Hemicraniectomy and Durotomy Upon Deterioration From Infarction-Related Swelling Trial
Randomized Pilot Clinical Trial

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Background and Purpose—Hemicraniectomy and Durotomy Upon Deterioration From Infarction-Related Swelling Trial (HeADDFIRST) was a randomized pilot study to obtain information necessary to design a Phase III trial to evaluate the benefit of surgical decompression for brain swelling from large supratentorial cerebral hemispheric infarction.

Methods—All patients with stroke were screened for eligibility (age 18–75 years, National Institutes of Health Stroke Scale ≥18 with Item 1a<2 [responsive to minor stimulation], and CT demonstrating unilateral, complete middle cerebral artery territory infarction by specific imaging criteria). All enrolled patients were treated using a standardized medical treatment protocol. Those with both ≥4 mm of pineal shift and deterioration in level of arousal or ≥7.5 mm of anteroseptal shift within 96 hours of stroke onset were randomized to continued medical treatment only or medical treatment plus surgery. Death at 21 days was the primary outcome measure.

Results—Among 4909 screened patients, only 66 (1.3%) patients were eligible for HeADDFIRST. Forty patients were enrolled, and 26 patients developed the requisite brain swelling for randomization. All who failed to meet randomization criteria were alive at 21 days. Mortality at 21 and 180 days was 40% (4/10) in the medical treatment only and 21% (3/14) and 36% (5/14) in the medical treatment plus surgery arms, respectively.

Conclusions—HeADDFIRST randomization criteria effectively distinguished low from high risk of death from large supratentorial cerebral hemispheric infarction. Lower mortality in the medical treatment only group than in other published trials suggests a possible benefit to standardizing medical management. These results can inform the interpretation of recently completed European trials concerning patient selection and medical management.

Clinical Trial Registration—This trial was not registered because enrollment began before July 1, 2005. (Stroke. 2014;45:00-00.)

Key Words: brain edema ▪ craniectomy ▪ stroke

Large supratentorial cerebral hemispheric infarctions can cause life-threatening brain swelling, frequently leading to death within the first week. The well-recognized and widely published high mortality with infarctions of this magnitude has led to increasing acceptance of the potential merits of surgical decompression in selected patients with hemicraniectomy and durotomy.

Hemicraniectomy and Durotomy Upon Deterioration From Infarction-Related Swelling Trial (HeADDFIRST) was a National Institute of Neurological Disorders and Stroke–sponsored pilot clinical trial designed to provide the information necessary to design and implement a Phase III study to evaluate the benefit of surgical decompression for life-threatening swelling from large supratentorial cerebral hemispheric infarction. The primary aims were the following: (1) to estimate the proportions of patients with stroke who would be eligible and of eligible patients who would deteriorate sufficiently to become randomizable (described below) using well-defined criteria appropriate for a Phase III trial, (2) to estimate the proportion of eligible patients whose families would consent to participate in a randomized trial, and to determine whether treatment assignment can be maintained without crossover, (3) to estimate the distribution of a variety of functional and quality-of-life outcomes at 21, 90, and 180 days in each treatment group, and (4) to determine whether outcome assessments can be performed in a blinded fashion.

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Since the completion of HeADDFIRST, there have been several published randomized clinical trials on the topic. However, several unique aspects of the design and performance of HeADDFIRST allow the results to critically supplement the findings of these important studies.

Methods

Participating Center Selection

Twenty centers in North America participated in HeADDFIRST, each with its own neurologist investigator. Only investigators (neurologists and neurosurgeons) who were comfortable with randomizing all eligible patients without bias were included, and only medical centers that could guarantee screening and considering all eligible patients were included. All principal investigators were neurologists, and the care organization of each participating center required a neurologist with expertise in neurocritical care to be the primary managing physician throughout the hospitalization. The study protocol was approved by the Institutional Review Board at each participating center and at the Data Coordinating Center located at the University of Chicago. A Performance and Safety Monitoring Board was constituted by National Institute of Neurological Disorders and Stroke to review study accrual and patient safety every 6 months.

Investigator Preparation and Protocol Development

Before study initiation, all medical and surgical investigators participated in a conference during which the study design and protocols were discussed and all treatment protocols were finalized. Although there was significant controversy and variability among the investigators about what constituted best medical and surgical management, all investigators agreed to adhere to the developed protocols for the purposes of HeADDFIRST. The minimal surgical decompression boundaries were anteriorly to 1 cm lateral to the superior sagittal sinus, and inferiorly to the foramen magnum (inclusion/exclusion criteria). Eligible patients who consented to participate were then registered in HeADDFIRST, a Standardized Medical Management Protocol (SMMP) was initiated, and registered patients were monitored clinically using serial CT scans at specified times from stroke onset. Registered patients who deteriorated sufficiently to meet randomization criteria were randomized at that point to continued medical treatment only (MTO) or medical treatment plus surgery (MTS). Registered patients who did not meet randomization criteria were managed according to the same SMMP as those who met randomization criteria. Functional and quality-of-life outcomes were evaluated at 21, 90, and 180 days postrandomization. Details of the study protocol omitted below are described in the online-only Data Supplement.

Overview of Study

All patients with ischemic stroke were screened for study eligibility (inclusion/exclusion criteria). Eligible patients who consented to participate were then registered in HeADDFIRST, a Standardized Medical Management Protocol (SMMP) was initiated, and registered patients were monitored clinically using serial CT scans at specified times from stroke onset. Registered patients who deteriorated sufficiently to meet randomization criteria were randomized at that point to continued medical treatment only (MTO) or medical treatment plus surgery (MTS). Registered patients who did not meet randomization criteria were managed according to the same SMMP as those who met randomization criteria. Functional and quality-of-life outcomes were evaluated at 21, 90, and 180 days postrandomization. Details of the study protocol omitted below are described in the online-only Data Supplement.

Patient Screening

All patients with ischemic stroke admitted to each participating center were screened for 4 criteria: unilateral middle cerebral artery (MCA) stroke, 18 to 75 years old, National Institutes of Health Stroke Scale (NIHSS) score of ≥18, and responsive to minor stimulation (NIHSS Item 1a ≤ 2). Those who met these 4 criteria satisfied the neuroimaging criterion of either hypodensity involving ≥50% of the MCA territory on a CT performed ≤ 5 hours after the stroke onset or hypodensity involving the complete MCA territory on a CT performed ≤ 48 hours after stroke onset, and those who met no exclusion criteria (Table 1) were deemed eligible, and those patients (or their surrogates) were approached for consent.

Consent, Registration, Randomization

On receipt of written informed consent, patients were registered into HeADDFIRST, admitted to a neuromonitoring or intensive care unit, and the SMMP and monitoring began. Registered patients who deteriorated sufficiently within 96 hours of stroke onset became randomizable, based on meeting one or both of the following criteria: (1) horizontal anterior septum pellucidum shift from the midline of ≥ 7.5 mm with unchanged or worse neurological examination or (2) ≥ 4 mm of horizontal pineal shift from the midline with depression of arousability to the level of effortful awakening with immediate subsequent sleepiness or worse (NIHSS Item 1a ≥ 2). Patients were randomized either to continued MTO using the SMMP or to MTS using an ipsilateral standardized hemicraniectomy and durotomy performed within 4 hours of meeting randomization criteria.

Table 1. Exclusion Criteria

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deterioration to randomizable condition before admission to the participating hospital</td>
</tr>
<tr>
<td>Confluent parenchymal hematoma</td>
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<tr>
<td>Subdural hematoma</td>
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<tr>
<td>Subarachnoid hemorrhage</td>
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<tr>
<td>PTT &gt; 40 s</td>
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<tr>
<td>INR &gt; 1.4</td>
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<tr>
<td>Platelet count &lt; 100 k/µL before correction with blood products</td>
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<tr>
<td>Pre-existing illness limiting life expectancy &lt; 6 mo</td>
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<tr>
<td>Pre-existing disability with modified Rankin &gt; 2</td>
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<tr>
<td>Pre-existing or concurrent brain injury with associated deficits in addition to principal stroke</td>
</tr>
</tbody>
</table>

Current participation in another clinical trial

Standardized Medical Management Protocol

All registered patients were cared for in a specialized neuromonitoring unit (intermediate or intensive care) with a consensus developed SMMP with the formal agreement of all investigators for required adherence to the protocol (not simply recommended) after in-person training and an examination that assessed an understanding of the protocols and required adherence. Randomization triggered transfer to a neurological intensive care unit (if not already in one) with placement of an arterial line, central venous catheter, and an ipsilateral parenchymal intracranial pressure (ICP) monitor. A comprehensive protocol specified detailed procedures for airway management, ventilator settings, blood pressure control and agents, fluid and electrolyte management, gastrointestinal and nutritional management, hematologic monitoring and management, ICP monitoring, sedation, use of mannitol, anticoagulants, prophylaxis against deep-vein thrombosis, and rehabilitation. (Full details of the protocol are contained in the online-only Data Supplement.)

Standardized Surgical Management Protocol

In patients who were randomized to surgical treatment, the standardized hemicraniectomy and durotomy required rapid initiation of surgery, with a target of ≤ 4 hours from meeting criteria for randomization, in addition to continued compliance with the SMMP. The minimal surgical decompression boundaries were anteriorly from the floor of the anterior cranial fossa at the midpupillary line, posteriorly to 4 cm posterior to the external auditory canal, superiorly to 1 cm lateral to the superior sagittal sinus, and inferiorly to the floor of the middle cranial fossa (Figure 1). All patients underwent a durotomy (circumferential or cruciate) with dural grafting recommended but not required. No brain amputation was allowed in any case. Perioperative antibiotics (unspecified) were required for the first 24 hours after surgery. Postoperative dressings were noncompressive. Ventricular drains could not be used. All randomized patients required an ipsilateral parenchymal ICP monitor, frontally located. All bone flaps were saved in a bone bank, frozen in an antibiotic solution to be replaced within 3 months or earlier for either safety, medical, or cosmetic indications.
Minor deviations were variances that related to minor medication substitutions. Major deviations related to variances of neurological specific and critical care treatments such as the use of mannitol, fluid and electrolyte management, ICP-directed treatment decisions, hemodynamic management, and airway and ventilation management.

### Data Analysis

Descriptive statistics (median, 25th and 75th percentiles, or frequency counts) were used to summarize the demographics, comorbidities, and disease characteristics of the study groups. Fisher exact test was used to evaluate differences in categorical measures between groups. Confidence intervals (CI) for mortality rates in each treatment group were calculated using exact binomial methods, and a confidence interval for the difference in mortality rates was calculated using the normal approximation. Statistical significance was defined as \( P < 0.05 \). Analyses and data management were performed using Stata.

### Results

From March 2000 to September 2002, 4909 patients with stroke were screened at 20 sites, representing all of the patients with stroke admitted to the participating centers during the study period. Of these, 73% were between ages of 18 and 75 years, and of these, 32% had unilateral MCA strokes. Of those with the unilateral MCA strokes, only 18% had an NIHSS score \( \geq 18 \), and of those, 56% had an item 1a \( < 2 \).

Of the 4909 screened patients, 118 (2.4%) patients met all 4 screening criteria. Of these, 66 patients met the remaining eligibility criteria for participation in HeADDFIRST (Figure 2). Among the excluded 52 patients, 40 patients failed to meet the hypodensity criteria, and another 12 patients met the hypodensity criteria but also met \( \geq 1 \) of the exclusion criteria. After 2 years, we determined together with the Performance Safety Monitoring Board that we had achieved our aims for the pilot study, and accrual was terminated.

Families for 3 of the eligible patients were not approached for participation because the patient or family had already decided to limit care (1), the family was not available (1), or for other reasons (1). Of the 63 patients who were approached, 40 (from 16 sites) patients consented to participate in the randomized portion of the trial. Common reasons for declining included making a decision to limit care (3), not wanting to...
Seven patients at 4 centers had minor violations related to for-
visit for the next registered patient which never occurred.
on 1 occasion thereby triggering a warning and planned site
involved the use of mannitol off protocol in an MTO patient
domized patients are provided in Table
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Median time from stroke onset to meeting randomization cri-
groups participating in the randomized portion of the trial.
data-collection-only group w
characteristics and comorbidities of each study group. The
ommunity differences at the respective centers.
participate in a research trial (6), not wanting treatment deter-
dined by randomization (6), wanting surgery (1), and not
ning surgery (5). Among the 23 patients who declined to
 Twenty-six patients progressed to meet the criteria for ran-
 one of whom was not randomized because of the
physician’s decision to limit treatment. The remaining 25 were
randomized to MTO (10) or MTS (15). One of the patients
who had a dominant hemispheric stroke and was randomized
to surgery was withdrawn because his wife, after reflection,
had come to believe that surgical treatment would be exces-
sive given his likely future level of disability.

Table 2 shows the demographic and disease character-
stics and comorbidities of each study group. The
data-collection-only group was similar in composition to the
groups participating in the randomized portion of the trial. The
Median time from stroke onset to meeting randomization cri-
teria was 52.5 hours in the medical group and 53.8 hours in the
surgical group, with 75th percentiles of 64.4 and 80.4, respec-
tively. Stroke characteristics and outcomes for individual ran-
randomized patients are provided in Table 3.

One center had a single major violation in one patient that
involved the use of mannitol off protocol in an MTO patient
on 1 occasion thereby triggering a warning and planned site
visit for the next registered patient which never occurred.
Seven patients at 4 centers had minor violations related to for-
mary differences at the respective centers.

Twenty-one day mortality was 40% (90% CI [15%, 70%]) in the
medical group and 21% (90% CI [6%, 47%]) in the
surgical group (difference=19%, 90% CI [-13%, 50%]). At
180 days, the mortality remained unchanged in the medical
group and had risen to 36% in the surgical group (Figure 3).
In contrast, among patients whose stroke did not progress suf-
ficiently to meet criteria for randomization, none died within
the first 21 days. The causes of death as reported on death
certificates in the medical group were the following: uncon-
trolled intracranial hypertension, brain stem compression,
cerebral infarction, and left middle cerebral artery stroke. The
causes of death in the surgical group were the following: mas-
sever right hemispheric stroke with malignant cerebral edema,
tractable intracranial hypertension, cardiac arrhythmia
(possibly secondary to sepsis), progression of disease, and
withdrawal of support. Three deaths in randomized patients
were because of medical complications or a decrease in treat-
ment aggressiveness. No deaths were attributable to surgical
complications.

The blinded examiners at 90 and 180 days were queried
about the effectiveness of the blind. Of the 9 patients in the
surgical group and 6 patients in the medical group who had
blinded exams, the examiner knew the treatment received with
certainty in only 2 cases (both in the surgical group) based on
physical clues and revealing conversations.

**Discussion**

Although large supratentorial cerebral infarctions involving at
least the majority of the MCA territory are known to be asso-
ciated with life-threatening cerebral edema (space-occupying
middle cerebral artery territory infarction, SOMCATI), their
actual risk of death is controversial. The majority of recent
publications suggest that medical management for SOMCATI
without surgical decompression is associated with a 70% to
80% mortality. This conclusion is predominantly derived
from surgical decompression series or retrospective reviews
without mandatory compliance (or monitoring of compliance)
with contemporary standardized medical or surgical treatment
protocols. Often it is presumed that either medical manage-
ment is uniform or that differences between physicians in
medical management do not importantly impact outcome; a
notion we have challenged previously.²

Because the treatment protocols in HeADDFIRST were
standardized and adherence was required, our results can pro-
vide unique insights into the potential relevance of the SMMP
used here to the outcome of SOMCATI. The HeADDFIRST
randomization criteria defined an extent of cerebral edema
of SOMCATI that was associated with increased mortality
(regardless of treatment) relative to the registered patients
who did not achieve randomization criteria (29% versus 0%,
P=0.03). These data suggest that the HeADDFIRST random-
ization criteria effectively distinguished between those at high
and low risk of 21-day mortality from SOMCATI.

The HeADDFIRST mortality for those randomized to MTO
was 40% at 21 days, whereas the mortality for all 35 patients
treated by the SMMP without hemicraniectomy (including
those registered without deterioration, randomized to MTO,
and registered to data collection only) was only 17% at 21
days. Randomization in HeADDFIRST required more signifi-
cant mass effect than that required for treatment assignment

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**Figure 2. Hemicraniectomy and Durotomy Upon Deterioration
From Infarction-Related Swelling Trial study flow diagram.**

(Flow diagram showing the progression of patients through the study, including eligibility, consent, randomization, and outcomes.)
in the 3 randomized European trials (DECIMAL, DESTINY, and HAMLET). In addition, many of the HeADDFIRST patients who were registered but never met randomization criteria (none of whom died) would have been randomized in the European trials. Table I in the online-only Data Supplement shows that many of the patients in this group would have fulfilled the inclusion criteria for randomization in the 3 European trials with a 12-month mortality in the pooled meta-analysis of conservative treatment of 71% and 76% (16 of 21) in another nonrandomized prospective study.

The lower mortality of the HeADDFIRST conservatively treated patients may be related to the fact that HeADDFIRST inclusion criteria allowed older patients than the randomized European trials (Table I in the online-only Data Supplement). The mean age (years) of the randomized patients in HeADDFIRST, DECIMAL, DESTINY, and HAMLET

| Table 2. Baseline and Prerandomization Characteristics |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | MTO             | MTS             | RC not met       | Data only       |
| N*                             | 10              | 14              | 14              | 11              |
| Background characteristics†    |                 |                 |                 |                 |
| Age                            | 57.9 (45.4–65.8) | 52.3 (45.5–59.0) | 61.7 (45.0–72.0) | 62.9 (54.1–69.8) |
| Age 60+, %                     | 50              | 21              | 54              | 55              |
| Male, %                        | 60              | 64              | 46              | 64              |
| History of stroke, %           | 10              | 7               | 8               | 0               |
| Hypertension, %                | 70              | 57              | 62              | 73              |
| CAD, %                         | 10              | 14              | 15              | 18              |
| Arrhythmia, %                  | 40              | 7               | 23              | 27              |
| Diabetes mellitus, %           | 30              | 7               | 15              | 0               |
| Current smoker, %              | 60              | 71              | 31              | 45              |
| Dominant hemisphere, %         | 50              | 36              | 50              | 55              |
| Registration                   |                 |                 |                 |                 |
| NIHSS                          | 19.0 (18.8–21.3) | 21.5 (18.8–23.3) | 19.5 (18.0–21.3) | 20.0 (18.0–22.0) |
| Pineal shift, mm‡              | 0.0 (0.0–2.0)   | 0.0 (0.0–2.0)   | 0.0 (0.0–0.0)   | 0.0 (0.0–3.0)   |
| Septal shift, mm‡              | 0.0 (0.0–6.0)   | 0.0 (0.0–5.0)   | 0.0 (0.0–0.0)   | 2.0 (0.0–5.0)   |
| Volume, cc‡                    | 163.0 (137.0–230.0) | 198.0 (183.0–214.0) | 150.0 (126.9–206.0) | 172.0 (126.0–227.0) |
| Randomization                  |                 |                 |                 |                 |
| Randomizable, %                | 100             | 100             | …               | …               |
| Onset to meeting RC, h         | 52.5 (29.5–64.4) | 53.8 (27.7–60.4) | …               | …               |
| <24 h, %                       | 10              | 21              | …               | …               |
| <48 h, %                       | 40              | 43              | …               | …               |
| NIHSS                          | 21.5 (19.5–23.8) | 23.0 (20.5–27.5) | …               | …               |
| Pineal shift, mm               | 6.0 (4.8–6.5)   | 5.5 (4.0–8.0)   | …               | …               |
| Septal shift, mm               | 9.5 (7.8–11.0)  | 9.0 (8.0–10.3)  | …               | …               |

Numbers in table are median (25%–75%) unless otherwise stated. CAD, coronary artery disease; MTO, medical treatment only; MTS, medical treatment+surgery; NIHSS, National Institutes of Health Stroke Scale; and RC, randomization criteria.

*One subject was not randomized because of MD preference, and another subject was randomized to surgery but did not receive it. These subjects are not included in the table.
†One subject in the RC not met group was missing all background characteristics except for whether it was a dominant hemispheric stroke.
‡Three MTO subjects and 1 MTS subject were excluded from these summaries because their eligibility CT scan was also used as their randomization CT scan.
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was 54.6, 43.4, 44.6, and 48.2, respectively. Older patients have more brain atrophy and are well recognized to tolerate their brain swelling better than younger patients. However, even with the older patient group, the lower mortality of the HeADDFIRST MTO patients relative to the other trials may be related to other factors. This is, in part, supported by the reported 76.2% conservative treatment mortality of a prospective nonrandomized trial that also included older patients.

Table 3. Clinical Characteristics and Outcomes of Randomized Patients

<table>
<thead>
<tr>
<th>Study Subject</th>
<th>Group</th>
<th>NIHSS at Randomization</th>
<th>Hemisphere</th>
<th>Imaging at Randomization</th>
<th>Onset to Meeting RC, h</th>
<th>Meeting RC to Surgery, h</th>
<th>Survival From Stroke Onset, d</th>
<th>Modified Rankin Score</th>
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<td>2.4</td>
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<tr>
<td>22</td>
<td>MTS</td>
<td>24</td>
<td>L</td>
<td>8</td>
<td>8</td>
<td>89.5</td>
<td>1.8</td>
<td>34</td>
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<tr>
<td>23</td>
<td>MTS</td>
<td>33</td>
<td>L</td>
<td>6</td>
<td>9</td>
<td>59.3</td>
<td>4.2</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>MTS</td>
<td>21</td>
<td>R</td>
<td>4</td>
<td>8</td>
<td>29.2</td>
<td>4.5</td>
<td>56</td>
</tr>
</tbody>
</table>

MTO, medical treatment only; MTS, medical treatment+surgery; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; and RC, randomization criteria. *Alive at 180 days.

Figure 3. Hemicraniectomy and Durotomy Upon Deterioration From Infarction-Related Swelling Trial modified Rankin scores at 21, 90, and 180 Days.
≥70 years old with a mean age of 58.4 years.11 None of the European trials required adherence to an SMMP. It is therefore plausible that required adherence to the HeADDFIRST standardized treatment protocols is responsible for the better survival in its nonsurgical patients, in contrast to the notion that differences in the execution of best medical management with a recommended protocol make no difference to the outcome.

The mortality for the HeADDFIRST MTS patients was 21% at 21 days compared with the 40% MTO mortality. Although this illustrates a favorable trend toward improved survival with surgical decompression, it did not reach statistical significance \( (P=0.39) \) because of the small sample size of this pilot clinical trial. Furthermore, any beneficial trend was diminished by 90 days because of additional deaths at day 34 (progression of disease) and day 56 (withdrawal of support) in the MTS group. Although HeADDFIRST only followed up patients for 180 days, subsequent studies should include a longer follow-up because some of the previously published trials of hemicraniectomy have shown that patients can continue to improve after this period.

Notably, HeADDFIRST allowed randomization of patients up to 96 hours after stroke onset, which was the same as HAMLET but significantly longer than DECIMAL (30 hours) and DESTINY (36 hours). Studies that allowed later randomization (with the time of randomization being linked to magnitude of mass effect and clinical deterioration as in HeADDFIRST) should be associated with higher mortality, a finding that could not be verified by our study.

HeADDFIRST also demonstrated that masking treatment for purposes of blinded outcome evaluation was feasible and should be incorporated in future randomized trials, as was successfully accomplished in the subsequent HAMLET study.

The recent series of randomized, controlled studies on surgical decompression for SOMCATI including HeADDFIRST have implications for management of patients with large supratentorial hemorrhagic infarctions. The European trials provide definitive evidence of the potential life-saving benefit of early hemicraniectomy and durotomy in selected younger patients, thereby allowing this procedure to become an integral part of the stroke management armamentarium. HeADDFIRST was completed >10 years ago; however, there have not been any major leaps forward in medical management of patients with SOMCATI that would diminish the significance of its results today in many key areas. The SMMP and required adherence in HeADDFIRST may have contributed to its lower mortality, emphasizing that the specifics of medical management may matter and potentially alter patient outcomes. Furthermore, the HeADDFIRST randomization criteria differentiated between early survivors and nonsurvivors with SOMCATI when patients are managed using the HeADDFIRST SMMP, and this can provide some useful clinical guidance about patient selection for the procedure and design of future trials relevant to the management of SOMCATI.

HeADDFIRST Trialists
Albany Medical College (Dr Gary Bernardini), The Cleveland Clinic Foundation (Dr John Andrefsky, Dr Derk Krieger), Columbia-Presbyterian Hospital (Dr Mitchell Elkind), Detroit Receiving Hospital (Dr William Coplin), Duke University Medical Center (Dr Carmelo Graffagnino), Indiana University Medical Center (Dr Joe Biller), OSF Saint Francis Medical Center (Dr David Wang), St. Louis University Health Sciences Center (Dr Salvador Cruz-Flores), Thomas Jefferson University (Dr David Brock), University of Calgary (Dr Andrew Demchuk), University of California Davis (Dr Piero Verro), University of Chicago (Dr Jeffrey Frank), University of Cincinnati (Dr Daniel Woo), University Hospitals of Cleveland (Dr Jose Suarez), University of Kentucky (Dr Creed Pettigrew), and University of Maryland (Dr Marian LaMonte).

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Disclosures
None.

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12. StataCorp. Stata: Release 12 Statistical Software. College Station, TX: StataCorp LP; 2011.
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Trial: Randomized Pilot Clinical Trial
Jeffrey I. Frank, L. Philip Schumm, Kristen Wroblewski, Douglas Chyatte, Axel J. Rosengart, Christi Kordeck and Ronald A. Thisted

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SUPPLEMENTAL MATERIAL

Additional Details of the HeADDFIRST Protocol
Patient Screening

For ambiguous cases of the imaging inclusion criterion, stroke volume of $\geq 90$ cc was considered representative of $\geq 50\%$ MCA territory and $\geq 180$ cc was considered representative of a complete MCA territory. Patients with ischemic stroke in additional vascular territories (anterior and posterior cerebral artery) were considered eligible if they also met the requisite MCA eligibility criteria. Stroke onset was defined as the last time the patient was known to be at baseline neurological function.

Consent, Registration, Randomization

Registration and randomization were both web-based and designed to provide balance for treatment assignment within each participating center. The investigators were unaware of the randomization scheme. Registration and randomization were available 24 hours per day, with a backup system in case the online application failed or was not accessible. Repeat CT scans were recommended every 12–24 hours to pace the brain swelling while patients were within the randomization time window. CT scans were the required brain imaging modality due to their consistent acute availability across participating centers and more favorable safety for patients with a wide range of severity of medical illness. On a case-by-case basis, Magnetic Resonance Imaging (MRI) scans of the head were permitted as eligibility and randomization scans as long as they matched the CT imaging thresholds for eligibility and randomization.

Standardized Management Protocols and Adherence

To ensure protocol compliance, the Principal Investigator (JF) conducted a site visit immediately following each center’s enrollment of its first patient while still hospitalized. Copies of the CT scans for each patient documenting eligibility and randomizability were provided to the DCC, and were read by the Principal Investigator and an independent, blinded neurologist (AR). Following hemicraniectomy and durotomy, the surgeon completed a detailed surgical report form and provided a CT scan documenting the surgical procedure; these were reviewed by a neurosurgeon (DC).

Because this was a pilot trial designed to obtain information about the outcomes of patients meeting the criteria described above, patients whose families did not wish to participate in the randomized portion of the trial were asked to participate in a parallel data collection only arm. This group received the same medical management as patients participating in the randomized portion of the trial, and was evaluated according to the primary endpoint.

Standardized Medical Management Protocol (SMMP)

Airway Management: Patients were orally intubated if they met one of the following criteria: 1. compromise of airway integrity through depression of protective reflexes and depressed level of consciousness; 2. depression of respiratory drive as evidenced by associated gas exchange abnormalities; 3. severe gas exchange abnormalities from pneumonia, atelectasis, or pulmonary edema; 4. consistent ICP elevation $> 15$ mm Hg if cerebral perfusion pressure (CPP) $< 70$ mm Hg; 5. met criteria for treatment initiation (randomization criteria) and assigned to the MTS group. Extubation was embraced if neurological stability was achieved for $> 48$ hours, with adequate spontaneous cough reflexes to clear secretions, and stable respiratory parameters and gas exchange on continuous positive airway pressure (CPAP) ventilator mode with pressure support $\leq 5$ cm H$_2$O for more than 12 hours.
**Ventilator Settings**: All intubated patients were placed on an assisted control mode of ventilation during the period of worsening brain swelling with tidal volumes 8-14 cc/kg/breath with a set ventilator rate 8-16 breaths per minute, positive end expiratory pressure of 5 cm H₂O. If a synchronized intermittent mandatory ventilation mode or CPAP mode was employed due to patient discomfort with assist control, pressure support of at least 5 cm H₂O was used. The FiO₂ was minimized to maintain consistent pO₂ > 75 mm Hg. The target pCO₂ levels were 30-35 mm Hg for gradual neurological worsening, 25-30 mm Hg for acute neurological worsening (e.g., signs of lateral transtentorial herniation such as development of a large, unreactive pupil), and 28-35 mm Hg for ICP > 15 mm Hg. If the pCO₂ was lowered too much, it was raised slowly (< 1 mm Hg/hour).

**Blood Pressure Control and Agents**: Blood pressure elevation was not treated unless the systolic blood pressure was > 200 mm Hg (assuming the CPP ≥ 70 mm Hg) and there was no compelling cardiac contraindication for this degree of hypertension. Higher blood pressure was tolerated if the CPP would be compromised to < 70 mm Hg with active blood pressure lowering. The antihypertensive medications of choice were intravenous labetalol (intermittent or drip), enalapril (intravenous or per nasogastric tube), or a continuous intravenous calcium channel blocker. The blood pressure was therapeutically elevated if the CPP was < 70 mm Hg using an intravenous phenylephrine drip (heart rate > 60 beats/minute) or dopamine (heart rate < 110 beats/minute). All patients on vasopressors required daily electrocardiograms, cardiac enzyme testing, and a baseline trans-thoracic echocardiogram. When vasopressors were employed, the target blood pressure was to achieve a CPP ≥ 70 mm Hg.

**Management of Fluid and Electrolytes**: The baseline intravenous fluid was 0.9% NaCl (without dextrose) with 20 mEq/Liter of KCl unless there was renal insufficiency and or hyperkalemia. The total daily fluid rate was individualized based on body weight and temperature: {1500 + [(ideal weight in kg – 20) x 20] + 0.5 cc/kg/degree > 38 degrees Centigrade} cc/day. No less than 80% of the calculated fluid maintenance was permitted unless there was pulmonary edema or oliguria/anuria. For the first week after registration, strict attention was focused on maintaining the fluid intake greater than fluid output of at least 300 cc/day. While electrolyte levels were maintained and corrected as needed, there was a permissive approach to sodium elevation when ≤ 155 mEq/Liter. Glucose was maintained < 200 with a sliding scale subcutaneous insulin regimen, and an insulin drip was utilized if the serum glucose was > 300 for more than 6 hours.

**Gastrointestinal and Nutritional Management**: Oral intake was not permitted for the first 72 hours, and was only progressed after formally cleared by a speech pathologist. For non-intubated patients who could not safely swallow, enteral nourishment was not provided until >48 hours of neurological stability when there were no prohibitive airway concerns. Intubated patients had enteral nutrition commenced within 36 hours of intubation or randomization. A small bore NG tube was employed (12-14 Fr) with a 1 Cal/cc full strength tube feeding formulation started @ 20 cc/hour and escalated @ 20 cc/hour every 8 hours until the target caloric goal was achieved. Gastric residuals were monitored every 4 hours, and tube feeding was held for two hours when > 80 cc until < 80 cc. If the high gastric residuals persisted >24-36 hours, promotility agents were initiated (metoclopramide or cisapride). The total fluid rate (intravenous fluid + tube feedings) was maintained based on fluid goal targets delineated in the fluid management section. Ulcer prophylaxis was used for the first week after registration with an H₂ blocker or sucralfate. All patients received docusate sodium daily (100 mg, oral or per nasogastric tube, bid), supplemented by a suppository if there was no bowel movement for 48 hours.

**Hematological Monitoring and Management**: Coagulation parameters (PT, INR, PTT) were monitored at least every other day. For mild elevations in PT or INR, vitamin K was administered while the etiology was investigated. Consistent decline in platelet count was investigated and corrected for counts < 50,000 or based on clinical judgment. Hemoglobin was maintained > 9.0 for the first 7 days after registration.

**Intracranial Pressure Monitoring**: While the use of intracranial pressure (ICP) monitors was optional (parenchymal only; no external ventricular drains) before randomization criteria were met, all patients had a parenchymal ICP monitor inserted ipsilateral to the stroke upon treatment initiation (post randomization) even if not assigned to the surgical group. The standard frontal location was used for patients assigned to the MTO arm,
and a frontal location anterior to the craniectomy site was used for those assigned to the MTS arm. Prophylactic antibiotic use was discouraged but optional. Monitors were removed after 72 hours of neurological stability.

**Sedation:** Propofol was the sedative of choice, and it was used only on intubated patients for one of the following indications: dangerous agitation or overt discomfort and ICP control for arousal/agitation related elevations. The propofol dosing was titrated using the Ramsay scale with a maximal dose of 50 mcg/kg/min. Fentanyl or morphine sulfate was added when necessary. All patients on sedation required vasopressors (phenylephrine or dopamine) readily available at the bedside to allow rapid response to any blood pressure dips.

**Mannitol:** Mannitol was only used in two specific circumstances: 1. acute neurological deterioration with life-threatening brainstem compression as evidence by asymmetric ipsilateral pupillary enlargement with diminished light reactivity, and/or 2. ICP plateaus challenging CPP to < 70 mm Hg after appropriate blood pressure augmentation (see below), verifying ICP accuracy, and addressing other conservative alternatives for limiting ICP plateaus related to body positioning, ventilator settings impacting mean airway pressure, blood pressure stability, and body temperature control. When CPP was < 70 mm Hg, the first approach was directed at augmenting the blood pressure to MAP > 90 mm Hg. When indicated, mannitol was dosed at 0.25-0.5 grams/kg and infused over a 15-30 minute period along with furosemide (5-20 mg, intravenous push). Repeat dosing could be utilized when indicated. When mannitol was used, vasopressor agents (phenylephrine and dopamine) were always maintained at the bedside to allow rapid response to precipitous blood pressure dips. Serum electrolyte monitoring was required at least twice daily during mannitol use. A permissive approach was taken toward hypernatremia (tolerance of sodium ≤ 155 mEq/L). Achieving serum osmolality > 315 mOsm/L was discouraged.

**Anticonvulsants:** All registered patients received intravenous phenytoin for seven days, and a longer duration of therapy was allowed for any patient with documented seizure episodes. A loading dose was used @ 18 mg/kg with a goal of maintaining free phenytoin in the 1.0 – 2.0 range.

**Deep Vein Thrombosis Prophylaxis:** At least one of the following treatments were mandatory: 1) TED hose, non compressive thigh high; 2) sequential compression boots; 3) Mini-dose heparin or low molecular weight heparin.

**Secondary Stroke Prevention with antithrombotics:** The use of antiplatelet agents and anticoagulation for secondary stroke prevention was left to the treating physician’s best clinical judgment.

**Rehabilitation:** Early consultations were required with physical therapy, occupational therapy, speech therapy, and rehabilitation medicine. All patients had advocacy to optimize their disposition into a stroke specialized acute rehabilitation environment when possible.

**Standardized Surgical Management Protocol (SHD)**

All neurosurgeons participated in an investigator training session and demonstrated detailed knowledge of the medical and surgical protocols and agreement to adhere to them even when there were personal variances in usual practice outside of the study setting.
References


Supplementary Table I. Comparison Of Selected Inclusion Criteria for HeADDFIRST with HAMLET\textsuperscript{1}, DESTINY\textsuperscript{2}, and DECIMAL\textsuperscript{3}

<table>
<thead>
<tr>
<th>TRIAL &amp; LOCATION</th>
<th>AGE (years)</th>
<th>STROKE ONSET TO TREATMENT (hrs)</th>
<th>NIHSS</th>
<th>Consciousness</th>
<th>Infarct Size</th>
<th>Cerebral Edema</th>
<th>Midline Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAMLET Netherlands</td>
<td>18-60</td>
<td>&lt; 96</td>
<td>&gt; 16 Right ≥ 21 Left</td>
<td>GCS &lt; 13 (Right) GCS (E&amp;M) ≤ 9 (Left)</td>
<td>&gt; 2/3 MCA (CT)</td>
<td>Required (not quantified)</td>
<td>NR</td>
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<tr>
<td>DESTINY Germany</td>
<td>18-60</td>
<td>12-36</td>
<td>&gt; 18 Right &gt; 20 Left</td>
<td>NIHSS 1a ≥ 1</td>
<td>&gt; 2/3 MCA (CT); Basal ganglia involvement required; Excluded if additional ACA or PCA</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>DECIMAL France</td>
<td>18-55</td>
<td>&lt; 30</td>
<td>≥ 16</td>
<td>NIHSS 1a ≥ 1</td>
<td>&gt; 50% MCA (CT) and ≥145 cm(^3) (MRI)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>HeADDFIRST U.S.A. &amp; Canada</td>
<td>18-70</td>
<td>&lt; 96</td>
<td>≥ 18</td>
<td>NIHSS 1a &gt; 1</td>
<td>Eligibility Requirement: &gt; 50% MCA (CT &lt; 5 hours) or Complete MCA (CT 5 - 48 hours); midline shift criteria not met yet</td>
<td>Required (see midline shift)</td>
<td>Randomization Requirement: ≥ 4 mm pineal shift from midline or ≥ 7.5 mm septal shift from midline</td>
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