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# MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

## ABSTRACT

***Background*** Cardiac arrest with widespread cerebral ischemia frequently leads to severe neurologic impairment. We studied whether mild systemic hypothermia increases the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation.

***Methods*** In this multicenter trial with blinded assessment of the outcome, patients who had been resuscitated after cardiac arrest due to ventricular fibrillation were randomly assigned to undergo therapeutic hypothermia (target temperature, 32°C to 34°C, measured in the bladder) over a period of 24 hours or to receive standard treatment with normothermia. The primary end point was a favorable neurologic outcome within six months after cardiac arrest; secondary end points were mortality within six months and the rate of complications within seven days.

***Results*** Seventy-five of the 136 patients in the hypothermia group for whom data were available (55 percent) had a favorable neurologic outcome (cerebral-performance category, 1 [good recovery] or 2 [moderate disability]), as compared with 54 of 137 (39 percent) in the normothermia group (risk ratio, 1.40; 95 percent confidence interval, 1.08 to 1.81). Mortality at six months was 41 percent in the hypothermia group (56 of 137 patients died), as compared with 55 percent in the normothermia group (76 of 138 patients; risk ratio, 0.74; 95 percent confidence interval, 0.58 to 0.95). The complication rate did not differ significantly between the two groups.

***Conclusions*** In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality. (N Engl J Med 2002;346:549-56.)

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AN estimated 375,000 people in Europe undergo sudden cardiac arrest yearly.[1] Recovery without residual neurologic damage after cardiac arrest with global cerebral ischemia is rare. After cardiac arrest with no blood flow for more than five minutes, the generation of free radicals, together with other mediators, during reperfusion creates chemical cascades that result in cerebral injury.[2] Until recently, there was no therapy with documented efficacy in preventing brain damage after cardiac arrest.

Several studies have shown that moderate systemic hypothermia (30°C)[3] or mild hypothermia (34°C)[4-8] markedly mitigates brain damage after cardiac arrest in dogs. The exact mechanism for this cerebral resuscitative effect is not clear. A reduction in cerebral oxygen consumption[9,10] and other multifactorial chemical and physical mechanisms during and after ischemia have been postulated.[11-16] These include retardation of destructive enzymatic reactions, suppression of free-radical reactions, protection of the fluidity of lipoprotein membranes, reduction of the oxygen demand in low-flow regions, reduction of intracellular acidosis, and inhibition of the biosynthesis, release, and uptake of excitatory neurotransmitters.

Preliminary clinical studies have shown that patients treated with mild hypothermia after cardiac arrest have an improved neurologic outcome, without important side effects, as compared with the outcome in historical controls.[17-20]

We compared mild hypothermia with standard normothermia in patients who had had cardiac arrest due to ventricular fibrillation. The primary end point

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*The investigators who participated in the Hypothermia after Cardiac Arrest Study Group are listed in the Appendix.



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was a favorable neurologic outcome within six months after cardiac arrest.[21-23] Secondary end points were mortality at six months and the incidence of complications during the first seven days. Nine centers in five European countries participated in the study.

## METHODS

### Patients

Patients seen consecutively in the emergency department in whom spontaneous circulation had been restored after cardiac arrest were eligible for the study. The criteria for inclusion were a witnessed cardiac arrest, ventricular fibrillation or nonperfusing ventricular tachycardia as the initial cardiac rhythm, a presumed cardiac origin of the arrest, an age of 18 to 75 years, an estimated interval of 5 to 15 minutes from the patient's collapse to the first attempt at resuscitation by emergency medical personnel, and an interval of no more than 60 minutes from collapse to restoration of spontaneous circulation.

Patients were excluded if they met any of the following criteria: a tympanic-membrane temperature below 30°C on admission, a comatose state before the cardiac arrest due to the administration of drugs that depress the central nervous system, pregnancy, response to verbal commands after the return of spontaneous circulation and before randomization, evidence of hypotension (mean arterial pressure, less than 60 mm Hg) for more than 30 minutes after the return of spontaneous circulation and before randomization, evidence of hypoxemia (arterial oxygen saturation, less than 85 percent) for more than 15 minutes after the return of spontaneous circulation and before randomization, a terminal illness that preceded the arrest, factors that made participation in follow-up unlikely, enrollment in another study, the occurrence of cardiac arrest after the arrival of emergency medical personnel, or a known preexisting coagulopathy.

### Study Design

The study was designed as a randomized, controlled trial with blinded assessment of the outcome. The protocol and consent procedure were approved by the institutional review board of each participating center. For all patients, the requirement of informed consent was waived in accordance with the ethical standards of the local institutional review board and the guidelines for good clinical practice of the European Agency for the Evaluation of Medicinal Products.[24] The patient's family was informed about the trial, and the protocol specified that if there were any objections, the patient would be withdrawn from the study. However, there were no objections.

Treatment assignments were randomly generated by computer in blocks of 10, with stratification according to center. Sealed envelopes containing the treatment assignments were provided by the biostatistics center. Immediately after a patient had been enrolled, an envelope was opened, and the patient was assigned to the specified group.

Personnel involved in the care of patients during the first 48 hours after cardiac arrest could not be blinded with respect to treatment assignments. However, the physicians responsible for assessing the neurologic outcome within the first six months after the arrest were unaware of the treatment assignments.

### Treatment

All patients received standard intensive care according to a detailed protocol. Sedation was induced by the intravenous administration of midazolam (0.125 mg per kilogram of body weight per hour initially) and fentanyl (0.002 mg per kilogram per hour initially), and the doses were adjusted as needed for 32 hours for the management of mechanical ventilation. To prevent shivering, paralysis was induced by the intravenous administration of pancuronium (0.1 mg per kilogram) every 2 hours for a total of 32 hours. Intracranial pressure was not monitored.

The temperature on admission was measured with an infrared tympanic thermometer (Ototemp LighTouch, Exergen, Watertown, Mass.). Further temperature measurements were made with a bladder-temperature probe (Foley catheter). Patients randomly assigned to the normothermia group were placed on a conventional hospital bed, and normothermia was maintained. Those randomly assigned to the hypothermia group were cooled to a target temperature of 32°C to 34°C with the use of an external cooling device (TheraKool, Kinetic Concepts, Wareham, United Kingdom). This device consists of a mattress with a cover that delivers cold air over the entire body. The goal was to reach the target bladder temperature within four hours after the return of spontaneous circulation. If this goal was not achieved, ice packs were applied. The temperature was maintained at 32°C to 34°C for 24 hours from the start of cooling, followed by passive rewarming, which we expected would occur over a period of 8 hours.

### Data Collection

Data on cardiac arrest for individual patients were recorded in the Utstein style.[25] Laboratory tests were performed at base line, 12 and 48 hours after cardiac arrest, and as clinically indicated. Risk factors for an unfavorable outcome (hypotension or a nonfatal cardiac arrest after resuscitation) were documented.

### Outcome

The primary outcome was a favorable neurologic outcome within six months, defined as a Pittsburgh cerebral-performance category of 1 (good recovery) or 2 (moderate disability) on a five-category scale; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death).[21-23] The neurologic outcome was determined without knowledge of the patient's treatment assignment. Patients with good recovery or moderate disability had sufficient cerebral function to live independently and work at least part-time.

Secondary end points were overall mortality at six months and the rate of complications during the first seven days after cardiac arrest. Bleeding of any severity, pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures, arrhythmias, and pressure sores were recorded. Since an individual patient might have more than one complication at a time, the occurrence of at least one complication of any kind per patient was also documented.

### Statistical Analysis

Continuous variables, which were not normally distributed, are reported as medians and interquartile ranges. Categorical variables are reported as counts and percentages. Primary and secondary outcomes were binary, and the chi-square test or Fisher's exact test, as appropriate, was used to compare outcomes in the hypothermia and normothermia groups. Trends across subgroups were measured with an extension of the Wilcoxon rank-sum test.[26] The difference in risk between the two groups, with the corresponding 95 percent confidence interval, was calculated as a measure of the absolute risk, which was then used to calculate the number needed to treat. Risk ratios are reported as a measure of relative risk.

We used a multivariate logistic-regression model to determine whether the association between the intervention and the primary and secondary outcomes (neurologic recovery and mortality) was confounded by base-line differences between the study groups. All the covariables listed in Table 1 were entered into the model, except for the dose of epinephrine, which was excluded because of collinearity with the interval from the patient's collapse to the restoration of spontaneous circulation. We converted odds ratios to risk ratios using the following formula:



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**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS.

| CHARACTERISTIC | NORMOTHERMIA (N=138) | HYPOTHERMIA (N=137) |
|---|---|---|
| Age — yr | | |
| Median | 59 | 59 |
| Interquartile range | 49–67 | 51–69* |
| Female sex — no./total no. (%) | 32/138 (23) | 33/137 (24) |
| Medical history — no./total no. (%) | | |
| Diabetes | 26/138 (19) | 11/135 (8) |
| Coronary heart disease | 59/138 (43) | 43/135 (32) |
| Cerebrovascular disease | 11/138 (8) | 10/135 (7) |
| NYHA class III or IV† | 16/132 (12) | 14/130 (11) |
| Location of cardiac arrest — no./total no. (%) | | |
| Home | 70/138 (51) | 69/135 (51) |
| Public place | 53/138 (38) | 48/135 (36) |
| Other‡ | 15/138 (11) | 18/135 (13) |
| Arrest witnessed — no./total no. (%)§ | 136/138 (99) | 134/137 (98) |
| Presumed cardiac origin of arrest — no./total no. (%)§ | 135/138 (98) | 135/137 (99) |
| Ventricular fibrillation or pulseless ventricular tachycardia — no./total no. (%)§ | 132/138 (96) | 133/137 (97) |
| Basic life support provided by bystander — no./total no. (%) | 68/138 (49) | 59/137 (43) |
| Interval between collapse and restoration of spontaneous circulation — min¶ | | |
| Median | 22 | 21 |
| Interquartile range | 17–33 | 15–28 |
| Total epinephrine dose — mg | | |
| Median | 3 | 3 |
| Interquartile range | 1–6 | 1–5* |
| Hypotension after resuscitation — no./total no. (%) | 68/138 (49) | 75/137 (55) |
| Subsequent nonfatal arrest — no./total no. (%) | 11/138 (8) | 15/137 (11) |
| Thrombolysis after resuscitation — no./total no. (%) | 24/133 (18) | 27/135 (20) |

*Data were not available for two patients.

†NYHA denotes New York Heart Association.

‡Other locations included a physician's office, the workplace, and the hospital.

§Although this was a criterion for inclusion in the study, in a few cases, the initial information was incorrect.

¶Data were not available for three patients in the normothermia group and four in the hypothermia group.

$$\text{risk ratio} = \text{odds ratio} \div ([1 - \text{incidence in normothermia group}] + \text{incidence in normothermia group} \times \text{odds ratio}).^{27}$$

Confounding can be assumed if the crude risk ratio differs from the adjusted risk ratio. Goodness of fit was assessed with the Hosmer–Lemeshow chi-square test. A reasonable fit can be assumed if the result is not significant at the 5 percent level. Analysis was carried out according to the intention-to-treat principle. Stata software (version 7, Stata, College Station, Tex.) was used to analyze the data.

## RESULTS

The study was carried out between March 1996 and January 2001. Since the enrollment rate was lower than expected and funding had ended by July 2000, enrollment was stopped at this date.

A total of 3551 patients were assessed for eligibility; 3246 of these patients did not meet the inclusion criteria, and 30 were not included because of logistic problems. Thus, 275 patients were enrolled, with 137 patients randomly assigned to the hypothermia group and 138 to the normothermia group (i.e., the group that received standard care after resuscitation). Hypothermia was discontinued early in 14 patients for the following reasons: death (6 patients), arrhythmia and hemodynamic instability (3), technical problems with the cooling device (2), liver rupture (1), previous random assignment to the hypothermia group (1), and an error in the duration of cooling (1). All randomized patients were included in the analysis of mortality. One patient in each group was lost to follow-up for neurologic status.

At base line, the patients in the two groups were generally similar, although the patients in the normothermia group were more likely to have a history of diabetes mellitus or coronary heart disease and to have received basic life support from a bystander than were those in the hypothermia group. These differences appear to have been due to random variation (Table 1).



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### Cooling

In patients randomly assigned to the hypothermia group, the median interval between the restoration of spontaneous circulation and the initiation of cooling was 105 minutes (interquartile range, 61 to 192). The median interval between the restoration of spontaneous circulation and the attainment of a temperature between 32°C and 34°C was 8 hours (interquartile range, 4 to 16). In 19 patients, the target temperature could not be reached. Ice packs were required for 93 of the 132 patients for whom data were available (70 percent). The median duration of cooling was 24 hours (interquartile range, 24 to 25), and among patients in whom the target temperature was reached, it was maintained for a median of 24 hours (interquartile range, 12 to 29). Passive rewarming to a temperature above 36°C lasted for a median of 8 hours (interquartile range, 8 to 12). The temperature curves for the normothermia and hypothermia groups are shown in Figure 1.

### Outcome at Six Months

A total of 75 of the 136 patients (55 percent) in the hypothermia group had a favorable neurologic outcome, as compared with 54 of the 137 (39 percent) in the normothermia group (risk ratio, 1.40; 95 percent confidence interval, 1.08 to 1.81) (Table 2). To prevent one unfavorable neurologic outcome, 6 patients would need to be treated with hypothermia (95 percent confidence interval, 4 to 25 patients). After adjustment for a history of diabetes mellitus, a history of coronary heart disease, and receipt of basic life support from a bystander, the risk ratio changed only marginally (data not shown). After adjustment for all the base-line variables shown in Table 1, the risk ratio increased slightly, to 1.47 (95 percent confidence interval, 1.09 to 1.82).

The rate of death six months after cardiac arrest was 14 percentage points lower in the hypothermia group than in the normothermia group (risk ratio for the hypothermia group, 0.74 [95 percent confidence interval, 0.58 to 0.95]) (Table 2 and Fig. 2). On the basis of the difference in the risk of death between the two groups, 7 patients would need to be treated with hypothermia (95 percent confidence interval, 4 to 33 patients) to prevent 1 death. After adjustment for base-line differences in the proportions of patients with a history of diabetes mellitus, a history of coronary heart disease, and receipt of basic life support from a bystander, the risk ratio changed only minimally (data not shown). After adjustment for all the base-line variables shown in Table 1, the effect

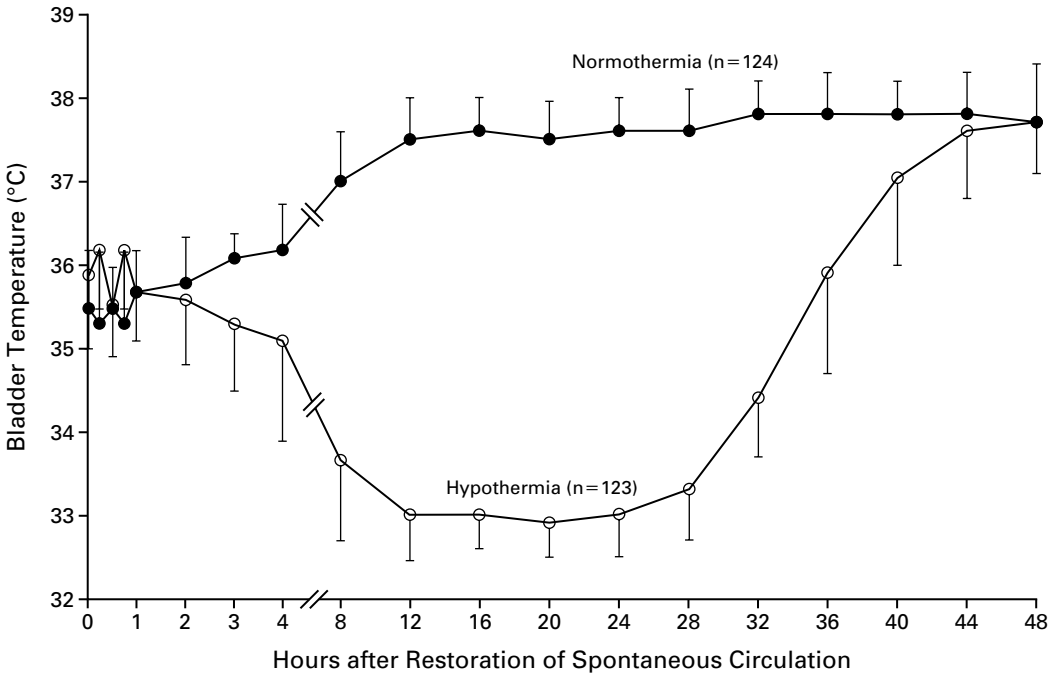


**Figure 1.** Bladder Temperature in the Normothermia and Hypothermia Groups.

The T bars indicate the 75th percentile in the normothermia group and the 25th percentile in the hypothermia group. The target temperature in the hypothermia group was 32°C to 34°C, and the duration of cooling was 24 hours. Only patients with recorded temperatures were included in the analysis.



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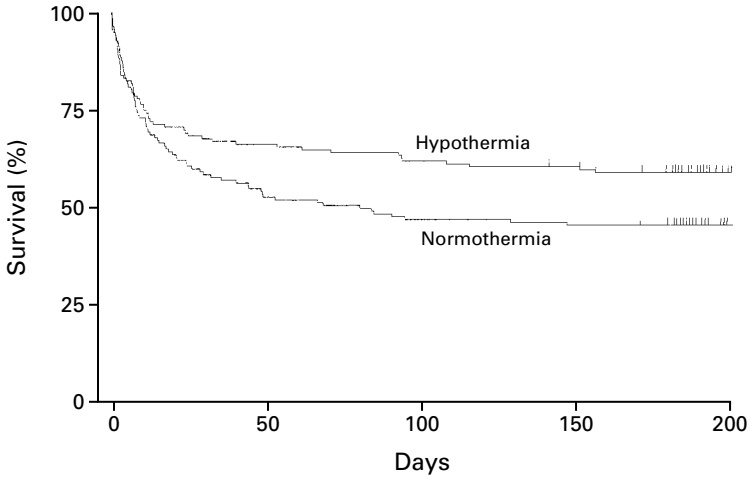
**TABLE 2.** NEUROLOGIC OUTCOME AND MORTALITY AT SIX MONTHS.

| OUTCOME | NORMOTHERMIA | HYPOTHERMIA | RISK RATIO (95% CI)* | P VALUE† |
|---|---|---|---|---|
| | no./total no. (%) | | | |
| Favorable neurologic outcome‡ | 54/137 (39) | 75/136 (55) | 1.40 (1.08–1.81) | 0.009 |
| Death | 76/138 (55) | 56/137 (41) | 0.74 (0.58–0.95) | 0.02 |

*The risk ratio was calculated as the rate of a favorable neurologic outcome or the rate of death in the hypothermia group divided by the rate in the normothermia group. CI denotes confidence interval.

†Two-sided P values are based on Pearson's chi-square tests.

‡A favorable neurologic outcome was defined as a cerebral-performance category of 1 (good recovery) or 2 (moderate disability). One patient in the normothermia group and one in the hypothermia group were lost to neurologic follow-up.




| NO. AT RISK | | | | | |
|---|---|---|---|---|---|
| Hypothermia | 137 | 92 | 86 | 83 | 11 |
| Normothermia | 138 | 74 | 66 | 64 | 9 |

**Figure 2.** Cumulative Survival in the Normothermia and Hypothermia Groups. Censored data are indicated by tick marks.

of hypothermia on mortality was slightly stronger (risk ratio, 0.62; 95 percent confidence interval, 0.36 to 0.95).

Most of the patients with unfavorable neurologic outcomes died within six months after discharge from the hospital. In this subgroup of patients, mortality after discharge did not differ significantly according to the assigned treatment (Table 3).

### Complications

The proportion of patients with any complication did not differ significantly between the two groups (93 of 132 patients in the normothermia group [70 percent] and 98 of 135 in the hypothermia group [73 percent], P=0.70). Sepsis was more likely to develop in the patients with hypothermia than in those with normothermia, although this difference was not statistically significant (Table 4). The total number of complications was not significantly higher in the hypothermia group than in the normothermia group (P=0.09).

## DISCUSSION

Our results show that among patients in whom spontaneous circulation had been restored after cardiac arrest due to ventricular fibrillation, systemic cool-



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**TABLE 3.** DEATHS BEFORE DISCHARGE AND DEATHS AFTER DISCHARGE ACCORDING TO THE CEREBRAL-PERFORMANCE CATEGORY.

| OUTCOME | NORMOTHERMIA | HYPOTHERMIA |
|---|---|---|
| Death in hospital — no. | 69 | 50 |
| Not discharged — no. | 2 | 2 |
| Death after discharge — no./ total no. discharged* | | |
| CPC 1 | 0/30 | 1/45 |
| CPC 2 | 0/12 | 0/19 |
| CPC 3 | 1/16 | 1/14 |
| CPC 4 | 6/8 | 4/6 |

*One patient in the normothermia group and one in the hypothermia group were lost to follow-up. There were no significant differences between the two groups (chi-square = 0.30, with 3 df; P = 0.96). A cerebral-performance category (CPC) of 1 indicates good cerebral performance (the patient is alert and has normal cerebral function). CPC 2 indicates moderate disability (the patient is alert and has sufficient cerebral function to live independently and work part-time). Such patients might have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory loss or other mental changes. CPC 3 indicates severe cerebral disability (the patient is conscious but dependent on others for daily support because of impaired brain function). CPC 4 indicates a vegetative state.

**TABLE 4.** COMPLICATIONS DURING THE FIRST SEVEN DAYS AFTER CARDIAC ARREST.*

| COMPLICATION | NORMOTHERMIA | HYPOTHERMIA |
|---|---|---|
| | no./total no. (%) | |
| Bleeding of any severity† | 26/138 (19) | 35/135 (26) |
| Need for platelet transfusion | 0/138 | 2/135 (1) |
| Pneumonia | 40/137 (29) | 50/135 (37) |
| Sepsis | 9/138 (7) | 17/135 (13) |
| Pancreatitis | 2/138 (1) | 1/135 (1) |
| Renal failure | 14/138 (10) | 13/135 (10) |
| Hemodialysis | 6/138 (4) | 6/135 (4) |
| Pulmonary edema | 5/133 (4) | 9/136 (7) |
| Seizures | 11/133 (8) | 10/136 (7) |
| Lethal or long-lasting arrhythmia | 44/138 (32) | 49/135 (36) |
| Pressure sores | 0/133 | 0/136 |

*None of the comparisons between the two groups, performed with the use of Pearson's chi-square test, indicated significant differences.

†The sites of bleeding were mucous membranes, the nose, the urinary tract, the gastrointestinal tract, subcutaneous tissue, and skin, as well as intracerebral and intraabdominal sites.

ing to a bladder temperature between 32°C and 34°C for 24 hours increased the chance of survival and of a favorable neurologic outcome (a cerebral-performance category of 1 or 2), as compared with standard normothermic life support.

The use of moderate hypothermia after cardiac arrest was initially reported in the late 1950s and early 1960s.[28-30] Although the target temperature was lower in these studies than in ours and the method and duration of cooling also differed from those in our study, the results were similar. However, the findings were inconclusive, and the rate of complications was higher than that observed with the mild hypothermia used in our study. There were no further investigations of hypothermia as a resuscitative measure until the 1990s, when laboratory studies demonstrated the benefit of mild hypothermia.[4-8,16] These studies led to preliminary clinical studies of mild hypothermia.

In the study by Bernard et al.,[17] cooling was induced more rapidly (with ice packs) and for a shorter period than in our study. Nevertheless, the results were similar to ours. The neurologic outcome has also been consistently favorable in studies of mild hypothermia in animals.[31-34] In the pilot studies by Yanagawa et al.[18] and Nagao et al.,[19] the frequency of a favorable neurologic outcome was similar to that in our study, although the method and duration of cooling in these studies differed from those in our study. In contrast to these encouraging findings, a study of hypothermia in patients with traumatic brain injury[35] showed no improvement in the neurologic outcome. The reasons for this discrepancy are thought to include the different pathogenesis of direct central nervous system injury, as well as the late initiation of cooling in some of the patients and variations in intensive care and life support among participating hospitals.[35,36]

Although the proportions of patients with any complication did not differ significantly between the two treatment groups in our study, a detailed analysis of the complications and an analysis of the total number of complications revealed a trend toward a higher rate of infectious problems in the hypothermia group. Nevertheless, the benefit of hypothermia exceeded its possible adverse effects.

One limitation of our study was the fact that the attending physicians could not be blinded to the treatment assignments. The relative risk may be slightly exaggerated in studies that are not double blind.[37] Although the outcome was assessed without knowledge of the treatment assignments, we did not verify that the blinding was successful. Even if it was not successful in a few cases, we do not believe that any bias that might have been introduced would have been strong enough to invalidate our findings.

The study population was restricted to a group of patients with a high risk of brain damage because of the specified interval between the patient's collapse and the first attempt at resuscitation by emergency



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medical personnel, as well as other factors, so only 8 percent of the patients assessed for eligibility were included in the trial. Further studies are warranted to determine whether our findings apply to patients at lower risk for brain damage and to those with cardiac arrest due to causes other than ventricular fibrillation.

Treatment with hypothermia may be of value in terms of public health. Each year, cardiac arrest occurs in approximately 375,000 people in Europe,[1] about 30,000 of whom would meet our inclusion criteria. We can be 95 percent confident that treatment with hypothermia would prevent an unfavorable neurologic outcome in 1200 to 7500 of these patients.

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## APPENDIX

The following investigators participated in the Hypothermia after Cardiac Arrest Study Group (the number of patients enrolled at each center is shown): **Chair, Central Coordinating Office** —M. Holzer (Universitätsklinik für Notfallmedizin, Vienna, Austria); **Steering Committee** — E. Cerchiari (Ospedale Niguarda Ca'Granda, Milan, Italy), P. Martens (A.Z. Sint Jan, Bruges, Belgium), R. Roine (Helsinki University Hospital, Helsinki, Finland), F. Sterz (Universitätsklinik für Notfallmedizin, Vienna, Austria); **Central Coordinating Office** — P. Eisenburger, C. Havel, J. Kofler, E. Oschatz, K. Rohrbach, W. Scheinecker, W. Schörkhuber; **hospital investigators** — W. Behringer, A. Zeiner (Universitätsklinik für Notfallmedizin, Vienna, Austria; 88 patients); A. Valentin (Krankenhaus Rudolfstiftung, Vienna, Austria; 2 patients); M. De Meyer (A.Z. Sint Jan, Bruges, Belgium; 35 patients); O. Takunen, M. Tiainen (Helsingin Yliopistollisen Keskussairaalan, Helsinki, Finland; 71 patients); S. Hachimi-Idrissi, L. Huyghens (Academisch Ziekenhuis van de Vrije Universiteit Brussel, Brussels, Belgium; 25 patients); M. Fischer, P. Walger (Medizinische Fakultat der Rheinischen Friedrich-Wilhems-Universitat Bonn, Bonn, Germany; 15 patients); A. Bartsch, M. Foedisch (Evangelisches Waldkrankenhaus Bonn, Bonn, Germany; 15 patients); E. Cerchiari (Ospedale Niguarda Ca'Granda, Milan, Italy; 12 patients); M. Bonizzoli, E. Pagni (Azienda Ospedalieria Careggi, Florence, Italy; 12 patients); **Monitoring Committee** — A.N. Laggner (Universitätsklinik für Notfallmedizin, Vienna, Austria), A. Kaff (Rettungs- und Krankenbeförderungsdienst der Stadt Wien, Vienna, Austria), B. Schneider (randomization procedure) (Institut für Medizinische Statistik, Universität Wien, Vienna, Austria); **Data Analysis** — M. Müllner (Universitätsklinik für Notfallmedizin, Vienna, Austria).

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