

## ORIGINAL ARTICLE

# Vasopressin and Epinephrine vs. Epinephrine Alone in Cardiopulmonary Resuscitation

Pierre-Yves Gueugniaud, M.D., Ph.D., Jean-Stéphane David, M.D., Ph.D., Eric Chanzy, M.D., Hervé Hubert, Ph.D., Pierre-Yves Dubien, M.D., Patrick Mauriacourt, M.D., Coralie Bragança, M.D., Xavier Billères, M.D., Marie-Paule Clotteau-Lambert, M.D., Patrick Fuster, M.D., Didier Thiercelin, M.D., Guillaume Debaty, M.D., Agnès Ricard-Hibon, M.D., Patrick Roux, M.D., Catherine Espesson, M.D., Emgan Querellou, M.D., Laurent Ducros, M.D., Patrick Ecollan, M.D., Laurent Halbout, M.D., Dominique Savary, M.D., Frédéric Guillaumée, M.D., Régine Maupoint, M.D., Philippe Capelle, M.D., Cécile Bracq, M.D., Philippe Dreyfus, M.D., Philippe Nouguier, M.D., Antoine Gache, M.D., Claude Meurisse, M.D., Bertrand Boulanger, M.D., Claude Lae, M.D., Jacques Metzger, M.D., Valérie Raphael, M.D., Arielle Beruben, M.D., Volker Wenzel, M.D., Comlavi Guinhouya, Ph.D., Christian Vilhelm, Ph.D., and Emmanuel Marret, M.D.

## ABSTRACT

**BACKGROUND**

During the administration of advanced cardiac life support for resuscitation from cardiac arrest, a combination of vasopressin and epinephrine may be more effective than epinephrine or vasopressin alone, but evidence is insufficient to make clinical recommendations.

**METHODS**

In a multicenter study, we randomly assigned adults with out-of-hospital cardiac arrest to receive successive injections of either 1 mg of epinephrine and 40 IU of vasopressin or 1 mg of epinephrine and saline placebo, followed by administration of the same combination of study drugs if spontaneous circulation was not restored and subsequently by additional epinephrine if needed. The primary end point was survival to hospital admission; the secondary end points were return of spontaneous circulation, survival to hospital discharge, good neurologic recovery, and 1-year survival.

**RESULTS**

A total of 1442 patients were assigned to receive a combination of epinephrine and vasopressin, and 1452 to receive epinephrine alone. The treatment groups had similar baseline characteristics except that there were more men in the group receiving combination therapy than in the group receiving epinephrine alone ( $P=0.03$ ). There were no significant differences between the combination-therapy and the epinephrine-only groups in survival to hospital admission (20.7% vs. 21.3%; relative risk of death, 1.01; 95% confidence interval [CI], 0.97 to 1.05), return of spontaneous circulation (28.6% vs. 29.5%; relative risk, 1.01; 95% CI, 0.97 to 1.06), survival to hospital discharge (1.7% vs. 2.3%; relative risk, 1.01; 95% CI, 1.00 to 1.02), 1-year survival (1.3% vs. 2.1%; relative risk, 1.01; 95% CI, 1.00 to 1.02), or good neurologic recovery at hospital discharge (37.5% vs. 51.5%; relative risk, 1.29; 95% CI, 0.81 to 2.06).

**CONCLUSIONS**

As compared with epinephrine alone, the combination of vasopressin and epinephrine during advanced cardiac life support for out-of-hospital cardiac arrest does not improve outcome. (ClinicalTrials.gov number, NCT00127907.)

From Service d'Aide Médicale Urgente (SAMU) 69, Hospices Civils de Lyon, University of Lyon 1, Lyon (P.-Y.G., J.-S.D.); SAMU 93, Bobigny (E.C.); Health Engineering Institute, University of Lille, Lille (H.H., C.G., C.V.); Service Mobile d'Urgence et de Réanimation (SMUR), Edouard Herriot Hospital, Lyon (P.-Y.D.); SAMU 59, Lille (P.M.); SAMU 33, Bordeaux (C. Bragança); Bataillon des Marins Pompiers, Marseille (X.B.); SAMU 44, Nantes (M.-P.C.-L.); SMUR, Centre Hospitalier Universitaire (CHU) Lyon-Sud, Lyon (P.F.); SAMU 06, Nice (D.T.); SAMU 38, Grenoble (G.D.); SMUR, Beaujon Hospital, Beaujon (A.R.-H.); SAMU 31, Toulouse (P.R.); SAMU 42, Saint-Etienne (C.E.); SAMU 29, Brest (E.Q.); SMUR, CHU Lariboisière, Paris (L.D.); SMUR, CHU Pitié-Salpêtrière, Paris (P.E.); SAMU 14, Caen (L.H.); SAMU 74, Annecy (D.S.); SMUR, Croix-Rousse Hospital, Lyon (F.G.); SAMU 01, Bourgen-Bresse (R.M.); SMUR, Maubeuge Hospital, Maubeuge (P.C.); SMUR, Dunkerque Hospital, Dunkerque (C. Bracq); SAMU 21, Dijon (P.D.); SAMU 13, Marseille (P.N.); SAMU 30, Nîmes (A.G.); SMUR, Valenciennes Hospital, Valenciennes (C.M.); SAMU 56, Vannes (B.B.); SMUR, Annemasse Hospital, Annemasse (C.L.); SMUR, Saint-Denis Hospital, Saint-Denis (J.M.); SMUR, Aulnay Hospital, Aulnay (V.R.); SMUR, Montfermeil Hospital, Montfermeil (A.B.); and Tenon Hospital, Paris (E.M.) — all in France; and Innsbruck Medical University, Innsbruck, Austria (V.W.). Address reprint requests to Dr. Gueugniaud at the Department of Anesthesiology and Critical Care Medicine, Pôle Urgence, CHU Lyon-Sud, Pierre Bénite, Lyon 69495, France, or at pierre-yves.gueugniaud@chu-lyon.fr.

N Engl J Med 2008;359:21-30.

Copyright © 2008 Massachusetts Medical Society.

**C**ARDIAC ARREST IS A MAJOR PUBLIC health problem, with more than 600,000 sudden deaths in North America and Europe each year. Although epinephrine is the vasopressor agent of choice for cardiopulmonary resuscitation, the prognosis of patients with cardiac arrest who require epinephrine remains extremely poor, regardless of the cumulative epinephrine dose given.<sup>1</sup>

Because endogenous vasopressin levels were found to be significantly higher in successfully resuscitated patients than in patients who died, Lindner et al. suggested that it might be beneficial to administer vasopressin during cardiopulmonary resuscitation.<sup>2</sup> Studies of cardiopulmonary resuscitation in animals demonstrated that vasopressin increased blood flow in vital organs,<sup>3</sup> cerebral oxygen delivery,<sup>4</sup> short-term survival,<sup>5</sup> and neurologic outcome,<sup>6</sup> as compared with epinephrine. In contrast to these observations, clinical studies of cardiopulmonary resuscitation in patients with in-hospital or out-of-hospital cardiac arrest showed that the effects of vasopressin and epinephrine were similar.<sup>7,8</sup> In one of these clinical studies,<sup>8</sup> however, successive administration of vasopressin and epinephrine in a subgroup of patients with refractory cardiac arrest resulted in significantly higher rates of survival to hospital discharge than repeated injections of epinephrine alone, a result suggesting that combined administration of vasopressin and epinephrine during cardiopulmonary resuscitation might be an effective strategy to improve the outcome in this subgroup. Although the concept of stimulating both catecholamine and vasopressin receptors to improve the perfusion of vital organs during cardiopulmonary resuscitation and to decrease vasopressor-mediated adverse effects makes sense, the promising results were based only on a subgroup analysis, and therefore a prospective clinical trial was required to assess this strategy.

We performed a large, randomized, clinical trial in France to prospectively test whether the combination of vasopressin and epinephrine is superior to epinephrine alone for advanced cardiac life support in out-of-hospital cardiac arrest.

## METHODS

### THE FRENCH EMERGENCY MEDICAL SYSTEM

As previously described,<sup>1,9</sup> the emergency medical service in France is a two-tiered system managed

by the Service d'Aide Médicale d'Urgente (SAMU). The first tier consists of emergency medical ambulances providing basic life support that are staffed by technicians and based at fire stations. The second tier consists of ambulances providing advanced cardiac life support that are staffed by physicians and based at major hospitals (Services Mobiles d'Urgence et de Réanimation [SMUR]). Because there are more fire stations than major hospitals, emergency medical technicians are frequently closer to the scene of cardiac arrest and start basic life support (including external defibrillation) before the arrival of a physician-staffed ambulance. In accordance with the 2000 European Resuscitation Council guidelines<sup>10</sup> that were in effect at the time of the study, cardiopulmonary resuscitation was performed until spontaneous circulation was restored at the scene or a decision was made by the physician to discontinue resuscitation efforts.

### STUDY PATIENTS

This study was conducted from May 1, 2004, through April 30, 2006, and involved 31 SAMU and SMUR units in France. Adult patients with out-of-hospital cardiac arrest presenting with ventricular fibrillation, pulseless electrical activity, or asystole requiring vasopressor therapy during cardiopulmonary resuscitation were included. The exclusion criteria were age under 18 years, successful defibrillation without administration of a vasopressor, traumatic cardiac arrest, pregnancy, documented terminal illness, presence of a do-not-resuscitate order, and obvious signs of irreversible cardiac arrest.

### STUDY DESIGN

The institutional review board of the University Hospitals of Lyon in Lyon approved the study for all participating study centers. Waiver of informed consent was authorized by the institutional review board because of the urgent need for treatment of cardiac arrest. The patients' relatives were informed about the trial, and for patients who survived until admission to the hospital, written informed consent for further participation in the trial was obtained, as prescribed by the hospital review board, from a family member or from patients who were capable of giving consent. Data from patients for whom consent was not obtained were excluded from the analysis.

The study drugs were manufactured, labeled,

and inspected by Laboratoire Aguettant, Lyon, according to Good Manufacturing Practice and Good Clinical Practice Guidelines; the composition of the drugs was confirmed by high-pressure liquid chromatography. Each set of study drugs consisted of either two 1-mg ampules of epinephrine and two 40-IU ampules of vasopressin (for the combination-therapy group) or two 1-mg ampules of epinephrine and two ampules of saline placebo (for the epinephrine-only group).

Treatment assignments were randomly generated in sets of 40 drug boxes, with stratification according to center. Randomization and distribution of study-drug sets were governed by a central randomization schedule. During the entire trial, all investigators and emergency medical service personnel were unaware of which study drugs were used and had no control over the order in which the study-drug sets were used. The possibility of making the physician aware of the identity of the study drugs was available in the case of adverse events, but it was never used. If all inclusion criteria were met and none of the exclusion criteria were present, patients presenting with pulseless electrical activity or asystole underwent randomization immediately; patients with ventricular fibrillation underwent randomization after three initial defibrillation attempts had failed. After randomization, the patients received either 1 mg of epinephrine and 40 IU of vasopressin or 1 mg of epinephrine and saline placebo in separate injections less than 10 seconds apart. If spontaneous circulation was not restored within 3 minutes after the first administration of the study drugs, the same combination of study drugs was administered again. If spontaneous circulation was still not restored within the following 3 minutes, patients in both the combination-therapy group and the epinephrine-only group were given additional open-label epinephrine at the discretion of the emergency-medical-service physician. All drugs were administered intravenously and were followed by the administration of 20 ml of normal saline. Amiodarone or fibrinolytic therapy was also administered at the discretion of the physician; no other drugs were administered.

#### DOCUMENTATION

Each patient's demographic characteristics and clinical data were recorded on a standardized paper form according to Utstein style recommenda-

tions<sup>11</sup> and subsequently entered into a secure national database. All case-record forms were subsequently collected in Lyon, where a random sample of 5% of the forms was assessed by the data and safety monitoring committee. Baseline characteristics and other clinically important features were documented. The primary end point was survival to hospital admission, which was defined as admission of a patient with a palpable pulse and measurable blood pressure to an intensive care unit. The secondary end points were return of spontaneous circulation (defined as the spontaneous return of a palpable pulse and measurable blood pressure for at least 1 minute),<sup>12</sup> survival to hospital discharge, good neurologic recovery (cerebral-performance category 1), and 1-year survival. Neurologic performance was assessed at hospital admission by the Glasgow Coma Scale (scores range from 3 to 15, with lower scores indicating reduced levels of consciousness) and at hospital discharge according to cerebral-performance categories<sup>13</sup> (1 indicates 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, and 5 brain-dead or dead).

#### STATISTICAL ANALYSIS

An estimate of the number of patients needed for the trial was derived from the analysis of a previous study of out-of-hospital cardiopulmonary resuscitation, in which the rate of survival to hospital admission in the control group (excluding patients with ventricular fibrillation) was 21%.<sup>1</sup> This calculation was based on a 25% improvement in outcome in the treatment group, a significance level of 0.05, a two-tailed analysis, and a power of 90%. According to this calculation, a sample size of 1146 patients in each group would be necessary to show a clinically significant difference in the rate of survival to hospital admission. The addition of a safety margin of 5.4% (corresponding to the proportion of patients excluded from analysis in the previous study) resulted in an estimate of 2416 patients needed for the entire trial. Analysis was performed according to the intention-to-treat principle. No interim analysis was performed during the study period.

The distribution of variables was tested by the Kolmogorov-Smirnov test. Continuous variables are expressed as means  $\pm$ SD or as medians and ranges. For categorical data, proportions within

groups and the relative risk of death in the combination-therapy group as compared with the epinephrine-only group were calculated, with 95% confidence intervals. The study end points were analyzed by the chi-square test with the Mantel-Haenszel formulation, Fisher's exact test, Student's t-test, or the Mann-Whitney U test, as appropriate. According to the guidelines for reporting subgroup analyses, 14 post hoc analyses were performed, including a test for interaction.<sup>14</sup> All tests were conducted with a two-sided alpha level of 0.05. All analyses were performed with the use of SPSS software, version 13.0. The data were analyzed by the data and safety monitoring committee; all authors reviewed the manuscript and vouch for the accuracy and completeness of the data.

---

## RESULTS

---

A total of 2956 patients underwent randomization. Sixty-two patients (2.1%) were excluded from analysis, including 26 in the combination-therapy group and 36 in the epinephrine-only group ( $P=0.22$ ). Twenty-six of the excluded patients did not consent to participation in the study, 29 had traumatic cardiac arrest, and 7 were treated but did not meet the inclusion criteria. Data from the remaining 2894 patients were analyzed; 1442 of these patients received vasopressin combined with epinephrine, and 1452 received epinephrine only. No treatment-related adverse events were reported. The characteristics of the patients in the two groups were similar, except that there were significantly more men in the combination-therapy group ( $P=0.03$ ) (Table 1). Patients with witnessed cardiac arrest were more likely to survive to hospital admission than were those with unwitnessed cardiac arrest (23.2% vs. 14.4%,  $P<0.001$ ). The rate of survival to hospital admission was also higher among patients who received basic life support less than 8 minutes and advanced cardiac life support less than 12 minutes after cardiac arrest than among patients in whom basic and advanced cardiac life support were delayed (38.3% vs. 20.5%,  $P=0.001$ ).

The rates of survival to hospital admission, return of spontaneous circulation, survival to hospital discharge, good neurologic recovery at discharge, and 1-year survival were similar in the combination-therapy and the epinephrine-only groups (Table 2). Subgroup analyses according to

various Utstein style categories also revealed no significant differences between the two groups<sup>11</sup> (Fig. 1, 2, and 3). There were no significant differences between the groups in cerebral performance at hospital admission, as measured by the percentage of patients with Glasgow Coma Scale scores of 3 (94.2% in the combination-therapy group vs. 93.1% in the epinephrine group,  $P=0.55$ ), and at hospital discharge, as measured by the percentage of patients in cerebral-performance categories 1 or 2 (53.6% in the combination-therapy group vs. 61.5% in the epinephrine-only group,  $P=0.51$ ). Among patients with an initial electrocardiographic (ECG) rhythm of ventricular fibrillation or asystole, there were no significant differences in any outcome between the combination-therapy group and the epinephrine-only group. However, a post hoc subgroup analysis showed that when the initial ECG rhythm was pulseless electrical activity, the rate of survival to hospital discharge was significantly higher in the epinephrine-only group than in the combination-therapy group (5.8% vs. 0%,  $P=0.02$ ). No significant differences were found in any other subgroup analyses (Fig. 3).

In 17.3% of admitted patients, hypothermia was immediately induced and maintained during the first 24 hours of the post-resuscitation phase. Although long-term survival without neurologic impairment was better in patients treated with hypothermia than in those not treated with hypothermia (9.6% vs. 3.2%,  $P=0.003$ ), conclusions about the efficacy of hypothermia cannot be drawn, since this intervention was not randomized.

---

## DISCUSSION

---

In studies in animals, vasopressors appear to be essential during cardiopulmonary resuscitation, with vasopressin generally producing better effects than epinephrine.<sup>15</sup> In contrast to these results, a meta-analysis of clinical studies of cardiopulmonary resuscitation showed no obvious benefit of vasopressin over epinephrine; there was also no evidence of harm from vasopressin given during cardiopulmonary resuscitation.<sup>16</sup> On the basis of these findings, the 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations concluded that "there is insufficient evidence to support or re-

**Table 1. Baseline Characteristics of the Study Patients.\***

Variable	Combination Treatment (N=1442)	Epinephrine Only (N=1452)	P Value
Age — yr	61±15	62±15	0.20
Male sex — no. (%)	1087 (75.4)	1041 (71.7)	0.03
Location of arrest — no. (%)			0.21
Home	1043 (72.3)	1080 (74.4)	
Public place	399 (27.7)	372 (25.6)	
Witnessed arrest — no. (%)	1072 (74.3)	1105 (76.1)	0.27
Bystander cardiopulmonary resuscitation — no. (%)	400 (27.7)	377 (26.0)	0.28
Suspected cause of arrest — no. (%)			
Cardiac	522 (36.2)	517 (35.6)	0.74
Noncardiac	303 (21.0)	335 (23.1)	0.18
Unknown	617 (42.8)	600 (41.3)	0.43
Medical history — no. (%)			
Coronary heart disease	295 (20.5)	310 (21.3)	0.56
Other cardiovascular disease	428 (29.7)	427 (29.4)	0.87
Respiratory disease	183 (12.7)	200 (13.8)	0.39
Other	431 (29.9)	479 (33.0)	0.08
Unknown	245 (17.0)	234 (16.1)	0.53
No history of disease	196 (13.6)	179 (12.3)	0.31
Initial cardiac rhythm — no. (%)			
Ventricular fibrillation	132 (9.2)	135 (9.3)	0.89
Pulseless electrical activity	111 (7.7)	120 (8.3)	0.57
Asystole	1199 (83.1)	1197 (82.4)	0.61
Time from collapse to treatment — min			
Time to arrival of emergency medical technicians	7.2±6.5	6.8±6.3	0.18
Time to arrival of advanced cardiac life support (SAMU)	16.3±9.0	16.3±8.9	0.84
Time to first injection of study drug	21.4±9.5	21.5±9.4	0.96
Total duration of advanced cardiac life support — min	38.0±15.1	37.6±15.4	0.17
Time to return of spontaneous circulation — min	44.0±16.0	43.7±16.3	0.28
Cardiopulmonary resuscitation initiated before arrival of advanced cardiac life support — no. (%)	1327 (92.0)	1353 (93.2)	0.23
Automated external defibrillation — no. (%)	1135 (78.7)	1168 (80.4)	0.25
Defibrillation administered by emergency medical technicians — no. (%)	343 (23.8)	362 (24.9)	0.69
End-tidal carbon dioxide monitoring — no. (%)	694 (48.1)	722 (49.7)	0.39
Additional drugs administered during advanced cardiac life support — no. (%)			
Amiodarone	204 (14.1)	188 (12.9)	0.35
Fibrinolytic drug	77 (5.3)	72 (5.0)	0.64

\* Plus-minus values are means ±SD. SAMU denotes Service d'Aide Médicale Urgente.

pute the use of vasopressin as an alternative to, or in combination with, adrenaline in any cardiac arrest rhythm.<sup>17</sup>

One hypothesis was that the combination of

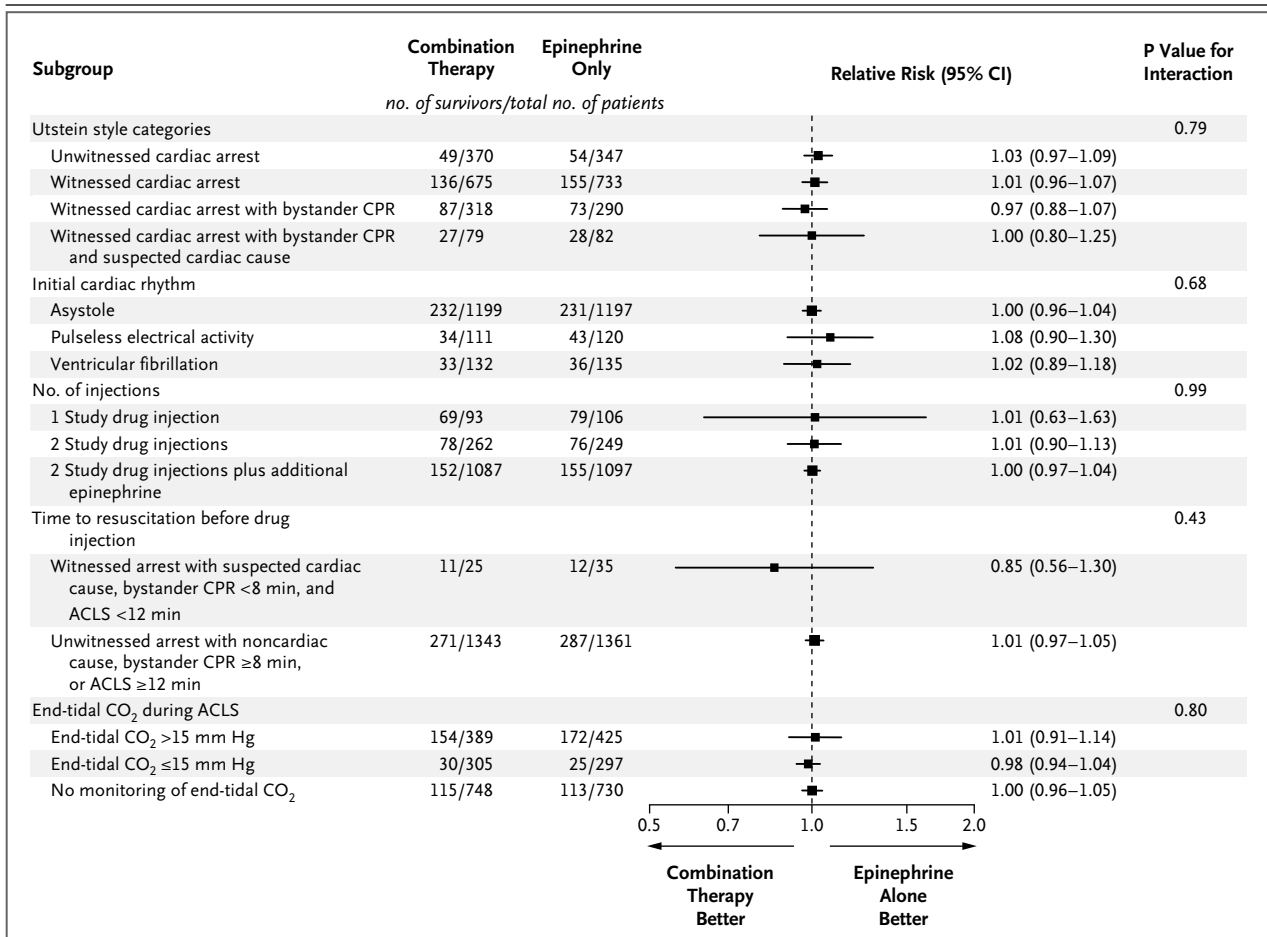
epinephrine and vasopressin would be more effective than either vasopressor alone; this combination had been extremely effective in an animal model of asphyxial cardiac arrest.<sup>18</sup> A previous

**Table 2. Survival Data for the 2894 Patients in the Intention-to-Treat Population.\***

End Point	Combination Treatment (N=1442)	Epinephrine Only (N=1452)	Relative Risk of Death (95% CI)	P Value
Survival to hospital admission — no. (%)	299 (20.7)	310 (21.3)	1.01 (0.97–1.05)	0.69
Survival to return of spontaneous circulation — no. (%)	413 (28.6)	428 (29.5)	1.01 (0.97–1.06)	0.62
Survival to hospital discharge — no./total no. (%)	24/1439 (1.7)	33/1448 (2.3)	1.01 (1.00–1.02)	0.24
1-Year survival — no./total no. (%)	18/1437 (1.3)	30/1447 (2.1)	1.01 (1.00–1.02)	0.09
Good neurologic recovery at hospital discharge — no./total no. (%)†	9/24 (37.5)	17/33 (51.5)	1.29 (0.81–2.06)	0.29

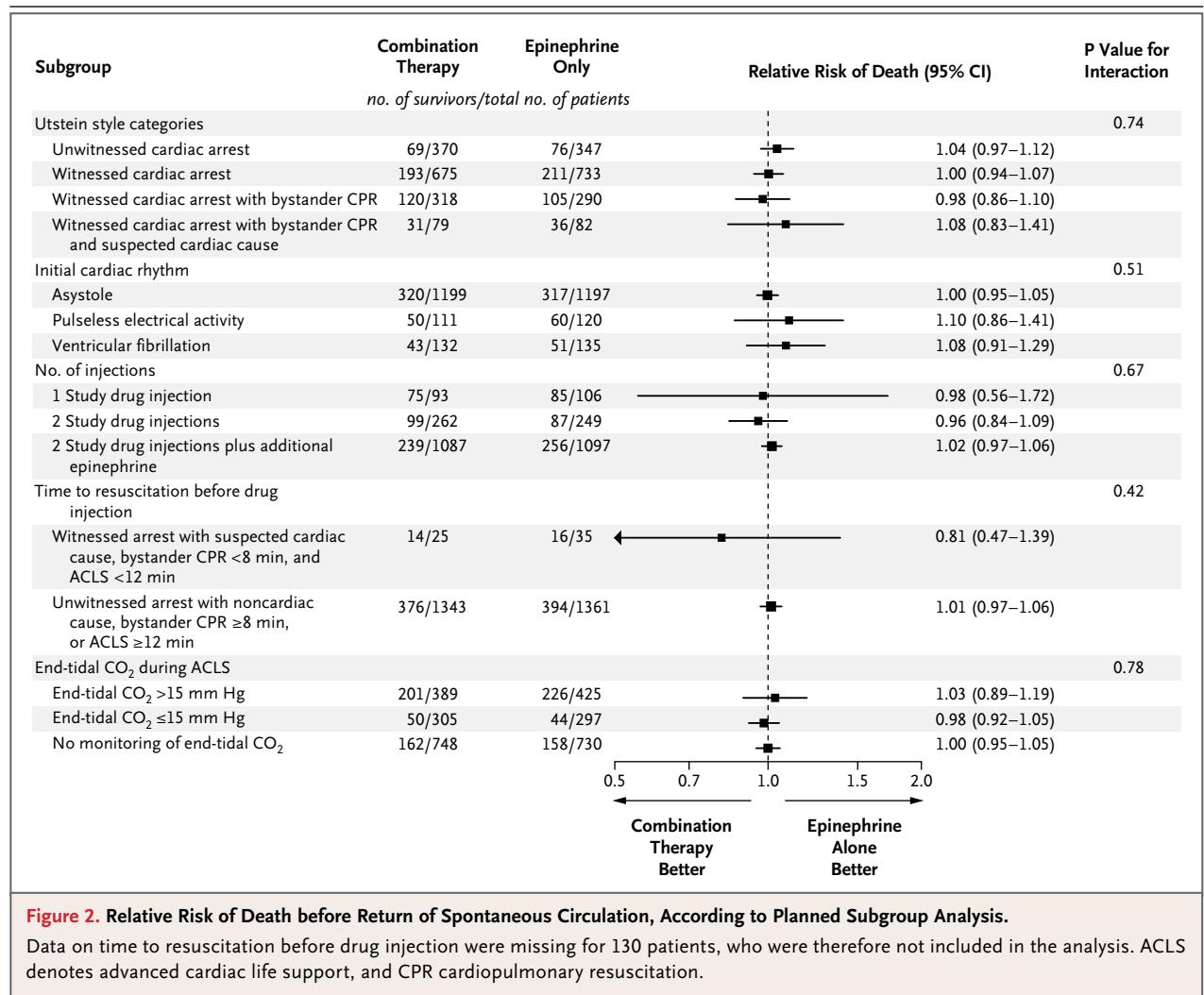
\* CI denotes confidence interval.

† Good neurologic recovery was defined as cerebral performance category 1 (conscious with normal function or only slight disability).



**Figure 1. Relative Risk of Death before Hospital Admission, According to Planned Subgroup Analysis.**

Data on time to resuscitation before drug injection were missing for 130 patients, who were therefore not included in the analysis. ACLS denotes advanced cardiac life support, and CPR cardiopulmonary resuscitation.



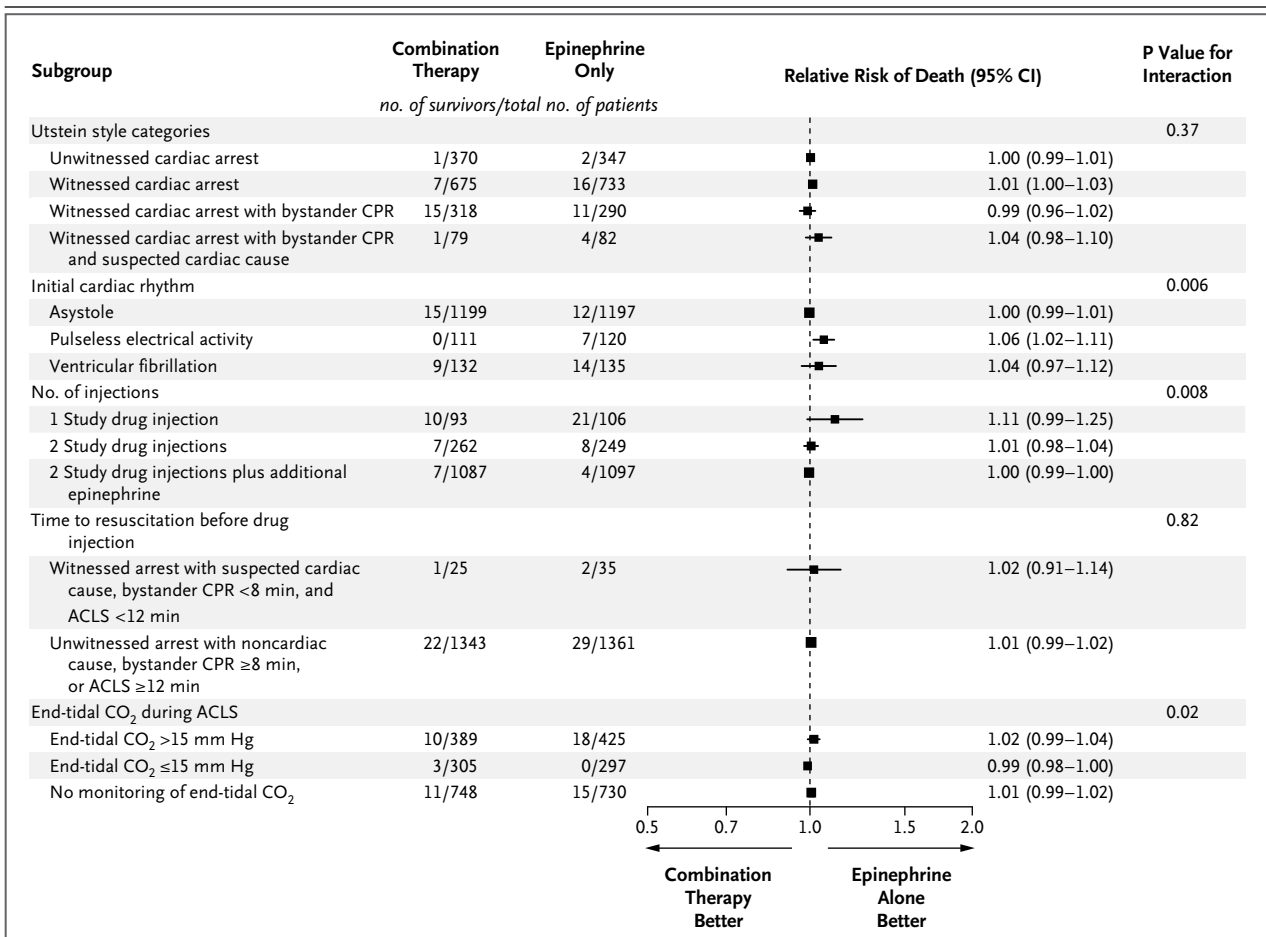
**Figure 2. Relative Risk of Death before Return of Spontaneous Circulation, According to Planned Subgroup Analysis.**

Data on time to resuscitation before drug injection were missing for 130 patients, who were therefore not included in the analysis. ACLS denotes advanced cardiac life support, and CPR cardiopulmonary resuscitation.

large, European study of out-of-hospital cardiopulmonary resuscitation by Wenzel et al. had confirmed this hypothesis, but only in a subgroup of patients that was not included for analysis in the initial study design; thus, the confirmation lacked statistical power.<sup>8</sup> In agreement with these observations, a recent retrospective study reported that treatment with a combination of vasopressin and epinephrine increased end-tidal carbon dioxide and mean arterial blood pressure during cardiopulmonary resuscitation; improvement in these surrogate measures of vital-organ perfusion may have been the mechanism for subsequent improvement in short-term survival.<sup>19</sup>

In contrast to these findings, a prospective,

randomized study of out-of-hospital cardiopulmonary resuscitation found similar outcomes when 40 IU of vasopressin or placebo was injected after an initial injection of 1 mg of epinephrine failed to restore spontaneous circulation.<sup>20</sup> However, the study protocol included only two vasopressor dosages and was underpowered (with 325 patients) to detect a difference in long-term survival.<sup>20</sup> Our trial enrolled almost 10 times as many patients as that study and used a more dynamic protocol of increasing vasopressor dosages, thus taking the underlying ischemia and the duration of ongoing cardiopulmonary-resuscitation efforts into account. Despite these efforts, the present study showed no benefit of the addition of vaso-



**Figure 3. Relative Risk of Death before Hospital Discharge, According to Planned Subgroup Analysis.**

Data on time to resuscitation before drug injection were missing for 130 patients, who were therefore not included in the analysis.  $P=0.02$  for patients with initial pulseless electrical activity. ACLS denotes advanced cardiac life support, and CPR cardiopulmonary resuscitation.

pressin to standard treatment with epinephrine during cardiopulmonary resuscitation of adults with out-of-hospital cardiac arrest. In contrast, in a post hoc subgroup analysis, we found a significant improvement in survival to hospital discharge in the epinephrine-only group as compared with the combined-therapy group among patients with pulseless electrical activity. Since the use of hypothermia was not randomized, we are unable to conclude whether inducing early hypothermia in the post-resuscitation phase improves neurologic recovery, as was shown in previous studies focused on the protective cerebral effects of hypothermia after cardiac arrest.<sup>21,22</sup>

To examine the effects of vasopressin treatment on patients with a better prognosis, we prospectively selected subgroups of patients with witnessed cardiac arrest, initial ventricular fibrillation, immediate cardiopulmonary resuscitation,

high end-tidal carbon dioxide levels during cardiopulmonary resuscitation, and return of spontaneous circulation after a single administration of study drugs. The lack of superiority of combination therapy over epinephrine alone, regardless of the patient subgroup, suggests that it may be futile to add vasopressin to epinephrine during cardiopulmonary resuscitation with advanced cardiac life support. In our study, the proportion of patients with asystole was higher, and therefore the rate of survival to hospital admission was lower, than in the study by Wenzel et al.<sup>8</sup> Since the benefit of vasopressin in the latter study was seen primarily in the subgroup of patients with asystole, it can be reasonably argued that our trial was conducted in a very appropriate population in which to test our hypothesis. More than 80% of our patients presented with asystole, and spontaneous circulation was restored an average



of 45 minutes later, facts that suggest that the combination of fundamentally depleted cardiac energy and a subsequent prolonged low-flow interval may reflect a degree of ischemia that determines survival to a greater degree than the quality and strategy of the ongoing cardiopulmonary-resuscitation efforts. This suggestion is in agreement with the finding that the greatest survival benefit was achieved in our study when a patient with witnessed cardiac arrest received basic life support within 8 minutes after the arrest and advanced cardiac life support within 12 minutes.

Because our patients were resuscitated in large and small cities and in rural areas by emergency medical services based in both university and county hospitals, the setting of the study was appropriate to determine the effects of a given drug during cardiopulmonary resuscitation under realistic conditions. However, our study has limitations, in particular the low overall survival rate. Although the rate of survival to hospital admission in our study was almost identical to that in a recent American trial of cardiopulmonary resuscitation (21.0% vs. 20.9%),<sup>20</sup> our rate of survival to hospital discharge was lower than that in the study by Wenzel et al. (2.0% vs. 9.7%).<sup>8</sup> This difference can be explained mainly by the low incidence of ventricular fibrillation in our trial as compared with that in the study by Wenzel et al. (9.2% vs. 39.8%), a reduction that was partly due to the efficacy of automated defibrillation that was performed before possible enrollment in our study. During a period of 14 years in France, the percentage of patients receiving automated defibrillation during basic cardiac life support increased from 13% to 80%, while the percentage of patients having ventricular fibrillation at the beginning of advanced life support decreased by 50%, from 35% to 17%.<sup>1</sup> A similar decline in the rate of initial ventricular fibrillation was observed in Seattle.<sup>23</sup> Thus, the “best” patients — those with a brief duration of ventricular fibrillation and therefore a high likelihood of survival and subsequent good cerebral recovery<sup>24</sup> — could not be included in the present study.

Unfortunately, the small number of patients with ventricular fibrillation in our study precludes a definitive conclusion against the use of vasopressin, even though a weak trend toward better outcomes with epinephrine alone was observed. The only cardiopulmonary-resuscitation interventions that have been proved to increase survival are rapid defibrillation and aggressive chest compression, both of which are performed during basic but not advanced cardiac life support.<sup>25</sup> The primary end point was not optimal, but it more realistically reflects the effects of cardiopulmonary-resuscitation interventions, because medical care in the intensive care units, wards, and rehabilitation facilities could not be standardized in our study protocol, although differences in care may have profoundly influenced the outcomes.<sup>26</sup> Moreover, because our study comparing the use of different vasopressors during cardiopulmonary resuscitation showed no difference in their effects on short-term survival, there is no reason to expect any difference in their effects on survival or neurologic recovery 1 year later. In conclusion, as compared with epinephrine alone, the combination of vasopressin and epinephrine did not improve outcome during advanced cardiac life support for out-of-hospital cardiac arrest.

Supported by the Programme Hospitalier de Recherche Clinique 2003 of the French Ministry of Health Research and the French Health Product Safety Agency and by the Research Delegation of the Hospices Civils de Lyon. The Research Delegation of the Hospices Civils de Lyon has received grant support from Aguetant Laboratories.

Presented in part at the Annual Congress of the French Society of Anesthesiology and Critical Care Medicine, Paris, September 26 to 29, 2007.

Dr. Wenzel reports receiving grant support from Boehringer Ingelheim. No other potential conflict of interest relevant to this article was reported.

We thank the physicians, nurses, and emergency medical service personnel of each participating center for their cooperation with the study and all involved SAMUs and SMURs for their participation; Bruno Riou (University Pierre et Marie Curie, Paris) for reviewing the manuscript; Brigitte Ladret (University Paul-Valérie, Montpellier, France) for her valuable help in translation; Elisabeth Pinelli for her continual technical assistance; Odile Gelpi and Catherine Cereser from the Clinical Research Delegation of the Hospices Civils de Lyon for their advice; Bertrand Camus at Aguetant Laboratories, Lyon, for his support; and our families and close relatives for their encouragement and extreme patience.

#### APPENDIX

The following investigators participated in the French Adrenaline-Vasopressin and Cardiac Arrest Study Group (the number of patients enrolled at each center is given in parentheses): **Data and safety monitoring committee** — H. Hubert (chair); C. Guinhouya; C. Vilhelm, Medical Decision Support, Health Engineering Institute, University of Lille, Lille; V. Piriou, Department of Anesthesiology, CHU Lyon-Sud, Lyon; **Central coordinating committee** — P.-Y. Gueugniaud (cochair), J.-S. David (cochair); E. Chanzy, P.-Y. Dubien, P. Mauriacourt, C. Brangança, X. Billères, M.-P. Clotteau-Lambert, P. Fuster, P. Goldstein, P. Petit; **Emergency medical service investigators** — J.-S. David, P. Petit, SAMU 69, Lyon (523), including three SMURs: P.-Y. Dubien, SMUR, Edouard Herriot Hospital (317), P. Fuster, SMUR, CHU Lyon-Sud (151), and F. Guillaumée, SMURs, Croix-Rousse Hospital (55); E. Chanzy, F. Adnet, SAMU 93, Bobigny (374), including four SMURs: E. Chanzy, SMUR, Avicenne Hospital (197), J. Metzger, SMUR, Saint-Denis Hospital (76), V. Raphael, SMUR,

Aulnay Hospital (62), and A. Beruben, SMUR, Montfermeil Hospital (39); P. Mauriaucourt, B. Chaybany, P. Goldstein, SAMU 59, Lille (237); C. Bragança, E. Tentillier, M. Thicoïpé, SAMU 33, Bordeaux (200); X. Billères, P. Le Dreff, C. Bar, D. Meyran, Bataillon des Marins Pompiers, Marseille (172); M.-P. Clotteau-Lambert, F. Berthier, SAMU 44, Nantes (164); D. Thiercelin, P. Benoît, C. Ichaï, SAMU 06, Nice (151); G. Debaty, B. Bourgeois, E. Menthonnex, P. Menthonnex, SAMU 38, Grenoble (143); A. Ricard-Hibon, I. Vassor, V. Bel-pomme, SMUR, Beaujon Hospital (130); P. Roux, M. Pujos, J.-L. Ducassé, SAMU 31, Toulouse (117); C. Espesson, J.-L. Blanc, J.-C. Bertrand, SAMU 42, Saint-Etienne (103); E. Querellou, D. L'Azou, A. Pennarguear, M. Veyne, SAMU 29, Brest (86); L. Ducros, C. Broche, P. Plaisance, SMUR, CHU Lariboisière, Paris (75); P. Ecollan, L. Fievet, B. Riou, SMUR, CHU Pitié-Salpêtrière, Paris (69); L. Halbout, E. Pondaven, J.-L. Gérard, SAMU 14, Caen (68); D. Savary, J.-P. Perfus, SAMU 74, Annecy (61); R. Maupoint, Y. Poncelin, L. Holzapfel, SAMU 01, Bourg-en-Bresse (40); P. Capelle, E. Boyez, C. Delassara, SMUR, Maubeuge Hospital (37); C. Bracq, J.-B. Campagne, SMUR, Dunkerque Hospital (35); P. Dreyfus, M. Freysz, SAMU 21, Dijon (33); P. Nouguier, J.-C. Devinat, J.-P. Auffray, SAMU 13, Marseille (26); A. Gache, J.-E. de la Coussaye, SAMU 30, Nîmes (18); C. Meurisse, SMUR, Valenciennes Hospital (12); B. Boulanger, D. Jan, SAMU 56, Vannes (10); C. Lae, SMUR, Annemasse Hospital (10).

## REFERENCES

- 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.
- Lindner KH, Strohmenger HU, Ensinger H, Hetzel WD, Ahnefeld FW, Georgieff M. Stress hormone response during and after cardiopulmonary resuscitation. *Anesthesiology* 1992;77:662-8.
- Lindner KH, Prengel AW, Pfenninger EG, et al. Vasopressin improves vital organ blood flow during closed-chest cardiopulmonary resuscitation in pigs. *Circulation* 1995;91:215-21.
- Prengel AW, Lindner KH, Keller A. Cerebral oxygenation during cardiopulmonary resuscitation with epinephrine and vasopressin in pigs. *Stroke* 1996;27:1241-8.
- Wenzel V, Lindner KH, Krismer AC, Miller EA, Voelckel WG, Lingnau W. Repeated administration of vasopressin but not epinephrine maintains coronary perfusion pressure after early and late administration during prolonged cardiopulmonary resuscitation in pigs. *Circulation* 1999;99:1379-84.
- Wenzel V, Lindner KH, Krismer AC, et al. Survival with full neurologic recovery and no cerebral pathology after prolonged cardiopulmonary resuscitation with vasopressin in pigs. *J Am Coll Cardiol* 2000;35:527-33.
- Stiell IG, Hebert PC, Wells GA, et al. Vasopressin versus epinephrine for in-hospital cardiac arrest: a randomised controlled trial. *Lancet* 2001;358:105-9.
- 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.
- Adnet F, Lapostolle F. International EMS systems: France. *Resuscitation* 2004; 63:7-9.
- Introduction to the International Guidelines 2000 for CPR and ECC: a consensus on science. *Resuscitation* 2000;46: 3-15.
- Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. *Ann Emerg Med* 1991;20:861-74.
- Brown CG, Martin DR, Pepe PE, et al. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. *N Engl J Med* 1992;327: 1051-5.
- The Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. *N Engl J Med* 1986; 314:397-403.
- Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine — reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;357:2189-94.
- Popp E, Vogel P, Teschendorf P, Böttiger BW. Vasopressors are essential during cardiopulmonary resuscitation in rats: is vasopressin superior to adrenaline? *Resuscitation* 2007;72:137-44.
- Aung K, Htay T. Vasopressin for cardiac arrest: a systematic review and meta-analysis. *Arch Intern Med* 2005;165:17-24.
- International Liaison Committee on Resuscitation. 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Part 4: advanced life support. *Resuscitation* 2005;67:213-47.
- Mayr VD, Wenzel V, Voelckel WG, et al. Developing a vasopressor combination in a pig model of adult asphyxial cardiac arrest. *Circulation* 2001;104:1651-6.
- Mally S, Jelantcev A, Grmec S. Effects of epinephrine and vasopressin on end-tidal carbon dioxide tension and mean arterial blood pressure in out-of-hospital cardiopulmonary resuscitation: an observational study. *Crit Care* 2007;11(2):R39.
- Callaway CW, Hostler D, Doshi AA, et al. Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac arrest. *Am J Cardiol* 2006;98: 1316-21.
- Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; 346:549-56. [Erratum, *N Engl J Med* 2002; 346:1756.]
- Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557-63.
- Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. *JAMA* 2002;288:3008-13.
- Bunch TJ, White RD, Gersh BJ, et al. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. *N Engl J Med* 2003;348:2626-33.
- Sanders AB, Ewy GA. Cardiopulmonary resuscitation in the real world: when will the guidelines get the message? *JAMA* 2005;293:363-5.
- Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007;73:29-39.

Copyright © 2008 Massachusetts Medical Society.

## RECEIVE THE JOURNAL'S TABLE OF CONTENTS EACH WEEK BY E-MAIL

To receive the table of contents of the *New England Journal of Medicine* by e-mail every Wednesday evening and access our archives of research articles (>6 months old), you can sign up through our Web site at: [www.nejm.org](http://www.nejm.org)