Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial

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Summary

Background Patients with space-occupying hemispheric infarctions have a poor prognosis, with case fatality rates of up to 80%. In a pooled analysis of randomised trials, surgical decompression within 48 h of stroke onset reduced case fatality and improved functional outcome; however, the effect of surgery after longer intervals is unknown. The aim of HAMLET was to assess the effect of decompressive surgery within 4 days of the onset of symptoms in patients with space-occupying hemispheric infarction.

Methods Patients with space-occupying hemispheric infarction were randomly assigned within 4 days of stroke onset to surgical decompression or best medical treatment. The primary outcome measure was the modified Rankin scale (mRS) score at 1 year, which was dichotomised between good (0–3) and poor (4–6) outcome. Other outcome measures were the dichotomy of mRS score between 4 and 5, case fatality, quality of life, and symptoms of depression. Analysis was by intention to treat. This trial is registered, ISRCTN94237756.

Findings Between November, 2002, and October, 2007, 64 patients were included; 32 were randomly assigned to surgical decompression and 32 to best medical treatment. Surgical decompression had no effect on the primary outcome measure (absolute risk reduction [ARR] 0%, 95% CI –21 to 21) but did reduce case fatality (ARR 38%, 15 to 60). In a meta-analysis of patients in DECIMAL (DEcompressive Craniectomy In MALignant middle cerebral artery infarction), DESTINY (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY), and HAMLET who were randomised within 48 h of stroke onset, surgical decompression reduced poor outcome (ARR 16%, –0·1 to 33) and case fatality (ARR 50%, 34 to 66).

Interpretation Surgical decompression reduces case fatality and poor outcome in patients with space-occupying infarctions who are treated within 48 h of stroke onset. There is no evidence that this operation improves functional outcome when it is delayed for up to 96 h after stroke onset. The decision to perform the operation should depend on the emphasis patients and relatives attribute to survival and dependency.

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Introduction

Patients with space-occupying hemispheric infarction have a poor prognosis. In intensive care-based series, the rates of case fatality were about 80%, and most survivors were left severely disabled.[1,2] No medical therapy has proved effective.[3] Decompressive surgery—removal of part of the skull and duraplasty—has been proposed as a way to accommodate shifts of brain tissue and normalise intracranial pressure, thereby preserving cerebral blood flow and preventing transtentorial herniation and secondary damage.[4] The results of observational studies that had historical controls suggest that surgical decompression reduces death rate, improves the functional outcome of patients with space-occupying hemispheric infarction, and has a greater benefit if done on the first day after stroke onset rather than later.[4,5]

In the randomised trials DECIMAL (DEcompressive Craniectomy In MALignant middle cerebral artery infarction[6]) and DESTINY (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY[7]), surgical decompression done within 30 or 36 h from stroke onset reduced case fatality compared with the best medical treatment; however, the numbers of patients were too small (38 and 32 patients, respectively) to prove the benefit of surgery on functional outcome.

In a meta-analysis of DECIMAL and DESTINY that included 23 patients from the then-ongoing randomised Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET),[8] surgical decompression within 48 h of stroke onset doubled the chance of a favourable functional outcome, which was defined as a modified Rankin scale (mRS) score of 3 or lower.[9] However, the effect of the operation on this outcome in patients categorised by the timing of treatment, age, or the presence of aphasia was uncertain. Furthermore, quality of life was assessed in only 12 of the 19 surviving patients in DECIMAL and in none of

the patients in DESTINY. Symptoms of depression were not assessed in either trial. In addition, the effect of surgery done later than the first 2 days after stroke onset was not assessed in DECIMAL, DESTINY, or the pooled analysis, whereas space-occupying oedema usually manifests on the second to fourth day after stroke onset.[1]

We present the final results of HAMLET, which was designed to assess the effect of decompressive surgery within 4 days of the onset of symptoms in patients with space-occupying hemispheric infarction, and an updated meta-analysis of the results from the three trials.

Methods

Patients

Patients were enrolled between November, 2002, and October, 2007, at six centres in the Netherlands, according to a previously published protocol.[10] The trial was approved by the institutional review board of each participating centre, and written informed consent was obtained from a legal representative of each patient. The eligibility criteria are summarised in panel 1.

Procedures

Patients were randomly assigned to surgical decompression or best medical treatment by use of a computerised randomisation service that was available 24 h a day. Randomisation was based on a published algorithm designed to prevent imbalance between treatment groups.[11] Many of the patients who were randomly assigned to surgical decompression would be admitted to an intensive care unit, as standard practice after craniectomy. To adjust for any potential benefits of treatment in an intensive care unit over treatment at a stroke unit, we aimed to study the effect of decompressive surgery in all patients who had received treatment in an intensive care unit and in a group of patients for whom the standard therapy was care at a stroke unit. For this reason, randomisation was stratified according to the intended mode of best medical treatment (ie, intensive care unit or stroke unit).

Treatment had to be started within 3 h of randomisation. Surgical decompression consisted of removal of a flap of bone of at least 12 cm diameter and including parts of the frontal, parietal, temporal, and occipital squama. If necessary, more temporal bone was removed so that the floor of the middle cerebral fossa could be assessed. The dura was opened, and an augmented dural patch was inserted. The position of the temporalis muscle and skin flap was then approximated and they were secured. Infarcted brain tissue was not resected. A sensor to measure intracranial pressure could be left in situ, if required. After the operation, patients were transferred to an intensive care unit. Drugs to prevent oedema were given at the discretion of the treating physician. Cranioplasty was done after at least 6 weeks of the operation with the stored bone flap or with acrylate.

Because no mode of medical treatment has been shown as superior,[3] best medical treatment was given at the discretion of the treating physician and could consist of treatment at an intensive care unit or at a stroke unit. To improve the consistency of treatment between centres, recommendations were made for treatment in the intensive care unit (panel 2).

The primary outcome measure was functional outcome, as measured by mRS score, at 1 year. Scores on the mRS ranged from 0 (no symptoms) through to 5 (severe disability); for statistical purposes, death was given a score of 6. Outcome was dichotomised as good (0–3) or poor (4–6). In a post-hoc analysis, good outcome was defined as an mRS score of 0–4 and poor outcome as an mRS score of 5 or 6 because this was the primary outcome measure in the previously published meta-analysis of the randomised trials.[8] To prevent observer bias, patients' scores on the mRS were decided independently by three blinded investigators on the basis of a narrative written by an unblinded and independent study nurse who had visited each patient and their relatives. In the case of

Panel 1: Eligibility criteria

Inclusion criteria

- Diagnosis of acute ischaemic stroke in the territory of the middle cerebral artery, with onset within 96 h of the start of the trial treatment
- Score on the National Institutes of Health stroke scale (NIHSS) of ≥16 for right-sided lesions or ≥21 for left-sided lesions
- Gradual decrease in consciousness to a score of ≤13 on the Glasgow coma scale for right-sided lesions or an eye and motor score of ≤9 for left-sided lesions
- Ischaemic changes on CT that affect two-thirds or more of the territory of the middle cerebral artery and the formation of space-occupying oedema; displacement of midline structures on CT was not required
- Age 18–60 years
- Able to start trial treatment within 3 h of randomisation
- Written, informed consent given by a legal representative of the patient

Exclusion criteria

- Ischaemic stroke of the whole cerebral hemisphere (anterior, middle, and posterior cerebral artery territories)
- Decrease in consciousness partially because of causes other than the formation of oedema, such as metabolic disturbances or medication
- Both pupils fixed and dilated
- Alteplase in the 12 h before randomisation
- Known systemic bleeding disorder
- Prestroke score on the modified Rankin scale of greater than 1 or less than 95 on the Barthel index
- Life expectancy is less than 3 years
- Other serious illness that might confound treatment assessment

***Panel 2:* Recommendations for treatment in intensive care units**

- Osmotherapy with mannitol or glycerol as soon as possible after randomisation and at a dose sufficient to reach a serum osmolality of 315–20 mOsm
- Intubation and mechanical ventilation if the patient's Glasgow coma score was ≤8, if there were signs of respiratory insufficiency, or if the airway was compromised
- Hyperventilation should be used only as a rescue measure in case of further neurological deterioration or an uncontrolled increase in intracranial pressure, with jugular bulb oximetry to maintain venous oxygen saturation at higher than 50% or to a target pCO_2 of 28–32 mm Hg
- Invasive monitoring of intracranial pressure, preferably on the same side as the infarct
- Sedation in the case of mechanical ventilation, further neurological deterioration, or an uncontrolled increase in intracranial pressure, preferably with propofol; the use of barbiturates was discouraged but, if necessary, muscle relaxants could be used
- Treatment of blood pressure higher than 220/120 mm Hg with labetolol or nitroprusside; hypotension or a reduction of cerebral perfusion pressure could be treated with catecholamines
- Elevation of the head to an angle of 30°
- Maintenance of normothermia, normoglycaemia, and normovolaemia

Treatment in the intensive care unit was continued at least until day 5 after stroke onset or until there was sufficient clinical improvement to permit transfer of the patient to a stroke unit. Recommendations for best medical treatment in a stroke unit were osmotherapy, elevation of the head, and maintenance of normothermia, normoglycaemia, and normovolaemia, as described above.

disagreement, the final mRS score was decided by consensus.

Secondary outcome measures were case fatality, functional dependence expressed as Barthel index (BI),[12] symptoms of depression measured by the Montgomery and Asberg depression rating scale (MADRS),[13] and quality of life measured with the Medical Outcomes Study 36-item short-form health survey (SF-36)[14] and a visual analogue scale (VAS)[15] at 1 year. The BI measures disability, from 0 (complete dependence on help with activities of daily living) to 100 (independence). The MADRS quantifies depressive symptoms in the presence of severe physical disorders. MADRS is an observer-rated, 10-item scale that ranges from 0 to 60 and places little emphasis on somatic symptoms. Mild symptoms of depression were defined as a MADRS score of 7 or more and symptoms of severe depression as a MADRS score of 19 or more.[16,17] The SF-36 assesses eight domains of health status: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Each domain was rated between 0 and 100, with high scores indicating a better quality of life. Two summary scores were calculated as a representation of physical and mental health.[18] The VAS ranges from 0 to 10, with a score of 10 representing perfect quality of life. The satisfaction of patients and their partners with the procedure was assessed after 1 year by interview.

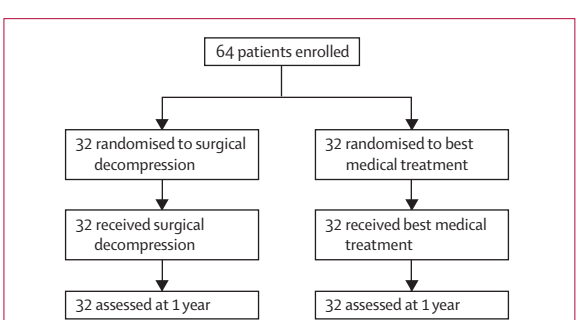

Figure 1: **Trial profile**

Statistical analysis

Sample size was calculated on the premise that the superiority of surgical decompression could be proved over best medical treatment in the group that received best medical treatment on a stroke unit and the group that received best medical treatment on an intensive care unit. A sample size of 112 was calculated (α=0·05, β=0·20) on the assumption that 60% of patients in the surgical group and 85% in each of the medical treatment groups would have a poor outcome. A predefined interim analysis was done by the independent data monitoring committee after 30 patients were assessed for the primary outcome. In February, 2008, a second interim analysis was done after the 50th patient had been seen at 1 year, on the advice of the data monitoring committee. Subsequently, the data monitoring committee advised that recruitment should stop. The final analyses were done after all 64 patients had completed the follow-up period of 1 year.

To assess the effect of surgical treatment, absolute risk reductions (ARR) and corresponding 95% CIs were calculated. Predefined subgroup analyses were done according to age (dichotomised at 50 years) and time of randomisation (dichotomised at 48 h). We did a subgroup analysis based on the presence of aphasia rather than a predefined analysis based on the side of the lesion, because one patient with aphasia had a right-sided infarct. Analyses were by intention to treat. To assess the effect of imbalances in age and time to randomisation at baseline, we also calculated adjusted effect estimates. A meta-analysis of data from patients in DECIMAL, DESTINY, and HAMLET who were randomised within 48 h of stroke onset was done. Only patients who were randomised within 48 h were included in this meta-analysis, because the previously published pooled analysis was explicitly limited to this time window.[8] This trial is registered, ISRCTN94237756.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or in the preparation of this manuscript, or the decision to submit for publication. The trial executive committee had full access to all data and had final responsibility for the decision to submit for publication.

Results

The data monitoring committee advised that recruitment of patients into HAMLET was stopped after 50 patients had been seen and graded 1 year after randomisation. The

reason for stopping the trial was that it was highly unlikely that a statistically significant difference would be seen for the primary outcome measure between the two treatment groups with the planned sample size. At this time, 64 patients had been recruited. During HAMLET, only one patient was operated on outside of the trial in one of the participating centres. Because most patients were referred for inclusion in HAMLET from general hospitals that did not participate in the trial, the number of patients who were screened for inclusion is unknown. Of the 64 patients in the trial, 32 were assigned to surgical decompression and 32 to best medical treatment. There was no cross-over between the intervention groups, and the follow-up rate was 100% (figure 1).

Table 1 shows the characteristics of patients. The patients who were treated surgically were slightly older, and those who were treated medically waited slightly longer for randomisation. In the subgroup of patients who were treated within 48 h, the mean interval from onset to randomisation was 31 h. Because all but three of the patients who were treated surgically were admitted to an intensive care unit, more of the patients in this group were ventilated, whereas more patients who were medically treated received osmotherapy.

Figure 2 shows the distribution of scores on the mRS for the two treatment groups after 1 year. Table 2 shows the distribution of all outcome measures. For the primary measure of outcome, an mRS score of 4–6, the ARR was 0%, 95% CI –21 to 21. The probability of a poor outcome, defined as an mRS score of 5 or 6, was slightly lower after surgical decompression, but this was not significant (ARR 19%, –5 to 43; p=0·13). Only risk of death was significantly lower in the patients who were treated surgically (ARR 38%, 15 to 60; p=0·002). These results were the same after adjustment for age and time to randomisation. Case fatality at 14 days was 5 of 32 (16%) in the surgically treated group and 18 of 32 (56%) in the medically treated group, which implies that most deaths occurred early. Transtentorial herniation was the cause of death in all patients who died in the first 2 weeks. Two patients who were treated surgically died between day 14 and 1 year due to myocardial arrest and pneumonia, respectively; one patient who was treated medically died from bronchial carcinoma within the same period. One patient developed a symptomatic epidural haematoma after surgical decompression and needed a second operation, which had no effect on final functional outcome. Two of the patients who were treated surgically had temporary CSF leaks. One patient who was treated surgically had epileptic seizures, which were treated with phenytoin.

The median BI score at 1 year was 47·5 in the surgically treated patients and 0 in the best medical treatment group (p=0·20). Table 2 shows the effects of surgery on mood, quality of life, and patient and caregiver satisfaction. There were no significant differences between the two treatment groups except for the physical summary score on the

	Surgical decompression (n=32)	Best medical treatment (n=32)
Demographics		
Men	20 (63%)	18 (56%)
Age (years)	50·0 (8·3)	47·4 (9·8)
Age 51–60 years	16 (50%)	10 (31%)
Time from symptom onset to randomisation (h)	41 (29–50)	45 (29–63)
>48 h between symptom onset and randomisation	11 (34%)	14 (44%)
Physical examination		
Systolic blood pressure (mm Hg)	147 (28)	151 (21)
Body temperature (°C)	37·6 (0·7)	37·4 (0·6)
Neurological examination		
NIHSS score	23 (17–34)	24 (20–36)
Glasgow coma score (eye-opening and motor)	7 (5–10)	7 (3–9)
Glasgow coma score (eye-opening, motor, and verbal)†	10 (6–13)	10 (4–13)
One pupil fixed and dilated	3 (10%)	3 (10%)
Aphasia	12 (38%)	12 (38%)
History		
Ischaemic stroke	2 (6%)	0 (0%)
Transient ischaemic attack	7 (22%)	6 (19%)
Diabetes mellitus	2 (6%)	0 (0%)
Hypertension	10 (31%)	9 (28%)
Current smoking	18 (56%)	15 (47%)
Past smoking	19 (59%)	19 (59%)
Territory of infarct		
Middle cerebral artery only	25 (78%)	21 (66%)
Middle cerebral artery plus posterior cerebral artery or anterior cerebral artery	7 (22%)	11 (34%)
Cause of stroke		
Large-vessel atherosclerosis	1 (3%)	2 (6%)
Cardiac embolism	6 (19%)	2 (6%)
Carotid dissection	5 (16%)	4 (13%)
Other known cause	0 (0%)	3 (9%)
Unknown (complete evaluation)	7 (22%)	2 (6%)
Unknown (incomplete evaluation)	13 (41%)	19 (59%)
Treatment		
Alteplase	10 (31%)	13 (41%)
Admitted to intensive care unit	29 (91%)	5 (16%)
Osmotherapy	17 (53%)	27 (84%)
Sedation	23 (72%)	5 (16%)
Monitoring of intracerebral pressure	4 (13%)	0 (0%)
Mechanical ventilation	27 (84%)	5 (16%)

Data are number (%), mean (SD), or median (IQR). †n=38 (19 surgical and 19 medical). NIHSS=National Institutes of Health stroke scale.

Table 1: **Patient demographics and treatments**

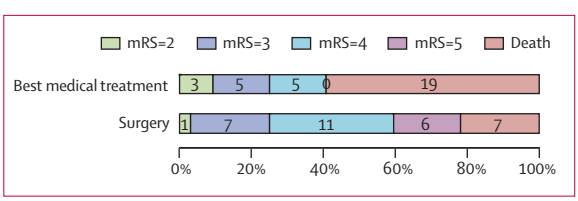

Figure 2: **Distribution of scores on the modified Rankin scale after 1 year**

	Surgical (n=32)	Best medical (n=32)	ARR (95% CI)	p
Modified Rankin scale score 4–6	24 (75%)	24 (75%)	0% (–21 to 21)	1·00
Modified Rankin scale score 5 or 6	13 (41%)	19 (59%)	19% (–5 to 43)	0·13
Death	7 (22%)	19 (59%)	38% (15 to 60)	0·002
Barthel index score	47·5 (0–100)	0 (0–100)		0·20*
Symptoms of depression†				
Montgomery and Asberg depression rating scale score ≥7	18 (78%)	7 (58%)	–20% (–53 to 13)	0·22
Montgomery and Asberg depression rating scale score ≥19	2 (9%)	0 (0%)	–9% (–20 to 3)	0·29
Quality of life (SF-36)†			Mean difference	
Physical summary	29 (7)	36 (11)	–8 (–14 to –1)	0·02
Mental summary	55 (12)	53 (11)	3 (–6 to 10)	0·59
Quality of life (visual analogue scale)†	55 (28)	62 (29)	–7 (–28 to 14)	0·49
At home after 1 year	14 (44%)	9 (28%)	–16% (–39 to 8)	0·19
Dissatisfied with treatment‡				
Patient	0 (0%)	1 (8%)	8% (–7 to 24)	0·18
Caregiver	2 (10%)	1 (8%)	–2% (–22 to 19)	0·88

Data are number (%), median (range), mean (SD), ARR (95% CI), or mean difference (95% CI). ARR=absolute risk reduction. SF-36=short form 36 questionnaire. *Mann-Whitney *U* test. †n=35 (23 surgical and 12 medical). ‡n=32 (20 surgical and 12 medical).

***Table 2*: Primary and secondary outcomes after 1 year**

	Surgical	Best medical	ARR (95% CI)%
Age ≤50 years (n=38)			
mRS=4–6	12/16 (75%)	14/22 (64%)	–11% (–41 to 18)
mRS=5 or 6	9/16 (56%)	13/22 (59%)	3% (–29 to 35)
Death	6/16 (38%)	13/22 (59%)	22% (–10 to 53)
Age 51–60 years (n=26)			
mRS=4–6	12/16 (75%)	10/10 (100%)	25% (4 to 46)
mRS=5 or 6	4/16 (25%)	6/10 (60%)	35% (–2 to 72)
Death	1/16 (6%)	6/10 (60%)	54% (21 to 86)
No aphasia (n=40)			
mRS=4–6	14/20 (70%)	15/20 (75%)	5% (–23 to 33)
mRS=5 or 6	6/20 (30%)	11/20 (55%)	25% (–5 to 55)
Death	3/20 (15%)	11/20 (55%)	40% (13 to 67)
Aphasia (n=24)			
mRS=4–6	10/12 (83%)	9/12 (75%)	–8% (–41 to 24)
mRS=5 or 6	7/12 (58%)	8/12 (67%)	8% (–30 to 47)
Death	4/12 (33%)	8/12 (67%)	33% (–4 to 71)
Randomisation <48 h (n=39)			
mRS=4–6	16/21 (76%)	14/18 (78%)	2% (–25 to 28)
mRS=5 or 6	10/21 (48%)	14/18 (78%)	30% (1 to 59)
Death	4/21 (19%)	14/18 (78%)	59% (33 to 84)
Randomisation >48 h (n=25)			
mRS=4–6	8/11 (73%)	10/14 (71%)	–1% (–37 to 34)
mRS=5 or 6	3/11 (27%)	5/14 (36%)	8% (–28 to 45)
Death	3/11 (27%)	5/14 (36%)	8% (–28 to 45)

Data are number (%) or ARR (95% CI). mRS=modified Rankin scale. ARR=absolute risk reduction.

***Table 3*: Subgroup analyses of primary and secondary outcomes at 1 year**

SF-36, which was better in medically treated patients. Quality of life and symptoms of depression were assessed in 35 of the 38 patients who survived to 1 year. Two surgically treated patients had aphasia that was so severe that quality of life and mood could not be assessed. One medically treated patient declined to answer these questions. All but one of the patients who had an mRS score of 2 or 3 lived at home after 1 year. Of the 16 patients with an mRS score of 4 at 1 year, eight lived at home, two were in rehabilitation centres, and six were in nursing homes. All six patients with an mRS score of 5 at 1 year lived in nursing homes.

Subgroup analyses were done according to age, the presence of aphasia, and time between stroke and randomisation (table 3). We found no significant differences in the effects of surgical decompression among any of the prespecified subgroups. However, there was a tendency towards a greater benefit of surgery in patients aged 51–60 years than there was in patients younger than 51 years. The reductions in absolute risk for patients with mRS scores of 4–6 and mRS scores of 5 or 6 were reduced by 6% after adjustment for age as a continuous variable. The effects did not change after further adjustment for other variables. The patients who were randomised within 48 h after stroke onset had a significant benefit of surgical decompression according to the secondary measure of outcome, in which poor outcome was defined as an mRS score of 5 or death, and case fatality was higher after best medical treatment. In patients who were randomised after 48 h from the onset of symptoms, we found no effect of surgical treatment on any outcome measure. Stroke severity, expressed as National Institutes of Health stroke scale (NIHSS) score[19] and the Glasgow coma score, was similar in the patients treated before 48 h and the patients treated after 48 h (data not shown). Because only five of the 32 patients in the medically treated group were treated in an intensive care unit—the others were treated at a stroke unit (table 1)—a subgroup analysis according to the location of treatment was not done.

A meta-analysis of the data from DECIMAL, DESTINY, and HAMLET shows a substantial reduction in the risk of poor outcome and case fatality after surgery in patients who were randomised within 48 h of stroke onset (figure 3).

Discussion

The results of HAMLET show that surgical decompression within 4 days of symptom onset does not reduce poor outcome in patients with space-occupying hemispheric infarction, despite a substantial reduction in case fatality in these patients. Surgical decompression does, however, reduce the probability of a poor outcome in patients who were randomised within 48 h of symptom onset. Whether there is any benefit of surgical decompression on the third or fourth day after stroke onset is unknown.

A trend towards a larger benefit was recorded in the published pooled analysis of trials of surgical

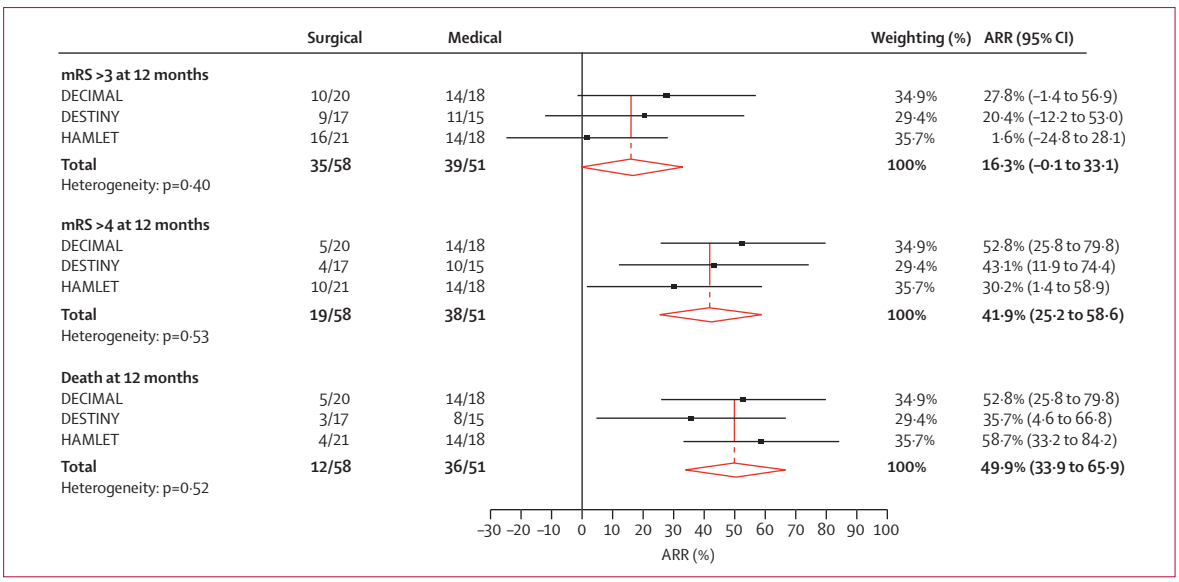

Figure 3: **Absolute risk reductions for poor outcomes after surgical decompression in patients from DECIMAL, DESTINY, and HAMLET who were randomised within 48 h of symptom onset and meta-analysis of these data**
mRS=modified Rankin scale. ARR=absolute risk reduction.

decompression within 48 h of stroke onset than was recorded in HAMLET: fewer patients in the surgical group than in the control group had an mRS score of 4 or more (ARR 23%, 95% CI 5 to 41), had an mRS score of 5 or more (ARR 51%, 34 to 69), or died (ARR 50%, 33 to 67).[8] The updated meta-analysis of the results of surgical decompression in patients randomised within 48 h of stroke onset still shows a benefit of the operation (figure 3), with numbers needed to treat of six to prevent poor outcome, two to prevent severe disability or death, and two to prevent death.

One reason for a smaller benefit of surgical decompression in HAMLET could be that the average time until randomisation was longer than it was in DECIMAL and DESTINY, even for the patients who were randomised within 48 h of symptom onset (31 h in HAMLET, 16 h in DECIMAL,[6] and 24 h in DESTINY[7]). The patients included in HAMLET had more severe strokes, as assessed by the NIHSS, with median values of 24, 21·5, and 22 for medically treated patients in HAMLET, DECIMAL, and DESTINY, respectively. The median eye and motor score of 7 also implies that the patients in HAMLET had severe strokes, but Glasgow coma scale scores are not available for patients in the other two trials.[6,7]

Adjudication of the score on the mRS includes a degree of subjectivity. The invasiveness of surgical decompression prevented a completely blinded assessment of outcome, and knowledge of a patient's treatment assignment might influence outcome assessment. For example, a prejudice that favours surgical decompression might lead to underestimation of the outcome with conservative treatment, and vice versa. The best assessment we could make of the primary outcome measure in HAMLET was semi-blinded; mRS score was assigned, on the basis of a standardised narrative from an unblinded and independent study nurse who had visited the patient and their relatives, by three neurologists who were unaware of the treatment. In DECIMAL, the mRS score raters were blinded to treatment assignment by covering the patients' heads with a surgical cap; in DESTINY, the outcome assessment was not blinded.[6,7]

In more than half of the patients with space-occupying infarction, clinical signs of herniation were seen later than the second day after stroke onset.[1] HAMLET assessed the effect of surgical decompression in patients who presented later than 48 h after stroke onset and had symptoms of massive oedema. In these patients, surgical decompression had no effect on any functional outcome measure, and case fatality with or without surgical treatment was also low. This implies that their infarcts were less life-threatening than those in the patients who were seen and included earlier, despite similar stroke severity assessed with the NIHSS and Glasgow coma score. However, because only 25 patients who presented after the first 2 days were included, the effects of chance cannot be excluded.

In a review of 13 uncontrolled studies of 138 patients, being older than 50 years was a strong predictor of poor functional outcome after surgical decompression. The timing of the operation, the side of the infarct, and the involvement of other vascular territories did not affect outcome.[20] We found a significant benefit of surgery in patients aged 51 to 60 years. This benefit was reduced after adjustment for age differences between the treatment groups and might be explained by chance or by the poor prognosis for older patients who are treated medically.

There is no unanimity on what constitutes a poor outcome. In most trials of acute stroke, an mRS score of 2 or less is deemed a favourable outcome. Because of the

severity of the infarcts under study in HAMLET, DECIMAL, and DESTINY, a good outcome was defined as an mRS score of 3 or less. In general, the difference between an mRS score of 3 and a score of 4 is the distinction between patients who can still live at home and those who are institutionalised or dead. Although 22 of the 38 survivors had an mRS score of 4 or 5 at 1 year, all but one of them were happy with the treatment they had received. This observation should be interpreted with caution because the question was not predefined, and the patient giving the desired answer cannot be excluded. However, this suggests that the definition of a good or poor outcome on the basis of disability might not indicate patient satisfaction.

Information on quality of life and symptoms of depression in survivors is misleading in a study of this kind. The 59% absolute reduction in case fatality after surgical decompression in patients randomised within 48 h came at the expense of an almost equivalent increase in the number of patients with moderately severe or severe disability (mRS score of 4 or 5). Symptoms of depression were seen in a large proportion of survivors at 1 year (78% after surgical decompression and 58% after best medical treatment). In a less-selected population of patients (ie, with infarcts of different sizes) with first-ever stroke, symptoms of depression (defined as a MADRS score of ≥7) were reported after 6 months in about half of the patients.[16] Because the severity of the symptoms of depression is related to infarct size,[21] the high rate of symptoms in patients who survive after space-occupying infarction is not surprising.

Life-threatening oedema is difficult to predict on the first day after stroke.[22] However, the 78% case fatality rate in medically treated patients who were randomised within 2 days of stroke onset is in line with previous observations[1,2] and implies that the inclusion criteria for HAMLET were sufficiently specific to predict fatal oedema within this time frame.

Before enrolment, the legal representatives of the patients in HAMLET were informed that the results of non-randomised studies suggested that surgical decompression was likely to reduce case fatality in patients with space-occupying hemispheric infarction.[4,5] Therefore, most of the representatives perceived the result of the randomisation procedure to be a matter of life or death. However, when asked at 1 year after enrolment, only 14% regarded participation in a randomised trial of this kind as unacceptable. A similar proportion was reported among the legal representatives who had given written informed consent for a relative to participate in a randomised trial that tested paracetamol as a treatment for acute stroke.[23]

Our study design had limitations. We had insufficient information about the patients who were screened for inclusion in HAMLET because most were referred from general hospitals. The small number of patients with aphasia suggests that there was some selection in the referral of patients for inclusion in this trial. Furthermore, although there are small differences at baseline between the groups with respect to age and the interval between stroke and randomisation, the results were similar after adjustment for these differences.

Although HAMLET is a large randomised trial of surgical decompression for space-occupying infarction, subgroup analyses are limited by the small number of patients recruited. Real, but undetected, differences in the benefit of surgery among patient subgroups can, therefore, not be excluded. Because the upper age for inclusion in HAMLET was 60 years, the effect of surgery in older patients is uncertain.

Medical treatment was mostly left to the discretion of the attending physician. Consequently, more patients who were treated medically received osmotherapy than did patients who were treated surgically, whereas more patients who were treated surgically were treated on an intensive care unit and were ventilated than were patients who were treated medically. However, none of these treatment modalities has convincingly shown an effect on case fatality or functional outcome after space-occupying infarction.[3] If osmotherapy was beneficial, the group differences would have been even smaller. Cerebral herniation was the cause of death in all of the patients who died in the first 2 weeks after stroke onset, and there is no evidence that treatment on an intensive care unit could have prevented this complication.

In conclusion, surgical decompression within 4 days of symptom onset did not reduce the probability of a poor functional outcome compared with best medical treatment. The updated pooled analysis of randomised trials strongly suggests that the operation increases the chance of a favourable functional outcome when initiated up to 48 h after stroke onset. Whether treatment is beneficial if it is delayed for up to 96 h after stroke onset is unknown. Surgical decompression should, therefore, be considered in patients up to 60 years old who deteriorate within 48 h from symptom onset. For these patients, the large reduction in death rate is associated with a reduction in severe disability. However, many survivors are left with moderately severe or severe disability and many have symptoms of depression. The decision of whether or not to perform surgical decompression can not be made uniformly and should be made only after a careful explanation of the results of randomised trials is given to each patient or their relatives.

HAMLET investigators

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Contributors
JH coordinated the trial and wrote the first draft of the paper. HBvdW, AA, JvG, and LJK thought of, designed, and supervised the study, and obtained funding and contributed to subsequent versions of the manuscript. GJA wrote the protocol for the operation. AA did the data analyses. All authors interpreted the data. All members of the steering committee approved the final report.

Conflicts of interest
We have no conflicts of interest.

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