Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials

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Summary

Background **Malignant infarction of the middle cerebral artery (MCA) is associated with an 80% mortality rate. Non-randomised studies have suggested that decompressive surgery reduces this mortality without increasing the number of severely disabled survivors. To obtain sufficient data as soon as possible to reliably estimate the effects of decompressive surgery, results from three European randomised controlled trials (DECIMAL, DESTINY, HAMLET) were pooled. The trials were ongoing when the pooled analysis was planned.**

Methods **Individual data for patients aged between 18 years and 60 years, with space-occupying MCA infarction, included in one of the three trials, and treated within 48 h after stroke onset were pooled for analysis. The protocol was designed prospectively when the trials were still recruiting patients and outcomes were defined without knowledge of the results of the individual trials. The primary outcome measure was the score on the modified Rankin scale (mRS) at 1 year dichotomised between favourable (0–4) and unfavourable (5 and death) outcome. Secondary outcome measures included case fatality rate at 1 year and a dichotomisation of the mRS between 0–3 and 4 to death. Data analysis was done by an independent data monitoring committee.**

Findings **93 patients were included in the pooled analysis. More patients in the decompressive-surgery group than in the control group had an mRS≤4 (75% *vs* 24%; pooled absolute risk reduction 51% [95% CI 34–69]), an mRS≤3 (43% *vs* 21%; 23% [5–41]), and survived (78% *vs* 29%; 50% [33–67]), indicating numbers needed to treat of two for survival with mRS≤4, four for survival with mRS≤3, and two for survival irrespective of functional outcome. The effect of surgery was highly consistent across the three trials.**

Interpretation **In patients with malignant MCA infarction, decompressive surgery undertaken within 48 h of stroke onset reduces mortality and increases the number of patients with a favourable functional outcome. The decision to perform decompressive surgery should, however, be made on an individual basis in every patient.**

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Introduction

Life-threatening, space-occupying brain oedema occurs in 1–10% of patients with a supratentorial infarct and usually manifests itself between the second and fifth day after stroke onset.[1–3] However, up to a third of patients can have neurological deterioration within 24 h of symptom onset.[4] The prognosis of these space-occupying or malignant middle cerebral artery (MCA) infarctions is poor, with case fatality rates in intensive care-based series of nearly 80%.[5,6] No medical treatment has been proven effective.[7] Different predictors of fatal brain oedema formation have been identified, such as major early CT hypodensity involving more than 50% of the MCA territory and other vascular territories.[8] However, up to now no single prognostic factor with sufficient prognostic value has been identified.

Non-randomised studies have suggested that decompressive surgery, consisting of a hemicraniectomy and duraplasty, reduces mortality in patients with malignant MCA infarction without increasing the number of severely disabled survivors.[9–12] However, evidence from randomised trials is lacking. Whereas most clinicians agree that the procedure is probably life-saving, no convincing data are available regarding functional outcome of survivors.

The effect of decompressive surgery on functional outcome in patients with malignant MCA infarction has been studied in three European randomised controlled trials: the French DECIMAL (decompressive craniectomy in malignant middle cerebral artery infarcts) trial; the German DESTINY (decompressive surgery for the treatment of malignant infarction of the middle cerebral artery) trial; and the Dutch trial HAMLET (hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial).[13] Two of these trials interrupted recruitment early in 2006: DECIMAL because of slow recruitment and a significant difference in mortality between the treatment groups favouring surgery; and DESTINY because a predefined sequential analysis showed a significant benefit of surgery on mortality. HAMLET is ongoing.

As the three trials have a similar design and share the same primary outcome measure—ie, favourable versus unfavourable functional outcome as determined by the

score on the modified Rankin scale (mRS)[14]—a collaborative protocol for a pooled analysis of individual patient data from the three trials was planned before the interruption of the first two trials. The principal aim of this pooled analysis was to obtain sufficient data to reliably estimate the effects of decompressive surgery as soon as possible so as to avoid unnecessary (and unethical) continuation of randomisation in the individual trials.

Methods

Trials

We combined individual patient data from DECIMAL (NCT00190203), DESTINY (ISRCTN01258591), and HAMLET (ISRCTN94237756), which are multicentre, randomised, controlled clinical trials assessing the effect of decompressive surgery in patients with space-occupying MCA infarction. When the pooled analysis was planned the trials were still ongoing and there was no knowledge of outcome data except for mortality rates in DECIMAL and DESTINY. At the time of the analysis, DECIMAL and DESTINY had been interrupted, whereas HAMLET was still ongoing. Randomisation, treatment, and outcome assessment were done according to the individual study protocols that were approved by the relevant institutional review boards. Informed consent was obtained from the patients or their legal representatives.

DECIMAL was designed to include a maximum of 60 patients, 30 in each group. Recruitment stopped after inclusion of 38 patients in March 2006, because of slow enrolment, a significant difference in mortality favouring decompressive surgery, and the opportunity of a pooled analysis with DESTINY and HAMLET. DESTINY aimed to include a maximum of 68 patients. Recruitment was interrupted in February, 2006, after a planned interim analysis including 32 patients showed a significant benefit of surgery on 30 day mortality, and the study was stopped definitively after a revised sample-size projection indicated that 188 patients would be needed to show a significant difference in the primary endpoint (mRS 0–3 *vs* 4 to death at 6 months). HAMLET aims to include 112 patients.[13]

The inclusion and exclusion criteria of the three trials were largely similar. The main differences included: a longer interval allowed from stroke onset to start of treatment in HAMLET (99 h) than in DECIMAL (30 h) and in DESTINY (36 h). For the pooled analysis, a maximum time window from stroke onset to randomisation of 45 h (ie, 48 h to treatment) was adopted. Neuroimaging criteria were too different between the three trials to be included in the pooled analysis. These criteria were an infarct volume on diffusion-weighted MRI of more than 145 cm^3 in DECIMAL, brain CT ischaemic changes affecting more than two-thirds of the MCA territory and including the basal ganglia in DESTINY, and brain CT ischaemic changes affecting at least two-thirds of the MCA territory with space-occupying oedema in HAMLET.

Patients were randomised to either decompressive surgery or conservative treatment in all trials. In DECIMAL, patients were centrally randomised in blocks of four using a pre-established randomisation list. In DESTINY, randomisation was done according to a central computer-generated randomisation list for each participating centre. In HAMLET, randomisation was done centrally with a computerised algorithm in which an element of chance was added to the treatment decision of minimisation.

Decompressive surgery consisted of a duraplasty and the creation of a large bone flap. In summary, a large (reversed) skin incision in the shape of a question mark based at the ear was made. A bone flap with a diameter of at least 12 cm (always including the frontal, temporal, and parietal bones) was removed. Additional temporal bone was removed so that the floor of the middle cerebral fossa could be reached. The dura was opened and a dural patch, consisting of pericranium or a commercially available dura substitute, was inserted and secured to enlarge the intradural space. To prevent epidural bleeding, dural tacking sutures were used when considered necessary. The temporal muscle and the skin flap were then reapproximated and sutured.

***Panel*: Eligibility criteria for the pooled analysis**

Inclusion criteria

Age 18–60 years

Clinical deficits suggestive of infarction in the territory of the MCA with a score on the National Institutes of Health stroke scale (NIHSS) >15

Decrease in the level of consciousness to a score of 1 or greater on item 1a of the NIHSS

Signs on CT of an infarct of at least 50% of the MCA territory, with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume >145 cm^3 as shown on diffusion-weighted MRI

Inclusion within 45 h after onset of symptoms

Written informed consent by the patient or a legal representative

Exclusion criteria

Prestroke score on the mRS ≥2

Two fixed dilated pupils

Contralateral ischaemia or other brain lesion that could affect outcome

Space-occupying haemorrhagic transformation of the infarct (≥parenchymal haemorrhage grade 2)

Life expectancy <3 years

Other serious illness that could affect outcome

Known coagulopathy or systemic bleeding disorder

Contraindication for anaesthesia

Pregnancy

Infarcted brain tissue was not resected. In surviving patients, cranioplasty was undertaken after at least 6 weeks with the stored bone flap or acrylate. After surgery, patients were transferred to an intensive-care unit, but anti-oedema treatment was usually not necessary.[15] In the conservative group, patients received best medical treatment on the basis of published guidelines for the management of acute ischaemic stroke and space-occupying brain oedema.[16–18]

The trials used largely similar outcome measures. In DECIMAL, outcomes were assessed by a neurologist unaware of treatment allocation; in DESTINY, outcome was assessed unblinded; and in HAMLET, the score on the mRS was determined independently by three investigators masked to treatment allocation on the basis of a narrative written by an unblinded independent study nurse and, if necessary, this process was followed by a consensus meeting.

Procedures

Patients included before Nov 1, 2005, in any of the three trials and fulfilling the prospectively defined eligibility criteria listed in the panel were used for this pooled analysis. A broad range of baseline characteristics and outcome measures was obtained in the individual trials. For the pooled analysis we used the following prespecified baseline characteristics: age; sex; time between stroke onset and randomisation; medical history; physical examination (blood pressure, body temperature); presence of aphasia; and score on the National Institutes of Health stroke scale (NIHSS) at randomisation.[19]

In the pooled analysis, the primary outcome measure was the score on the mRS at 1 year dichotomised between favourable (mRS 0 to 4) and unfavourable (mRS 5 and death). Secondary analyses included a dichotomisation of the mRS, in which favourable outcome was defined as a score of 0–3 and unfavourable outcome as a score of 4 to death, and case fatality at 1 year. The mRS measures functional outcome after stroke.[14] Scores range from 0 to 6: 0 indicating no symptoms at all; 1 indicating no significant disability despite symptoms, being able to carry out all usual duties and activities; 2 indicating slight disability, being unable to carry out all previous activities, but able to look after own affairs without assistance; 3 indicating moderate disability, requiring some help, but being able to walk without assistance; 4 indicating moderately severe disability, being unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 indicating severe disability, being bedridden, incontinent, and requiring constant nursing care and attention; and 6 indicating death.

Statistical analyses

Data analysis was undertaken according to a prespecified protocol by an independent data monitoring committee. The distributions of the mRS were compared between

	DECIMAL			DESTINY			HAMLET			Comparison of treatment groups		
	Surgery (n=20)	Conservative (n=18)	Total (n=38)	Surgery (n=17)	Conservative (n=15)	Total (n=32)	Surgery (n=14)	Conservative (n=9)	Total (n=23)	DECIMAL p	DESTINY p	HAMLET p
Age (mean[SD])	43·4 (9·7)	43·4 (7·3)	43·4 (8·5)	43·2 (9·7)	46·1 (8·4)	44·6 (9·1)	51·6 (6·1)	43·0 (12·6)	48·2 (9·9)	0·98†	0·39†	0·086†
Male sex	9 (45%)	9 (50%)	18 (47%)	8 (47%)	7 (47%)	15 (47%)	9 (64%)	3 (33%)	12 (52%)	1·00	1·00	0·21
History of TIA or stroke	2/19 (11%)	0 (0%)	2/37 (5%)	0 (0%)	0 (0%)	0 (0%)	3 (21%)	2/8 (25%)	5 (22%)	0·49	1·00	1·00
Ischaemic heart disease	0/19 (0%)	1 (6%)	1/37 (3%)	3 (18%)	4 (27%)	7 (22%)	2 (14%)	0 (0%)	2 (9%)	0·49	0·68	0·50
Atrial fibrillation	0/19 (0%)	1 (6%)	1/37 (3%)	3 (18%)	3 (20%)	6 (19%)	4 (29%)	0 (0%)	4 (17%)	0·49	1·00	0·13
Hypertension	6/19 (32%)	5 (28%)	11/37 (30%)	9 (53%)	7 (47%)	16 (50%)	4 (29%)	1 (11%)	5 (22%)	1·00	1·00	0·61
Diabetes	0/19 (0%)	4 (22%)	5/37 (14%)	2 (12%)	3 (20%)	5 (16%)	2 (14%)	0 (0%)	2 (9%)	0·18	0·65	0·50
Current smoker	9/18 (50%)	4/16 (25%)	13/34 (38%)	7 (41%)	5 (33%)	12 (38%)	5/12 (42%)	4 (44%)	9/21 (43%)	0·17	0·73	1·00
Temperature (mean[SD])	36·9 (0·5)	37·0 (0·6)	37·0 (0·6)	37·0 (0·5)	37·2 (0·6)	37·1 (0·5)	37·5 (0·6)	37·5 (0·5)	37·5 (0·5)	0·55†	0·34†	0·96†
Systolic blood pressure (mean[SD])	135·5 (19·3)	154·0 (25·1)	144·2 (23·8)	139·4 (16·6)	133·3 (14·2)	136·6 (15·6)	147·5 (27·4)	148·1 (23·0)	147·7 (25·2)	0·014†	0·28†	0·96†
Diastolic blood pressure (mean[SD])	75·8 (15·6)	83·4 (15·1)	79·4 (15·6)	74·7 (15·6)	72·3 (11·2)	73·6 (13·5)	74·6 (16·5)	76·3 (21·9)	75·3 (18·3)	0·13†	0·63†	0·83†
Aphasia	12 (60%)	11 (61%)	23 (61%)	10 (59%)	11 (73%)	21 (66%)	6 (43%)	3 (33%)	9 (39%)	1·00	0·47	1·00
NIHSS (median[IQR])	21·5 (18–25)	21·5 (18–26)	21·5 (18–25)	21 (19·5–23)	24 (22–26)	22 (20·3–24)	23 (21·8–27)	27 (22·5–32)	24 (22–28)	0·77‡	0·0033‡	0·13‡
Hours to randomisation (median[IQR])	16·1 (10·8–21·0)	15·5 (11·1–20)	15·8 (10·9–20·5)	24 (18·1–29·1)	22·5 (17·3–32·5)	24 (17·6–29·2)	30·5 (22·8–39·3)	29·5 (20·1–40·8)	29·5 (24–40)	0·90‡	0·65‡	0·91‡

Data are number (%) unless otherwise indicated. Group comparisons are Fisher's exact tests unless otherwise indicated. †t test or ANOVA as appropriate. ‡Mann-Whitney U or Kruskal-Wallis test as appropriate.

Table: **Baseline characteristics**

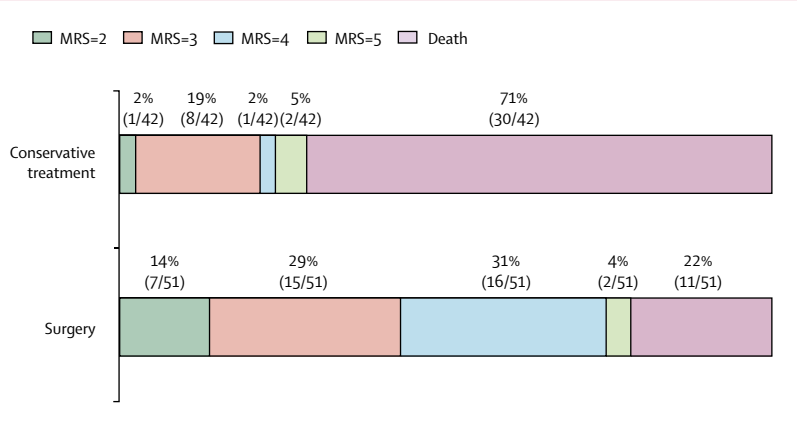

Figure 1: **Distributions of the scores on the mRS and death after 12 months for patients treated with or without decompressive surgery**

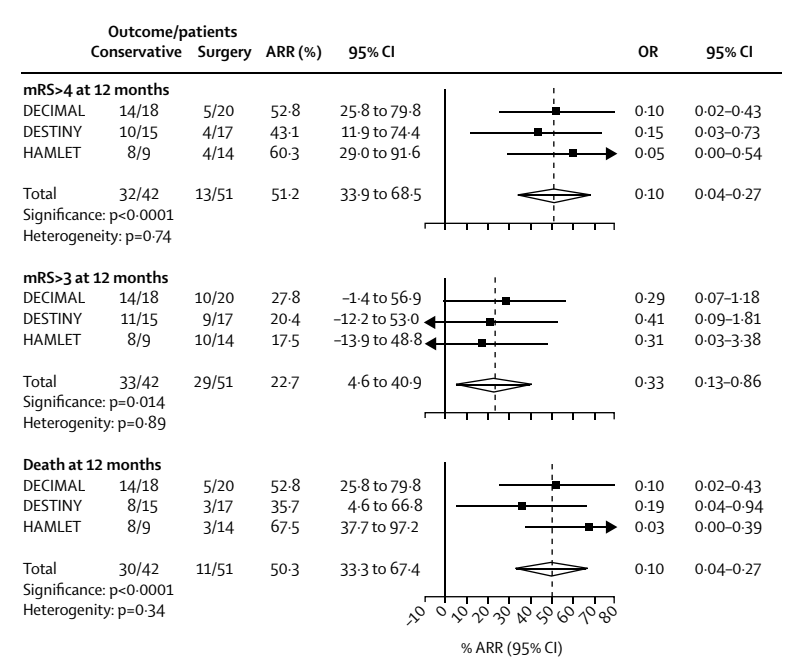

Figure 2: **Absolute risk reductions and odds ratios for unfavourable outcome at 12 months**

the treatment groups with the Mann-Whitney *U* test. To assess the effect of surgical treatment absolute risk reductions (ARRs), odds ratios (ORs), and 95% CIs were calculated for the specified outcomes in each trial and then pooled by the Mantel-Haenszel method. Heterogeneity of ARRs and ORs between trials was determined by the Breslow-Day test. The effect of baseline differences between the treatment groups was assessed by the comparison of crude and adjusted ORs. Data were also analysed in a cumulative logit model.[20] These ORs represent the odds of obtaining higher rather than lower mRS scores after surgical treatment compared with conservative treatment. Subgroup analyses were undertaken according to age (dichotomised at 50 years), timing of randomisation (dichotomised at 24 h), and presence of aphasia. Analyses were done on an intention-to-treat basis. The SPSS software package was used for all analyses. The criterion for statistical significance was set at $\alpha=0\cdot05$.

Role of the funding source

The funding bodies of the individual trials 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 and had final responsibility for the decision to submit for publication.

Results

All patients randomised in DECIMAL (38 patients) and DESTINY (32 patients) and 23 patients randomised in HAMLET were eligible for the pooled analysis. From HAMLET, 34 of a total of 57 patients were excluded because they were randomised after 45 h from stroke onset or were included after Nov 1, 2005. For all other patients there were no missing data on primary or secondary outcome measures. Thus, 93 patients were included, of whom 51 were randomised to decompressive surgery and 42 to conservative treatment. There was one crossover in DESTINY from conservative treatment to decompressive surgery. There were no crossovers in the other trials. The primary outcome measure for two patients from DESTINY was assessed at 10 months.

Treatment groups within the individual trials had broadly similar baseline characteristics (table). There were two minor differences: in DESTINY, the conservatively treated group had a higher NIHSS score than the surgically treated group, and in DECIMAL, mean systolic blood pressure was higher in the conservatively treated group than in the surgically treated group. There were baseline differences between the three trials. Time to randomisation in DESTINY and HAMLET was significantly longer than in DECIMAL; time to randomisation in HAMLET was also longer than in DESTINY. NIHSS scores in DESTINY and DECIMAL were lower than in HAMLET. Body temperature was lower in DESTINY and DECIMAL than in HAMLET. History of transient ischaemic attack or stroke was more common in HAMLET than in DESTINY, and a history of ischaemic heart disease was more common in DESTINY than in DECIMAL. In all trials combined, 25 (60%) of the conservatively treated patients and 28 (55%) of the surgically treated patients had aphasia.

Figure 1 shows the distributions of the scores on the mRS after 12 months according to randomised treatment. Distribution of the scores on the mRS between the two treatment groups differed significantly ($p<0\cdot001$). Significantly fewer patients had an unfavourable outcome, defined as an mRS score of 5 or

death at 12 months, after surgery than after conservative treatment (figure 2). Significantly fewer patients had an mRS score greater than 3 at 12 months after surgical treatment than after conservative treatment. The survival rate at 12 months was higher after surgical treatment than after conservative treatment. The results of our analyses remained essentially the same after adjustment for baseline incomparabilities.

With regard to all three outcome measures, there was no significant heterogeneity between the three trials. If baseline differences between the treatment groups were taken into account, the reduction in ORs remained essentially the same for all three analyses. The resulting numbers needed to treat for the three outcomes are 2 (95% CI 1·5–3) for the prevention of mRS 5 or death, 4 (2–22) for the prevention of mRS 4 to death, and 2 (1·5–3) for survival.

Surgery was beneficial (p<0·01) in all predefined subgroups (age [above and below 50 years], presence of aphasia, and time to randomisation [above and below 24 h]), as measured by mRS of 4 or less at 12 months, with no significant subgroup-treatment effect interactions (figure 3).

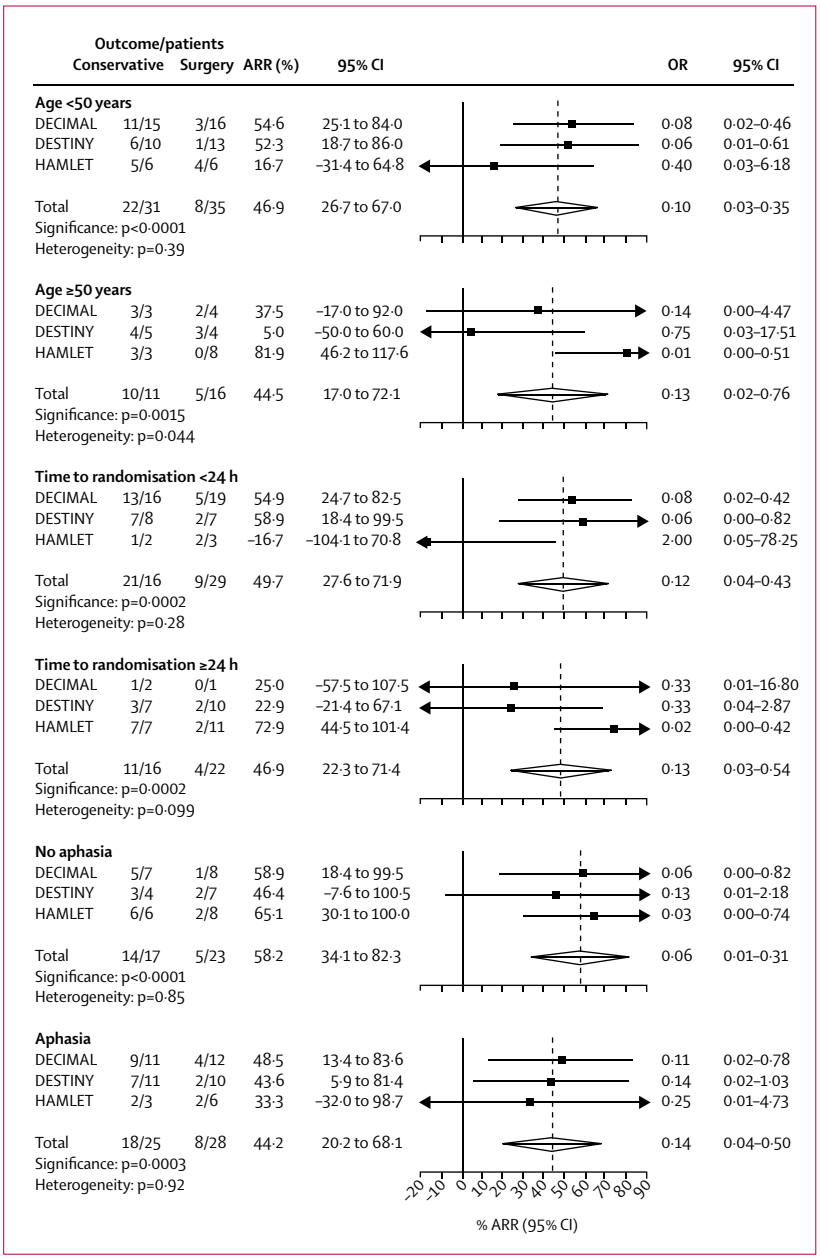

Figure 3: **Subgroup analyses of outcome according to age, timing of randomisation, and presence of aphasia**

Discussion

This pooled analysis of randomised trials confirms suggestions from non-randomised studies that decompressive surgery undertaken within 48 h of stroke onset reduces mortality and increases the number of patients with a favourable functional outcome after malignant hemispheric infarction.[9,10,12] Patients with massive space-occupying hemispheric infarction have a poor prognosis: in intensive-care based series of patients not treated with decompressive surgery, the case fatality rate was about 80%.[5,6] Several conservative treatment strategies have been proposed to limit brain tissue shifts and reduce intracranial pressure, including sedation, hyperventilation, osmotic therapy, and hypothermia. However, no randomised clinical trials have addressed the efficacy of these treatments to improve functional outcome, and several reports suggest that they are ineffective or even detrimental.[7]

In the past decades, several case reports and retrospective case series have described the effects of decompressive surgery on functional outcome after space-occupying infarction. In a review of these studies, 58% of the patients died or were severely disabled after a minimum follow-up of 4 months,[12] suggesting a substantial benefit from surgery. Of the 63 patients aged 50 years or younger, only 32% had a poor outcome.[12] However, all of these studies were retrospective and uncontrolled. Additionally, case series are prone to publication bias and the benefit of surgery might have been overestimated.

In two prospective German studies including a total of 63 patients, mortality was reduced from 78% in historical controls to 34% and 16% in surgically treated patients. Poor outcome, defined as a score lower than 60 on the Barthel index, occurred in 95% of the controls and in 50% and 16% of patients after surgery.[9,10] The benefit of decompressive surgery suggested by these studies is now supported by evidence from randomised clinical trials.

The present study is the first in the field of stroke in which a pooled analysis of individual patient data from three independent randomised trials was planned while these trials were still ongoing. This approach has the obvious advantage of being able to keep the number of patients included to a minimum and to report the

results several years earlier than would have been possible based on the individual trials alone. The results of this pooled analysis have led to premature termination of DESTINY. DECIMAL had been terminated after the difference in mortality had become significant and the data monitoring committee had recommended stopping enrolment.

Although a score on the mRS of ≤3 is generally accepted as a favourable outcome in stroke research, an mRS ≤4 after 12 months was chosen as the primary outcome in this pooled analysis. Given that survival with no or only slight disability after large MCA infarction is rare, the primary aim of the study was to assess whether decompressive surgery reduced mortality without an increase in the number of severely disabled survivors (mRS score of 5). However, decompressive surgery did in fact result in a significant increase in survival with an mRS ≤3 after 12 months.

The present study shows that after decompressive surgery the probability of survival increases from 28% to nearly 80% and the probability of survival with an mRS of ≤3 doubles. However, the probability of surviving in a condition requiring assistance from others (mRS of 4) increases more than ten times, although the risk of very severe disability (mRS of 5) is not increased. The choice of performing decompressive surgery in an individual patient with space-occupying hemispheric infarction will therefore depend on the willingness to accept survival with moderate disability. Information about quality of life of survivors is essential for guiding such decisions. Previous studies on quality of life after decompressive surgery for space-occupying infarction have reported divergent results.[21–23] Even patients with aphasia may improve significantly.[24] Information about quality of life will be provided in the separate publications of the trials.

In the three trials under study, patients were excluded if they were older than 55 years or 60 years of age. The results can probably not be generalised to patients who are older. In a systematic review of uncontrolled studies on decompressive surgery, 80% of the patients older than 50 years were dead or remained severely disabled compared with 32% of the patients aged 50 years or younger.[12] Moreover, quality of life can remain impaired, especially in older patients.[22,23]

Data from a large non-randomised series have suggested that outcome is substantially improved if treatment is initiated within 24 h of stroke onset as compared with longer time windows for treatment.[10] In the above-mentioned systematic review, the timing of surgery did not affect outcome. Similar observations were made in a recent series of patients, in which the mean interval from stroke onset to surgery was 47 h.[25] In the present study, in view of the limited patient numbers, no difference in outcome was found between patients treated on the first and those treated on the second day. In most patients, clinical signs of herniation appear after 2 days of stroke onset.[5] Whether decompressive surgery is also beneficial if undertaken after the first 48 h is currently being tested in HAMLET.[13]

The present study has limitations. First, as a result of slightly different eligibility criteria between the individual trials, there were differences in baseline characteristics of the patients included. However, there was no statistically significant heterogeneity between the trials in the effect of surgery on any of the outcome measures. Second, as with most surgical trials, the nature of the treatment under study prevented a fully blinded outcome assessment. Although observer bias cannot be excluded, the consistency of results across the three trials, of which two used some form of blinding, argues against any major bias. Third, subgroup analyses on expected prognostic factors, such as age and the interval between the onset of symptoms and treatment, were not powered to show quantitative differences in treatment effect between groups. However, surgery was significantly beneficial in all subgroups, suggesting that there are unlikely to be any qualitative subgroup-treatment effect interactions—ie, harm in one group and benefit in another. Fourth, group effects might be a result of baseline differences. However, analyses adjusted for baseline differences provided essentially the same results. Finally, CT or MRI characteristics of the infarct were not included in the present analyses because of substantial differences between the trials in imaging modalities and timing of imaging. The effect of infarct characteristics on outcome will be reported in the separate publications of the individual trials.

In conclusion, decompressive surgery increases the probability of survival without increasing the number of very severely disabled survivors. Still, the decision to perform decompressive surgery should be made on an individual basis in every patient.

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KV, JH, and EJ contributed equally to the manuscript. KV, JH, EJ, and PMR wrote the first draft of the paper. MGB, WH, and HBvdW conceived, designed, and supervised the individual trials, obtained funding, and contributed to subsequent versions of the manuscript. The present pooled analysis was a joint initiative of KV, JH, EJ, MGB, WH, and HBvdW. PMR analysed the data. EV, BG, AA, GJA, PS, and SS played an important role in design, patient recruitment, and the operative procedures in the individual trials. All authors approved the final report.

Conflicts of interest
We have no conflicts of interest.

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