

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

DECEMBER 17, 2015

VOL. 373 NO. 25

## Hypothermia for Intracranial Hypertension after Traumatic Brain Injury

Peter J.D. Andrews, M.D., M.B., Ch.B., H. Louise Sinclair, R.G.N., M.Sc., Aryelly Rodriguez, M.Sc., Bridget A. Harris, R.G.N., Ph.D., Claire G. Battison, R.G.N., B.A., Jonathan K.J. Rhodes, Ph.D., M.B., Ch.B., and Gordon D. Murray, Ph.D., for the Eurotherm3235 Trial Collaborators\*

### ABSTRACT

#### BACKGROUND

In patients with traumatic brain injury, hypothermia can reduce intracranial hypertension. The benefit of hypothermia on functional outcome is unclear.

#### METHODS

We randomly assigned adults with an intracranial pressure of more than 20 mm Hg despite stage 1 treatments (including mechanical ventilation and sedation management) to standard care (control group) or hypothermia (32 to 35°C) plus standard care. In the control group, stage 2 treatments (e.g., osmotherapy) were added as needed to control intracranial pressure. In the hypothermia group, stage 2 treatments were added only if hypothermia failed to control intracranial pressure. In both groups, stage 3 treatments (barbiturates and decompressive craniectomy) were used if all stage 2 treatments failed to control intracranial pressure. The primary outcome was the score on the Extended Glasgow Outcome Scale (GOS-E; range, 1 to 8, with lower scores indicating a worse functional outcome) at 6 months. The treatment effect was estimated with ordinal logistic regression adjusted for prespecified prognostic factors and expressed as a common odds ratio (with an odds ratio <1.0 favoring hypothermia).

#### RESULTS

We enrolled 387 patients at 47 centers in 18 countries from November 2009 through October 2014, at which time recruitment was suspended owing to safety concerns. Stage 3 treatments were required to control intracranial pressure in 54% of the patients in the control group and in 44% of the patients in the hypothermia group. The adjusted common odds ratio for the GOS-E score was 1.53 (95% confidence interval, 1.02 to 2.30;  $P=0.04$ ), indicating a worse outcome in the hypothermia group than in the control group. A favorable outcome (GOS-E score of 5 to 8, indicating moderate disability or good recovery) occurred in 26% of the patients in the hypothermia group and in 37% of the patients in the control group ( $P=0.03$ ).

#### CONCLUSIONS

In patients with an intracranial pressure of more than 20 mm Hg after traumatic brain injury, therapeutic hypothermia plus standard care to reduce intracranial pressure did not result in outcomes better than those with standard care alone. (Funded by the National Institute for Health Research Health Technology Assessment program; Current Controlled Trials number, ISRCTN34555414.)

From the Centre for Clinical Brain Sciences (P.J.D.A.), Department of Anaesthesia, Critical Care, and Pain Medicine (H.L.S., B.A.H., C.G.B., J.K.J.R.), and Centre for Population Health Sciences (A.R., G.D.M.), University of Edinburgh, and Critical Care, Western General Hospital, NHS Lothian (B.A.H., J.K.J.R.) — all in Edinburgh. Address reprint requests to Dr. Andrews at Ward 20, Intensive Care Unit, Western General Hospital, Crewe Rd., Edinburgh EH4 2XU, United Kingdom, or at p.andrews@ed.ac.uk.

\*A complete list of investigators in the European Study of Therapeutic Hypothermia (32–35°C) for Intracranial Pressure Reduction after Traumatic Brain Injury (the Eurotherm3235 Trial) is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 7, 2015, at NEJM.org.

N Engl J Med 2015;373:2403-12.

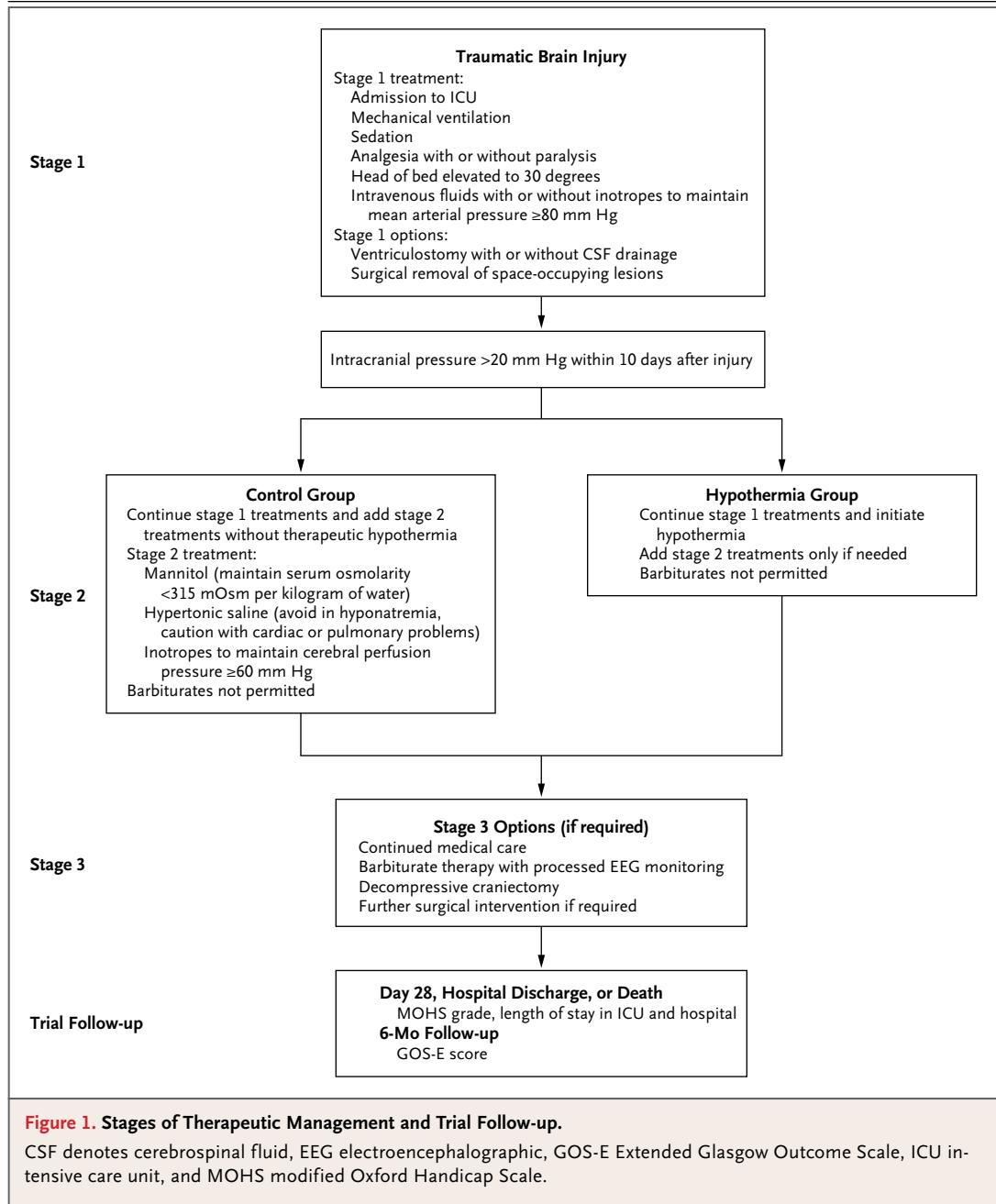
DOI: 10.1056/NEJMoa1507581

Copyright © 2015 Massachusetts Medical Society.

**I**N EUROPE, TRAUMATIC BRAIN INJURY IS the most common cause of permanent disability in people younger than 40 years of age, with the annual cost exceeding €33 billion (approximately \$37.5 billion in U.S. dollars).<sup>1,2</sup> Recent statistics show a 21% increase in the incidence of traumatic brain injury during the past 5 years — three times greater than the increase in population. Despite this, management of traumatic brain injury has been underrepresented in

medical research as compared with other health problems.<sup>3</sup> Consequently, there are few data to support the commonly used stage 2 interventions (Fig. 1) for the management of traumatic brain injury,<sup>4-6</sup> with even the use of intracranial-pressure monitoring being debated.<sup>7</sup>

Hypothermia is one treatment option for this patient group.<sup>8-12</sup> Some previous trials of early induction of prophylactic hypothermia have shown benefit, but the trials of hypothermia for



neuroprotection that were judged to be higher in quality and to have a lower risk of bias (on the basis of assessment of randomization procedures, blinding, outcome assessment, and completeness of the data)<sup>11</sup> have shown trends toward unfavorable outcomes<sup>13,14</sup> or were stopped for futility.<sup>15,16</sup> Although hypothermia is routinely used to treat elevated intracranial pressure in patients with traumatic brain injury in some intensive care units (ICUs), its effect on outcome in this context has limited evaluation.<sup>17</sup> We conducted a trial of therapeutic hypothermia for elevated intracranial pressure in which we tested hypothermia in the way that many clinicians currently use it.<sup>18-21</sup>

## METHODS

### TRIAL DESIGN AND OVERSIGHT

The European Study of Therapeutic Hypothermia (32–35°C) for Intracranial Pressure Reduction after Traumatic Brain Injury (the Eurotherm3235 Trial) aimed to recruit 600 patients who had a traumatic brain injury. The first patient was enrolled in November 2009, and the trial was stopped early in October 2014 for participant safety.

The trial protocol was developed by the first, second, fourth, and last authors in consultation with an international advisory board. The trial was conducted and reported with fidelity to the study protocol. Full details of the trial protocol have been published previously,<sup>22</sup> and the protocol is available with the full text of this article at NEJM.org. After the pilot phase of the trial, the inclusion criteria and power calculation were refined as described below. The authors vouch for the accuracy and completeness of the data and analyses. Data were gathered by investigators at the trial sites (see the Supplementary Appendix, available at NEJM.org).

Ethical approval was obtained from the Scotland A Research Ethics Committee, the Bradford Research Ethics Committee, and ethics committees in another 14 countries. Owing to the incapacitated state of the potential participants, it was not possible to obtain consent directly from them. Written informed consent was therefore sought from each eligible patient's nearest relative or person designated to give consent. Early consent was obtained when possible to prevent a delay between a rise in intracranial pressure and potential randomization.

An independent steering committee and independent data and safety monitoring committee reviewed the trial regularly, assessing conduct, progress, and safety (see the Supplementary Appendix). Trial recruitment was stopped on the advice of the data and safety monitoring committee after its ninth meeting (Table S11 in the Supplementary Appendix).

### PARTICIPANTS

All patients admitted to the ICU after a traumatic brain injury who had intracranial-pressure monitoring in place were screened. Eligible patients were believed to be of legal age for consent. Other inclusion criteria were a primary, closed traumatic brain injury; an intracranial pressure of more than 20 mm Hg for at least 5 minutes after stage 1 treatments (Fig. 1), with no obvious reversible cause; an initial head injury that had occurred no more than 10 days earlier; the availability of a cooling device or technique for more than 48 hours; a core temperature of at least 36°C (at the time of randomization); and an abnormal computed tomographic scan of the brain. Patients who were already receiving therapeutic hypothermia or who were unlikely to survive for the next 24 hours were excluded. Other exclusion criteria were the administration of barbiturate infusion before randomization, a temperature of 34°C or less at hospital admission, and pregnancy.

The inclusion criteria were changed in January 2012, on the basis of the pilot-phase findings,<sup>23</sup> to remove an upper age limit (previously 65 years) and to increase the time from injury from 72 hours to 10 days. These changes allowed the enrollment of older patients and those with evolving brain swelling.

ICUs in hospitals that provide specialist neurologic treatment for traumatic brain injury were recruited (25 centers in the United Kingdom and 39 elsewhere). Evidence of expertise with intracranial-pressure monitoring and therapeutic cooling were necessary.

### DATA COLLECTION

An online case-report form (Lincoln, Paris) was used for collection of data (Fig. S8 in the Supplementary Appendix), including baseline demographic information and data on completion of stage 1 interventions; intracranial pressure and temperature at randomization; intracranial pres-

sure, mean arterial pressure, cerebral perfusion pressure, and temperature measured hourly on days 1 through 7; failure of stage 2 therapy to control intracranial pressure; new pneumonia; and functional outcome. This trial was pragmatic, with a focus on patient-oriented outcomes; therefore, we did not collect data on which stage 2 therapies were delivered to patients.<sup>5</sup>

#### RANDOMIZATION AND STUDY TREATMENT

Participants were randomly assigned to standard care (control group) or therapeutic hypothermia plus standard care (intervention group). Randomization was performed with the use of a minimization procedure to balance assignments according to center, age, Glasgow Coma Scale (GCS) motor score, time from injury, and pupillary response. The online case-report form ensured minimization (with a random element) and concealment of allocation to study groups. The trial had an open-label design, with patients, families, and treating clinicians aware of the study-group assignments. Scoring of the primary outcome measure (described below) was blinded.

According to the study protocol, hypothermia was induced by a bolus of intravenous, refrigerated 0.9% sodium chloride (20 to 30 ml per kilogram of body weight) and thereafter maintained with the usual cooling technique of each site. Guidelines were provided for induction and maintenance of hypothermia, rewarming, and detection and treatment of shivering in the intervention group (Fig. S1, S2, and S3 in the Supplementary Appendix).

Core temperature in the hypothermia group was reduced by the minimum required to maintain an intracranial pressure of 20 mm Hg or less (in keeping with guidelines of the Brain Trauma Foundation<sup>24</sup>), within the limits of 32 to 35°C. Stage 2 treatments were added if hypothermia failed to control intracranial pressure. Stage 3 treatments were used for patients whose intracranial pressure was not controlled by hypothermia and all other stage 2 treatments.

Hypothermia was maintained for at least 48 hours in the intervention group and continued for as long as necessary to control intracranial pressure. Rewarming was considered after 48 hours at a rate of 0.25°C per hour, provided that intracranial pressure was 20 mm Hg or less. The control group also received stage 2 and 3 treatments but without hypothermia (Fig. 1).

#### OUTCOMES

The primary outcome measure was the score on the Extended Glasgow Outcome Scale (GOS-E) at 6 months after injury.<sup>25,26</sup> The eight-point scale assesses the effects of traumatic brain injury on function in major areas of life. A GOS-E score of 1 indicates death, 2 indicates a vegetative state, 3 or 4 indicates severe disability, 5 or 6 indicates moderate disability, and 7 or 8 indicates good recovery (Table S2 in the Supplementary Appendix). The GOS-E questionnaire (Fig. S4 in the Supplementary Appendix) was sent by mail to surviving participants from the trial office in Edinburgh. When this was not possible, a local staff member contacted the patient by telephone to complete the questionnaire. An investigator who was unaware of the study-group assignments scored all outcomes according to the standardized approach (Fig. S4 in the Supplementary Appendix). The manually calculated scores were automatically checked in the trial database with the use of a specially developed algorithm. An independent expert was consulted in the few cases in which adjudication was needed.

Secondary outcomes were 6-month mortality, lack of intracranial-pressure control (failure of all stage 2 therapies to control intracranial pressure to  $\leq 20$  mm Hg), incidence of pneumonia during days 1 through 7 after randomization, length of ICU stay, and grade on the modified Oxford Handicap Scale (MOHS; a score of 0 indicates no symptoms, 1 minor symptoms, 2 some restriction, 3 dependent, 4 fully dependent, and 5 death) (Table S3 in the Supplementary Appendix)<sup>27</sup> at 28 days or discharge from an acute-care hospital (whichever came first).

Data were collected on serious adverse events, including bleeding, cardiovascular instability, thermal burns, and a cerebral perfusion pressure of less than 50 mm Hg. Data on other adverse events were not collected, because many untoward events are expected in patients with traumatic brain injury who are admitted to the ICU.

#### STATISTICAL ANALYSIS

As a result of the internal pilot phase, the sample size for the full trial was reduced from 1800 to 600 patients.<sup>23</sup> Two factors contributed to this decision: our original sample size may have underestimated the possible benefit of hypothermia because, unlike participants in most previous trials, participants in the Eurotherm3235 Trial

had evidence of brain swelling (raised intracranial pressure); and we showed that an enhanced cooling intervention could be delivered, as described by Peterson et al.<sup>28</sup> These data therefore informed the revised power calculation.

Using an ordinal analysis of the GOS-E scores together with covariate adjustment (primary efficacy analysis), we were able to increase the statistical efficiency of the analysis,<sup>29,30</sup> so that a trial involving 600 patients would have power equivalent to that of a trial involving 1000 patients that assessed a binary outcome. We calculated that with such an analysis, the study would have the equivalent of 80% power to detect a rate of unfavorable outcome (GOS-E score of 1 to 4) that was 9 percentage points lower with hypothermia than with standard care (51% vs. 60%), at the 5% significance level (two-sided).

All analyses were performed with SAS software, version 9.3 (SAS Institute). Analyses were performed on an intention-to-treat basis, incorporating all patients who underwent randomization and for whom outcome data were available, with patients evaluated according to their assigned intervention.

For the primary analysis, the distribution of the 6-month GOS-E scores between the two groups (hypothermia vs. control) was compared with the use of ordinal logistic regression<sup>30</sup> and with adjustment for the following baseline covariates: age (included as a continuous variable, with the use of a linear term in the regression model), postresuscitation GCS motor score (1 or 2 [no or extensor response] vs. 3 to 6 [flexion or better response]) (Table S1 in the Supplementary Appendix), time from injury (<12 hours vs. ≥12 hours), and pupillary response (both reacting vs. one reacting vs. neither reacting; included as an unordered categorical variable in the regression model).

For this analysis, we collapsed the eight-point GOS-E to six categories by pooling death with a vegetative state and lower severe disability. This ensured that the analysis would not favor an intervention that reduced mortality at the expense of increasing the proportion of severely disabled survivors.

Prespecified subgroups for the primary analysis were defined on the basis of the baseline covariates described above, the location of the center (United Kingdom vs. elsewhere), and the volume of the center (≥10 vs. <10 patients).

We performed these analyses by including an interaction term between intervention and the relevant covariate in the ordinal logistic-regression model; a stricter level of statistical significance ( $P < 0.01$ ) was used owing to their exploratory nature.

MOHS grades were analyzed in the same way as GOS-E scores, but we collapsed the six grades to four categories by grouping dependent, fully dependent, and death (Table S9B in the Supplementary Appendix). In the analysis of the between-group difference in mortality, Cox proportional-hazards regression was used to estimate the intervention effect.

Other continuous outcomes were tested with an analysis of covariance; for binary outcomes, logistic regression was used. Intracranial pressure, core temperature, mean arterial pressure, and cerebral perfusion pressure on days 1 through 7 were analyzed post hoc with the use of a linear model, with study days as repeated measurements with a compound-symmetry covariance matrix. All these analyses used the same covariates as were prespecified for GOS-E scores together with the baseline value of the relevant variable.

## RESULTS

### RECRUITMENT

A total of 2498 patients at 55 centers in 18 countries were assessed for trial eligibility, and 387 patients at 47 centers in 18 countries underwent randomization, of whom 205 (53.0%) were recruited in the United Kingdom (Table S4 in the Supplementary Appendix). Patients underwent randomization between November 2009 (pilot phase to September 15, 2011) and October 2014, at which time recruitment was stopped (Fig. S6 in the Supplementary Appendix). The most common reasons for exclusion from the trial were an intracranial pressure of 20 mm Hg or less (41% of 2111 exclusions), the unlikelihood of survival (8%), and current receipt of therapeutic hypothermia (6%). Recruitment was stopped after the steering committee concluded that there were signs of harm with the treatment being evaluated and that a result of futility, at best, would be expected if the trial were to continue. These findings became apparent when the committee examined the designated primary outcome measure analyzed according to the prespecified statistical

analysis plan (Table S11 in the Supplementary Appendix).

On an intention-to-treat basis, 195 participants were randomly assigned to the hypothermia group and 192 to the control group. Of the 387 randomly assigned patients, 386 received the intended treatment (1 patient in the hypothermia group was withdrawn before receiving the intervention), and 376 (188 in each group) were evaluated for the primary outcome (Fig. S6 in the Supplementary Appendix). Baseline characteristics of the two groups were similar in all respects (Table 1, and Table S5 in the Supplementary Appendix). There were no significant differences between groups with respect to pre-randomization neurosurgery for single or multiple procedures (Table S6 in the Supplementary Appendix).

#### INTRACRANIAL PRESSURE AND CORE TEMPERATURE

Mean daily intracranial pressure was similar in the two groups (Fig. 2 and Table 2). Core temperature was substantially lower in the hypothermia group than in the control group during the first 4 days after randomization. During that time period, there were fewer first occurrences of failure of stage 2 therapy to control intracranial pressure in the hypothermia group than in the control group (57 vs. 84) (Table S7 in the Supplementary Appendix). This resulted in more frequent use of stage 3 treatments on days 1 through 7 in the control group than in the hypothermia group (102 of 189 patients [54.0%] vs. 84 of 192 patients [43.8%]). Barbiturate-infusion therapy was used more often in the control group than in the hypothermia group (41 patients vs. 20 patients) during days 1 through 4 after randomization, but decompressive craniectomy was not used more often (27 patients in each group) (Table S8 in the Supplementary Appendix).

A repeated-measures analysis was performed to compare the difference between the groups with respect to the change from day 1 to day 7 after randomization in core temperature, intracranial pressure, mean arterial pressure, and cerebral perfusion pressure. There was a significant difference with respect to core temperature only (Table 2 and Fig. 2).

#### PRIMARY OUTCOME

Six months after injury, the distribution of GOS-E scores was shifted in an unfavorable direction in

the hypothermia group (adjusted common odds ratio, 1.53; 95% confidence interval [CI], 1.02 to 2.30;  $P=0.04$ ) (Table 2, and Table S9A in the Supplementary Appendix). Favorable outcomes (GOS-E score of 5 to 8, indicating moderate disability or good recovery) occurred in 49 of 191 patients (25.7%) in the hypothermia group and in 69 of 189 patients (36.5%) in the control group ( $P=0.03$ ). The results without adjustment for prespecified covariates were similar for the GOS-E score (unadjusted common odds ratio, 1.55; 95% CI, 1.05 to 2.29;  $P=0.03$ ). The risk of death (hazard ratio, 1.45; 95% CI, 1.01 to 2.10;  $P=0.047$ ) favored the control group (Table 2, and Table S9A and Fig. S7 in the Supplementary Appendix).

Subgroup analysis showed no significant interaction effect between the intervention and prespecified subgroups (Fig. S5 in the Supplementary Appendix). The rate of adherence, defined as more than 80% of core temperature measurements within range for days 1 through 4, was 64.8% in the hypothermia group (32 to 35°C) and 68.8% in the control group ( $\geq 36^\circ\text{C}$ ). Serious adverse events were reported more often in the hypothermia group than in the control group (33 events vs. 10 events) (Table S10 in the Supplementary Appendix).

## DISCUSSION

In this trial involving patients with traumatic brain injury and an intracranial pressure of more than 20 mm Hg for at least 5 minutes despite stage 1 therapy, hypothermia plus standard care did not result in outcomes better than those with standard care alone. The trial was stopped early owing to safety concerns, which introduces the risk of bias, but the results suggest that outcomes were worse with hypothermia than with standard care alone.

The Eurotherm3235 Trial was a large randomized, controlled trial that tested therapeutic hypothermia as the primary (stage 2) intervention to reduce intracranial pressure after brain trauma. Literature at the time of protocol development showed that at least one episode of intracranial pressure of more than 20 mm Hg occurred in 50% of patients with traumatic brain injury who received mechanical ventilation and intracranial-pressure monitoring.<sup>31</sup> In contrast, data collected during the screening of patients for this trial

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

Characteristic	Hypothermia (N=195)	Control (N=192)
Age <45 yr — no. (%)	131 (67.2)	131 (68.2)
Age — yr	37.4±15.4	36.7±14.9
GCS motor score — no. (%)†		
1 or 2	56 (28.7)	51 (26.6)
3–6	139 (71.3)	141 (73.4)
Pupillary response — no. (%)		
Both reacting	144 (73.8)	143 (74.5)
One or neither reacting	51 (26.2)	49 (25.5)
Time from injury — no. (%)		
<12 hr	19 (9.7)	15 (7.8)
≥12 hr	176 (90.3)	177 (92.2)
Intracranial pressure at randomization — mm Hg	25.2±4.8	25.5±6.4
Core temperature at randomization — °C	37.0±0.72	37.1±0.72
Isolated TBI — no. (%)	123 (63.1)	133 (69.3)
Marshall classification — no. (%)‡		
Diffuse axonal injury I–III	72 (36.9)	78 (40.6)
Diffuse axonal injury IV	21 (10.8)	15 (7.8)
Any lesion surgically removed	46 (23.6)	52 (27.1)
High-density or mixed-density lesion	56 (28.7)	47 (24.5)
Mechanism of injury — no. (%)§		
Road-traffic accident, pedestrian	22 (11.3)	31 (16.1)
Road-traffic accident, motor vehicle	68 (35.1)	51 (26.6)
Bicycling accident	7 (3.6)	10 (5.2)
Fall	78 (40.2)	78 (40.6)
Sports injury	1 (0.5)	1 (0.5)
Assault	18 (9.3)	21 (10.9)

\* Plus–minus values are means ±SD. There were no significant differences between groups for these baseline measures. Other baseline characteristics are presented in Tables S5 and S6 in the Supplementary Appendix. TBI denotes traumatic brain injury.

† The Glasgow Coma Scale (GCS) motor score was measured on hospital admission. A score of 1 indicates that the patient makes no movements, a score of 2 indicates extension to painful stimuli, a score of 3 indicates abnormal flexion, a score of 4 indicates normal flexion, a score of 5 indicates that the patient localizes painful stimuli, and a score of 6 indicates that the patient obeys commands.

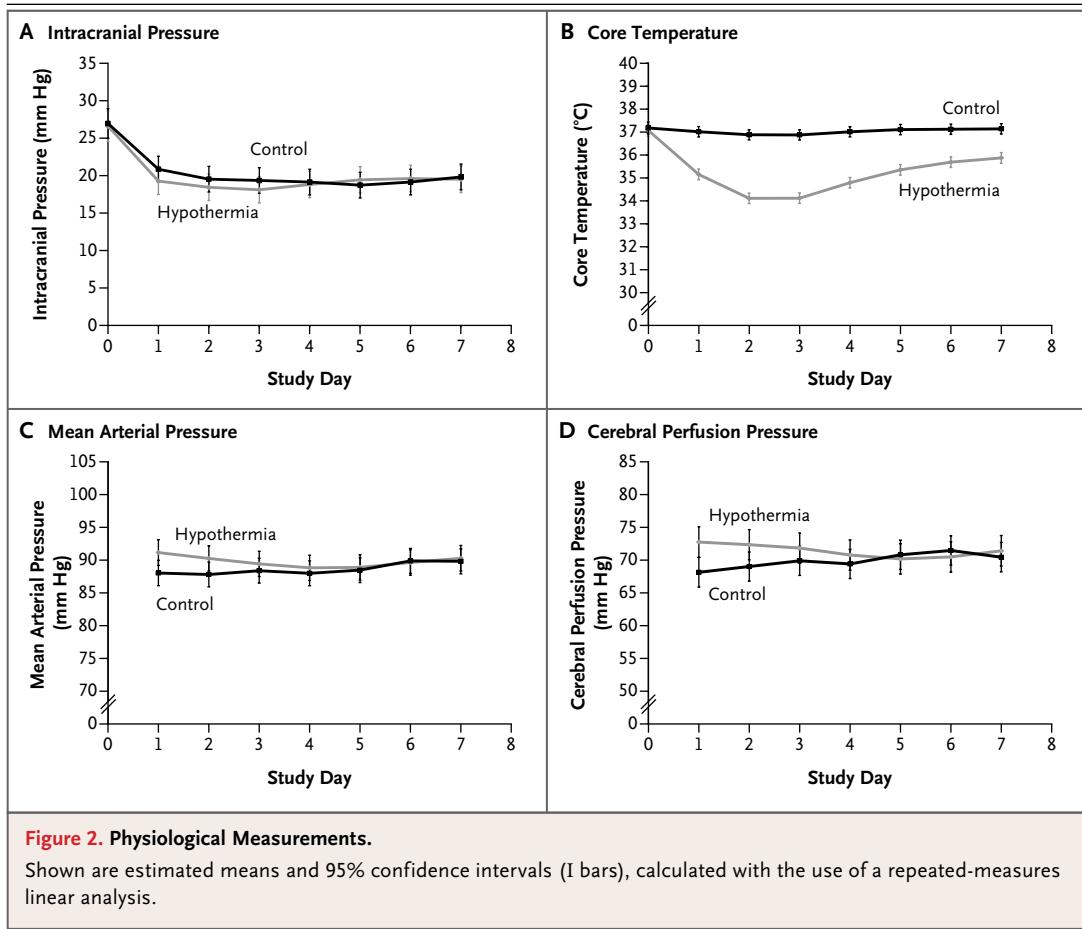
‡ The Marshall classification of traumatic brain injury is based on a review of computed tomographic scans, which were obtained at the screening visit. A diffuse injury indicates that no high-density or mixed-density lesions of more than 25 mm<sup>3</sup> are present. Diffuse injury I indicates no visible intracranial pathologic features, diffuse injury II indicates that cisterns are present with a midline shift of 0 to 5 mm or that lesion densities are present, diffuse injury III indicates that cisterns are compressed or absent with a midline shift of 0 to 5 mm, and diffuse injury IV indicates a midline shift of more than 5 mm.

§ Data were missing for one patient in the hypothermia group.

indicated that fewer patients than expected had a rise in intracranial pressure.

Standard care followed best practice (Brain Trauma Foundation guidelines) but was not prescribed in the protocol. There were guidelines

for hypothermia maintenance and control of shivering, but only induction of hypothermia, rather than a specific maintenance technique, was prescribed in the protocol. Centers used whichever cooling technique they would normally



use. Therefore, the results are not due to any one cooling method or to any treatment prescribed as part of the trial protocol. We believe this enhances the validity and generalizability of the trial and its results, because the intervention studied is already used in clinical practice and was tested in the way that centers currently use it.

In this trial, barbiturate infusion was reserved for patients who had uncontrolled intracranial pressure despite all stage 1 and stage 2 treatments; barbiturate infusion to reduce intracranial pressure<sup>32</sup> was used more frequently and earlier in the control group than in the hypothermia group (Table S8 in the Supplementary Appendix). It is plausible that barbiturate infusion may have been beneficial, but that hypothesis requires further testing. There was no difference in the use of decompressive craniectomy<sup>33</sup> between the two groups.

We found no significant between-group difference according to the time from injury to

initiation of hypothermia (<12 or ≥12 hours), a finding that is contrary to that of a previous review.<sup>34</sup> However, there were too few patients who underwent randomization less than 12 hours after injury to be confident of having excluded a subgroup effect for the time from injury. The trials of hypothermia for neuroprotection that were judged to be of higher quality and to have a lower risk of bias<sup>11</sup> have shown trends toward unfavorable outcomes<sup>13,14</sup> or were stopped for futility.<sup>15,16</sup>

The trial sponsor and steering committee accepted the recommendation of the data and safety monitoring committee in full and terminated recruitment early. Early stopping of any trial can potentially reduce the external validity of the results; however, the burden of proof required for early stopping for possible harm is considerably lower than that for overwhelming evidence of efficacy.<sup>35</sup> In this case, the remaining GOS-E scores collected after the “stopping”

**Table 2. Analysis of Primary and Secondary Outcomes for Hypothermia versus Control.\***

Variable	Estimate (95% CI)	P Value
Physiological measurements†		
Adjusted mean difference in ICP on days 1–7 — mm Hg	−0.48 (−2.04 to 1.08)	0.55
Adjusted mean difference in core temperature on days 1–7 — °C	−2.14 (−2.34 to −1.94)	<0.001
Adjusted mean difference in mean arterial pressure on days 1–7 — mm Hg	1.20 (−0.46 to 2.86)	0.16
Adjusted mean difference in cerebral perfusion pressure on days 1–7 — mm Hg	1.61 (−0.36 to 3.58)	0.11
Primary analysis: adjusted common odds ratio for GOS-E score at 6 mo‡	1.53 (1.02 to 2.30)¶	0.04
Adjusted odds ratio for unfavorable outcome‡	1.69 (1.06 to 2.70)¶	0.03
Unadjusted hazard ratio for death at 6 mo	1.45 (1.01 to 2.10)	0.047
Adjusted mean difference in squared proportion of ICP measurements of ≤20 mm Hg on days 1–7‡	440 (−160 to 1000)	0.47
Adjusted odds ratio for presence of pneumonia on days 3–7‡	1.04 (0.69 to 1.58)¶	0.84
Adjusted mean difference in log-transformed length of ICU stay — log hours‡	0.05 (0.11 to 0.22)	0.54
Adjusted common odds ratio for MOHS grade at 28 days‡**	1.65 (0.91 to 3.02)¶	0.10

\* CI denotes confidence interval, ICP intracranial pressure, and ICU intensive care unit.

† Values were calculated with the use of a repeated-measures model adjusted for age, postresuscitation GCS motor score, time from injury, pupillary response, study day, and (when available) baseline value. These are post hoc analyses.

‡ Results were adjusted for age, postresuscitation GCS motor score, time from injury, and pupillary response.

§ The eight-point Extended Glasgow Outcome Scale (GOS-E) was collapsed to six categories by pooling death (score of 1) with vegetative state (score of 2) and lower severe disability (score of 3) (Table S9A in the Supplementary Appendix).

¶ An odds ratio or common odds ratio of less than 1 corresponds to a benefit for hypothermia over control.

|| The eight-point GOS-E was collapsed to two categories: favorable outcome (score of 5 to 8) and unfavorable outcome (score of 1 to 4) (Table S9A in the Supplementary Appendix).

\*\* The six grades of the modified Oxford Handicap Scale (MOHS) were collapsed to four categories by pooling dependent, fully dependent, and death (Table S9B in the Supplementary Appendix).

decision confirmed the result and did not show regression to the mean and a resultant lack of evidence (Table S11 in the Supplementary Appendix).

A limitation of the study is the lack of blinding to the intervention, which is problematic in all trials of therapeutic hypothermia. However, because cooling to normothermia was permitted in the standard-care group, it is possible that there was masking of the intervention to patients and relatives in some cases. Outcome scoring was blinded. Lack of blinding was why, in our opinion, more serious adverse events were reported in the hypothermia group. In the control group, the same clinical events may have been considered expected and may not have been reported as serious adverse events.

The trial was designed to be pragmatic, focused on functional outcome rather than on detailed mechanistic pathways. The intensity of a stage 2 therapy is adjusted according to the effect on intracranial pressure, mean arterial pressure, and cerebral perfusion pressure. There were no clinically important differences in these

variables between the two groups. Given that there were no or limited data on the benefits and harms of standard stage 2 interventions, we elected not to record which stage 2 therapies were delivered to patients. The findings suggesting possible harm of hypothermia could be due to a biologic effect of hypothermia or due to the harms or benefits of the other therapies used differentially in the two groups. This trial did not assess the benefits and risks of hypothermia used in patients with traumatic brain injury who have severe intracranial hypertension that is refractory to all stage 2 treatments before initiation of hypothermia.

The benefits and harms of other interventions that successfully reduce intracranial pressure have not been assessed. More adequately powered clinical trials of hypertonic therapy, barbiturates, and hyperventilation are required.<sup>5</sup>

In patients with traumatic brain injury, therapeutic hypothermia plus standard care successfully reduced intracranial pressure. This intervention, however, did not improve functional recovery as compared with standard care alone.

Supported by the National Institute for Health Research Health Technology Assessment program, which funded the main phase of the study. The European Society of Intensive Care Medicine funded the pilot phase. The trial sponsors, the University of Edinburgh and NHS Lothian, provided research governance.

Dr. Andrews reports receiving lecture fees from C.R. Bard and Integra LifeSciences; and Dr. Rhodes, lecture fees from C.R. Bard. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who participated in this trial and their families, Lindsay Wilson, Ph.D., for support with training and adjudication of Extended Glasgow Outcome Scale scoring, Corrie Roberts and Dawn Gray for assistance with trial management and administration, and Jill Harris and the staff of the Wellcome Trust Clinical Research Facility for research nurse support.

## REFERENCES

- Olesen J, Gustavsson A, Svensson M, et al. The economic cost of brain disorders in Europe. *Eur J Neurol* 2012;19:155-62.
- Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011;21:718-79.
- The Lancet Neurology. A rally for traumatic brain injury research. *Lancet Neurol* 2013;12:1127.
- Roberts I, Schierhout G, Alderson P. Absence of evidence for the effectiveness of five interventions routinely used in the intensive care management of severe head injury: a systematic review. *J Neurol Neurosurg Psychiatry* 1998;65:729-33.
- Ker K, Perel P, Blackhall K, Roberts I. How effective are some common treatments for traumatic brain injury? *BMJ* 2008;337:a865.
- Le Roux P, Menon DK, Citerio G, et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Intensive Care Med* 2014;40:1189-209.
- Chestnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2012;367:2471-81.
- McIntyre LA, Fergusson DA, Hébert PC, Moher D, Hutchison JS. Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. *JAMA* 2003;289:2992-9.
- Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. *Cochrane Database Syst Rev* 2009;2:CD001048.
- Henderson WR, Dhingra VK, Chittock DR, Fenwick JC, Ronco JJ. Hypothermia in the management of traumatic brain injury: a systematic review and meta-analysis. *Intensive Care Med* 2003;29:1637-44.
- Crossley S, Reid J, McLatchie R, et al. A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury. *Crit Care* 2014;18:R75.
- Harris OA, Colford JM Jr, Good MC, Matz PG. The role of hypothermia in the management of severe brain injury: a meta-analysis. *Arch Neurol* 2002;59:1077-83.
- Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med* 2008;358:2447-56.
- Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *Lancet Neurol* 2011;10:131-9.
- Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 2001;344:556-63.
- Maekawa T, Yamashita S, Nagao S, Hayashi N, Ohashi Y. Prolonged mild therapeutic hypothermia versus fever control with tight hemodynamic monitoring and slow rewarming in patients with severe traumatic brain injury: a randomized controlled trial. *J Neurotrauma* 2015;32:422-9.
- Shiozaki T, Sugimoto H, Taneda M, et al. Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *J Neurosurg* 1993;79:363-8.
- Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM. The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. *J Neurosurg* 1993;79:354-62.
- Zhi D, Zhang S, Lin X. Study on therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. *Surg Neurol* 2003;59:381-5.
- Jiang JY, Xu W, Li WP, et al. Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. *J Cereb Blood Flow Metab* 2006;26:771-6.
- Tokutomi T, Miyagi T, Takeuchi Y, Karukaya T, Katsuki H, Shigemori M. Effect of 35 degrees C hypothermia on intracranial pressure and clinical outcome in patients with severe traumatic brain injury. *J Trauma* 2009;66:166-73.
- Andrews PJ, Sinclair HL, Battison CG, et al. European Society of Intensive Care Medicine study of therapeutic hypothermia (32-35°C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm3235Trial). *Trials* 2011;12:8.
- Andrews PJ, Sinclair LH, Harris B, et al. Study of therapeutic hypothermia (32 to 35°C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm 3235Trial): outcome of the pilot phase of the trial. *Trials* 2013;14:277.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *J Neurotrauma* 2007;24:Suppl 1:S55-S58.
- Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. *J Neurol Neurosurg Psychiatry* 1981;44:285-93.
- Wilson JT, Edwards P, Fiddes H, Stewart E, Teasdale GM. Reliability of postal questionnaires for the Glasgow Outcome Scale. *J Neurotrauma* 2002;19:999-1005.
- Bamford JM, Sandercock PA, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989;20:828.
- Peterson K, Carson S, Carney N. Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. *J Neurotrauma* 2008;25:62-71.
- Murray GD, Barer D, Choi S, et al. Design and analysis of phase III trials with ordered outcome scales: the concept of the sliding dichotomy. *J Neurotrauma* 2005;22:511-7.
- Roozenbeek B, Lingsma HF, Perel P, et al. The added value of ordinal analysis in clinical trials: an example in traumatic brain injury. *Crit Care* 2011;15:R127.
- Stocchetti N, Colombo A, Ortolano F, et al. Time course of intracranial hypertension after traumatic brain injury. *J Neurotrauma* 2007;24:1339-46.
- Nordby HK, Nesbakken R. The effect of high dose barbiturate decompression after severe head injury: a controlled clinical trial. *Acta Neurochir (Wien)* 1984;72:157-66.
- Timofeev I, Czosnyka M, Nortje J, et al. Effect of decompressive craniectomy on intracranial pressure and cerebrospinal compensation following traumatic brain injury. *J Neurosurg* 2008;108:66-73.
- Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet* 2008;371:1955-69.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1-39.

Copyright © 2015 Massachusetts Medical Society.