

ORIGINAL ARTICLE

Thrombolysis during Resuscitation for Out-of-Hospital Cardiac Arrest

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ABSTRACT

BACKGROUND

Approximately 70% of persons who have an out-of-hospital cardiac arrest have underlying acute myocardial infarction or pulmonary embolism. Therefore, thrombolysis during cardiopulmonary resuscitation may improve survival.

METHODS

In a double-blind, multicenter trial, we randomly assigned adult patients with witnessed out-of-hospital cardiac arrest to receive tenecteplase or placebo during cardiopulmonary resuscitation. Adjunctive heparin or aspirin was not used. The primary end point was 30-day survival; the secondary end points were hospital admission, return of spontaneous circulation, 24-hour survival, survival to hospital discharge, and neurologic outcome.

RESULTS

After blinded review of data from the first 443 patients, the data and safety monitoring board recommended discontinuation of enrollment of asystolic patients because of low survival, and the protocol was amended. Subsequently, the trial was terminated prematurely for futility after enrolling a total of 1050 patients. Tenecteplase was administered to 525 patients and placebo to 525 patients; the two treatment groups had similar clinical profiles. We did not detect any significant differences between tenecteplase and placebo in the primary end point of 30-day survival (14.7% vs. 17.0%; $P=0.36$; relative risk, 0.87; 95% confidence interval, 0.65 to 1.15) or in the secondary end points of hospital admission (53.5% vs. 55.0%, $P=0.67$), return of spontaneous circulation (55.0% vs. 54.6%, $P=0.96$), 24-hour survival (30.6% vs. 33.3%, $P=0.39$), survival to hospital discharge (15.1% vs. 17.5%, $P=0.33$), or neurologic outcome ($P=0.69$). There were more intracranial hemorrhages in the tenecteplase group.

CONCLUSIONS

When tenecteplase was used without adjunctive antithrombotic therapy during advanced life support for out-of-hospital cardiac arrest, we did not detect an improvement in outcome, in comparison with placebo. (ClinicalTrials.gov number, NCT00157261.)

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OUT-OF-HOSPITAL CARDIAC ARREST IS A major public health concern. According to one estimate, 155,000 persons have an out-of-hospital cardiac arrest annually in the United States, of whom less than 10% survive.¹ These statistics underscore a need for improvement in cardiopulmonary-resuscitation strategies.

Cardiac arrest is caused by acute myocardial infarction or pulmonary embolism in approximately 70% of out-of-hospital cases,^{2,3} and cardiac arrest itself activates systemic coagulation.⁴ Thrombolytic therapy during cardiopulmonary resuscitation can dissolve intravascular blood clots and has beneficial effects on cerebral microcirculatory reperfusion⁵; it may therefore improve survival⁶ and neurologic recovery⁷ after cardiac arrest. In a previous randomized, controlled trial, no advantage could be shown for thrombolysis in patients with pulseless electrical activity,⁸ but a recent meta-analysis suggested that thrombolysis during cardiopulmonary resuscitation can improve the rate of survival to discharge and neurologic function.⁹ Although thrombolytic therapy in general is associated with an increased bleeding rate, the data currently available do not indicate that it contributes to an increase in risk when administered during cardiopulmonary resuscitation.¹⁰

Current cardiopulmonary-resuscitation guidelines state that thrombolytic therapy should be considered in adult patients who have cardiac arrest with pulmonary embolism but that there are insufficient data to make a recommendation for or against the use of thrombolysis in cardiac arrest from other causes.^{11,12} We therefore performed a prospective, multicenter trial to determine whether thrombolysis with the use of tenecteplase during cardiopulmonary resuscitation can improve survival in adults with witnessed out-of-hospital arrest of presumed cardiac origin.

METHODS

STUDY DESIGN

We performed this prospective, placebo-controlled, double-blind, randomized trial in 66 emergency-medical-service (EMS) systems in Austria, Belgium, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and Switzerland. The study protocol was approved by the institutional review boards of all participating centers. The requirement for informed consent before enrollment was waived in accordance with national legal regula-

tions, ethics standards of local institutional review boards, and guidelines for good clinical practice of the European Agency for the Evaluation of Medicinal Products.¹³ Surviving patients, patients' families, or legal representatives were informed about the trial and retrospectively provided written informed consent.

Funding for this trial and the matching study drug and placebo were provided by Boehringer Ingelheim. The sponsor and the executive committee were responsible for the design and conduct of the trial; analysis of the data was performed by two of the academic authors. The academic authors vouch for the integrity and completeness of the data and analyses.

STUDY PATIENTS

Patients eligible for inclusion in the study were adults with witnessed out-of-hospital cardiac arrest of presumed cardiac origin and with initiation of basic or advanced life support within 10 minutes after collapse. The exclusion criteria were suspected noncardiac cause of the arrest, known internal bleeding, neurologic impairment, coagulation disorders, pregnancy, participation in any other clinical study, hypersensitivity to the study medication, institutionalization of the patient, or any other condition that the investigator believed would place the patient at increased risk if included in the trial. Treatment with open-label thrombolytic therapy rather than randomization into the trial was permitted for cases in which pulmonary embolism was suspected to be the cause of the cardiac arrest.

STUDY PROCEDURES

On receipt of an emergency call for suspected cardiac arrest, the EMS dispatching center dispatched a mobile intensive care unit (ICU) (an EMS vehicle equipped with advanced cardiac life-support capability) to the scene. All mobile-ICU personnel participating in this trial had been trained in the conduct of the study protocol. On arrival, staff of the mobile ICU determined whether basic life support was being performed and initiated advanced cardiac life-support measures. At the same time, one member of the team evaluated the patient for eligibility for the trial.

If the selection criteria were met, patients presenting with asystole or pulseless electrical activity as the initial electrocardiographic rhythm underwent randomization immediately after in-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Tenecteplase Group (N=525)	Placebo Group (N=525)	P Value
Age — yr	64.9±13.2	64.7±13.7	0.82
Body-mass index†	27.3±4.2	27.1±4.3	0.30
	<i>no./total no. (%)</i>		
Female sex	108/518 (20.8)	110/514 (21.4)	0.89
Race‡			0.25
White	490/501 (97.8)	480/498 (96.4)	
Other	11/501 (2.2)	18/498 (3.6)	
Medical history			
Current or former smoker	249/360 (69.2)	238/352 (67.6)	0.72
Hypertension	250/484 (51.7)	218/477 (45.7)	0.08
Acute coronary syndrome	179/481 (37.2)	169/483 (35.0)	0.51
Hyperlipidemia	133/479 (27.8)	112/466 (24.0)	0.22
Diabetes	109/482 (22.6)	96/477 (20.1)	0.39
Heart failure	90/479 (18.8)	102/479 (21.3)	0.38
Respiratory disorder	85/480 (17.7)	84/476 (17.6)	>0.99
Arrhythmias	82/475 (17.3)	93/475 (19.6)	0.40
Neurologic disorder	55/479 (11.5)	68/474 (14.3)	0.22
Long-term medication			
Angiotensin-converting-enzyme inhibitor	156/454 (34.4)	138/440 (31.4)	0.38
Aspirin	135/455 (29.7)	132/446 (29.6)	>0.99
Beta-blocker	129/452 (28.5)	121/440 (27.5)	0.79
Statin	108/454 (23.8)	86/440 (19.5)	0.14
Calcium-channel blocker	59/450 (13.1)	62/437 (14.2)	0.71
Coumarin or warfarin	46/450 (10.2)	43/441 (9.8)	0.90
Antiarrhythmic drug	39/450 (8.7)	38/442 (8.6)	>0.99
Clopidogrel or ticlopidine	27/450 (6.0)	15/441 (3.4)	0.10

* Plus-minus values are means ±SD.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Race was determined by the investigators.

travenous cannulation. Patients with ventricular fibrillation or pulseless ventricular tachycardia underwent randomization if up to three initial defibrillation attempts failed to achieve the return of spontaneous circulation. The treatment assignments of study drugs were randomly generated and stratified according to individual mobile ICU in blocks of four to ensure proper randomization at any time.

When a patient underwent randomization, either tenecteplase, dosed according to estimated body weight (30 mg for patients weighing less than 60 kg, 35 mg for patients weighing between

60 kg and 69 kg, 40 mg for patients weighing between 70 kg and 79 kg, 45 mg for patients weighing between 80 kg and 89 kg, and 50 mg for patients weighing 90 kg or more), or matching placebo (Boehringer Ingelheim) was injected intravenously during ongoing cardiopulmonary resuscitation by the mobile ICU team. If required, cardiopulmonary resuscitation according to international guidelines¹⁴ was continued for at least 30 minutes after administration of the study drug. Subsequent care, including transport to the hospital, followed standard EMS practice. Heparin was not allowed during cardiopulmonary resus-

Table 2. Number of Minutes from Collapse to Event and from Randomization to Event.*

Interval	Tenecteplase Group (N=525)		Placebo Group (N=525)		P Value
	no. of patients	median no. of minutes (interquartile range)	no. of patients	median no. of minutes (interquartile range)	
From collapse to:					
Emergency call	357	1 (0–3)	369	1 (0–3)	0.92
Basic-life-support CPR	385	2 (0–7)	365	2 (0–5)	0.39
Dispatch of EMS unit	385	3 (2–5)	398	3 (2–6)	0.70
Arrival of EMS unit	450	9 (6–12)	455	9 (6–12)	0.49
Advanced-life-support CPR	507	9 (6–13)	510	9 (6–12)	0.86
First defibrillation attempt	346	12 (8–16)	353	11 (8–16)	0.67
Intubation of the trachea	492	13 (9–17)	495	13 (9–17)	0.79
Intravenous access	481	14 (10–18)	483	14 (10–18)	0.82
First vasopressor injection	484	14 (10–18)	496	14 (10–18)	0.55
Randomization	513	16 (12–20)	512	17 (11–21)	0.55
Administration of study drug	483	18 (14–23)	485	18 (13–23)	0.94
From randomization to:					
Return of spontaneous circulation	259	8 (4–14)	246	10 (5–15)	0.18
Hospital admission	274	36 (25–53)	279	35 (25–50)	0.22

* CPR denotes cardiopulmonary resuscitation, and EMS emergency medical services.

citation, and its use was discouraged until hospital admission, unless it was considered mandatory for further treatment. For patients undergoing percutaneous coronary intervention within 12 hours after randomization, glycoprotein IIb/IIIa antagonists were not permitted; the use of clopidogrel or ticlopidine and aspirin was discouraged unless they were considered mandatory.

STUDY END POINTS

All trial data were documented according to the Utstein style.¹⁵ The primary end point was 30-day survival; the secondary end points were hospital admission, return of spontaneous circulation, 24-hour survival, survival to hospital discharge, and neurologic outcome of surviving patients.¹⁶ Neurologic outcome was categorized according to cerebral performance category, with level 1 indicating good cerebral performance and level 5 indicating brain death.¹⁷ The safety end points were symptomatic intracranial hemorrhage or major bleeding complications that were considered life-threatening or fatal or that led to hemodynamic compromise requiring intervention. Safety assessments included all complications occurring until hospital discharge or day 30, whichever came first.

The original trial data were reviewed during the

study by an independent data and safety monitoring board. Planned data reviews by the data and safety monitoring board were to take place after approximately 50, 100, 200, 400, and 800 patients had been recruited. However, no formal statistical assessments of efficacy, safety, or futility were planned in advance and no a priori criteria were formulated for amending the design or stopping the trial prematurely. Instead, the decisions of the data and safety monitoring board, including decisions to obtain specific interim analyses, were based on review of the observed data. During the trial, the data and safety monitoring board did not reveal any of the results to the investigators.

STATISTICAL ANALYSIS

On the basis of a multicenter trial in patients with cardiac arrest,¹⁸ it was estimated that 30-day survival in the placebo group would be about 10%. It was calculated that 1000 patients would be needed for the trial, on the assumption of a drug-related improvement in outcome of 7 percentage points (the assumed risk difference), a significance level of 0.05 (for a two-tailed analysis), and a power of approximately 90%. Trial recruitment began on January 24, 2004.

A blinded review of the data by the data and

Table 3. Circumstances of Cardiac Arrest and Patient Treatment.*

Variable	Tenecteplase Group (N=525) <i>no./total no. (%)</i>	Placebo Group (N=525) <i>no./total no. (%)</i>	P Value
Presumed cause of cardiac arrest			<0.01
Acute myocardial infarction	377/504 (74.8)	343/501 (68.5)	
Primary arrhythmia	65/504 (12.9)	82/501 (16.4)	
Pulmonary embolism	30/504 (6.0)	55/501 (11.0)	
Other cardiac cause	32/504 (6.3)	21/501 (4.2)	
Initial electrocardiographic rhythm			0.79
Ventricular fibrillation	283/516 (54.8)	272/514 (52.9)	
Pulseless electrical activity	112/516 (21.7)	125/514 (24.3)	
Pulseless ventricular tachycardia	8/516 (1.6)	7/514 (1.4)	
Asystole	113/516 (21.9)	110/514 (21.4)	
Basic-life-support CPR performed before arrival of advanced-life-support team			0.09
None	115/517 (22.2)	144/514 (28.0)	
By relatives or bystanders	157/517 (30.4)	150/514 (29.2)	
By professional rescuers	245/517 (47.4)	220/514 (42.8)	
Arrest witnessed by EMS personnel	100/517 (19.3)	85/512 (16.6)	0.29
Defibrillation administered by first responders	116/516 (22.5)	123/514 (23.9)	0.63
Drugs given during or after CPR in the out-of-hospital setting			
Epinephrine (adrenaline)	498/516 (96.5)	501/514 (97.5)	0.47
Atropine	257/517 (49.7)	244/514 (47.5)	0.51
Amiodarone	190/517 (36.8)	201/514 (39.1)	0.48
Sodium bicarbonate	205/517 (39.7)	181/514 (35.2)	0.16
Lidocaine	41/517 (7.9)	51/514 (9.9)	0.31
Aspirin	45/517 (8.7)	44/514 (8.6)	>0.99
Vasopressin	31/517 (6.0)	35/514 (6.8)	0.69
Heparin	26/517 (5.0)	33/514 (6.4)	0.41
Postresuscitation interventions			
Percutaneous coronary intervention	62/269 (23.0)	74/252 (29.4)	0.12
Coronary-artery bypass grafting	6/242 (2.5)	4/234 (1.7)	0.79

* CPR denotes cardiopulmonary resuscitation, and EMS emergency medical services.

safety monitoring board considered the results from the first 443 enrolled patients, with 30-day survival data available for 300 patients, on December 21, 2004. On the basis of this review, an ad hoc recommendation was made to discontinue enrollment of asystolic patients because of an extremely low 30-day survival rate in this subgroup (1 of 103). The study protocol was then amended accordingly. The number of patients to be enrolled was increased to 1300 to maintain the power of the study after an increase of 15% in the expected

survival rate in the placebo group. The significance level was reduced to 0.045, because a non-negligible alpha penalty of 0.005 was deemed reasonable.

Subsequently, on observing nearly identical survival rates in the two treatment groups, the data and safety monitoring board requested that a formal futility analysis be performed. With the use of data from 653 patients who were evaluated (after 209 patients with asystole had been excluded and a total of 1014 patients had undergone randomization), futility analyses performed on March

Table 4. Outcomes.				
Outcome	Tenecteplase Group (N = 525) no./total no. (%)	Placebo Group (N = 525) no./total no. (%)	Relative Risk (95% CI)	P Value
Primary end point				
30-Day survival	77/525 (14.7)	89/525 (17.0)	0.87 (0.65–1.15)	0.36
Secondary end points				
Return of spontaneous circulation	283/515 (55.0)	279/511 (54.6)	1.01 (0.90–1.13)	0.96
Hospital admission	281/525 (53.5)	289/525 (55.0)	0.97 (0.87–1.09)	0.67
24-Hr survival	158/517 (30.6)	171/514 (33.3)	0.92 (0.77–1.10)	0.39
Survival to hospital discharge	78/517 (15.1)	90/514 (17.5)	0.86 (0.65–1.14)	0.33
Neurologic outcome*				0.69
Good cerebral performance	41/86 (47.7)	45/96 (46.9)	1.02 (0.75–1.38)	
Moderate cerebral disability	13/86 (15.1)	9/96 (9.4)	1.12 (0.88–1.42)	
Severe cerebral disability	10/86 (11.6)	16/96 (16.7)	1.02 (0.86–1.21)	
Coma	14/86 (16.3)	18/96 (18.8)	0.99 (0.90–1.08)	
Brain death	8/86 (9.3)	8/96 (8.3)	1.00	
Safety end points				
Symptomatic intracranial hemorrhage	4/518 (0.8)	0/514	8.93 (0.48–165.45)	0.13
Any intracranial hemorrhage	14/518 (2.7)	2/514 (0.4)	6.95 (1.59–30.41)	0.006
Major nonintracranial hemorrhage	40/517 (7.7)	33/514 (6.4)	1.21 (0.77–1.88)	0.48
Ischemic stroke	4/518 (0.8)	3/514 (0.6)	1.32 (0.30–5.88)	1.00

* Neurologic outcome is measured by cerebral performance category; categories range from 1 to 5, with 1 indicating good cerebral performance and 5 indicating brain death. The relative risks and associated 95% confidence intervals (CIs) are based on cumulative rates.

20, 2006, yielded conditional power for a successful completion of the study of less than 1%. The data and safety monitoring board therefore recommended suspension of the trial on March 23, 2006, and the executive committee immediately directed all investigators to stop enrolling patients. At a final meeting on July 4, 2006, on the basis of the results for all 1050 patients who had undergone randomization, the data and safety monitoring board recommended that the trial be stopped. The final decision by the executive committee to follow the recommendation of the data and safety monitoring board was made on July 15, 2006.

Baseline characteristics are reported as means \pm SD, medians with interquartile ranges, or percentages, as appropriate. Analysis of the primary end point was performed with the log-rank test. All secondary end points were analyzed with a continuity-corrected chi-square test. Nine prespecified subgroup analyses¹⁶ and one post hoc subgroup analysis were performed. Missing end-point

data were imputed according to a worst-case scenario. All analyses were performed with the use of SAS software, version 8.02.

RESULTS

PATIENT CHARACTERISTICS

From January 24, 2004, to March 23, 2006, a total of 1050 patients were enrolled in the trial. Of these, 525 were assigned to tenecteplase and 525 to placebo. Fifty-eight patients (29 assigned to tenecteplase and 29 assigned to placebo) did not receive the study drug; in 33 of these 58 patients (18 assigned to receive tenecteplase and 15 assigned to receive placebo), the return of spontaneous circulation had already occurred; in 19 (8 and 11, respectively), exclusion criteria were detected after randomization; and in 6 (3 and 3, respectively), the study drug was not administered for other, miscellaneous reasons.

The two trial groups were similar in almost all

respects with regard to clinical profile, event intervals, and concomitant medications before and during cardiopulmonary resuscitation (Tables 1, 2, and 3). The mean age of the patients was 65 years, and 21.1% were women. The median time from collapse to administration of study drug was 18 minutes. Acute myocardial infarction was the assumed cause of cardiac arrest in a larger proportion of the tenecteplase group than of the placebo group; this was the only baseline characteristic for which there was a statistically significant difference between the two treatment groups (Table 3).

FOLLOW-UP

Protocol violations with regard to inclusion or exclusion criteria (mostly violations of timelines) occurred in 86 patients in the tenecteplase group (16.4%) and 74 patients in the placebo group (14.1%, $P=0.34$). Treatment assignment was unblinded in 33 patients who had received tenecteplase (6.3%) and in 22 who had received placebo (4.2%, $P=0.17$). Unblinding was generally performed for safety reasons. Sixteen patients who subsequently underwent a percutaneous coronary intervention were believed to need a glycoprotein IIb/IIIa inhibitor, the treating investigator decided to use open-label thrombolytic treatment in 9 patients with prolonged unsuccessful cardiopulmonary resuscitation or suspected pulmonary embolism, 7 patients had bleeding complications, and 23 patients received unblinded treatment for other reasons.

Complete follow-up data were available for 1032 study patients. The relatives of 18 deceased patients were unwilling to give consent for the patients' data to be used. For 11 of these patients, permission to use their 30-day survival status was obtained, and for the remaining 7 patients, the missing primary end point was imputed to be "death." No patient was lost to 30-day follow-up.

OUTCOMES

At 30 days, 77 of 525 patients in the tenecteplase group (14.7%) and 89 of 525 patients in the placebo group (17.0%) were alive (relative risk of survival, 0.87; 95% confidence interval, 0.65 to 1.15; $P=0.36$). Thus, we did not detect a significant difference between the two treatment groups in the primary end point (Table 4 and Fig. 1). There were also no statistically significant differences in any of the secondary end points, including return of spontaneous circulation, hospital admission, 24-hour survival, survival to hospital discharge, and neu-

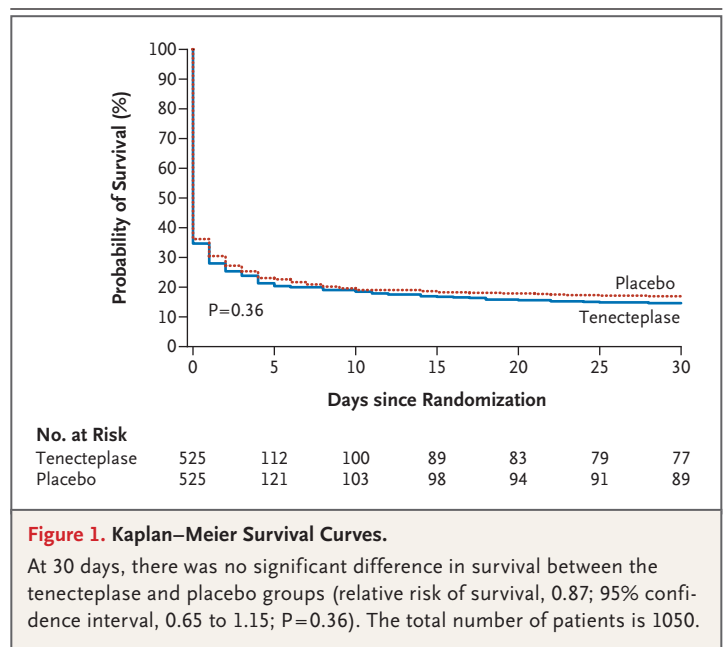


Figure 1. Kaplan–Meier Survival Curves.

At 30 days, there was no significant difference in survival between the tenecteplase and placebo groups (relative risk of survival, 0.87; 95% confidence interval, 0.65 to 1.15; $P=0.36$). The total number of patients is 1050.

rologic outcome (Table 4). Subgroup analysis did not reveal any significant differences between groups in the primary end point, except for those patients who received cardiopulmonary resuscitation from a bystander (Fig. 2).

Intracranial hemorrhage occurred with significantly greater frequency in the tenecteplase group (14 of 518 [2.7%]) than in the placebo group (2 of 514 [0.4%], $P=0.006$). Four patients with intracranial hemorrhage (all in the tenecteplase group) were symptomatic (Table 4) ($P=0.13$).

A separate analysis was performed excluding the 223 patients with asystole who had been included in the trial before the decision of the data and safety monitoring board to stop further enrollment of such patients. The results were similar to those of the primary analysis (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

DISCUSSION

We evaluated the potential benefit of thrombolytic therapy during cardiopulmonary resuscitation for out-of-hospital cardiac arrest. There were no significant differences between the tenecteplase and placebo groups in the efficacy end points that we evaluated, including the primary end point of 30-day survival and the secondary end points of return of spontaneous circulation, hospital admis-

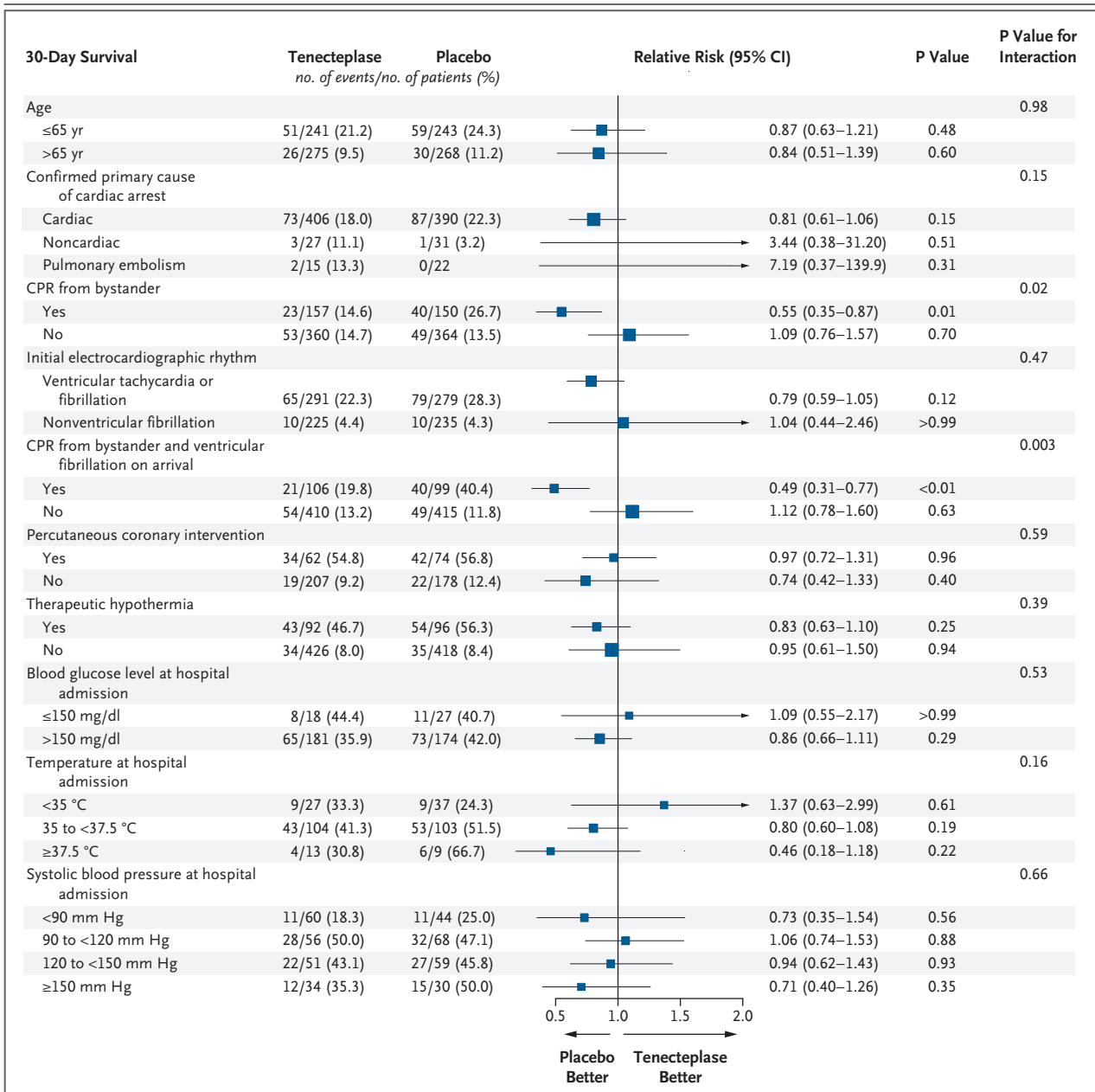


Figure 2. Subgroup Analyses.

CPR denotes cardiopulmonary resuscitation. The relative risk of the primary end point is shown for nine prespecified subgroups and one post hoc subgroup (CPR from a bystander and ventricular fibrillation on arrival of the emergency responders). The size of the squares is proportional to the size of the corresponding subgroup.

sion, 24-hour survival, survival to hospital discharge, and neurologic outcome.

Our trial did not confirm the beneficial effects of thrombolytic therapy during cardiopulmonary resuscitation that were described in several previous reports.^{6,19-21} However, the previous studies were much smaller than the present trial and most

were not randomized trials. We enrolled only patients with witnessed arrest that was presumed to be cardiac in origin. In addition, the thrombolytic agent used in the present trial was tenecteplase, whereas either alteplase or streptokinase was used in some of the previous studies.

The fact that antithrombin and antiplatelet

agents were not administered during cardiopulmonary resuscitation and before hospital admission may have contributed to the lack of efficacy of tenecteplase in the present trial. Like other thrombolytic agents, tenecteplase increases platelet activation.²² Heparin was administered with the thrombolytic agent in some of the previous studies. In the present study, the use of heparin was discouraged in the prehospital phase, primarily because of the fear of an increased risk of bleeding but also because we believed that the pharmacodynamic profile of tenecteplase made the use of heparin unnecessary. The adjunctive use of aspirin was also considered to be unnecessary. Platelet activation, however, is a key mechanism not only in the genesis of acute coronary syndromes²³ but also during cardiopulmonary resuscitation.²⁴ Activated platelets release von Willebrand factor, various cytokines, and plasminogen-activator inhibitor, all of which may inhibit thrombolysis. Activated platelets also interact with neutrophils and endothelial cells, which may — together with increased concentrations of complement and adhesion molecules in patients with cardiac arrest — exacerbate microcirculatory impairment.^{5,25,26}

In the present study, the interval between collapse and administration of the study drug was much shorter than in many previous reports (18 minutes vs. typically more than 30 minutes). This is in part a consequence of the administration of the thrombolytic agent only by the mobile ICU, without participation of emergency department personnel. Other response intervals were also shorter than in previous reports. The short response intervals may explain the fact that, even though patients with a successful response to initial defibrillation were excluded, our hospital-discharge rate was two to five times as high as that in other studies that focused on patients with cardiac arrest and that had similar inclusion criteria.^{18-21,27-29} The surprisingly high overall survival rate may have contributed to the inability to demonstrate an additional survival advantage for tenecteplase, since the scope for improvement with any new strategy is limited if existing therapy is unusually successful (a ceiling effect).

Other possible reasons for the lack of efficacy of tenecteplase must also be considered. Although thrombolytic therapy dissolves intravascular thrombi, perfusion of vital organs during cardiopulmonary resuscitation is restricted,³⁰ which may have hampered the delivery of tenecteplase to blood

clots in the coronary arteries. Sustained perfusion pressure may be necessary to induce benefit from thrombolysis, as is suggested by the reduced efficacy of thrombolysis in patients with ST-segment elevation myocardial infarction presenting with severe hypotension or cardiogenic shock.³¹

The risk of intracranial hemorrhage in this study was greater than that expected from the use of thrombolysis after myocardial infarction.³² Information related to possible contraindications to the use of a lytic agent could not be elicited from patients in cardiac arrest. More important, intracranial hemorrhage can cause circulatory arrest. Indeed, the site investigators reported intracranial bleeding as the cause of cardiac arrest in six patients, although such a causal relationship could not be proved with certainty. In fact, two of the six patients with intracranial hemorrhage as the reported cause of arrest did not receive the study drug after they had been randomly assigned to tenecteplase. Finally, since indications for cranial computer scanning were not predefined, a detection bias cannot be ruled out. Skeletal and other injuries are common during cardiopulmonary resuscitation,³³ but an increased risk of nonintracranial bleeding was not observed.

Our findings do not suggest that thrombolytic therapy should be withheld in patients with cardiac arrest if the primary pathologic condition is known to be responsive to such treatment.^{10,34} A retrospective analysis showed excellent survival in patients with myocardial infarction who had cardiac arrest and received thrombolytic therapy after the return of spontaneous circulation³⁵; thus, a more selective strategy may improve outcome. Since the study protocol permitted open-label thrombolytic therapy in patients with suspected pulmonary embolism as the cause of cardiac arrest, only 37 patients with confirmed pulmonary embolism were enrolled in the randomized trial — a number that was unfortunately too small to permit final conclusions about the value of tenecteplase in this subgroup.

The limitations of the study must be recognized. Prehospital emergency care is a very difficult setting for research. Because of the natural history of cardiac arrest and the limited number of autopsies, it is impossible to confirm the causes and circumstances of the underlying disease in all patients. Although the treatment of patients with cardiac arrest followed international guidelines,¹⁴ which were modified by the use of a trial

medication only, postresuscitation care differs between different hospitals.³⁶ For practical reasons, the trial did not include a registry of patients with cardiac arrest who could have been included, so any effect on the overall results due to bias in patient selection cannot be completely ruled out.

In conclusion, we did not detect an improvement in outcome when, in comparison with placebo, tenecteplase was used without adjunctive antithrombotic therapy during advanced life support for out-of-hospital cardiac arrest.

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APPENDIX

The following investigators participated in the Thrombolysis in Cardiac Arrest (TROICA) trial (the number of patients enrolled is given in parentheses). **Germany (199)**: Charité, Campus Benjamin Franklin, Berlin — H.R. Arntz, J. Breckwoldt, D. Müller; Charité, Campus Rudolf Virchow, Berlin — U. Frei, L. Nibbe; Charité, Campus Humboldt, Berlin — S. Behrens, B. Lehmke; Deutsches Rotes Kreuz Kliniken Westend, Berlin — M. Toursarkissian; Städtische Kliniken, Bielefeld — H.P. Milz, A. Roeper; Knappschafts-Krankenhaus, Dortmund — U. Schniedermeier; Albert-Ludwig-University, Freiburg — C. Bode, T. Schwab; Georg-August University, Göttingen — M. Roessler; Martin-Luther University, Halle/Saale — S. Grond, O. Meyer; Ruprecht-Karls University, Heidelberg — B.W. Böttiger, A. Gries, J. Motsch, F. Spöhr; Friedrich-Schiller-University, Jena — K. Pahlke, J. Reichel, K. Reinhardt; University Hospital Schleswig Holstein, Kiel — A. Seidenstücker, R. Simon; Berufsfeuerwehr, Kiel — M. 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REFERENCES

1. Rea TD, Eisenberg MS, Sinibaldi G, White RD. Incidence of EMS-treated out-of-hospital cardiac arrest in the United States. *Resuscitation* 2004;63:17-24.
2. Silfvast T. Cause of death in unsuccessful prehospital resuscitation. *J Intern Med* 1991;229:331-5.
3. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med* 1997;336:1629-33.
4. Böttiger BW, Motsch J, Böhrer H, et al. Activation of blood coagulation after cardiac arrest is not balanced adequately by activation of endogenous fibrinolysis. *Circulation* 1995;92:2572-8.
5. Fischer M, Böttiger BW, Popov-Cenic S, Hossmann KA. Thrombolysis using plasminogen activator and heparin reduces cerebral no-reflow after resuscitation from cardiac arrest: an experimental study in the cat. *Intensive Care Med* 1996; 22:1214-23.
6. Böttiger BW, Bode C, Kern S, et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. *Lancet* 2001;357:1583-5.
7. Lederer W, Lichtenberger C, Pechlaner C, Kinzl J, Kroesen G, Baubin M. Long-term survival and neurological outcome of patients who received recombinant tissue plasminogen activator during out-of-hospital cardiac arrest. *Resuscitation* 2004;61: 123-9.
8. Abu-Laban RB, Christenson JM, Innes GD, et al. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. *N Engl J Med* 2002;346:1522-8. [Erratum, *N Engl J Med* 2003;349:1487.]
9. Li X, Fu QL, Jing XL, et al. A meta-analysis of cardiopulmonary resuscitation with and without the administration of thrombolytic agents. *Resuscitation* 2006;70: 31-6.
10. Spöhr F, Böttiger BW. Safety of thrombolysis during cardiopulmonary resuscitation. *Drug Saf* 2003;26:367-79.
11. Nolan JP, Deakin CD, Soar J, Böttiger BW, Smith G. European Resuscitation Council guidelines for resuscitation 2005. Section 4: adult advanced life support. *Resuscitation* 2005;67:Suppl 1:S39-S86.
12. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112:Suppl:IV1-IV203.
13. Human Medicines Evaluation Unit. Guidelines for good clinical practice. London: European Agency for the Evaluation of Medicinal Products, 1995:1-58. (Accessed November 24, 2008, at <http://www.emea.europa.eu/pdfs/human/ich/013595en.pdf>)
14. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. *Resuscitation* 2000;46:1-447.
15. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style — a statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991;84:960-75.
16. Spöhr F, Arntz HR, Bluhmki E, et al. International multicentre trial protocol to assess the efficacy and safety of tenecteplase during cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest: the Thrombolysis in Cardiac Arrest (TROICA) Study. *Eur J Clin Invest* 2005;35:315-23.
17. Stiell IG, Hebert PC, Weitzman BN, et al. High-dose epinephrine in adult cardiac arrest. *N Engl J Med* 1992;327:1045-50.
18. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004;350:105-13.
19. Fatovich DM, Dobb GJ, Clugston RA. A pilot randomised trial of thrombolysis in cardiac arrest (the TICA trial). *Resuscitation* 2004;61:309-13.
20. Bozeman WP, Kleiner DM, Ferguson KL. Empiric tenecteplase is associated with increased return of spontaneous circulation and short term survival in cardiac arrest patients unresponsive to standard interventions. *Resuscitation* 2006;69:399-406.
21. Lederer W, Lichtenberger C, Pechlaner C, Kroesen G, Baubin M. Recombinant tissue plasminogen activator during cardiopulmonary resuscitation in 108 patients with out-of-hospital cardiac arrest. *Resuscitation* 2001;50:71-6.
22. Gurbel PA, Hayes K, Bliden KP, Yoho J, Tantry US. The platelet-related effects of tenecteplase versus alteplase versus reteplase. *Blood Coagul Fibrinolysis* 2005; 16:1-7.
23. Fitzgerald DJ, Roy L, Catella F, Fitzgerald GA. Platelet activation in unstable coronary disease. *N Engl J Med* 1986; 315:983-9.
24. Böttiger BW, Böhrer H, Böker T, Motsch J, Aulmann M, Martin E. Platelet factor 4 release in patients undergoing cardiopulmonary resuscitation — can reperfusion be impaired by platelet activation? *Acta Anaesthesiol Scand* 1996;40:631-5.
25. Afshar-Kharghan V, Thiagarajan P. Leukocyte adhesion and thrombosis. *Curr Opin Hematol* 2006;13:34-9.
26. Böttiger BW, Motsch J, Braun V, Martin E, Kirschfink M. Marked activation of complement and leukocytes and an increase in the concentrations of soluble endothelial adhesion molecules during cardiopulmonary resuscitation and early reperfusion after cardiac arrest in humans. *Crit Care Med* 2002;30:2473-80.
27. Hallstrom A, Rea TD, Sayre MR, et al. Manual chest compression vs use of an automated chest compression device during resuscitation following out-of-hospital

- tal cardiac arrest: a randomized trial. *JAMA* 2006;295:2620-8.
28. Ong ME, Ornato JP, Edwards DP, et al. Use of an automated, load-distributing band chest compression device for out-of-hospital cardiac arrest resuscitation. *JAMA* 2006;295:2629-37.
29. Gueugniaud PY, Mols P, Goldstein P, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. *N Engl J Med* 1998;339:1595-601.
30. Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. *JAMA* 2005;293:299-304.
31. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-22. [Erratum, *Lancet* 1994;343:742.]
32. Van de Werf F, Barron HV, Armstrong PW, et al. Incidence and predictors of bleeding events after fibrinolytic therapy with fibrin-specific agents: a comparison of TNK-tPA and rt-PA. *Eur Heart J* 2001;22:2253-61.
33. Hoke RS, Chamberlain DA. Skeletal chest injuries secondary to cardiopulmonary resuscitation. *Resuscitation* 2004;63:327-38.
34. Janata K, Holzer M, Kırkcıyan I, et al. Major bleeding complications in cardiopulmonary resuscitation: the place of thrombolytic therapy in cardiac arrest due to massive pulmonary embolism. *Resuscitation* 2003;57:49-55.
35. Arntz HR, Wenzel V, Dissmann R, Marschalk A, Breckwoldt J, Müller D. Out-of-hospital thrombolysis during cardiopulmonary resuscitation in patients with high likelihood of ST-elevation myocardial infarction. *Resuscitation* 2008;76:180-4.
36. Langhelle A, Tyvold SS, Lexow K, Hapnes SA, Sunde K, Steen PA. In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest: a comparison between four regions in Norway. *Resuscitation* 2003;56:247-63.

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