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Decompressive Craniectomy vs Craniotomy for Traumatic Acute Subdural Hematoma

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ABSTRACT

Background

Traumatic acute subdural hematomas frequently require surgical evacuation via a craniotomy (bone flap replaced) or decompressive craniectomy (bone flap not replaced). Craniectomy may prevent intracranial hypertension, but it is unclear if it is associated with better outcomes. We conducted a trial to compare the two techniques.

Methods

Patients undergoing surgery for traumatic acute subdural hematoma were randomly assigned in a 1:1 ratio to craniotomy or decompressive craniectomy of ≥11 cm anteroposterior diameter in both groups. Patients with intra-operative brain swelling that would be anticipated to prevent replacement of the bone flap without compressing the brain were not enrolled. The primary outcome was the Extended Glasgow Outcome Scale (GOSE) (an 8-point scale, ranging from death [1] to “upper good recovery”, reflecting no problems, [8]) at 12 months, obtained by questionnaires. Secondary outcomes included GOSE at 6 months and quality of life on the EQ-5D-5L scale.

Results

A total of 450 patients were enrolled; 228 assigned to craniotomy and 222 to craniectomy. The median size of the bone flap was 13 cm (IQR 12 to 14) in both groups. The common odds ratio for the differences across GOSE scores at 12 months was 0.85 (95% confidence interval, 0.6 to 1.18; p=0.324). Results were similar at 6 months. At 12 months death had occurred in 30.2% in the craniotomy group versus 32.2% in the craniectomy group; vegetative state occurred in 2.3% versus 2.8%, and good recovery occurred in 25.6% versus 19.9%, respectively. EQ-5D-5L scores were similar in the two trial groups at 12 months. Additional cranial surgery within 2 weeks after

randomization was required in 14.5% of patients in the craniotomy group and 6.9% of patients in the craniectomy group. Wound complications, including surgical site infections, occurred in 3.9% patients in the craniotomy group and 12.1% patients in the craniectomy group.

Conclusions

Among patients undergoing evacuation of acute traumatic subdural hematoma with decompressive craniectomy or craniotomy of the sizes used in this trial, disability and quality of life outcomes were similar in both groups. Additional surgery was required in a higher proportion of the craniotomy group but more wound complications occurred in the craniectomy group.

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INTRODUCTION

Decompressive craniectomy is a surgical procedure in which a large skull section is removed, and the underlying dura mater is opened widely.[1] It has been shown to reduce mortality when used as a last-tier treatment for post-traumatic intracranial hypertension[2] but is associated with a higher rate of unfavorable outcomes[3] when used as a second-tier treatment. However, the most common indication for a decompressive craniectomy is a traumatic subdural hematoma.[4 - 7]

As acute subdural hematomas are often associated with underlying parenchymal brain injury, brain swelling can be encountered intra-operatively or post-operatively.[8,9] Therefore, a primary decompressive craniectomy is often performed at the time of evacuating an acute subdural hematoma, either due to brain swelling that does not allow replacement of the bone flap without compressing the brain or pre-emptively in anticipation of swelling in the ensuing days based on clinician judgement.[10] In the former situation, the bone flap must be left out. However, there is limited evidence with respect to the added value of performing a decompressive craniectomy pre-emptively in this setting.[11] The effectiveness of a primary decompressive craniectomy (bone flap left out) compared to a craniotomy (bone flap replaced) for evacuation of acute subdural hematomas has not been adequately studied but it is important to address this choice in a trial, particularly because craniectomy necessitates storage of the bone flap and and/or subsequent operation for reconstructing the skull (termed cranioplasty) that has risks.[12] We conducted a multi-center, randomized, controlled trial to compare the outcomes of craniotomy versus decompressive craniectomy in adult patients with acute traumatic subdural hematoma.

METHODS

Trial design and oversight

The RESCUE-ASDH trial (Randomized Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Hematoma) was an investigator initiated, international, multi-center, pragmatic, randomized trial in adult head-injured patients undergoing evacuation of an acute subdural hematoma. Ethical approval was obtained from the North West - Haydock Research Ethics Committee (14/NW/1076) in the United Kingdom, and ethics committees in the participating countries. The funder was the National Institute for Health and Care Research Health Technology Assessment Programme, which had no involvement in design or analysis but required approval of substantial changes to the study design (see below). The trial protocol was designed by a team of neurosurgeons, intensivists and methodologists from several hospitals and universities worldwide led by the first and senior authors. The analysis was conducted by the penultimate author who is the trial statistician. The first draft of the manuscript was written by the first two authors and the last author and was revised by all the authors, who collectively agreed to submit the manuscript for publication.

An internal pilot phase, which enrolled 92 patients at 19 trial sites, confirmed the feasibility of the overall trial. The pilot phase did not aim to assess efficacy or re-estimate the overall sample size. These 92 patients were included in the final analysis of the current trial.

It was anticipated that most patients would lack capacity to consent for participation in the trial. When possible, written informed consent was obtained from their legal representative. Due to the time-sensitive nature of evacuating acute subdural hematomas, patients whose legal representative was not available could be enrolled in the trial with the agreement of an independent doctor. When a legal representative became available, their consent was sought retrospectively. When patients regained capacity, their retrospective consent was also sought. An independent trial steering committee and an independent data monitoring and ethics committee reviewed the trial every 6 to 12 months to assess conduct, progress, and safety. The trial protocol

was designed in a collaborative fashion by clinicians and researchers from several hospitals and universities internationally with methodological input from the Cambridge Clinical Trials Unit. The trial protocol is available as part of the appendix. The trial was conducted in accord with the Helsinki Harmonisation Guidelines and investigators vouch for the accuracy and completeness of the data and the analyses and for the fidelity of this report to the trial protocol and the statistical analysis plan and full reporting of adverse events.

Patients

To be eligible for enrolment, patients had to be over 16 years old and have an acute subdural hematoma on a computed tomography (CT) scan of the brain that required evacuation with a large bone flap either by a craniotomy or decompressive craniectomy according to the opinion of the admitting neurosurgeon. There was no restriction in the time from injury or development of a subdural hematoma to eligibility for enrollment. Patients with additional cerebral lesions (such as intracerebral hematoma or contusions) could be included. Patients with bilateral acute subdural hematomas both requiring evacuation, severe pre-existing disability or severe comorbidity which would lead to a poor outcome even if the patient made a full recovery from the head injury were excluded from trial participation. Trial sites were hospitals with acute neurosurgical services for patients with traumatic brain injury (See Supplementary Appendix available at NEJM.org).

Treatment and randomization

Enrolled patients underwent evacuation of the acute subdural hematoma in the operating room under general anesthesia. In both trial groups, a bone flap of recommended size ≥ 11 cm in anteroposterior diameter ipsilateral to the hematoma was raised, the dura opened, and the hematoma evacuated. Other lesions, such as intracerebral hematoma or contusions, could be evacuated at the surgeon's discretion. After evacuating the subdural hematoma, patients were randomly assigned to a trial treatment group in the operating room with the use of a central

telephone or web-based randomization service. The process of randomization took place intra-operatively. If the brain was too swollen to allow replacement of the bone flap without compressing it, the bone flap was left out and the patient was not randomized.

Block randomization was used, with a block size of 4 and allocation ratio of 1:1; subjects were allocated randomly within each block. Allocation was stratified by geographical region, age group, severity of injury and CT findings (see Protocol for further details available at NEJM.org). Patients in the craniotomy group could undergo a decompressive craniectomy at a later time at the discretion of their treating clinician if their condition deteriorated after their index procedure. It was not possible to mask patients, relatives and treating doctors as the skull defect is noticeable until a cranioplasty is undertaken. However, outcomes were adjudicated centrally by investigators masked to treatment assignment.

Patients randomized to craniotomy had their bone flap replaced and fixed to the surrounding skull with an appropriate fixation system prior to scalp closure. Patients randomized to decompressive craniectomy had their dura left open or there was a non-constricting duraplasty prior to scalp closure, and their bone flap was left out. The type of the incision, method used to close the dura in the craniotomy group, use of wound drains and intracranial pressure monitors, and method for scalp closure were left to the discretion of the surgeons. At U.K sites, most reconstructions of the craniectomy were later done with titanium or synthetic materials; In India, most cranioplasty replacements were later performed from the autologous bone flap with storage of the flap in the abdominal wall. Management of the patients, pre-, intra- and post-operatively was undertaken according to each center’s standard practice for head-injured patients.

Outcomes

The primary outcome measure was the extended Glasgow Outcome Scale (GOSE) at 12 months post-injury. The GOSE is an ordinal outcome scale assessing functional independence, work, social and leisure activities, and personal relationships.[13] Its eight outcome categories are as follows: death (1), vegetative state (2; unable to obey commands), lower severe disability (3; dependent on others for care), upper severe disability (4; independent at home), lower moderate disability (5; independent at home and outside the home but with some physical or mental disability), upper moderate disability (6; independent at home and outside the home but with some physical or mental disability, with less disruption than lower moderate disability), lower good recovery (7; able to resume normal activities with some injury-related problems), and upper good recovery (8; no problems).

Postal questionnaires were used to follow up surviving participants and collated centrally by the Cambridge Clinical Trials Unit.[14] If no response was received, a member of the research team contacted the patient or a caregiver by telephone to complete the questionnaire. Two trial team investigators, who were unaware of the trial-group assignments, centrally adjudicated outcomes based on the GOSE questionnaires independently of each other according to a standardized approach. Disagreements were resolved by consensus between them or with the consultation of a third trial team investigator who was also unaware of the trial-group assignments.

There were 12 secondary outcomes: GOSE at 6 months post-injury; EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L) utility index score at discharge, 6 months and 12 months after randomization (responses on the EQ-5D-5L were converted into a utility index score with the use of the cross-walk algorithm; scores range from −0.594 [health state worse than death] to 1 [perfect health state] — patients who died were given a score of zero);[15,16] Glasgow Coma Scale (GCS) on discharge from the intensive care unit (ICU) and from the neurosurgical unit; length of stay in ICU, neurosurgical and rehabilitation unit; therapy intensity level (TIL) in the ICU (TIL scores were

collected during the ICU stay after randomization; daily TIL basic scores range are TIL 0 – no specific ICP-directed therapy, TIL 1 – basic ICU care, TIL 2 – mild, TIL 3 – moderate, and TIL 4 – extreme ICP lowering measures);[17] discharge destination from neurosurgical unit; mortality at 30 days, 6 and 12 months post-injury; serious adverse events and surgical complications during index admission; further cranial surgery within 2 weeks after randomization; subsequent readmissions to the neurosurgical unit within the 12 month follow-up period for a cranioplasty; hydrocephalus requiring shunt insertion within the 12 month follow-up period, and economic evaluation. The economic evaluation has not been analyzed and will be reported separately.

Statistical analysis

A formal sample size calculation was performed using a Wilcoxon-Mann-Whitney rank-sum test for ordered categories (nQuery Advisor Version 7.0) and it was estimated that a sample of 990 patients with an ordinal analysis would allow us to detect the equivalent of an absolute difference of 8 percentage points in the proportion of participants at 12 months after randomization with a favorable outcome [difference in favorable outcome rate of 35% vs. 43%;number needed to treat (NNT) 12.5; see the definition of favorable outcome later in this section] with 90% power at the 5% significance level (two-sided), allowing for a loss to follow-up of up to 10%. The 8-percentage points difference was determined to be a clinically relevant treatment effect based on estimates of a favorable outcome in 35% of patients in previous studies.[9,18] Due to previous work by the International Mission for Prognosis and Analysis of Clinical Trials in TBI project (IMPACT-TBI project), it was decided that the primary analysis of the GOSE should use an ordinal approach, based on proportional odds methodology.[19]

However, after the trial started, many participating surgeons expressed the view that a larger treatment effect would be required to encourage them to change practice, especially since the “experimental” intervention in question (i.e. craniectomy) necessitates a second operation (i.e.

cranioplasty). Thus, it became clear that a NNT of 12.5 with its corresponding sample size of 990 may not be appropriate. To address this matter, a survey amongst 28 principal investigators who were neurosurgeons with expertise in neurotrauma was undertaken. This process was undertaken over several months, during which approximately 200 patients had been enrolled and randomized but before unblinding of any outcome data. The survey showed that the mean NNT that would lead to these surgeons to change their practice was 7, which is equivalent to a 14 percentage point treatment effect. Thus, the sample size was re-estimated in 2018 using a 14 percentage point treatment effect giving an updated sample size of 440, allowing for a 10% loss to follow-up. A sample size of 440 had more than 90% power for a 14 percentage point treatment effect with ordinal analysis and more than 80% power for a 14 percentage point treatment effect with binary analysis. This change was discussed with and approved by the independent trial steering committee, independent data monitoring and ethics committee and trial funder.

Outcome analyses were performed in the modified intention-to-treat population, which included all randomly assigned patients except those who withdrew consent for participation in the trial and those lost to follow-up. Patients were retained in the group to which they were originally allocated, regardless of protocol adherence. The main analysis was undertaken as an ordinal analysis based on the proportional odds model, with the results presented as the estimated common odds ratio with its corresponding 95% confidence interval and P value. The goodness-of-fit of the unadjusted proportional odds model was tested and the model's assumptions were met. Further pre-specified secondary analyses were planned, including a fixed dichotomy analysis and a sliding dichotomy. The former compared the proportion of patients achieving a 'favorable' outcome (defined as upper severe disability or better on GOSE) between the two arms using the chi-squared test. The latter used a sliding dichotomy to define favorable outcome; if the randomization GCS was between 3 and 8, a favorable GOSE outcome was defined as upper

severe disability or better but if the randomization GCS was between 9 and 15, a favorable GOSE outcome was defined as lower moderate disability or better.

There was no prespecified plan for imputation of missing data but we performed a post hoc analysis comparing the groups for death, vegetative state and lower severe disability vs the better outcome grades and assuming patients lost to follow up with an initial GCS ≥9 had a good outcome and those with GCS ≤8 had poor outcome. Because there was no prespecified plan for adjustment of the widths of confidence intervals for secondary outcome comparison, no definite conclusions can be drawn from these results. Details can be found in the Statistical Analysis Plan available at NEJM.org.

RESULTS

Patients

Patients were enrolled into the trial from September 2014 through April 2019 in 40 centers in 11 countries (UK, India, Canada, Malaysia, Germany, Spain, USA, Australia, Hungary, Pakistan, and Singapore). A total of 3566 patients were screened for eligibility, and 462 were enrolled. Twelve patients were withdrawn due to lack of valid informed consent or withdrawal of consent. This resulted in a total of 228 in the craniotomy arm and 222 in the decompressive craniectomy arm. Out of 228 in the craniotomy arm, 208 received the allocated intervention and 20 received a decompressive craniectomy but were included in their original assignment group. Out of 222 in the decompressive craniectomy arm, 210 received the allocated intervention and 12 received a craniotomy. The primary outcome was reported in 426 patients (215 in the craniotomy arm and 211 in the decompressive craniectomy arm; Figure 1).

The baseline characteristics were similar in both groups (Table 1). Severity of brain injury assessed by GCS, pupil reactivity, mechanism of injury, presence of major non-cranial injury and past medical history were similar in both groups. Approximately 15% in both groups had been receiving anticoagulant or antiplatelet medications. Approximately 65% had a GCS between 3 and 8 at baseline. Baseline CT brain findings were also similar in both groups; 56% of patients in the craniotomy group had an acute subdural hematoma located over the right hemisphere and 54% of patients in the craniectomy group had a hematoma located over the left hemisphere. The median size of the bone flap was 13 cm (IQR 12 to 14) in both groups (See Supplemental Appendix Table S6). The representativeness of the trial population is shown in Table S17. Approximately 2% in both trial groups were Black. Primary outcome data was missing for 13 patients in the craniotomy group and 11 in the craniectomy group (Figure 1).

Primary outcome

In the modified intention-to-treat ordinal analysis of GOSE scores at 12 months, the common odds ratio across outcome categories was 0.845 (95% confidence interval [CI], 0.6 to 1.18; P=0.324) (Table 2 and Figure 2). The GOSE distributions were as follows: death, 30.2% among 215 patients in the craniotomy group versus 32.2% among 211 patients in the craniectomy group; vegetative state, 2.3% versus 2.8%; lower severe disability (dependent on others for care), 17.7% versus 19.4%; upper severe disability (independent at home), 13.0% versus 12.8%; moderate disability, 11.2% versus 12.8%; and good recovery, 25.6% versus 19.9%.

In the pre-specified secondary fixed dichotomy analysis, unfavorable outcomes at 12 months (defined as upper severe disability or better on the GOSE scale) were reported in 108/215 (50.2%) of the patients in the craniotomy group and 115/211 (54.5%) in the craniectomy group (odds ratio 0.84 (95% CI, 0.58 to 1.23). In the sliding dichotomy analysis, the odds ratio for unfavorable outcome with craniotomy was 0.77 (95% CI, 0.53 to 1.14). Covariate adjustment of the ordinal

analysis produced results similar to the unadjusted ordinal analysis (common odds ratio 0.843 (95% CI, 0.59 to 1.19). In the post hoc sensitivity analysis accounting for missing data as described above, the OR for dichotomous groups was 0.84 (95% CI, 0.58 to 1.23) and results with sliding dichotomy and ordinal analyses were also similar to the primary analysis.

Secondary outcomes

At 6 months, the GOSE scores were similar between the 2 groups in the ordinal analysis (common odds ratio 0.836; 95% confidence interval, 0.59 to 1.18; Table 2 and Figure 2). Results for the 30-day, 6 months or 12 months mortality were similar between groups. A time-to-event analysis of length of stay, with follow-up data censored at death for patients who died in the ICU, showed that the median length of stay in ICU was 10 days in both groups.

Additional cranial surgery within two weeks after randomization was performed in 28/192 patients (14.6%) in the craniotomy group and 13/188 (6.9%) in the craniectomy group (Table 2). In the craniotomy group, most additional operations (18/28) were decompressive craniectomies. Other secondary outcomes were similar between trial groups.; full results are presented in Table 2 and the appendix (Tables S7-S15). The results of exploratory subgroup analyses are provided in the appendix (Table S16).

Safety

Procedure-related adverse events occurred in 60/228 patients (26.3%) in the craniotomy group and 57/222 patients (25.7%) in the craniectomy group (P=0.438). However, wound-related complications were reported in 4 patients in the craniotomy and 17 in the decompressive craniectomy group, while surgical site infections were reported in 5 in the craniotomy and 10 in the decompressive craniectomy group. Non-cranial adverse events (pulmonary, cardiac, renal,

hepatobiliary, gastrointestinal, thrombotic, miscellaneous) were reported in 113/228 (49.6%) craniotomy patients and 104/222 (46.8%) craniectomy patients (P=0.282).

DISCUSSION

In this trial involving adult patients with traumatic acute subdural hematomas requiring surgical evacuation, we found no significant difference across GOSE outcomes between the craniotomy (bone flap replaced) and decompressive craniectomy (bone flap left out) at 12 months and similar results between groups for most secondary outcomes. To our knowledge, there are no uniformly accepted criteria that predict the development of post-operative brain swelling and elevated intracranial pressure in this setting and inform the choice of craniotomy for evacuation of the hematoma vs craniectomy. Systematic reviews of the literature have identified no randomized trials that address the issue that led to this trial and in non-randomized studies, conclusions have been limited due to confounding by indication with more severely injured patients undergoing craniectomy more frequently than craniotomy.[11,20] Therefore, the role of a pre-emptive decompressive craniectomy in this setting is not known and has been identified as a research priority.[21]

Although the present trial found no significant difference in mortality or GOSE outcomes between the decompressive craniectomy and the craniotomy groups, additional cranial operations within two weeks after randomization were performed more frequently in the craniotomy group and most of them were decompressive craniectomy for brain swelling. However, patients in the decompressive craniectomy group had more wound-related complications and surgical site infections. Even though disability and other outcomes were similar between the groups, the trial may have practical implications. If the bone flap can be replaced without compressing the brain,

surgeons may consider doing so, as opposed to performing a pre-emptive decompressive craniectomy. These findings may not be relevant for resource-limited or military settings, where pre-emptive craniectomy is often used due to the absence of advanced ICU facilities for post-operative care.[22,23]

Our trial has limitations. First, the clinicians caring for patients were not masked to trial-group assignments. However, outcome adjudication was performed by personnel who were unaware of the group assignments. Outcome results were obtained by postal questionnaires or telephone interviews and may not reflect findings on clinical examination and personal interview. Second, 8.8% of patients allocated to craniotomy had a craniectomy and 5.4% of patients allocated to craniectomy had a craniotomy. This non-adherence with the allocation did not influence the primary analysis, which was based on the modified intention-to-treat principle. Third, 36 patients (8%) who were randomized were not included in the final analysis due to consent withdrawal and/or loss to follow-up. However, the sample size calculation for powering of the trial allowed for a loss to follow-up up to 10%. Finally, the trial did not formally examine other surgical techniques, such as a floating/hinge craniotomy, lager-size craniectomies, removal of contusions, cisternal opening and irrigation, that may have a role in this setting.

In conclusion, among adult patients undergoing evacuation of acute traumatic subdural hematoma, decompressive craniectomy and craniotomy gave similar results in in overall outcomes at 12 months. Additional craniectomies were required more frequently in the craniotomy group but wound complications and surgical-site infections occurred more frequently in the craniectomy group.

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

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Figure 1. Screening, Randomization, and Follow-up

* 407 patients were not randomized but followed up as part of the observational study

[a] The main reason for non-adherence was intra-operative brain swelling

[b] The main reason for non-adherence was a relaxed brain

[c] Of those, 8 were known to be alive

[d] Of those, 5 were known to be alive

[e] Of those, 9 were known to be alive

[f] Of those, 9 were known to be alive

Figure 2. Stacked Bar Chart of Extended Glasgow Outcome Scale (GOSE) Results at 6 Months and 12 Months.

Table 1. Characteristics of the Patients at Baseline. *		
Characteristic	**Craniotomy** (N=228)	**Decompressive craniectomy** (N=222)
Age — yr	48.3±16.5	48.8±16.6
Male sex — no/total no. (%)	178/228 (78.1)	179/222 (80.6)
Ethnicity [a]		
White — no./total no. (%)	117/227 (51.5%)	117/219 (53.4%)
Asian — no./total no. (%)	100/227 (44.1%)	90/219 (41.1%)
Black — no./total no. (%)	4/227 (1.8%)	4/219 (1.8%)
Other — no./total no. (%)	6/227 (2.6%)	8/219 (3.7%)
Any antithrombotic medication — no./total no. (%) [b]	30/209 (14.4)	31/202 (15.3)
Presence of major non-cranial injury requiring admission — no./total no. (%)	90/225 (40.0)	83/220 (37.7)
GCS 3-8 [c]	148/228 (64.9)	146/222 (65.8)
Initial CT brain findings		
Presence of midline shift > 5mm — no./total no. (%)	195/226 (86.3)	189/221 (85.5)
Compression / absence of basal cisterns —	197/226 (87.2)	192/221 (86.9)
Presence of parenchymal contusions ≤25cc —	109/227 (48.0)	104/221 (47.1)

* Plus–minus values are means ±SD. Total number of patients that are less than 228 in the craniotomy group and less than 222 in the decompressive craniectomy group indicate that data were missing / unknown for some patients

[a] Distribution across countries was similar for the two groups

[b] Includes antiplatelets and anticoagulants

[c] Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating a worse injury. The median GCS for the craniotomy group was 8 (IQR 4, 11) and the median GCS for the craniectomy group was 7.5 (IQR 6, 11).

Table 2. Efficacy and Safety Outcomes.					
Variable	**Craniotomy** (N=228)	**Decompressive craniectomy** (N=222)	**Measure of Effect**	**Difference or Odds Ratio (95%CI)**	**P Value**
Primary outcome					
Extended Glasgow Outcome Scale (GOSE) at 12 mo — no./ total no. (%)					
Ordinal outcomes					
Dead	65/215 (30.2)	68/211 (32.2)	Common odds ratio	0.85 (0.6 to 1.18)	0.324
Vegetative state (VS)	5/215 (2.3)	6/211 (2.8)			
Lower severe disability (LSD)	38/215 (17.7)	41/211 (19.4)			
Upper severe disability (USD)	28/215 (13.0)	27/211 (12.8)			
Lower moderate disability (LMD)	12/215 (5.6)	11/211 (5.2)			
Upper moderate disability (UMD)	12/215 (5.6)	16/211 (7.6)			
Lower good recovery (LGR)	17/215 (7.9)	13/211 (6.2)			

Upper good recovery (UGR)	38/215 (17.7)	29/211 (13.7)			
Secondary outcomes					
Extended Glasgow Outcome Scale (GOSE) evaluated at 6 mo — no./ total no. (%)[b]					
Dead	63/206 (30.6)	57/201 (28.4)	Common odds ratio	0.84 (0.59 to 1.18)	-
Vegetative	7/206 (3.4)	14/201 (7.0)			
Lower severe disability	34/206 (16.5)	45/201 (22.4)			
Upper severe disability	28/206 (13.6)	29/201 (14.4)			
Lower moderate disability	16/206 (7.8)	9/201 (4.5)			
Upper moderate disability	17/206 (8.3)	16/201 (8.0)			
Lower good recovery	16/206 (7.8)	15/201 (7.5)			
Upper good recovery	25/206 (12.1)	16/201 (8.0)			
Mortality at 30 days — no./ total no. (%)	48/225 (21.3)	44/220 (20.0)	Odds ratio	1.09 (0.69 to 1.72)	-
Further cranial surgery within 2 weeks after randomization — no./ total no. (%)[a]	28/192 (14.6)	13/188 (6.9)	Percentage-point difference	7.6 (0.01 to 0.14)	-

Mean EQ-5D-5L utility index score					
At discharge (no)	0.247 (179)	0.271 (185)	Difference (95% CI)	-0.024 (-0.098 to 0.049)	-
At 6 mo (no)	0.434 (193)	0.386 (188)		0.048 (-0.031 to 0.126)	-
At 12 mo (no)	0.455 (197)	0.397 (199)		0.058 (-0.024 to 0.141)	-

[a] A total of 49 cranial operations within 2 weeks after randomization were reported in 41 patients across both groups; 5/28 patients in the craniotomy group and 2/13 patients in the craniectomy group had more than one cranial operation within 2 weeks after randomization. Of the 49 operations, 19 were decompressive craniectomies (38.8%); 18 of those occurred in the craniotomy group.

[b] Primary outcome data was missing for 24/450 patients (5.3%). No imputation was undertaken for missing data but results of sensitivity analyses are given in the text.. Because there was no prespecified plan for adjustment of the widths of confidence intervals for secondary outcomes, no definite conclusions can be drawn from these results.

Table 3. Adverse events					
Variable	**Craniotomy** (N=228)	**Decompressive craniectomy** (N=222)	**Measure of Effect**	**Difference or Odds Ratio (95%CI)**	**P Value**
Non-cranial — no./ total no. (%)[a]	113/228 (49.6)	104/222 (46.8)	Percentage-point difference	2.7 (-0.07 to 0.12)	0.282
Procedure related — no./ total no. (%)[b]	60/228 (26.3)	57/222 (25.7)	Percentage-point difference	0.64 (-0.07 to 0.08)	0.438

[a] 270 non-cranial adverse events were reported for 113/228 patients in the craniotomy group, whereas 289 adverse events were reported for 104/222 patients in the decompressive craniectomy group. There were no differences in the types of adverse events experienced between the two groups.

[b] 9/228 (3.9%) patients in the craniotomy group had a wound complication (including surgical site infection) versus 27/222 (12.1%) in the craniectomy group (P=0.0013, Chi-square).