for the 443 patients who underwent randomization at invasive-treatment centers, and Panel C for all 1572 patients in the study. P values were calculated with the use of the log-rank test.

would need to be treated in order to avoid one death, clinical reinfarction, or disabling stroke in a 30-day period was 17 for referral hospitals and 18 for invasive-treatment centers. The rate of the primary composite end point was consistently lower with angioplasty than with fibrinolysis in a number of prespecified subgroups (Fig. 2). No significant interactions between subgroups and treatment were detected. The relative benefit of angioplasty remained constant among the 646 patients whose symptoms had lasted less than two hours, the 549 patients whose symptoms had lasted two to four hours, and the 377 patients whose symptoms had lasted four hours or more.

Among the 62 patients who had clinical reinfarction during follow-up, 30-day mortality was 24.2 percent, as compared with 6.5 percent among the remaining 1510 patients (P<0.001). Procedure-related reinfarctions occurred in 10 patients randomly assigned to fibrinolysis and 5 patients randomly assigned to angioplasty — after coronary-bypass surgery in 11 cases and after angioplasty in 4 cases. Inclusion of these procedure-related reinfarctions in the analysis of clinical reinfarctions did not change the results.

The types of medication prescribed at discharge did not differ between patients randomly assigned to angioplasty and those assigned to fibrinolysis. A total of 96 percent of patients received aspirin, 87 percent received beta-blockers, 51 percent received lipid-lowering drugs, and 36 percent received angiotensin-converting–enzyme inhibitors.

REPEATED CORONARY REVASCULARIZATION DURING FOLLOW-UP

In the fibrinolysis group, 26 patients underwent repeated fibrinolysis within 12 hours after randomization, and 15 patients underwent rescue angioplasty (P=0.22). During the 30 days of follow-up, 148 patients randomly assigned to fibrinolysis underwent mechanical revascularization (coronary-bypass surgery in 20 patients and angioplasty in 129 patients), as did 72 patients randomly assigned to angioplasty (coronary-bypass surgery in 30 patients and angioplasty in 45 patients) (P<0.001 for the comparison between groups); some patients had more than one procedure.

DISCUSSION

In a large cohort, we found that primary angioplasty is superior to fibrinolysis for patients who have my-

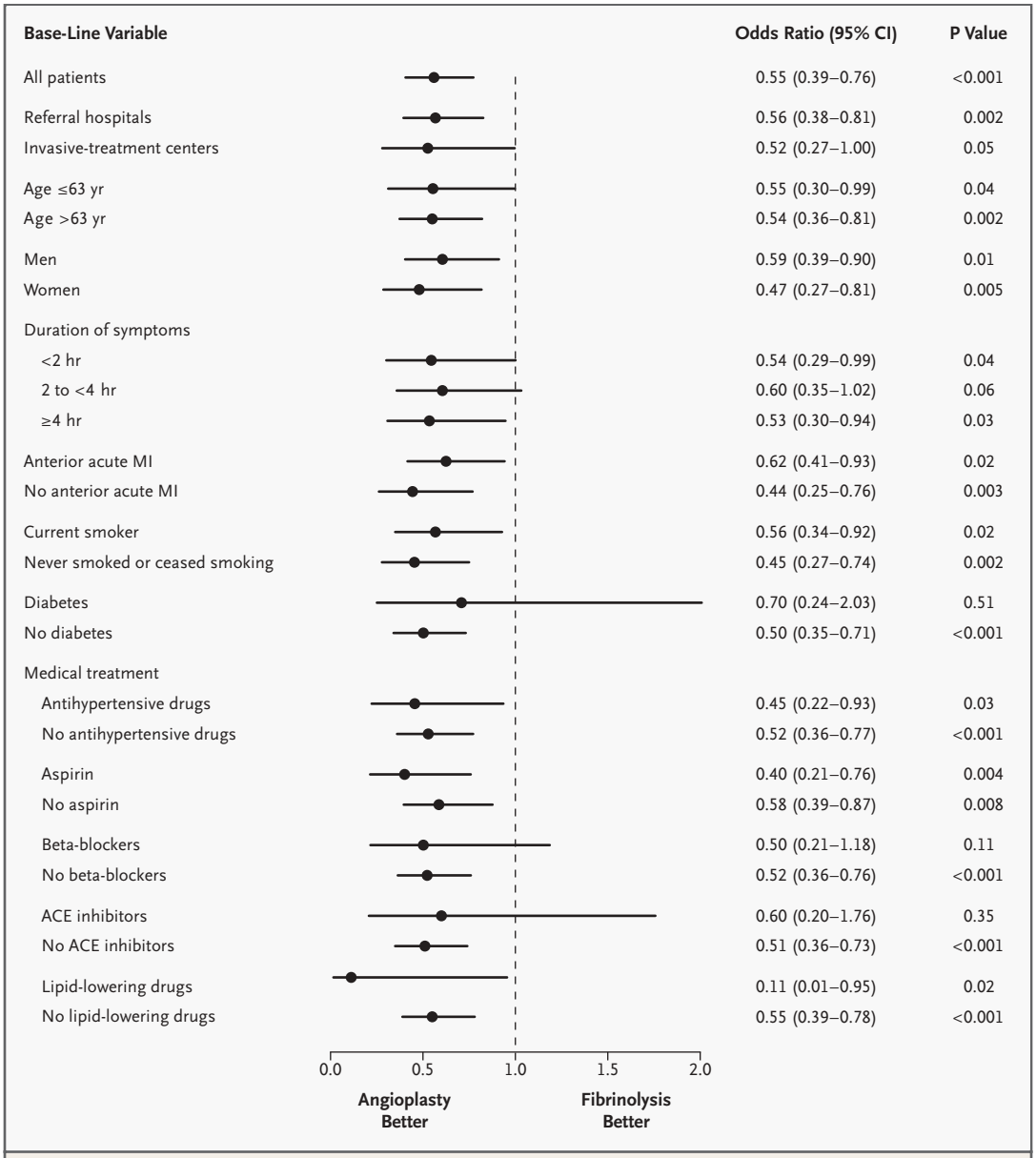

Figure 2. Odds Ratios for the Primary Composite End Point of Death, Reinfarction, or Disabling Stroke at 30 Days of Follow-up among All 790 Patients Randomly Assigned to Primary Angioplasty as Compared with All 782 Patients Randomly Assigned to Fibrinolysis, According to Base-Line Characteristics.

For analysis according to age, the median value of 63 years was used to dichotomize the variable. CI denotes confidence interval, MI myocardial infarction, and ACE angiotensin-converting enzyme.

ocardial infarction with ST-segment elevation, even when patients are admitted to a local hospital without angioplasty capabilities and must be transported to an invasive-treatment center. Our study demonstrates that it is possible to implement a new treatment strategy with 24-hour invasive-treatment services in a community that has not previously offered primary angioplasty as routine treatment. The benefit of treatment with primary angioplasty was the same for patients transferred from community hospitals as for patients admitted directly to an interventional-treatment center.

The transfer of patients was found to be safe. Only 4 percent of the screened patients were con-

sidered to be unable to tolerate being transported. Our results extend the findings of the recent PRAGUE-2 study.[7]

Our study was designed to minimize all components of the delay in treatment. At the primary admission, patients were brought directly to the coronary care unit by the ambulance staff, thus bypassing the emergency ward. Interhospital transportation was provided by the same ambulance, and the angioplasty center was alerted immediately on the initiation of transportation to ensure direct access to the catheterization room. Even with this algorithm, the median time from admission to the start of transportation was 50 minutes, which still compares favorably with the delay of approximately 75 minutes in the recent Air Primary Angioplasty in Myocardial Infarction study.[8] The time required for transfer by ambulance between hospitals constituted only 14 percent of the total time between the onset of symptoms and the start of treatment, despite the fact that 70 percent of the patients were transported farther than 25 km. Almost all patients enrolled at community hospitals arrived in the catheterization laboratory within two hours after randomization. This fact makes our results applicable to most Western communities and opens the way for more widespread use of primary angioplasty in the treatment of patients who have myocardial infarction with ST-segment elevation.

Although the rates of death, clinical reinfarction, and stroke were all reduced with angioplasty, the better overall outcome after angioplasty was driven primarily by the reduction in the rate of reinfarction. Our finding of a higher 30-day mortality rate among patients with reinfarction accords with recent results by Gibson et al.[9] and indicates that clinical reinfarction in our trial was a severe event. The prognostic significance of procedure-related ischemic events is uncertain.[10] The inclusion in the analysis of procedure-related reinfarctions strengthened, rather than weakened, the evidence of a favorable outcome after angioplasty.

Our angiographic success rate, with the achievement of a flow of TIMI grade 3 in 83 percent of our patients, is similar to the success rates in experienced centers.[11-13] It is well documented that the benefit of primary angioplasty depends on the volume of procedures performed and the level of experience of the physician.[14,15] Although all five invasive-treatment centers in our study were high-volume interventional-treatment centers (performing 600 to 1600 angioplasty procedures per year), they had had limited experience in performing primary angioplasty at the beginning of the study. However, they were all able to adapt the training program and obtain and maintain the necessary skills.

The frequency of rescue angioplasty was low. Although one may argue that our approach was too conservative, there is no published evidence of a treatment benefit of rescue angioplasty in patients who have been treated with fibrinolysis at referral hospitals. At 30 days of follow-up, one fifth of the patients who had been treated with fibrinolysis had undergone ischemia-guided mechanical revascularization, in accordance with the protocol of our previous study.[16]

Future attempts to improve the clinical outcome associated with primary angioplasty should focus on the logistics of transferring patients and on adjunctive medication. One approach might be to obtain an electrocardiogram in the ambulance and then to transfer the patient directly to a center with facilities for primary angioplasty, with or without surgical backup.[17] There has been great interest in "facilitated" angioplasty involving the use of a reduced dose of a fibrinolytic drug in combination with more aggressive antithrombotic treatment before angioplasty. Trials dealing with such strategies have not yet provided convincing evidence of their effectiveness.[18]

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APPENDIX

The following are participants in DANAMI-2. *Steering Committee:* T.T. Nielsen (chair), H.R. Andersen, L. Thuesen, H. Kelbaek, P. Grande, J.K. Madsen, P. Thayssen, T. Haghfelt, K. Rasmussen, T. Vesterlund, O. Amtorp, U. Abildgaard, F.H. Pedersen, K. Egstrup, and H.K. Kjaergard. *End Points Committee:* E. Steinmetz (chair), L.R. Krusell, K.N. Hansen, P.R. Hansen, P. Clemmensen, and I. Christiansen. *Audit Committee:* P. Clemmensen (chair), S. Galatius, and C. Sundgreen. *Safety and Ethics Committee:* H. Ibsen (chair), K. Mellemgaard (chair), S. Strandgaard, J.S. Christiansen, L.S. Mortensen, M.L. Simoons, F. Zijlstra, C.L. Grines, L. Ekström, and G.W. Stone. *Participating hospitals and principal investigators* (the number in parenthesis is the number of patients randomized): Aalborg University Hospital, K. Rasmussen (181), Horsens Hospital, E. Vigholt (127), Randers Hospital, P. Lomholt (117), Aarhus Amtssygehus, S. Husted (110), Bispebjerg Hospital, N. Gadsboell (88),

Odense University Hospital, P. Thayssen (88), Skejby Sygehus, Aarhus University Hospital, H.R. Andersen (83), Viborg Hospital, O. Lederballe (71), Hjoerring Hospital, N. Falstie-Jensen (56), Gentofte Hospital, U. Abildgaard (51), Glostrup Hospital, J.R. Nielsen (47), Grenaa Hospital, H. Rickers (42), Skive Hospital, S.E. Stentebjerg (41), Silkeborg Hospital, F. Roemer (40), Herning Hospital, D. Dalsgaard (40), Rigshospitalet, K. Saunamäki (40), Nykoebing Mors, A.N. Davidson (38), Kolding Hospital, M. Asklund (38), Vejle Hospital, B. Engby (37), Frederiksberg Hospital, P. Hildebrandt (37), Odder Hospital, B. Jastrup (37), Amager Hospital, H. Nielsen (34), Frederikshavn Hospital, H. Sejersen (31), Hilleroed Hospital, J. Launbjerg (27), Haderslev Hospital, P. Wiggers (26), Fredericia Hospital, J. Markenvard (23), Hvidovre Hospital, S.L. Rasmussen (19), Skagen Hospital, H. Sejersen (4), and Brovst Hospital, E. Steinmetz (2). *Angioplasty centers* (the number in parenthesis is the number of patients treated with angioplasty): Skejby Hospital, L. Thuesen, H.R. Andersen (421), Aalborg University Hospital, K. Rasmussen, A.B. Villadsen (135), Rigshospitalet, J.K. Madsen, K. Saunamäki (108), Gentofte Hospital, U. Abildgaard, E. Kassis (63), and Odense University Hospital, P. Thayssen (55).

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