

Sequential-Design, Multicenter, Randomized, Controlled Trial of Early Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarction (DECIMAL Trial)

Katayoun Vahedi, MD; Eric Vicaut, MD, PhD; Joaquim Mateo, MD; Annie Kurtz, MS; Mikael Orabi, MD; Jean-Pierre Guichard, MD; Carole Boutron, BS; Gregory Couvreur, MD; François Rouanet, MD; Emmanuel Touzé, MD; Benoît Guillon, MD; Alexandre Carpentier, MD; Alain Yelnik, MD; Bernard George, MD; Didier Payen, MD, PhD; Marie-Germaine Bousser, MD; on behalf of the DECIMAL Investigators

Background and Purpose—There is no effective medical treatment of malignant middle cerebral artery (MCA) infarction. The purpose of this clinical trial was to assess the efficacy of early decompressive craniectomy in patients with malignant MCA infarction.

Methods—We conducted in France a multicenter, randomized trial involving patients between 18 and 55 years of age with malignant MCA infarction to compare functional outcomes with or without decompressive craniectomy. A sequential, single-blind, triangular design was used to compare the rate of development of moderate disability (modified Rankin scale score ≤ 3) at 6 months' follow-up (primary outcome) between the 2 treatment groups.

Results—After randomization of 38 patients, the data safety monitoring committee recommended stopping the trial because of slow recruitment and organizing a pooled analysis of individual data from this trial and the 2 other ongoing European trials of decompressive craniectomy in malignant MCA infarction. Among the 38 patients randomized, the proportion of patients with a modified Rankin scale score ≤ 3 at the 6-month and 1-year follow-up was 25% and 50%, respectively, in the surgery group compared with 5.6% and 22.2%, respectively, in the no-surgery group ($P=0.18$ and $P=0.10$, respectively). There was a 52.8% absolute reduction of death after craniectomy compared with medical therapy only ($P<0.0001$).

Conclusions—In this trial, early decompressive craniectomy increased by more than half the number of patients with moderate disability and very significantly reduced (by more than half) the mortality rate compared with that after medical therapy. (*Stroke*. 2007;38:2506-2517.)

Key Words: clinical trials ■ craniectomy ■ middle cerebral artery

Malignant middle cerebral artery (MCA) infarction is a large hemispheric infarction with poor outcome attributable to the ischemic edema that causes an early rise in intracranial pressure and subsequent brain herniation and death.^{1,2} No medical therapy has proven effective in preventing brain herniation and improving patient outcome. As an alternative therapy, surgical decompression techniques (large hemicraniectomy with durotomy) have been proposed to relieve the high intracranial pressure, but this strategy remains controversial in the absence of randomized, controlled trials and the fear of severe and “unacceptable” residual disability.^{3–12} This controversy in the

medical literature was also apparent in the national survey that we performed in 47 French Neurology Departments in 2000, showing that only 2 centers were convinced of the efficacy of decompressive craniectomy. The majority of centers (77%) approved the concept of a randomized trial evaluating the benefit of decompressive craniectomy in patients with malignant MCA infarction (K. Vahedi, unpublished data, 2000). Therefore, we conducted in France a multicenter, randomized, controlled trial that aimed to assess the efficacy of early decompressive craniectomy on functional outcomes in patients <55 years of age with malignant MCA infarction.

Received February 22, 2007; final revision received April 24, 2007; accepted April 26, 2007.

From Service de Neurologie (K.V., A.K., M.-G.B.), Unité de Recherche Clinique (E.V., C.B.), Département d'Anesthésie Réanimation et Réanimation Chirurgicale (J.M., D.P.), Service de Neurochirurgie (M.O., A.C., B.G.), and Service de Neuroradiologie (J.-P.G.), Assistance Publique-Hôpitaux de Paris, Hôpital Lariboisière, Paris; Service de Neurologie (G.C.), Centre Hospitalier Universitaire de Dijon, Dijon; Service de Neurologie (F.R.), Centre Hospitalier Universitaire de Bordeaux, Bordeaux; Service de Neurologie (E.T.), Centre Hospitalier Sainte-Anne, Paris; Service de Neurologie (B.G.), Centre Hospitalier Universitaire de Nantes, Nantes; and Service de Rééducation et de Réadaptation Fonctionnelles (A.Y.), Assistance Publique-Hôpitaux de Paris, Hôpital Fernand-Widal, Paris, France.

Correspondence to Katayoun Vahedi, MD, Assistance Publique-Hôpitaux de Paris, Hôpital Lariboisière, Service de Neurologie, 2 rue Ambroise Paré, 75010 Paris, France. E-mail katayoun.vahedi@lrh.aphp.fr

© 2007 American Heart Association, Inc.

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

DOI: 10.1161/STROKEAHA.107.485235

Patients and Methods

Study Design and Patient Eligibility

The *DE*compressive Craniectomy In *MAL*ignant MCA Infarction (DECIMAL) Trial was a multicenter, prospective, randomized, open (but with blind evaluation of the primary end point) study comparing early decompressive craniectomy plus standard medical therapy versus standard medical therapy alone in patients with malignant MCA infarction. The study protocol was approved by a national ethics committee (CCPRB Hôpital Saint-Louis, Paris, No. 2001/36). The study was conducted in 13 selected stroke centers (including a stroke unit and a neurosurgery department in France) and was funded by the French Ministry of Health and the Assistance Publique–Hôpitaux de Paris (Programme Hospitalier de Recherche Clinique AOM 00148, P001004). The patient or a close relative gave written, informed consent for participation in the trial. The first patient was enrolled in December 2001 and the last patient in November 2005. An independent data safety monitoring committee monitored the safety, progress, and ethics of the trial.

Patients between 18 and 55 years of age were included within 24 hours of a malignant MCA infarction defined by the association of 3 criteria: a National Institutes of Health Stroke Scale score ≥ 16 , including a score ≥ 1 for item 1a (level of consciousness); brain computed tomography ischemic signs involving $>50\%$ of the MCA territory; and a diffusion-weighted imaging (DWI) infarct volume $>145 \text{ cm}^3$.

Exclusion criteria included preexisting significant disability defined by a modified Rankin Scale (mRS) score ≥ 2 , a significant contralateral infarction, a severe secondary hemorrhagic infarction involving $>50\%$ of the MCA territory, any known coagulopathy (including use of recombinant tissue-type plasminogen activator), life expectancy <3 years or any serious illness that could confound treatment assessment, pregnancy, and any magnetic resonance imaging (MRI) contraindication.

Eligible patients were randomly assigned to receive standard medical therapy alone or standard medical therapy plus decompressive craniectomy and durotomy. For patients in the surgical group, decompressive craniectomy had to be done no later than 6 hours after randomization and up to 30 hours after the onset of symptoms.

Surgical Procedure

Decompressive surgery consisted of a large hemicraniectomy that removed, ipsilateral to the stroke, a bone flap as large as possible including temporal, frontal, parietal, and some occipital bones. The dura had to be open, and duraplasty was left to the discretion of the neurosurgeon.

Standard Medical Therapy

In both groups of patients, standard medical therapy was based on published guidelines for the early management of patients with ischemic stroke.^{13–15} Non–evidence-based therapeutics such as hypothermia were discouraged. Continuous invasive intracranial pressure monitoring was not recommended. Endotracheal intubation was recommended to maintain adequate tissue oxygenation in patients with severely increased levels of intracranial pressure. It was also recommended to avoid factors that might exacerbate brain edema, including hyperthermia and hyperglycemia, and to keep the head of the bed elevated at 30° to assist venous drainage. Intravenous fluid restriction of 500 mL/d with normal saline was also recommended, but the use of intravenous glucose solutions was discouraged unless necessary. Administration of intravenous mannitol (0.25 to 0.5 g/kg) or furosemide was recommended only in patients whose condition was rapidly worsening because of brain edema, without additional recommendations on loading doses. Intravenous antihypertensive agents were recommended when systolic blood pressure was $>220 \text{ mm Hg}$ or diastolic blood pressure was $>120 \text{ mm Hg}$. Prophylactic use of anticonvulsants was at the discretion of each investigating center.

Follow-Up and Assessment of End Points

The primary end point was a “favorable” functional outcome, defined by patient survival with an mRS score ≤ 3 at 6 months.¹⁶ Secondary end points were survival, a favorable functional outcome defined as an mRS score ≤ 3 or a Barthel Index >85 at 12 months, the National Institutes of Stroke Scale, and quality of life assessed by the French version of the Stroke Impact Scale 2.0 (SIS) at 12 months.^{17,18} The SIS consists of 8 domains, 4 physical domains (including strength, hand function, mobility, and activities of daily living/instrumental activities of daily living) and 4 psychosocial domains (including emotion, communication, memory, and social participation), and includes the patient’s global assessment of the percentage of recovery on a visual analog scale. The score of each domain ranges from 0 to 100, with 100 being the best.

Patients were assessed at study inclusion; at 7 days; at 4, 8, and 12 weeks; and at 3, 6, 9, and 12 months. At all visits after the 12-week visit, a neurologist blinded to the therapeutic arm assignment of the patient assessed the mRS (primary outcome). To keep the investigator neurologist blinded to therapeutic assignment, the head of each patient (in both groups) was covered with a surgical cap. Adverse events were recorded at each visit. For the surgical group, cranioplasty was not performed before the 6-month visit to avoid interfering with the evaluation of the primary outcome measure, unless the patient had reached the primary end point (mRS score ≤ 3) at an earlier visit.

Before inclusion into the study, all patients had a brain MRI performed in a head coil, including the following sequences: diffusion ($b=1000 \text{ s/mm}^2$), T2 fluid-attenuated inversion recovery, T2 gradient echo, and 3-dimensional time of flight. All images were acquired in the axial plane with a 6-mm section thickness, no gap, and 20 sections, thus ensuring whole brain coverage. The 3-dimensional time of flight sequence covered the intracranial carotid arteries to the MCAs.

DWI Infarct Volume Evaluation

Patients were enrolled in DECIMAL on the basis of MR DWI that demonstrated an infarct volume of $>145 \text{ cm}^3$ (Figure 1). The infarct volume (DWI volume) was measured on the DWI scans (b value = 1000 s/mm^2) as previously described.¹⁹ All images in which the infarcted area was displayed as a region of bright signal were first selected. On each of the slices, the area of hypersignal was then delineated with a semiautomatic thresholding method as follows. The cursor was initially positioned on the most hyperintense pixel. The intensity threshold was then progressively enlarged until the total selected area matched the hyperintense area that would have been manually contoured. Whenever >1 lesion was present, each additional lesion was contoured with the same method. Hemorrhagic transformation, displayed as areas of low signal inside the infarcted area, was added to the surface of measure. Then, the surface of each area was added, and DWI volume was obtained by multiplying the total surface by the slice thickness (slice thickness = 6 mm, intersection gap = 0).

Each center, before inclusion of its first patient, had to send to the MRI validation committee a measurement sample of a large MCA infarction for validation. After each randomization, the inclusion MR DWI image was centrally reevaluated for measurement of DWI infarct volume by a neuroradiologist (J.-P.G.) who was unaware of the treatment allocation.

Statistical Analysis

Because of ethical considerations (especially the possibility of early termination of the trial in case of a high benefit of craniectomy), we used a sequential design based on a triangular test.²⁰

Sequential methods are appealing because they allow early study termination in case of either treatment efficacy or lack of efficacy. With these methods, type I and type II errors are correctly maintained to their desired values despite the multiple analyses occurring during the trial. The triangular test used here was based on a comparison of statistics calculated at each analysis and threshold values that can be considered as boundaries limits. This approach can

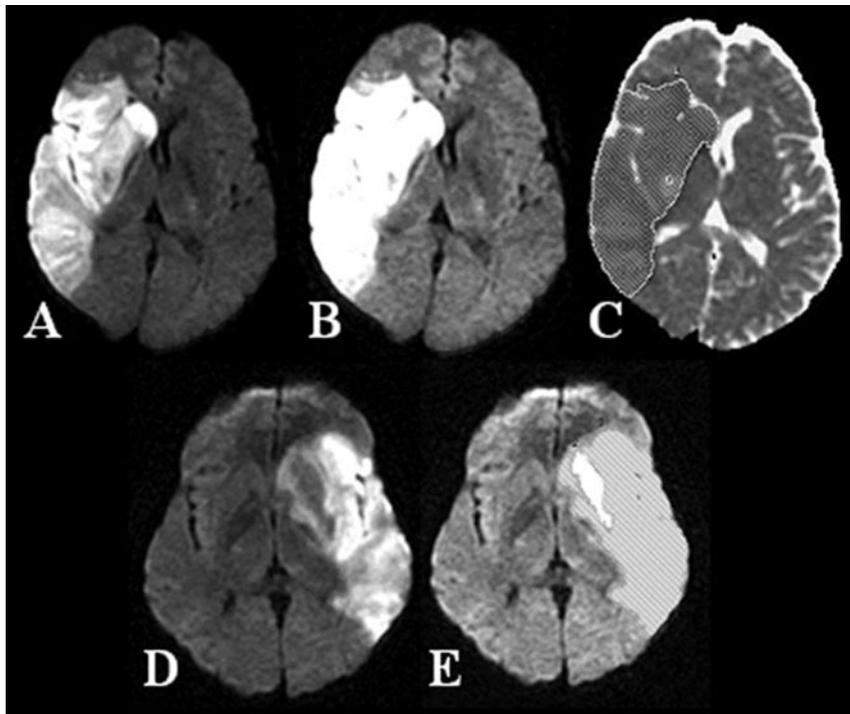


Figure 1. Illustrative method of DWI infarct volume measurement in the DECIMAL trial. Infarct volume was measured on the DWI images (A). For each slice, the area of hypersignal was delineated with a semiautomatic thresholding method. Contrast was forced for better demarcation of the area of hypersignal (B). The area was compared with the apparent diffusion coefficient map to confirm the result (C). When a zone of hemorrhagic transformation was present, it was added to the entire surface (D and E). In the same way, when some non-contiguous zones were present, each area was measured and then added to the final volume.

be considered in a graphical manner. In brief, a sequential plan defined by 2 perpendicular axes is considered. The horizontal axis corresponds to a first statistic V , which represents the quantity of information accumulated since the beginning of the trial (Fisher's information for the parameter of interest). The vertical axis corresponds to a second statistic Z , which represents the benefit compared with the null hypothesis. Two straight lines, the boundaries of the test, delineate a continuation region (situated between these lines) from the region of nonrejection of the null hypothesis (situated beneath the bottom line) and of rejection of the null hypothesis (situated above the top line). For both tests, the boundaries are convergent, thus defining a closed continuation region with a triangular shape, giving the name of the test. Both statistics Z and V are computed under the null hypothesis. They are calculated after each group of patients has been evaluated. The trial is continued as long as the sample path remains in the continuation region. A conclusion is reached as soon as the sample path crosses 1 of the boundaries of the test.

On the basis of data from previous open studies of decompressive craniectomy in malignant MCA infarction and under the assumption that the percentage of patients with an mRS score ≤ 3 would be close to 10% in the medical therapy only group and close to 40% in the surgical group, we anticipated a median sample size of 30 patients per group for 90% power and a 5% 2-sided significance level (calculated with Planning and Evaluation of Sequential Trial Software, University of Reading, Reading, UK). All statistical analyses were done on an intention-to-treat basis.

Patients were centrally randomized in blocks of 4 according to a preestablished randomization list. There was no predefined stratification per center. Each sequential procedure and set of termination rules were based on evaluation of the primary end point of the study (ie, percentage of patients with no moderately severe or severe residual disability [mRS ≤ 3] at 6 months). Interim analyses were carried out after every 4 patients were randomized. The final analysis was performed after the data safety monitoring committee decision after 38 patients had been enrolled. Monitoring and analysis of the trial were performed with PEST 3 software (PEST4 operating manual, MPS Research Unit, Reading University, Reading, UK; 1996). No interim analysis was planned for the secondary criteria that were analyzed at the end of the trial.

The frequency of qualitative parameters or categories of mRS scores were compared between the 2 groups by an exact probability test. Comparison of outcomes according to nondichotomized scores on the mRS was made with the Mann-Whitney test. Correlations were done only for exploratory purposes with Spearman's nonparametric correlation coefficient. Only descriptive analyses were provided for baseline characteristics and for exploratory subgroup analyses. For DWI infarct volumes, interrater reliability between the local investigators and the validation committee was tested with an intraclass correlation coefficient. All tests were 2-sided with a 5% significance level. This trial has been registered at www.clinicaltrials.gov; No. NCT00190203.

Results

Characteristics of the Patients

Thirty-eight patients from 7 stroke centers had been enrolled in the DECIMAL trial when it was prematurely stopped on recommendation from the data safety monitoring committee. On the basis of interim data, the data safety monitoring committee recommended first, to stop the trial, mainly because of slow recruitment and a high difference in mortality between the 2 groups, and second, to organize a pooled analysis of the individual data from DECIMAL and the 2 other ongoing European randomized trials of decompressive craniectomy in malignant MCA infarction (DESTINY and HAMLET).²¹

Of the 38 enrolled patients, 18 were assigned to receive standard medical therapy only and 20 were assigned to have decompressive craniectomy in addition to standard medical therapy (Figure 2). All patients assigned to the surgical group underwent decompressive craniectomy with a mean delay of 20.5 ± 8.3 hours (range, 7 to 43 hours) after the onset of symptoms (Figure 3). Duraplasty was performed in 11 of 20 patients. No patient assigned to the no-surgery group underwent decompressive surgery at any time during follow-up.

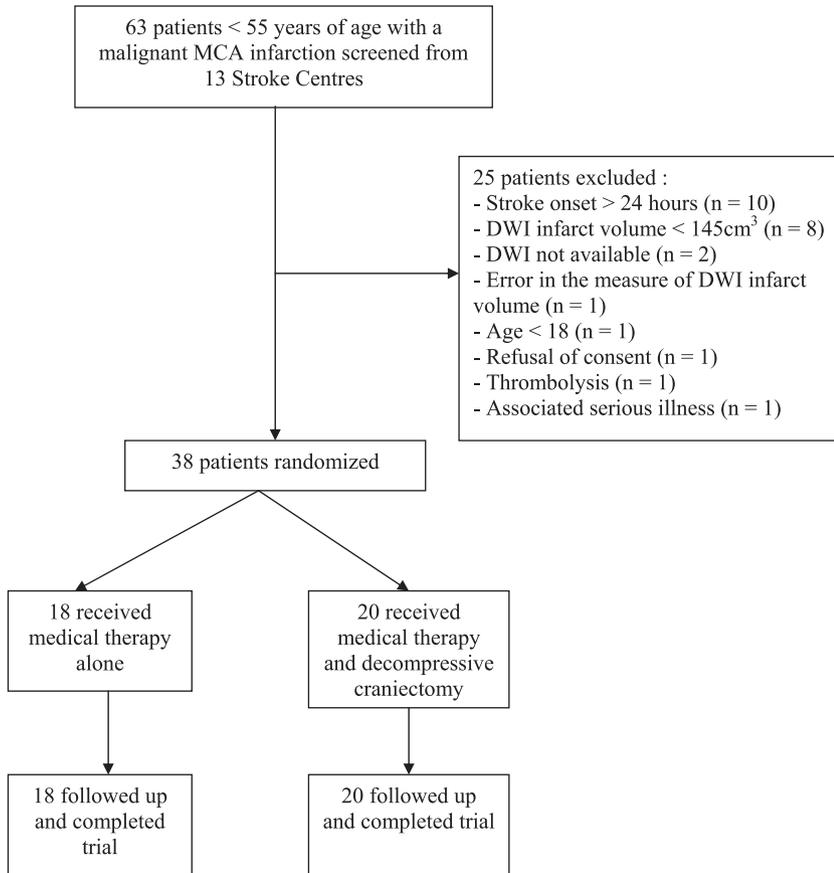


Figure 2. Flow chart of patient group assignment and treatment.

Baseline characteristics of the patients are listed in Table 1. Before inclusion into the study, all patients had their DWI infarct volumes calculated by the local neuro-radiologist. All measurements except 1 were validated by

the central validation committee to be >145 cm³. Interrater reliability between the local neuroradiologist and the central validation committee was excellent, with an intra-class correlation coefficient of 0.94. Enrolled patients had

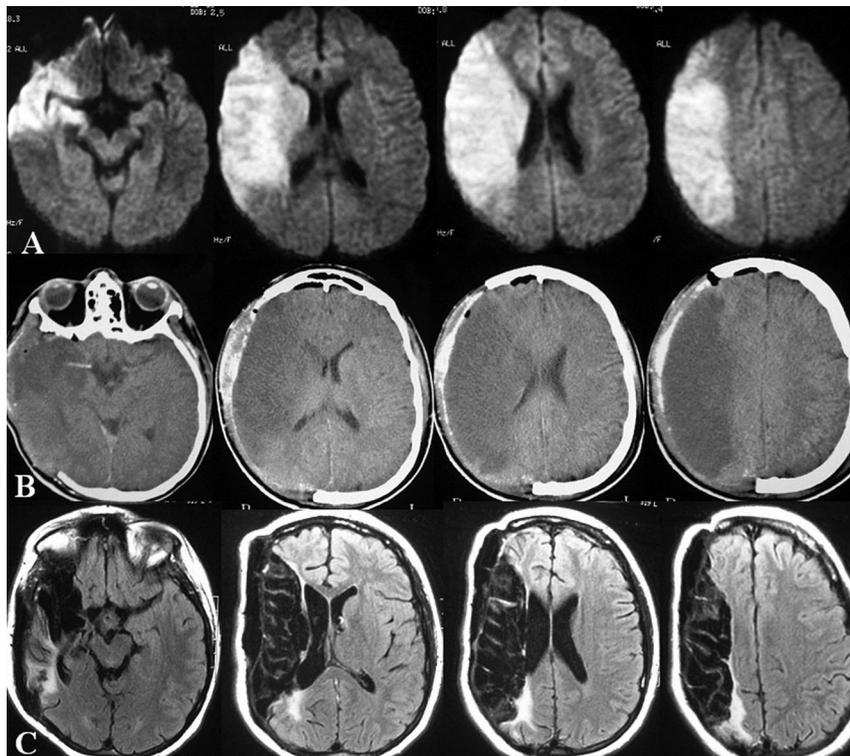


Figure 3. Baseline MRI scans (A) of a 22-year-old woman in the surgery group with a DWI infarct volume of 173 cm³. A large right hemispheric craniectomy including temporal, frontal, parietal, and occipital bone ipsilateral to the stroke was performed (B). At 1-year follow-up, 6 months after reconstruction of the large bone defect, her mRS score was 3, and fluid-attenuated inversion recovery imaging revealed right hemisphere atrophy (C).

TABLE 1. Baseline Characteristics of Patients

	Surgery Group (n=20)	No-Surgery Group (n=18)
Age, y		
Mean±SD, range	43.5±9.7, 22–55	43.3±7.1, 29–53
Male, No. (%)	9 (45%)	9 (50%)
NIHSS score		
Mean±SD, range	22.5±5.4, 16–35	23.4±6.2, 17–38
SBP, mm Hg		
Mean±SD, range	135.5±19.3, 103–169	154.0±25.1, 102–200
DBP, mm Hg		
Mean±SD, range	75.8±15.6, 48–98	83.4±15.1, 64–120
Heart rate, beats/min		
Mean±SD, range	73.0±17.0, 46–113	82.2±25.0, 40–140
Respiratory rate, breaths/min		
Mean±SD, range	20.9±14.1, 13–73	24.8±17.1, 13–84
Temperature, °C		
Mean±SD, range	36.9±0.5, 36.1–37.8	37.0±0.6, 35.8–38.2
DWI infarct volume, cm ³		
Mean±SD, range	211.5±67.1, 146–381	214.7±45.2, 150–308
Magnetic resonance angiography, No. (%)		
Carotid occlusion	12 (60%)	10 (56%)
MCA occlusion	4 (20%)	4 (22%)
Other	...	2 (11%)
Not done	4 (20%)	2 (11%)
Time from onset of stroke to craniectomy, h		
Mean±SD, range	20.5±8.3, 7–43	...
History, No. (%)		
Cigarette smoking	11 (58%)	7 (41%)
Hypertension	6 (31%)	4 (22%)
Diabetes	1 (5%)	3 (17%)
Hypercholesterolemia	...	1 (6%)
Prior stroke	2 (10%)	...
Atrial fibrillation	...	1 (6%)
Stroke etiologies, No. (%)		
Carotid dissection	5 (20%)	2 (11%)
Cardioembolic	3 (15%)	3 (17%)
Atherosclerotic	1 (5%)	2 (11%)
Drepanocytosis	...	1 (6%)
Not determined	11 (55%)	10 (56%)

NIHSS indicates National Institutes of Health Stroke Scale; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

few cardiovascular risk factors except for cigarette smoking and hypertension (Table 1). The 2 most common causes were carotid dissection and cardiac emboli. In 55% of patients, no cause was found.

Clinical Outcomes

The trial did not reach a stopping boundary for the primary outcome measure (mRS ≤ 3 at 6-month follow-up) after the 10th interim analysis. The proportion of patients with an mRS score ≤ 3 at the 6-month follow-up was 25% in the surgery group and 5.6% in the no-surgery group ($P=0.18$; Figure 4). At the 1-year follow-up, 10 of 20 patients (50%)

in the surgery group had an mRS score ≤ 3 , whereas 4 of 18 (22.2%) in the no-surgery group had an mRS score ≤ 3 ($P=0.10$). A comparison of outcomes according to nondichotomized scores on the mRS differed significantly between the 2 groups at 6 and 12 months' follow-up in favor of craniectomy ($P=0.011$ and $P=0.0024$, respectively). The number of patients surviving with no severe disability (mRS score ≤ 4) also differed significantly between the 2 groups at 6 ($P=0.0011$) and 12 months' follow-up: 15 of 20 patients (75%) in the surgery group had an mRS score ≤ 4 at the 1-year follow-up compared with 4 of 18 patients (22.2%) in the no-surgery group ($P=0.0029$).

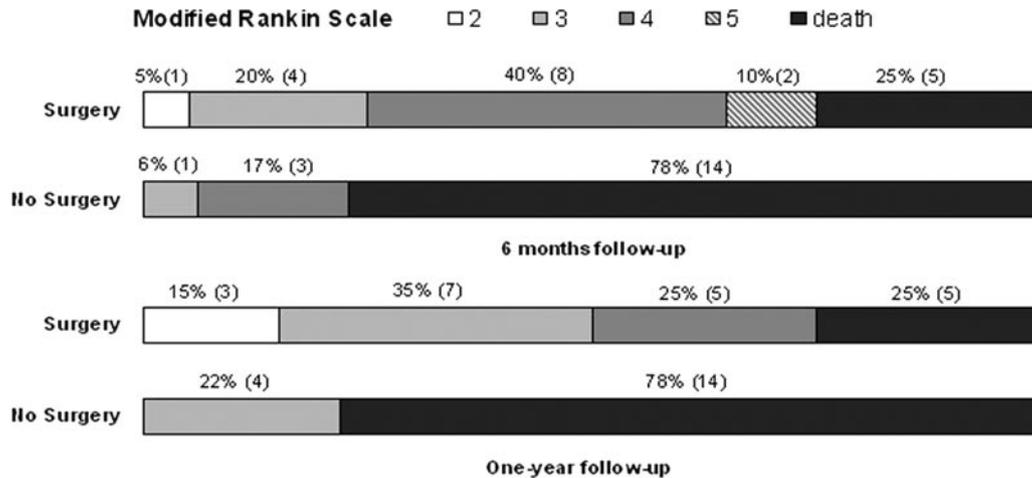


Figure 4. mRS score distribution in the 2 therapeutic groups at the 6-month and 1-year follow-up. (Numbers of patients are shown in parentheses.)

There was a dramatic life-saving effect of surgery with a highly significant absolute reduction of 52.8% in the death rate in the surgery group compared with the no-surgery group ($P < 0.0001$; Figure 5). Only 4 of 18 patients (22.2%) in the no-surgery group survived (Figure 6). All deaths occurred during the first 4 weeks of follow-up and were mainly attributable to temporal brain herniation and brain death secondary to the ischemic edema (Table 2 and Figure 7). Only 1 patient in the surgery group died of another cause, an acute myocardial infarction at the 2-week follow-up. The mean interval between stroke onset and death was 3.1 ± 1.9 days in the no-surgery group and 9.2 ± 4.4 days in the surgery group. Other major but nonfatal adverse events were inhalation pneumonia, venous thromboembolic complications, and seizures (Table 2). During the 1-week follow-up, 14 of 19 survivors in the surgery group were still being ventilated (Table 3). In the no-surgery group, 1 of 6 survivors was still being ventilated, but this patient subsequently died of brain herniation. At the 4-week follow-up, no patients in either

group were still in the intensive care unit. Medical treatment characteristics in both groups are detailed in Table 4.

At the 1-year follow-up, 33.3% (5 of 15 patients) in the surgery group and 50% (2 of 4 patients) in the no-surgery group had a Barthel Index > 85 ($P = 0.6$). There was no difference between the 2 groups in terms of mean National Institutes of Health Stroke Scale scores at the 1-year follow up (10.3 ± 4 in the surgery group and 10.3 ± 5.2 in the no-surgery group). Ten surviving craniectomy patients and 2 surviving medically treated patients underwent a quality of life evaluation with the SIS 1 year after treatment (Table 5). SIS measurement was not possible because of aphasia in 6 surviving patients and refusal in 1. All 10 craniectomy patients acknowledged that “life is worth living” (“all of the time” in 4, “most of the time” in 4, and “some of the time” in 2). The 2 medically treated patients also felt that “life is worth living” (“all of the time” in 1 and “some of the time” in the other). At the end of follow-up, 10 of 15 (67%) survivors in the surgery group and 2 of 4 (50%) survivors in the no-surgery group were at home (Table 3).

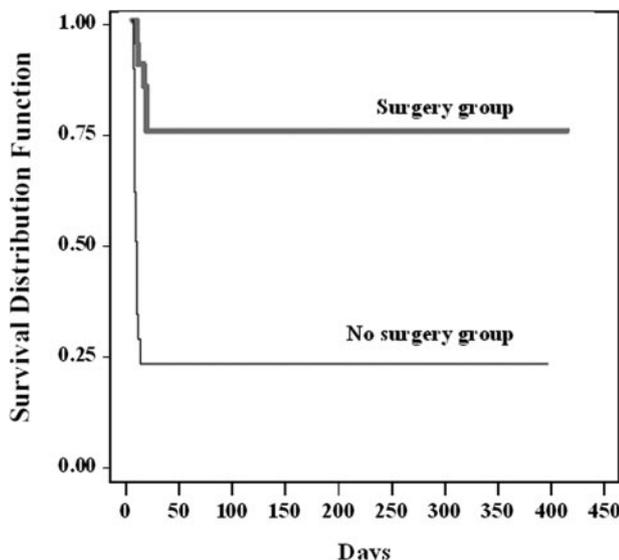


Figure 5. Kaplan–Meier survival curves for the 2 treatment groups.

Subgroup Analysis

Three predefined subgroup analyses were performed. In the no-surgery group, DWI infarct volume at inclusion was positively correlated with outcome as measured by the mRS (0 to 6) at 6 months’ follow-up (Spearman correlation coefficient $R = 0.52$, $P = 0.03$; Figure 8). In the surgery group, there was a trend, though not significant, toward a worse outcome in patients with higher infarct volumes at inclusion (Spearman correlation coefficient $R = 0.38$, $P = 0.09$).

In the surgery group, younger age was correlated with favorable outcome as measured by the mRS at 6 months’ follow-up (Spearman correlation coefficient $R = 0.64$, $P = 0.0018$; Figure 8). In the no-surgery group, there was no correlation between age and outcome. There was no significant difference in outcome as evaluated by the distribution of mRS scores after 1 year of follow-up between all living patients with dominant (10 patients) and nondominant (9 patients) hemisphere infarction.

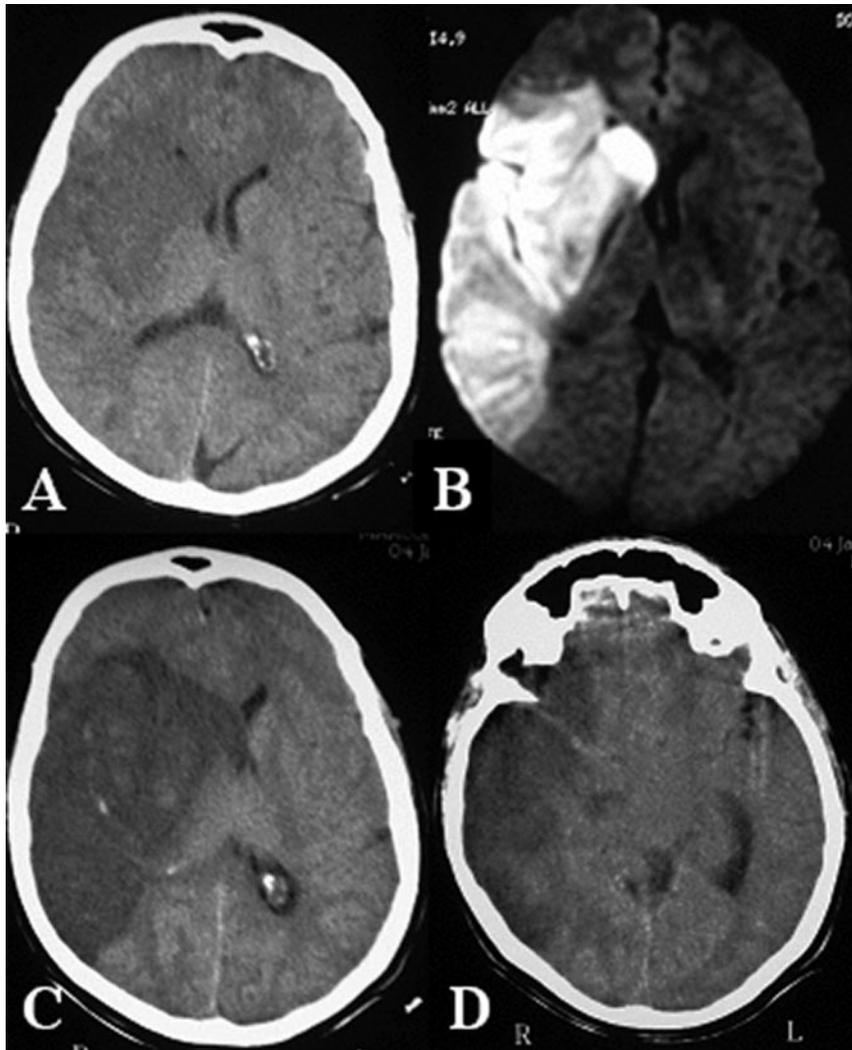


Figure 6. Baseline computed tomography and MRI scans of a 48-year-old woman in the no-surgery group (A and B) showing a DWI infarct volume of 154 cm³. Follow-up brain computed tomography scan 51 hours after stroke onset shows a mass effect with moderate hydrocephalus. The patient survived without mechanical ventilation or osmotherapy.

Discussion

This prospective, randomized, controlled trial showed in young patients <55 years of age with malignant MCA infarction selected on the basis of a DWI infarct volume

≥145 cm³, first, great benefit from early decompressive hemicraniectomy on survival and second, better functional outcome as defined by the mRS score distribution at 6 and 12 months of follow-up after craniectomy.

TABLE 2. Safety Outcomes

Serious and Other Major Adverse Events, No. of Patients (%)	At 1-Week Follow-Up		From 1 to 4 Weeks' Follow-Up		From 4 Weeks' to 12 Months' Follow-Up	
	Surgery Group (n=20)	No-Surgery Group (n=18)	Surgery Group (n=19)	No-Surgery Group (n=6)	Surgery Group (n=15)	No-Surgery Group (n=4)
Death from brain herniation	1 (5)	12 (67)	3 (16)	2 (33)	0	0
Death from other causes	0	0	1 (5)	0	0	0
Inhalation pneumonia	5 (25)	1 (6)	3 (16)	0	1 (7)	0
Venous thromboembolic complications	1 (5)	0	4 (21)	1 (17)	2 (13)	1 (25)
Seizures	1 (5)	0	0	0	6 (40)	2 (50)
Depression	0	0	2 (11)	1 (17)	3 (20)	2 (50)
Urinary tract infection	2 (10)	1 (6)	0	1 (17)	2 (13)	2 (50)
Cerebral abscess	0	0	0	0	1 (7)	0
Jejunostomy	0	0	0	0	1 (7)	0
Tracheostomy	0	0	1 (5)	0	0	0
Neuroalgodystrophy	0	0	0	0	4 (26)	1 (25)
Gastric ulcer	0	0	0	0	1 (7)	0

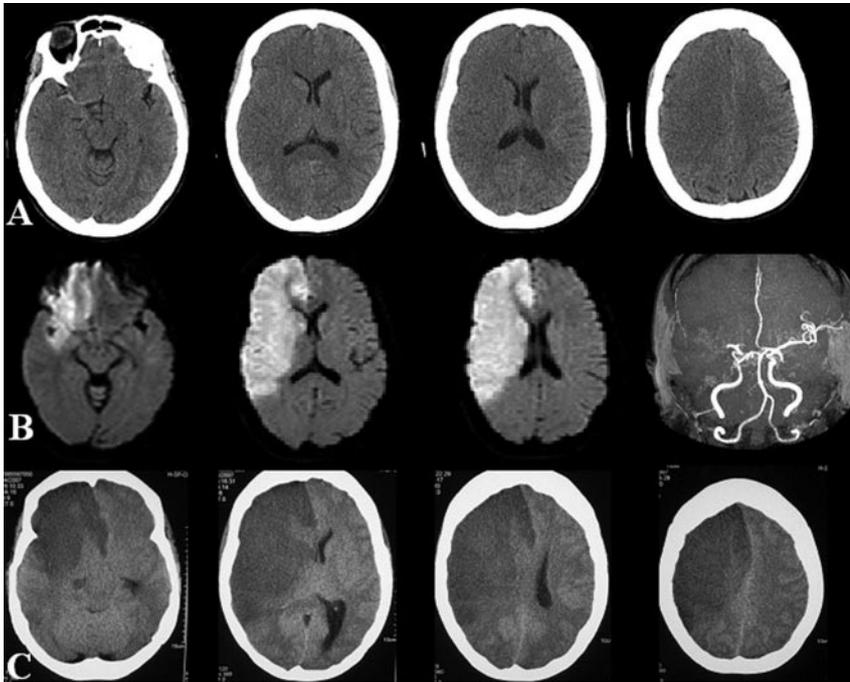


Figure 7. Baseline and follow-up brain imaging of a 50-year-old woman in the no-surgery group. A, Early computed tomography images show signs of right hemisphere infarction including an MCA hyperdense sign, gray matter hypoattenuation, and effacement of the cortical sulci. B, Brain MRI scans performed 5 hours after symptom onset show a 281-cm³ DWI infarct volume with MCA and anterior cerebral artery occlusion. C, Follow-up computed tomography scans performed 28 hours after symptom onset show severe brain edema with a mass effect, hydrocephalus, and temporal herniation. The patient died on day 3.

As expected from the results of open studies of decompressive hemicraniectomy in malignant MCA infarction, the DECIMAL trial showed an impressive life-saving effect of craniectomy. Among the 38 patients randomized, the absolute death rate was significantly decreased by more than half in the surgical group compared with that in the medical group. Although mortality was not the primary end point of the trial, if recruitment had been prolonged, the impressive efficacy of surgery on survival would

probably have created a major source of bias in the recruitment of subsequent eligible patients because of ethical disagreements among investigators.

The major aim of our study was to evaluate the effect of hemicraniectomy on functional outcome. This is why we based the primary outcome on the mRS. After long discussions about what might be an “acceptable” disability, we choose to dichotomize the results at an mRS score ≤3. For this primary outcome, although the number of

TABLE 3. Patient Management at Admission and During Trial Follow-Up

	At Admission		At 1-Week Follow-Up			At 4 Weeks' Follow-Up		At 12 Months' Follow-Up
	Surgery Group (n=20)	No-Surgery Group (n=18)	Surgery Group (n=19)	No-Surgery Group (n=6)	Surgery Group (n=15)	No-Surgery Group (n=4)	Surgery Group (n=15)	No-Surgery Group (n=4)
Patients hospitalized in the intensive care unit, No. (%)	3 (15)	2 (11)	14 (74)	1 (17)	0	0	0	0
Patients hospitalized in the Neurology Department, No. (%)	11 (55)	12 (67)	5 (26)	5 (83)	13 (87)	1 (25)	1 (7)	0
Patients hospitalized in the Emergency Department, No. (%)	6 (30)	3 (17)	0	0	0	0	0	0
Patients hospitalized in the Rehabilitation Department, No. (%)	0	0	0	0	2 (13)	2 (50)	4 (27)	2 (50)
Patients hospitalized in other departments, No. (%)	0	1 (6)	0	0	0	1 (25)	0	0
Patients at home, No. (%)	0	0	0	0	0	0	10 (67)	2 (50)

TABLE 4. Medical Treatment Characteristics in the Acute Phase of Malignant MCA Infarction in Both Groups of Patients

	Surgery Group (n=20)	No-Surgery Group (n=18)
Mechanical ventilation, No. of patients (%)	20 (100)	11 (61)
Length of mechanical ventilation, d		
Mean±SD, range	11.3±6.6, 3–24	2.6±2, 1–8
Mannitol administration, No. of patients (%)	7 (35)	14 (78)

patients was increased by nearly 5 times after decompressive craniectomy compared with medical therapy only, the difference was not statistically significant because of the lack of sufficient statistical power at the time of early termination of the trial. Had an mRS score ≤ 4 been chosen as the primary end point, the present trial would have been

stopped at the eighth interim analysis. Additionally, in the craniectomy group, there was no patient who sustained severe disability (mRS score of 5), and 67% of survivors were at home 1 year after treatment. It is notable that in this trial, no patient had an mRS score of 4 or 5 at the 1-year follow-up in the medical group. This means that because of the extremely important effect of hemicraniectomy on survival, more patients will survive after surgery with a moderately severe disability (mRS score of 4). The clinical features of survivors with an mRS score of 4 at the 1-year follow-up are detailed in Table 6. It is likely that more time will be needed to evaluate the quality of life of these patients and the neuropsychological impact of surviving to a severe stroke.

The patients in our trial received evidence-based medical therapy. They were all managed by a stroke team in a stroke or an intensive care unit. Other than brain edema, the incidence of serious or major adverse events was high, as expected, because of stroke severity leading to a high risk of

TABLE 5. Assessment of Quality of Life at 1-Year Follow-Up

SIS	Surgery Group	No Surgery Group
Strength		
No. of patients	10	2
Score, mean±SD, range	19.4±13.3, 0.0–43.8	15.6, 6.3–25.0
Hand function		
No. of patients	10	2
Score, mean±SD, range	1.0±2.1, 0.0–5.0	0.0, 0.0–0.0
Mobility		
No. of patients	10	2
Score, mean±SD, range	60.8±22.4, 25.0–91.7	73.6, 63.9–83.3
ADL/IADL		
No. of patients	10	2
Score, mean±SD, range	52.5±18.1, 22.5–85.0	66.3, 65.0–67.5
Physical combined score*		
No. of patients	10	2
Score, mean±SD, range	33.4±12.5, 16.7–80	38.9, 33.8–44
Emotion		
No. of patients	10	2
Score, mean±SD, range	57.0±13, 44.4–77.8	59.7, 52.8–66.7
Memory		
No. of patients	10	2
Score, mean±SD, range	70.4±28, 15.0–100.0	100.0, 100.0–100.0
Communication		
No. of patients	10	2
Score, mean±SD, range	82.5±25.3, 25.0–100.0	100.0, 100.0–100.0
Participation		
No. of patients	9	2
Score, mean±SD, range	32.6±17.2, 12.5–59.4	42.2, 37.5–46.9
Stroke recovery (visual analog scale)		
No. of patients	10	2
Score, mean±SD, range	36.0±15.6, 10–60	60, 40–80

ADL/IADL indicates activities of daily living/instrumental activities of daily living.

*The combined physical score was calculated from the strength, hand function, and mobility domain scores.

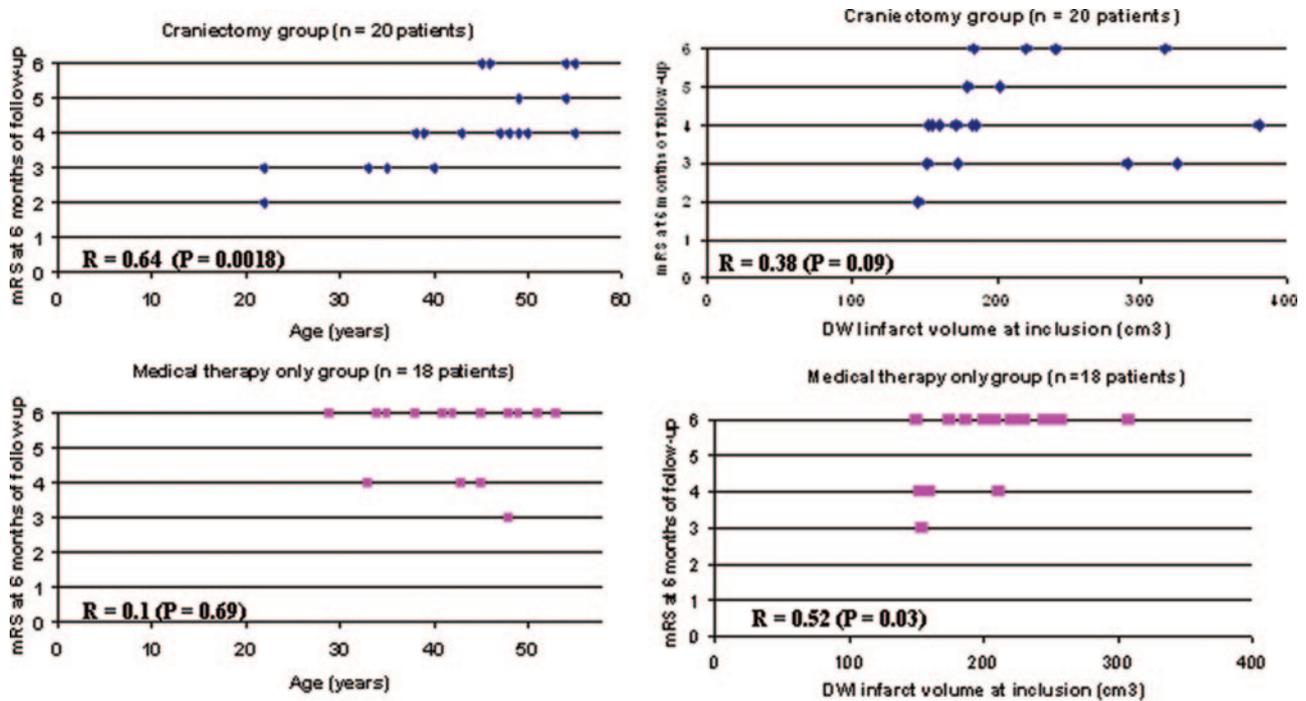


Figure 8. The Spearman correlation test showed a significant correlation between age and outcome (according to the mRS score distribution at the 6-month follow-up) in the surgery group ($R=0.64$, $P=0.0018$; top left). There was no such correlation between age and outcome in the no-surgery group ($R=0.1$, $P=0.69$; bottom left). The Spearman correlation test showed a significant correlation between DWI infarct volume at inclusion and outcome according to the mRS score distribution at the 6-month follow-up in the no-surgery group ($R=0.52$, $P=0.03$; bottom right) but not in the surgery group, although there was a trend toward better outcome with lower infarct volume in this group of patients ($R=0.38$, $P=0.09$; top right).

inhalation pneumonia and thromboembolic complications. No patient in either group needed >4 weeks of hospitalization in an intensive care unit. However, we excluded from this trial patients with severe associated comorbidities who are at much greater risk of general complications after a severe stroke and who would probably have needed prolonged intensive care unit management and might have had worse outcomes. It is notable that seizures were particularly frequent in both groups of patients (nearly 50% of all patients had at least 1 seizure), but these occurred mainly after the first 4 weeks of follow-up and needed long-term anticonvulsant therapy (data not shown).

Predefined subgroup analysis showed that young age was significantly correlated with better outcome in the craniectomy group but not in the no-surgery group, in which the main prognostic factor of survival was baseline DWI infarct volume. No patient with an infarct volume >210 cm³ survived without craniectomy. For DWI infarct volumes between 145 and 210 cm³, there was still a high death rate attributable to brain herniation in the absence of surgery. On the contrary, among the 8 patients screened but not randomized because of a DWI infarct volume <145 cm³, none died (data not shown). These data indicate that the cut-off value of 145 cm³ for DWI early infarct

TABLE 6. Clinical Features of Patients According to Their mRS Score Distribution at 1-Year Follow-Up

	Surgery Group, mRS score, No.			No-Surgery Group, mRS score, No.		
	2 (n=3)	3 (n=7)	4 (n=5)	2 (n=0)	3 (n=4)	4 (n=0)
Age, y	28±10, 22–40	42±7, 33–50	49±6, 39–54	...	42±6, 33–48	...
Mean±SD, range						
NIHSS	8±4, 5–12	9±3, 5–14	13±4, 8–18	...	10±5, 4–15	...
Mean±SD, range						
Barthel Index	98±3, 95–100	87±9, 75–100	36±15, 20–55	...	86±14, 70–100	...
Mean±SD, range						
Patients at home	3 (100)	6 (86)	1 (20)	...	2 (50)	...
No. (%)						
Patients in the Rehabilitation Department	0	1 (14)	3 (60)	...	2 (50)	...
No. (%)						

NIHSS indicates National Institutes of Health Stroke Scale.

volume that has been previously suggested as predictive of malignant ischemic edema is valid and should be used for the selection of patients in whom early surgery is warranted.¹⁹ In addition, there was an excellent correlation between the DWI infarct volumes calculated by the investigator neuroradiologists and the validation committee, indicating the good reproducibility of this measure, which can be done even on an emergency basis. In the craniectomy group, there was also a trend toward better functional outcome with lower DWI infarct volume. Further studies are needed to confirm this correlation between infarct volume and residual disability after craniectomy.

In conclusion, in young (≤ 55 years) patients with malignant MCA infarction selected on the basis of a DWI infarct volume >145 cm³, early decompressive craniectomy first, had a great benefit on survival and second, led to a better functional outcome as defined by the mRS score distribution at 6 and 12 months' follow-up. Furthermore, none of the patients in the surgery group remained bedridden or had severe residual disability. Younger patients had a significantly better outcome after surgery, but none had a complete recovery (mRS ≤ 1). Thus, in patients similar to those included in the DECIMAL trial, early decompressive craniectomy should be considered and fully discussed with the patient and close relatives. These data were confirmed in the recently published pooled analysis of individual data from DECIMAL, DESTINY, and HAMLET trials.²¹

Appendix: The DECIMAL Investigators

Coordinating center: AP-HP, Hôpital Lariboisière, Paris, France: K. Vahedi, M.-G. Bousser, E. Vicaut, A. Kurtz, J.-P. Guichard, J. Mateo, A. Yelnik, A. Carpentier.

Participating institutions and investigators (numbers of patients enrolled at each center are given in parentheses): AP-HP, Hôpital Lariboisière, Paris, France (18): K. Vahedi, M.-G. Bousser, A. Kurtz, G. Lutz, D. Hervé, P. Favrole, C. Stapf, H. Chabriat, I. Crassard, J. Mateo, D. Payen, A.-C. Lukaszewicz, M.-R. Losser, S. Welschbillig, M. Rossignol, M. Orabi, A. Carpentier, A. Blanquet, G. Lot, M. Archilli, Y. Cornélius, B. George, J.P. Guichard, M. Boukobza, D. Reizine, A. Yelnik, M.-C. Gellez, F. Colle; Hôpital Général, Dijon, France (5): M. Giroud, G.V. Osseby, T. Moreau, F. Benatru, G. Couvreur, A. Fromont, M. Lemesle, K.L. Mourier, J.L. Sautreaux, J. Beaurain, F. Ricolfi, D. Krause, D. Martin, N. Baudouin, D. Ben Salem, B. Blettery, H. Aube, J.P. Quenot, J.M. Doize, P. Gras; Hôpital Sainte-Anne, Paris, France (4): J.L. Mas, E. Touze, M. Zuber, C. Lamy, D. Ranoux, B. Devaux, C. Oppenheim, A. Sermet, Ph. Page, F. Nataf; Groupe Hospitalier Pellegrin Tripode, Bordeaux, France (4): F. Rouanet, E. Cuny, P. Ménégon, I. Sibon, X. Barreau, J. Berge, M.E. Petitjean, P. Lassie, C. Pellerin, A. Bouju, C. Balleau, Ph. Dabadie, J.P. Castel, V. Dousset, J.M. Orgogozo; Hôpital Laennec, Nantes, France (4): B. Guillon, Ph. Damier, M. Vercelletto, Ch. Magne, P. Derkinderen, S. Wiertlewski, Y. Lajat, D. Menegalli, S. Martin, M. Al Hammad Ibrahim, S. Raoul, A. de Kersaint-Gilly, H. Desal, E. Auffray-Calvier, Y. Blanloeil, C. Peneau, R.J. Daudet, B. Perrouin-Verbe, J. Rome, E. Bord; Centre Hospitalier Universitaire (CHU), Nancy, France (2): X. Ducrocq, T. Civit, O. Klein, C. Pinelli, S. Colnat-Coulbois, R. N'Seir, S. Bracard, P.E. Bollaert, L. Nace, J. Bocquet, A. Cravoisy, S. Gibot, B. Levy, B. Dusang; Hôpital E. Muller, Mulhouse-Hôpital L. Pasteur, Colmar, France (1): G. Rodier, E. Cohen, E. Baldauf, P.M. Schatz, M.H. Dugay-Arentz, F. Vuillemet, B. Stilhart, R.

Spour, C. Bizette, A. Klinkert, H. Oesterle, C. Riquelme, T. Tajahmady, Ph. Feuerstein, O. Martinet, G. Lungu.

Other participating institutions: Unité de Recherche Clinique, Hôpital Fernand Widal, Paris, France: E. Vicaut, C. Boutron-Labreuche, F. Thevot, V. Jouis, S. Leclerc; Direction Régionale à la Recherche Clinique, Hôpital Saint-Louis, Paris, France: A. Ouslimani, O. Chassany, P. Pastor, P. Cimermann; Banque de tissu, Hôpital Saint-Louis, Paris, France: H. Jarraya.

Acknowledgments

We thank all of the physicians who referred patients to the investigating centers and all physicians, nurses, and physiotherapists who took care of the patients and their relatives. We also thank Mapi Research Institute, Lyon, France, for providing the French version of the SIS 2.0 (Duncan et al, University of Kansas Medical Center) and S. Hello and M. Gicquel for technical assistance.

Sources of Funding

This study was supported by grants from the Programme Hospitalier de Recherche Clinique of the French Ministry of Health. The study was sponsored by Département de la Recherche Clinique et du Développement of Assistance Publique-Hôpitaux de Paris (AOM 00148, P001004).

Disclosures

None.

References

- Ropper AH, Shafran B. Brain edema after stroke: clinical syndrome and intracranial pressure. *Arch Neurol*. 1984;41:26–29.
- Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol*. 1996;53:309–315.
- Rengachary SS, Batnitzky S, Morantz RA, Arjunan K, Jeffries B. Hemispherectomy for acute massive cerebral infarction. *Neurosurgery*. 1981; 8:321–328.
- Kondziolka D, Fazl M. Functional recovery after decompressive craniectomy for cerebral infarction. *Neurosurgery*. 1988;23:143–147.
- 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.
- Carter BS, Ogilvy CS, Candia GJ, Rosas HD, Buonanno F. One year outcome after decompressive surgery for massive nondominant hemispheric infarction. *Neurosurgery*. 1997;40:1168–1176.
- Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, Hacke W. Early hemicraniectomy in patients with complete middle cerebral artery infarction. *Stroke*. 1998;29:1888–1893.
- 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.
- Walz B, Zimmermann C, Bottger S, Haberl RL. Prognosis of patients after hemicraniectomy in malignant middle cerebral artery infarction. *J Neurol*. 2002;249:1183–1190.
- Foerch C, Lang JM, Krause J, Raabe A, Sitzer M, Seifert V, Steinmetz H, Kessler KR. Functional impairment, disability, and quality of life outcome after decompressive hemicraniectomy in malignant middle cerebral artery infarction. *J Neurosurg*. 2004;101:248–254.
- Nicholas CD, Eivind Berge M, Cruz-Flores S, Whittle IR. Surgical decompression for cerebral edema in acute ischemic stroke. *Cochrane Library*. 2002;3.
- Vahedi K, Benoist L, Kurtz A, Mateo J, Blanquet A, Rossignol M, Amarenco P, Yelnik A, Vicaut E, Payen D, Bousser MG. Quality of life after decompressive craniectomy for malignant middle cerebral artery infarction. *J Neurol Neurosurg Psychiatry*. 2005;76:1181–1182.

13. Adams HP Jr, Brott TG, Crowell RM, Furlan AJ, Gomez CR, Grotta J, Helgason CM, Marler JR, Woolson RF, Zivin JA, et al. Guidelines for the management of patients with acute ischemic stroke: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Circulation*. 1994;90:1588–1601.
14. Hacke W, Kaste M, Skyhoj Olsen T, Orgogozo JM, Bogousslavsky J. European Stroke Initiative (EUSI) recommendations for stroke management: the European Stroke Initiative Writing Committee. *Eur J Neurol*. 2000;7:607–623.
15. Adams HP Jr, Adams RJ, Brott T, del Zeppo G, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. *Stroke*. 2003;34:1056–1083.
16. Bonita R, Beaglehole R. Modification of Rankin Scale: Recovery of motor function after stroke. *Stroke*. 1988;19:1497–1500.
17. Loewen SC, Anderson BA. Predictors of stroke outcome using objective measurement scales. *Stroke*. 1990;21:78–81.
18. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Jacobs Laster J. The Stroke Impact Scale 2.0: evaluation of reliability, validity, and sensitivity to change. *Stroke*. 1999;30:2131–2140.
19. Oppenheim C, Samson Y, Manai R, Vandamme X, Crozier S, Cornu P, Dormont D, Rancurel G, Marsault C. Prediction of malignant middle cerebral artery infarction by diffusion-weighted imaging. *Stroke*. 2000;31:2175–2181.
20. Jennison C, Turnbull BW. *Group Sequential Methods With Applications to Clinical Trials*. Boca Raton, Fla: Chapman & Hall/CRC; 1999.
21. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Boussier MG, van der Worp HB, Hacke W, for the DECIMAL, DESTINY, and HAMLET investigators. Early decompressive surgery in malignant middle cerebral artery infarction: a pooled analysis of three randomised controlled trials. *Lancet Neurol*. 2007;6:215–222.

Sequential-Design, Multicenter, Randomized, Controlled Trial of Early Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarction (DECIMAL Trial)

Katayoun Vahedi, Eric Vicaut, Joaquim Mateo, Annie Kurtz, Mikael Orabi, Jean-Pierre Guichard, Carole Boutron, Gregory Couvreur, François Rouanet, Emmanuel Touzé, Benoît Guillon, Alexandre Carpentier, Alain Yelnik, Bernard George, Didier Payen and Marie-Germaine Bousser
on behalf of the DECIMAL Investigators

Stroke. 2007;38:2506-2517; originally published online August 9, 2007;
doi: 10.1161/STROKEAHA.107.485235

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/38/9/2506>

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/>