

## A COMPARISON OF REPEATED HIGH DOSES AND REPEATED STANDARD DOSES OF EPINEPHRINE FOR CARDIAC ARREST OUTSIDE THE HOSPITAL

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**ABSTRACT**

**Background** Clinical trials have not shown a benefit of high doses of epinephrine in the management of cardiac arrest. We conducted a prospective, multicenter, randomized study comparing repeated high doses of epinephrine with repeated standard doses in cases of out-of-hospital cardiac arrest.

**Methods** Adult patients who had cardiac arrest outside the hospital were enrolled if the cardiac rhythm continued to be ventricular fibrillation despite the administration of external electrical shocks, or if they had asystole or pulseless electrical activity at the time epinephrine was administered. We randomly assigned 3327 patients to receive up to 15 high doses (5 mg each) or standard doses (1 mg each) of epinephrine according to the current protocol for advanced cardiac life support.

**Results** In the high-dose group, 40.4 percent of 1677 patients had a return of spontaneous circulation, as compared with 36.4 percent of 1650 patients in the standard-dose group ( $P=0.02$ ); 26.5 percent of the patients in the high-dose group and 23.6 percent of those in the standard-dose group survived to be admitted to the hospital ( $P=0.05$ ); 2.3 percent of the patients in the high-dose group and 2.8 percent in the standard-dose group survived to be discharged from the hospital ( $P=0.34$ ). There was no significant difference in neurologic status according to treatment among those discharged. High-dose epinephrine improved the rate of successful resuscitation in patients with asystole, but not in those with ventricular fibrillation.

**Conclusions** In our study, long-term survival after cardiac arrest outside the hospital was no better with repeated high doses of epinephrine than with repeated standard doses. (N Engl J Med 1998;339:1595-601.)

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**E**PINEPHRINE remains the first-line adrenergic agent used for cardiac arrest, but the dose remains controversial.<sup>1-3</sup> Almost all experimental studies suggest that high-dose epinephrine is more effective than the currently recommended doses; higher doses increase myocardial and cerebral blood flow and improve rates of survival in animals.<sup>4-9</sup> In contrast, with the exception of a recent multinational study,<sup>10</sup> multicenter clinical trials have generally failed to demonstrate any difference in outcome between standard and high doses.<sup>11,12</sup> A French study found a nonsignificant improvement in the rates of initial resuscitation, admission to the hospital, and survival at six months in the high-dose group.<sup>13</sup>

To pursue this question further, we conducted a prospective, multicenter, randomized, double-blind study to compare the efficacy of repeated 1-mg doses of epinephrine with that of repeated 5-mg doses of epinephrine in adults with out-of-hospital cardiac arrest.

**METHODS****The French and Belgian Emergency Medical Systems**

Cardiac arrest occurring outside the hospital in France and Belgium is managed by the Service d'Aide Médicale Urgente.<sup>14,15</sup> Each medical region has a dispatching center located in a major hospital that controls several units, called Services Mobiles d'Urgence et de Réanimation, that are based in other hospitals within the region. Each hospital is equipped with several ambulances that carry a physician, a nurse, and a trained driver. The telephone number is a national emergency number. Switchboard operators, available 24 hours a day, receive all calls related to cardiac arrest in the dispatching centers and forward them to the dispatching physician, who decides whether to send out a team of emergency medical technicians (who are members of the fire-department rescue services) and, at the same time, an ambulance staffed by the medical team. Because of the greater numbers of emergency medical technicians, they are frequently closer to the patient and can start basic life support before the arrival of the medical team. The medical units provide advanced cardiac life support, according to the American Heart Association guidelines adapted for Europe by the European Resuscitation Council, until a return of spontaneous circulation is observed on the scene or a decision is made by the team physician to stop cardiopulmonary resuscitation.

**Study Design**

The study was approved by the ethics committees of the university hospitals in Lyons and Brussels and by the Consultative Council for the Protection of Persons Volunteering for Biomedical Research of our institution; approval was valid for each of the participating study centers. Waiver of informed consent was accepted by the council because of the urgency of the situation of the subjects with cardiac arrest and the lack of availability of family members.

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\*Other members of the European Epinephrine Study Group are listed in the Appendix.

TABLE 1. PRIMARY OUTCOMES ACCORDING TO THE INTENTION-TO-TREAT ANALYSIS.

OUTCOME	STANDARD-DOSE GROUP (N = 1938)	HIGH-DOSE GROUP (N = 1969)	DIFFERENCE BETWEEN GROUPS (95% CI)*	P VALUE
	number (percent)		percent	
Return of spontaneous circulation	666 (34.4)	749 (38.0)	3.6 (0.6 to 6.6)	0.02
Admission to hospital	439 (22.7)	499 (25.3)	2.6 (0 to 5.4)	0.05
24-Hr survival	288 (14.9)	299 (15.2)	0.3 (-1.9 to 2.5)	0.78
Discharge from hospital	46 (2.4)	38 (1.9)	-0.5 (-1.4 to 0.4)	0.34

\*CI denotes confidence interval.

This trial involved 12 centers: those in Lyons, Lille, Paris, Toulouse, Grenoble, Saint Etienne, Bobigny, Dijon, and Privas in France and Brussels, Liege, and Auvelais-Jolimont in Belgium. These centers cover a population of approximately 8.2 million. The study was conducted from September 1, 1994, to September 1, 1996. All patients 18 years of age or older who had cardiac arrest outside the hospital were eligible for inclusion in the study. Cardiac arrest was defined as the absence of both spontaneous respiration and palpable pulse. Patients with cardiac arrest were included in the study if they remained in ventricular fibrillation despite three successive countershocks or if they had asystole or pulseless electrical activity (defined as any organized electrocardiographic complex in the absence of palpable pulse) at the time epinephrine was administered. Patients were excluded if they were under 18 years of age; if they had traumatic cardiac arrest; if they had obvious signs of irreversible cardiac arrest; or if epinephrine had been injected before the study resuscitation.

### Treatment Protocol

All included patients were treated according to standard American Heart Association and European Resuscitation Council guidelines,<sup>1,2</sup> except for epinephrine injections. Patients were randomly assigned to receive up to 15 high doses (5 mg each) or standard doses (1 mg each) of epinephrine at three-minute intervals, according to recent standard protocols.<sup>3</sup>

Drugs were usually given intravenously by the peripheral (antecubital) or central route, but they were occasionally administered through an endotracheal tube when an intravenous catheter was not immediately available. In order to keep drug administration totally blinded, the two regimens of epinephrine were provided in packages of 15 coded 5-ml ampules with the same dosage of epinephrine. Each package was used for one person with cardiac arrest. Study packages were available in special sets of 10 randomized packages in all the medical ambulances of the 12 centers. The distribution of sets and packages inside the sets was governed for each center by a central randomization schedule determined in Lyons. During the course of the trial, all investigators and personnel providing care outside the hospital remained blinded as to which dose was administered and had no control over the order in which the sets were used.

### Outcome Measures

Demographic and clinical data were obtained from a standardized form completed according to the recommendations of the Utstein Consensus Conference.<sup>16</sup> Base-line characteristics, such as sex, age, location of arrest, suspected cause of arrest, whether the arrest was witnessed, initial electrical rhythm, medical history, principal event-to-event intervals, and other clinically important characteristics, were recorded. The primary end points were the return of spontaneous circulation, defined as the return of spontaneous palpable pulse and blood pressure for at least one minute<sup>12</sup>;

admission to the hospital, defined as the admission of a patient to an intensive care unit as an inpatient with a palpable pulse and blood pressure; the number of admissions after the administration of only a single dose of epinephrine; and discharge from the hospital. The secondary end points were survival and the neurologic outcome of patients, according to the template suggested by the Utstein Consensus Conference.<sup>16</sup> Cardiac arrests were categorized as witnessed arrests, witnessed arrests with suspected cardiac causes, and witnessed arrests with suspected cardiac causes in which bystanders administered cardiopulmonary resuscitation. Survival and outcome variables were admission to the intensive care unit, 24-hour survival, one-week survival, one-month survival, one-year survival, discharge from the hospital, and discharge from the hospital with no neurologic impairment or moderate impairment.

Neurologic function was assessed at the time of admission and at one week according to the highest score on the Glasgow Coma Scale (from 3, worst, to 15, best) and at hospital discharge according to a system for grading cerebral performance.<sup>17,18</sup> The cerebral-performance categories<sup>19</sup> were as follows: 1, conscious with normal function or only slight disability; 2, conscious with moderate disability; 3, conscious with severe disability; 4, comatose or in a vegetative state; 5, brain-dead or dead. Each patient's cerebral-performance category at the time of hospital discharge was determined retrospectively from hospital records.

Finally, the survival rates were also assessed according to the initial cardiac rhythm and the kind of cardiopulmonary resuscitation (standard or nonstandard — i.e., when active compression-decompression cardiopulmonary resuscitation was used). The initial rhythm was categorized as pulseless electrical activity, asystole if the electrical amplitude was no more than 0.1 mV, and ventricular fibrillation if the waveform amplitude was more than 0.1 mV, with the following classification: coarse ventricular fibrillation if the waveform amplitude was at least 0.8 mV, and fine-to-medium ventricular fibrillation if the waveform amplitude ranged from 0.1 to 0.8 mV.<sup>20</sup>

### Statistical Analysis

Continuous variables are given as means  $\pm$ SD. For categorical data, however, the proportions in the groups as well as the absolute differences between percentages in the 5-mg group and the 1-mg group were calculated, with 95 percent confidence intervals of the differences. Statistical tests included the chi-square test with the Mantel-Haenszel formulation and Fisher's exact test (when needed) for categorical data. Analysis of variance, Student's t-test, or the Wilcoxon test was used for continuous variables.<sup>21</sup> All tests were conducted with a two-sided alpha risk level of 0.05. The statistical software packages we used included SAS, SPSS, StatXact, Statistica, and Epi Info.

## RESULTS

During the study period, a total of 3946 epinephrine packages were assigned to patients. Thirty-nine

packages were not used properly for cardiac arrests, and 580 patients were subsequently excluded from the final analysis (by two investigators unaware of treatment assignment): 45 patients who did not meet the eligibility criteria or who received the study medication inappropriately, 190 patients for whom essential data were not available or who were lost to follow-up, and 345 patients who had traumatic cardiac arrest. The principal outcomes were first analyzed on a true intention-to-treat basis, with all enrolled patients included (Table 1).

The population for the final analysis consisted of 3327 patients, with 1650 randomly assigned to the standard-dose group and 1677 to the high-dose group. The characteristics of the patients in the two groups were similar, except for the number of epinephrine doses administered, which was higher in the standard-dose group (P=0.04) (Table 2).

The 5-mg group had a higher rate of return of spontaneous circulation than the 1-mg group (40.4 percent vs. 36.4 percent, P=0.02) and a higher rate of survival to hospital admission (26.5 percent vs. 23.6 percent, P=0.05). In contrast, the rate of survival to hospital admission after a single injection of epinephrine was similar in both groups (5.0 percent in the high-dose group vs. 4.6 percent in the standard-dose group, P=0.59) (Table 3). The rate of survival to discharge was similar in the two groups (2.3 percent in the high-dose group and 2.8 percent in the standard-dose group, P=0.34); 76.3 percent of the 38 survivors in the high-dose group and 71.7 percent of the 46 survivors in the standard-dose group were conscious without major disability (cerebral-performance category 1 or 2) at the time of discharge (P=0.64) (Table 4).

Patients who were resuscitated had similar neurologic outcomes in the high-dose and standard-dose groups. The median Glasgow Coma Scale scores were 3.9±2.6 for the high-dose group and 4.3±3.1 for the standard-dose group at 24 hours (P=0.18); at one week, they were 8.0±5.2 for the high-dose group and 8.6±5.2 for the standard-dose group (P=0.40). There was no significant difference between the high-dose and standard-dose groups in the proportion of patients who survived to discharge after admission to the intensive care unit (Table 4). The percentage of patients admitted to the intensive care unit who died before discharge (in-hospital mortality) was similar in the two groups (91.4 in the high-dose group and 88.2 in the standard-dose group, P=0.12). Nevertheless, there was a higher in-hospital mortality rate in the high-dose group during the first 24 hours (38.7 percent, as compared with 32.4 percent in the standard-dose group; P=0.06).

There were no significant differences in long-term survival between subgroups of patients, as defined according to the Utstein Consensus Conference. In contrast, within certain subgroups there were sub-

TABLE 2. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.\*

CHARACTERISTIC	STANDARD-DOSE GROUP (N=1650)	HIGH-DOSE GROUP (N=1677)
Age — yr		
Mean	66.7±14.8	64.5±15.1
Range	18–92	18–92
Male sex — no. (%)	1151 (69.8)	1173 (69.9)
Location of arrest — no. (%)		
Home	1217 (73.8)	1249 (74.5)
Public place	433 (26.2)	428 (25.5)
Suspected cause of arrest — no. (%)		
Cardiac	1171 (71.0)	1211 (72.2)
Noncardiac	479 (29.0)	466 (27.8)
Witnessed arrest — no. (%)	1297 (78.6)	1326 (79.1)
Bystander CPR — no. (%)	153 (9.3)	173 (10.3)
Medical history — no. (%)		
Cardiovascular disease	760 (46.1)	789 (47.0)
Respiratory disease	175 (10.6)	160 (9.5)
Other	734 (44.5)	732 (43.6)
Unknown	312 (18.9)	314 (18.7)
No history of disease	93 (5.6)	94 (5.6)
Initial cardiac rhythm — no. (%)		
Ventricular fibrillation	262 (15.9)	302 (18.0)
Pulseless electrical activity	157 (9.5)	159 (9.5)
Asystole	1231 (74.6)	1216 (72.5)
Time from collapse to treatment — min		
Bystander CPR†	5.7±5.8	5.2±5.6
ACLS	18.9±11.1	18.7±11.6
Epinephrine	20.7±12.9	20.6±14.1
Total duration of ACLS — min	28.2±15.5	28.1±15.7
Time to return of spontaneous circulation — min‡	31.0±14.7	29.6±15.4
Type of ACLS — no. (%)		
Standard	1154 (69.9)	1158 (69.1)
ACD	496 (30.1)	519 (30.9)
Automated external defibrillation — no. (%)§	221 (13.4)	208 (12.4)
Epinephrine administered		
No. of doses	6.1±3.7	5.8±3.7¶
Total dose — mg	6.1±3.7	29.0±18.5
Route of administration of epinephrine — no. (%)		
Peripheral intravenous	1546 (93.7)	1581 (94.3)
Central intravenous	80 (4.8)	66 (3.9)
Endotracheal tube alone	24 (1.5)	30 (1.8)

\*Plus-minus values are means ±SD. CPR denotes cardiopulmonary resuscitation, ACLS advanced cardiac life support, and ACD active compression–decompression. Percentages do not always sum to 100 when patients belong to several groups.

†Data for 326 patients were considered in this analysis.

‡Data for 1279 patients were considered in this analysis.

§Data for 429 patients were considered in this analysis.

¶P=0.04 for the comparison between the groups by Student's t-test. No other difference between the groups was significant.

stantial differences between the high-dose group and the standard-dose group in the proportions of patients who regained spontaneous circulation and who were admitted to the hospital. For witnessed cardiac arrests, 45.1 percent of patients in the high-dose group and 40.1 percent of those in the standard-dose group regained spontaneous circulation (P=0.009); 29.7 per-

**TABLE 3. PRIMARY OUTCOMES ACCORDING TO THE FINAL ANALYSIS.**

OUTCOME	STANDARD-DOSE GROUP (N=1650)	HIGH-DOSE GROUP (N=1677)	DIFFERENCE BETWEEN GROUPS (95% CI)*	P VALUE
	number (percent)		percent	
Return of spontaneous circulation	601 (36.4)	678 (40.4)	4.0 (0.7 to 7.3)	0.02
Admission to hospital	389 (23.6)	444 (26.5)	2.9 (0 to 5.8)	0.05
Admission after a single epinephrine injection	76 (4.6)	84 (5.0)	0.4 (-1 to 1.8)	0.59
Discharge from hospital	46 (2.8)	38 (2.3)	-0.5 (-1.6 to 0.6)	0.34

\*CI denotes confidence interval.

**TABLE 4. SURVIVAL AND NEUROLOGIC OUTCOME OF PATIENTS IN THE TWO RANDOMIZED GROUPS.\***

VARIABLE	ALL PATIENTS			WITNESSED ARRESTS			WITNESSED ARRESTS WITH SUSPECTED CARDIAC CAUSE			WITNESSED ARRESTS WITH SUSPECTED CARDIAC CAUSE AND BYSTANDER CPR		
	STANDARD-DOSE GROUP (N=1650)	HIGH-DOSE GROUP (N=1677)	P VALUE	STANDARD-DOSE GROUP (N=1297)	HIGH-DOSE GROUP (N=1326)	P VALUE	STANDARD-DOSE GROUP (N=954)	HIGH-DOSE GROUP (N=985)	P VALUE	STANDARD-DOSE GROUP (N=132)	HIGH-DOSE GROUP (N=161)	P VALUE
Return of spontaneous circulation — no. (%)	601 (36.4)	678 (40.4)	0.02	520 (40.1)	598 (45.1)	0.009	357 (37.4)	422 (42.8)	0.02	56 (42.4)	82 (50.9)	0.15
ICU admission — no. (%)	389 (23.6)	444 (26.5)	0.05	338 (26.1)	394 (29.7)	0.04	213 (22.3)	260 (26.4)	0.04	39 (29.5)	54 (33.5)	0.47
Survival — no. (%)												
24 hr	263 (15.9)	272 (16.2)	0.83	229 (17.7)	246 (18.6)	0.55	151 (15.8)	163 (16.5)	0.67	22 (16.7)	39 (24.2)	0.11
1 wk	103 (6.2)	84 (5.0)	0.12	94 (7.2)	78 (5.9)	0.16	66 (6.9)	54 (5.5)	0.19	6 (4.5)	11 (6.8)	0.41
1 mo	60 (3.6)	49 (2.9)	0.25	57 (4.4)	47 (3.5)	0.26	40 (4.2)	34 (3.5)	0.39	4 (3.0)	6 (3.7)	1.00†
1 yr	43 (2.6)	35 (2.1)	0.32	33 (2.5)	27 (2.0)	0.38	30 (3.1)	25 (2.5)	0.42	1 (0.8)	3 (1.9)	0.62†
Hospital discharge — no. (%)	46 (2.8)	38 (2.3)	0.34	44 (3.4)	36 (2.7)	0.31	30 (3.1)	28 (2.8)	0.70	2 (1.5)	3 (1.9)	1.00†
Discharge without neurologic impairment (CPC 1) — no. (% of discharged patients)	26 (56.5)	26 (68.4)	0.95	26 (59.1)	25 (69.4)	0.83	23 (76.7)	20 (71.4)	0.65	2 (100)	2 (66.7)	1.00†

\*CPR denotes cardiopulmonary resuscitation, ICU intensive care unit, and CPC cerebral-performance category.

†The P value was calculated with Fisher's exact test.

cent of patients in the high-dose group and 26.1 percent of those in the standard-dose group were admitted to the hospital (P=0.04). For witnessed arrests with suspected cardiac causes, 42.8 percent of patients in the high-dose group and 37.4 percent of those in the standard-dose group regained spontaneous circulation (P= 0.02); 26.4 percent of patients in the high-dose group and 22.3 percent of those in the standard-dose group were admitted to the hospital (P=0.04). For witnessed arrests with suspected cardiac causes in which a bystander administered the first cardiopulmonary resuscitation, 50.9 percent of patients in the high-dose group and 42.4 percent of those in the standard-

dose group regained spontaneous circulation (P= 0.15); 33.5 percent of patients in the high-dose group and 29.5 percent of those in the standard-dose group were admitted to the hospital (P=0.47) (Table 4).

Similarly, when the initial rhythm was asystole, 36.9 percent of patients in the high-dose group and 32.2 percent of those in the standard-dose group regained spontaneous circulation (P=0.01); 25.2 percent of patients in the high-dose group and 20.3 percent of those in the standard-dose group were admitted to the hospital (P=0.004) (Table 5). When standard cardiopulmonary resuscitation was administered, 39.8 percent of patients in the high-dose group and 34.7 per-

**TABLE 5.** SUCCESSFUL RESUSCITATION ACCORDING TO INITIAL CARDIAC RHYTHM.

OUTCOME	ASYSTOLE			PULSELESS ELECTRICAL ACTIVITY			COARSE VF*			FINE OR MEDIUM VF*		
	STANDARD-DOSE GROUP (N=1231)	HIGH-DOSE GROUP (N=1216)	P	STANDARD-DOSE GROUP (N=157)	HIGH-DOSE GROUP (N=159)	P	STANDARD-DOSE GROUP (N=115)	HIGH-DOSE GROUP (N=118)	P	STANDARD-DOSE GROUP (N=147)	HIGH-DOSE GROUP (N=184)	P
	no. (%)			no. (%)			no. (%)			no. (%)		
Return of spontaneous circulation	396 (32.2)	449 (36.9)	0.01	71 (45.2)	87 (54.7)	0.09	74 (64.3)	66 (55.9)	0.19	60 (40.8)	76 (41.3)	0.93
Admission to hospital	250 (20.3)	306 (25.2)	0.004	44 (28.0)	45 (28.3)	0.96	52 (45.2)	43 (36.4)	0.17	43 (29.2)	50 (27.2)	0.68
Discharge from hospital	18 (1.5)	13 (1.1)	0.38	4 (2.5)	7 (4.4)	0.37	13 (11.3)	9 (7.6)	0.34	11 (7.5)	9 (4.9)	0.33

\*VF denotes ventricular fibrillation; VF is coarse if wave-form amplitude is  $\geq 0.8$  mV and fine or medium if wave-form amplitude is  $< 0.8$  mV.

**TABLE 6.** INTERACTION BETWEEN ACTIVE COMPRESSION–DECOMPRESSION CARDIOPULMONARY RESUSCITATION AND DOSE OF EPINEPHRINE IN SUCCESSFUL RESUSCITATION.\*

TYPE OF CPR	NO. OF PATIENTS		RETURN OF SPONTANEOUS CIRCULATION			ADMISSION TO HOSPITAL			DISCHARGE FROM HOSPITAL		
	STANDARD-DOSE GROUP	HIGH-DOSE GROUP	STANDARD-DOSE GROUP	HIGH-DOSE GROUP	P	STANDARD-DOSE GROUP	HIGH-DOSE GROUP	P	STANDARD-DOSE GROUP	HIGH-DOSE GROUP	P
	no. (%)		no. (%)			no. (%)			no. (%)		
Standard ACLS	1154	1158	400 (34.7)	461 (39.8)	0.01	242 (21.0)	291 (25.1)	0.02	28 (2.4)	29 (2.5)	0.90
Active compression–decompression ACLS	496	519	201 (40.5)	217 (41.8)	0.68	147 (29.6)	153 (29.5)	0.96	18 (3.6)	9 (1.7)	0.06
P value	—	—	0.023	0.44	—	$< 0.001$	0.062	—	0.17	0.33	—

\*CPR denotes cardiopulmonary resuscitation, and ACLS advanced cardiac life support.

cent of those in the standard-dose group regained spontaneous circulation ( $P=0.01$ ); 25.1 percent of patients in the high-dose group and 21.0 percent of those in the standard-dose group were admitted to the hospital ( $P=0.02$ ) (Table 6). In contrast, there was no significant difference between the groups when active compression–decompression cardiopulmonary resuscitation was used, and an advantage of standard-dose epinephrine was observed when the initial rhythm was ventricular fibrillation, particularly coarse ventricular fibrillation (Table 5). There was an advantage in long-term survival when standard doses were associated with active compression–decompression cardiopulmonary resuscitation ( $P=0.06$ ).

**DISCUSSION**

During the past decade, experimental<sup>4-9</sup> and uncontrolled<sup>22-26</sup> clinical studies have suggested that epinephrine in doses higher than those currently recommended may improve the outcome after cardiac

arrest. Unfortunately, although a few single-center studies yielded positive results,<sup>27,28</sup> two multicenter clinical trials did not demonstrate any significant difference in initial and final survival rates between patients treated with high doses of epinephrine and those treated with standard doses.<sup>11,12</sup> The multicenter trials have some limitations, however. In one study, only a single injection of a very high dose of epinephrine was administered.<sup>12</sup> In the other study, the number of cardiac arrests was small, and advanced life support was not available outside the hospital.<sup>11</sup> The aim of our trial was to evaluate the efficacy of repeated high doses of epinephrine (up to 15 doses) for the treatment of cardiac arrest in patients receiving advanced cardiac life support outside the hospital in a protocol suitable to our European system of prehospital care for emergencies.<sup>29</sup> We found that the initial survival rate was slightly higher than usually reported when care is provided by emergency technicians who do not offer advanced cardiac life support, whereas

the rate of discharge from the hospital was as poor as that usually reported.<sup>30-33</sup>

Our results demonstrate that in cases of cardiac arrest outside the hospital, the rates of return of spontaneous circulation and survival to hospital admission are markedly improved with high doses of epinephrine. In contrast, there was no beneficial effect on long-term survival or neurologic outcome. In-hospital mortality was actually higher in the high-dose group than in the standard-dose group.

When we investigated the subgroups of patients with cardiac arrest, selected according to the Utstein Consensus Conference, improvement in the rates of return of spontaneous circulation and admission to the hospital with high-dose epinephrine was still observed for those with witnessed cardiac arrests and witnessed cardiac arrests of cardiac origin, but there were no longer differences between the effects of high and standard doses on long-term survival and neurologic outcome.

Among other relevant subgroups of patients, high-dose epinephrine improved the rate of successful resuscitation only with standard cardiopulmonary resuscitation, whereas among patients who received active compression–decompression cardiopulmonary resuscitation, survival rates were higher in the standard-dose group. Study of the initial cardiac rhythm indicated that the rates of return of spontaneous circulation and admission to the hospital were increased with high-dose epinephrine mainly in patients with asystole — that is, usually those with the most prolonged cardiac arrests, who represented three out of four patients in our study. In contrast, standard-dose epinephrine slightly improved the rate of successful resuscitation in the case of coarse ventricular fibrillation, which usually represents the shortest cardiac arrests. Consequently, we conclude that, except for patients with ventricular fibrillation, repeated high doses of epinephrine increase the likelihood of the return of spontaneous circulation and of initial survival after out-of-hospital cardiac arrest, but they do not improve the final outcome.

Unfortunately, the overall survival rate was poor in both groups in our study; the very long duration of cardiac arrest before advanced cardiopulmonary resuscitation (almost 20 minutes in each group) could explain that finding, in contrast to the results in animal models in which the duration of cardiac arrest was shorter.<sup>5-9</sup> Since high-dose epinephrine did not prove to be advantageous in the management of all cardiac arrests, other promising vasopressors should be studied in patients with cardiac arrest outside the hospital.<sup>34-37</sup>

In conclusion, high doses of epinephrine resulted in a significant improvement in the rate of successful resuscitation but did not have beneficial effects on long-term survival or neurologic outcome. Therefore, standard doses of epinephrine are still recommend-

ed, particularly in the management of ventricular fibrillation, whereas high doses of epinephrine may be considered in the management of prolonged out-of-hospital cardiac arrest.

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## APPENDIX

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