Trial of Early Minimally Invasive Removal of Intracerebral Hemorrhage


BACKGROUND
Trials of surgical evacuation of supratentorial intracerebral hemorrhages have generally shown no functional benefit. Whether early minimally invasive surgical removal would result in better outcomes than medical management is not known.

METHODS
In this multicenter, randomized trial involving patients with an acute intracerebral hemorrhage, we assessed surgical removal of the hematoma as compared with medical management. Patients who had a lobar or anterior basal ganglia hemorrhage with a hematoma volume of 30 to 80 ml were assigned, in a 1:1 ratio, within 24 hours after the time that they were last known to be well, to minimally invasive surgical removal of the hematoma plus guideline-based medical management (surgery group) or to guideline-based medical management alone (control group). The primary efficacy end point was the mean score on the utility-weighted modified Rankin scale (range, 0 to 1, with higher scores indicating better outcomes, according to patients’ assessment) at 180 days, with a prespecified threshold for posterior probability of superiority of 0.975 or higher. The trial included rules for adaptation of enrollment criteria on the basis of hemorrhage location. A primary safety end point was death within 30 days after enrollment.

RESULTS
A total of 300 patients were enrolled, of whom 30.7% had anterior basal ganglia hemorrhages and 69.3% had lobar hemorrhages. After 175 patients had been enrolled, an adaptation rule was triggered, and only persons with lobar hemorrhages were enrolled. The mean score on the utility-weighted modified Rankin scale at 180 days was 0.458 in the surgery group and 0.374 in the control group (difference, 0.084; 95% Bayesian credible interval, 0.005 to 0.163; posterior probability of superiority of surgery, 0.981). The mean between-group difference was 0.127 (95% Bayesian credible interval, 0.035 to 0.219) among patients with lobar hemorrhages and −0.013 (95% Bayesian credible interval, −0.147 to 0.116) among those with anterior basal ganglia hemorrhages. The percentage of patients who had died by 30 days was 9.3% in the surgery group and 18.0% in the control group. Five patients (3.3%) in the surgery group had postoperative rebleeding and neurologic deterioration.

CONCLUSIONS
Among patients in whom surgery could be performed within 24 hours after an acute intracerebral hemorrhage, minimally invasive hematoma evacuation resulted in better functional outcomes at 180 days than those with guideline-based medical management. The effect of surgery appeared to be attributable to intervention for lobar hemorrhages. (Funded by Nico; ENRICH ClinicalTrials.gov number, NCT02880878.)
CURRENT TREATMENT GUIDELINES FOR spontaneous intracerebral hemorrhage support surgical evacuation of the hematoma by means of conventional craniotomy only as life-saving treatment, because randomized trials have shown no improvement in functional outcomes with surgical evacuation, with the exception of results in some trials involving patients who had superficially located lobar hemorrhages. Several minimally invasive surgical options have been investigated in meta-analyses as alternatives to conventional craniotomy. Catheter-based evacuation with thrombolysis, tested in the MISTIE-III (Minimally Invasive Surgery Plus Rt-PA [recombinant tissue plasminogen activator] for ICH [intracerebral hemorrhage] Evacuation Phase III) trial, did not result in improved scores on the modified Rankin scale at 1 year. Minimally invasive trans-sulcal parafascicular intracerebral hemorrhage evacuation with access through a port in a sulcus oriented along the long axis of the white-matter tracts has been shown in preliminary studies to be safe, and the surgery has been successful at removing a large amount of hematoma. We conducted the Early Minimally Invasive Removal of Intracerebral Hemorrhage (ENRICH) trial to assess outcomes of minimally invasive trans-sulcal parafascicular surgery plus guideline-based medical management as compared with guideline-based medical management alone.

METHODS

TRIAL DESIGN AND OVERSIGHT

ENRICH was a prospective, multicenter, adaptive, randomized trial with end-point adjudication. The trial design and conduct were overseen by a multidisciplinary team of academic investigators at Emory University. The sponsor of the trial was Nico (Indianapolis), the manufacturer of the devices used in the trial. Devices and associated disposable items were purchased by each site as part of its clinical operations (Nico did not provide the devices for free or at a reduced cost), and these purchases were unrelated to trial participation. The sponsor did not participate in data collection or data analysis, nor did it contribute to the design of the trial, its scientific concepts, or the decision to submit the manuscript for publication. No confidentiality agreements were made between the investigators and the sponsor. Surgeons completed a prerequisite training course that was organized by the manufacturer. (This course was developed and conducted independent of the trial and before the trial had begun.) The adaptive trial methodology was designed and data analyses were performed by the authors who are statisticians from Berry Consultants (Austin, Texas). The first three authors wrote the first draft of the manuscript, and all the authors reviewed and contributed to subsequent versions. Data analyses and interpretation were performed by the authors without input from the sponsor. The authors had independent access to the database, and they vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Additional details regarding trial governance and responsibilities are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, and the trial protocol, available at NEJM.org, was approved by the institutional review board at each site. Patients were enrolled after written informed consent was obtained.

PATIENTS

Persons 18 to 80 years of age were eligible to enroll in the trial if they had computed tomographic (CT) evidence of a supratentorial, spontaneous, acute intracerebral hemorrhage with a hematoma volume of 30 to 80 ml (estimated by the local investigator by means of the following calculation: volume = [length × width × height]/2); a score on the Glasgow Coma Scale (GCS) between 5 and 14, indicating mild-to-severe neurologic deficits (scores range from 3 to 15, with higher scores indicating better neurologic status); a score on the National Institutes of Health (NIH) stroke scale of more than 5, representing moderate-to-severe disability (scores range from 0 to 42, with higher scores indicating worse neurologic deficit); and a score before the hemorrhage occurred of 0 to 1 on the modified Rankin scale, representing little or no disability (scores range from 0 to 6, with a score of 0 indicating no deficit, 1 indicating minimal deficit, and 6 indicating death), that was obtained by an investigator by means of an interview with the patient’s representative. In addition, patients were eligible only if surgery could be initiated within 24 hours after the time that they were last known to be well. Patients
were excluded if they had an uncorrectable coagulopathy, a need for long-term anticoagulation, very poor or very good results on neurologic examinations, an intraventricular hemorrhage involving more than 50% of either lateral ventricle, a primary thalamic or infratentorial hemorrhage, or any secondary cause of intracerebral hemorrhage. Full inclusion and exclusion criteria have been published previously and are listed in Table S1 in the Supplementary Appendix. The trial was paused because of the coronavirus disease 2019 pandemic, at which time 220 patients had been enrolled, from March through November 2020.

**RANDOMIZATION**

Patients were randomly assigned, in a 1:1 ratio, to undergo minimally invasive trans-sulcal parafascicular surgery plus guideline-based medical management (surgery group) or to receive guideline-based medical management alone (control group) (Fig. 1). Randomization was performed through a central, online electronic data-capture system, with stratification according to the GCS score (<9 or ≥9) and the location of the hemorrhage (anterior basal ganglia or lobar).

The term “lobar” refers to a lesion superficially located in the main lobes of the brain, typically the parietal, temporal, or frontal lobes. The anterior basal ganglia include the caudate, putamen, and pallidum to the capsula externa and excludes the thalamus. The leadership team established a clinical standardization guideline, based on the guidelines regarding intracerebral hemorrhage from the American Heart Association and the American Stroke Association, that included a surgical manual, which the surgeons treating patients in the surgery group used (see the Supplementary Appendix). The surgery was performed with the patient under general anesthesia. A small craniotomy and a durotomy provided access to the sulcus, and the trajectory to the hematoma was planned with the use of imaging guidance. The hematoma was accessed by means of the BrainPath minimal access port that allowed a bimanual technique with visualization; the hematoma was evacuated with suction and the Myriad device (both are FDA-cleared devices manufactured by Nico). Hemostasis in the hemorrhage cavity was performed according to the judgment of the surgeon. Bone flaps were repositioned and secured, and incisions were closed in standard fashion as previously described. The treatment of every patient was reviewed and monitored by the leadership team for adherence to the clinical standardization guideline. The surgeries were video-recorded; the first two cases at each site were reviewed by the leadership team to ensure consistency with the surgical manual; additional recordings were reviewed on a case-by-case basis by the leadership team. Crossover from the control group to the surgery group was prohibited; however, lifesaving conventional craniotomy or decompressive hemicraniectomy could be performed as needed, a practice consistent with the guidelines regarding intracerebral hemorrhage referenced above.

Each participating center had one neurosurgeon and one neurointensivist principal investigator who had had experience with the surgical intervention before the trial began. Site investigators and personnel were trained regarding the protocol and clinical standardization guidelines.

**ADJUDICATION AND MASKING**

The NIH stroke scale and modified Rankin scale assessments were performed by certified trial personnel at each site. The score on the modified Rankin scale was obtained by site personnel for each patient by means of an audio-recorded structured interview at 30, 90, and 180 days after randomization. Caregivers often accompanied the patients and would provide additional contextual or environmental information to the assessor when necessary, including when the patients were unable to communicate. Site personnel were aware of the patients’ trial group because of the physical evidence of surgery or inadvertent disclosure by patients. In order to mask the trial data with respect to the primary end point, a third party uploaded the audio recordings of the interviews to the electronic data-capture system and removed any identifying information and the group assignment. The redacted file was uploaded to a central end-point-adjudication form in the electronic data-capture system. An author who is an independent neuropsychologist with specialized training and experience in stroke outcomes reviewed the redacted audio recordings of the structured interviews and entered the adjudicated scores into the electronic data-capture system. For patients who could not participate in an in-person assessment, the structured
The interview was performed and recorded by means of a telephone call with patients, caregivers, or both.\textsuperscript{13}

Neuroimaging was adjudicated centrally. Classification of the hemorrhage location (lobar or anterior basal ganglia) and hematoma volume were determined by the site investigator. Neuroimages were deidentified and uploaded to a central online platform. The core imaging laboratory personnel interpreted and adjudicated the qualifying CT, initial CT angiogram, and follow-up neuroimages (either CT or magnetic resonance imaging).

\textbf{Figure 1. Enrollment, Randomization, and Follow-up.}

Scores on the Glasgow Coma Scale (GCS) range from 3 to 15, with lower scores indicating a more severe depression of mental status. Scores on the National Institutes of Health (NIH) stroke scale range from 0 to 42, with higher scores indicating a more severe neurologic deficit. Scores on modified Rankin scale range from 0 to 6, with a score of 1 or lower indicating no or minimal deficit and 6 indicating death. ICH denotes intracerebral hemorrhage.

11,603 Patients were assessed for eligibility

11,303 Were excluded

10,611 Did not meet inclusion criteria or met exclusion criteria

1,259 Were <18 or >80 yr of age

3,618 Had a secondary cause of ICH: hemorrhagic conversion, trauma, ruptured aneurysm, arteriovenous malformation, vascular anomaly, Moyamoya disease, venous sinus thromboses, a mass or tumor, recurrent ICH within 1 yr, or primary thalamic or infratentorial ICH

2,635 Had ICH volume <30 or >80 ml

406 Had intraventricular hemorrhage >50\% of either lateral ventricle

474 Were >24 hr from last known normal

821 Had GCS <5 or >14 or NIHSS <5

333 Had score on the modified Rankin scale >1 before the hemorrhage occurred

821 Had GCS <5 or >14 or NIHSS <5

214 Had do-not-resuscitate or comfort-measures-only order

168 Were unable or declined to give consent

246 Did not provide a reason

692 With anterior basal ganglia hemorrhage were excluded after adaptation of enrollment criteria

300 Underwent randomization

(adaptation of enrollment criteria occurred after 175 patients were enrolled)

150 Were assigned to the surgery group

48 Had anterior basal ganglia ICH

102 Had lobar ICH

150 Were assigned to the control group

44 Had anterior basal ganglia ICH

106 Had lobar ICH

1 Was lost to follow-up

2 Withdrew consent

147 Had observed score on the modified Rankin scale at 180 days

139 Had observed score on the modified Rankin scale at 180 days

150 Were included in the intention-to-treat primary analysis

150 Were included in the intention-to-treat primary analysis

7 Were lost to follow-up

4 Withdrew consent
imaging) 24 hours after the surgery had been performed. The qualifying hematoma volumes on CT were adjudicated by two neuroradiologists, of whom one was aware of the patients' trial group and one was unaware. Safety and procedure-related events were reviewed by the leadership team. A physician whose training involved neurocritical care and stroke served as the independent medical monitor adjudicating serious adverse events and deaths at each site; this physician was aware of the patients' trial group.

END POINTS
The primary efficacy end point was the score on the utility-weighted modified Rankin scale at 180 days. The modified Rankin scale is a seven-level ordinal scale that ranges from 0 (no symptoms) to 6 (death); we assigned the following utility weights to the seven levels: 1.0, 0.91, 0.76, 0.65, 0.33, 0.0, and 0.0 (with higher scores indicating a better outcome, according to patients' assessment). These utility weights have been used previously in trials involving ischemic stroke. The primary safety end points were death within 30 days after enrollment and the change in hematoma volume from the initial to the follow-up neuroimaging.

Prespecified secondary end points were postoperative rebleeding associated with neurologic deterioration, defined as an increase of 4 or more points on the NIH stroke scale or a decrease of 2 or more points on the GCS; length of stay in the intensive care unit; length of stay in the hospital; ordinal score on the modified Rankin scale at 7 days or at discharge (whichever came first) and at 30, 90, and 180 days; the change in the hematoma volume after completion of surgery, expressed as a percentage; the hematoma volume (in milliliters) after the completion of surgery; the dichotomized score on the modified Rankin scale at 24 hours after the surgery had been performed. The qualifying hematoma volumes on CT were adjudicated by two neuroradiologists, of whom one was aware of the patients' trial group and one was unaware. Safety and procedure-related events were reviewed by the leadership team. A physician whose training involved neurocritical care and stroke served as the independent medical monitor adjudicating serious adverse events and deaths at each site; this physician was aware of the patients' trial group.

STATISTICAL ANALYSIS
Simulations were conducted in the design stage of the trial to evaluate power and type I error over a wide range of assumptions. With an adaptive sample size of 150 to 300 patients, the Bayesian primary analysis was shown in a simulation to have approximately 90% or greater power for detecting superiority of surgery over control, with a between-group difference in the mean score on the utility-weighted modified Rankin scale in both hemorrhage locations of 0.15 or higher (i.e., a 15% absolute increase in utility-weighted modified Rankin scale), with an approximate one-sided type I error of less than 0.025. In addition, the trial design and analysis would provide approximately 60 to 90% power for detecting superiority of surgery with respect to the between-group difference in one of the two locations of 0.15 or higher in the mean score on the utility-weighted modified Rankin scale. This model included scenarios in which the surgery effect would be homogeneous and heterogeneous with respect to hemorrhage locations.

We compared the groups with respect to the score on the utility-weighted modified Rankin scale with the use of a Bayesian analysis with pooling of data from the two hemorrhage locations. The prespecified threshold for showing the superiority of surgery plus medical management over medical management alone at 180 days was a posterior probability of superiority of at least 0.975, with the posterior probability of superiority defined as the probability that the mean difference in the score on the utility-weighted modified Rankin scale (surgery group minus control group) is greater than 0 (i.e., the probability that surgery would be superior to control). The model provided an estimate of the mean difference in the score on the utility-weighted modified Rankin scale between groups with a corresponding 95% Bayesian credible interval. The primary analysis model included Bayesian multiple imputation for missing scores on the modified Rankin scale at 180 days on the basis of the scores on the modified Rankin scale at 90 days (for more details, see the Supplementary Appendix). To control the type I error, a decision of superiority was made on the basis of the Bayesian pooled estimate under an assumption of equal surgery benefit across hemorrhage locations. In addition, a complementary prespecified Bayesian hierarchical model provided an estimate
of the surgery benefit within each location by means of partial pooling and enabled adaptive decisions of enrichment. This hierarchical model provided a more reliable estimate of the groups than either a pooled analysis or an independent analysis of each location (see the Supplementary Appendix). All prespecified Bayesian prior distributions were intended to be noninformative, with the primary objective of allowing the observed data to drive the estimation of key model variables.

The original statistical plan called for the use of complete cases for the secondary end-point analyses (i.e., ignoring missing data, under the assumption that data were missing completely at random) and the use of frequentist analyses. However, to ensure that our methods were consistent with the Bayesian primary analysis, we conducted corresponding Bayesian analyses on all secondary end points and report them here; we provide the prespecified frequentist analyses of the secondary and exploratory end points in the Supplementary Appendix. To align with the strategy we used for missing data in the primary analysis, we used a Bayesian model for multiple imputation of missing data for all secondary analyses involving the modified Rankin scale (using the scores that we collected at previous time points to impute missing values at subsequent time points); this model included an assumption that data were missing at random. Because data on other secondary end points and exploratory end points (e.g., length of stay and number of days receiving mechanical ventilation) were collected either at or before hospital discharge, complete case analyses were used for these secondary and exploratory end points. These analyses did not account for the competing risk of death, implying an assumption that data were missing completely at random. Because there was no prespecified plan for adjustment of Bayesian credible intervals (or for frequentist confidence intervals) for multiple comparisons, no definitive conclusions can be drawn from these intervals for secondary and exploratory end points.

The adaptive trial design allowed for a sample size ranging from 150 to 300 patients, with interim analyses triggered when 150, 175, 200, 225, 250, and 275 patients had undergone randomization. Prespecified decision rules were used to evaluate each interim analysis with the use of a Bayesian hierarchical model of the estimated surgery effect within each hemorrhage-location subgroup. Decisions related to the adaptation of enrollment criteria were made at the recommendation of an independent data and safety monitoring board. The design included the following three possible adaptive decisions: stop for futility the new enrollment of patients with a hemorrhage in either the anterior basal ganglia or the lobar location, stop for predicted success all new enrollment (both hemorrhage locations) and continue with follow-up, or continue enrollment (both hemorrhage locations) (Fig. S1).

The criteria to stop new enrollment for predicted success at any interim analysis required a minimum of 60 patients and a Bayesian posterior probability of superiority of at least 0.99. Futility criteria were met with regard to one or both hemorrhage locations if at least 30 patients had a score on the modified Rankin scale obtained at 180 days and the Bayesian posterior probability of meaningful effect was 0.20 or less (i.e., the probability of a surgery benefit >0.075 for a hemorrhage location was <0.20).

A clinically meaningful effect was defined as a between-group difference in the mean score on the utility-weighted modified Rankin scale of at least 0.075, a difference that was chosen on the basis of effect sizes observed in other positive clinical trials of acute stroke and design simulations that achieved adequate operating characteristics (see the Adaptive Design Report in the Supplementary Appendix for more details). The futility criteria would be met if there were insufficient evidence of a meaningful benefit among patients in a hemorrhage-location subgroup.

For patients with missing values for the primary end point (the score on the utility-weighted modified Rankin scale at 180 days), we used multiple imputation in the Bayesian primary analysis on the basis of the scores collected at 90 days and treatment group. This approach was prespecified and assumed that missing 180-day values were missing at random, conditional on observed data at 90 days and treatment group.

To control the overall false positive rate (i.e., type 1 error) in the context of the adaptive design, the primary analysis to evaluate the surgery benefit included all patients who underwent randomization. Statistical analyses were conducted with the use of FACTS (Fixed and Adaptive Clinical Trial Simulator), version 6.5,19 and R software,
version 4.3,20 with the use of the rstan package, version 2.26.21

RESULTS

ENROLLMENT AND PATIENT CHARACTERISTICS
Between December 1, 2016, and August 24, 2022, a total of 11,605 patients were assessed for eligibility; 300 patients at 37 centers in the United States that included 59 treating neurosurgeons were randomly assigned to either the surgery group (150 patients) or the control group (150 patients) (Fig. 1). Trial groups were similar with respect to demographic and baseline characteristics, including hematoma volume, score on the NIH stroke scale, and GCS score (Table 1 and Table S3). The representativeness of the trial population is shown in Table S2. The median number of hours from the time that the patient was last known to be well to randomization was 12.8 hours in the surgery group and 12.9 hours in the control group, and the median number of hours from randomization to surgery was 1.5 hours (Table 1). At the second interim analysis (after 175 patients had been enrolled), the prespecified futility criterion was met for the anterior basal ganglia location (the posterior probability of meaningful effect equaled 0.177, which met the 0.20 threshold) and the decision was made to cease enrollment of patients with a hemorrhage in the anterior basal ganglia location. Subsequently, all patients who underwent randomization met the inclusion criteria for lobar hemorrhage, which led to a total number of 92 of 300 patients (30.7%) with hemorrhage in the anterior basal ganglia location and 208 of 300 (69.3%) with hemorrhage in the lobar location. The score on the modified Rankin scale at 180 days was obtained in 286 patients (95.3%) — 139 in the control group (40 with hemorrhage in the anterior basal ganglia and 99 in the lobar location) and 147 in the surgery group (47 with hemorrhage in the anterior basal ganglia and 100 in the lobar location), with all patients who underwent randomization included in the primary analysis.

EFFICACY END POINTS
The mean score on the utility-weighted modified Rankin scale at 180 days (the primary efficacy end point) was 0.458 in the surgery group and 0.374 in the control group, for a between-group difference of 0.084 (95% Bayesian credible interval, 0.005 to 0.163) in the total population (posterior probability of superiority, 0.981, exceeding the 0.975 prespecified threshold to conclude superiority of surgery) (Fig. 2). Because the data did not support the assumption of equal surgery benefit across hemorrhage locations in the primary analysis model, a prespecified Bayesian hierarchical model was used to estimate the mean difference between groups for each location with Bayesian partial pooling. The between-group difference was −0.013 (95% Bayesian credible interval, −0.147 to 0.116) among patients with hemorrhage in the anterior basal ganglia location and 0.127 (95% Bayesian credible interval, 0.035 to 0.219) among patients with hemorrhage in the lobar location (Table 2).

Bayesian analyses for the secondary and exploratory end points are shown in Table 2 (frequentist analyses of secondary end points are shown in Table S8, but no conclusions can be drawn from these results). Among patients in the surgery group, the mean (±SD) percent reduction in hematoma volume from baseline to 24 hours was 73.2±37.8, with a mean volume after the completion of surgery of 14.9±21.7 ml. A volume of 15 ml or less after the completion of surgery was observed in 109 patients (72.7%) (this was not a prespecified end point, but it is provided for comparison with other trials and guidelines).1 Calculation of odds ratios for modified Rankin scale values by means of a Bayesian ordinal logistic-regression model among patients in the surgery group as compared with those in the control group resulted in posterior mean odds ratios of 0.376 (95% Bayesian credible interval, 0.230 to 0.577) at 7 days or discharge, 0.504 (95% Bayesian credible interval, 0.326 to 0.741) at 30 days, 0.665 (95% Bayesian credible interval, 0.437 to 0.970) at 90 days, and 0.658 (95% Bayesian credible interval, 0.433 to 0.957) at 180 days. In the surgery group, 74 patients (50.3%) had a score on the modified Rankin scale of 0 to 3 and 73 (49.7%) had a score of 4 to 6 at 180 days; in the control group, 57 patients (41.0%) had a score of 0 to 3 and 82 (59.0%) had a score of 4 to 6 (Table 2). Results of prespecified subgroup analyses are shown in Table S7.

The mean length of stay in the intensive care unit, the mean length of stay in the hospital, and
the mean number of days that patients received mechanical ventilation are shown in Table 2. Decompressive hemicraniectomy was performed in 5 patients (3.3%) in the surgery group and in 30 patients (20%) in the control group (Table 2).

**SAFETY END POINTS**

Among patients in the surgery group, 9.3% had died by 30 days (primary safety end point) and 4.7% died in the hospital after randomization, and among patients in the control group, 18.0% had died by 30 days and 12.7% died in the hospital after randomization (Table 3). Death from any cause at the final follow-up at 180 days had occurred in 30 patients (20%) in the surgery group and in 35 (23%) in the control group. In the surgery group, one or more serious adverse events occurred in 95 patients (63.3%), and 5 patients (3.3%) had rebleeding associated with neurologic deterioration after surgery; in the control group, 118 patients (78.7%) had one or more serious adverse events. Table S12 provides details on serious adverse events; seizures and cerebral edema appeared to be numerically more common in the control group than in the surgery group. Cardiac arrest occurred in 9 patients in the surgery group (8 of the arrests occurred after discharge), as compared with 2 in the control group.

### Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Surgery Group (N = 150)</th>
<th>Control Group (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) — yr</td>
<td>64 (56–72)</td>
<td>62 (51–73)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>72 (48)</td>
<td>78 (52)</td>
</tr>
<tr>
<td>Median score on NIH stroke scale (IQR)†</td>
<td>16 (11–22)</td>
<td>18 (13–22)</td>
</tr>
<tr>
<td>Score on the Glasgow Coma Scale at randomization — no. (%)‡</td>
<td>4–8</td>
<td>25 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29 (19)</td>
</tr>
<tr>
<td></td>
<td>9–14</td>
<td>125 (83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>121 (81)</td>
</tr>
<tr>
<td>Median hematoma volume (IQR) — ml§</td>
<td>54 (39–72)</td>
<td>55 (40–73)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage present — no. (%)§</td>
<td>65 (43)</td>
<td>59 (39)</td>
</tr>
<tr>
<td>ICH location — no. (%)¶</td>
<td>48 (32)</td>
<td>44 (29)</td>
</tr>
<tr>
<td>Anterior basal ganglia</td>
<td>102 (68)</td>
<td>106 (71)</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>73 (49)</td>
<td>79 (53)</td>
</tr>
<tr>
<td>Median ICH score (IQR) [</td>
<td>2 (1–2)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>Median FUNC score (IQR)**</td>
<td>8 (6–8)</td>
<td>8 (6–8)</td>
</tr>
<tr>
<td>Median APACHE II score (IQR)††</td>
<td>12 (10–14)</td>
<td>12 (11–14)</td>
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<tr>
<td>Median CCI score (IQR)††</td>
<td>3 (1–4)</td>
<td>2 (1–4)</td>
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<tr>
<td>Score on modified Rankin scale of ≤1 before ICH</td>
<td>29 (19)</td>
<td>17 (11)</td>
</tr>
<tr>
<td>occurred — no. (%)§§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history — no./total no. (%)¶¶</td>
<td>123/150 (82)</td>
<td>117/150 (78)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>45/150 (30)</td>
<td>42/150 (28)</td>
</tr>
<tr>
<td>Central nervous system disease</td>
<td>42/150 (28)</td>
<td>39/150 (26)</td>
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<tr>
<td>Endocrine or renal disorder</td>
<td>59/152 (45)</td>
<td>53/152 (40)</td>
</tr>
<tr>
<td>Cigarette smoking, current or former</td>
<td>38/148 (26)</td>
<td>46/144 (32)</td>
</tr>
<tr>
<td>Daily alcohol use</td>
<td></td>
<td></td>
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<tr>
<td>Time from patient last known to be well to randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8 hr — no. (%)</td>
<td>42 (28)</td>
<td>38 (25)</td>
</tr>
<tr>
<td>≤12 hr — no. (%)</td>
<td>73 (49)</td>
<td>69 (46)</td>
</tr>
<tr>
<td>Median (IQR) — hr</td>
<td>12.8 (7.8–18.7)</td>
<td>12.9 (7.5–17.7)</td>
</tr>
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</table>
In this randomized trial involving patients with an acute supratentorial intracerebral hemorrhage, a functional benefit of minimally invasive surgery plus guideline-based medical management as compared with guideline-based medical management alone was observed at 180 days on a weighted scale of disability after minimally invasive surgical evacuation of the hematoma within 24 hours after the time that the patient was last known to be well. Death by 30 days occurred in fewer patients in the surgery group than in the control group. Seizures and cerebral edema were more common in the control group than in the surgery group. The results in the pooled analysis appeared to be attributable to the surgery effect in the lobar hemorrhage location. In that respect, the results affirm tentative conclusions from previous randomized trials.3,4 The generalizability of these results is limited to the restricted population meeting the trial entry criteria with respect to the size and location of the hemorrhage and the time from onset of symptoms to surgery.

The Bayesian adaptive design, rather than a traditional frequentist approach, was chosen as the analytic method for the primary end point in part because of similar trials in patients with acute ischemic stroke17,22 that had population heterogeneity (i.e., with respect to time of sur-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Surgery Group (N = 150)</th>
<th>Control Group (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time from patient last known to surgery (IQR) — hr</td>
<td>16.75 (10.70–21.25)</td>
<td>NA</td>
</tr>
<tr>
<td>Median time from randomization to surgery (IQR) — hr</td>
<td>1.48 (0.97–2.43)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* ICH denotes intracerebral hemorrhage, IQR interquartile range, and NA not applicable.
† Scores on the National Institutes of Health (NIH) stroke scale range from 0 to 42, with higher scores indicating a more severe neurologic deficit. Data were available for 150 patients in the surgery group and 149 patients in the control group.
‡ Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating a more severe depression of mental status.
§ This information was provided by the core imaging laboratory personnel who interpreted and adjudicated the neuroimaging.
¶ The ICH location was determined by site investigators at the time of randomization.
†† The ICH score estimates the risk of death in patients with ICH and ranges from 0 to 6, with a score of 6 estimating a 100% risk of death from the ICH. Data were available for 149 patients in the surgery group and 150 patients in the control group.
‡‡ The Functional Outcome in Patients with Primary Intracerebral Hemorrhage (FUNC) score predicts functional independence after ICH and ranges from 0 to 11, with higher scores representing a greater likelihood to achieve functional independence at 90 days. Data were available for 144 patients in the surgery group and 150 patients in the control group.
‖ The Acute Physiology and Chronic Health Evaluation II (APACHE II) score estimates the severity of disease, and ranges from 0 to 71, with higher scores associated with a greater risk of death. Data were available for 36 patients in the surgery group and 16 patients in the control group.
‡‡‡ The Charlson comorbidity index (CCI) predicts 10-year survival of patients with multiple coexisting conditions. The score ranges from 0 to 37, with any score greater than 6 representing a 0% estimated 10-year survival.
§§ Scores on the modified Rankin scale range from 0 to 6, with a score of 1 or lower indicating no or minimal deficit and 6 indicating death.
¶¶ A full list of all medical history is provided in Table S6.
Table 2. Efficacy End Points.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>No. of Patients</th>
<th>Value for Surgery Group</th>
<th>Value for Control Group</th>
<th>Estimated Difference (95% Credible Interval)†</th>
<th>Posterior Probability of Superiority‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Control</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score on the utility-weighted modified Rankin scale at 180 days§</td>
<td>147</td>
<td>139</td>
<td>286</td>
<td>0.458</td>
<td>0.374</td>
</tr>
<tr>
<td>Anterior basal ganglia hemorrhage location</td>
<td>40</td>
<td>47</td>
<td>87</td>
<td>0.340</td>
<td>0.381</td>
</tr>
<tr>
<td>Lobar hemorrhage location</td>
<td>99</td>
<td>100</td>
<td>199</td>
<td>0.513</td>
<td>0.371</td>
</tr>
<tr>
<td><strong>Secondary end points¶</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Odds Ratio (95% Credible Interval)‖</td>
</tr>
<tr>
<td>ICU length of stay — days**</td>
<td>141</td>
<td>132</td>
<td>273</td>
<td>6.9±6.8</td>
<td>9.7±7.6</td>
</tr>
<tr>
<td>Hospital length of stay — days**</td>
<td>141</td>
<td>132</td>
<td>273</td>
<td>14.9±11.2</td>
<td>18.1±11.9</td>
</tr>
<tr>
<td>Surgery effect on modified Rankin scale at discharge or 7 days††</td>
<td>148</td>
<td>144</td>
<td>292</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 30 days</td>
<td>147</td>
<td>146</td>
<td>293</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 90 days</td>
<td>143</td>
<td>139</td>
<td>282</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 180 days</td>
<td>147</td>
<td>139</td>
<td>286</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma reduction after completion of surgery — %‡‡</td>
<td>147</td>
<td>NA</td>
<td>NA</td>
<td>73.2±37.8</td>
<td>NA</td>
</tr>
<tr>
<td>Hematoma volume after completion of surgery — ml‡‡</td>
<td>147</td>
<td>NA</td>
<td>NA</td>
<td>14.9±21.7</td>
<td>NA</td>
</tr>
<tr>
<td>Score of ≤3 on modified Rankin scale at 180 days — no. (%)§§</td>
<td>147</td>
<td>139</td>
<td>286</td>
<td>74 (50.3)</td>
<td>57 (41.0)</td>
</tr>
<tr>
<td><strong>Exploratory end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation** — no. (%)</td>
<td>150</td>
<td>150</td>
<td>300</td>
<td>88 (58.7)</td>
<td>78 (52.0)</td>
</tr>
<tr>
<td>No. of days receiving mechanical ventilation**</td>
<td>141</td>
<td>132</td>
<td>273</td>
<td>5.3±6.3</td>
<td>8.8±6.6</td>
</tr>
<tr>
<td>Decompressive hemicraniectomy — no. (%)</td>
<td>5 (3.3)</td>
<td>30 (20.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median hematoma reduction (IQR) — %</td>
<td>87.7</td>
<td></td>
<td></td>
<td>(65.15–96.61)</td>
<td>NA</td>
</tr>
<tr>
<td>Median volume after completion of surgery (IQR) — ml</td>
<td>7.17</td>
<td></td>
<td></td>
<td>(1.95–17.34)</td>
<td>NA</td>
</tr>
<tr>
<td>Volume after completion of surgery ≤15 ml — no. (%)</td>
<td>109</td>
<td>72.7</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The estimates were derived from a Bayesian hierarchical model.
† The estimated difference is the difference between the means of the surgery and control groups.
‡ The posterior probability is the probability that the surgery group is superior to the control group.
§ The utility-weighted modified Rankin scale is a measure of disability.
¶ Secondary end points
‖ Odds Ratio (95% Credible Interval)
** ICU length of stay, hospital length of stay, and mechanical ventilation are measured in days.
†† At discharge or 7 days
‡‡ Hematoma reduction and volume after completion of surgery are measured in percentage and ml, respectively.
§§ Score of ≤3 on modified Rankin scale at 180 days
§§§ Volume after completion of surgery ≤15 ml is measured as a binary outcome.
Plus-minus values are means ±SD. ICU denotes intensive care unit.

† The estimated between-group difference in scores on the utility-weighted modified Rankin scale (surgery group minus control group) is greater than 0 (i.e., that results in the surgery group are superior to those in the control group).

‡ The estimated posterior probability of superiority of surgery over control is defined as the probability that the mean difference in the score on the utility-weighted modified Rankin scale (surgery group minus control group) is greater than 0 (i.e., that results in the surgery group are superior to those in the control group).

§ Data from the 180-day assessment are missing for 3 of 150 patients (2%) in the surgery group and for 11 of 150 patients (7%) in the control group.

¶ Secondary end points were prespecified. No conclusions can be drawn from results of secondary or exploratory end-point analyses because there was no prespecified plan for adjustment of confidence intervals for multiple comparisons.

‖ Odds ratios were calculated with the use of a Bayesian ordinal logistic-regression model with noninformative prior distributions. A value less than 1 represents a favorable effect.

** Percentages were compared across treatment groups with the use of a Bayesian beta-binomial model with noninformative prior distributions. The mean number of days receiving mechanical ventilation was compared across treatment groups with the use of a Bayesian linear-regression model with noninformative prior distributions.

†† The surgery effect was evaluated at discharge or 7 days, whichever occurred first.

‡‡ These data were analyzed with the use of a Bayesian ordinal logistic-regression model with noninformative prior distributions for known scores on the modified Rankin scale at 180 days; in the surgery group, for every 10% of blood removed or every 10 ml of blood removed, the outcome was more favorable.

gery after onset, size of the hematoma, and lesion location). After 175 patients had been enrolled (58% of the anticipated sample), the enrollment criteria were adapted, in accordance with the prespecified plan, to enroll only patients who had lobar hemorrhage, because the interim results for the anterior basal ganglia location met the futility criterion for surgery benefit.

Reduction in hematoma volume has been associated with improved survival and has been hypothesized to be associated with improved outcomes in previous studies.3,5 Approximately two thirds of patients in the surgery group had a hematoma volume of 15 ml or less after completion of surgery.1 Surgical hemostasis was durable, with few rebleeding events despite inclusion of patients with imaging findings of active contrast extravasation suggestive of active bleeding.23,24

We can make no conclusions with respect to the results being specific to the surgical technique we used, because there is no comparison group for different techniques. The surgical technique and trial design differed from that of previous randomized trials of conventional craniotomy,7,8 and catheter aspiration plus thrombolysis6 and of a small, uncontrolled study of minimally invasive trans-sulcal parafascicular surgery,7 and no claims can be made with respect to differences from results with conventional surgical approaches as used in previous trials. Early reduction in hematoma volume, hemostasis, intracranial pressure control, and amelioration of secondary inflammation are potential advantages of minimally invasive approaches that could minimize white-matter injury12; however, this trial did not test these hypotheses, and no claims are made about these issues. The trial also differed from previous trials of surgical evacuation of intracerebral hemorrhage by requiring intervention less than 24 hours after the onset of symptoms and by consideration of differential end points according to hemorrhage location. The STICH-II and STICH-II' trials (Surgical Trial in Intracerebral Haemorrhage I and II) informed our trial design by suggesting that results of surgical evacuation may differ by hemorrhage location. Previous reports7,8 and results from the MiSPACE (Minimally Invasive Subcortical Parafascicular Access for Clot Evacuation) registry have suggested that evacuation could be beneficial for lobar and anterior basal ganglia locations.

This trial has several important limitations.
ENRICH was an open-label trial and excluded patients with hematoma volumes less than 30 ml or more than 80 ml and hemorrhages with substantial thalamic or intraventricular extension; therefore, the results cannot be applied to hematomas with those volumes or situated in those locations. Because recruitment of patients with basal ganglia hemorrhages was halted for futility after relatively few patients had been enrolled, inferences of potential benefit in basal ganglia are limited. The method we used for calculation of hematoma volume is crude. To address this limitation, qualifying CT and follow-up neuroimaging were centrally adjudicated by neuroradiologists. The modified Rankin scale is widely used as a stroke outcome measure, and the utility-weighted scale that we used as the primary end point has been used in ischemic stroke trials that included some patients with intracerebral hemorrhage but has not been validated specifically for this purpose. Bayesian analyses have the potential to be overly influenced by the prespecified prior distributions. However, sensitivity analyses of the prior distributions suggested that the results of the primary analysis were consistent with the choice of reasonable alternative prior distributions (see the Supplementary Appendix).

In this trial of minimally invasive surgical evacuation of intracerebral hemorrhage of 30 to 80 ml within 24 hours after onset, weighted disability scores were better with surgery plus medical management than with medical management alone. The result was apparently attributable to intervention for lobar supratentorial hemorrhages.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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### Table 3. Safety End Points.‡

<table>
<thead>
<tr>
<th>End Point</th>
<th>Surgery Group (N = 150)</th>
<th>Control Group (N = 150)</th>
<th>Estimated Difference (95% Credible Interval)</th>
<th>Posterior Probability of Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death by 30 days — no. (%)</td>
<td>14 (9.3)</td>
<td>27 (18.0)</td>
<td>-8.7 (−16.4 to −1.0)</td>
<td>0.987</td>
</tr>
<tr>
<td>Postoperative rebleeding associated with neurologic deterioration — no. (%)†</td>
<td>5 (3.3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Change in hematoma volume — ml‡</td>
<td>-43.9±30.09</td>
<td>4.0±17.82</td>
<td>-47.91 (−53.59 to −42.36)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>One or more serious adverse events — no. (%)</td>
<td>95 (63.3)</td>
<td>118 (78.7)</td>
<td>-15.3 (−25.4 to −5.2)</td>
<td>0.998</td>
</tr>
<tr>
<td>Death in the hospital after randomization — no. (%)</td>
<td>7 (4.7)</td>
<td>19 (12.7)</td>
<td>-8.0 (−14.5 to −1.8)</td>
<td>0.994</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Percentages were compared across treatment groups with the use of a Bayesian beta-binomial model with noninformative prior distributions. Details regarding safety events are provided in Table S12.
† Rebleeding was defined as growth in hematoma volume between the initial CT and follow-up neuroimaging. Neurologic deterioration was defined as an increase of 4 or more points on the NIH stroke scale or a decrease of up to 2 points on the GCS that was not explained by planned medical interventions (e.g., sedatives, analgesics, and procedures).
‡ The absolute change in hematoma volume was calculated as the follow-up neuroimaging volume minus the baseline volume. This was a safety measure (i.e., increase in volume can be an early sign of inadequate surgical procedures). One value was missing in the control group.

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APPENDIX

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REFERENCES


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