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A CLINICAL TRIAL COMPARING PRIMARY CORONARY ANGIOPLASTY WITH TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE MYOCARDIAL INFARCTION

THE GLOBAL USE OF STRATEGIES TO OPEN OCCLUDED CORONARY ARTERIES IN ACUTE CORONARY SYNDROMES (GUSTO IIb) ANGIOPLASTY SUBSTUDY INVESTIGATORS*

ABSTRACT

Background Among physicians who treat patients with acute myocardial infarction, there is controversy about the magnitude of the clinical benefit of primary (i.e., immediate) coronary angioplasty as compared with thrombolytic therapy.

Methods As part of the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) trial, we randomly assigned 1138 patients from 57 hospitals who presented within 12 hours of acute myocardial infarction (with ST-segment elevation on the electrocardiogram) to primary angioplasty or accelerated thrombolytic therapy with recombinant tissue plasminogen activator (t-PA). We also randomly assigned 1012 patients to heparin or hirudin treatment in a factorial design. The primary study end point was a composite outcome of death, nonfatal reinfarction, and nonfatal disabling stroke at 30 days.

Results The incidence of the primary end point in the angioplasty and t-PA groups was 9.6 percent and 13.7 percent, respectively (odds ratio, 0.67; 95 percent confidence interval, 0.47 to 0.97; P = 0.033). Death occurred in 5.7 percent of the patients assigned to angioplasty and 7.0 percent of those assigned to t-PA (P = 0.37), reinfarction in 4.5 percent and 6.5 percent (P = 0.13), and disabling stroke in 0.2 percent and 0.9 percent (P = 0.11). At six months, there was no significant difference in the incidence of the composite outcome (14.1 percent vs. 16.1 percent, P not significant). The primary end point was observed in 10.6 percent of the patients in the angioplasty group assigned to heparin and 8.2 percent of those assigned to hirudin (P = 0.37).

Conclusions This trial suggests that angioplasty provides a small-to-moderate, short-term clinical advantage over thrombolytic therapy with t-PA. Primary angioplasty, when it can be accomplished promptly at experienced centers, should be considered an excellent alternative method for myocardial reperfusion. (N Engl J Med 1997;336:1621-8.)

PROMPT, complete restoration of coronary flow is the principal mechanism by which reperfusion therapy improves survival and other clinical outcomes in patients with acute myocardial infarction in whom there is electrocardiographic evidence of ST-segment elevation.[1-3] At selected centers, coronary angioplasty can be performed expeditiously in such patients, resulting in better coronary flow[4,5] and 30-day survival rates[2,4-12] than are obtained with intravenous thrombolytic therapy.

Intravenous thrombolytic therapy is, however, the standard of care for patients with acute myocardial infarction, because of its widespread availability, its ability to reduce mortality, and its use in more than a million patients over the past decade.[6,13-15] Recently, two large studies of registry data[16,17] raised doubt about whether the apparent superiority of angioplasty over thrombolytic therapy would be sustained in general clinical practice, because treatment delays and technical failures appear to be more common than in the selected centers that have participated in randomized trials.

The use of "front-loaded" (accelerated), weight-adjusted treatment with recombinant tissue plasminogen activator (t-PA)[6] instead of other lytic regimens used in previous trials[4,5,7-12] might further reduce the differences in outcome between these two therapies. Also, the adjunctive use of direct inhibitors of thrombin, which have several potential advantages over heparin but have not been proved beneficial in this setting,[18,19] might also influence the outcomes of these two strategies. Therefore, we performed an in-

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*The investigators and centers participating in the GUSTO IIb Angioplasty Substudy are listed in the Appendix.

ternational, multicenter, randomized trial comparing primary angioplasty with thrombolytic therapy (and hirudin with heparin, in the patients treated with primary angioplasty) in the initial management of acute myocardial infarction.

METHODS

Study Organization

This study was a prospective substudy of the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) trial.[20] Fifty-seven hospitals in nine countries participated (see the Appendix). To participate, each site was required to perform at least 200 angioplasties yearly, to have at least one cardiologist who had performed at least 50 angioplasties yearly, a 24-hour on-call team, and a system for operating-room backup if emergency bypass surgery was required. Eighty-five percent of sites performed more than 400 angioplasties yearly, and 85 percent of operators performed more than 75 angioplasties yearly.

Study Patients

Patients presenting within 12 hours after the onset of symptoms (chest pain lasting at least 20 minutes, accompanied by electrocardiographic signs of ST-segment elevation of at least 0.2 mV in two or more contiguous leads or left bundle-branch block) were eligible for enrollment. The exclusion criteria were identical to those used in the main GUSTO IIb trial.[20] All the patients gave informed consent, and the protocol was approved by the institutional review board at each hospital.

Randomization and Treatment Strategies

The investigators and study coordinators telephoned or faxed a 24-hour-a-day, seven-day-a-week randomization center to review the eligibility of patients and receive their assignments to treatment. Eligible patients were randomly assigned to either primary coronary angioplasty or accelerated t-PA (an intravenous bolus of 15 mg, followed by an infusion of 0.75 mg per kilogram of body weight [not to exceed 50 mg] over a 30-minute period and then 0.50 mg per kilogram [not to exceed 35 mg] over the next 60 minutes, for a maximal total dose of 100 mg). The first 1012 patients were also randomly assigned, in a two-by-two factorial design, to either heparin or hirudin given intravenously as part of the GUSTO IIb trial (these patients were included in the main trial).[20] The protocol for the administration of the study drug in this trial has been reported previously[20]; in brief, patients were assigned to receive an infusion of either heparin or hirudin for three to five days; the dose was adjusted to keep the activated partial-thromboplastin time within the 60-to-85-second range.

At the recommendation of the Data and Safety Monitoring Board and the GUSTO IIb Steering Committee, enrollment in this substudy was extended, without a review of the end-point data, beyond the completion of enrollment in the GUSTO IIb trial, to January 1, 1996, in order to reach the intended sample size. All the patients enrolled thereafter were treated with heparin as the thrombin inhibitor.

All the patients were also to receive standard medical care, including chewable aspirin, at the time of enrollment.[20] Other cardiac medications were administered at the discretion of the physician. Angiography within three days of study entry was discouraged in patients randomly assigned to t-PA, except to manage refractory ischemia or hemodynamic deterioration.

Primary Angioplasty

Angioplasty was performed according to local standards, with the intention of reestablishing blood flow in the infarct-related artery as soon as possible. After securing arterial access and verifying that angioplasty was indicated, we titrated the study thrombin inhibitor in a double-blind fashion in increments of 3000 U of heparin or 30 mg of hirudin to reach an activated clotting time of at least 350 seconds. The infarct-related artery was the only target, except in patients whose hemodynamic values deteriorated despite restoration of the patency of that artery. After angioplasty, the study drug was temporarily stopped to permit early removal of the sheath. The study protocol acknowledged that in some patients, particularly those with stenoses of the left main artery or critical three-vessel disease, bypass surgery should be strongly considered instead of angioplasty. In patients whose infarct-related arteries had Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow at first angiography, whether or not to perform angioplasty was left to the judgment of the operator.

Angiographic Analyses

The cineangiograms obtained at study entry for all patients randomly assigned to angioplasty were forwarded to the Angiographic Core Laboratory for quantitative analyses by a validated edge-detection method (Artrek, version 1.60, Quinton Imaging Systems, Bothell, Wash.).[21] Technical success was defined as a residual stenosis of less than 50 percent and a final TIMI flow grade of 2 or 3.

Data Management and Quality Assurance

Case-report forms were forwarded to either the international coordinating center (Catholic University, Leuven, Belgium) or the main coordinating center (Duke University, Durham, N.C.) for data entry and the generation of queries about missing or inconsistent data. Patient follow-up at 30 days and 6 months was performed by means of a self-administered questionnaire, telephone interview, or follow-up visit to the physician. The quality of the data was ensured by auditing 10 percent of the data forms and by having an independent Clinical Events Committee adjudicate decisions on all possible primary-end-point events. A data-based algorithm was developed to capture all the events that might constitute part of the primary end point and trigger a review of chart information by this committee, whose members remained unaware of the initial treatment assignments.

End Points

The primary end point was a composite outcome of death, nonfatal reinfarction, and nonfatal disabling stroke within 30 days, as confirmed by the Clinical Events Committee. The prespecified secondary end points were mortality from all causes at 30 days; mortality from all causes and nonfatal reinfarction at 30 days; a composite end point consisting of death, reinfarction, disabling stroke, and congestive heart failure at 30 days; recurrent, medically refractory ischemia; and major bleeding.[20] Follow-up electrocardiograms and creatine kinase and MB isoenzyme levels were to be obtained at the time of any suspected myocardial reinfarction.[20] Computed tomography or magnetic resonance imaging of the brain was requested for all patients with suspected stroke. Severe bleeding was defined as intracranial hemorrhage or bleeding that caused hemodynamic compromise. Moderate bleeding was defined as bleeding that required blood transfusion but that did not lead to hemodynamic compromise.

Statistical Analysis

The primary study hypothesis was that immediate angioplasty would result in a lower incidence of death, nonfatal reinfarction, and nonfatal disabling stroke at 30 days than thrombolytic therapy. The incidence of the primary end point in the t-PA group was expected to be approximately 12 percent. Although studies had suggested that the incidence of major end points would be more than 60 percent lower with angioplasty than with thrombolytic therapy,[4,5,7-12] the size of this study population was chosen to ensure that a relative reduction of 40 percent could be detected with an alpha error of 0.05 and a beta error of 0.20.

Continuous data are presented as medians with 25th and 75th percentiles unless otherwise stated. Selected base-line character-

istics and clinical outcomes were compared between treatment groups by the chi-square test in the case of discrete variables and by nonparametric analysis of variance in the case of continuous variables. Odds ratios and 95 percent confidence intervals were used to compare treatments with regard to major clinical outcomes. Kaplan–Meier survival curves were used to characterize the timing of the primary study end point and its components during the follow-up period. Logistic-regression models were used to assess prespecified interactions.

Prespecified subgroups classified according to the following variables were studied in relation to the primary and secondary end points: age and time to randomization, as continuous variables; and anterior as compared with nonanterior location of the infarct, high as compared with low risk,[5] and the hospital's experience with angioplasty (with the number of procedures dichotomized at the median), as discrete variables.

An interim analysis of safety was performed by an independent Data and Safety Monitoring Board when the enrollment reached 750 patients, as specified in the protocol. Efficacy was compared with the use of two-sided, symmetric O'Brien–Fleming boundaries generated by the Lan–DeMets approach to group-sequential testing.[22,23] All tests of significance were two-tailed, and the treatments were compared according to the intention-to-treat principle.

RESULTS

Recruitment began on July 5, 1994, and ended on January 1, 1996, after 1138 patients had been enrolled. The patients tended to be middle-aged and male, presenting without hypotension or pulmonary edema (Table 1). Among the patients randomly assigned to angioplasty, 94 percent had angiography and 82 percent had angioplasty (5 percent also received stents); among the patients randomly assigned to t-PA, 98 percent received that therapy and only 1.4 percent had primary angioplasty. Balloon inflation was first performed in the patients undergoing angioplasty a median of 1.3 hours after randomization (interquartile range, 1.0 to 1.6). The activated partial-thromboplastin times at 6 hours were longer in the angioplasty group because of periprocedural dosing to achieve an activated clotting time of more than 350 seconds, but the times in the two groups were similar by 12 hours after the initial drug therapy.

In the patients randomly assigned to angioplasty, 83 percent of the infarct-related arteries were initially occluded (TIMI grade 0 or 1 flow) according to the on-site interpretation (Table 2). The median peak activated clotting time during the procedure was 381 seconds (interquartile range, 329 to 480). TIMI grade 3 flow was obtained in 73 to 88 percent of the patients (depending on whether the angiograms were read at the core laboratory or at the site). Seventeen of 465 patients (3.7 percent) who were randomly as-

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT BASE LINE, ACCORDING TO TREATMENT ASSIGNMENT.*

CHARACTERISTIC	t-PA (N=573)	ANGIOPLASTY (N=565)	HEPARIN PLUS ANGIOPLASTY (N=247)	HIRUDIN PLUS ANGIOPLASTY (N=256)
Median age — yr	61.9 (52.0, 70.1)	63.5 (52.5, 71.0)	64 (50, 71)	63 (54, 71)
Age >75 yr — no. (%)	79 (13.8)	82 (14.5)	32 (13.0)	39 (15.2)
Female sex — no.(%)	121 (21.5)	139 (24.6)	65 (26.3)	66 (25.8)
Current smoker — no. (%)†	255 (60.9)	235 (63.7)	102 (61.1)	108 (69.2)
Diabetes — no. (%)†	77 (13.4)	99 (17.5)	45 (18.2)	50 (19.5)
Median heart rate — beats/min	74.5 (62, 86)	75 (63, 87)	75 (63, 87)	75 (64, 86)
Hypertension — no. (%)†	218 (38.0)	225 (39.8)	100 (40.5)	101 (39.5)
Killip class — no. (%)†				
1	524 (91.4)	507 (89.7)	220 (89.1)	228 (89.1)
2	41 (7.2)	47 (8.3)	22 (8.9)	23 (9.0)
3	4 (0.7)	2 (0.4)	1 (0.4)	1 (0.4)
4	2 (0.3)	5 (0.9)	3 (1.2)	2 (0.8)
Prior bypass surgery — no. (%)	16 (2.8)	12 (2.1)	2 (0.8)	10 (3.9)
Prior myocardial infarction — no. (%)†	85 (14.8)	73 (12.9)	25 (10.1)	38 (14.8)
Prior angioplasty — no. (%)	28 (4.9)	29 (5.1)	9 (3.6)	17 (6.6)
Median systolic blood pressure — mm Hg	130 (116, 148)	130 (116, 147)	130 (118, 150)	130 (113, 144)
Median time to arrival at hospital — hr‡	1.8 (1.0, 3.1)	1.9 (1.1, 3.0)	2.0 (1.1, 3.2)	1.9 (1.2, 2.8)
Median time to treatment — hr‡	3 (2.0, 4.3)	3.8 (3.0, 5.3)	3.9 (3.0, 5.4)	3.9 (3.0, 5.1)
Median weight — kg	76 (68, 86)	75 (67, 86)	76 (67, 86)	75 (67, 86)

*Median values are given with interquartile ranges (the 25th and 75th percentiles).

†Data were not available for some patients.

‡Times shown are from the onset of symptoms.

TABLE 2. RESULTS OF ANGIOPLASTY, AS DETERMINED IN THE CORE LABORATORY AND AT THE CLINICAL SITE.*

VARIABLE†	CORE LABORATORY	CLINICAL SITE
Before angioplasty		
Median percent stenosis	100 (81.9, 100)	100 (99, 100)
TIMI flow grade — no. (%)		
0	308 (60.4)	325 (70.3)
1	66 (12.9)	52 (11.3)
2	96 (18.8)	40 (8.7)
3	40 (7.8)	37 (8.0)
0 or 1	—	4 (0.9)
2 or 3	—	4 (0.9)
After angioplasty		
Median percent stenosis	39.2 (30.7, 48.8)	23 (10, 30)
<50% stenosis — no. (%)	343 (77.4)	423 (91.4)
<60% stenosis — no. (%)	406 (91.7)	438 (94.6)
TIMI flow grade — no. (%)		
0	28 (5.5)	12 (2.7)
1	7 (1.4)	9 (2.0)
2	101 (19.9)	32 (7.1)
3	372 (73.2)	385 (85.4)
Open (TIMI 2 or 3, not specified)	—	13 (2.9)
Peak intraprocedural activated clotting time — sec	—	381 (329, 480)

*Median values are given with interquartile ranges (the 25th and 75th percentiles).

†Data were not available for some patients.

TABLE 3. CONCOMITANT MEDICATIONS AND IN-HOSPITAL PROCEDURES IN THE STUDY GROUPS.

MEDICATION OR PROCEDURE	t-PA	ANGIOPLASTY
	no. of patients (%)	
Angiotensin-converting–enzyme inhibitor	253 (45.1)	225 (40.3)
Aspirin	559 (98.1)	550 (98.0)
Beta-blocker		
Intravenous	171 (30.1)	151 (26.9)
Oral	409 (72.7)	388 (69.9)
Calcium-channel blocker	163 (29.1)	158 (28.4)
Digitalis	61 (10.8)	72 (12.9)
Nitrate		
Intravenous	491 (86.3)	468 (83.1)
Oral	427 (76.1)	410 (74.0)
Nonstudy heparin*	267 (51.1)	208 (40.7)
Warfarin	80 (14.1)	61 (11.0)
Angiography		
Emergency	82 (14.4)	22 (4.0)
Elective	270 (47.3)	19 (3.5)
Specified by protocol	6 (1.1)	532 (94.4)
None	213 (37.3)	13 (2.3)
Coronary-artery bypass surgery	47 (8.3)	42 (7.5)
Intraaortic balloon pump	39 (6.8)	78 (13.8)
First angioplasty		
Emergency	60 (16.8)	19 (3.5)
Elective	61 (17.0)	5 (0.9)
Specified by protocol	5 (1.4)	446 (81.1)
None	228 (63.7)	79 (14.4)

*In these patients, heparin was given before infusion of the study drug.

signed to angioplasty and who underwent that procedure required bypass surgery on the same day. The results of angioplasty did not differ significantly between the patients assigned to heparin and those assigned to hirudin. The medications received during hospitalization are shown in Table 3.

As compared with t-PA, angioplasty resulted in 13 fewer deaths (95 percent confidence interval, −15 to 41; $P=0.37$) and 41 fewer deaths, infarctions, or disabling strokes (95 percent confidence interval, 3 to 78; $P=0.033$) at day 30 per 1000 patients (Tables 4 and 5). Most of the relative benefit of angioplasty seemed to occur between days 5 and 10 (Fig. 1). Among patients undergoing delayed elective angioplasty, 7 of 61 (11 percent) in the t-PA group and 2 of 5 (40 percent) in the angioplasty group subsequently died or had a reinfarction or a nonfatal, disabling stroke. Angioplasty was associated with more bleeding events than t-PA, with the notable exception of intracranial hemorrhage. Death, reinfarction, or disabling stroke occurred in 10.6 percent of patients assigned to angioplasty and heparin, as compared with 8.2 percent of those assigned to angioplasty and hirudin ($P=0.37$). Bleeding complications in the hirudin and heparin groups were similar.

Eighteen percent of the patients assigned to angioplasty did not undergo that procedure. At least 9.3 percent had acceptable reasons for not undergoing primary angioplasty: 1.2 percent died early, 6.9 percent had an open infarct-related artery, and 1.2 percent had early bypass surgery with left main or three-vessel coronary disease. Another 3.4 percent had early catheterization with no reason noted for refraining from primary angioplasty; 3.6 percent did not undergo early catheterization, had received thrombolytic therapy before catheterization (often because of delays in patient transfer), or both; and for the remaining 1.6 percent, information about the time of catheterization was missing. Among the patients assigned to primary angioplasty who did not undergo the procedure, 14.1 percent died within 30 days and 20.7 percent died or had a nonfatal reinfarction or nonfatal, disabling stroke.

In the angioplasty group, the correlations between mortality within 30 days and the final TIMI flow grades as determined in the core laboratory were as follows: TIMI flow grade 0, 21.4 percent mortality; grade 1, 14.3 percent; grade 2, 19.9 percent; and grade 3, 1.6 percent ($P<0.001$).

The relation between the risk of death within 30 days and assignment to angioplasty or accelerated t-PA in several prospectively defined subgroups of patients is shown in Figure 2.

Six months after randomization, with follow-up complete in 96.9 percent of the eligible patients, the incidence of the composite adverse outcome was 15.7 percent in the t-PA group and 13.3 percent in the angioplasty group (P not significant).

TABLE 4. OCCURRENCE OF THE PRIMARY END POINT AT 30 DAYS.

END POINT	t-PA	ANGIOPLASTY	ODDS RATIO (95% CONFIDENCE INTERVAL)	P VALUE	ANGIOPLASTY PLUS HIRUDIN	ANGIOPLASTY PLUS HEPARIN	ODDS RATIO (95% CONFIDENCE INTERVAL)	P VALUE
	no. (%)				no. (%)			
Death	40 (7.0)	32 (5.7)	0.80 (0.49–1.30)	0.37	12 (4.7)	15 (6.1)	0.77 (0.34–1.67)	0.50
Reinfarction	37 (6.5)	25 (4.4)	0.67 (0.40–1.12)	0.13	11 (4.3)	11 (4.5)	0.97 (0.41–2.27)	0.94
Disabling stroke	5 (0.9)	1 (0.2)	0.20 (0.02–1.73)	0.11	0	1 (0.4)	—	—
Any of the above	78 (13.6)	54 (9.6)	0.67 (0.47–0.97)	0.033	21 (8.2)	26 (10.6)	0.76 (0.42–1.39)	0.37

TABLE 5. OCCURRENCE OF SECONDARY END POINTS AT 30 DAYS.

END POINT	t-PA	ANGIOPLASTY
Bleeding — no. (%)		
Any	195 (34.2)	227 (40.3)
Severe or life-threatening	11 (1.9)	15 (2.7)
Moderate	44 (7.7)	57 (10.1)
Moderate or worse	54 (9.5)	69 (12.3)
Transfusion required	51 (8.9)	64 (11.3)
Congestive heart failure — no. (%)	28 (4.9)	24 (4.3)
Intracranial hemorrhage — no. (%)	8 (1.4)	0
Median length of stay — days*		
Intensive care unit	3.5 (2.5, 5)	3 (2, 4)
Hospital	10 (7, 14)	8 (6, 12)
Recurrent ischemia — no. (%)	48 (9.0)	29 (5.5)
Shock — no. (%)	26 (4.6)	34 (6.1)
Any stroke — no. (%)	11 (1.9)	6 (1.1)
Death, myocardial infarction, stroke, or congestive heart failure — no. (%)	94 (16.5)	71 (12.6)

*Median values are given with interquartile ranges (the 25th and 75th percentiles).

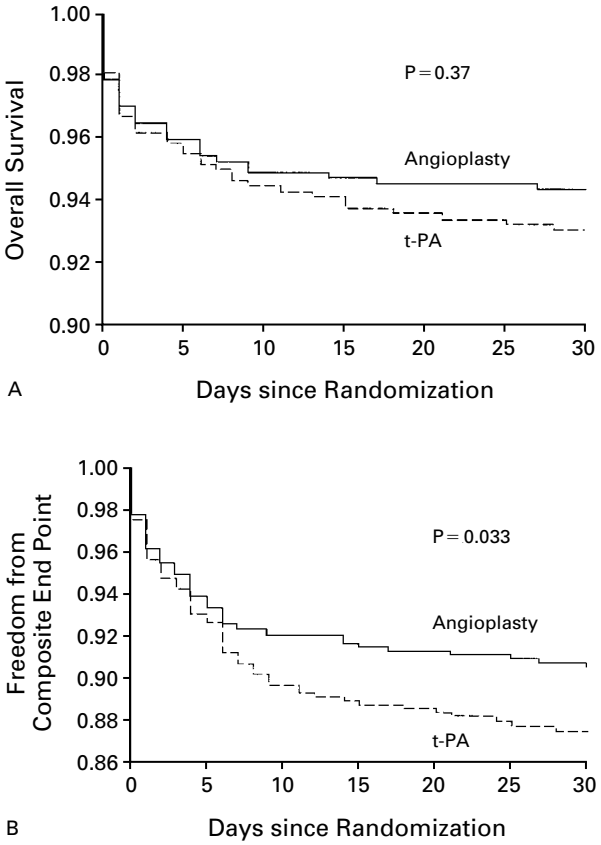

Figure 1. Kaplan–Meier Curves for Survival (Panel A) and Freedom from the Composite End Point of Death, Reinfarction, and Disabling Stroke (Panel B) in the Study Patients within the 30 Days after Randomization, According to Treatment Group.

DISCUSSION

In this international trial comparing primary angioplasty with thrombolytic therapy for acute myocardial infarction, there was a relative benefit at 30 days with angioplasty with respect to all elements of the primary study end point — death, reinfarction, and disabling stroke. The aggregate outcome occurred significantly less often in the angioplasty group — in 9.6 percent of patients, as compared with 13.7 percent in the t-PA group (odds ratio, 0.67; $P = 0.033$). The extent of this benefit and of the benefit with regard to mortality alone ($P = 0.37$) was far less than was seen in eight previous, small, randomized trials but larger than in recent data reported from large registries.[16,17]

Previous randomized trials, albeit with considerable apparent heterogeneity, suggested that there was a significant improvement in major clinical outcomes with angioplasty, with an estimated 40 lives saved (95 percent confidence interval, 2 to 63) per 1000 patients treated.[4,5,7-12] This benefit is larger than the benefit of streptokinase as compared with placebo (in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico trial, 23 lives saved at 21 days; in the Second International Study of Infarct Survival, 29 lives saved at 35 days) in the same types of patients,[13,15] a finding that revolutionized the care of patients with acute myocardial infarction. However, these trials were performed at se-

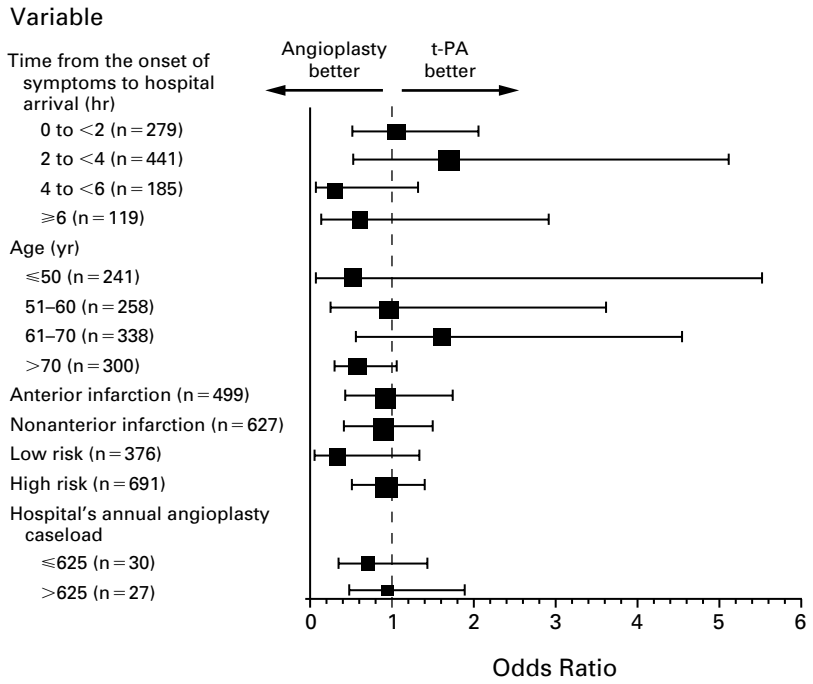

Figure 2. Point Estimates and 95 Percent Confidence Intervals for the Odds Ratios for Death within 30 Days in Several Prospectively Defined Subgroups of Patients, According to Treatment Assignment.

Odds ratios below 1 indicate that angioplasty is preferable, and odds ratios above 1 that thrombolysis is preferable. High-risk patients were those with an anterior infarction, an age of 70 years or older, or a heart rate of 100 beats per minute or higher at admission. The hospitals were subdivided according to the median annual angioplasty caseload (625 angioplasties). The size of the solid squares corresponds roughly to the number of patients studied. Complete data were not available for all the patients.

lected hospital sites, involved few patients, and except in one case, used thrombolytic regimens that are suboptimal by today's standards.

Another difference in outcome between this and other trials[4,5] may relate to the technical results of the angioplasty itself. Technical success, with restoration of TIMI grade 3 flow, was reported in 92 to 97 percent of patients in previous trials,[5,24] albeit without independent confirmation by a core angiographic laboratory. Technical success, as determined by the core laboratory, was obtained in 93 percent of the patients in GUSTO IIb, with TIMI grade 3 flow restored in 73 percent. These differences may be due to the more globally representative outcome in GUSTO IIb or to the fact that even at established core angiographic laboratories, determinations of TIMI flow are frequently discrepant.[25] Recent reported rates for the success of primary angioplasty in the community range from 46 to 93 percent.[26,27]

Although there was no significant relation between the operator's experience with angioplasty and the effect of treatment, 85 percent of angioplasties in this study were performed by operators who performed more than 75 such procedures per year. In the light of some reports of a relation between higher volume of angioplasty and better outcome for patients,[28] the results of this study should not be extrapolated to operators with lower angioplasty volumes.

The results of this study also differ from those of certain previous trials in that the patients in the higher-risk groups did not appear to gain greater benefit from angioplasty. In the first Primary Angioplasty Myocardial Infarction Study (PAMI-I),[5] the patients found in a post hoc analysis to be at high risk (those older than 70, with anterior infarctions, or with heart rates greater than 100 beats per minute at admission) had a far lower in-hospital mortality with angioplasty (2.0 percent) than patients receiving thrombolytic therapy (10.4 percent), and others did not appear to benefit. No significant differential effect was observed in this study. It should be acknowledged that patients at highest risk, those in Killip class 3 or 4, are represented in very small numbers in this and other trials.[4,5] Subgroup analyses — from small trials in particular — should be interpreted with caution, and it will require further study to resolve this issue. The small but definite excess of hemorrhagic strokes with t-PA in this study is consistent with the findings of the PAMI-I trial,[5] but the risk associated with t-PA appears to be considerably greater than what might

be expected on the basis of the findings of far larger studies[6] (e.g., 1.4 percent in this substudy, as compared with 0.5 percent in the main study[20]). This finding may be a reason to suggest that angioplasty would be preferable in patients at highest risk for intracranial hemorrhage.[29]

A further and perhaps unexpected finding was the timing of the benefit of angioplasty (Fig. 1). If the mechanism of this benefit is the early restoration of TIMI grade 3 flow, the importance of which was demonstrated in the GUSTO-I trial, then a benefit should have been evident within 24 hours.[23] The delayed benefit, particularly with respect to reinfarction, suggests that either spontaneous or procedure-related reinfarction between day 5 and day 10 in the t-PA group accounted for much of the difference in outcome, as Stone and colleagues also suggested.[30]

The attenuation of the benefit of angioplasty at six months is notable. Smaller trials have reported mixed results after discharge from the hospital.[31-33] This finding may have been a consequence of the relatively high rate of coronary reocclusion after angioplasty, which has been noted in serial angiographic studies.[34]

Given the striking reduction in adverse outcomes in patients treated with inhibitors of the platelet glycoprotein IIb/IIIa receptor as an adjunct to angioplasty[35,36] and the possible benefit of these agents combined with thrombolytic therapy,[37] the possible improvement in outcome early after infarction with primary stenting as compared with angioplasty alone,[38-41] and the reduction in intermediate-term revascularization in selected patients treated with stents,[42,43] this study should be regarded as only a step in the continued development of optimal reperfusion strategies. The speed, completeness, and durability of reperfusion, and thus outcomes for patients, will probably improve with both angioplasty and thrombolytic therapy.

At present, physicians deciding which therapy to offer a patient who is eligible for either treatment should return to fundamentals established in multiple large studies. The rapid restoration of brisk antegrade coronary flow is critical in reducing mortality.[1,2] The time from presentation to angioplasty in GUSTO IIb (1.9 hours) was greater than the time from randomization in the PAMI and Dutch trials (1.0 hour in each)[4,5] and nearly the same as in the more broadly representative Second National Registry of Myocardial Infarction (2.0 hours).[17] If a skilled cardiologist is readily available and the patient can be treated rapidly, angioplasty may be preferable. Patients with severe hypertension, advanced age, or symptomatic cerebrovascular disease should also be treated with angioplasty, if available, to lower the risk of intracranial hemorrhage.[29] In most situations, however, thrombolytic therapy should still be regarded as an excellent strategy of reperfusion. The important point is not to delay in restoring myocardial reperfusion in suitable candidates with two attractive alternatives.

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APPENDIX

The following centers and investigators collaborated in this study (values in parentheses denote the number of patients enrolled). **Principal Investigators:** A. Betriu, H. Phillips, and S. Ellis. **Steering Committee:** E. Topol (Study Chairman), R. Califf (Clinical Director, Coordinating Center), F. Van der Werf (Director, Intermediate Coordinating Center), A. Betriu (International Clinical Coordinator), D. Ardissino, P.W. Armstrong, P. Aylward, E. Bates, K. Beatt, J. Cheseboro, J. Col, S. Ellis, H. Emanuelsson, V. Fuster, W.B. Gibler, J. Gore, A. Guerci, J. Hochman, D. Holmes, N. Kleiman, D. Morris, K. Neuhaus, M. Ohman, M. Pfisterer, H. Phillips, W. Rutsch, J. Simes, M. Simoons, A. Vahanian, W.D. Weaver, and H. White. **Coordinating Center:** *Duke University Medical Center, Durham, N.C.* — *Clinician Coordinators:* C. Granger, H. Phillips, J. Hochrein, and R. Califf; *Coordinators:* B. Fraulo, I. Moffie, and L. Paraschos; *Statisticians:* A. Stebbins, L. Woodlief, K. Lee, and K. Pieper; *Electrocardiographic Core Laboratory:* G.S. Wagner (Director) and K. Gates. **Angiographic Core Laboratory:** *Cleveland Clinic Foundation, Cleveland* — S. Ellis (Director), D. Debowey, R. Poliszczuk, and H. Vilsack. **International:** *Clinical Coordinator:* A. Betriu, Spain; *Coordinators:* A. Luyten, Belgium; L. Tobback, Belgium; M. Kava, Australia; and W. Sutherland, Canada. **Data Safety and Monitoring Committee:** R. Frye (Chairman), M. Cheitlin, D. DeMets, L. Fisher, J. Hirsh, P. Serruys, and L. Walters.

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