

## ORIGINAL ARTICLE

# Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction

Paul W. Armstrong, M.D., Anthony H. Gershlick, M.D., Patrick Goldstein, M.D., Robert Wilcox, M.D., Thierry Danays, M.D., Yves Lambert, M.D., Vitaly Sulimov, M.D., Ph.D., Fernando Rosell Ortiz, M.D., Ph.D., Miodrag Ostojic, M.D., Ph.D., Robert C. Welsh, M.D., Antonio C. Carvalho, M.D., Ph.D., John Nanas, M.D., Ph.D., Hans-Richard Arntz, M.D., Ph.D., Sigrun Halvorsen, M.D., Ph.D., Kurt Huber, M.D., Stefan Grajek, M.D., Ph.D., Claudio Fresco, M.D., Erich Bluhmki, M.D., Ph.D., Anne Regelin, Ph.D., Katleen Vandenberghe, Ph.D., Kris Bogaerts, Ph.D., and Frans Van de Werf, M.D., Ph.D., for the STREAM Investigative Team\*

## ABSTRACT

**BACKGROUND**

It is not known whether prehospital fibrinolysis, coupled with timely coronary angiography, provides a clinical outcome similar to that with primary percutaneous coronary intervention (PCI) early after acute ST-segment elevation myocardial infarction (STEMI).

**METHODS**

Among 1892 patients with STEMI who presented within 3 hours after symptom onset and who were unable to undergo primary PCI within 1 hour, patients were randomly assigned to undergo either primary PCI or fibrinolytic therapy with bolus tenecteplase (amended to half dose in patients  $\geq 75$  years of age), clopidogrel, and enoxaparin before transport to a PCI-capable hospital. Emergency coronary angiography was performed if fibrinolysis failed; otherwise, angiography was performed 6 to 24 hours after randomization. The primary end point was a composite of death, shock, congestive heart failure, or reinfarction up to 30 days.

**RESULTS**

The primary end point occurred in 116 of 939 patients (12.4%) in the fibrinolysis group and in 135 of 943 patients (14.3%) in the primary PCI group (relative risk in the fibrinolysis group, 0.86; 95% confidence interval, 0.68 to 1.09;  $P=0.21$ ). Emergency angiography was required in 36.3% of patients in the fibrinolysis group, whereas the remainder of patients underwent angiography at a median of 17 hours after randomization. More intracranial hemorrhages occurred in the fibrinolysis group than in the primary PCI group (1.0% vs. 0.2%,  $P=0.04$ ; after protocol amendment, 0.5% vs. 0.3%,  $P=0.45$ ). The rates of nonintracranial bleeding were similar in the two groups.

**CONCLUSION**

Prehospital fibrinolysis with timely coronary angiography resulted in effective reperfusion in patients with early STEMI who could not undergo primary PCI within 1 hour after the first medical contact. However, fibrinolysis was associated with a slightly increased risk of intracranial bleeding. (Funded by Boehringer Ingelheim; ClinicalTrials.gov number, NCT00623623.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Van de Werf at the Department of Cardiovascular Sciences, University Hospitals Leuven, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium, or at frans.vandewerf@med.kuleuven.be.

\*Committees and investigators for the Strategic Reperfusion Early after Myocardial Infarction (STREAM) study are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on March 10, 2013, at NEJM.org.

N Engl J Med 2013.

DOI: 10.1056/NEJMoa1301092

Copyright © 2013 Massachusetts Medical Society.

**A**LTHOUGH CONTEMPORARY GUIDELINES for patients with acute ST-segment elevation myocardial infarction (STEMI) recommend primary percutaneous coronary intervention (PCI) as the preferred reperfusion strategy, this approach is contingent on performing PCI in a timely fashion.<sup>1,2</sup> Since most patients do not present to a PCI-capable hospital, this factor presents a major logistic challenge in many regions.<sup>3</sup> Despite substantial effort directed toward addressing this issue, the large majority of patients with STEMI who present to non-PCI facilities do not subsequently receive primary PCI within guideline-recommended times.<sup>4</sup> This delay results in a commensurate increase in morbidity and mortality.<sup>5,6</sup>

A second major therapeutic challenge is the persisting delay from the time of symptom onset to hospital presentation.<sup>7</sup> This factor has spawned major advances in prehospital care that include the performance of prehospital electrocardiography, the delivery of prehospital fibrinolysis, and the informed triage of such patients to PCI-capable hospitals when appropriate.<sup>7</sup> In our trial, called the Strategic Reperfusion Early after Myocardial Infarction (STREAM) study, we evaluated whether a fibrinolytic-therapy approach consisting of prehospital or early fibrinolysis with contemporary antiplatelet and anticoagulant therapy, coupled with timely coronary angiography, provides a clinical outcome similar to that with primary PCI in patients with STEMI who present early after symptom onset.

## METHODS

### STUDY DESIGN AND OVERSIGHT

The design of this open-label, prospective, randomized, parallel-group, multicenter trial has been reported previously.<sup>8</sup> The study organization is provided in the Supplementary Appendix (available with the protocol and the full text of this article at NEJM.org). Study data were collected with an electronic-record form and were managed by Pierrel Research independent of the sponsor (Boehringer Ingelheim). Final data were transferred to the University of Leuven, Belgium, for independent statistical analysis. The first and last authors wrote the first draft of the manuscript, and the executive and steering committees participated in writing subsequent drafts. The last author vouches for the accuracy of the data and for the fidelity of this report to the study proto-

col. The decision to submit the manuscript for publication was made by the executive committee and approved by the sponsor. The study protocol was approved by national regulatory authorities as well as the local ethics committee at each study center.

### PATIENTS

Patients were eligible for enrollment if they presented within 3 hours after the onset of symptoms, had evidence of acute STEMI on their qualifying electrocardiogram (at least 2 mm in two contiguous peripheral or precordial leads), and could not undergo primary PCI within 1 hour after the first medical contact. With an emphasis on prehospital randomization, patients who were initially treated medically received tenecteplase along with antiplatelet and anticoagulant therapy, followed by coronary angiography within 6 to 24 hours. In the event that there was less than 50% ST-segment resolution in the single lead with maximum elevation or clinical evidence of failed reperfusion within 90 minutes after fibrinolysis, rescue coronary intervention was performed. All patients provided written informed consent.

### STUDY THERAPIES

We compared the fibrinolytic strategy with primary PCI performed according to guideline-based local practice, with early use of concomitant antiplatelet and anticoagulant medications, as well as additional discretionary glycoprotein IIb/IIIa antagonists. Tenecteplase was administered in a weight-based dose (30 mg if the weight was 55 to <60 kg, 35 mg if the weight was 60 to <70 kg, 40 mg if the weight was 70 to <80 kg, 45 mg if the weight was 80 to <90 kg, and 50 mg if the weight was ≥90 kg) and was combined with low-molecular-weight enoxaparin (30-mg intravenous bolus followed by subcutaneous injection of 1 mg per kilogram of body weight [0.75 mg per kilogram for patients ≥75 years of age] every 12 hours) except for patients 75 years of age or older, in whom the intravenous bolus was omitted. Antiplatelet therapy consisted of clopidogrel in a 300-mg loading dose (omitted for patients ≥75 years of age) followed by 75 mg daily and aspirin (150 to 325 mg) immediately followed by 75 to 325 mg daily. Urgent coronary angiography in the fibrinolysis group was permitted at any time in the presence of hemodynamic or electrical instability, worsening ischemia, or progressive or sustained

ST-segment elevation requiring immediate coronary intervention, according to the investigator's judgment.

Randomization was performed by an interactive voice-response system. All patients were transferred to a PCI-capable hospital; for all non-PCI community hospitals participating in the study, a well-developed hub-and-spoke relationship with a PCI-capable site was required. All strokes were centrally adjudicated by a stroke review panel whose members were unaware of study-group assignments.

#### PRIMARY END POINT

The primary end point of the trial was a 30-day composite of death from any cause, shock, congestive heart failure, or reinfarction. Single efficacy end points as well as safety end points consisting of ischemic stroke, intracranial hemorrhage, nonintracranial bleeding, and other serious clinical events were recorded and are defined in the Supplementary Appendix.

#### STATISTICAL ANALYSIS

A sample size of 1000 patients per study group was planned, and the rate of the primary end point in the primary PCI group was projected to be 15.0%.<sup>8</sup> After 21% of the ultimate population had been enrolled, the executive committee, with the advice of the data and safety monitoring board, amended the protocol on August 24, 2009, to reduce the dose of tenecteplase by 50% in patients 75 years of age or older because of an excess of intracranial hemorrhage in that age group. This approach was informed by a previous study by Larsen et al.<sup>9</sup> In addition, at that time, in order to better align the electrocardiographic entry criteria with contemporary STEMI trials, the inclusion criterion for inferior myocardial infarction was changed from an ST-segment elevation of at least 3 mm in two contiguous inferior leads to an elevation of at least 2 mm.

This trial was designed as a proof-of-concept study. All statistical tests were of an exploratory nature. Baseline characteristics are reported as means ( $\pm$ SD) or numbers and percentages, as appropriate. Time differences are reported as medians and interquartile ranges and compared by means of a Wilcoxon test. We analyzed efficacy and safety end points by calculating the event rates for each study group and comparing them using relative risks with two-sided 95%

confidence intervals obtained by means of a Poisson regression model with robust error variance. For the primary end point, we also performed prespecified subgroup analyses according to age, sex, Killip class, time to randomization, place of randomization, infarct location, systolic blood pressure, weight, status with respect to a history of diabetes or hypertension, Thrombolysis in Myocardial Infarction (TIMI) risk score, and randomization before or after adoption of the protocol amendment. We evaluated the interactions between treatment and subgroups. For the primary end point, we also compared Kaplan-Meier curves using a log-rank test.

An observed case analysis was performed except for analyses in which there was a proportion of missing data of more than 1% and for which a multiple imputation analysis was performed. The imputation model was based on baseline characteristics together with all single efficacy and safety end points. All analyses were performed on an intention-to-treat basis with the use of either SAS software, version 9.2, or R software (aregImpute function in the Hmisc package).<sup>10</sup> P values are provided for descriptive purposes only.

## RESULTS

#### PATIENTS

From March 19, 2008, to July 26, 2012, we enrolled 1915 patients at 99 sites in 15 countries (Fig. S1 in the Supplementary Appendix). A total of 1892 patients underwent randomization and provided written informed consent. In the fibrinolysis group, 4 patients were lost to follow-up, and 1 patient withdrew consent. In the primary PCI group, 2 patients were lost to follow-up. Most patients (81%) underwent randomization in an ambulance setting. Baseline characteristics were similar, except that previous congestive heart failure was more frequent in patients in the primary PCI group (Table 1).

The median time delay from the onset of symptoms to first medical contact and randomization was similar in the two study groups. The median times between symptom onset and start of reperfusion therapy (bolus tenecteplase or arterial sheath insertion) were 100 minutes and 178 minutes, respectively ( $P < 0.001$ ). As expected, the median time from randomization to angiography was longer in the fibrinolysis group than in the primary PCI group, with a delay of 2.2 hours for

**Table 1. Characteristics of the Patients at Baseline and Key Time Intervals.\***

Characteristic	Fibrinolysis (N=944)	Primary PCI (N=948)	P Value†
<b>Age</b>			
Mean — yr	59.7±12.4	59.6±12.5	0.86
≥75 yr — no. (%)	134 (14.2)	121 (12.8)	0.36
Female sex — no. (%)	194 (20.6)	208 (21.9)	0.46
Weight — kg	80.5±14.8	80.0±14.9	0.49
<b>Killip class — no./total no. (%)</b>			
I	842/895 (94.1)	844/894 (94.4)	
II or III	52/895 (5.8)	47/894 (5.3)	
IV	1/895 (0.1)	3/894 (0.3)	
Heart rate — beats/min	74.9±18.4	75.5±18.1	0.48
Systolic blood pressure (mm Hg)	135.0± 22.7	135.9±23.3	0.38
<b>Infarct location — no./total no. (%)</b>			
Anterior	453/942 (48.1)	431/946 (45.6)	
Inferior	468/942 (49.7)	497/946 (52.5)	
Other	21/942 (2.2)	18/946 (1.9)	
<b>Cardiovascular history — no./total no. (%)</b>			
Previous congestive heart failure	3/939 (0.3)	16/945 (1.7)	0.004
Previous PCI	60/942 (6.4)	83/944 (8.8)	0.06
Previous myocardial infarction	81/940 (8.6)	98/947 (10.3)	0.20
Previous coronary-artery bypass grafting	2/944 (0.2)	3/946 (0.3)	0.99
Hypertension	434/930 (46.7)	414/932 (44.4)	0.33
Diabetes	113/934 (12.1)	123/939 (13.1)	0.51
<b>Median time delay (interquartile range) — min</b>			
Symptom onset to first medical contact: ambulance or emergency department	62 (40–100)	61 (35–100)	0.36
Symptom onset to randomization	91 (68–132)	92 (65–132)	0.89
Symptom onset to hospital admission	150 (110–202)	140 (100–185)	<0.001
Randomization to arrival in catheterization laboratory	483 (135–1140)	67 (45–98)	<0.001
Randomization to arterial sheath insertion	492 (148–1157)	77 (57–112)	<0.001
Symptom onset to arrival in catheterization laboratory	600 (245–1235)	170 (125–220)	<0.001
Symptom onset to start of reperfusion treatment: tenecteplase or arterial sheath insertion‡	100 (75–143)	178 (135–230)	<0.001

\* Plus-minus values are means ±SD.

† P values were calculated with the use of a t-test, an exact test, or a Wilcoxon test, as appropriate.

‡ Median time delays for patients who underwent randomization in an ambulance setting were 96 minutes for the fibrinolysis group and 165 minutes for the primary PCI group; median values for patients who underwent randomization in a community hospital were 130 minutes and 230 minutes, respectively.

the 36% of patients who required rescue or urgent intervention and 17 hours for the remaining 64% of patients.

#### PRIMARY END POINTS

The primary end point (death from any cause, shock, congestive heart failure, or reinfarction up to 30 days) occurred in 116 of 939 patients (12.4%) in the fibrinolysis group and 135 of 943

patients (14.3%) in the primary PCI group (relative risk in the fibrinolysis group, 0.86; 95% confidence interval [CI], 0.68 to 1.09; P=0.21) (Fig. 1). The 95% confidence interval of the relative risk in the fibrinolysis group would exclude a relative increase of 9% (or an absolute increase of 1.1 percentage points) as compared with the primary PCI group. The incidence of the primary end point in the prespecified subgroups was generally similar

to the overall result (Fig. 2). No significant treatment interactions were found.

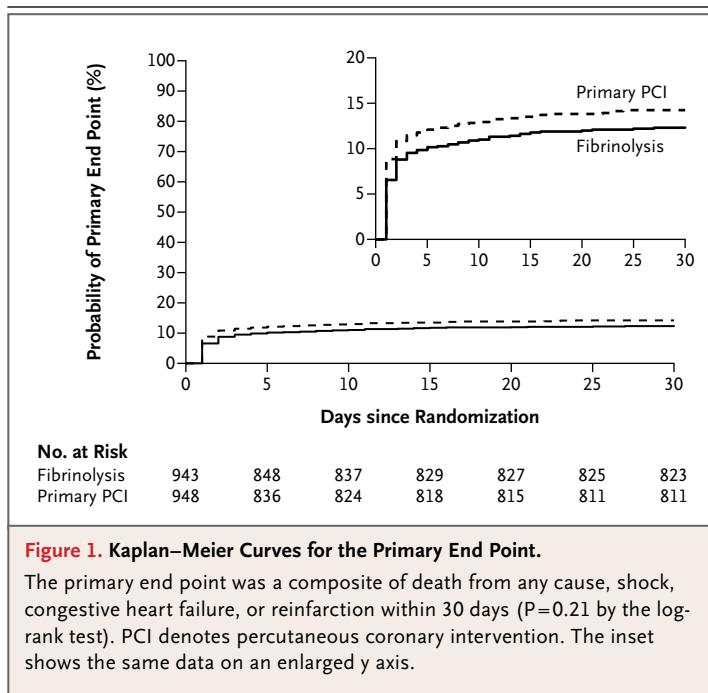
The individual components of the primary end point, other major clinical end points, and interventions up to 30 days are shown in Table 2. Cardiogenic shock and congestive heart failure tended to occur more frequently in the primary PCI group than in the fibrinolysis group. For other clinical end points, the rates in the two groups were very similar. Significantly more open vessels were found on first angiography before PCI in the fibrinolysis group than in the primary PCI group (Table 2).

Among patients in whom urgent angiography was required, the target vessel showed TIMI flow grade 0 or 1 in 46.5% of patients. Among patients who underwent nonurgent angiography, TIMI flow grades 2 and 3 were present in 13.2% and 72.8% of patients, respectively. After PCI, patency rates were high and almost identical in the two study groups. Of those undergoing PCI, 96% in the two groups received one or more stents. Overall, significantly more bypass surgeries and fewer PCIs were performed in the fibrinolysis group than in the PCI group.

Rates of stroke were low in the two study groups, but both intracranial hemorrhagic and primary ischemic strokes were more frequent in the fibrinolysis group than in the primary PCI group (Table 3). After the dose reduction of tecteplase in patients 75 years of age or older, there were no cases of intracranial hemorrhage (0 of 97 patients), as compared with 3 of 37 patients (8.1%) in this age group before the amendment. The rate of major nonintracranial bleeding was 6.5% in the fibrinolysis group, and 4.8% in the primary PCI group, a difference that was not significant (P=0.11). The rates of blood transfusions were also similar in the two study groups (2.9% and 2.3%, respectively; P=0.47).

DISCUSSION

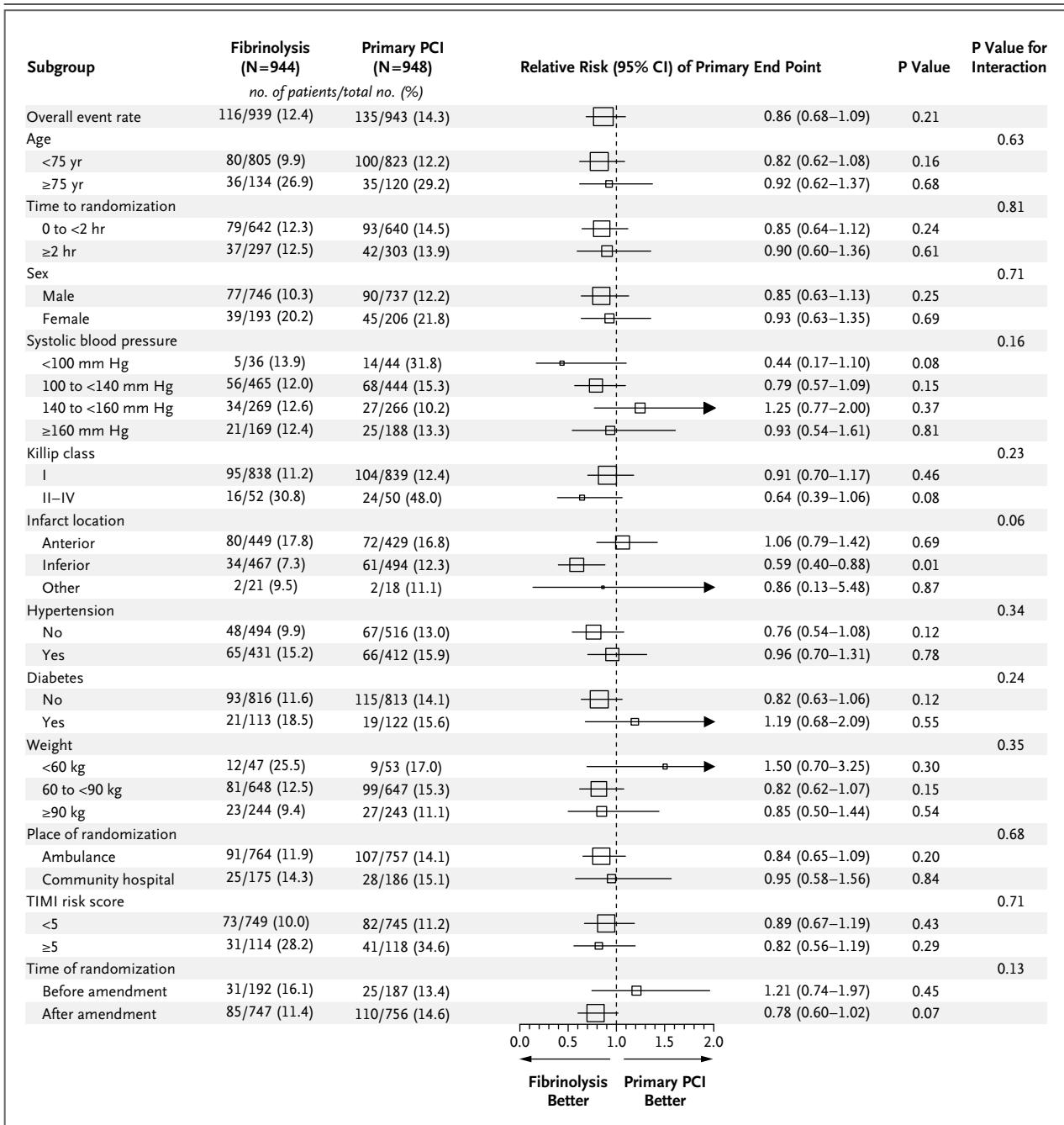
In this study, patients with STEMI who presented early after symptom onset with an ST-segment elevation of at least 2 mm in two contiguous leads had similar rates of the primary composite end point of death, shock, congestive heart failure, or reinfarction at 30 days, regardless of whether they underwent prehospital fibrinolysis or primary PCI. This outcome was consistent across prespecified subgroups.



**Figure 1. Kaplan–Meier Curves for the Primary End Point.**  
The primary end point was a composite of death from any cause, shock, congestive heart failure, or reinfarction within 30 days (P=0.21 by the log-rank test). PCI denotes percutaneous coronary intervention. The inset shows the same data on an enlarged y axis.

Our strategy resulted in remarkably short delay times from symptom onset to each of the two reperfusion approaches, with an expected between-group delay of more than 1 hour for primary PCI, as compared with fibrinolytic therapy. It is interesting to compare the times from symptom onset until reperfusion in our study with those in analogous treatment groups in the Danish Trial in Acute Myocardial Infarction 2 (DANAMI-2),<sup>11</sup> the largest previous clinical trial that favored primary PCI over in-hospital fibrinolysis. In our study, the median times until reperfusion were 100 minutes in the fibrinolysis group and 178 minutes in the primary PCI group, which are more than 1 hour shorter than the corresponding times reported in DANAMI-2. Moreover, the interval between fibrinolytic therapy and primary PCI in DANAMI-2 was substantially shorter than that observed in our study.

Each therapy in our study was delivered with contemporary adjunctive medical therapy. Diligent protocol-mandated use of urgent angiography in approximately one third of the patients in the fibrinolysis group, combined with angiography within 24 hours followed by additional revascularization, if indicated, in the remainder of the patients, probably contributed to the overall satisfactory clinical result. The more frequent performance of coronary bypass surgery among



**Figure 2. Subgroup Analyses.**

Shown are the rates of the primary end point among patients undergoing early fibrinolysis or primary PCI. The size of each square is proportional to the number of patients in the comparison. The arrows indicate that the upper limit of the 95% confidence interval is more than 2.0. The overall rate of the primary end point is provided for patients who were 75 years of age or older, although the study protocol was amended to reduce the dose of tenecteplase by 50% because of an excess of intracranial hemorrhage in this age group. Before the amendment, among patients in this age group, the rate of the primary end point was 29.7% in the fibrinolysis group and 31.3% in the primary PCI group; after the amendment, the rates were 25.8% and 28.4%, respectively. The Thrombolysis in Myocardial Infarction (TIMI) risk score ranges from 0 to 10, with higher scores indicating greater risk. In cases of missing data for more than 1% of patients, a multiple imputation analysis (100 imputations) was performed, so all percentages may not have been calculated with the use of simple fractions.

**Table 2. Clinical Efficacy End Points, Angiographic Findings, and Procedures Performed within 30 Days.\***

Variable	Fibrinolysis (N=944)	Primary PCI (N=948)	P Value
	<i>no./total no. (%)</i>		
<b>End Point</b>			
Primary composite end point: death, shock, congestive heart failure, or reinfarction at 30 days	116/939 (12.4)	135/943 (14.3)	0.21
Death from any cause	43/939 (4.6)	42/946 (4.4)	0.88
Cardiogenic shock	41/939 (4.4)	56/944 (5.9)	0.13
Congestive heart failure	57/939 (6.1)	72/943 (7.6)	0.18
Reinfarction	23/938 (2.5)	21/944 (2.2)	0.74
Death from cardiovascular causes	31/939 (3.3)	32/946 (3.4)	0.92
Rehospitalization for cardiac causes	45/939 (4.8)	41/943 (4.3)	0.64
<b>TIMI blood flow on angiography†</b>			
Before PCI			<0.001
0	141/884 (16.0)	534/900 (59.3)	
1	88/884 (10.0)	91/900 (10.1)	
2	138/884 (15.6)	89/900 (9.9)	
3	517/884 (58.5)	186/900 (20.7)	
After PCI			0.41
0	18/819 (2.2)	24/884 (2.7)	
1	12/819 (1.5)	11/884 (1.2)	
2	43/819 (5.3)	33/884 (3.7)	
3	746/819 (91.1)	816/884 (92.3)	
<b>Procedure</b>			
Urgent coronary angiography	331/911 (36.3)	NA	
PCI	736/915 (80.4)	838/933 (89.8)	<0.001
Coronary-artery bypass grafting after study angiography or PCI	44/943 (4.7)	20/947 (2.1)	0.002
Stent placement	704/736 (95.7)	801/838 (95.6)	0.95

\* NA denotes not applicable.

† The level of coronary blood flow was measured with the use of Thrombolysis in Myocardial Infarction (TIMI) grade flow, a scoring system ranging from 0 to 3, as follows: 0, absence of antegrade flow beyond a coronary occlusion; 1, faint antegrade coronary flow beyond the occlusion with incomplete filling of the distal coronary bed; 2, delayed or sluggish antegrade flow with complete filling of the distal coronary bed; and 3, normal flow that completely fills the distal coronary bed.

patients in the fibrinolysis group is probably related to the nonurgent circumstances in which the angiography was performed and revascularization decisions were made. We observed lower rates of shock and heart failure, as well as more complete surgical coronary revascularization, among the patients undergoing fibrinolysis.

The increased risk of intracranial bleeding in the fibrinolysis group among patients 75 years of age or older was recognized promptly after approximately one fifth of our planned enrollment

and led to a reduction in the dose of tenecteplase in these patients, with an acceptable subsequent safety profile in this age group.

It is useful to reflect on our findings in the context of the Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) trial, which evaluated facilitated fibrinolysis versus primary PCI. That study was terminated early because of an excess of strokes and early thrombotic complications when mandatory routine

**Table 3. Strokes and Nonintracranial Bleeding Events within 30 Days.**

Event	Fibrinolysis (N=944)	Primary PCI (N=948)	P Value
	no./total no. (%)		
Total strokes	15/939 (1.6)	5/946 (0.5)	0.03
Intracranial hemorrhage			
Any	9/939 (1.0)	2/946 (0.2)	0.04
After protocol amendment*	4/747 (0.5)	2/758 (0.3)	0.45
Primary ischemic stroke			
Without hemorrhagic conversion	5/939 (0.5)	3/946 (0.3)	0.51
With hemorrhagic conversion	1/939 (0.1)	0/946	0.50
Nonintracranial bleeding			
Major	61/939 (6.5)	45/944 (4.8)	0.11
Minor	205/939 (21.8)	191/944 (20.2)	0.40
Blood transfusion	27/937 (2.9)	22/943 (2.3)	0.47

\* On August 24, 2009, the study protocol was amended to reduce the dose of tenecteplase by 50% in patients 75 years of age or older because of an excess of intracranial hemorrhage in this age group.

PCI was undertaken within 1 to 3 hours after fibrinolysis, regardless of evidence of successful reperfusion.<sup>12</sup> In addition, unlike the use of adjunctive therapies in our trial, which were specified in the protocol, suboptimal use of adjunctive antiplatelet and anticoagulant therapies were reported in the ASSENT-4 PCI trial. Our findings are supported by other trials in which lytic therapy was administered very early after symptom onset<sup>13</sup> and was combined with frequent additional revascularization.<sup>14</sup>

Our study has some strengths and limitations that deserve attention. No single prospective study of adequate size has previously addressed this relevant and common patient population at such an early stage in its evolution. We chose a moderate-sized sample and an exploratory statistical approach without a primary hypothesis, after taking into account various challenges in undertaking the study, including available funding, a global shift toward primary PCI, and the capacity for prehospital randomization and administration of fibrinolytic therapy. Because we excluded patients with STEMI who were able to undergo primary PCI within 1 hour after the first medical contact, our findings do not apply to this population. Similarly, we cannot comment on the applicability of our findings to patients with STEMI who present more than 3 hours after symptom onset or who do not have the specific characteristics for inclusion in our study.

Our objective was to compare the two reperfusion strategies aligned with current guidelines in patients with early STEMI who had a substantial amount of myocardium at risk and for whom immediate PCI was not possible. We prespecified our intent to portray our composite end point with 95% confidence limits and found that patients in the fibrinolysis group had a relative risk of the primary end point of 0.86 (95% CI, 0.68 to 1.09), as compared with the primary PCI group. On the basis of our findings, applied post hoc, the 95% confidence interval of the relative risk of the primary end point in the fibrinolysis group would exclude a relative increase of 9% (or an absolute increase of 1.1 percentage points), as compared with the primary PCI group. Although our study did not prespecify noninferiority boundaries, it is noteworthy that generally accepted proportional margins for noninferiority trials currently fall in the range of 15 to 20%.<sup>15</sup>

In summary, we found that a strategic alignment of prehospital or early fibrinolysis and contemporary antithrombotic cotherapy coupled with timely coronary angiography resulted in effective reperfusion in patients with STEMI who presented within 3 hours after symptom onset and who could not undergo PCI within 1 hour after the first medical contact. However, early fibrinolysis was associated with a slightly increased risk of intracranial bleeding.

Supported by Boehringer Ingelheim.

Dr. Armstrong reports receiving consulting fees from Eli Lilly, Merck, and Roche, payment for the development of educational presentations from AstraZeneca and Eli Lilly, and grant support through his institution from Merck; Dr. Goldstein, serving as a board member for Eli Lilly, Daiichi Sankyo, and the Medicines Company and receiving consulting fees from Eli Lilly, Daiichi Sankyo, the Medicines Company, and AstraZeneca, lecture fees from Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, AstraZeneca, the Medicines Company, Sanofi, and Bayer, and payment for the development of educational presentations from AstraZeneca and Boehringer Ingelheim; Dr. Wilcox, being a board member for and receiving consulting fees through his institution from Schering-Plough, Eli Lilly, Daiichi Sankyo, and AstraZeneca; Drs. Danays, Bluhmki, and Regelin, being employees of Boehringer Ingelheim; Dr. Lambert, receiving lecture fees from Boehringer Ingelheim; Dr. Sulimov, receiving lecture fees from Boehringer Ingelheim, Sanofi-Aventis, AstraZeneca, Bayer, Bristol-Myers Squibb, and Abbott; Dr. Rosell Ortiz, receiving lecture fees from Daiichi Sankyo and AstraZeneca; Dr. Welsh, receiving consulting fees from AstraZeneca, Eli Lilly, Roche, Medtronic, and Bayer, lecture fees from AstraZeneca and Eli Lilly, grant support from AstraZeneca and Edwards Lifesciences, and payment for the development of educational presentations from Bayer, AstraZeneca, and Eli Lilly; Dr. Nanas, receiving payment from Novartis, Sanofi-Aventis, and Actelion as principal investigator and to his institution for each patient enrolled in a multicenter trial; Dr. Halvorsen, receiving lecture fees from Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Boehringer Ingelheim, and Bayer, travel reimbursement from Bristol-Myers Squibb, Eli Lilly,

and Bayer, and payment for the development of educational presentations from AstraZeneca; Dr. Grajek, receiving consulting fees and payment for manuscript preparation from AstraZeneca and Servier, lecture fees from AstraZeneca, Servier, and Bayer, and payment for the development of educational presentations from AstraZeneca, Servier, Bayer, Merck, Sanofi-Aventis, and Berlin-Chemie; Dr. Fresco, receiving consulting fees from Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and the Medicines Company and lecture fees from Boehringer Ingelheim, Eli

Lilly, the Medicines Company, Pfizer, Bristol-Myers Squibb, and AstraZeneca; Dr. Bogaerts, receiving consulting fees through his institution from Boehringer Ingelheim; and Dr. Van de Werf, receiving consulting and lecture fees from Boehringer Ingelheim and grant support through his institution from Boehringer Ingelheim. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

#### APPENDIX

The authors' affiliations are as follows: the Canadian Virtual Coordinating Centre for Global Collaborative Cardiovascular Research (P.W.A.) and Mazankowski Alberta Heart Institute (R.C.W.), University of Alberta, Edmonton, Canada; National Institute for Health Research, Leicester Cardiovascular Biomedical Research Unit, University Hospitals of Leicester Trust, Leicester (A.H.G.), and the Department of Cardiovascular Medicine, University of Nottingham, Nottingham (R.W.) — both in the United Kingdom; the Emergency Department and Service d'aide Medicale Urgente (SAMU), Lille University Hospital, Lille (P.G.), Boehringer Ingelheim, Reims (T.D.), and Centre Hospitalier de Versailles, SAMU 78 and Mobile Intensive Care Unit, Versailles (Y.L.) — all in France; the Department of Internal Diseases, First Moscow State Medical University, Moscow (V.S.); Empresa Pública de Emergencias Sanitarias, Almería, Spain (F.R.O.); Medical School, University of Belgrade, Belgrade, Serbia (M.O.); Cardiology Division, Department of Medicine, Federal University of São Paulo, São Paulo (A.C.C.); 3rd Department of Cardiology, University of Athens, Athens (J.N.); Charité, Benjamin Franklin Medical Center, Berlin (H.-R.A.); the Department of Cardiology, Oslo University Hospital Ullevål, Oslo (S.H.); 3rd Department of Medicine, Cardiology and Emergency Medicine, Wilhelminenhospital, Vienna (K.H.); the Department of Cardiology, Karol Marcinkowski University of Medical Science, Poznan, Poland (S.G.); the Department of Cardiothoracic Sciences, Azienda Ospedaliero Universitaria di Udine, Udine, Italy (C.F.); Boehringer Ingelheim, Biberach, Germany (E.B.); Boehringer Ingelheim, Basel, Switzerland (A.R.); and the Department of Cardiovascular Sciences (K.V., F.V.W.) and Interuniversity Institute for Biostatistics and Statistical Bioinformatics (K.B.), KU Leuven, Leuven, and University Hasselt, Hasselt (K.B.) — both in Belgium.

#### REFERENCES

1. Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569-619.
2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61(4):e78-e140.
3. Armstrong PW, Boden WE. Reperfusion paradox in ST-segment elevation myocardial infarction. *Ann Intern Med* 2011;155:389-91.
4. Roe MT, Messenger JC, Weintraub WS, et al. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J Am Coll Cardiol* 2010;56:254-63.
5. Terkelsen CJ, Sørensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA* 2010;304:763-71.
6. Pinto DS, Frederick PD, Chakraborti AK, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. *Circulation* 2011;124:2512-21.
7. Armstrong PW, Westerhout CM, Welsh RC. Duration of symptoms is the key modulator of the choice of reperfusion for ST-elevation myocardial infarction. *Circulation* 2009;119:1293-303.
8. Armstrong PW, Gershlick A, Goldstein P, et al. The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study. *Am Heart J* 2010;160(1):30.e1-35.e1.
9. Larson DM, Duval S, Sharkey SW, et al. Safety and efficacy of a pharmacoinvasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. *Eur Heart J* 2012;33:1232-40.
10. Harrell FE Jr. Hmisc: Harrell Miscellaneous — R package, version 3.8-3. 2010 (<http://cran.r-project.org/package=Hmisc>).
11. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;349:733-42.
12. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;367:569-78.
13. Brouwer MA, Martin JS, Maynard C, et al. Influence of early prehospital thrombolysis on mortality and event-free survival (the Myocardial Infarction Triage and Intervention [MITI] Randomized Trial). *Am J Cardiol* 1996;78:497-502.
14. Westerhout CM, Bonnefoy E, Welsh RC, Steg PG, Boutitie F, Armstrong PW. The influence of time from symptom onset and reperfusion strategy on 1-year survival in ST-elevation myocardial infarction: a pooled analysis of an early fibrinolytic strategy versus primary percutaneous coronary intervention from CAPTIM and WEST. *Am Heart J* 2011;161:283-90.
15. Kaul S, Diamond GA, Weintraub WS. Trials and tribulations of non-inferiority: the ximelagatran experience. *J Am Coll Cardiol* 2005;46:1986-95.

Copyright © 2013 Massachusetts Medical Society.