

# Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial

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See Comment page 361

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## Summary

**Background** Spontaneous supratentorial intracerebral haemorrhage accounts for 20% of all stroke-related sudden neurological deficits, has the highest morbidity and mortality of all stroke, and the role of surgery remains controversial. We undertook a prospective randomised trial to compare early surgery with initial conservative treatment for patients with intracerebral haemorrhage.

**Methods** A parallel-group trial design was used. Early surgery combined haematoma evacuation (within 24 h of randomisation) with medical treatment. Initial conservative treatment used medical treatment, although later evacuation was allowed if necessary. We used the eight-point Glasgow outcome scale obtained by postal questionnaires sent directly to patients at 6 months follow-up as the primary outcome measure. We divided the patients into good and poor prognosis groups on the basis of their clinical status at randomisation. For the good prognosis group, a favourable outcome was defined as good recovery or moderate disability on the Glasgow outcome scale. For the poor prognosis group, a favourable outcome also included the upper level of severe disability. Analysis was by intention to treat.

**Findings** 1033 patients from 83 centres in 27 countries were randomised to early surgery (503) or initial conservative treatment (530). At 6 months, 51 patients were lost to follow-up, and 17 were alive with unknown status. Of 468 patients randomised to early surgery, 122 (26%) had a favourable outcome compared with 118 (24%) of 496 randomised to initial conservative treatment (odds ratio 0·89 [95% CI 0·66–1·19],  $p=0\cdot414$ ); absolute benefit 2·3% (–3·2 to 7·7), relative benefit 10% (–13 to 33).

**Interpretation** Patients with spontaneous supratentorial intracerebral haemorrhage in neurosurgical units show no overall benefit from early surgery when compared with initial conservative treatment.

## Introduction

Spontaneous supratentorial intracerebral haemorrhage affects 20 in 100 000 people every year and community-based studies have indicated a mortality of more than 40%.<sup>1</sup> Most survivors are disabled. The role of medical and surgical treatment continues to be controversial. Much of this controversy relates to the penumbra of functionally impaired (but potentially viable) tissue around the haematoma. Such an ischaemic penumbra is associated with brain oedema related to the presence of thrombin.<sup>2–6</sup> Simulated removal of the mass lesion improves perfusion in the surrounding brain tissue.<sup>7,8</sup>

However, clinical studies have yielded conflicting results regarding the importance of such a penumbra.<sup>9,10</sup> If a penumbra exists in patients with spontaneous intracerebral haemorrhage, clot evacuation could then restore function to the surrounding brain tissue and improve outcome, but clinical imaging studies have so far failed to provide conclusive evidence for or against this theory. Elevated intracranial pressure and reduced cerebral perfusion pressure have been associated with poor outcome,

lending support to a possible benefit from early surgical intervention.<sup>11</sup>

In 1961, McKissock and colleagues<sup>12</sup> reported the first prospective randomised controlled trial in neurosurgery and showed that operative treatment was associated with a worse outcome than conservative treatment for patients with spontaneous supratentorial intracerebral haemorrhage. That trial has affected the management of this disorder for most of the past half century. In 1989, Auer and co-workers<sup>13</sup> reported the opposite result in a trial of endoscopic removal of haemorrhage in 100 patients. In the same year, this finding was contradicted by Juvela and colleagues<sup>14</sup> (who supported the view of the McKissock group) but the trial was too small to detect less than a substantial effect of surgery.

Since these three initial trials, a further six have been reported and meta-analysis of the first seven has shown no firm conclusions regarding the role of operative treatment.<sup>15</sup> A recent trial that used intracavity thrombolysis<sup>16</sup> did not suggest a benefit from surgery, whereas a trial of CT-guided mechanical aspiration did,<sup>17</sup> but again in a small number of patients. Many non-randomised

studies, including a large observational study of more than 7000 patients from Japan,<sup>18</sup> have identified important prognostic criteria in patients with intracerebral haemorrhage.

Improved surgical techniques, neuroimaging, neuroanaesthesia, and perioperative monitoring and care have all led to improved outcomes from surgery in many conditions. Hence, a randomised trial of the management of patients with spontaneous supratentorial intracerebral haemorrhage was timely. The International Surgical Trial in Intracerebral Haemorrhage (STICH) aimed to assess whether a policy of early surgical evacuation of the haematoma in patients with spontaneous supratentorial intracerebral haemorrhage would improve outcome, in terms of death and disability, compared with a policy of initial conservative treatment. Additionally, it aimed to improve definitions of the indications for early surgery. STICH was designed as an international, multicentre, parallel-group study.

## Methods

### Patients

Randomisation commenced in 1995 in Newcastle, UK, with initial funding from the Stroke Association (UK). By the beginning of 1998, 11 centres were registered and further funding was then obtained from the Medical Research Council (MRC) in the UK for an international, multicentre trial. By the end of recruitment in February, 2003, 107 centres were registered with the trial and 1033 patients had been recruited. The full trial protocol was published in 1999.<sup>19</sup> Every centre obtained written ethical approval according to national and local guidelines before being eligible to join the study, and recorded consent to participation as required by local procedures. Patients were eligible for inclusion if they had CT evidence of a spontaneous supratentorial intracerebral haemorrhage that had arisen within 72 h and if the responsible neurosurgeon was uncertain about the benefits of either treatment (the clinical uncertainty principle). Study guidelines recommended that eligible patients should have a minimum haematoma diameter of 2 cm and a Glasgow coma score of five or more.

Patients were not eligible if: the haemorrhage was probably due to an aneurysm or an angiographically proven arteriovenous malformation; the haemorrhage was secondary to a tumour or trauma; patients had a cerebellar haemorrhage or extension of a supratentorial haemorrhage into the brainstem; patients had severe pre-existing physical or mental disability or severe comorbidity that might interfere with the assessment of outcome; surgery could not be undertaken within 24 h of randomisation.

Informed consent according to the criteria set by the local research ethics committee in every centre had to be obtained in writing before randomisation. If consent could not be obtained because the patient was in coma,

confused, or dysphasic, assent was obtained from relatives (if this was regarded by the local ethics committee as an acceptable alternative).

### Procedures

We used the 24-h telephone randomisation service provided by the Clinical Trial Service Unit (CTSU) at the University of Oxford. The responsible neurosurgeon, having obtained consent or assent, completed a one-page randomisation form before telephoning the CTSU. These key baseline data were recorded before treatment was allocated by the CTSU. A deterministic minimisation algorithm, based on side of haematoma and minimum depth from cortical surface, was initially used to ensure balance between the two groups, within every country where patients were recruited. However, the algorithm was later reprogrammed by the CTSU independently of the trial steering and trial management committees. As a result, at least 50% of patients were allocated using simple randomisation alone. This procedure did not compromise the study, and the recorded imbalance in overall numbers was entirely consistent with randomisation when so many strata were included.

Patients randomised to early surgery had their haematoma evacuated within 24 h of randomisation by the method of choice of the responsible neurosurgeon, combined with the appropriate and best medical treatment. Patients randomised to initial conservative treatment had the best medical treatment. Later evacuation had to be allowed if it became necessary because of neurological deterioration. Primary outcome was death or disability using the extended Glasgow outcome scale 6 months after ictus. Secondary outcomes included mortality, the Barthel index, and the modified Rankin scale.

Structured postal questionnaires included questions required to assess the Glasgow outcome scale,<sup>20</sup> Barthel index, and modified Rankin scale. Questionnaires were sent directly to the surviving patients or carers for completion at 6 months as a technique of masking surgeons to the outcome. They were translated into German, Czech, Spanish, Hungarian, Polish, Russian, Ukrainian, Swedish, Dutch, Chinese, Hindi, Greek, Turkish, Latvian, and Lithuanian. Patients' family practitioners (in the UK) or consultants (outside the UK) were contacted at 4 months to confirm that the patient was still alive and to confirm his or her place of residence.

Questionnaires were sent to patients at 5 months for completion by the patient, relative, or carer, and a reminder was sent at 6 months. In a few countries where the postal system was poor, patients were requested to attend a follow-up clinic where the questionnaires could be distributed and obtained. Also in some countries where literacy or language (or dialect) was problematic, an independent, masked interviewer questioned the

patients. Further reminders were sent if needed and exhaustive inquiries were made with neurosurgeons to confirm the status of patients who failed to respond, including whether they were still alive or had changed their address.

In the UK, resource use data relating to types of surgery, length of stay, and use of services after discharge were obtained from questionnaires sent to patients at 3 and 6 months. Hospital records supplemented these data. Patients in the UK were also asked to complete the EuroQol at 6 months to rate their health outcomes. A case report form was completed at 2 weeks or discharge (depending on which was earlier) to record place of discharge, operative procedures, when and why procedures took place, and any adverse events. These forms were also used to record patients' Glasgow coma scores and Glasgow outcome scales, which were used by the independent data monitoring and ethics committee to monitor the progress of the trial. These forms were then returned to the trial office in Newcastle, together with copies of the randomisation forms and prerandomisation CT scans. Measurements were made on the prerandomisation scans following a strict protocol,<sup>21</sup> which could be used to confirm the data reported on the randomisation forms. Postoperative CT scans were not requested from centres.

Our trial was undertaken in accordance with MRC guidelines for good clinical practice in clinical trials. Monitoring visits were undertaken to the major recruiting centres to ensure adherence to the protocol. All completed forms were entered onto password-protected databases and extensively checked for errors. Any data omissions or deviations from protocol were notified immediately to the centre investigators for correction. Extensive logic checking ensured that the data were validated before the unmasking of the results.

### Statistical analysis

Calculations for sample size were based on the outcome distribution expected from published work and from a prospective sample of 259 patients with intracerebral haemorrhage admitted to Newcastle General Hospital between Jan 1, 1994, and July 31, 1996. Therefore, with a favourable outcome of 40% from initial conservative treatment, a sample size of 800 would be needed to show a 10% absolute benefit from surgery (two-sided significance level of 0.05) with 80% power. A safety margin of 25% was built in to allow for protocol violations and crossovers, making a total sample size of 1000.

We anticipated that problems with compliance would arise (patients might withdraw consent for the operation, demand surgery after randomisation, or refuse to complete follow-up questionnaires) and that complete outcome information would be obtained for 90% of survivors. Potential crossovers included patients allocated to initial conservative treatment, who were

deemed by the responsible neurosurgeon to need surgery within the first 72 h because their condition deteriorated, and some patients allocated to early surgery who deteriorated and died before surgery could take place or whose surgery was delayed because the operating theatre was needed by another patient. All analyses were undertaken with SPSS software or RevMan Analyses 1.0.2.

Analysis was on an intention-to-treat basis using all available data. Primary outcome analysis was a simple categorical frequency comparison using a  $\chi^2$  test for favourable and unfavourable outcomes at 6 months. Patients were assigned to one of two groups on the basis of clinical status at randomisation. Prognosis was estimated from the following equation, which was derived from observational studies of non-STICH patients with spontaneous intracerebral haemorrhage: Prognostic score = (10 × admission Glasgow coma score) – age (years) – (0.64 × volume [mL]). Patients were divided into good and poor prognosis groups by the median prognostic score. For patients with a poor prognosis, a favourable outcome included the good recovery, moderate disability, and upper severe disability categories of the extended Glasgow outcome scale, whereas for those with a good prognosis, favourable outcome encompassed good recovery and moderate disability. This prognosis-based outcome for International STICH was declared before the results were unmasked.<sup>22–24</sup> The notion that a different outcome threshold is justified for more severely affected patients is familiar to clinicians who normally judge the quality of an outcome with respect to the severity of the disorder at presentation. This prognosis-based methodology has been proposed by several researchers.<sup>25,26</sup>

Secondary outcomes included mortality, which was analysed by a simple categorical frequency comparison and a survival analysis. Prognosis-based outcome analysis was also used for both the Barthel index and the modified Rankin scale. For the good prognosis group, a Barthel index of 95/100 or higher, or a Rankin score of two or below, were regarded as favourable outcomes, whereas for those with a poor prognosis, the equivalent thresholds were 65 or higher for the Barthel index and three or below for the Rankin score. For all patients, death was classified as an unfavourable outcome.

All prespecified subgroup analyses were by intention to treat and compared the primary outcome across the subgroups with formal interaction tests. The variables and prespecified subgroups were: age (<65 vs ≥65 years); haematoma volume (≤50 mL vs >50 mL); Glasgow coma score (≤8 vs 9 to 12 vs ≥13); lobar vs basal ganglia/thalamic haematoma, or both; thrombolytic or anticoagulant treatment (any vs none); severity of neurological deficit (normal or weak vs paralysed arm, normal or weak vs paralysed leg, normal speech vs dysphasia or aphasia); type of intended operation (craniotomy vs other). Furthermore, side of

haematoma (left vs right), depth from the cortical surface ( $\leq 1$  cm vs  $>1$  cm), and country were used as minimisation criteria.

A cost analysis covering a period of up to 6 months after randomisation was undertaken for UK patients. The unit costs used (base year 2001) were an amalgam of local costs from one participating centre (Newcastle) and nationally published figures in those circumstances where individual unit costs were not available.<sup>27</sup>

The protocol for this study was peer reviewed and accepted by *The Lancet*; a summary of the protocol was published on the journal's website, and the journal then made a commitment to peer-review the primary clinical manuscript.<sup>19</sup>

	Early surgery (n=503)	Initial conservative treatment (n=530)
Men	285 (57%)	306 (58%)
Age (years)	62 (52–70)	62 (53–71)
Pre-ICH modified Rankin index		
0	387 (79%)	397 (76%)
1	81 (16%)	92 (18%)
2	20 (4%)	21 (4%)
3	4 (1%)	13 (2%)
4	0	2
5	0	0
Pre-ICH mobility		
1 200 m or more outdoors	477 (97%)	499 (96%)
2 Walk indoors	13 (3%)	13 (3%)
3 Unable to walk	1	6 (1%)
Time between ictus and randomisation (h)	22 (10–36)	20 (10–35)
Glasgow coma score		
5–8	99 (20%)	106 (20%)
9–12	199 (40%)	211 (40%)
13–15	205 (41%)	213 (40%)
Affected arm		
Normal or weak	195 (39%)	225 (42%)
Paralysed	300 (60%)	298 (56%)
Not assessable	8 (2%)	7 (1%)
Affected leg		
Normal or weak	245 (49%)	269 (51%)
Paralysed	250 (50%)	251 (47%)
Not assessable	8 (2%)	10 (2%)
Speech		
Normal	130 (26%)	142 (27%)
Dysphasic or aphasic	296 (59%)	314 (59%)
Not assessable	77 (15%)	74 (14%)
Any anticoagulation or thrombolytic treatment contributing to ICH	39 (8%)	55 (10%)
Past medical history*		
Hypertension	341 (69%)	378 (72%)
On antihypertensives	225 (46%)	263 (50%)
Previous myocardial infarction	28 (6%)	44 (8%)
Previous stroke	30 (6%)	43 (8%)
Smoker	146 (30%)	134 (26%)
Other medical disorders	132 (27%)	143 (27%)
Prognostic score	27.0 (–4.1 to 50.0)	29.2 (–3.1 to 56.9)
Good prognosis†	245 (49%)	271 (51%)

ICH=intracerebral haemorrhage. Data are number of patients (%) or median (IQR).  
\*Data missing for between nine and 14 patients in early surgery and between three and ten cases in initial conservative treatment groups. †Good prognosis is a score greater than 27–672.

**Table 1: Baseline characteristics**

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study after unmasking and had final responsibility for the decision to submit for publication.

### Results

1033 patients from 83 centres in 27 countries were randomised: 503 to early surgery and 530 to initial conservative treatment. Details of all patients' age, sex, previous medical history, and Glasgow coma score at presentation are shown in table 1. The groups were well matched at baseline. More than half the patients were men and ages ranged between 19 and 93 years, with a median of 62 years (IQR 52–70). Time from ictus to randomisation varied from 2 to 72 h, with half being randomised within 20 h (10–36). A fifth of patients presented in coma (ie, Glasgow coma score  $\leq 8$ ), whereas two-fifths had a score of 13 or above. Haematoma characteristics at randomisation are shown in table 2. About two-fifths of the haematomas were lobar and a similar number were located in the basal ganglia or thalamic regions, with the rest extending through both sites. Slightly more haematomas were located on the left side than the right. The volume, using the Broderick method,<sup>28</sup> varied from 4 mL to 210 mL (median 38 mL [24–62]) and the median depth from the cortical surface was 1 cm (0–2).

The trial profile is shown in figure 1. Eight patients were withdrawn from the study after randomisation: one was recruited by an ineligible centre, one was withdrawn by the centre, five withdrew consent, and the centre lost all data for one. Thus, process data were available for 496 patients randomised to early surgery and 529 to initial conservative treatment. Another 43 patients were lost between the 2-week follow-up and 6-month follow-up. For a further 17 patients, their status at 6 months was not recorded but they were known to have died after 6 months. These 17 patients were included in the survival analysis as they were known to have been alive at follow-up, but were excluded from all other analyses because their Glasgow outcome scales at 6 months were

	Early surgery (n=503)	Initial conservative treatment (n=530)
Site of haematoma		
Lobar	196 (39%)	214 (40%)
Basal ganglia/thalamic	210 (42%)	224 (42%)
Both	94 (19%)	90 (17%)
Not assessable	3 (1%)	2
Left side of haematoma	265 (53%)	285 (54%)
Haematoma volume (mL)*	40 (24–63)	37 (23–60)
Minimum depth from cortical surface (cm)	1.0 (0.1–2.0)	1.0 (0.0–2.0)

Data are number (%) or median (IQR). \*Volume=length×width×height/2.<sup>28</sup>

**Table 2: Haematoma characteristics**

	Early surgery (n=465)	Initial conservative treatment (n=140)
Time between ictus and surgery (h)	30 (16–49)	60 (27–99)
Surgery, <12 h from ictus	74 (16%)	7 (5%)
Time between randomisation and surgery (h)	5 (2–12)	31 (11–82)
Surgery, <12 h from randomisation	339 (73%)	35 (25%)
<b>Surgical method</b>		
Craniotomy	346 (75%)	119 (85%)
Burrhole	37 (8%)	10 (7%)
Endoscopy	31 (7%)	7 (5%)
Stereotaxy	34 (7%)	3 (2%)
Other	16 (3%)	1 (1%)
Not recorded	1	0
<b>Additional neuro procedure</b>		
Re-evacuation	27 (6%)	8 (6%)
External ventricular drain	18 (4%)	8 (6%)
Intracranial pressure monitoring	10 (2%)	4 (3%)
Other	12 (3%)	4 (3%)
Not recorded	5 (1%)	0
<b>Status before evacuation</b>		
Paralysed and sedated	64 (14%)	23 (16%)
Glasgow coma score		
3–8	94 (24%)	85 (73%)
9–12	157 (40%)	25 (22%)
13–15	145 (37%)	6 (5%)
Affected arm		
Normal	42 (9%)	3 (2%)
Weak	113 (24%)	17 (12%)
Paralysed	239 (51%)	88 (63%)
Not assessable/not recorded	71 (15%)	32 (23%)
Affected leg		
Normal	49 (11%)	3 (2%)
Weak	129 (28%)	22 (16%)
Paralysed	216 (46%)	83 (59%)
Not assessable/not recorded	71 (15%)	32 (23%)
Speech		
Normal	102 (22%)	11 (8%)
Dysphasic	93 (20%)	11 (8%)
Aphasic	130 (28%)	37 (26%)
Not assessable/not recorded	140 (30%)	81 (58%)

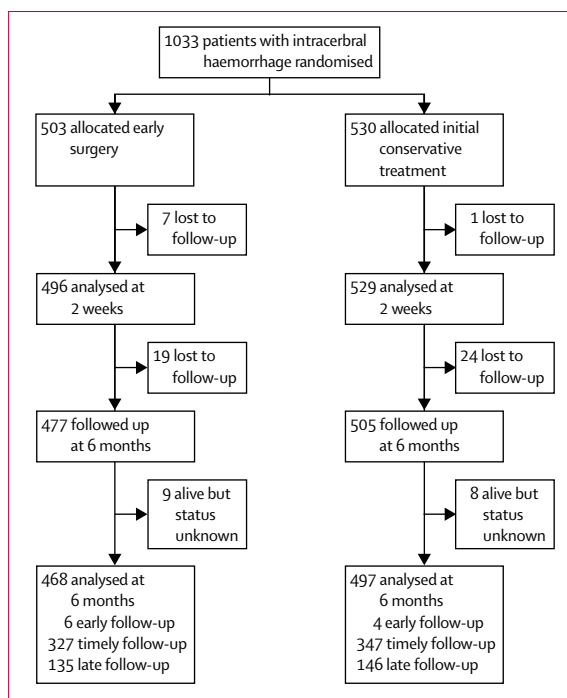
Data are number (%) or median (IQR).

**Table 3: Surgery details**

unknown. Losses to follow-up balanced between the two groups. Thus, 965 patients had complete follow-up data for the primary outcome analysis.

Of 496 assessable patients randomised to early surgery, 465 (94%) underwent surgery (table 3). However, in 28 (6%), surgery was undertaken more than 24 h after randomisation. Reasons for patients not receiving surgery were: condition deteriorated (six patients), second intracerebral haemorrhage or extension (four), other major clinical event (three), improvement (four), refusal by relative (six), confusion over allocation (two), uncertain haematoma size and location (two), and reason not recorded (four).

Of 529 assessable patients randomised to initial conservative treatment, 140 (26%) underwent surgery after an initial period of observation (table 3). Reasons for these patients undergoing operations were: rebleeding (17 patients), neurological deterioration (82), clinical deterioration (20), no improvement on



**Figure 1: Trial profile**

conservative treatment (four), raised intracranial pressure (three), oedema (five), altered consciousness (three), coma (one), aneurysm (one), not waking after external ventricular drain (one), family request (one), and reason not recorded (three). The most frequently used surgical technique was craniotomy (465 patients [77%]) and table 3 shows details of the patients' status immediately before surgery.

Comparison of tables 1 and 3 shows that patients in the initial conservative treatment group who received surgery had deteriorated substantially from their randomisation level; in fact 59% had deteriorated by three or more points on the Glasgow coma score. Additionally, those in this group who went on to have clot evacuation (n=140) compared with those who did not (n=389) were more likely to be men (91 [65%] vs 214 [55%], p=0.0403), and have haematomas with a volume greater than 50 mL (81 [58%] vs 107 [27%], p<0.0001), be superficial (102 [73%] vs 180 [46%], p<0.0001), be lobar (71 [51%] vs 142 [37%], p<0.0001), and haematomas were more likely on the right side (76 [54%] vs 169 [43%], p=0.0274).

With the prognosis-based dichotomy of the extended Glasgow outcome scale, 122 (26%) patients allocated to early surgery had a favourable outcome at 6 months, compared with 118 (24%) allocated to initial conservative treatment (odds ratio 0.89 [95% CI 0.66–1.19], p=0.414). Early surgery had an absolute benefit of 2.3% and a relative benefit of 10% (–13 to 33; table 4). The mortality rate at 6 months for the early surgery group was 36% compared with 37% for the initial conservative treatment group (odds ratio 0.95 [0.73–1.23], p=0.707);

	Early surgery (n=468)	Initial conservative treatment (n=497)	Absolute benefit (95% CI)
<b>Primary outcome</b>			
Favourable	122 (26%)	118 (24%)	2.3 (-3.2 to 7.7)
Unfavourable	346 (74%)	378 (76%)	..
Not recorded		1	..
<b>Secondary outcomes</b>			
<b>Mortality</b>			
Alive*	304 (64%)	316 (63%)	1.2 (-4.9 to 7.2)
Dead	173 (36%)	189 (37%)	..
<b>Prognosis-based modified Rankin index</b>			
Favourable	152 (33%)	137 (28%)	4.7 (-1.2 to 10.5)
Unfavourable	312 (67%)	351 (72%)	..
Not recorded	4	9	..
<b>Prognosis-based Barthel index</b>			
Favourable	124 (27%)	110 (23%)	4.1 (-1.4 to 9.5)
Unfavourable	341 (73%)	377 (77%)	..
Not recorded	3	10	..

Data are number (%). \*Includes 17 patients who were alive at 6 months but status was unknown.

**Table 4: Outcomes at 6 months**

early surgery had an absolute benefit of 1.2% and a relative benefit of 2% (-8 to 11; table 4). Survival during the first 6 months did not significantly differ between the two groups (log-rank test,  $p=0.678$ ; figure 2).

With the prognosis-based modified Rankin scale, 152 (33%) in the early surgery group had a favourable outcome compared with 137 (28%) in the initial conservative treatment group ( $p=0.116$ ); early surgery had an absolute benefit of 4.7% and a relative benefit of 17% (95% CI -4 to 37; table 4). With the prognosis-based Barthel index, 124 (27%) in the early surgery group had a favourable outcome compared with 110 (23%) in the initial conservative treatment group ( $p=0.144$ ); early surgery had an absolute benefit of 4.1% and a relative benefit of 18% (-6 to 42; table 4).

Results of the subgroup analyses are shown in figure 3. The only subgroup to show heterogeneity of

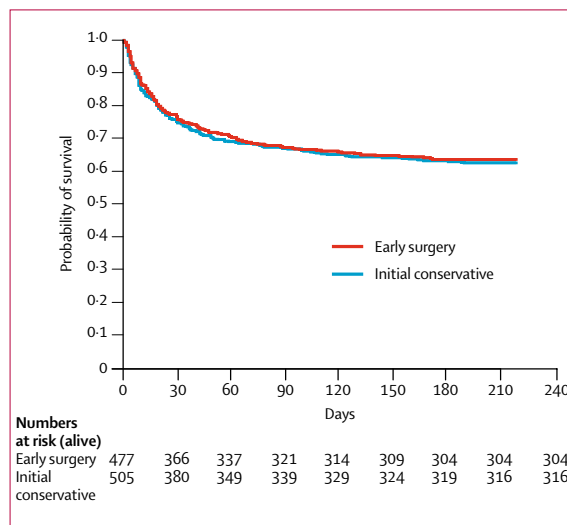


Figure 2: Kaplan-Meier survival curves

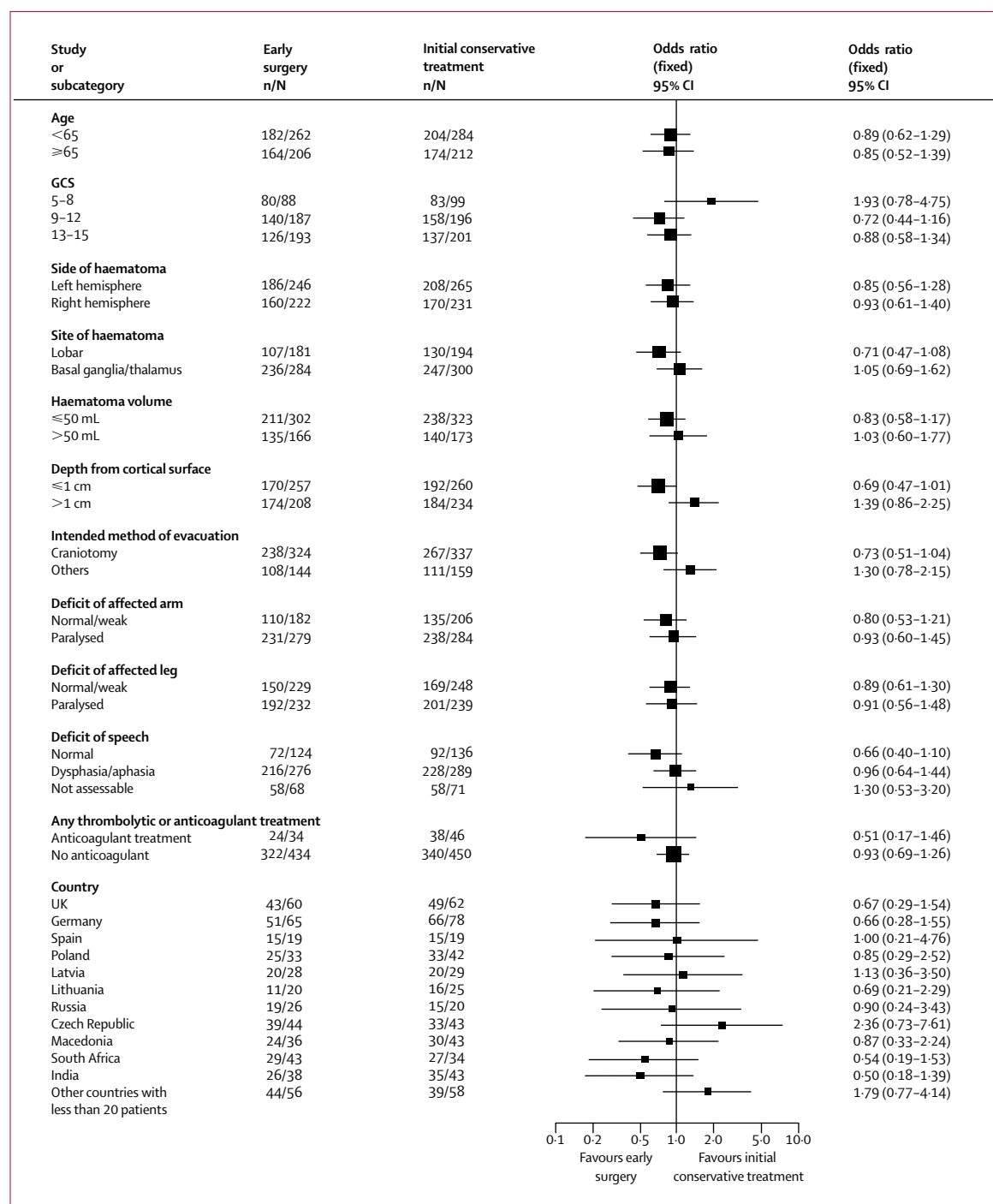
treatment response was depth of haematoma from cortical surface. A favourable outcome from early surgery was more likely if the haematoma was 1 cm or less from the cortical surface (absolute benefit 8%; 0-15); interaction between depth from cortical surface and treatment was significant ( $p=0.02$ ). A favourable outcome from early surgery was also more likely if the intended method of evacuation was craniotomy (absolute benefit 6%; -1 to 12), but interaction between intended method of surgery and treatment was not significant ( $p=0.07$ ). Open craniotomy was chosen for 346 (75%) patients given early surgery and was associated with a non-significant relative benefit of 28% (-3 to 59). A uniformly poor outcome was seen in patients in coma (Glasgow coma score  $\leq 8$ ): early surgery increased the relative risk of poor outcome for comatose patients by 8% (-3 to 20).

Patients in the early surgery group who did not have surgery tended to have a poor outcome: favourable outcomes for this group applied to only five (20%) of 25 patients with outcome assessed (7-41). 29 (22%) of 130 patients with outcome assessed (15-30) in the initial conservative treatment group who went on to have surgery afterwards, had a favourable outcome.

Our cost analysis included 77 UK patients (37 early surgery, 40 initial conservative treatment) for whom complete details of hospital stay could be obtained. All early surgery patients in this UK substudy had surgery: nine (24%) had a favourable outcome; 12 (30%) patients who received initial conservative treatment had surgery: eight (20%) had a favourable outcome. Total costs per patient were calculated from surgery, hospital and long-term stay, and allied service costs (physiotherapy, occupational therapy, speech therapy, and day hospital) after discharge.

As expected, surgery costs were higher in the early surgery group than the initial conservative treatment group (mean £2250 [SD 922] vs £797 [1091],  $t$  test  $p<0.0001$ ; £1=US \$1.83) because these patients were more likely to have surgery. In the initial conservative treatment group, total hospital stay costs were non-significantly higher than in the early surgery group (£15 507 [11 593] vs £18 599 [13 911]  $t$  test,  $p=0.29$ ), because of a non-significantly extended stay in hospital (60.9 [55.6] vs 78.5 [57.7] days,  $t$  test,  $p=0.18$ ; median 34 [IQR 17-93] vs 73 [20-114]). Allied service costs were also non-significantly higher in the initial conservative treatment group than early surgery (mean £695 [SD 1268] vs £1118 [1620],  $t$  test,  $p=0.21$ ). Mean total cost for early surgery was £18 452 (12 123) compared with £20 514 (14 163) for initial conservative treatment ( $t$  test,  $p=0.50$ ) during the first 6 months after randomisation, but again this difference was not significant.

CT scans were returned for 958 (93%) patients. Of these, measurements could not be made on eight (of which one was aneurysmal and another a subdural haemorrhage). Additionally, another 12 (two cerebellar,



**Figure 3: Prespecified subgroup analysis**

n=number of unfavourable outcomes using prognosis-based outcome. N=number randomised in group. GCS=Glasgow coma score.

nine with brainstem involvement, and one glioblastoma multiforme) did not fulfil the inclusion and exclusion criteria but were included in the intention-to-treat analysis. There were very high intraclass correlations (ICC) between measurements reported on the randomisation form and those made on

the CT scans (volume ICC=0.73 [95% CI 0.70-0.77]; depth from cortical surface ICC=0.81 [0.74-0.85]).

## Discussion

Our findings show that favourable outcomes (from prognosis-based indices) in patients with intracerebral

haemorrhage treated with early surgery or initial conservative treatment do not differ significantly. Prespecified subgroup analysis also showed little difference between the two treatments, except for depth of the haematoma. Patients with haematomas 1 cm or less from the cortical surface were more likely to have a favourable outcome from early surgery than those with deep haematomas.

Randomised controlled trials in surgical patients with severe neurological disorders, especially those causing disturbance of consciousness, are difficult to undertake and probably will become even more problematic in the near future because of new legislation such as the European Clinical Trials Directive. International STICH has taken 8 years to recruit over 1000 patients in a rigorous attempt to define the role of early surgery for patients with spontaneous supratentorial intracerebral haemorrhage. Although the number of patients randomised in International STICH exceeds the total number of patients in all nine previous randomised controlled trials, our results still leave much uncertainty.

Careful consideration was given to outcome assignment in this trial.<sup>24</sup> The traditional split into favourable and unfavourable outcomes using the five-point Glasgow outcome scale is useful in trials of younger patients with diffuse brain injury. However, patients in this study tended to be older (median 62 years) and all had focal neurological deficits. For young patients recovering from head injury or subarachnoid haemorrhage, any outcome short of independence outside the home can be classified as unfavourable, whereas for an older stroke victim, independence achieved within the home is worthwhile compared with dependence on 24-h care.

The eight-point Glasgow outcome scale divides the severe disability category into those who are dependent and independent within the home. To achieve an outcome of moderate disability, patients have to be able to use public transport and shop independently.<sup>20</sup> Although this outcome might be expected for a patient with a minor bleed, a patient initially in coma (Glasgow coma score <9) or with a severe hemiplegia would not be expected to reach that kind of independence. We therefore set out to differentiate treatment targets for patients according to their initial prognosis (on the basis of an independently derived formula). This prognosis-based dichotomy substantially improved the power of the study to detect a modest treatment effect. However, we still cannot give a definite answer to the question: can a policy of early surgical intervention for patients with ICH be recommended and, if so, under what conditions?

The decision to compare a policy of early surgery with one of initial conservative treatment, including an option for delayed surgery if necessary, was dictated by practical and ethical considerations. Recruitment of centres would have been exceedingly difficult and probably unethical if

the protocol prevented neurosurgeons from operating on patients in the initial conservative treatment group, even if patients' conditions deteriorated.<sup>29,30</sup>

In fact, this operative intervention took place in about a quarter of patients in the initial conservative treatment group. By contrast, only 6% of patients randomised to the early surgery group did not undergo operation, and 6% had the operation more than 24 h after randomisation. Patients in the early surgery group who did not have surgery tended to have a poor outcome: patients in the initial conservative treatment group who later had surgery also did not have good outcomes. However, whether this difference would have been substantial enough to show a significant difference between the two groups is unlikely.

Potential bias in the trial was reduced by use of concealed randomisation through the CTSU and with follow-up by postal questionnaire. Investigators had to provide details of patients before being told of treatment group assignments and had to provide prerandomisation CT scans that were used as confirmation. Postal questionnaires sent to patients for outcome assessment ensured that this masking was not biased by investigator perceptions.

There was little difference in mortality (1%) between the two demographically well-balanced groups. Stroke physicians might prefer to consider the other secondary outcome measures (ie, modified Rankin scales and Barthel indices), because they are commonly used in stroke trials. However, the potential absolute benefit from early surgery was only 4.7% for the Rankin scale and 4.1% for the Barthel index even with the more sensitive prognosis-based outcome assignment. Previously published screening-log data<sup>30</sup> set these STICH results in context with other non-randomised intracerebral haemorrhage patients.

The overall results of the trial suggest that surgeons were justified in their uncertainty. Therefore, the subgroups that might emerge from such a wide spectrum of clinically relevant characteristics are clinically important to consider. These subgroups were prespecified in the protocol but few differences were seen except in three groups of patients: first, in patients in whom the intracerebral haemorrhage reached to within 1 cm of the cortical surface. In this subgroup (the first of three minimisation criteria), there was a 29% relative benefit for early surgery. Can this be interpreted as a group of patients who might benefit from this policy? Traditional statistical and mathematical opinion would say no, because subgroup analysis, even if prespecified, must reach a level of significance that is much greater than in the trial itself.<sup>31,32</sup> Correction for 12 pre-specified subgroups would require multiplication of the p value by 12 and thus the significance would disappear. Therefore, statistical opinion would conclude that evidence is insufficient to recommend either policy, even in this prespecified subgroup.

Second, there are good clinical reasons for the assumption that craniotomy (compared with stereotaxic aspiration or endoscopy) might do harm in deep-seated intracerebral haemorrhage, whereas in superficial haematomas, craniotomy is easy and less complicated. Most operative procedures in this trial were open craniotomies, so the beneficial result for superficial haematomas might indicate the advantage of clot evacuation via craniotomy and the disadvantage of open craniotomy for any haematomas that have not reached the cortical surface. Trauma of open craniotomy for deep haematomas might thus offset any benefit. This assumption can be seen, to some extent, by the superior results in the craniotomy subgroup. For patients allocated to early surgery in International STICH, the type of operation was left to the discretion of the admitting surgeon. Three-quarters of these patients had open craniotomy, which was associated with a non-significant relative benefit of 28%.

Third, perhaps the clearest and most disappointing result was the uniformly poor outcome in patients presenting with intracerebral haemorrhage in coma. In those with initial Glasgow coma scores of eight or below, nearly all were classified as having unfavourable outcomes (ie, lower severe disability or worse on the prognosis-based outcome scale). Early surgery raised the relative risk of poor outcome for these patients by 8%. Thus, a relative benefit of over 3% from surgery, or an absolute benefit of about 2.5%, can effectively be excluded, which means that, for patients in coma, surgery is probably harmful, and even at the most optimistic estimate, about 40 operations would be needed to achieve one more favourable outcome (probably upper severe disability) in such patients.

The philosophy of subgroup analysis needs to be considered in the context of a pragmatic surgical trial such as International STICH. Although post-hoc analysis can generate significant differences that are meaningless,<sup>32</sup> the main problem arises if significant differences are generated that are meaningful, but are dependent on how the data are classified or analysed. This problem is especially the case in surgical trials in which interventions have great risk: so subgroup analyses need to be considered carefully. If one accepts that argument, then surgeons, clinicians, and statisticians need to set the threshold for post-hoc subgroup analyses and for the prespecified subgroup analyses. No post-hoc analyses have yet been undertaken with these data.

Our economic analysis, although limited to UK patients, suggests that early surgery is less costly than initial conservative treatment, but again this difference was not significant. This reduced cost is associated with a shorter hospital stay and use of less costly or fewer services after discharge into the community. Since this result is not related to a raised mortality rate, patients having early surgery could recover more quickly than

those with initial conservative treatment, but a much more detailed study would be needed to investigate this difference.

These results need to be interpreted with respect to the nine previous randomised controlled trials in supratentorial intracerebral haemorrhage.<sup>12–14,16,17,33–36</sup> If all ten trials are analysed, no net benefit from surgery is seen. However, although some studies<sup>12,34</sup> can be omitted,<sup>15</sup> still no overall benefit accrues from early surgery. In future, operative trials of image-guided, stereotaxically-assisted evacuation of intracerebral haemorrhage might be justified, especially for deep basal ganglia haematomas. With superficial haematomas, craniotomy might be the preferred method for neurosurgeons comparing the need for early surgery with a wait and watch conservative policy.

There is insufficient evidence to justify a general policy of early operative intervention in patients with spontaneous supratentorial intracerebral haemorrhage, compared with one of initial conservative treatment. Patients with superficial haematomas might benefit from surgery, especially by craniotomy, but this beneficial effect needs to be established. The results of International STICH should encourage surgeons to organise such trials.

#### Contributors

A D Mendelow and the steering committee conceived the study. All listed collaborators contributed to the trial design and interpretation of the data. B A Gregson and G D Murray analysed the study. A D Mendelow and B A Gregson drafted the paper, but all listed collaborators edited and revised the report.

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#### Conflict of interest statement

There is a potential conflict of interest in countries where neurosurgeons undertake fee for service medicine. Some members of the management team were funded by the MRC or the Stroke Association to undertake the study. There are no other conflicts of interest.

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#### References

- Dennis M. Outcome after brain haemorrhage. *Cerebrovas Dis* 2003; 16 (suppl 1): 9–13.
- Yang GY, Betz AL, Hoff JT. The effects of blood or plasma clot on brain edema in the rat with intracerebral hemorrhage. *Acta Neurochirurgica supplement* 1994; 60: 555–57.
- Lee KR, Colon GP, Betz AL, Keep RF, Kim S, Hoff JT. Edema from intracerebral hemorrhage: the role of thrombin. *J Neurosurg* 1996; 84: 91–96.
- Lee KR, Kawai N, Kim S, Sagher O, Hoff JT. Mechanisms of edema formation after intracerebral hemorrhage: effects of thrombin on cerebral blood flow, blood-brain barrier permeability, and cell survival in a rat model. *J Neurosurg* 1997; 86: 272–28.
- Xi G, Wagner KR, Keep RF, et al. Role of blood clot formation on early edema development after experimental intracerebral hemorrhage. *Stroke* 1998; 29: 2580–86.
- Xi G, Keep RF, Hoff JT. Erythrocytes and delayed brain edema formation following intracerebral hemorrhage in rats. *J Neurosurg* 1998; 89: 991–96.
- Nehls DG, Mendelow AD, Graham DI, Teasdale GM, McCulloch J. Experimental intracerebral haemorrhage: early removal of a spontaneous mass lesion improves late outcome. *Neurosurgery* 1990; 27: 675–82.
- Kingman TA, Mendelow AD, Graham DI, Teasdale GM. Experimental intracerebral mass: time-related effects on local cerebral blood-flow. *J Neurosurg* 1987; 67: 732–38.
- Siddique MS, Fernandes HM, Wooldridge TD, Fenwick JD, Slomka P, Mendelow AD. Reversible ischemia around intracerebral hemorrhage: a single-photon emission computerized tomography study. *J Neurosurg* 2002; 96: 736–41.
- Heiss WD. Ischemic penumbra: evidence from functional imaging in man. *J Cereb Blood Flow Metab* 2000; 20: 1276–93.
- Fernandes HM, Siddique S, Banister K, et al. Continuous monitoring of ICP and CPP following ICH and its relationship to clinical, radiological, and surgical parameters. *Acta Neurochirurgica* 2000; 76 (suppl): 463–66.
- McKissock W, Richardson A, Taylor J. Primary intracerebral haemorrhage: a controlled trial of surgical and conservative treatment in 180 unselected cases. *Lancet* 1961; 278: 221–26.
- Auer LM, Deinsberger W, Niederkorn K, et al. Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. *J Neurosurg* 1989; 70: 530–35.
- Juvela S, Heiskanen O, Poranen A, et al. The treatment of spontaneous intracerebral hemorrhage: a prospective randomized trial of surgical and conservative treatment. *J Neurosurg* 1989; 70: 755–58.
- Fernandes HM, Gregson B, Siddique S, Mendelow AD. Surgery in intracerebral hemorrhage: the uncertainty continues. *Stroke* 2000; 31: 2511–16.
- Teernstra O, Evers S, Lodder J, Leffers P, Franke C, Blaauw G. Stereotactic treatment of intracerebral hematoma by means of plasminogen activator: a multicentre randomized controlled trial (SICHPA). *Stroke* 2003; 34: 968–74.
- Hosseini H, Leguerinel C, Hariz M, et al. Stereotactic aspiration of deep intracerebral hematomas under computed tomographic control: a multicentric prospective randomised trial. 12th European Stroke Conference 2003, Valencia, Spain: 57.
- Kanaya H, Kuroda K. Intracerebral hematomas. In: Kaufman HH, ed. Development in neurosurgical approaches to hypertensive intracerebral haemorrhage in Japan. New York: Raven Press, 1992: 197–209.
- Anon. Protocol 99PRT/7 International STICH (Surgical Trial in Intracerebral Haemorrhage). *Lancet*, 1999.
- Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow outcome scale and the extended Glasgow outcome scale: guidelines for their use. *J Neurotrauma* 1998; 15: 573–85.
- Bhattachari PS, Gregson B, Prasad KS, et al. Reliability assessment of computerized tomography scanning measurements in intracerebral hematoma. *Neurosurg Focus* 2003; 15: E6.
- Anon. Protocol 99PRT/7 International STICH (Surgical Trial in Intracerebral Haemorrhage). *Lancet*, 2003. <http://www.thelancet.com/info/info.isa?n1=authorinfo&n2=Protocol+reviews&uid=14545> (July 14, 2003).
- Shaw MDM, Mendelow AD, Teasdale GM, Murray GD, Gregson BA. Alterations to STICH protocol. *Lancet* 2003; 362: 1244.

- 24 Mendelow AD, Teasdale GM, Barer D, Fernandes HM, Murray GD, Gregson BA. Outcome assignment in the international surgical trial in intracerebral haemorrhage. *Acta Neurochirurgica (Eur J Neurosurg)* 2003; **145**: 679–81.
- 25 Berge E, Barer D. Could stroke trials be missing important treatment effects. *Cerebrovasc Dis* 2002; **13**: 73–75.
- 26 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* (in press).
- 27 Netten A, Rees T, Harrison G. Unit costs of health and social care. Canterbury: Personal Social Services Research Unit, University of Kent at Canterbury, 2001.
- 28 Broderick JP, Brott TG, Grotta JC. Intracerebral hemorrhage volume measurement. *Stroke* 1994; **25**: 1081.
- 29 Fernandes HM, Mendelow AD. Spontaneous intracerebral haemorrhage: a surgical dilemma. *Br J Neurosurg* 1999; **13**: 389–94.
- 30 Gregson BA, Mendelow AD, on behalf of the STICH Investigators. International variations in surgical practice for spontaneous intracerebral haemorrhage. *Stroke* 2003; **34**: 2593–98.
- 31 Altman DG, Matthews JN. Statistics notes. Interaction 1: heterogeneity of effects. *Br Med J* 1996; **313**: 486.
- 32 ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **332**: 349–60.
- 33 Batjer HH, Reisch JS, Allen BC, Plaizier LJ, Su CJ. Failure of surgery to improve outcome in hypertensive putaminal hemorrhage: a prospective randomized trial. *Arch Neurol* 1990; **47**: 1103–06.
- 34 Chen X, Yang H, Cheng Z. The comparative study of the total medical and surgical treatment of hypertensive intracerebral haemorrhage. *Acta Academiae Medicinae Shanghai* 1992; **19**: 234–40.
- 35 Zuccarello M, Brott T, Derex L, et al. Early surgical treatment for supratentorial intracerebral haemorrhage: a randomized feasibility study. *Stroke* 1999; **30**: 1833–39.
- 36 Morgenstern LB, Frankowski RF, Shedden P, Pasteur W, Grotta JC. Surgical treatment for intracerebral hemorrhage (STICH). A single-center, randomized clinical trial. *Neurology* 1998; **51**: 1359–63.