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Facilitated PCI in Patients with ST-Elevation Myocardial Infarction

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ABSTRACT

BACKGROUND

We hypothesized that percutaneous coronary intervention (PCI) preceded by early treatment with abciximab plus half-dose reteplase (combination-facilitated PCI) or with abciximab alone (abciximab-facilitated PCI) would improve outcomes in patients with acute ST-segment elevation myocardial infarction, as compared with abciximab administered immediately before the procedure (primary PCI).

METHODS

In this international, double-blind, placebo-controlled study, we randomly assigned patients with ST-segment elevation myocardial infarction who presented 6 hours or less after the onset of symptoms to receive combination-facilitated PCI, abciximab-facilitated PCI, or primary PCI. All patients received unfractionated heparin or enoxaparin before PCI and a 12-hour infusion of abciximab after PCI. The primary end point was the composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomization, cardiogenic shock, and congestive heart failure during the first 90 days after randomization.

RESULTS

A total of 2452 patients were randomly assigned to a treatment group. Significantly more patients had early ST-segment resolution with combination-facilitated PCI (43.9%) than with abciximab-facilitated PCI (33.1%) or primary PCI (31.0%; P=0.01 and P=0.003, respectively). The primary end point occurred in 9.8%, 10.5%, and 10.7% of the patients in the combination-facilitated PCI group, abciximab-facilitated PCI group, and primary-PCI group, respectively (P=0.55); 90-day mortality rates were 5.2%, 5.5%, and 4.5%, respectively (P=0.49).

CONCLUSIONS

Neither facilitation of PCI with reteplase plus abciximab nor facilitation with abciximab alone significantly improved the clinical outcomes, as compared with abciximab given at the time of PCI, in patients with ST-segment elevation myocardial infarction. (ClinicalTrials.gov number, NCT00046228.)

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*The investigators who participated in the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) study are listed in the Appendix.

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Effective and rapid reperfusion is the most important goal in the treatment of patients with acute ST-segment elevation myocardial infarction.[1,2] When feasible and when performed in a timely and expert fashion, primary percutaneous coronary intervention (PCI) is the preferred strategy for reperfusion in the treatment of ST-segment elevation myocardial infarction, because it has been shown to produce superior clinical outcomes as compared with fibrinolytic therapy.[3-13] Primary PCI has not, however, become the treatment of choice in many locales because of logistical difficulties, including the inability to offer this treatment strategy in a timely fashion.

The time to treatment with primary PCI is an important determinant of the clinical outcome among patients who have had an acute myocardial infarction,[14-18] and current guidelines from the American College of Cardiology call for a time of less than 90 minutes from the first medical contact to inflation of the balloon.[19] In the United States, the average door-to-balloon time for patients who require a hospital transfer for PCI is 139 minutes (French WJ: personal communication). Times in Europe vary by country but can be as long as those in the United States.[20-22] Conceptually, the door-to-balloon time may be most important for patients with potentially large infarcts who present early, since they have the most myocardium to salvage.[23]

The question of the optimal pharmacologic therapy for reperfusion before and in conjunction with primary PCI, especially when there is a delay in the initiation of therapy, remains unanswered. Fibrinolytic therapy alone was found to be harmful among patients in the Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) trial (ClinicalTrials.gov number, NCT00168792),[24] possibly owing to the deleterious effects of early activation of platelets by the fibrinolytic agents without effective antiplatelet treatment or plaque hemorrhage at the time of PCI. Glycoprotein IIb/IIIa inhibitors alone, and especially in conjunction with fibrinolytic therapy, have been evaluated in relatively small numbers of patients. The results of these studies have been inconclusive,[25-30] although there is evidence of an increase in major bleeding, particularly among the elderly.[31]

The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) study was designed to test the hypothesis that PCI that is facilitated with the use of a combination of abciximab and reduced-dose reteplase would be more effective than primary PCI, in which abciximab is administered in the catheterization laboratory immediately before PCI. A group for whom PCI was facilitated by abciximab alone was included to help clarify the contribution of this component of the combination therapy to the clinical outcome.

METHODS

PARTICIPANTS

We enrolled patients who presented within 6 hours after the onset of signs and symptoms of cardiac ischemia, who had ST-segment elevation suggestive of an acute myocardial infarction, who were eligible for fibrinolytic therapy or primary PCI, and for whom the estimated time to diagnostic catheterization was 1 to 4 hours after randomization. Details of the study design have been reported previously.[32] Patients were excluded if they were at low risk (i.e., if they were less than 60 years of age and had a localized inferior infarction [ST-segment elevation in the inferior leads only]), if they had received more than the 40 U of heparin per kilogram of body weight that was specified by the protocol (and were therefore at potentially greater risk for bleeding), or if they had any other risk factors for bleeding. The study was approved by the local institutional review boards, and all patients provided written informed consent.

PROCEDURES AND DESIGN

Patients from 20 countries were randomly assigned through a central randomization center, in a 1:1:1 ratio, to receive reteplase plus abciximab (combination-facilitated PCI), abciximab alone (abciximab-facilitated PCI), or placebo (primary PCI). Immediately after randomization, patients in the combination-facilitated–PCI group received intravenous doses of abciximab (0.25 mg per kilogram) and reteplase (two 5-U boluses separated by 30 minutes, for those younger than 75 years of age, or one 5-U dose, for those 75 years of age or older); patients in the abciximab-facilitated–PCI group received an intravenous bolus of abciximab at a dose of 0.25 mg per kilogram.

Before participation in the study, each enrolling center was required to state whether low-molecular-weight heparin or unfractionated heparin would be used as the adjunct antithrombin therapy. To minimize the risk of bleeding, the dose of unfrac-

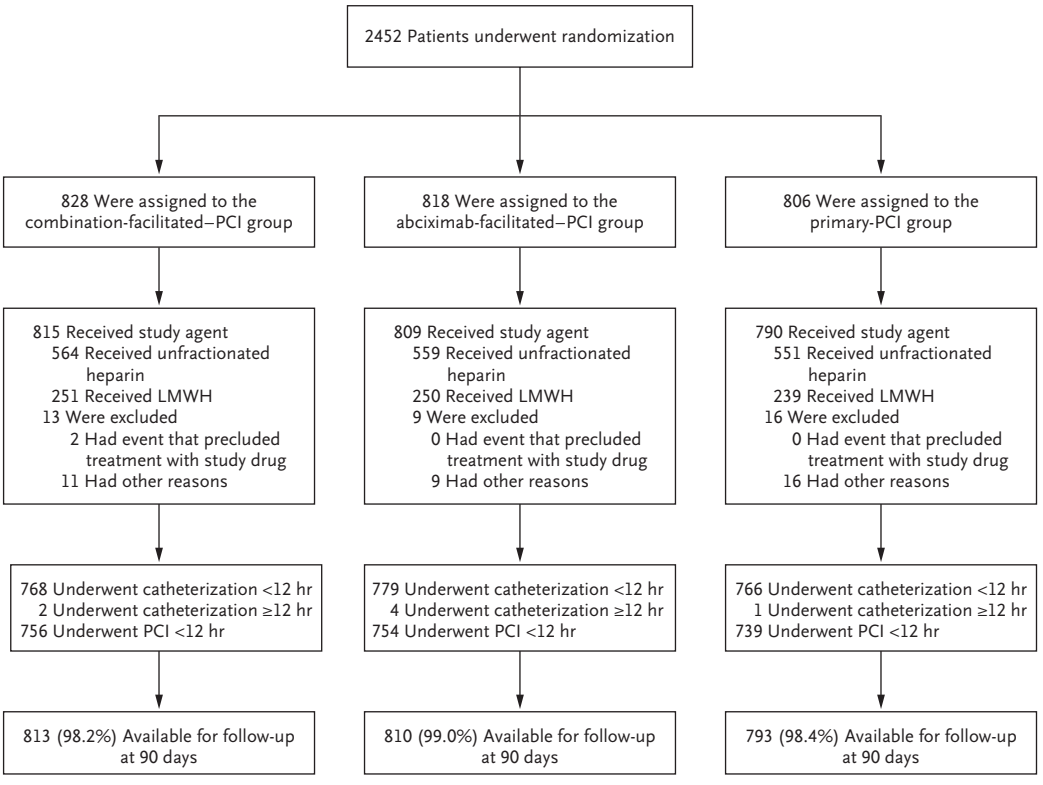

Figure 1. Numbers of Patients Who Underwent Randomization, Received the Assigned Treatment, and Were Available for Follow-up at 90 Days.

LMWH denotes low-molecular-weight heparin, and PCI percutaneous coronary intervention.

tionated heparin was limited to 40 U per kilogram (maximum dose, 3000 U), with a target activated clotting time of 200 to 250 seconds. At sites that participated in the low-molecular-weight–heparin substudy, 0.5 mg of enoxaparin per kilogram was administered intravenously, and 0.3 mg per kilogram was administered subcutaneously, with no target for the activated clotting time. All of the patients received 81 to 325 mg of aspirin orally or 250 to 500 mg intravenously.

No abciximab or heparin infusions were started unless PCI was to be delayed by up to 2 hours. Transfer of the patient to the cardiac catheterization laboratory was expedited, and procedures were performed according to local standards. Immediately before PCI, patients in the placebo (primary-PCI) group received blinded therapy with abciximab (a bolus of 0.25 mg per kilogram delivered intravenously). After PCI, all patients were treated with 0.125 μg of abciximab per kilogram per minute (maximum dose, 10 μg per minute) for 12 hours. "Dummy" placebo medications were administered at all time points to ensure that the study remained blinded.

The primary end point was a composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomization, cardiogenic shock, and congestive heart failure requiring rehospitalization or an emergency room visit through 90 days. Major secondary end points were complications of myocardial infarction through 90 days (as in the primary end point), death from all causes through 90 days, and ST-segment resolution of more than 70% from baseline as assessed at 60 to 90 minutes after randomization. Major safety end points were nonintracranial major or minor bleeding as assessed by the Thrombolysis in Myocardial Infarction (TIMI) classification and intracranial hemorrhage through discharge or day 7, whichever was sooner. Cardiogenic shock, congestive heart failure, and stroke (in all patients), as well as ST-segment resolution (in a randomly selected cohort of 50% of the patients for whom data were available within the

Table 1. Baseline Characteristics of the Patients and Initial Treatment.*

Characteristic and Treatment	Primary PCI (N=806)	Abciximab-Facilitated PCI (N=818)	Combination-Facilitated PCI (N=828)
Female sex — no. (%)	207 (25.7)	216 (26.4)	219 (26.4)
Age — yr	62.5±11.4	61.9±11.8	62.6±11.4
<75 yr — no. (%)	678 (84.1)	695 (85.0)	691 (83.5)
≥75 yr — no. (%)	128 (15.9)	123 (15.0)	137 (16.5)
Race — no. (%)†			
White	786 (97.5)	798 (97.6)	812 (98.1)
Black	4 (0.5)	4 (0.5)	5 (0.6)
Asian	6 (0.7)	6 (0.7)	2 (0.2)
Other	10 (1.2)	10 (1.2)	9 (1.1)
Weight — kg	78.7±13.9	79.6±13.8	78.1±13.5
Body-mass index‡	27.1±4.2	27.3±4.1	27.0±4.0
Family history of CAD (diagnosed at <55 yr of age) — no. (%)	149 (18.5)	187 (22.9)	190 (22.9)
Cigarette smoker — no. (%)			
Past or current	524 (65.0)	549 (67.1)	537 (64.9)
Current	357 (44.3)	363 (44.4)	347 (41.9)
Diabetes — no. (%)			
All patients	133 (16.5)	119 (14.5)	128 (15.5)
Patients treated with insulin	29 (3.6)	28 (3.4)	32 (3.9)
Previous MI — no. (%)	82 (10.2)	80 (9.8)	104 (12.6)
Previous CHF — no. (%)	13 (1.6)	9 (1.1)	12 (1.4)
Hypertension — no. (%)	374 (46.4)	405 (49.5)	394 (47.6)
Hypercholesterolemia — no. (%)			
All patients	276 (34.2)	249 (30.4)	291 (35.1)
Patients treated	131 (16.3)	125 (15.3)	144 (17.4)
Location of infarction — no. (%)§			
Anterior	370 (45.9)	403 (49.3)	400 (48.3)
Inferior or posterior	358 (44.4)	358 (43.8)	378 (45.7)
Other	141 (17.5)	117 (14.3)	110 (13.3)
Not localized	10 (1.2)	4 (0.5)	6 (0.7)
Killip class — no. (%)			
I	713 (88.5)	714 (87.3)	741 (89.5)
II	67 (8.3)	81 (9.9)	68 (8.2)
III	11 (1.4)	6 (0.7)	3 (0.4)
IV	2 (0.2)	0	3 (0.4)
Unknown	13 (1.6)	17 (2.1)	13 (1.6)
Interval from symptom onset to qualifying ECG obtained in the ER — hr			
Median	2.1	2.2	2.1
Interquartile range	1.2–3.3	1.2–3.5	1.3–3.3
Door-to-balloon time — hr			
Median	2.2	2.2	2.2
Interquartile range	1.8–2.8	1.8–2.8	1.8–2.8

Table 1. (Continued.)

Characteristic and Treatment	Primary PCI (N=806)	Abciximab-Facilitated PCI (N=818)	Combination-Facilitated PCI (N=828)
Peak procedural ACT — sec			
Mean	229	230	223
Interquartile range	196–273	200–275	178–262
ACE inhibitors through hospital discharge or day 7 — %	75.1	77.5	76.6
Beta-blockers through hospital discharge or day 7 — %	86.1	86.9	85.0

* Plus–minus values are means ±SD. Percentages do not sum to 100 because of rounding. ACE denotes angiotensin-converting enzyme, ACT activated clotting time, CAD coronary artery disease, CHF congestive heart failure, ECG electrocardiogram, ER emergency room, MI myocardial infarction, and PCI percutaneous coronary intervention.
† Race was reported by the investigator.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Some patients had an infarct that extended to more than one location.

time window), were centrally adjudicated, without knowledge of the assigned treatment. The size of the infarct was estimated on the basis of the area under the curve and the trapezoidal rule for measurements of total creatine kinase levels obtained at baseline and at 8, 16, and 24 hours.

STUDY ORGANIZATION, OVERSIGHT, AND MONITORING

The study protocol was principally designed by three of the authors (Drs. Ellis, Barnathan, and Topol), with assistance from others. The steering committee was responsible for the scientific content of the protocol, oversight of the trial, and the preparation of manuscripts arising from the study. The source documentation for the primary end-point data was verified for all patients. The study was monitored by an independent data and safety monitoring committee, with prespecified data analyses after a 90-day follow-up of 1000 patients. The executive committee received recommendations from the data monitoring committee and rendered decisions regarding the conduct of the study. The Clinical Events Committee of Cleveland Clinic Cardiovascular Coordinating Center adjudicated the clinical end points. The Mayo Clinic ECG Core Laboratory assessed ST-segment resolution in a randomly selected subgroup of 745 patients who had electrocardiograms that could be evaluated for ST-segment resolution at 60 to 90 minutes. Final study data were stored and analyzed separately by the sponsor and the Cleveland Clinic Cardiovascular Coordinating Center. Dr. Ellis wrote the first draft of the manuscript, coordinated edits based on recommendations by the steering committee and other authors, and takes responsibility for the integrity of the data and analysis on behalf of the FINESSE investigators.

STATISTICAL ANALYSIS

All efficacy analyses were conducted on the basis of the intention-to-treat principle. Safety analyses were performed according to the treatment received. A two-sided log-rank test was used to assess the difference in the primary end point between the combination-facilitated–PCI and the primary-PCI groups, assuming a 15% event rate in the primary-PCI group and a relative risk reduction with active treatment of 28% or more at an alpha level of 0.05 (two-sided), at approximately 83% power. One formal interim efficacy analysis evaluated either futility or efficacy ($P<0.001$ on the basis of a two-sided test). A final P value of 0.049 or less was considered to indicate statistical significance. Kaplan–Meier analyses were performed for components of the primary end point. Formal secondary comparisons between combination-facilitated PCI and abciximab-facilitated PCI or between abciximab-facilitated PCI and primary PCI were to be performed if the primary hypothesis was met. Adjustment for multiple comparisons was performed with the use of a modified Hochberg procedure.

Prespecified subgroup analyses to further evaluate the primary efficacy end point included analyses according to sex, age (<75 years vs. ≥75 years), Killip class (I vs. II through IV), presence or absence of a history of diabetes, previous or no previous myocardial infarction, infarct location (anterior vs. nonanterior), geographic location (North America vs. rest of the world), hub site (capable of performing PCI) or spoke site, time

from onset of symptoms to randomization (>3 hours vs. ≤3 hours), PCI performed or not performed, time to balloon inflation (in thirds, from slowest to fastest), unfractionated heparin or low-molecular-weight heparin, and moderate risk or high risk (age >70 years, anterior myocardial infarction, heart rate >100 beats per minute, or Killip class >I); low-risk patients were excluded from the study. All subgroup analyses were considered to be exploratory and descriptive.

PREMATURE TERMINATION OF THE STUDY

Complexities arising from the recruitment of patients in community hospitals and their subsequent transfer to hub centers that had the capability to perform PCI, rapidly changing patterns of patient referral, strict limitations (as specified by the protocol) on the initial dosing of heparin (which was often administered before the patient was considered for study enrollment), and the concern at sites in the United States that the time needed for assignment of patients to study groups would adversely affect the new "quality indicator" of door-to-balloon time led to a recruitment rate that was much slower than expected and to substantial cost overruns. Consequently, the sponsors of the study mandated closure of the study before the planned enrollment of 3000 patients was met. (Data from the meta-analysis by Keeley et al.[25] for combination therapy [involving 194 patients] were perceived to be inconclusive and did not influence this decision.) The steering and executive committees concurred with the decision to terminate the study.

RESULTS

PATIENTS

Between August 2002 and December 2006, a total of 2452 patients were randomly assigned to one of the treatment groups (Fig. 1). Baseline characteristics of the patients and the initial treatments received were similar across all groups (Table 1). At randomization, 66.7% of the patients were considered to be at high risk. Treatment intervals are provided in Table 1 and Figure 2. The median door-to-balloon time for all patients was 2.2 hours (interquartile range, 1.8 to 2.8), and 92.0% of the patients underwent PCI. Data on 90-day follow-up were available for 813 of the patients in the combination-facilitated–PCI group (98.2%), 810 of the patients in the abciximab-facilitated–PCI group (99.0%), and 793 of the patients in the primary-PCI group (98.4%); there were no significant differences among the groups.

EFFICACY

Significantly more patients in the combination-facilitated–PCI group than in the abciximab-facilitated–PCI group or the primary-PCI group had ST-segment resolution that was greater than 70% in 60 to 90 minutes (43.9% vs. 33.1% and 31.0%, respectively; $P=0.003$ for combination-facilitated PCI vs. primary PCI, and $P=0.01$ for combination-facilitated PCI vs. abciximab-facilitated PCI). Significantly more patients in the group that received reteplase plus abciximab than in the group that received abciximab alone or underwent primary PCI had a TIMI flow grade of 3, as determined by the site investigator, before PCI was performed (32.8% vs. 14.1% and 12.0%, respectively; $P<0.001$ for both comparisons). No substantial difference among treatment groups was seen for TIMI flow grade after PCI or for ST-segment resolution at 180 to 240 minutes.

The 90-day primary composite end point occurred in 9.8% of the patients in the combination-facilitated–PCI group, 10.5% of the patients in the abciximab-facilitated–PCI group, and 10.7% of the patients in the primary-PCI group (hazard ratio in the combination-facilitated–PCI group as compared with the primary-PCI group, 0.91; 95% confidence interval [CI], 0.67 to 1.23). Complications of myocardial infarction occurred in 7.4%, 7.5%, and 9.0% of patients in the three groups, respectively, with no significant differences. The individual components of the primary end point did not differ significantly among the combination-facilitated–PCI, abciximab-facilitated–PCI, and primary-PCI groups; the respective rates were 5.2%, 5.5%, and 4.5% for death from all causes; 0.6%, 0.2%, and 0.4% for ventricular fibrillation occurring more than 48 hours after randomization; 5.3%, 4.8%, and 6.8% for cardiogenic shock; and 1.9%, 2.9%, and 2.2% for rehospitalization or an emergency room visit for congestive heart failure. The Kaplan–Meier estimate of the composite primary end point is shown in Figure 3. There were no substantive differences among the subgroups (Fig. 4).

The area under the curve for creatine kinase was significantly reduced with combination-facilitated PCI (1625 IU per liter per hour) as compared with both abciximab-facilitated PCI (1782 IU per

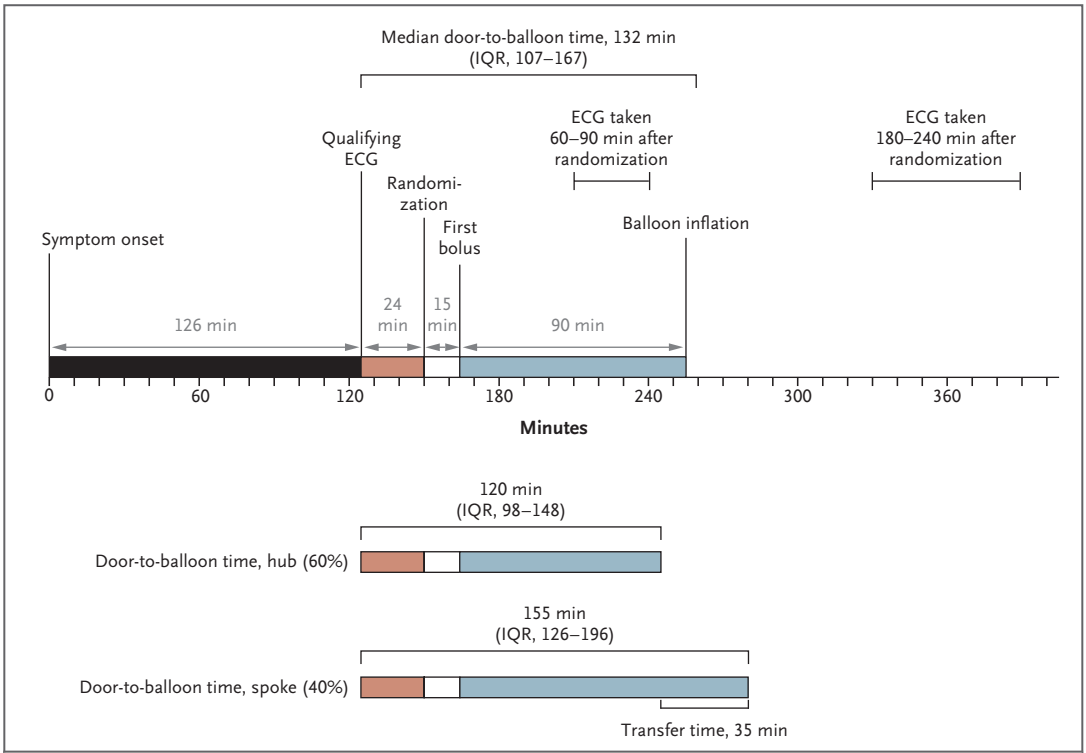

Figure 2. Key Median Treatment Intervals.

Door-to-balloon times are shown according to the type of center: hub (capable of performing PCI) or spoke. ECG denotes electrocardiogram, and IQR interquartile range.

liter per hour) and primary PCI (1860 IU per liter per hour) (P=0.01 and P<0.001, respectively). The combination-facilitated–PCI group did not have improvement over the primary-PCI group for any other secondary efficacy end points (Table 2).

SAFETY

Safety end points, through discharge or day 7, are summarized in Table 3. Nonintracranial TIMI major or minor bleeding, assessed on the basis of the TIMI classification, occurred in 14.5%, 10.1%, and 6.9% of the patients in the combination-facilitated–PCI, abciximab-facilitated–PCI, and primary-PCI groups, respectively (P<0.001 for the comparison of combination-facilitated PCI with primary PCI). Intracranial hemorrhage occurred in 0.6% of the patients in the combination-facilitated–PCI group (four patients with cerebral hemorrhage and one with cerebral infarction and major hemorrhage), no patients in the abciximab-facilitated–PCI group, and 0.1% of the patients in the primary-PCI group (one patient with cerebral infarction with hemorrhagic transformation); ischemic stroke occurred in 0.5% of the patients in each of the facilitated groups and in 0.9% of the patients in the primary-PCI group. Three fatal strokes occurred, all in the combination-facilitated–PCI group; two involved intracranial hemorrhage and one was ischemic. No intracranial hemorrhages occurred in patients who were 75 years of age or older. Overall, there was a graded increase in the rates of bleeding, intracranial hemorrhage, and transfusions in the PCI-facilitated groups. In all three treatment groups combined, the rate of death was associated with the extent of bleeding (18.2% with TIMI major bleeding, 6.1% with TIMI minor bleeding, and 2.6% with little or no bleeding; P<0.001).

DISCUSSION

A therapy for acute ST-segment elevation myocardial infarction that could initiate reperfusion before PCI without increasing complications might be expected to provide a clinical benefit. To date, however, trials that have tested the concept of "fa-

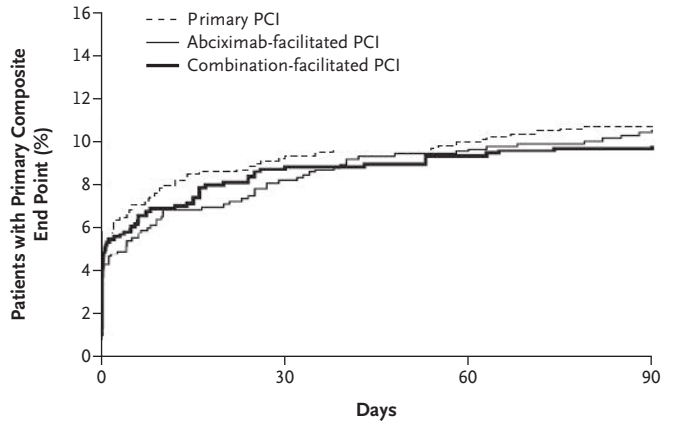

Figure 3. Kaplan–Meier Estimates of the Proportion of Patients with the Composite End Point.

The composite end point included death from all causes and complications of myocardial infarction from randomization through day 90. Data are shown for all patients randomly assigned to a treatment group. P=0.55 for the comparison of primary percutaneous coronary intervention (PCI) with reteplase-plus-abciximab–facilitated (combination-facilitated) PCI. P=0.86 for the comparison of primary PCI with abciximab-facilitated PCI. P=0.68 for the comparison of abciximab-facilitated PCI with combination-facilitated PCI.

cilitated angioplasty" with fibrinolytic agents and glycoprotein IIb/IIIa inhibitors have been limited by small numbers of enrollees, the risk of bleeding among patients receiving the therapy, enrollment of a low-risk cohort, and perhaps an excess risk associated with PCI.[25-27] Our trial, which enrolled 2452 patients, addressed several of these shortcomings but did not show any significant reduction in the combined clinical end point at 90 days with treatment with abciximab plus reteplase (hazard ratio, 0.91; 95% CI, 0.67 to 1.23). Furthermore, the incidence of major hemorrhage was increased. Treatment with early abciximab alone had no benefit and was also associated with a trend toward increased bleeding.

Previous studies have suggested that the addition of a combination of reduced-dose fibrinolytic therapy and glycoprotein IIb/IIIa inhibitors would improve early TIMI flow and ST-segment resolution as compared with treatment with aspirin and antithrombin therapy alone.[26-29,33] The results of our trial confirm these observations. Significantly greater TIMI 3 flow before PCI and ST-segment resolution 60 to 90 minutes after the initiation of treatment were seen in the group that received treatment with abciximab plus reteplase as compared with the groups that received placebo or abciximab alone.

The question remains, then, why enhanced early reperfusion did not significantly improve clinical outcomes. At least four reasons can be postulated. First, as summarized by Gersh et al.,[23] differences in the time to reperfusion may affect major myocardial salvage only during approximately the first 2 hours after the onset of infarction, an interval that is shorter than that in which many patients can be treated; after 2 hours, the time-dependency of PCI-mediated salvage may be considerably attenuated. Treatment was initiated 3 hours or less after the onset of symptoms in only 60% of the patients in our study, and among these patients, there was a very modest trend toward more clinical benefit from treatment with abciximab plus reteplase (hazard ratio for the composite end point, 0.83; 95% CI, 0.56 to 1.21) as compared with patients who presented later (hazard ratio, 1.12; 95% CI, 0.67 to 1.86).

Second, studies by Schömig et al.,[34] Brodie et al.,[35] Kastrati et al.,[36] and Pinto et al.[37] suggest that the importance of the timing of treatment for myocardial salvage may not be as great with PCI as it is with thrombolysis. That being the case, in most instances, opening the infarct-related artery 30 to 60 minutes earlier with pharmacologic therapy than with PCI alone would not be expected to provide a dramatic benefit.

Third, as suggested by Antoniucci et al.[18] and Brodie et al.,[38] only high-risk patients are likely to have a major benefit from early reperfusion with PCI. Indeed, among the patients in our study who were classified as being at high risk (those older than 70 years of age and those with anterior myocardial infarction, Killip class >I, or a presenting heart rate >100 beats per minute), accounting for 67% of all the patients in the study, there was a weak trend toward a greater benefit of combined therapy, as compared with treatment with primary PCI, with abciximab administered in the catheterization laboratory immediately before PCI (hazard ratio for the composite end point, 0.84; 95% CI, 0.60 to 1.17), whereas there was no benefit for lower-risk patients (hazard ratio, 1.22; 95% CI, 0.56 to 2.63). These subgroup analyses should not, however, be used to justify the use of combination-facilitated PCI in higher-risk patients, given the absence of an effect on mortality and the excess bleeding observed in this study.

Fourth, the rates of major complications and of death among patients with ST-segment elevation myocardial infarction who are undergoing primary PCI with adjunctive abciximab are quite low and

Subgroup	Primary PCI	Combination-Facilitated PCI	Hazard Ratio (95% Confidence Interval)
	no. (%)		
All patients	806 (10.7)	828 (9.8)	0.91 (0.67–1.23)
Sex			
Female	207 (17.0)	219 (13.3)	0.76 (0.47–1.25)
Male	599 (8.6)	609 (8.6)	1.00 (0.68–1.48)
Age			
≥75 yr	128 (20.5)	137 (16.1)	0.76 (0.43–1.35)
<75 yr	678 (8.9)	691 (8.6)	0.96 (0.67–1.38)
Baseline Killip class			
>I	80 (21.3)	74 (23.0)	1.09 (0.56–2.13)
I	713 (9.7)	741 (8.0)	0.81 (0.57–1.15)
History of diabetes mellitus			
Yes	133 (12.8)	128 (13.4)	1.05 (0.54–2.06)
No or unknown	673 (10.3)	700 (9.2)	0.88 (0.63–1.24)
Previous myocardial infarction			
Yes	82 (9.9)	104 (19.3)	2.07 (0.91–4.69)
No or unknown	724 (10.8)	724 (8.5)	0.77 (0.55–1.08)
Infarct location			
Anterior	370 (14.4)	400 (11.8)	0.80 (0.54–1.19)
Not anterior	436 (7.6)	428 (8.0)	1.05 (0.65–1.70)
Geographic location			
North America	72 (8.3)	56 (7.1)	0.85 (0.24–3.02)
Rest of the world	734 (11.0)	772 (10.0)	0.91 (0.67–1.24)
Site			
Hub	489 (9.9)	488 (9.2)	0.93 (0.62–1.40)
Spoke	317 (12.0)	340 (10.7)	0.88 (0.56–1.39)
Time from symptom onset to randomization			
>3 hr	310 (9.0)	318 (10.1)	1.12 (0.67–1.86)
≤3 hr	492 (11.7)	508 (9.7)	0.83 (0.56–1.21)
Time from qualifying ECG to balloon inflation			
Slowest third	250 (8.1)	255 (10.3)	1.31 (0.73–2.34)
Middle third	254 (10.3)	219 (6.9)	0.66 (0.35–1.25)
Fastest third	233 (11.2)	275 (11.3)	0.99 (0.59–1.67)
Time from symptom onset to balloon inflation			
Slowest third	242 (7.5)	240 (8.8)	1.18 (0.63–2.21)
Middle third	248 (10.9)	265 (10.3)	0.94 (0.55–1.60)
Fastest third	245 (11.1)	244 (9.9)	0.88 (0.51–1.52)
Index PCI performed			
Yes	740 (9.8)	758 (9.8)	1.00 (0.72–1.39)
No	66 (21.2)	70 (10.0)	0.45 (0.18–1.12)
PCI delay due to low risk			
Yes	0 (0.0)	0 (0.0)	—
No	740 (9.8)	758 (9.8)	1.00 (0.72–1.39)
Enrollment in LMWH substudy			
Yes	246 (8.2)	258 (10.5)	1.29 (0.72–2.30)
No	560 (11.8)	570 (9.5)	0.80 (0.56–1.14)
High risk			
Yes	523 (14.2)	555 (12.1)	0.84 (0.60–1.17)
No	283 (4.3)	273 (5.1)	1.22 (0.56–2.63)

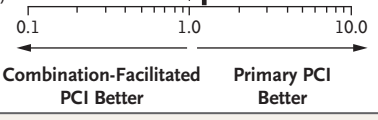

Figure 4. Results of Prespecified Subgroup Analysis for the Primary End-Point Comparison.

P>0.10 for all subgroup interaction analyses except for an interaction of treatment with prior myocardial infarction (P=0.02) and PCI performed (P=0.09). For the time from ECG or symptom onset to balloon inflation, the 1st third is the shortest interval. ECG denotes electrocardiogram, LMWH low-molecular-weight heparin, and PCI percutaneous coronary intervention.

Table 2. Additional Efficacy End Points through 90 Days.*

End Point	Primary PCI (N=806)	Abciximab-Facilitated PCI (N=818)	Combination-Facilitated PCI (N=828)
		number (percent)	
Atrial fibrillation or flutter	46 (5.7)	43 (5.3)	40 (4.8)
Asystole	10 (1.2)	6 (0.7)	18 (2.2)
Second- or third-degree atrioventricular block	19 (2.4)	22 (2.7)	9 (1.1)
Electromechanical dissociation or pulseless electrical activity	8 (1.0)	6 (0.7)	6 (0.7)
Heart failure (index hospitalization)	52 (6.5)	45 (5.5)	54 (6.5)
Myocardial rupture	2 (0.2)	5 (0.6)	5 (0.6)
Papillary muscle rupture	1 (0.1)	0	0
Pericarditis or pericardial effusion	15 (1.9)	12 (1.5)	15 (1.8)
Any subsequent revascularization	111 (13.8)	111 (13.6)	111 (13.4)
Percutaneous coronary intervention	78 (9.7)	85 (10.4)	81 (9.8)
Coronary-artery bypass grafting	37 (4.6)	26 (3.2)	31 (3.7)
Recurrent myocardial infarction	15 (1.9)	16 (2.0)	17 (2.1)
Severe recurrent ischemia requiring urgent IRA revascularization	15 (1.9)	8 (1.0)	12 (1.4)
Sustained ventricular tachycardia	20 (2.5)	10 (1.2)	19 (2.3)
Tamponade	2 (0.2)	5 (0.6)	2 (0.2)
Ventricular septal defect	0	2 (0.2)	0

* IRA denotes infarct-related artery, and PCI percutaneous coronary intervention.

therefore difficult to improve. One concern at the initiation of the study was that combination therapy might not be given sufficient time to be effective if PCI were undertaken quickly. A subgroup analysis that evaluated the time from randomization to balloon inflation does not substantiate this concern.

Finally, the lack of benefit from the early administration of abciximab as compared with administration in the catheterization laboratory with respect to major clinical end points is consistent with the results of systematic overviews.[25,27]

These findings should be considered in the context of certain limitations of the study. First, it was terminated prematurely owing to slow enrollment, for reasons noted above. However, the early termination was unlikely to have changed the outcome of the study. Given the observed results in 2452 enrolled patients, there was less than a 2% chance that the primary treatment-group difference would be significant if the trial continued, assuming a relative benefit of 27% for the remainder of the 3000 patients. In addition, the study was originally powered on the basis of an assumed event rate of 15% in the primary-PCI group. One might argue, therefore, that the trial should more aptly be described as inconclusive. However, in light of recent data from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) study, which showed a strong relationship of in-hospital bleeding with long-term mortality,[39] it seems unlikely that the combination therapy as it was administered in the FINESSE study will be adopted in clinical practice because of the major risk of bleeding associated with this therapy (occurring in more than 25 of 1000 patients treated) relative to the reduction in the ischemic composite end point (9 of 1000 patients treated). Furthermore, the results apply only to the patient population we studied. Whether a different population of patients would have had a different response is a matter of conjecture, but as noted, the results of secondary analyses should be considered as only hypothesis-generating.

In summary, the use of a facilitated pharmacologic strategy for reperfusion, with either abciximab alone or abciximab plus reduced-dose reteplase, in anticipation of urgent PCI for patients

Table 3. Safety End Points through Discharge or Day 7.*

End Point	Primary PCI (N=795)	Abciximab-Facilitated PCI (N=805)	Reteplase/Abciximab-Facilitated PCI (N=814)
Nonintracranial TIMI bleeding, major or minor — no. (%)	55 (6.9)	81 (10.1)†	118 (14.5)†
Major	21 (2.6)	33 (4.1)	39 (4.8)†
Minor	34 (4.3)	48 (6.0)	79 (9.7)†
Stroke — no. (%)	8 (1.0)	4 (0.5)	9 (1.1)
Intracranial hemorrhage	1 (0.1)	0	5 (0.6)
Ischemic	7 (0.9)	4 (0.5)	4 (0.5)
Transfusions — no. (%)	24 (3.0)	31 (3.9)	52 (6.4)†
Packed red cells or whole blood	19 (2.4)	28 (3.5)	46 (5.7)†
Platelets	13 (1.6)	7 (0.9)	11 (1.4)
Thrombocytopenia — no./total no. (%)			
<100,000 platelets/mm^3	31/794 (3.9)	40/800 (5.0)	36/810 (4.4)
<50,000 platelets/mm^3	11/795 (1.4)	16/805 (2.0)	16/814 (2.0)
<20,000 platelets/mm^3	4/795 (0.5)	8/805 (1.0)	5/814 (0.6)

* PCI denotes percutaneous coronary intervention, and TIMI Thrombolysis in Myocardial Infarction.
† P<0.05 for the comparison with primary PCI.

with an ST-segment elevation myocardial infarction cannot be justified by the results of this trial. Primary PCI with abciximab administered in the catheterization laboratory provides a better benefit-to-risk ratio than the two facilitated strategies among patients with ST-segment elevation myocardial infarction who can undergo PCI within 4 hours after the first medical contact. The limitations of these facilitated approaches should provide further impetus both to develop triage systems that can shorten the door-to-balloon time for high-quality primary PCI when impediments to rapid PCI exist[40-42] and to evaluate other treatment strategies.

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