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# Aspirin Continuation or Discontinuation in Surgically Treated Chronic Subdural Hematoma
## A Randomized Clinical Trial

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**IMPORTANCE** Discontinuation of low-dose acetylsalicylic acid (ASA) during the perioperative phase of treatment for chronic subdural hematoma (cSDH) may reduce recurrence rates but may also increase the risk of cardiovascular or thromboembolic events. However, the efficacy and safety of discontinuing ASA in this patient population remain unclear.

**OBJECTIVE** To assess the risk of recurrence of cSDH and cardiovascular events in patients undergoing surgical treatment of cSDH with continuous vs discontinuous ASA treatment.

**DESIGN, SETTING, AND PARTICIPANTS** The SECA (Surgical Evacuation of Chronic Subdural Hematoma and Aspirin) trial was an investigator-initiated, multicenter, placebo-controlled randomized clinical trial conducted from February 2018 to June 2023 at 6 neurosurgical centers in Switzerland. Adults undergoing burr hole drainage for cSDH and receiving ASA treatment prior to cSDH onset were included. Of 1363 screened patients, 155 were included. Both assessors and participants were blinded to the treatment arms.

**INTERVENTION** Participants were randomized 1:1 to receive either continuous ASA or placebo for 12 days during the perioperative phase.

**MAIN OUTCOME AND MEASURES** The main outcome was the recurrence rate of cSDH necessitating reoperation within 6 months. An intention-to-treat analysis was performed, calculating risk differences. Secondary outcomes were cardiovascular or thromboembolic events, other bleeding events, and mortality.

**RESULTS** Of 155 participants, 78 were assigned to continuous ASA and 77 to placebo treatment. The mean (SD) participant age was 77.9 (8.2) years and 77.6 (9.7) years for the ASA and placebo groups, respectively, and 25 participants (16.1%) were female. A primary outcome event occurred in 13.9% of participants for the ASA group and 9.5% for the placebo group (weighted risk difference, 4.4%; 95% CI, −7.2% to 15.9%; $P = .56$). The incidence of any cardiovascular or thromboembolic event was 0.27 per person half-year in the ASA group and 0.28 in the placebo group. The incidence of a cardiovascular event indicating ASA treatment was 0.02 per person half-year in the ASA group and 0.06 in the placebo group. Other bleeding events showed an incidence of 0.10 per person half-year in the ASA group and 0.08 in the placebo group. All-cause mortality occurred at an incidence of 0.06 per person half-year in the ASA group and 0.03 in the placebo group.

**CONCLUSIONS AND RELEVANCE** The SECA randomized clinical trial suggests that discontinuing ASA treatment did not reduce the recurrence rate of surgically treated cSDH within 6 months. Recurrence risk estimates for continuous ASA treatment in this trial were distinctly lower than previously reported.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT03120182

Supplemental content

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Low-dose acetylsalicylic acid (ASA) is widely prescribed for treating and reducing the risk of cardiovascular events.[1-4] Chronic subdural hematoma (cSDH) is a common neurosurgical condition, which is particularly prevalent in individuals aged 65 years and older.[5] Consequently, a substantial proportion of patients presenting with cSDH are concurrently receiving ASA therapy.[6]

This overlap between patients needing surgical treatment for cSDH and those receiving ASA therapy presents a significant medical dilemma. On one hand, continuing ASA during the perioperative phase of cSDH treatment is estimated to increase recurrence rates from 7% to 10% to 25% to 33%.[7,8] On the other hand, discontinuing ASA may elevate the risk of postoperative cardiovascular events, including nonfatal myocardial infarction, cardiac arrest, and cardiac death.[9,10] The in-hospital mortality rate due to perioperative myocardial infarction ranges from 15% to 25%.[10-12]

Despite the high incidence of patients receiving ASA treatment presenting with symptomatic cSDH, there is a lack of high-quality data assessing the effects of continuing vs discontinuing ASA treatment in those undergoing surgical treatment of cSDH.[13,14] Historically, most clinical studies evaluating bleeding risks with continuous ASA treatment during the perioperative period have excluded neurosurgical patients.[10,15-17] Surveys indicate that in surgically treated cSDH cases, most physicians prefer to discontinue and/or reverse ASA therapy perioperatively for 12 to 30 days due to concerns about elevated risks of recurrence or intracranial bleeding.[18]

To address this gap, the SECA (Surgical Evacuation of Chronic Subdural Hematoma and Aspirin) randomized clinical trial was conducted. The trial aimed to assess the risk of recurrence of cSDH and cardiovascular events in patients undergoing surgical treatment of cSDH with continuous vs discontinuous ASA treatment.

### Key Points

**Question** Does discontinuation of low-dose acetylsalicylic acid (ASA) during the perioperative phase of surgical treatment of chronic subdural hematoma (cSDH) reduce recurrence rates?

**Findings** In this randomized clinical trial of 155 adults, the proportion with recurrence of cSDH at 6 months was 13.9% in the ASA group and 9.5% in the placebo group, showing no statistical difference.

**Meaning** Discontinuing ASA treatment did not seem to reduce the recurrence rate of surgically treated cSDH within 6 months, while recurrence risk estimates for continuous ASA treatment in this trial were distinctly lower than previously reported.

## Methods

### Trial Design and Oversight

This national multicenter trial was overseen by the Department of Neurosurgery at the University Hospital of Basel and was funded by the Swiss National Science Foundation and others. The trial protocol has been published previously[19] and is available in Supplement 1. The protocol was approved by all responsible national ethics committees (EKNZ 2016-02003). The participant, their next of kin or other legal representative, or an independent physician provided written informed consent before enrollment. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonization E6 requirements and the Declaration of Helsinki.

The trial design, analysis, and data collection were overseen by the leading center. Site investigators gathered the data. Data analysis was performed by a trial statistician (M.C.) who attests to the integrity of the analysis and the accuracy and completeness of the reported data. The leading center and all investigators guarantee the accuracy and completeness of the data, adherence to the trial protocol, and precise reporting of adverse events. There was no industry involvement in the trial.

### Participants

The trial was conducted at 6 neurosurgical centers in Switzerland. Eligible patients were male or female, older than 18 years, receiving ASA treatment, and presented with a symptomatic cSDH diagnosed by computed tomography (CT) and/or magnetic resonance imaging (MRI) requiring surgical evacuation. Participants treated with additional anticoagulant or antithrombotic agents were also included, with the management of these agents defined within the trial protocol (eTable 1 in Supplement 3). Patients treated with surgical techniques other than burr hole drainage (eg, craniotomy), those with cSDH caused by a preexisting condition (eg, overdrainage of a ventriculoperitoneal shunt), or those without informed consent were excluded. Additionally, patients with major cardiac events (eg, unstable angina, myocardial infarction, or coronary revascularization) or active bleeding events within 30 days prior to randomization and patients with known bleeding disorders (eg, hemophilia) were excluded from the study. Detailed eligibility criteria are provided in the trial protocol (Supplement 1).

### Trial Treatment

Participants were randomly assigned in a 1:1 ratio to either continuous ASA treatment (100 mg/day, ASA group) or a 12-day placebo treatment (placebo group) using a centralized web-based system. Both the placebo and ASA were provided in identical blister packs to facilitate double-blind outcome assessment. The study medication was administered on the first postoperative day for emergency operations occurring the same day, preoperatively for emergency operations scheduled 24 hours after the last ASA intake, and 5 days prior to the operation for elective surgeries. The study medication was administered for 12 days, after which ASA treatment was resumed. The surgical procedure involved 2-burr hole trephination, hematoma evacuation via rinsing, and insertion of a drain, without any other adjuvant therapies. Prophylactic anticonvulsant medication was not used, but all participants received a single dose of antibiotics 30 minutes before the skin incision. Bilateral hematomas were treated as a single case, with both

sides receiving identical surgical treatment. If the surgeon determined intraoperatively that a craniotomy was necessary (eg, due to a clotted hemorrhage that could not be adequately evacuated through burr hole drainage), the participant was excluded from the trial.

## Outcomes

The primary outcome was recurrence of the cSDH within 6 months after randomization. Recurrent cSDH was defined as an ipsilateral hematoma observed on a CT scan that required surgical evacuation due to symptoms. Secondary outcomes assessed at 6 months included cardiovascular or thromboembolic events, intracranial bleeding events, clinical outcomes, radiological outcomes, and mortality. Adverse events were monitored for 6 months and categorized as mild, moderate, or severe. Cardiovascular events included perioperative myocardial infarction or injury (PMI), defined as a rise in high-sensitivity cardiac troponin T concentration of at least 0.014 ng/mL above preoperative concentrations (to convert troponin T from ng/mL to µg/L, multiply by 1)[20]; ST-segment elevation myocardial injury (STEMI); non-ST-elevation myocardial infarction (NSTEMI); cerebrovascular insult (CVI); peripheral arterial occlusion (PAO); deep vein thrombosis (DVT); or pulmonary embolism (PE). Additionally, the events were dichotomized into cardiovascular or cerebrovascular events (including PMI, STEMI, NSTEMI, CVI, and PAO) and thromboembolic events (including DVT and PE). Major cardiovascular or cerebrovascular events were defined as all cardiovascular or cerebrovascular events, excluding PMI. Further, cardiovascular or cerebrovascular events indicating initiation of ASA treatment were documented. Bleeding events included any type of intracranial bleeding other than recurrent cSDH. Postoperative anemia was defined as hemoglobin less than 0.0008 g/dL at any point during the study medication period (to convert hemoglobin from g/dL to g/L, multiply by 10) or the need for intraoperative or postoperative blood transfusion. Clinical outcome was assessed using the modified Rankin scale (mRS), dichotomized into favorable (mRS 0-2) and unfavorable (mRS 3-6) outcomes; the Glasgow Outcome Scale (GOS), dichotomized into favorable (GOS 4-5) and unfavorable (GOS 1-3) outcomes; and the Markwalder score.[21-23]

## Statistical Analysis

Existing literature at the time of study planning suggested that continuation of ASA during the perioperative phase of cSDH increases recurrence rates from 7% to 10% to 25% to 33%. Assuming a 28% recurrence rate under ASA, the sample size was set to identify an absolute difference of 18% in recurrence rates between the study arms (ie, reducing risk to 10% with placebo) at a 2-sided significance level of 5%. Using a resampling procedure in which different sample sizes were each evaluated 999 times by drawing random samples of events based on these assumptions and examining whether the 2-sided 95% confidence interval for the difference in proportions between the arms contains 0, it was concluded that 142 participants should be randomized to ensure 80% power to identify the effect. Due to a 10% dropout rate observed after randomizing 142 patients, the ethics committee approved the inclusion of an additional 15 participants, raising the final number of participants randomized to 157.

The primary outcome of interest was the difference in recurrence rates between participants treated with ASA and those treated with placebo. All enrolled participants were analyzed according to their assigned treatment regardless of loss to follow-up or protocol violations, such as incomplete adherence to medication. The difference in 6-month recurrence rates was calculated using inverse probability of censoring weights (IPCW) to account for participants who did not have a final follow-up observation due to withdrawal of consent or death. Censoring weights were derived from a logistic regression model that included predetermined potential confounders as predictors (Supplement 1). Observed participants were reweighted based on their censoring probability, and the difference in weighted proportions was calculated, along with its 95% confidence intervals, using Yates continuity correction. A $\chi^2$ test was then performed on the weighted data to obtain a $P$ value. $P < .05$ was considered significant.

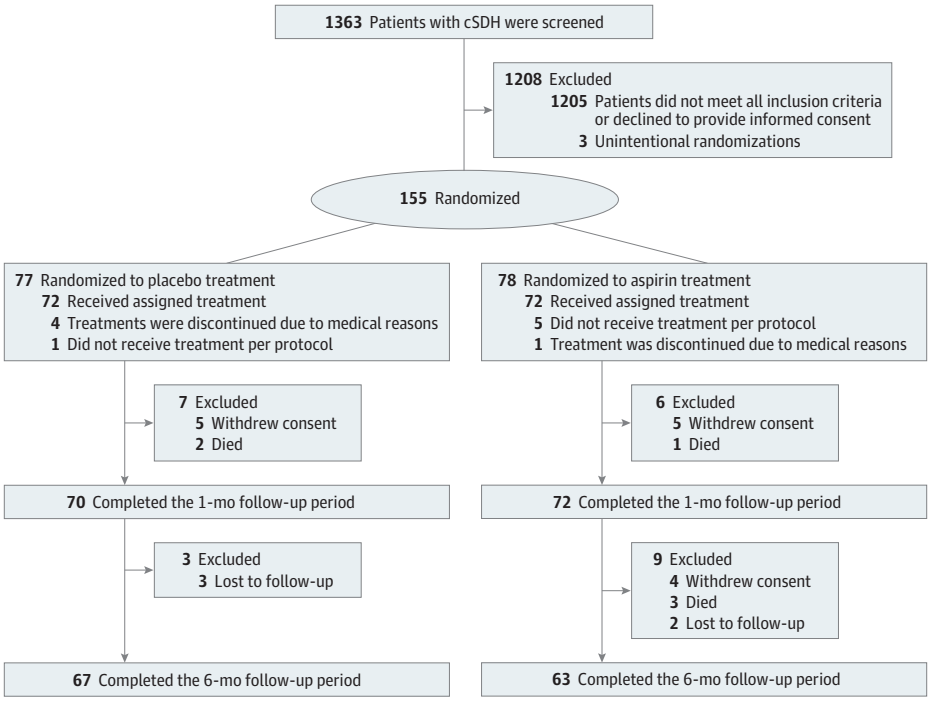
In addition to the primary outcome, other estimands of interest were defined, all focused on the IPCW-weighted risk difference between ASA treatment and placebo in various analysis sets or for specific composite end points. These include the difference in 6-month cSDH recurrence rates between those receiving ASA or placebo treatments as per protocol, the effect of ASA treatment on the composite outcome of recurrence or loss to follow-up for any reason, and the effect of ASA on the composite outcome of recurrent cSDH or any bleeding event. Additional sensitivity analyses are detailed in the report and analysis plan in Supplement 1, as well as in the eAppendix in Supplement 3.

As a secondary analysis, the time to recurrence up to 6 months was examined using a Fine-Gray competing risks regression model, considering withdrawal of consent, loss to follow-up, or death as competing risks. The cumulative incidence function and the subdistribution hazard ratio (HR) are presented. Predefined subgroup analyses used Fine-Gray models to test the interaction between subgroups and treatment, providing within-subgroup HRs for ASA vs placebo. Time-to-event analyses reporting incidence rates and fitting cause-specific Cox proportional hazards models to obtain HR, censoring patients at their last observation if an event was not observed, were performed for other predefined secondary outcomes, including other bleeding events, cardiovascular or cerebrovascular and TE events, and mortality. For clinical outcome, descriptive statistics are provided. Full details of the statistical analysis are provided in Supplement 1.

# Results

A total of 1363 patients were screened, and 157 participants were enrolled at 6 sites in Switzerland between February 2018 and June 2023. The distribution between the trial groups is shown in **Figure 1**. Of these participants, 2 were excluded from the analysis: 1 withdrew consent prior to any study-related interventions, and 1 underwent randomization but did not meet the inclusion criteria. This resulted in 155 participants in the full

Figure 1. Flowchart of the Participants in the Intention-to-Treat Population




The screening list for 1 center was collected retrospectively. cSDH indicates chronic subdural hematoma.

analysis set, with 77 randomized to the placebo group and 78 to the ASA group. At the 6-month follow-up, 3 participants in the placebo group and 2 in the ASA group were lost to follow-up. Additionally, 2 participants in the placebo group and 4 in the ASA group died during the trial period, while 5 participants in the placebo group and 9 in the ASA group withdrew their consent.

Baseline demographic and clinical characteristics were similar in both treatment groups (**Table 1**; eTable 2 in Supplement 3). The mean (SD) participant age was 77.6 (9.7) years for the placebo group and 77.9 (8.2) years for the ASA group, with 25 participants (16.1%) being female. The median (IQR) Glasgow Coma Scale (GCS) scores at presentation were 15 (14-15) and 15 (14-15) for the placebo and ASA groups, respectively, while the median (IQR) Markwalder score was 1 (1-2) in the placebo group and 1 (1-2) in the ASA group. The most frequent symptom at presentation was ataxia, occurring in 59% of participants, followed by motor function deficit in 56% of participants. Most participants (92.5%) underwent emergency surgery within 24 hours. At the time of admission, 6.5% of participants were receiving concomitant anticoagulants in addition to ASA.

## Primary Outcome

A primary outcome event was observed in 8 participants (10.3%) in the ASA group and in 7 participants (9.1%) in the placebo group. The IPCW-weighted recurrence rates were 13.9% in the ASA group and 9.5% in the placebo group (risk difference, 4.4%; 95% CI, −7.2% to 15.9%; $P = .56$) by 6 months (**Figure 2**). The risk difference in the per-protocol set was estimated at 2.4% (95% CI, −10.9% to 15.8%; $P = .89$; Figure 2).

## Secondary Outcomes

The subdistribution HR for time to recurrence by 6 months in the ASA group over the placebo group was estimated at 1.31 (95% CI, 0.49-3.50), considering any loss to follow-up as a competing risk (**Figure 3**). Cardiovascular events indicating ASA treatment occurred in 1 participant from the ASA group and 4 participants from the placebo group (HR, 0.24; 95% CI, 0.03-2.12; Figure 2). Cardiovascular or cerebrovascular or thromboembolic events occurred in 15 participants from the ASA group and in 16 participants from the placebo group (HR, 0.91; 95% CI, 0.45-1.83). Eleven and 14 participants suffered a cardiovascular or cerebrovascular event in the ASA and placebo groups, respectively (HR, 0.76; 95% CI, 0.34-1.67). Major cardiovascular or cerebrovascular events (MACCE) occurred in 3 participants from the ASA group and 6 participants from the placebo group (HR, 0.48; 95% CI, 0.12-1.91). Thromboembolic events were seen in 4 and 2 participants from the ASA and placebo groups, respectively (HR, 1.90; 95% CI, 0.35-10.40). Time to event of cardiovascular and thromboembolic events are shown in eFigures 9-13 in Supplement 3. Intracranial bleeding events other than recurrent cSDH occurred in 6 participants from the ASA group and 5 participants from the placebo group (HR, 1.16; 95% CI, 0.36-3.82), leading to 2 revision surgeries in each group, while no mortality was caused. Postoperative anemia was found in 2 participants (2.6%) in the ASA group and in 1 participant (1.3%) in the placebo group. No participants in either group required a blood transfusion. All-cause mortality was seen in 4 participants from the ASA group and 2 participants from the placebo group (HR, 1.92; 95% CI, 0.35-10.51). Favorable mRS at 6 months was seen in 89.1% of participants in the ASA group and 86.7% of partici-

Table 1. Characteristics of the Participants at Baseline

| Characteristic | Participants, No. (%) | |
|---|---|---|
| | Placebo group (n = 77) | ASA group (n = 78) |
| Age, mean (SD), y | 77.58 (9.7) | 77.90 (8.2) |
| Sex | | |
| Female | 13 (16.9) | 12 (15.4) |
| Male | 64 (83.1) | 66 (84.6) |
| GCS score at admission, mean (SD) | 14.5 (1.2) | 14.4 (1.0) |
| GCS category | | |
| 3-8 | 0 | 1 (1.3) |
| 9-13 | 6 (7.8) | 6 (7.7) |
| 14-15 | 71 (92.2) | 71 (91.0) |
| mRS, mean (SD) | 2.2 (1.2) | 2.3 (1.2) |
| mRS category | | |
| 1-2 | 47 (61.0) | 42 (53.8) |
| 3-5 | 30 (39.0) | 36 (46.2) |
| GOS, mean (SD) | 4.2 (0.8) | 4.2 (0.8) |
| GOS category | | |
| 1-3 | 20 (26.0) | 16 (20.5) |
| 4-5 | 56 (72.7) | 62 (79.5) |
| NA | 1 (1.3) | 0 |
| Markwalder score, mean (SD) | 1.4 (0.6) | 1.5 (0.7) |
| Markwalder score category | | |
| 0 | 3 (3.9) | 3 (3.8) |
| 1 | 39 (50.6) | 39 (50) |
| 2 | 33 (42.9) | 33 (42.3) |
| 3 | 2 (2.6) | 2 (2.6) |
| 4 | 0 | 1 (1.3) |
| Operation type | | |
| Elective | 6 (7.8) | 5 (6.4) |
| Emergency (ASA >24 h) | 38 (49.4) | 28 (35.9) |
| Emergency on the same day | 33 (42.9) | 45 (57.7) |
| Hematoma side | | |
| Bilateral | 14 (18.2) | 24 (30.8) |
| Left | 33 (42.9) | 29 (37.2) |
| Right | 30 (39.0) | 25 (32.1) |
| Hematoma characteristics | | |
| Acute on chronic | 20 (26) | 16 (20.5) |
| Chronic | 39 (50.6) | 47 (60.3) |
| Subacute | 13 (16.9) | 12 (15.4) |
| Hygroma | 1 (1.3) | 1 (1.3) |
| Other | 4 (5.2) | 2 (2.6) |

Abbreviations: ASA, acetylsalicylic acid; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; mRS, modified Rankin scale; NA, not available.

pants in the placebo group. Further secondary outcomes and analysis are described in **Table 2** and in eTables 3-7 and eFigures 3-14 in Supplement 3.

### Safety

Any severe adverse event by 6 months occurred in 6 participants (7.7%) from the ASA group and in 2 participants (2.6%) from the placebo group. Further details regarding adverse events are provided in eTables 6 and 7 in Supplement 3.

### Sensitivity, Per-Protocol, and Subgroup Analyses

Secondary estimands of interest showed similar results to those of the primary analysis (Figure 2). Results of the per-protocol analysis were similar to those in the main analysis (Figure 2; eFigure 2 in Supplement 3). Additional sensitivity analyses did not alter the main conclusions. No heterogeneity of effects within prespecified subgroups was seen; however, the trial was not powered to detect differences within the subgroups (eFigure 3 and eTables 9 and 10 in Supplement 3).

## Discussion

The trial was designed to determine whether discontinuing ASA treatment during the perioperative phase of burr hole drainage for cSDH reduced recurrence rates within 6 months. We report some evidence that discontinuation of ASA did not reduce the recurrence rates following burr hole drainage of cSDH within 6 months. In addition, there might be a trend toward a higher rate of cardiovascular events in patients with discontinuous vs continuous ASA treatment.

The recurrence rate in the placebo group (9.5%) was slightly lower than in the ASA group (13.9%) without showing a significant difference. Based on the width of the 95% confidence intervals, it is difficult to draw firm conclusions, as data indicate a 7.2% lower to 15.9% higher risk for continuous vs discontinuous ASA treatment. However, considering our own retrospective data and other literature reports showing recurrence rates of up to 33% with continuous ASA treatment, the lower rates found in this trial suggest that previous estimates may have been overstated.[7,8,19]

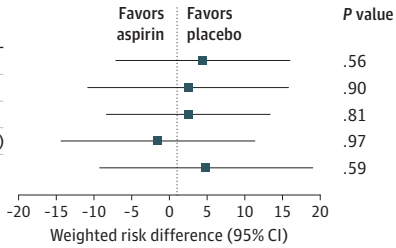
Intracranial bleeding events other than recurrent cSDH occurred slightly more frequently in the ASA group (0.10% per person half-year) compared to the placebo group (0.08% per person half-year). In 36% of cases, these bleeding events were managed surgically without impacting clinical outcomes or resulting in mortality. Overall, the intracranial bleeding rates in both groups fell within the range described in the literature (2%-10%).[24]

The occurrence of cardiovascular or cerebrovascular events was 2-fold higher in the placebo group, with 6 participants (0.10% per person half-year), compared to the ASA group, with 3 participants (0.05% per person half-year), while PMI was seen in 8 participants in each group. Cardiovascular or cerebrovascular events indicating ASA treatment showed a 3-fold lower incidence with continuous ASA treatment (0.06% vs 0.02% per person half-year). Venous thromboembolic events occurred in 4 participants (0.06% per person half-year) from the ASA group and in 2 participants (0.03% per person half-year) from the placebo group. No events showed an effect on mortality or clinical outcomes at 6 months. The risk MACCE in patients undergoing noncardiac surgery is estimated at 2% to 3%, with neurosurgical patients exhibiting one of the highest rates of MACCE (6%) compared to other noncardiac surgeries.[25] Recent studies have identified PMI as a significant factor influencing the risk of MACCE and mortality within 1 year after noncardiac

Figure 2. Primary and Secondary Outcomes, Main Estimands, and Weighted Risk Difference of Primary Outcome (A) and Number and Incidence Rate of Secondary Outcomes (B)

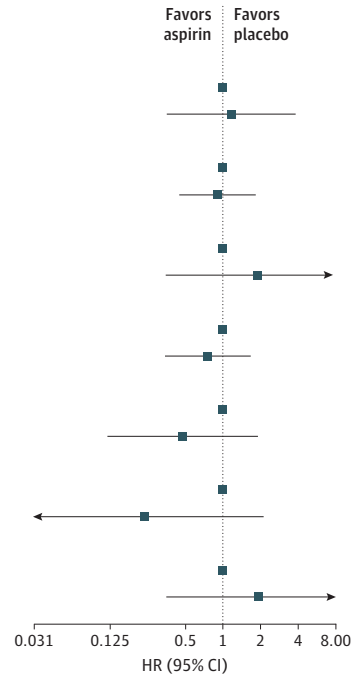
A Weighted event numbers and risk of the primary outcome, main estimands, and weighted risk difference with 95% CIs

| Estimand | Event No. (weighted, %) | | Risk difference (95% CI) | P value |
|---|---|---|---|---|
| | Aspirin | Placebo | | |
| Treatment policy[a] | 10.5 (13.9) | 7.1 (9.5) | 4.4 (-7.2 to 15.9) | .56 |
| Per-protocol set[b] | 8.0 (13.6) | 7.0 (11.1) | 2.4 (-10.9 to 15.8) | .90 |
| Composite: recurrence or any loss to follow-up[c] | 9.0 (11.5) | 7.0 (9.1) | 2.4 (-8.4 to 13.3) | .81 |
| Composite: recurrence or restart ASA[d] | 11.4 (14.8) | 12.3 (16.4) | -1.5 (-14.4 to 11.3) | .97 |
| Composite: recurrence or any bleeding[e] | 17.9 (23.1) | 14.1 (18.3) | 4.8 (-9.3 to 18.8) | .59 |




B Number and incidence rate of secondary events of interest

| Secondary outcome | Events | Person half-years | Incidence | HR (95% CI) |
|---|---|---|---|---|
| Bleeding events other than cSDH | | | | |
| Placebo | 5 | 61.12 | 0.08 | 1 [Ref] |
| Aspirin | 6 | 59.77 | 0.10 | 1.16 (0.36-3.82) |
| CC or TE events | | | | |
| Placebo | 16 | 57.02 | 0.28 | 1 [Ref] |
| Aspirin | 15 | 54.79 | 0.27 | 0.91 (0.45-1.83) |
| TE events | | | | |
| Placebo | 2 | 64.11 | 0.03 | 1 [Ref] |
| Aspirin | 4 | 61.95 | 0.06 | 1.90 (0.35-10.40) |
| CC events | | | | |
| Placebo | 14 | 57.19 | 0.24 | 1 [Ref] |
| Aspirin | 11 | 57.06 | 0.19 | 0.76 (0.34-1.67) |
| Major CC events | | | | |
| Placebo | 6 | 62.57 | 0.10 | 1 [Ref] |
| Aspirin | 3 | 61.41 | 0.05 | 0.48 (0.12-1.91) |
| CC events indicating aspirin treatment | | | | |
| Placebo | 4 | 61.73 | 0.06 | 1 [Ref] |
| Aspirin | 1 | 63.72 | 0.02 | 0.24 (0.03-2.12) |
| Mortality | | | | |
| Placebo | 2 | 71.09 | 0.03 | 1 [Ref] |
| Aspirin | 4 | 68.60 | 0.06 | 1.92 (0.35-10.51) |




Hazard ratios (HRs) of acetylsalicylic acid (ASA) over placebo treatment calculated from Cox proportional hazards models. CC indicates cardiovascular or cerebrovascular; cSDH, chronic subdural hematoma; Ref, reference; TE, thromboembolic.

[a]Represents the weighted analysis of the primary outcome for the intention-to-treat population.

[b]Represents the weighted analysis of the primary outcome for the per-protocol population.

[c]Represents the effect of the composite end point recurrence of cSDH of being lost to follow-up.

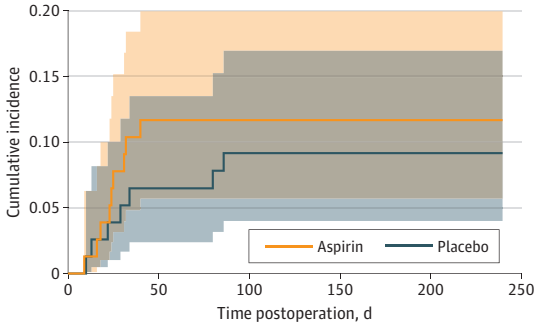
[d]Represents the effect of the composite end point recurrence of cSDH or cardiac event indicating treatment with aspirin.

[e]Represents the effect of the composite end point recurrence of cSDH or other postoperative bleeding event.

surgery.[26,27] In neurosurgical patients, the rate of PMI remains unclear, as studies assessing the risk of MACCE after noncardiac surgery, which included neurosurgical patients, did not evaluate PMI rates, and studies analyzing PMI rates in noncardiac surgery excluded neurosurgical patients.[26] Further, the rate of MACCE and thromboembolic events after discontinuation of ASA in neurosurgical patients, and in particular in those undergoing surgery for cSDH, as well as the potential benefit of continuing ASA treatment in those at risk for MACCE, remains unclear. This trial provides qualitative data on the rates of cardiovascular or cerebrovascular events, including PMI, and thromboembolic events, in patients undergoing surgical treatment of cSDH, although it was not primarily designed to estimate these event rates.

Current clinical practice in cSDH is to discontinue blood thinner treatment, including ASA, before surgical treatment and to delay the resumption of ASA for at least 12 to 30 days after surgery.[18,28-30] Our data demonstrated that if ASA is discontinued for 12 days during the perioperative phase, the recurrence rate (9.5%) appears comparable to the general surgically treated population with cSDH (approximately 10%).[31,32] Therefore, extending the discontinuation period, as practiced in many centers, appears to be unjustified.[18] Since the concomitant use of anticoagulants is of gen-

Figure 3. Cumulative Incidence of the Primary Outcome of the Intention-to-Treat Population, Considering Any Loss to Follow-Up as a Competing Risk




| | | | | | | |
|---|---|---|---|---|---|---|
| No. at risk | | | | | | |
| Aspirin | 78 | 64 | 60 | 59 | 18 | 0 |
| Placebo | 77 | 62 | 59 | 55 | 21 | 0 |
| No. of events | | | | | | |
| Aspirin | 0 | 9 | 9 | 9 | 9 | 9 |
| Placebo | 0 | 5 | 7 | 7 | 7 | 7 |

eral concern in neurosurgical patients, these patients have been systematically excluded from large randomized clinical trials examining the effect of anticoagulants in the perioperative phase.[10,15,17] Therefore, it is not surprising that this trial is the first randomized clinical trial to our knowledge to investigate the effect of continuous ASA treatment in neurosurgical patients. These findings should encourage researchers to include neurosurgical patients in similar studies and to design large prospective trials specifically analyzing the risks associated with continuous or early resumption of anticoagulants in this patient population.

Based on this trial's data concerning the risk of recurrence and bleeding events vs the risk of cardiovascular or cerebrovascular and thromboembolic events, clinicians can conduct a data-driven risk-benefit analysis regarding the continuation or discontinuation of ASA in patients undergoing surgical treatment of cSDH. Furthermore, these data should serve as a foundation for future studies analyzing the benefits and risks of continuous blood thinner treatment in patients surgically treated for cSDH.

## Limitations

The limitations of this trial include limited statistical power due to overestimated recurrence rates in the ASA group during the trial design, which affected the sample size estimation. This overestimation, based on the available literature at the time, directly influenced the trial design, wherein the superiority of discontinuous (placebo) over continuous ASA treatment was assumed. Consequently, the trial also lacks sufficient statistical power to explore subgroups, and no definitive conclusions can be drawn from these results. Patients lost to follow-up can introduce potential bias; to mitigate this, IPCW calculations were used. This trial recruited in central Europe and therefore may have limited generalizability to non-European populations. Additionally, although this was a multicenter trial with a predefined surgical procedure (burr hole drainage with drain insertion), some technical nuances of the surgery might have varied among the centers and even within centers, potentially affecting the primary outcome. Covert ischemic lesions may have been missed, since no imaging was performed at the final follow-up examination, and routine MRI was not conducted during imaging visits, potentially limiting detection. Since this study focused on patients undergoing burr hole drainage and drain insertion under aspirin therapy, the results cannot be extrapolated to other surgical treatment groups or medication groups.

Table 2. Primary and Secondary Outcomes

| Outcome | Participants, No. (%) | |
|---|---|---|
| | Placebo group (n = 77) | ASA group (n = 78) |
| Primary outcome | | |
| Recurrent cSDH needing revision surgery at 6 mo | 7 (9.1) | 8 (10.2) |
| Recurrent cSDH needing revision surgery at 6 mo (IPCW weighted) | 7.1 (9.5) | 10.5 (13.9) |
| Secondary outcomes | | |
| Cardiovascular or cerebrovascular events | 14 (18.2) | 11 (14.1) |
| PMI | 8 (10.4) | 8 (10.3) |
| STEMI or NSTEMI | 2 (2.6) | 0 |
| APAO | 1 (1.3) | 0 |
| CVI or TIA | 2 (2.6) | 3 (3.9) |
| Tachycardia | 1 (1.3) | 0 |
| Thromboembolic events | 2 (2.6) | 4 (5.1) |
| DVT | 0 | 1 (1.3) |
| PE | 2 (2.6) | 3 (3.9) |
| Cardiovascular events indicating ASA treatment | 4 (5.2) | 1 (1.3) |
| Non-cSDH bleeding events | 2 (2.6) | 5 (6.4) |
| Mortality | 2 (2.6) | 4 (5.1) |
| Clinical outcomes at 6 mo | | |
| GCS category | | |
| 3-8 | 0 | 0 |
| 9-13 | 1 (1.5) | 3 (4.4) |
| 14-15 | 59 (86.8) | 62 (91.2) |
| mRS category | | |
| 0-2 | 62 (91.2) | 55 (80.9) |
| 3-6 | 6 (8.8) | 9 (13.2) |
| GOS category | | |
| 1-3 | 3 (4.4) | 6 (8.8) |
| 4-5 | 65 (95.6) | 58 (85.3) |
| Markwalder score | | |
| 0 | 44 (64.7) | 41 (60.3) |
| 1 | 21 (30.9) | 20 (29.4) |
| 2 | 3 (4.4) | 2 (2.9) |
| 3 | 0 | 1 (1.5) |
| 4 | 0 | 0 |

Abbreviations: APAO, acute peripheral arterial occlusion; ASA, acetylsalicylic acid; cSDH, chronic subdural hematoma; CVI, cerebrovascular insult; DVT, deep vein thrombosis; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; IPCW, inverse probability of censoring weights; mRS, modified Rankin scale; PE, pulmonary embolism; PMI, perioperative myocardial infarction/injury; STEMI, ST-segment elevation myocardial injury; NSTEMI, non–ST-segment elevation myocardial infarction; TIA, transitory ischemic attack.

## Conclusions

In conclusion, discontinuous ASA treatment did not appear to reduce the recurrence rate of surgically treated cSDH within 6 months. The risk difference was estimated at 4.4%, with 95% confidence intervals ranging from 7.2% lower to 15.9% higher for continuous vs discontinuous ASA treatment. Notably, recurrence risk estimates for continuous ASA treatment in this trial were distinctly lower than previously reported.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