Effects of Thrombolysis During Out-of-Hospital Cardiopulmonary Resuscitation

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In this post hoc analysis, we assessed effects of thrombolysis during out-of-hospital cardiopulmonary resuscitation. The original study was designed as a double-blinded, prospective, multicenter, randomized, controlled clinical trial. In this report, 1,219 patients were randomized, but 33 patients were excluded due to missing study drug codes. Thus, 1,186 patients were analyzed based on receipt (n = 99) versus nonreceipt (n = 1,087) of thrombolysis; the primary end point was hospital admission, and the secondary end point was hospital discharge. Patients who received thrombolysis versus those who did not were significantly younger (mean ± SD 62.7 ± 13.3 vs 66.5 ± 14.3 years of age, p = 0.01) and more likely to have had an acute myocardial infarction (75.3% vs 54.6%, p <0.01) or pulmonary embolism (20.2% vs 12.0%, p = 0.03) as the suspected underlying cause for cardiac arrest. In patients who underwent thrombolysis versus those who did not, cardiac arrest was more often witnessed (86.9% vs 77.5%, p = 0.03), initial ventricular fibrillation was more likely (59.6% vs 38.0%, p <0.01), and a short estimated interval (0 to 5 minutes) between collapse and initiation of basic life support was more likely (51.3% vs 29.2%, p <0.01). In patients who received thrombolysis, sodium bicarbonate (45.5% vs 33.0%, p = 0.01), lidocaine (32.3% vs 18.1%, p <0.01), and amiodarone (30.3% vs 12.2%, p <0.01) were administered significantly more often. Hospital admission rates were significantly higher in patients who underwent thrombolysis than in patients who did not (45.5% vs 32.7%, p = 0.01), and there was a trend to higher hospital discharge rates (14.1% vs 9.5%, p = 0.14). In patients who had suspected myocardial infarction, hospital admission and discharge rates were significantly higher in patients who underwent thrombolysis than in patients who did not. In logistic regression models after adjusting for confounding variables (e.g., age, initial electrocardiographic rhythm, and initiation of basic life support), hospital admission and discharge rates did not differ significantly. In conclusion, even when being employed in patients with a potentially better chance to survive, thrombolysis in patients with cardiac arrest resulted in an increased hospital admission but not discharge rate in this post hoc analysis. **(Am J Cardiol 2006;97:305–308)**

In a recent trial that was designed to assess the effects of vasopressin versus epinephrine in out-of-hospital cardiac arrest,[1] injection of thrombolysis was a patient intervention. In this post hoc analysis, we investigated 2 nonrandomized subgroups of patients who received or did not receive thrombolysis to evaluate thrombolysis as a cardiopulmonary resuscitation (CPR) treatment.

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The original study was performed in 33 communities with 44 physician-manned emergency medical service units in Austria, Germany, and Switzerland.[1] The criteria for inclusion were out-of-hospital cardiac arrest in adult patients who presented with ventricular fibrillation, pulseless electrical activity, or asystole that required CPR with a vasopressor. Exclusion criteria were successful defibrillation without a vasopressor, documented terminal illness, no intravenous access, hemorrhagic shock, pregnancy, cardiac arrest after trauma, age <18 years, or presence of a do-not-resuscitate order.

The original study was designed as a blinded, prospective, multicenter, randomized, controlled clinical trial; the primary end point was hospital admission and the secondary

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Table 1
Demographic data of patients (n = 1,186)

Characteristic	Thrombolysis		p Value
	No (n = 1,087)	Yes (n = 99)	
Age (yrs)	66.5 ± 14.3	62.7 ± 13.3	0.01
Men	747/1,072 (69.7%)	76/99 (76.8%)	0.14
Coronary heart disease	345/864 (39.9%)	20/66 (30.3%)	0.12
Hypertension	154/880 (17.5%)	12/69 (17.4%)	0.98
Diabetes mellitus	145/884 (16.4%)	11/69 (15.9%)	0.92
Left ventricular failure	113/869 (13.0%)	5/66 (7.6%)	0.20
Peripheral vascular disease	89/880 (10.1%)	11/69 (15.9%)	0.13
Cardiac arrhythmias	57/868 (6.57%)	7/67 (10.5%)	0.23
Pacemaker	36/879 (4.1%)	2/69 (2.9%)	0.63
Valvular heart disease	23/868 (2.7%)	4/68 (5.9%)	0.13
Cardiomyopathy	16/869 (1.8%)	1/67 (1.5%)	0.84
Suspected cause of cardiac arrest			
Myocardial infarction	444/814 (54.6%)	67/89 (75.3%)	<0.01
Primary arrhythmia	198/818 (24.2%)	10/89 (11.2%)	0.01
Pulmonary embolism	99/822 (12.0%)	18/89 (20.2%)	0.03

Age data are presented as mean ± SD; all other data are presented as number/total number of patients (percentage). Percentages are provided for known data.

end point was hospital discharge rate. The protocol was approved by the institutional review board of each participating center. When a patient underwent randomization, 1 mg of epinephrine or 40 IU of vasopressin was injected. If spontaneous circulation was not restored within 3 minutes after the first injection of the study drug, the same drug at the same dose was injected again. If spontaneous circulation was still not restored, the patient was given additional injections of epinephrine at the discretion of the emergency physician managing the CPR attempt. Full details of the original study are described elsewhere.[1]

A total of 1,219 patients was randomized, but 33 patients were excluded due to missing study drug codes. Of all included patients (n = 1,186), 2 new groups were formed for this post hoc analysis; namely, patients who received thrombolysis during CPR (n = 99) and patients who did not (n = 1,087). The type of the thrombolytic agent in most patients was tenecteplase or reteplase, depending on the center; the given dosage was adapted to the patient's weight. These groups underwent additional post hoc analysis, with the primary end point being hospital admission and the secondary end point being hospital discharge.

Comparisons of patient characteristics and survival outcomes were tested with chi-square or Student's *t* test, as appropriate. To assess for confounding effects of variables, logistic regression analysis was applied. All p values are 2-sided, and a type I error level of 5% was used. No corrections were made for multiple comparisons. All statistical calculations were performed with SPSS 11.5 for Windows (SPSS, Inc., Chicago, Illinois).

Ninety-nine of 1,186 patients (8.3%) received thrombolysis during or after CPR. During CPR, vasopressin was used in 54 patients with thrombolysis, and 45 received epinephrine (p = NS); among patients without thrombolysis, 535 received vasopressin and 552 received epinephrine as a vasopressor (p = NS). Patients who received thrombolysis were significantly younger, and in more patients acute myocardial infarction or pulmonary embolism was the suspected underlying cause for cardiac arrest compared with patients who received no thrombolysis (Table 1). In patients who underwent thrombolysis, cardiac arrest was more often witnessed, ventricular fibrillation was more likely to be the initial electrocardiographic rhythm, and the estimated interval between collapse and initiation of basic life support was significantly shorter (Table 2). Additional drugs such as sodium bicarbonate, lidocaine, and amiodarone were administered significantly more often in this cohort of patients (Table 2). Hospital admission rates were significantly higher in patients who underwent thrombolysis than in patients who did not, but hospital discharge rates were comparable between groups (Figure 1). In patients who had suspected myocardial infarction, hospital admission and discharge rates were significantly higher in patients who underwent thrombolysis (Figure 2). In logistic regression models that were adjusted for confounding variables such as age, initial electrocardiographic rhythm, and initiation of basic life support, hospital admission and discharge rates did not differ significantly.

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In a recent retrospective study of 27 discharged patients who underwent thrombolysis during CPR, 22 (81%) had an excellent neurologic outcome, which is unusually high for cardiac resuscitation.[2] Similar to other reports,[3] this may indicate that thrombolysis during CPR does not result in fundamental bleeding complications but is feasible, safe, and effective.[4] However, only 1 randomized CPR trial employing thrombolysis has been performed to date, which

Table 2
Cardiopulmonary resuscitation management data of patients (n = 1,186)

Characteristic	Thrombolysis		p Value
	No (n = 1,087)	Yes (n = 99)	
Initiation of cardiac arrest			
Arrest witnessed	834/1,076 (77.5%)	86/99 (86.9%)	0.03
CPR by bystander or family	197/1,079 (18.3%)	21/99 (21.2%)	0.47
Initial cardiac rhythm			
Ventricular fibrillation	413/1,087 (38.0%)	59/99 (59.6%)	<0.01
Pulseless electrical activity	175/1,087 (16.1%)	11/99 (11.1%)	0.19
Asystole	499/1,087 (45.9%)	29/99 (29.3%)	<0.01
Estimated interval of untreated cardiac arrest to initiation of basic life support			
0–5 min	235/805 (29.2%)	41/80 (51.3%)	<0.01
5–10 min	254/805 (31.6%)	24/80 (30.0%)	0.78
10–15 min	187/805 (23.2%)	8/80 (10.0%)	0.01
>15 min	129/805 (16.0%)	7/80 (8.8%)	0.09
Additional drugs given during CPR			
Heparin	35/1,084 (3.2%)	24/99 (24.2%)	<0.01
Sodium bicarbonate	358/1,084 (33.0%)	45/99 (45.5%)	0.01
Atropine	258/1,084 (23.8%)	32/99 (32.3%)	0.06
Lidocaine	196/1,084 (18.1%)	32/99 (32.3%)	<0.01
Amiodarone	133/1,087 (12.2%)	30/99 (30.3%)	<0.01

Data are presented as number/total number of patients (percentage). Percentages are provided for known data.

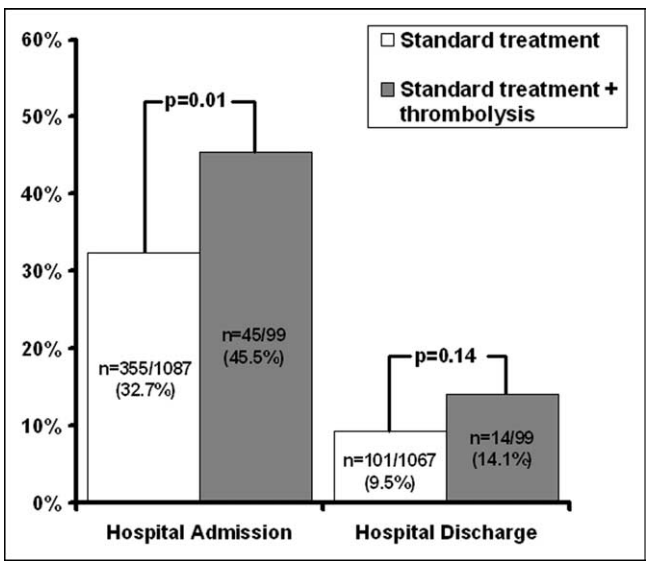

Figure 1. Hospital admission and discharge rates after resuscitation without thrombolysis *(white bars)* versus resuscitation with thrombolysis *(gray bars)* during out-of-hospital CPR. Y-scale range is 0% to 60%. No corrections were made for multiple comparisons.

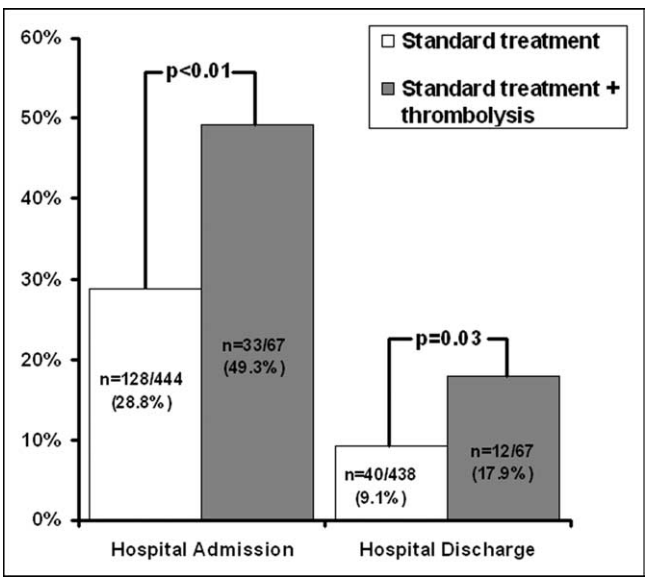

Figure 2. Hospital admission and discharge rates after resuscitation without thrombolysis *(white bars)* versus resuscitation with thrombolysis *(gray bars)* in patients with suspected myocardial infarction. Y-scale range is 0% to 60%. No corrections were made for multiple comparisons.

had simply too few patients (n = 35) to definitely assess effects on hospital discharge rate.[5,6]

In our post hoc analysis, patients who received thrombolysis were admitted alive to the hospital significantly more often than were patients who did not receive thrombolysis (p = 0.01), but there was only a trend toward higher hospital discharge rates (p = 0.14). No adverse effects such as intracranial bleeding were reported in patients who received thrombolysis in our study. It is quite obvious in our previous study[1] that patients were more likely to receive thrombolysis if ventricular fibrillation was the initial rhythm, were younger, or had received basic life support within the first 5 minutes after collapse. Moreover, ~75% of patients who received thrombolysis had suspected myocardial infarction, which is a major indication for thrombolysis. This may indicate that thrombolysis was preferentially employed in patients who had potentially better chances to survive per se.

Our original trial had few exclusion criteria and relatively open inclusion criteria. This explains why many pa-

tients were randomized who had statistically small chances to survive due to limiting circumstances, such as asystole, unwitnessed cardiac arrest, and severe underlying diseases that make successful CPR unlikely. As indicated by the aforementioned clinical characteristics, patients who received thrombolysis may have been subject to selection bias. However, there was no significant increase in hospital discharge rates in patients who received thrombolysis, except those with myocardial infarction. Thus, at least in this post hoc analysis, thrombolysis seems to be not as effective as previously believed.

Limitations need to be noted. Our retrospective analysis represents nonrandomized groups, and thrombolysis was a patient intervention without verification of the reason for the decision in that patient. Further, we were not able to assess whether thrombolysis was given before or after return of spontaneous circulation. In addition, clinical management of successfully resuscitated patients in the emergency room, intensive care unit, ward, and rehabilitation facilities that may differ from 1 hospital to the next may have profoundly influenced outcome. This trial was a multicenter study in 44 different centers in 3 countries and, unfortunately, it was not possible to obtain all information about the in-hospital treatment of this cohort of patients.

In spring 2004, the Thrombolysis In Cardiac Arrest (TROICA) trial was initiated in Europe with the goal to randomize 1,300 patients to investigate the effects of thrombolysis versus placebo when administered immediately after the first vasopressor drug during out-of-hospital CPR.

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