

Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY)

A Randomized, Controlled Trial

Eric Jüttler, MD; Stefan Schwab, MD, PhD; Peter Schmiedek, MD, PhD;
Andreas Unterberg, MD, PhD; Michael Hennerici, MD, PhD; Johannes Woitzik, MD;
Steffen Witte, PhD; Ekkehart Jenetzky, MD; Werner Hacke, MD, PhD;
for the DESTINY Study Group*

Background and Purpose—Decompressive surgery (hemicraniectomy) for life-threatening massive cerebral infarction represents a controversial issue in neurocritical care medicine. We report here the 30-day mortality and 6- and 12-month functional outcomes from the DESTINY trial.

Methods—DESTINY (ISRCTN01258591) is a prospective, multicenter, randomized, controlled, clinical trial based on a sequential design that used mortality after 30 days as the first end point. When this end point was reached, patient enrollment was interrupted as per protocol until recalculation of the projected sample size was performed on the basis of the 6-month outcome (primary end point=modified Rankin Scale score, dichotomized to 0 to 3 versus 4 to 6). All analyses were based on intention to treat.

Results—A statistically significant reduction in mortality was reached after 32 patients had been included: 15 of 17 (88%) patients randomized to hemicraniectomy versus 7 of 15 (47%) patients randomized to conservative therapy survived after 30 days ($P=0.02$). After 6 and 12 months, 47% of patients in the surgical arm versus 27% of patients in the conservative treatment arm had a modified Rankin Scale score of 0 to 3 ($P=0.23$).

Conclusions—DESTINY showed that hemicraniectomy reduces mortality in large hemispheric stroke. With 32 patients included, the primary end point failed to demonstrate statistical superiority of hemicraniectomy, and the projected sample size was calculated to 188 patients. Despite this failure to meet the primary end point, the steering committee decided to terminate the trial in light of the results of the joint analysis of the 3 European hemicraniectomy trials. (*Stroke*. 2007;38:2518-2525.)

Key Words: decompressive surgery ■ malignant middle cerebral artery infarction ■ randomized trials

The treatment of life-threatening, space-occupying brain edema after massive cerebral infarction is still a controversial issue in neurology and neurosurgery. Such massive hemispheric infarctions occur in 1% to 10% of patients with a supratentorial infarct.¹ Life-threatening brain edema usually becomes manifest between the second and fifth day after stroke onset,^{2,3} and the prognosis for these patients is poor despite maximal intensive care treatment. In larger intensive care-based prospective series, the case fatality rate was ≈70% to 80%.^{3,4} Therefore, the term “malignant middle cerebral artery (MCA) infarction” was introduced for these massive cerebral infarcts.³ Several conservative treatment

strategies, such as sedation, hyperventilation, steroids, barbiturates, and osmotic therapy with glycerol, mannitol, or hydroxyethyl starch, have been proposed to reduce the development of brain edema and intracranial pressure. So far, though, insufficient evidence of efficacy from randomized clinical trials is available to support any of these therapeutic strategies.^{5–7} Several reports suggest that these therapies may be ineffective or even detrimental.^{7–10}

Because of the limitations of medical therapies, decompressive surgery has been proposed for patients with space-occupying hemispheric infarction. The rationale of this therapy is to create compensatory space to accommodate the

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

Received February 22, 2007; final revision received April 27, 2007; accepted May 3, 2007.

From the Department of Neurology (E.J., S.S., W.H.), University Hospital Heidelberg, University of Heidelberg, Heidelberg; the Department of Neurology (S.S.), University Hospital Erlangen, University of Erlangen, Erlangen; the Department of Neurosurgery (P.S., J.W.), University Hospital Mannheim, University of Heidelberg, Heidelberg; the Department of Neurosurgery (A.U.), University Hospital Heidelberg, University of Heidelberg, Heidelberg; the Department of Neurology (M.H.), University Hospital Mannheim, University of Heidelberg, Heidelberg; and the Institute of Medical Biometry and Informatics (S.W., E.J.), University of Heidelberg, Heidelberg, Germany.

*For list of the DESTINY Study Group, please see the supplemental Appendix, available online at <http://stroke.ahajournals.org>.

Correspondence to Werner Hacke, MD, PhD, Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany. E-mail werner.hacke@med.uni-heidelberg.de

© 2007 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.107.485649

swollen brain, thereby normalizing intracranial pressure, reverting brain tissue shifts, and preventing secondary tissue damage.¹¹

Findings from animal studies and numerous case reports are supported by a number of uncontrolled, nonrandomized, prospective case series suggesting a substantial benefit of decompressive surgery on mortality, from 67% to 88%, to 0% to 34% compared with historical controls.¹² This effect may even be more pronounced if treatment is started earlier, before signs of herniation appear.^{13,14} These studies also suggest that hemicraniectomy may reduce poor functional outcome (modified Rankin Scale [mRS] score 4 to 6, Barthel Index 0 to 25, or Glasgow Outcome Scale score 1 to 3) from 95% in conservatively treated patients to 8% to 50% in surgically treated patients.^{3,12,13,15}

None of those reports, however, was a randomized clinical trial. In addition, most of the control groups consisted of patients who were significantly older, had more comorbidity, and more often had lesions of the dominant hemisphere.^{12,15} Nevertheless, the promising results of nonrandomized studies encouraged the use of decompressive surgery to treat space-occupying infarcts. However, owing to the lack of conclusive evidence of efficacy from randomized clinical trials, there is still controversy about the benefit of hemicraniectomy and hence, large regional differences in the use of the procedure.

Five randomized trials have been designed to investigate the efficacy of decompressive surgery: The Hemicraniectomy And Durotomy On Deterioration From Infarction-Related Swelling Trial (HeADDFIRST) randomized 26 patients between 2000 and 2003. The final results have not been published yet.¹⁶ Between 2001 and 2004, 4 other studies were initiated: one trial, the Hemicraniectomy For Malignant Middle Cerebral Artery Infarcts (HeMMI) performed in the Philippines, and 3 European trials. HAMLET (Hemicraniectomy After Middle Cerebral Artery Infarction With Life-Threatening Edema Trial)¹⁷ is being performed in the Netherlands, DECIMAL (Decompressive Craniectomy In Malignant Middle Cerebral Artery Infarcts) has been conducted in France, and DESTINY (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery) has been performed in Germany.¹⁸

Meanwhile, a pooled analysis of data from DECIMAL, DESTINY, and HAMLET has been published that included 93 patients.¹⁹ Results for the dichotomized end points mRS score ≤ 4 , mRS score ≤ 3 , and survival showed a pooled absolute risk reduction of 51%, 23%, and 50%, respectively. We report here the results of the main end points of the DESTINY trial.

Patients and Methods

DESTINY is a prospective, multicenter, randomized, controlled, clinical trial based on a sequential design and registered in the Current Controlled Trials registry (ISRCTN01258591). The study protocol was approved by the ethics committees of all participating centers.

Patients and Interventions

For eligibility criteria see Table 1. Written, informed consent was obtained from the patient or an authorized representative before randomization and the performance of any protocol-specific proce-

TABLE 1. Eligibility Criteria

Inclusion criteria
Age 18–60 years
Clinical signs of infarction of the MCA territory with an NIHSS ²⁰ score > 18 for lesions of the nondominant hemisphere and >20 for lesions of the dominant hemisphere
Decrease in the level of consciousness to a score of ≥ 1 on item 1a of the NIHSS
Computed tomography–documented unilateral MCA infarction, including at least 2/3 of the territory and including at least part of the basal ganglia, with or without additional ipsilateral infarction of the anterior or posterior cerebral artery
Onset of symptoms >12 and <36 hours before a possible surgical intervention
Possibility to start treatment/surgery within 6 hours after randomization
Written, informed consent by the patient or legal representative
Exclusion criteria
Prestroke mRS score ≥ 2 ²¹
Prestroke score on the Barthel Index <95 ²²
Score on the Glasgow Coma Scale <6
Both pupils fixed and dilated
Any other coincidental brain lesion that might affect outcome
Space-occupying hemorrhagic transformation of the infarct
Life expectancy <3 years
Other serious illness that might affect outcome
Known coagulopathy or systemic bleeding disorder
Contraindication for anesthesia
Pregnancy

NIHSS indicates National Institutes of Health Stroke Scale.

dures. Patients were randomized to either surgical plus conservative treatment or to conservative treatment alone. Blocked randomization codes, stratified for each center, were provided by an institute in sealed envelopes. Conservative treatment and decompressive surgery were conducted according to a consensus protocol of all participating neurologic, neurosurgical, and intensive care physicians (Table 2).^{23–25} All patients were ventilated and treated on an intensive care unit.

Study Design and Statistics

The trial design has a unique feature, as defined by the difficulty of establishing the most important outcome after massive MCA infarction: survival, functional outcome, or both. Given the expected magnitude of the intervention on survival, it was considered highly likely that the superiority of surgery regarding survival could be established with a small number of randomized patients. On the other hand, it was still unclear as to what extent one could expect an effect on functional outcome. Therefore, DESTINY was based on a sequential design, taking mortality after 30 days as the first, but not the primary, efficacy end point.

Sample size calculation was planned with the use of PEST 2.2 software, and statistical analysis was performed with this same validated software.²⁶ Based on the previously published review in the Cochrane Library, the difference in mortality after 30 days between the 2 groups was estimated at 40% absolute with a mortality rate of 85% in the conservative treatment group (level of significance 5%, power of 90%).¹² In this sequential design, exploratory analysis was performed after reaching this end point in each individual patient.

The study protocol defined that thereafter patient enrollment would be interrupted until the 6-month functional outcome (primary end point, dichotomized between mRS score 0 to 3 versus 4 to 6) had

TABLE 2. Treatment Protocol**Conservative Treatment**

Osmotherapy: Indication—Any clinical or neuroradiologic signs of space-occupying brain edema. Mannitol (0.5 g/kg $4\times$ /day, every 4 to 6 hours; maximum daily dose, 2.5 g/kg), glycerol (250 mL, 10% solution, $4\times$ /day), or hydroxyethyl starch (6% hetastarch in 0.9% NaCl injection, 100–250 mL every 8 hours; maximum daily dose, 750 mL); target serum osmolality=315 to 320 mOsm

Intubation and mechanical ventilation: Indication—Glasgow Coma Scale score <8 , any signs of respiratory insufficiency ($P_{O_2} <60$ mm Hg, $P_{CO_2} >48$ mm Hg), or compromised airway. Ventilation mode left at discretion of the treating physician. Target parameters= $P_{O_2} >75$ mm Hg, P_{CO_2} 36–44 mm Hg. In case of raised intracranial pressure, target parameters= $P_{O_2} >100$ mm Hg, P_{CO_2} 35–40 mm Hg, tidal volume 8–10 mL/kg, 10–12 breaths per minute, minimum of 5 cm H_2O of positive end-expiratory pressure

Hyperventilation: Ultimate ratio in case of further neurologic deterioration and/or uncontrolled increase in intracranial pressure. Target P_{CO_2} 28–32 mm Hg. Venous oxygenation (jugular bulb oxymetry, saturation $>50\%$)

Intracranial pressure monitoring: Invasive measurement in the ipsilateral hemisphere

Sedation: Mode including use of muscle relaxants left at the discretion of the treating physician. Propofol recommended. Use of barbiturates discouraged

Blood pressure: Target parameters in formerly hypertensive patients=180/100–105 mm Hg, in formerly normotensive patients=160–180/90–100 mm Hg. Target parameters during the first 8 hours after decompressive surgery=140–160 mm Hg

Positioning: Plane head positioning, elevation of 15° – 30° recommended in case of severely increased intracranial pressure, depending on CPP, or in patients at high risk of infection

Body core temperature: Target=normothermia. Treatment started at $>37.5^\circ\text{C}$. Use of antipyretics, external or intravasal cooling left at the discretion of the treating physician

Blood glucose level: Target parameters=80–110 mg/dL. Treatment started at >140 mg/dL with insulin. Hypoglycemia treated with 10% or 20% glucose

Fluid management: Target=normovolemia; avoid hyponatremia

Prophylaxis of deep venous thrombosis: Weight-adjusted low-molecular-weight heparin

No seizure prophylaxis

Decompressive surgery

Large (reversed) question mark-shaped skin incision based at the ear

Removal of a bone flap (diameter >12 cm, including the frontal, parietal, temporal, and parts of the occipital squama)

Removal of additional temporal bone so that the floor of the middle cerebral fossa can be explored

Opening of the dura and insertion of an augmented dural patch consisting of either homologous periost and/or temporal fascia

No resection of infarcted brain tissue

Fixation of the dura at the margin of the craniotomy

Reapproximation and securing of the temporal muscle and skin flap

Insertion of a sensor for registration of intracranial pressure

Cranioplasty in surviving patients after 6–8 weeks, with the stored bone flap or artificial bone flap

CPP indicates cerebral perfusion pressure.

been assessed.²¹ For analysis of the primary end point, a 2-sided χ^2 test with an error level of 0.05 was defined. Thereafter, depending on the observed difference in functional outcome, the final sample size was recalculated for a second exploratory trial stage. All ethics committees of the participating centers agreed that this was an appropriate way to minimize the number of patients needed to be randomized in this trial.

Six-month and 1-year follow-ups were conducted by 1 single investigator, who was not involved in screening, randomization, or patient care. No blinding was applied. Before the last patient was enrolled, several publications had underlined the usefulness of analyzing the whole spectrum of the mRS.²⁷ We therefore decided, before the mortality and outcome results were disclosed to the steering committee, to analyze the distribution of scores of the mRS with the Wilcoxon U test. In addition, we entered the mRS dichotomization (between 0 and 4 versus 5 to 6) and an interview assessment of the retrospective agreement and the perceived usefulness of the surgical procedure among survivors and caregivers in the surgical treatment group as secondary analyses to further understand the results of the trial. Because substantial recovery, especially regarding aphasia, activities of daily living, and quality of life, seems to extend into the 3-year period after stroke in patients enrolled in this trial, the steering committee also decided to additionally analyze functional outcome, the quality of life as measured by the SF-36²⁸ and the Stroke Impact Scale,²⁹ and aphasia with the Aachen Aphasia Test³⁰ at 2 and 3 years in a blinded fashion to avoid bias.

All analyses were carried out on an intention-to-treat (ITT) and per-protocol basis. All treatment procedures were documented for the per-protocol analysis, which was conducted by a case adjudication committee consisting of an experienced neurologist, neuroradiologist, neurosurgeon, and statistician. Patients were included in the per-protocol analysis only when the case adjudication committee confirmed that all eligibility criteria had been fulfilled and no major protocol violation had occurred.

Results

We report here the ITT results of the 30-day mortality end point and functional outcome after 6 months and 1 year. The first patient was enrolled in February 2004, and the last 2 patients were enrolled in October 2005. One hundred twenty-six patients were screened, 48 fulfilled all eligibility criteria, 32 patients or their relatives consented to randomization, and all 32 were included (20 at Heidelberg; 6 at Mannheim; 2 at Leipzig; 2 at Greifswald; 1 at Würzburg; and 1 at Cologne). Patient characteristics are detailed in Table 3. There were some imbalances in characteristics, such as a higher median National Institutes of Health Stroke Scale score in the conservative treatment arm (24, versus 21 in the surgical treatment arm), which was due to a statistically nonsignificant

TABLE 3. Baseline Patient Characteristics by Group

	Surgery Group n=17	Conservative Treatment Group n=15	Total n=32	P Value
Sex				
Male	47%	47%	47%	$P=0.98^*$
Female	53%	53%	53%	
Age, y				
Mean±SD	43.2±9.7	46.1±8.4	44.6±9.1	$P=0.44^\dagger$
Median	43.0	46.0	44.5	
Range	30.0–60.0	29.0–59.0	29.0–60.0	
Hemisphere				
Dominant	53%	73%	63%	$P=0.23^*$
Nondominant	47%	27%	38%	
NIHSS score on admission				
Median	21	24	22	$P<0.01$
Range	19–26	19–31	19–31	
Time from symptom onset to treatment start, h				
Mean±SD	24.4±6.9	23.8±7.8	24.1±7.2	$P=0.66$
Median	24.0	22.5	24.0	
Range	13.5–36.0	12.0–35.0	12.0–36.0	

NIHSS indicates National Institutes of Health Stroke Scale.

* χ^2 test.

†*U* test.

higher proportion of patients with infarction of the dominant hemisphere in the conservative treatment arm. There were 2 major protocol violations: One patient had been randomized to conservative treatment but underwent surgery (beyond the 36-hour time window) because another surgeon strongly recommended surgery. One patient did not receive hemicraniectomy according to the protocol. Both patients survived.

After inclusion of 32 patients, the trial was interrupted according to the protocol, after significance for the 30-day mortality end point was reached. In the ITT analysis, 15 of 17 (88%; 95% CI, 64% to 99%) patients randomized to hemicraniectomy had survived, whereas in the conservative treatment arm, 7 of 15 (47%; 95% CI, 21% to 73%) patients had survived after 30 days ($P=0.02$; median unbiased odds ratio [OR]=6.37; 95% CI, 1.35 to 29.17). All deaths occurred within 8 days except for 1 patient in the decompressive surgery group, who died after 157 days due to a fatal postoperative pulmonary embolism, 1 day after having received cranioplasty. No further deaths occurred thereafter. Survival after 6 and 12 months was 82% in the surgical group versus 47% in the conservative treatment group ($P=0.03$; OR=5.33; 95% CI, 1.07 to 26.61).

The ITT results for functional outcome after 6 months are given in Table 4 and Figures 1a and 2. Analysis of the distribution of mRS scores showed positive results in favor of surgery ($P=0.04$). Forty-seven percent of patients in the surgical arm versus 27% of patients in the conservative treatment arm reached an mRS score of 0 to 3 ($P=0.23$; OR=2.44; 95% CI, 0.55 to 10.83). Seventy-seven percent in the surgical arm versus 33% in the conservative treatment arm reached an mRS score of 0 to 4 ($P=0.01$; OR=6.50; 95%

CI, 1.38 to 30.68). Eight-two percent in the surgical arm versus 47% in the conservative treatment arm were alive ($P=0.03$; OR=5.33; 95% CI, 1.07 to 26.61).

Sample-size projection for the primary end point, from estimation of a 20% difference in mRS scores of 4 to 6 between the 2 groups, suggested that 94 patients be included in each arm (188 patients total). With this projection and in light of an ongoing pooled analysis of a prespecified subset of patients included into the 3 European hemicraniectomy trials, HAMLET, DECIMAL, and DESTINY, the steering committee decided to stop the trial in April 2006.

The results of 12-month functional outcomes are given in Table 4 and Figures 1b and 2. Analysis of the distribution of mRS scores again showed positive results in favor of surgery ($P=0.04$). Analyses of the dichotomized mRS scores (0 to 3 versus 4 to 6; 0 to 4 versus 5 to 6) and mortality were identical to those after 6 months. In the interview with patients and caregivers, there was 100% agreement with the procedure after 12 months in all surviving surgically treated patients.

Discussion

Even after decades, no agreement has been reached among experts concerning the question of whether decompressive surgery should be performed in patients with malignant MCA infarction. Several reports noted a reduction in mortality to $\approx 30\%$ after “delayed” hemicraniectomy and an even higher reduction of mortality to $\approx 20\%$ after “early” hemicraniectomy (before signs of herniation were present) with a moderate to good functional outcome in 83% of surviving patients.^{13,15,32} On the other hand, other reports have questioned the benefit of decompressive surgery, especially with

TABLE 4. Patient Outcomes

	Surgery Group n=17	Conservative Treatment Group n=15	Total n=32	Statistics
Survival after 30 days				
Alive	88%	47%	69%	$P=0.02$
Dead	12%	53%	31%	Median unbiased OR=6.37 (1.35, 29.17)‡
mRS score after 6 months				
Median	4	6	4	$P=0.04†$
Range	2–6	3–6	2–6	
mRS 2	6%	0%	3%	Difference mRS 0–3 vs 4–6=20% $P=0.23^*$
mRS 3	41%	27%	34%	OR=2.44 (0.55, 10.83)
mRS 4	29%	7%	19%	Difference mRS 0–4 vs 5–6=43% $P=0.01^*$
mRS 5	6%	13%	9%	OR=6.50 (1.38, 30.68)
mRS 6	18%	53%	34%	Difference alive vs dead=36% $P=0.03^*$ OR=5.33 (1.07, 26.61)
Barthel Index score after 6 months				
Median	50	0	35	$P=0.08^*$
Range	0–85	0–85	0–85	
Median difference 20 (0, 55)				
NIHSS score after 6 months				
Median	14	42	16	$P=0.04†$
Range	10–19	12–42	5–42	
Median difference –7 (–27, 0)				
mRS score after 12 months				
Median	4	6	4	$P=0.04†$
Range	2–6	2–6	2–6	
mRS 2	24%	7%	16%	Difference mRS 0–3 vs 4–6=20% $P=0.23^*$
mRS 3	24%	20%	22%	OR=2.44 (0.55, 10.83)
mRS 4	29%	7%	19%	Difference mRS 0–4 vs 5–6=43% $P=0.01^*$
mRS 5	6%	13%	9%	OR=6.50 (1.38, 30.68)
mRS 6	18%	53%	34%	Difference alive vs dead=36% $P=0.03^*$ OR=5.33 (1.07, 26.61)
Barthel Index score after 12 months				
Median	45	0	30	$P=0.07†$
Range	0–95	0–95	0–95	
Median difference 25 (0, 55)				
NIHSS score after 12 months				
Median	13	42	14	$P=0.05†$
Range	5–42	6–42	5–42	
Median difference –7 (29, 0)				

NIHSS indicates National Institutes of Health Stroke Scale.

* χ^2 test.† U test.

‡Sequential test.

No. in parentheses indicate 95% CI.

Median difference indicates median difference between surgery and conservative treatment group.

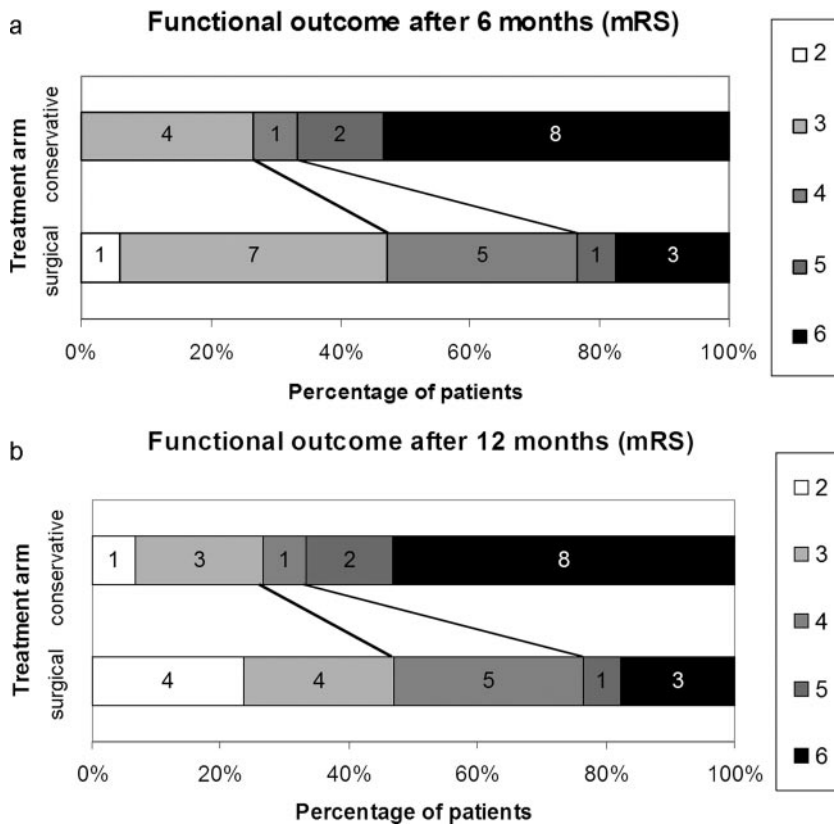


Figure 1. Functional outcome according to the mRS after 6 (a) and 12 (b) months (ITT analysis). Lines indicate the differences between both treatment arms: mRS score 0 to 3 versus 4 to 6 (primary end point) and 0 to 4 versus 5 to 6 (secondary end point).

respect to long-term survival and functional outcome, with overall mortality rates after 12 months as high as 50% and a favorable outcome in only $\approx 20\%$ of survivors, especially in older patients.^{15,33} However, all available data have come from nonrandomized, observational, or single-center studies.

Great efforts have been undertaken in the past to develop an appropriate study protocol for a randomized trial that is accepted by both neurosurgeons and neurologists. By choosing a sequential design, DESTINY is the first randomized, prospective trial to show that hemicraniectomy significantly reduces mortality in large hemispheric stroke by including the minimum number of patients that was absolutely necessary to address this question.

However, most neurologists and neurosurgeons agree that mortality alone is not the only important issue in these trials. The concern of many clinicians is not about survival but rather about clinical outcome and quality of life. Thus, the primary end point in DESTINY was not mortality but functional outcome according to the mRS after 6 months. There was a long discussion about the cutpoint for dichotomization of the mRS score to be used as the primary end point; ie, which grade of dependence distinguishes an “acceptable” from an “unacceptable” outcome. One primary aim of DESTINY was to demonstrate reduced mortality without an increase in disastrous outcome, eg, complete dependency or permanent vegetative state, congruent with an mRS score of 5. Therefore, we assessed mRS dichotomization not only at ≤ 3 but also at ≤ 4 and the mRS score distribution as secondary end points.

Hacke et al³ and Berrouschot et al⁴ reported a median mRS score of 3 in conservatively treated patients surviving a

malignant MCA infarction. Studies with comparative data report unfavorable outcomes (mRS score of 4 to 6, Barthel Index of 0 to 25, or Glasgow Outcome Scale score of 1 to 3) in 55% to 100% of patients treated by hemicraniectomy versus 63% to 100% of patients treated conservatively.^{34–37} Compared with most of these previous findings, DESTINY showed a better outcome in surgically treated patients, with 47% with an mRS score of ≤ 3 after 6 and 12 months. Only 27% in the conservative treatment group had an mRS score ≤ 3 . This finding contradicts the view of critics of early hemicraniectomy, who have argued that the better outcome seen in previous studies might reflect the selection of patients who were destined to do well regardless of surgery or not.

Although DESTINY failed to show statistically significant results for the primary end point because of the low number of patients, the steering committee decided to stop the trial: There was not only a major effect on mortality but also evidence that the fear of many critics that a reduction in mortality by hemicraniectomy might be outweighed by leaving survivors in a “vegetative state,” facing a life of dependency, pain, and hopelessness was unsubstantiated. Of the 14 survivors in the surgical arm, only 1 showed an mRS of 5 (7%) compared with 2 of 7 survivors in the conservative treatment arm (28%). In addition, analysis of the distribution of mRS scores showed a statistically significant benefit in functional outcome. Substantial recovery extends into the second half year and thereafter, and none of the surgical patients or their closest relatives, given the choice of being treated or not, would have chosen otherwise. Recalculation of the sample size for the primary end point, an mRS score ≤ 3 , suggested the need for almost 200 patients to be randomized.

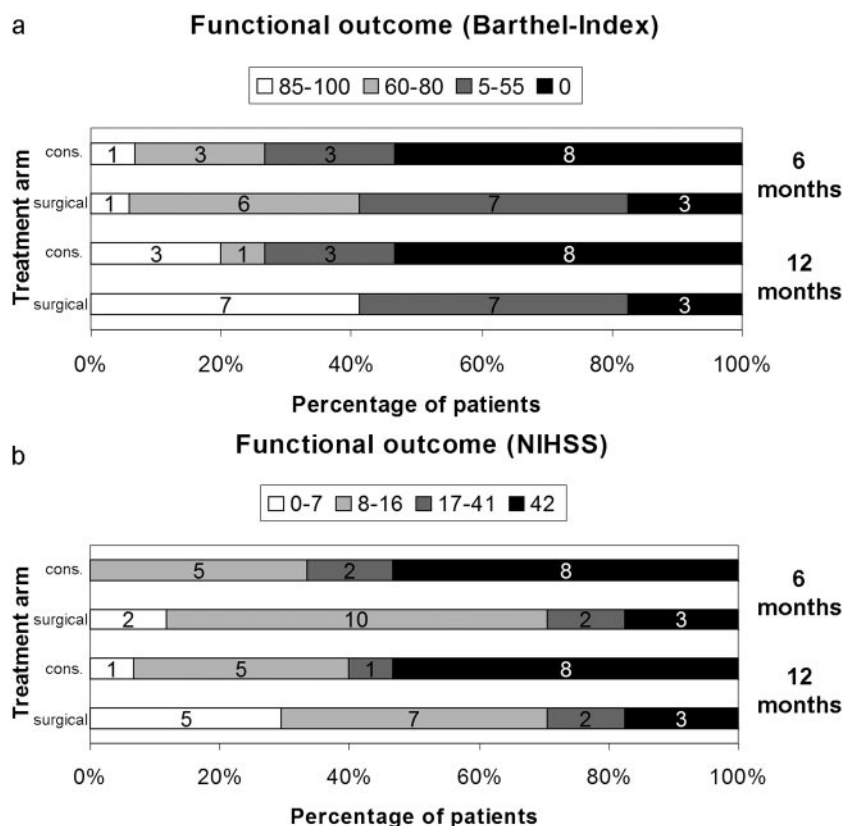


Figure 2. Functional outcome according to the Barthel Index (a), wherein scores of 85 to 100 indicate independent outcome; 60 to 80, mild to moderate disability; 5 to 55, severe disability; and 0, total dependence or death,¹⁵ and the National Institutes of Health Stroke Scale (b), wherein patients were grouped into no or mild (<8), moderate, (8–16) or severe (17–41) neurologic deficit, and coma and quadriplegia or death (42)³¹ after 6 and 12 months (ITT analysis).

All investigators agreed that further randomization of this large number of patients was no longer justifiable. This decision was facilitated by the expectations of the prospectively designed pooled analysis of data from the 3 individual European trials. The results of this pooled analysis support the DESTINY findings: After decompressive surgery, the probability of survival increased from 22% to 71%, the probability of survival with an mRS score ≤ 4 increased from 24% to 75%, and the probability of survival with an mRS score ≤ 3 almost doubled. At the same time, very severe disability (mRS score of 5) was not increased.¹⁹

DESTINY has several shortcomings. First, 81% of patients originated from 2 centers only. As a matter of fact, this makes DESTINY an oligocenter rather than a multicenter trial. Blinded evaluation of clinical outcome was not possible, which may have introduced bias for the outcome assessment. There were 2 major protocol violations, which were included in the ITT analysis. After excluding these patients from the preliminary per-protocol analysis, the results were not changed substantially. Finally, DESTINY does not provide data on older patients with malignant MCA infarction. Based on the results of several reports suggesting that patients >60 years may not profit from decompressive surgery, DESTINY only included patients 18 to 60 years of age.^{33,34} From the available data, it is currently impossible to define an upper age limit above which decompressive surgery should not be performed. More data from randomized trials will be needed to address this question in the future.

Disclosures

None.

References

- Heinsius T, Bogousslavsky J, Van Melle G. Large infarcts in the middle cerebral artery territory: etiology and outcome patterns. *Neurology*. 1998; 59:341–350.
- Ropper AH, Shafar B. Brain edema after stroke: clinical syndrome and intracranial pressure. *Arch Neurol*. 1984;41:26–29.
- Hacke W, Schwab S, Horn M, Spranger M, DeGeorgia M, von Kummer R. 'Malignant' middle cerebral artery infarction: clinical course and prognostic signs. *Arch Neurol*. 1996;53:309–315.
- Berrouschot J, Sterker M, Bettin S, Koster J, Schneider D. Mortality of space-occupying (malignant) middle cerebral artery infarction under conservative intensive care. *Intensive Care Med*. 1998;24:620–623.
- Bereczki D, Liu M, do Prado GF, Fekete I. Mannitol for acute stroke. *Cochrane Database Syst Rev*. 2004;CD001153.
- Righetti E, Celani MG, Cantisani T, Sterzi R, Boysen G, Ricci S. Glycerol for acute stroke. *Cochrane Database Syst Rev*. 2000;CD000096.
- Hofmeijer J, van der Worp HB, Kappelle LJ. Treatment of space-occupying cerebral infarction. *Crit Care Med*. 2003;31:617–625.
- Schwab S, Schwab M, Bertram M, Aschoff A, Hacke W. Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. *Stroke*. 1998;29: 1550–1555.
- Schwab S, Georgiadis D, Aschoff A, Schwab S. Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. *Stroke*. 2002;33:497–501.
- Schwab S, Spranger M, Schwarz S, Hacke W. Barbiturate coma in severe hemispheric stroke: useful or obsolete? *Neurology*. 1997;48:1608–1613.
- Schwab S, Rieke K, Aschoff A, Albert F, von Kummer R, Hacke W. Hemispherectomy in space-occupying hemispheric infarction: useful early intervention or desperate activism? *Cerebrovasc Dis*. 1996;6: 325–329.
- Morley NC, Berge E, Cruz-Flores S, Whittle IR. Surgical decompression for cerebral oedema in acute ischaemic stroke. *Cochrane Database Syst Rev*. 2002;3:CD003435.
- Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, Hacke W. Early hemispherectomy in patients with complete middle cerebral artery infarction. *Stroke*. 1998;29:1888–1893.
- Cho DY, Chen TC, Lee HC. Ultra-early decompressive craniectomy for malignant middle cerebral artery infarction. *Surg Neurol*. 2003;60: 227–232.

15. Gupta R, Connolly ES, Mayer S, Elkind MS. Hemicraniectomy for massive middle cerebral artery territory infarction: a systematic review. *Stroke*. 2004;35:539–543.
16. Frank JI, Krieger D, Chyatte D. Hemicraniectomy and durotomy upon deterioration from massive hemispheric infarction: a proposed multicenter, prospective, randomized study. *Stroke*. 1999;30:243.
17. Hofmeijer J, Amelink GJ, Algra A, van Gijn J, Macleod MR, Kappelle LJ, van der Worp HB, the HAMLET investigators. Hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial (HAMLET): protocol for a randomised controlled trial of decompressive surgery in space-occupying hemispheric infarction. *Trials*. 2006;7:29.
18. Major ongoing stroke trials. *Stroke*. 2006;37:e18–e26.
19. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedek P, Schwab S, Rothwell PM, Boussier MG, van der Worp HB, Hacke W, the DECIMAL, DESTINY, and HAMLET investigators. Early decompressive surgery in malignant middle cerebral artery infarction: pooled analysis of three randomized controlled trials. *Lancet Neurol*. 2007;6:215–222.
20. Brott T, Adams H, Olinger C, Marler J, Barsan W, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864–870.
21. Rankin J. Cerebral vascular accidents in people over the age of 60, II: prognosis. *Scott Med J*. 1957;2:200–215.
22. Mahoney GI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J*. 1965;14:61–65.
23. The European Stroke Initiative Executive Committee and the EUSI Writing Committee. European Stroke Initiative Recommendations for Stroke Management—update 2003. *Cerebrovasc Dis*. 2003;16:311–337.
24. Steiner T, Ringleb P, Hacke W. Treatment options for large hemispheric stroke. *Neurology*. 2001;57(suppl):61–68.
25. Demchuk AM, Krieger DW. Mass effect with cerebral infarction. *Curr Treat Options Neurol*. 1999;1:189–199.
26. Whitehead J, Brunier H. The PEST project, University of Reading, 1989: the design and analysis of sequential clinical trials. In: *Planning and Evaluation of Sequential Trials*. New York: Wiley; 1997.
27. Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. *Arch Neurol*. 2004;61:1066–1070.
28. <http://www.sf-36.org/tools/sf36.shtml>.
29. http://www1.va.gov/rorc/stroke_impact.cfm.
30. Huber W, Poeck K, Willmes K. The Aachen Aphasia Test. *Adv Neurol*. 1984;42:291–303.
31. Briggs D, Felberg R, Malkoff M, Bratina P, Grotta J. Should mild or moderate strokes be admitted to an intensive care unit? *Stroke*. 2001;32:871–876.
32. Rieke K, Schwab S, Krieger D, von Kummer R, Aschoff A, Schuchardt V, Hacke W. Decompressive surgery in space-occupying hemispheric infarction: results of an open, prospective trial. *Crit Care Med*. 1995;23:1576–1587.
33. Uhl E, Kreth FW, Elias B, Goldammer A, Hempelmann RG, Liefner M, Nowak G, Oertel M, Schmieder K, Schneider HH. Outcome and prognostic factors of hemicraniectomy for space occupying cerebral infarction. *J Neurol Neurosurg Psychiatry*. 2004;75:270–274.
34. Holtkamp M, Buchheim K, Unterberg A, Hoffmann O, Schielke E, Weber JR, Masuhr F. Hemicraniectomy in elderly patients with space occupying media infarction: improved survival but poor functional outcome. *J Neurol Neurosurg Psychiatry*. 2001;70:226–228.
35. Delashaw JB, Broaddus WC, Kassell NF, Haley EC, Pendleton GA, Vollmer DG, Maggio WW, Grady MS. Treatment of right hemispheric cerebral infarction by hemicraniectomy. *Stroke*. 1990;21:874–881.
36. Maramattom BV, Bahn MM, Wijdicks EMF. Which patient fares worse after early deterioration due to swelling from hemispheric stroke? *Neurology*. 2004;63:2142–2145.
37. Mori K, Nakao Y, Yamamoto T, Maeda M. Early external decompressive craniectomy with duroplasty improves functional recovery in patients with massive hemispheric embolic infarction: timing and indication of decompressive surgery for malignant cerebral infarction. *Surg Neurol*. 2004;62:420–429.

Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): A Randomized, Controlled Trial

Eric Jüttler, Stefan Schwab, Peter Schmiedek, Andreas Unterberg, Michael Hennerici, Johannes Woitzik, Steffen Witte, Ekkehart Jenetzky and Werner Hacke
for the DESTINY Study Group

Stroke. 2007;38:2518-2525; originally published online August 9, 2007;
doi: 10.1161/STROKEAHA.107.485649

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://stroke.ahajournals.org/content/38/9/2518>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>