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# Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy
## A Randomized Clinical Trial

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**IMPORTANCE** Optimal management of sedation and airway during thrombectomy for acute ischemic stroke is controversial due to lack of evidence from randomized trials.

**OBJECTIVE** To assess whether conscious sedation is superior to general anesthesia for early neurological improvement among patients receiving stroke thrombectomy.

**DESIGN, SETTING, AND PARTICIPANTS** SIESTA (Sedation vs Intubation for Endovascular Stroke Treatment), a single-center, randomized, parallel-group, open-label treatment trial with blinded outcome evaluation conducted at Heidelberg University Hospital in Germany (April 2014-February 2016) included 150 patients with acute ischemic stroke in the anterior circulation, higher National Institutes of Health Stroke Scale (NIHSS) score (>10), and isolated/combined occlusion at any level of the internal carotid or middle cerebral artery.

**INTERVENTION** Patients were randomly assigned to an intubated general anesthesia group (n = 73) or a nonintubated conscious sedation group (n = 77) during stroke thrombectomy.

**MAIN OUTCOMES AND MEASURES** Primary outcome was early neurological improvement on the NIHSS after 24 hours (0-42 [none to most severe neurological deficits; a 4-point difference considered clinically relevant]). Secondary outcomes were functional outcome by modified Rankin Scale (mRS) after 3 months (0-6 [symptom free to dead]), mortality, and peri-interventional parameters of feasibility and safety.

**RESULTS** Among 150 patients (60 women [40%]; mean age, 71.5 years; median NIHSS score, 17), primary outcome was not significantly different between the general anesthesia group (mean NIHSS score, 16.8 at admission vs 13.6 after 24 hours; difference, −3.2 points [95% CI, −5.6 to −0.8]) vs the conscious sedation group (mean NIHSS score, 17.2 at admission vs 13.6 after 24 hour; difference, −3.6 points [95% CI, −5.5 to −1.7]); mean difference between groups, −0.4 (95% CI, −3.4 to 2.7; $P$ = .82). Of 47 prespecified secondary outcomes analyzed, 41 showed no significant differences. In the general anesthesia vs the conscious sedation group, substantial patient movement was less frequent (0% vs 9.1%; difference, 9.1%; $P$ = .008), but postinterventional complications were more frequent for hypothermia (32.9% vs 9.1%; $P$ < .001), delayed extubation (49.3% vs 6.5%; $P$ < .001), and pneumonia (13.7% vs 3.9%; $P$ = .03). More patients were functionally independent (unadjusted mRS score, 0 to 2 after 3 months [37.0% in the general anesthesia group vs 18.2% in the conscious sedation group $P$ = .01]). There were no differences in mortality at 3 months (24.7% in both groups).

**CONCLUSIONS AND RELEVANCE** Among patients with acute ischemic stroke in the anterior circulation undergoing thrombectomy, conscious sedation vs general anesthesia did not result in greater improvement in neurological status at 24 hours. The study findings do not support an advantage for the use of conscious sedation.

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Supplemental content

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Several randomized clinical trials (RCTs) and an individual patient data meta-analysis have recently shown that thrombectomy using stent retrievers combined with standard treatment was more effective than standard treatment (most often including intravenous thrombolysis) alone for severe acute ischemic stroke caused by large-vessel occlusion in the anterior circulation.[1-6] International guidelines were recently updated to include recommendation of this treatment.[7,8] Choice of sedation and airway modes are among the unresolved issues in periinterventional management of thrombectomy.[9,10] Options include general anesthesia with intubation and mild (conscious) sedation or local anesthesia without intubation. Some interventionalists and stroke physicians prefer general anesthesia with intubation,[11-13] assuming it may be associated with less pain, anxiety, agitation and movement and lower aspiration risk.[11] Others favor conscious sedation to save time, evoke less hemodynamic instability, and risk fewer ventilation-associated complications.[9]

In the recent positive thrombectomy RCTs, general anesthesia was used in less than 40% of cases,[1,4,5] and it was used in less than 10% of cases in ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times)[2] and REVASCAT (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset),[3] which indicated a preference for conscious sedation. Moreover, several retrospective studies suggested that general anesthesia may be associated with lower reperfusion rates, more respiratory complications, higher mortality, and poorer functional outcome.[14] A recent posthoc analysis of MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) showed loss of thrombectomy superiority over intravenous thrombolysis if patients were treated while receiving general anesthesia vs nongeneral anesthesia.[15] Most of these studies, however, were not balanced for baseline parameters, carried risk of bias, and did not report procedural details on general anesthesia or conscious sedation. The recent THRACE (Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke) trial confirmed the superiority of combined intravenous thrombolysis and thrombectomy over intravenous thrombolysis alone with no significant effect of general anesthesia or conscious sedation, which were reported as secondary outcomes and used in balanced frequency by the centers.[16]

Given the current equipoise and expected increase in thrombectomy for patients with acute stroke, an RCT to address this question was considered timely and necessary. A single-center trial design was selected to allow for strict standardization in both treatment groups.

### Key Points

**Question** Does conscious sedation during stroke thrombectomy result in better early neurological improvement compared with general anesthesia?

**Findings** In this single-center randomized clinical trial, 150 patients with acute ischemic stroke were randomized to receive general anesthesia with intubation or conscious sedation without intubation during thrombectomy. There was no significant difference in the score change on the 42-point National Institutes of Health Stroke Scale between groups at 24-hour follow-up (−3.6 points for conscious sedation vs −3.2 points for general anesthesia).

**Meaning** Conscious sedation did not result in better early neurological outcome compared with general anesthesia.

## Methods

### Trial Design

SIESTA (Sedation vs Intubation for Endovascular Stroke Treatment) was a single-center, parallel-group, open-label RCT with blinded end point evaluation (PROBE [prospective, randomized, open, blinded end point] design). The details of the study protocol were published previously (trial protocol in Supplement 1).[17] In this trial, patients selected for thrombectomy were preliminarily randomized 1:1 (using sealed, opaque envelopes based on a computer-generated list not allowing for sequence guessing) to receive either conscious sedation or general anesthesia, standardized according to institutional treatment protocols (Supplement 1).

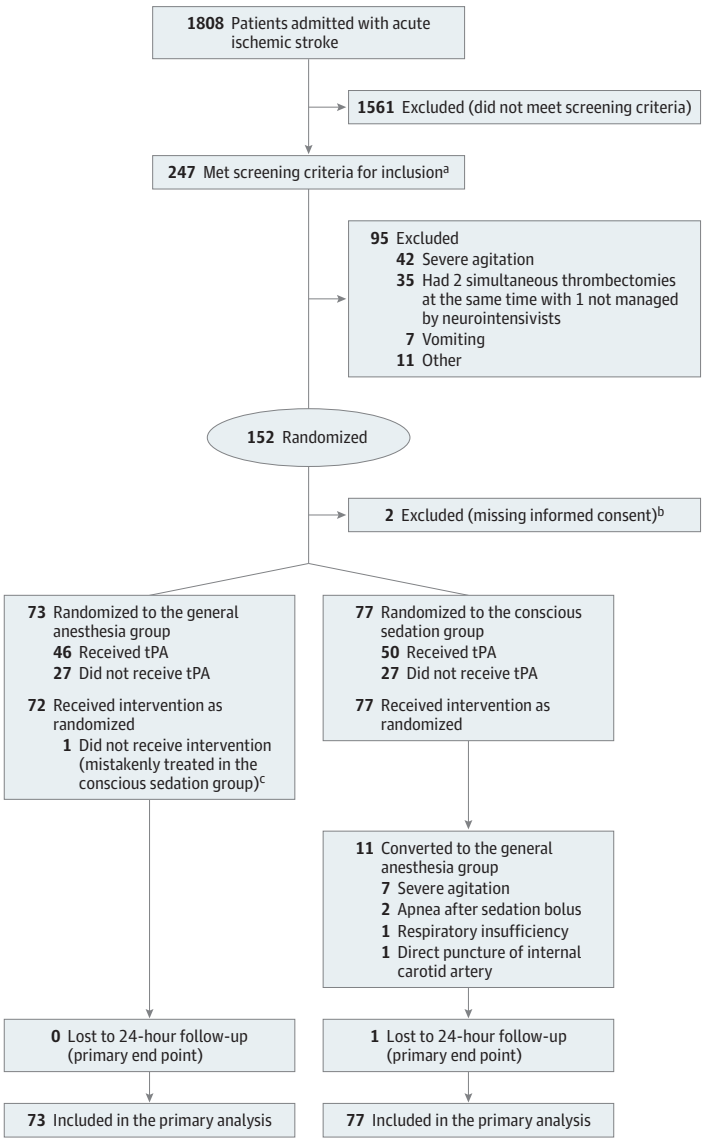
The study was performed using deferred consent for emergency circumstances research. Patients were allocated to the randomization group after meeting study entry criteria (**Figure 1**). Within the first 72 hours of treatment, explicit oral and written research informed consent was obtained from the patient or the patient's legal representative. Investigators evaluating the primary (early neurological improvement) and certain secondary outcomes (long-term functional outcome and causes of mortality) were blinded to allocation. The study protocol (Supplement 1) and the form of consent was approved by the institutional review board (Ethikkommission Medizinische Fakultät Heidelberg, ID S-650/2013).

### Patients

Patients with the following criteria were included: severe ischemic stroke defined by a National Institutes of Health Stroke Scale (NIHSS) score greater than 10 (range, 0-42 with higher scores indicating more severe neurological deficits [a difference of 4 points was considered to be clinically relevant]), isolated or combined occlusion at any level of the internal carotid artery or the middle cerebral artery, decision for thrombectomy according to the internal protocol for acute recanalizing stroke treatment of the Heidelberg University Hospital (Supplement 1) and at the discretion of the physician in charge.

Patients were excluded from the trial if diagnostic imaging results did not clearly depict site of vessel occlusion; their clinical or imaging findings suggested occlusion of a cerebral vessel that was not an internal carotid artery or a middle cerebral artery, or imaging showed intracerebral hemorrhage; coma at admission (Glasgow Coma Scale [GCS] score <8 [range, 3-15 points with 3 being the worst and 15 the best, composed of 3 parameters: best eye response, best verbal response, and best motor response]); severe agitation at admission (making groin and vascular access impossible); loss of airway-protective reflexes of at least absence of gag reflex, insufficient saliva handling, observed aspiration, vomiting, or a combination thereof

Figure 1. Flow of Participation in the SIESTA Trial of Conscious Sedation vs General Anesthesia During Thrombectomy




tPA indicates tissue-type plasminogen activator.

[a] Screening criteria for inclusion were severe acute ischemic anterior circulation stroke, as defined by the National Institutes of Health Stroke Scale score (>10 on a 0- to 42-point scale); decision for thrombectomy at the discretion of the physician in charge; nonintubation on admission; and noncandidacy for other intervention trial.

[b] One patient was randomized to the general anesthesia group, and 1 was randomized to the conscious sedation group. Both patients received the intervention.

[c] Indicates the only major protocol violation.

at admission; obviously or known difficult airway; or known intolerance of certain medications for sedation, analgesia, or both.

## Intervention

Thrombectomy technique, such as usage of a stent retriever or direct thrombus aspiration (all devices CE-marked [European conformity]), was chosen at the discretion of the interventionalist and adapted to occlusion site, vascular status (eg, vessel tortuosity, stenosis), and clot burden in each patient. The interventionalist announced reperfusion times and grades, and the neurointensivist documented these in the angiography protocol. Reperfusion grades were assessed according to the modified TICI (Thrombolysis in Cerebral Infarction) perfusion scale grade[18] (range, 0-3 [0, no antegrade flow beyond the occlusion; 1, minimal perfusion; 2a, perfusion of <50% of the vascular distribution of the occluded artery; 2b, perfusion of ≥50% of the vascular distribution of the occluded artery; 3, complete perfusion).

## Study Treatment

The study flow chart summarizes the main elements of the trial (eFigure 2 in Supplement 2). Peri-interventional management followed in-house protocols for general anesthesia or conscious sedation (Supplement 1). All randomized patients were noninvasively monitored for the same hemodynamic and respiratory targets. Patients in the conscious sedation group received intravenous, low-dose, short-acting analgesics and sedatives. Patients in the general anesthesia group received the same medication at higher doses or alternative or additional medications if necessary. In cases of interventional emergency or intolerable difficulty, respiratory failure, coma, or loss of airway-protective

reflexes, patients receiving conscious sedation were immediately converted to general anesthesia. After thrombectomy, all patients were first transferred to the neurological intensive care unit and soon thereafter to the stroke unit. After general anesthesia, extubation was aimed for as early as feasible, according to the in-house protocol for neurocritical care patients (eg, as soon as completely free of sedation, normothermic, fulfilling specified respiratory criteria).

### Study Outcomes

Evaluation of the primary outcome was performed by one of several NIHSS-certified examiners blinded to each patient's treatment group (4-point difference considered clinically relevant). Another blinded modified Rankin Scale–certified investigator not involved in patients' clinical treatment conducted a structured telephone interview[19] with the respective caregiver, institution, or patient at a mean (SD) time frame of 3 months (2 weeks) after stroke onset.

The primary outcome was early neurological improvement defined by change in NIHSS score between admission and a mean (SD) of 24 (3) hours. The NIHSS classifies neurological deficit on a scale from 0 (no deficit) to 42 (most severe deficit).[20] A score of 35 was assigned to patients intubated and receiving mechanical ventilation at the time of assessment.[21]

There were 52 prespecified secondary outcomes, including functional outcome at 3 months assessed by the modified Rankin Scale, which is a 7-point scale ranging from 0 (free of symptoms) to 6 (dead). Functional independence was defined as a modified Rankin Scale score of 0 to 2. Delayed extubation was defined as exceeding 2 hours after cessation of sedation and analgesia. Other secondary outcomes included in-hospital and 3-month mortality, peri-interventional safety (assessed by critical hypertension or hypotension, ventilation or oxygenation disturbance, and procedural complications [eg, vessel perforations]), and feasibility (assessed by substantial patient movement and difficulty of recanalization). Of the 52 prespecified secondary outcomes, 47 were analyzed, and there are plans for the 5 that were not analyzed (respiratory parameters, cerebral and systemic physiology monitor parameters, penumbra fate, relevant medication types, and treatment costs) to be reported separately after further analysis. No significant differences were shown for 41 of the prespecified secondary outcomes. All prespecified secondary outcomes are listed in the trial protocol (Supplement 1 and eAppendix 1 in Supplement 2).

### Statistical Analysis

Sample size was calculated to provide a 90% power to detect a treatment group difference of 4 points in NIHSS score from admission to 24-hour follow-up at a 2-sided significance level of .05 when applying a baseline NIHSS-adjusted analysis of covariance. A decrease of 4 points in the NIHSS score at 24 hours after treatment was defined and found to be clinically relevant on an individual patient's level in a similar setting.[22] Taking this consideration into account, a treatment group difference of 4 points was considered to be clinically relevant in SIESTA, and this difference was used as a basis for sample size calculation. A comprehensive literature search showed a high variability in the standard deviation of the NIHSS score at baseline (4.5-7.3 points)[23-26] and at 24-hour follow-up (4.5-6.7 points).[25]

To account for uncertainty associated with residual variance, an internal pilot study design was implemented.[27] Based on a preplanned interim analysis using the pooled data of the first 75 patients, residual variance was estimated in a blinded fashion and was used in the analysis of covariance sample size formula,[27,28] giving a total sample size of 150 patients.

The primary analysis was performed according to the intent-to-treat (ITT) principle. Adjusted treatment effects together with 95% CIs were calculated from the prespecified analysis of covariance model that included the NIHSS score at admission as covariate and that was applied for primary analysis. Sensitivity analyses comprised evaluation of the per-protocol population of those patients without major protocol violations and an as-treated analysis. Furthermore, primary outcome was analyzed in following prespecified subgroups: baseline NIHSS score (≤17 and >17); age (≤70 years and >70 years); sex (men and women); recombinant tissue-type plasminogen activator (tPA [yes and no]); ASPECTS (Alberta Stroke Program Early CT [computed tomographic] Score [<8 and 8-10]); and TICI score (2b/3).

Secondary outcomes were evaluated by descriptive data analysis.[29] Mean (SD) or median (interquartile range [IQR]) values were calculated for continuous outcomes, and absolute and relative frequencies were calculated for ordinal and categorical variables. For continuous variables, treatment-group differences were assessed by using the 2-sample *t* test based on original or log-transformed data. Ordinal variables were compared using the Mann-Whitney *U* statistic, and the $\chi^2$ test was used for analysis of categorical data. Statistical analyses were implemented using SAS software (SAS Institute Inc), version 9.4 and R software (R Development Core Team 2016),[30] version 3.2.2.

## Results

### Patient Characteristics

Of 1808 patients admitted between April 2014 and February 2016 with acute ischemic stroke, 247 who seemed to qualify for thrombectomy were screened for SIESTA. Of these, 150 patients were enrolled and randomized into the general anesthesia group (73 [48.6%]) or the conscious sedation group (77 [51.4%]). In the study population, mean age was 71.5 years, baseline median NIHSS score was 17, and 46 (63%) in the general anesthesia group and 50 (65%) in the conscious sedation group received intravenous thrombolysis with recombinant tPA. One patient who was randomized to the general anesthesia group was mistakenly treated under conscious sedation, representing the only major protocol violation (Figure 1). Twenty-eight patients received additional stenting of the proximal internal carotid artery because of high-grade stenosis (16 in the general anesthesia group and 12 in the conscious sedation group). Outcome-relevant risk factors were evenly distributed between the 2 treatment groups. Baseline, demographic, and clinical characteristics are displayed in **Table 1** and **Table 2**.

### Primary Outcome

Early improvement in neurological function was not significantly different between treatment groups. At 24-hour follow-up, the

Table 1. Baseline Demographics and Medical History

| Characteristic | No. (%) General Anesthesia (n = 73) | Conscious Sedation (n = 77) |
|---|---|---|
| Age, mean (SD), y | 71.8 (12.9) | 71.2 (14.7) |
| Women | 25 (34.2) | 35 (45.5) |
| Premedication | | |
| Antiplatelets | | |
| Aspirin | 16 (22.5) | 19 (26.0) |
| Clopidogrel | 0 | 1 (1.4) |
| Aspirin and clopidogrel | 4 (5.6) | 4 (5.5) |
| No | 51 (71.8) | 49 (67.1) |
| Missing data | 2 | 4 |
| Oral anticoagulants | | |
| Yes | 14 (19.7) | 17 (22.3) |
| No | 57 (80.3) | 59 (77.6) |
| Missing data | 2 | 1 |
| Statin | | |
| Yes | 23 (33.3) | 21 (28.0) |
| No | 46 (66.7) | 54 (72.0) |
| Missing data | 4 | 2 |
| Vascular risk factors | | |
| Hypertension | 53 (72.6) | 54 (70.1) |
| Atrial fibrillation | 36 (49.3) | 36 (46.8) |
| Hyperlipidemia | 20 (27.4) | 24 (31.2) |
| Heart failure | 17 (23.3) | 21 (27.3) |
| Diabetes mellitus | 17 (23.3) | 17 (22.1) |
| Smoking | 9 (12.3) | 13 (17.1)[a] |
| Peripheral artery occlusive disease | 4 (5.6)[b] | 6 (8.0)[b] |

[a] Percent is based on a denominator of 76 patients.

[b] Percent is based on a denominator of 71 patients for the general anesthesia group and a denominator of 75 for the conscious sedation group.

Table 2. Clinical Characteristics Assessed at Admission

| Characteristic | No. (%) General Anesthesia (n = 73) | Conscious Sedation (n = 77) |
|---|---|---|
| Pretreatment imaging | | |
| CT | 57 (78.1) | 57 (74.0) |
| MRI | 10 (13.7) | 16 (20.8) |
| CT and MRI | 6 (8.2) | 4 (5.2) |
| ASPECTS[a] | | |
| 10-8 | 52 (71.2) | 42 (56.7) |
| 7-6 | 16 (21.9) | 24 (32.5) |
| <6 | 5 (6.8) | 8 (10.8) |
| Median (IQR) | 8 (7-9) | 8 (6.25-9) |
| Missing data | 0 | 3 |
| Premorbid modified Rankin Scale[b] | | |
| 0 | 40 (54.8) | 39 (50.6) |
| 1 | 14 (19.2) | 19 (24.7) |
| 2 | 10 (13.7) | 13 (16.9) |
| >2 | 9 (12.3) | 6 (7.8) |
| NIHSS[c] | | |
| Mean (SD) | 16.8 (3.9) | 17.2 (3.7) |
| Median (IQR) | 17 (13-20) | 17 (14-20) |
| Glasgow Coma Scale[d] | | |
| 12 | 6 (8.2) | 3 (3.9) |
| 13 | 38 (52.1) | 41 (53.2) |
| 14-15 | 29 (39.8) | 33 (42.9) |
| Occlusion | | |
| Middle cerebral artery | 46 (63.0) | 47 (61.0) |
| M1 | 39 (53.4) | 43 (55.8) |
| M2 | 7 (9.6) | 4 (5.2) |
| Internal carotid artery | 1 (1.4) | 9 (11.7) |
| Internal carotid and middle cerebral artery | 26 (35.6) | 21 (27.3) |
| Internal carotid artery and M1 | 25 (34.2) | 21 (27.3) |
| Internal carotid artery and M2 | 1 (1.4) | 0 |
| Right-side occlusion | 28 (38.4) | 35 (45.5) |
| Reperfusion treatments | | |
| Intravenous thrombolysis and endovascular stroke treatment | 46 (63.0) | 50 (64.9) |
| Endovascular stroke treatment alone | 26 (35.6) | 27 (35.1) |
| No intervention | 1 (1.4) | 0 |
| Types of endovascular stroke treatment | | |
| Stent retriever | 60 (82.2) | 66 (85.7) |
| Direct aspiration | 6 (8.2) | 4 (5.2) |
| Cervical stent/angioplasty[e] | 16 (21.9) | 12 (15.6) |
| Onset-to-door time, mean (SD), min | 145.0 (83.8) | 118.1 (61.5) |

Abbreviations: ASPECTS, Alberta Stroke Program Early CT (computed tomography) Score; IQR, interquartile range, MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale.

[a] ASPECTS measures the extension of stroke; score range of 0 to 10 (higher scores indicating fewer early ischemic changes). ASPECTS assessed manually in 114 (76%) patients based on CT and 36 (24%) patients based on MRI.

[b] Modified Rankin Scale score range: 0 to 6 (0 = symptom free to 6 = dead).

[c] The NIHSS classifies neurological deficit from 0 (no deficit) to 42 (most severe).

[d] The Glasgow Coma Scale was scored between 3 and 15 points with 3 indicating the worst and 15 the best. It is composed of 3 parameters: best eye response, best verbal response, and best motor response.

[e] Indicates cervical stent and percutaneous transluminal angioplasty in combination with stent-retriever/aspiration-thrombectomy or stent alone.

mean NIHSS score decreased from 16.8 to 13.6 in the general anesthesia group, and decreased from 17.2 to 13.6 in the conscious sedation group. The mean difference in decline (adjusted for baseline NIHSS) between the groups was −0.4 (95% CI, −3.4 to 2.7; $P$ = .82; **Table 3**). No significant differences for the primary outcome were observed between the treatment groups in the sensitivity analyses (eTable 1 and eTable 2 in Supplement 2) or in any of the subgroup analyses, including the subgroup with successful reperfusion (TICI 2b/3; **Figure 2** and eTable 1 in Supplement 2). Eleven patients (9.2%) were intubated at the time of evaluation of NIHSS. Reasons for intubation were severe cerebral infarction with midline shift, additional cerebral hemorrhage, or both (n = 7); pneumonia (n = 3); and severe fluctuations of blood pressure including necessity of high-dose vasopressors (n = 1). One of these patients was converted from conscious sedation to general anesthesia during the intervention because of respiratory insufficiency, and 10 were primarily randomized to the general anesthesia group. Two of these were extubated after the intervention and had to be reintubated because of their severe cerebral lesions. All of these 11 patients required mechanical ventilation for more than 4 days after the intervention.

Table 3. Primary and Secondary Outcome Results

| Variable | General Anesthesia (n = 73) | Conscious Sedation (n = 77) | Difference (95% CI) | *P* Value[a] |
|---|---|---|---|---|
| **Primary Outcome** | | | | |
| Change in NIHSS[b], mean (95% CI) | −3.2 (−5.6 to −0.8) | −3.6 (−5.5 to −1.7) | −0.4 (−3.4 to 2.7) | .82[c] |
| Change in NIHSS, median (IQR) | −5.0 (−10.0 to 2.0) | −4.0 (−10 to 2.0) | | |
| NIHSS after 24 h, mean (SD) | 13.6 (11.1) | 13.6 (9.0) | 0.0 (−3.3 to 3.3) | >.99[d] |
| **Secondary Outcomes** | | | | |
| Clinical | | | | |
| Modified Rankin Scale after 3 mo, mean (SD) | 3.5 (1.9) | 3.7 (1.8) | 0.2 (3.3 to 3.9) | .41[e] |
| Modified Rankin Scale after 3 mo, median (IQR) | 4 (2 to 5) | 4 (3 to 5) | | |
| Modified Rankin Scale 0-2 after 3 mo, No. (%) | 27 (37) | 14 (18.2) | −18.8 (−32.8to−4.8) | .01[f] |
| In-hospital mortality, No. (%) | 5 (6.8) | 6 (7.8) | 0.9 (−7.4 to 9.3) | .83[f] |
| Mortality after 3 mo, No. (%) | 18 (24.7) | 19 (24.7) | 0.0 (−13.8 to 13.8) | >.99[f] |
| Logistics, mean (SD) | | | | |
| Length of stay in hospital, d | 5.9 (4.2) | 5.2 (4.0) | −0.7 (−2.0 to 0.6)[g] | .19[e] |
| Length of stay in intensive care unit, h | 71.6 (106.4) | 54.5 (82.2) | −17.0 (−50.4 to 15.0)[g] | .23[e] |
| Length of ventilation, h[h] | 30.9 (90.9) | 45.4 (126.8) | 14.5 (−31.6 to 173.3)[g] | .91[e] |
| Length of stay on stroke unit, h[i] | 87.4 (51.2) | 85.4 (46.9) | −2.0 (−20.9 to 15.3)[g] | .89[e] |
| Door-to-arterial puncture time, min | 75.6 (29.3) | 65.6 (19.9) | −10.0 (−19.2 to −2.9)[g] | .03[e] |
| Door-to-reperfusion time, min[j] | 165.2 (59.4) | 174.4 (56.3) | 9.2 (−10.0 to 28.5)[g] | .29[e] |
| Duration of EST, min | 111.6 (62.5) | 129.9 (62.5) | −18.2 (−38.4 to 2.0) | .04[e] |
| Feasibility of EST, No. (%)[k] | | | | |
| Reperfusion grade (TICI)[l] | | | | |
| 0-1 | 4 (5.5) | 7 (9.1) | | .68[l] |
| 2a | 4 (5.5) | 8 (10.4) | | |
| 2b | 30 (41.1) | 36 (46.8) | | |
| 3 | 35 (47.9) | 26 (33.8) | | |
| Substantial reperfusion grade 2b-3 (TICI) | 65 (89.0) | 62 (80.5) | −8.5 (−19.9 to 2.9)[l] | |
| Substantial patient movement[m] | 0 | 7 (9.1) | 9.1 (2.7 to 15.5) | .01[f] |
| Difficult vascular approach[n] | 6 (8.2) | 9 (11.7) | 3.5 (−6.1 to 13.0) | .48[f] |
| Other[o] | 5 (7.2) | 1 (1.4) | −5.8 (−12.5 to 0.9) | .09[f] |

*(continued)*

Table 3. Primary and Secondary Outcome Results (continued)

| Variable | General Anesthesia (n = 73) | Conscious Sedation (n = 77) | Difference (95% CI) | *P* Value[a] |
|---|---|---|---|---|
| Safety, No. (%) | | | | |
| Complications before EST | | | | |
| Incomplete cardiovascular monitoring | 1 (1.4) | 0 | −1.4 (−4.0 to 1.3) | .30[f] |
| Difficulties of arterial puncture | 0 | 1 (1.3) | 1.3 (−1.2 to 3.8) | .33[f] |
| Other complications[p] | 1 (1.4) | 0 | −1.4 (−4.0 to 1.3) | .30[f] |
| Complications during EST | | | | |
| Critical hypertension or hypotension (>180 mm Hg or <120 mm Hg) | 2 (2.7) | 0 | −2.7 (−6.5 to 1.0) | .14[f] |
| Critical ventilation or oxygenation disturbance[q] | 3 (4.1) | 3 (3.9) | −0.2 (−6.5 to 6.1) | .95[f] |
| Intervention-associated complications | 2 (2.7) | 2 (2.6) | −0.1 (−5.3 to 5.0) | .96[f] |
| Vessel perforation with ICH, SAH, or both | 1 (1.4) | 2 (2.6) | 1.2 (−3.2 to 5.7) | .59[f] |
| Allergic reaction after application of contrast agent | 1 (1.4) | 0 | −1.4 (−4.0 to 1.3) | .30[f] |
| Complications after EST | | | | |
| Hypertension or hypotension (>180 mm Hg or <120 mm Hg) | 17 (23.3) | 10 (13.0) | −10.3 (−22.6 to 2.0) | .10[f] |
| Hyperthermia or hypothermia (>37.2°C or <36.0°C) | 24 (32.9) | 7 (9.1) | −23.8 (−36.3 to −11.2) | <.001[f] |
| Delayed extubation[r] | 36 (49.3) | 5 (6.5) | −42.8 (−55.5 to −30.1) | <.001[f] |
| Ventilation-associated complications[s] | 10 (13.7) | 3 (3.9) | −9.8 (−18.8 to −0.8) | .03[f] |

Abbreviations: EST, endovascular stroke treatment; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage; TICI, Thrombolysis in Cerebral Infarction.

[a] All *P* values except for the primary outcome were unadjusted.

[b] The NIHSS classifies neurological deficit from 0 (none) to 42 (most severe).

[c] Adjusted estimates, 95% CIs, and 2-sided *P* value from analysis of covariance with NIHSS baseline value as covariate.

[d] Calculated using the *t* test but not on log-transformed data.

[e] Calculated using the *t* test, 2-sided, on log-transformed data.

[f] Calculated using the $\chi^2$ test, 2-sided.

[g] Bootstrap CIs were based on 10 000 iterations.

[h] 11 Converted from conscious sedation to general anesthesia and 72 for the general anesthesia group.

[i] 54 For the general anesthesia group and 64 for the conscious sedation group.

[j] 65 For the general anesthesia group and 69 for the conscious sedation group. Reperfusion was defined as a TICI score of 2b or 3.

[k] Indicates performance of the complete intervention, as planned, without technically related interruptions or delays for more than 30 minutes and without major complications

[l] TICI score range is 0 to 3 with 0 indicating no antegrade flow beyond the occlusion through 3, complete perfusion. The 95% CI indicates categories 2b and 3. *P* value calculated using $\chi^2$ test, was 2-sided for category 0 to 1 and 2a vs 2b and 3.

[m] Indicates repeated uncontrollable or unpredictable movement of the patient (especially head and neck) causing delay, pausing, interruption, or technical changes in the intervention, or any combination of the listed movements.

[n] Indicates difficulty in establishing a secure vascular access or introducing a guidewire or catheter or device due to anatomical, medical (or both) conditions causing substantial delay or termination of the intervention

[o] Indicates spontaneous recanalization (n = 4), severe disturbances with monitor installation (n = 1), or catheter tear-off in the middle cerebral artery (n = 1).

[p] Bronchospasm occurred in another patient with known chronic obstructive pulmonary disease before initiation of intubation.

[q] Prespecified as oxygen saturation <90% and end expiratory carbon dioxide <35 mm Hg or >45 mm Hg.

[r] Delayed extubation was prespecified as extubation >2 h after cessation of sedation and analgesia

[s] Ventilation-associated complications were prespecified as tube-related injury, pneumothorax, or ventilation-associated pneumonia (onset <48 hours after ventilation and included any kind of pneumonia [eg, community-acquired manifesting after admission, aspiration, or ventilation-associated pneumonia]).

## Secondary Outcomes

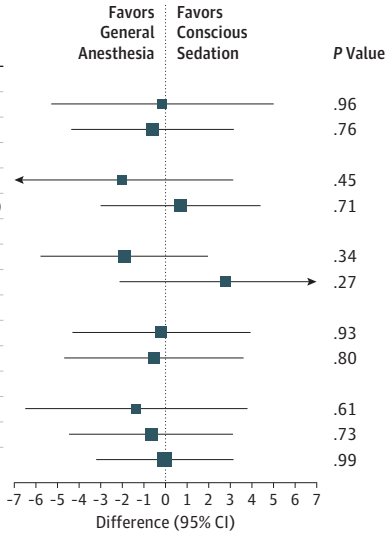
### Mortality and Long-term Function

Of the 52 prespecified secondary outcomes, 47 were analyzed and 41 showed no significant differences (Table 3). There was no significant difference in in-hospital mortality between the general anesthesia group (5 [6.8%]) and the conscious sedation group (6 [7.8%]) (rate difference, 0.9% [95% CI, −7.4% to 9.3%]; *P* = .83) or in mortality after 90 days between the general anesthesia group (18 [24.7%]) and the conscious sedation group (19 [24.7%]) (rate difference, 0.0% [95% CI, −13.8% to 13.8%]; *P* > .99).

Functional independence at 90 days, as reflected by a modified Rankin Scale score of 0 to 2, was significantly more frequent in the general anesthesia group (37%) than in the

Figure 2. Primary Outcome as the Improvement of NIHSS Score in Prespecified Subgroups[a]

| Subgroup | No. of Patients by Group | | Change in NIHSS Score | | Difference (95% CI) | P Value |
|---|---|---|---|---|---|---|
| | General Anesthesia | Conscious Sedation | General Anesthesia | Conscious Sedation | | |
| NIHSS score[b] | | | | | | |
| >17 | 30 | 31 | -3.4 (-7.5 to 0.8) | -3.5 (-6.9 to -0.2) | -0.14 (-5.29 to 5.01) | .96 |
| ≤17 | 43 | 46 | -3.1 (-6.1 to -0.1) | -3.6 (-6.0 to -1.2) | -0.60 (-4.36 to 3.16) | .76 |
| Age, y | | | | | | |
| ≤70 | 29 | 31 | -1.3 (-5.6 to 3.0) | -3.3 (-6.5 to -0.1) | -2.01 (-7.15 to 3.13) | .45 |
| >70 | 44 | 46 | -4.5 (-7.4 to -1.6) | -3.8 (-6.2 to -1.3) | 0.70 (-3.01 to 4.40) | .71 |
| Sex | | | | | | |
| Men | 48 | 42 | -1.7 (-4.9 to 1.5) | -3.6 (-5.8 to -1.4) | -1.91 (-5.79 to 1.97) | .34 |
| Women | 25 | 35 | -6.2 (-9.7 to -2.7) | -3.5 (-7.0 to -0.1) | 2.75 (-2.13 to 7.64) | .27 |
| Recombinant tissue-type plasminogen activator | | | | | | |
| No | 27 | 27 | -3.4 (-6.4 to -0.3) | -3.4 (-6.4 to -0.5) | -0.19 (-4.31 to 3.94) | .93 |
| Yes | 46 | 50 | -3.1 (-6.6 to 0.3) | -3.7 (-6.2 to -1.1) | -0.54 (-4.69 to 3.61) | .80 |
| ASPECTS score[c] | | | | | | |
| <8 | 21 | 32 | -1.0 (-6.0 to 3.9) | -2.4 (-5.3 to 0.6) | -1.35 (-6.49 to 3.80) | .61 |
| 8-10 | 52 | 42 | -4.1 (-6.9 to -1.3) | -4.8 (-7.4 to -2.3) | -0.67 (-4.46 to 3.12) | .73 |
| TICI 2b/3[d] | 65 | 62 | -4.7 (-7.1 to -2.4) | -4.8 (-6.9 to -2.6) | -0.03 (-3.21 to 3.15) | .99 |




Size of the data markers is proportional to the precision of the estimates (ie, the area is proportional to the inverse of the squared standard errors).

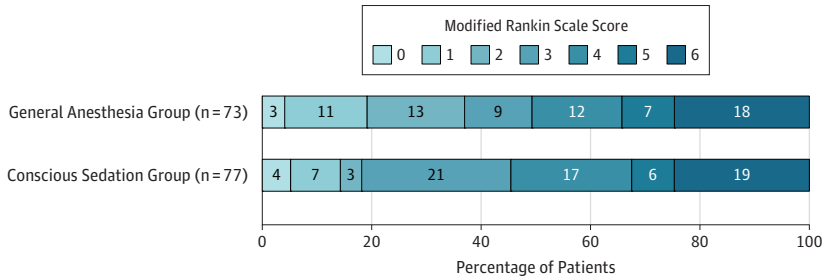
[a] For the detailed analysis of the prespecified subgroups see eTable 11 in Supplement 2.

[b] The National Institutes of Health Stroke Scale (NIHSS) ranges from 0 to 42 with higher scores indicating more severe neurological deficits.

[c] ASPECTS (Alberta Stroke Program Early CT [computed tomographic] Score) is a measure of the extension of stroke. Scores range from 0 to 10 with higher scores indicating fewer early ischemic changes.

[d] The TICI (Thrombolysis in Cerebral Infarction) scale ranges from 0 to 3 (0 indicates no antegrade flow beyond the occlusion; 1, minimal perfusion; 2a, perfusion of less than 50% of the vascular distribution of the occluded artery; 2b, perfusion of at least 50% of the vascular distribution of the occluded artery; 3, complete perfusion).

Figure 3. Functional Outcome at 90-Day Follow-up in the Intent-to-Treat Population




Modified Rankin Scale range, 0 to 6 (0, no symptoms; 1, no clinically relevant disability; 2, slight disability [able to look after own affairs without assistance but not to the full extent]; 3, moderate disability [requires some help but able to walk unassisted]; 4, moderately severe disability [requires assistance and unable to walk unassisted]; 5, severe disability [requires constant nursing care]; 6, dead). Distribution of modified Rankin Scale categories were additionally tested using the Mann-Whitey *U* (Wilcoxon) statistic (*P* = .41).

conscious sedation group (18.2%) (rate difference, -18.8% [95% CI, -32.8% to -4.8%]; *P* = .01), but post-hoc analysis showed the differences for a modified Rankin Scale score of 0 to 1 (19.2% in the general anesthesia group vs 14.3% in the conscious sedation group; rate difference, 4.9% [95% CI, -7.1% to 16.8%]; *P* = .42) and for a modified Rankin Scale score of 0 to 3 (49.3% in the general anesthesia group vs 45.5% for the conscious sedation group; rate difference, 3.9% [95% CI, -12.1% to 19.8%]; *P* = .64) were not significant between the groups. Table 3 summarizes all clinical primary and secondary outcomes. **Figure 3** presents the modified Rankin Scale scores after 90 days.

### Peri-interventional Feasibility and Safety

The analysis of prespecified feasibility criteria did not yield any significant differences between the groups, except that substantial patient movement was less frequent in the general anesthesia group (0%) than in the conscious sedation group (9.1%) (rate difference, 9.1% [95% CI, 2.7% to 15.5%]; *P* = .008). Likewise, prespecified safety criteria, complications, or both showed no statistically significant differences before or during the intervention (for detailed descriptions of the complications that were well-balanced between the 2 groups, see eAppendix 2, eTable 3, and eTable 4 in Supplement 2). The analysis

of the postprocedural period, however, revealed significantly more complications in the general anesthesia group: more hypothermia (32.9% vs 9.1%; rate difference, −23.8% [−36.3% to −11.2%]; $P < .001$), delayed extubation (49.3% vs 6.5%; rate difference, −42.8% [−55.5% to −30.1%]; $P < .001$), and pneumonia (13.7% vs 3.9%; rate difference, −9.8% [−18.8% to −0.8%]; $P = .03$) than in the conscious sedation group (Table 3 and eTable 3 in Supplement 2).

Conscious sedation was converted to general anesthesia in 11 patients (14.3%) due to severe agitation (n = 7), apnea after sedation bolus (n = 2), respiratory insufficiency (n = 1), and elective intubation for direct puncture of the proximal internal carotid artery (n = 1) (eTable 5 in Supplement 2).

Most findings in time intervals and process durations were not significantly different between study groups. However, a mean 10-minute time gain in favor of conscious sedation was found for door-to-arterial puncture time in the conscious sedation group (mean difference, −10.0 [95% CI, −19.2 to −2.9], $P = .03$). Achievement of successful reperfusion (TICI grades 2b and 3) was not significantly different between the study groups (89.0% in the general anesthesia group vs 80.6% in the conscious sedation group) (rate difference, −8.5% [95% CI, −19.0% to 2.9%]; $P = .67$; Table 3).

Mean systolic blood pressure during the intervention (144.9 mm Hg in general anesthesia vs 147.2 mm Hg in conscious sedation; $P = .34$) as well as the variability of systolic blood pressure (9.8 mm Hg in general anesthesia vs 8.9 mm Hg in conscious sedation; $P = .32$) were not significantly different between the 2 treatment groups. Nearly 50% of all documented measurements per patient of the systolic blood pressure in both groups were within the narrow range targeted by protocol (140 mm Hg-160 mm Hg) (47.2% for the general anesthesia group vs 49.4% for the conscious sedation group; $P = .59$; eTable 6 and eTable 7 in Supplement 2).

## Discussion

In this single-center RCT, 150 patients with acute ischemic stroke in the anterior circulation were randomized to receive either general anesthesia with intubation or conscious sedation without intubation during thrombectomy. Early neurological improvement, according to NIHSS score change after 24 hours, was not significantly better for patients in the conscious sedation group.

To the best of our knowledge, this study is the first RCT evaluating the peri-interventional management of stroke thrombectomy. The strengths of the study include (1) standardized treatment in both groups for achieving comparability; (2) good balance of baseline characteristics between the study groups; (3) robust data regarding many prespecified feasibility and safety criteria from a broad practice setting; and (4) very few missing data with no patient loss to follow-up.

The findings of SIESTA were in contrast to data from several retrospective studies that strongly suggested that general anesthesia for thrombectomy decreases neurological recovery and increases morbidity and mortality compared with conscious sedation.[14,31] Pathophysiological considerations supporting this include general anesthesia-associated hypotension and hypocapnia, the latter potentially causing cerebral vasoconstriction.[9,31-34] Conversely, it was proposed that insufficient airway protection in nonintubated patients with acute ischemic stroke may lead to higher aspiration rates and, subsequently, pneumonia in these patients. All previous studies addressing this question had been retrospective, hence reported associations only and were prone to selection bias since general anesthesia was often chosen for the patients with more severe illness. Moreover, these studies did not report protocols or details on peri-interventional management, limiting their potential to clarify the controversy and to compare with our findings.

The main objectives of SIESTA were to determine whether conscious sedation was superior to general anesthesia with regard to early neurological improvement and to assess short-term differences of the peri-interventional clinical course, feasibility, and safety between conscious sedation and general anesthesia in a balanced group of patients with major ischemic stroke undergoing thrombectomy. The patient population in this trial shares many characteristics with those of the prior thrombectomy RCTs. However, patients with poorer premorbid condition could be enrolled and decisions for thrombectomy were not based strictly on predefined clinical or radiological selection processes. The SIESTA population and setting, therefore, better reflect broad practice; hence, clinical outcomes cannot be expected to mirror the HERMES meta-analysis.[6] If at all, this study population may be fairly comparable with the MR CLEAN population, which had less rigid inclusion criteria.[1] By adhering to protocols for work flow, monitoring, set-up, and physiological parameter targets in both groups of SIESTA, only few significant differences were observed in the secondary outcomes regarding timing, feasibility, and safety. For example, similar to the results of previous studies,[24,35,36] a conversion rate from conscious sedation to general anesthesia of only 14% was observed and may support the approach of starting the intervention in conscious sedation. Patients who were converted to receiving general anesthesia on an emergency basis did not develop more complications or have longer stays in the intensive care unit (eTable 9 and eTable 10 in Supplement 2). Delay in starting the intervention was previously proposed as an important disadvantage of general anesthesia.[23] Berkhemer et al found, in a post-hoc analysis of MR CLEAN, that a general anesthesia-related time delay of 32 minutes was associated with worse outcome.[15] In SIESTA, the mean delay in door-to-arterial puncture time by general anesthesia was only 10 minutes. Moreover, this was possibly offset by a trendwise shorter door-to-reperfusion time in general anesthesia (9.2 minutes [not significant]). The relevance of the higher postprocedural frequency of pneumonia in the general anesthesia group, most probably related to intubation and ventilation and in line with previous studies,[37,38] remains uncertain given that pneumonia was treated with antibiotics immediately upon detection per in-house standards.

With regard to the primary outcome of early neurological improvement, conscious sedation was not superior to general anesthesia. Decrease in NIHSS score after 24 hours was previously applied as an early outcome variable and correlated

with long-term outcome in stroke studies.[14,22,23,25,26,39] Decrease in NIHSS score after 24 hours was also reported in prior thrombectomy RCTs and ranged from 5 to 13[1-5] in the intervention groups. In comparison, the NIHSS score decrease in SIESTA may appear quite small, barely reaching the widely accepted difference of 4 points of the NIHSS that is thought to be clinically meaningful.[40] However, the inclusion criteria of this trial allowed a broader patient population to undergo the procedure without strict radiological selection (eg, according to collateral status); hence, early NIHSS changes in the magnitude reported in the HERMES meta-analysis could not be expected. Assignment of NIHSS scores of 35 to patients (still) being intubated or reintubated at the time of assessment is a potential confounder but was only necessary in 11 patients, mostly caused by cerebral deterioration after unsuccessful reperfusion. Sensitivity analysis excluding these patients revealed no statistically significant difference (eTable 1 in Supplement 2).

Unadjusted long-term outcome was better in patients in the general anesthesia group, with 37% achieving independence after 3 months compared with 18.2% in the conscious sedation group. This is in contrast to what retrospective studies suggested for general anesthesia.[14,15] However, since the difference in modified Rankin Scale score of 0 to 2 was not paralleled by a consistent shift over all modified Rankin Scale categories, this result should be interpreted with caution. Of note, SIESTA was not powered and designed to primarily investigate long-term functional outcome, and slight imbalances in ASPECTS and reperfusion grades, although not reaching statistical significance, may still have influenced that result, possibly reflecting that local interventionalists performed slightly better for patients in general anesthesia, which was the preferred sedation regimen in the years before the study. However, this finding is a signal to suggest that the concern about worse outcome after general anesthesia, based on retrospective comparisons, may not be justified. In essence, the findings from SIESTA do not support superiority of conscious sedation over general anesthesia on short-term peri-interventional management, mortality, and long-term outcome.

These findings suggest that, clinically, both peri-interventional regimens for thrombectomy appear applicable, provided strict protocols are in place and performed by physicians trained in this setting. To start the thrombectomy procedure using conscious sedation may allow better clinical monitoring of recanalization success or complications and may save time.[41] This approach appears reasonable as long as contraindications, such as severe agitation, vomiting, or coma with loss of airway-protective reflexes are absent and an immediate conversion to general anesthesia is possible. In that case general anesthesia may be equally feasible. It would be desirable to avoid emergency conversion to general anesthesia by using primary general anesthesia according to certain clinical or radiological predictors that need to be identified by further research. A multicenter future RCT, including at least basic agreement on standards, directed at functional outcome after 3 months and such predictors, and possibly designed to compare 3 groups (general anesthesia, conscious sedation, and no sedation), would be desirable.

This study has several limitations. First, SIESTA was a single-center study, and the results cannot be generalized. Patients were treated by neurointensivists trained in the interventional setting and a specialized neurocritical care nursing team according to standard operating procedures established over years and continuously adapted to local conditions. Second, since general anesthesia was generally more frequently used before study inception, personnel had more experience with that regimen, which may have put the general anesthesia group at an advantage not fully reflected by the secondary outcomes we chose. The small sample size may have further limited study power to detect moderate but clinically relevant differences in outcome. Third, by including older premorbid patients without strict radiological selection and who had considerably longer times to reperfusion than in some other thrombectomy reference trials, outcomes may have been overall worse and smaller effects of general anesthesia or conscious sedation masked. Fourth, the primary outcome was assessed quite early after the procedure, risking that some patients may not have sufficiently recovered from the intervention, sedatives, or both and may not have been extubated after 24 hours. Fifth, current definitions of general anesthesia and conscious sedation are heterogeneous and allow for a very diverse choice of drugs and measures. This trial tested 2 possible ways of applying general anesthesia and conscious sedation, deliberately using the same drugs in both study groups at different doses, with intubation being the most decisive difference. The option of using no sedation, which is potentially time-saving and practiced in some centers, was also not addressed in this study but may be worth investigating.

## Conclusions

Among patients with acute ischemic stroke in the anterior circulation undergoing thrombectomy, the use of conscious sedation compared with general anesthesia did not result in greater improvement in neurological status at 24 hours. The study findings do not support an advantage for the use of conscious sedation.

ARTICLE INFORMATION

**Correction:** This article was corrected online on February 7, 2017, for incorrect information in Table 3.

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**Author Contributions:** Drs Bösel and Schönenberger had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Möhlenbruch and Bösel contributed equally.

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