Trials

STUDY PROTOCOL

Open Access

Restarting anticoagulation early versus late in patients with chronic subdural hematoma and atrial fibrillation (RELACS): a phase III international multicenter, randomized controlled, two-arm, assessor-blinded trial

Rahul Raj[1*], Pihla Tommiska[1], Riku Kivisaari[1], Miikka Korja[1], Teemu Luostarinen[2], Jyri J. Virta[2], Simo Taimela[3,4], Teppo L.N Järvinen[3,4], Mika Niemelä[1], Timo Koivisto[5], Ville Leinonen[5], Bjartur Saemundsson[6,7], Alexander Fletcher-Sandersjöö[6,7], Tommi Korhonen[8], Sami Tetri[8], Minna Rauhala[9], Dan Laukka[10], Tomasz Czuba[12,13], Jiri Bartek[6,7†], Nils Danner[5†], Oula Knuutinen[8†], Teemu Luoto[9†], Jussi P. Posti[10,11†] and Jarno Satopää[1†]

Abstract

Background Chronic subdural hematoma (CSDH) is a rapidly growing neurosurgical condition, driven primarily by an aging population and the increasing use of antithrombotic medications. Approximately 25% of CSDH patients are on anticoagulants due to atrial fibrillation (AF). The postoperative management of these patients presents a significant clinical challenge, as clinicians must balance the risks of thromboembolic and hemorrhagic complications. Currently, no evidence-based guidelines exist regarding the optimal timing for resuming anticoagulation therapy after surgery. This study aims to evaluate the net effect of early versus late postoperative resumption of oral anticoagulation in CSDH patients with AF. We hypothesize that early resumption will result in fewer thromboembolic complications and vascular deaths, without increasing the risk of hemorrhagic complications.

Methods This is an investigator-initiated, international, multicenter, superiority, two-arm, assessor-blinded, phase 3 trial with 1:1 randomization, comparing early resumption (defined as 5 days) and late resumption (defined as 30 days) of oral anticoagulation medication after CSDH surgery in patients with AF. The primary outcome is a composite outcome that combines thromboembolic events, hemorrhagic events, and vascular death within 90 days of the surgery. Secondary outcomes include reoperations, functional outcome, and adverse events. The estimated sample size is 332 patients to achieve an 80% power and a two-sided alpha of 0.05 for the primary outcome, including potential dropouts.

[†]Jiri Bartek, Nils Danner, Oula Knuutinen, Teemu Luoto, Jussi P Posti, and Jarno Satopää share equal contributions.

*Correspondence:
Rahul Raj
rahul.raj@hus.fi
Full list of author information is available at the end of the article

Discussion This is the first large-scale RCT addressing the critical evidence gap in anticoagulation timing after CSDH surgery. If early resumption proves superior, it could transform clinical practice by reducing thromboembolic complications without increasing hemorrhagic risk, potentially improving outcomes for the growing population of CSDH patients with AF worldwide.

Trial registration The study is registered on June 4, 2025. The EU Clinical Trials Register (EUCTR) under identifier EUCT 2025-521179-29-00 (https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2025-521179-29-00).

Keywords Chronic subdural hematoma, Surgical evacuation, Atrial fibrillation, Stroke, Hemorrhage

Introduction

Chronic subdural hematoma (CSDH) is one of the fastest-growing neurosurgical diseases worldwide, anticipated to become the most common type of intracranial surgery by 2030 [1]. This rise is largely driven by an aging population and increased use of antithrombotic medications, with as many as 50% of CSDH patients being on antithrombotic medication at diagnosis [2–4]. Up to half of these, or 25% of all CSDH patients being operated, are on oral anticoagulants due to atrial fibrillation (AF) [5–9]. Moreover, the rising number of patients on oral anticoagulation medication for AF suggests a growing proportion of CSDH cases involving anticoagulation therapy for AF in the future. [10, 11].

CSDH patients with AF requiring surgery face a significant clinical challenge. When a patient on anticoagulation medication presents with CSDH, the standard approach is to withhold their anticoagulation therapy to prevent hematoma expansion, which could result in severe neurological impairment or death. However, withholding anticoagulation therapy exposes the patients to an increased risk of thromboembolic complications. Data show that the thromboembolic risk is especially high after surgery for CSDH, with a rate of early postoperative thromboembolic events ranging from 2 to 23% [12–19].

Despite the importance of the issue, there is a critical lack of evidence-based guidelines to determine the optimal timing for resuming anticoagulation therapy after CSDH surgery. For example, recent randomized controlled trials (RCTs) for CSDH show varied anticoagulation resumption protocols, ranging from 2 to 10 weeks post-surgery [5, 8, 20], with some trials lacking specific protocols [6, 21–23]. The lack of evidence-based guidelines on when to resume anticoagulation after CSDH surgery remains a significant controversy, constituting a daily clinical dilemma for neurosurgeons, balancing between the perceived risk of hemorrhagic complications versus thromboembolic complications [12, 24–26]. A thromboembolic event significantly worsens patient outcomes with up to 70% of those experiencing thromboembolic complications after CSDH surgery have poor functional outcomes at 6 months [27, 28]. Meanwhile, the association between resuming antithrombotic medication and risk of hemorrhagic complications and CSDH recurrences is uncertain. Some studies report no increased risk of hemorrhagic complications [12–14, 29, 30] or CSDH recurrences [15, 29–36], while others report an increased risk of CSDH recurrences [24, 37–40]. Furthermore, the association between CSDH recurrence and functional outcome is inconsistent, with some studies reporting an association between CSDH recurrence and poorer functional outcome [41–43], while some studies did not find any association [44, 45]. Overall, the balance of risks and benefits appears to favor early resumption of anticoagulation therapy. However, even as emerging evidence suggests that middle meningeal artery (MMA) embolization may be a treatment option for CSDH patients on anticoagulation medication, it does not provide immediate relief of compression symptoms caused by the hematoma [46–48]. Thus, the necessity of surgical evacuation of CSDHs, even in patients with anticoagulation medication, remains essential, underscoring the need for a well-designed RCT.

This study aims to address the net effect of early versus late resumption of anticoagulation in operated CSDH patients with AF. We hypothesize that early resumption will reduce the incidence of thromboembolic complications without increasing the risk of hemorrhage.

Materials and analysis

Primary objective

The primary objective of the RELACS trial is to estimate the net effect of early resumption versus late resumption of oral anticoagulation medication in patients with AF undergoing surgery for CSDH. Net effect is estimated by a composite outcome that combines thromboembolic events (ischemic stroke, systemic embolism), hemorrhagic events (intracranial hemorrhage, major extracranial bleeding) and vascular death.

Secondary objectives

The secondary objectives are to assess reoperations, functional outcome, all-cause mortality, separate vascular events and healthcare service use after early versus late resumption in patients with AF undergoing surgery for CSDH.

Hypothesis

The trial hypothesis is that early resumption (5 days) compared to late resumption (30 days) of oral anticoagulation medication will result in fewer thromboembolic complications and vascular deaths with no increase in hemorrhagic complications in patients with AF undergoing CSDH surgery.

Overview of study design

RELACS is an international, multicenter, superiority randomized controlled, two-arm, assessor-blinded, phase 3 trial with the primary aim to compare early resumption of oral anticoagulation medication versus late resumption after surgery for CSDH in patients with AF. Eligible patients will be block randomized in a 1:1 allocation rate to one of two arms: (1) oral anticoagulation medication resumption 5 days after the surgery and (2) oral anticoagulation medication resumption 30 days after the surgery.

The study is registered at EU Clinical Trials (EU CT number: 2025-521179-29-00). The protocol has been written according to the Standard Protocols Items: Recommendations for Interventional Trials (SPIRIT) guidelines for reporting a RCT study protocol (the SPIRIT Checklist is available in the Online Material, p2 [49].

Study settings

Participating sites are all five neurosurgical departments in Finland and Karolinska University Hospital (Stockholm, Sweden). The Finnish centers are Helsinki University Hospital (Helsinki, Finland), Kuopio University Hospital (Kuopio, Finland), Tampere University Hospital (Tampere, Finland), Turku University Hospital (Turku, Finland), and Oulu University Hospital (Oulu, Finland). All participating sites are tertiary neurosurgical referral centers.

Participant selection and recruiting process

We will screen all patients who are referred for CSDH surgery to the recruiting centers for trial eligibility. A standard clinical examination and a brain computed tomography (CT) or magnetic resonance imaging (MRI) examination will be performed. Patients with clinical and imaging findings consistent with a diagnosis of symptomatic CSDH and considered to benefit from operative treatment of CSDH by single burr-hole evacuation will be asked to participate in the trial. The local research team at each site will be responsible for enrolling participants and obtaining informed consent.

All patients considered for recruitment are to be on an oral anticoagulation medication due to permanent, persistent or paroxysmal spontaneous AF that was previously known. All types of oral anticoagulation medications are considered (warfarin (Marevan®), rivaroxaban (Xarelto®), dabigatran (Pradaxa®), apixaban (Eliquis®), edoxaban (Lixiana®)).

Inclusion and exclusion criteria

Adult patients with oral anticoagulation medication due to previously known permanent, persistent or paroxysmal spontaneous AF with a symptomatic unilateral or bilateral CSDH requiring burr-hole evacuation are eligible for the trial. The specific inclusion criteria are:

- Age ≥ 18 years
- Patients with a symptomatic unilateral or bilateral CSDH requiring burr-hole evacuation
  - ■ CSDH is predominantly hypodense or isodense on imaging (CT/MRI)
  - ■ Clinical symptoms attributable to the CSDH
  - ■ If bilateral symptomatic hematomas are present and require bilateral surgery, both sides will be treated using burr-hole evacuation (patients with bilaterally operated CSDHs will be treated with the same protocol on both sides and analyzed as a single study participant).
- Patients that are on an oral anticoagulation medication due to permanent, persistent or paroxysmal spontaneous AF previously known
- Randomization done within 4 days of the surgery
- Patients with cognitive impairment, including mild cognitive impairment or dementia, are eligible if a legally authorized representative can provide informed consent on their behalf, as detailed in the informed consent section
- Patients on standard or reduced doses of oral anticoagulants for stroke prevention in atrial fibrillation are eligible. Reduced doses must be in accordance with approved dosing recommendations and clinical practice guidelines based on patient-specific factors such as renal function, age, and body weight.

Exclusion criteria are:

- Intraoperative or immediate postoperative hemorrhagic complication
  - ■ Reason: If there is an acute procedure-related hemorrhagic complication, resumption of anticoagulation medication after the surgery may not be safe.
- Chronic subdural hematoma (CSDH) requiring surgical treatment other than burr-hole evacuation (e.g., craniotomy)

■ Reason: Craniotomy is a more invasive procedure than burr-hole evacuation and resumption of oral anticoagulation medication after 5 days may not be safe. Further, craniotomy is often reserved for patients with acute and/or subacute subdural hematomas.

– Prior CSDH surgery within 12 months
  ■ Reason: To avoid including early recurrences that have a higher likelihood of further recurrences.
– Cerebrospinal fluid shunt
  ■ Reason: CSF drainage may impact the natural history and recovery of CSDH by altering the CSF resorption and flow.
– CSDH is in an arachnoid cyst
  ■ Reason: CSDHs in arachnoid cysts probably follow a different pathogenesis and natural history than normal CSDHs.
– If the operated hematoma reveals to be a cerebrospinal fluid collection (hygroma)
  ■ Reason: Hygroma is a different entity from CSDH.
– Conditions other than atrial fibrillation (AF) that require anticoagulation, including therapeutical dose of low molecular-weight heparin or heparin (for example, pulmonary embolism, deep vein thrombosis, hypercoagulability syndromes)
  ■ Reason: Other indications for current anticoagulation medication in addition to AF increase the overall thromboembolic risk and resuming anticoagulation medication after 30 days may not be safe.
– Mechanical heart valve(s)
  ■ Reason: DOACs are contraindicated for mechanical prosthetic valves and for moderate to severe mitral stenosis [50].
– Moderate or severe mitral stenosis (other valvular diseases and biological valves are eligible)
  ■ Reason: DOACs are contraindicated for mechanical prosthetic valves and for moderate to severe mitral stenosis [50].
– Contraindication to anticoagulation medication (for example bleeding disorder, documented high risk of fall (e.g., due to severe alcoholism), severe thrombocytopenia, severe anemia)
  ■ Reason: Anticoagulation medication may need to be discontinued after surgery if a contraindication is detected or diagnosed. Randomization cannot be carried out.
– Concomitant use of antiplatelet medication
  ■ Reason: Patients on concomitant antiplatelet and anticoagulation therapy (e.g., due to recent coronary stenting) are at a high risk of thromboembolic complications and these patients' anticoagulation medication often need to be individualized. Randomization cannot safely be carried out.
– Moderate to severe renal insufficiency (creatinine clearance < 30 ml/min or on dialysis)
  ■ DOACs are contraindicated in severe renal insufficiency or in end-stage renal disease [50].
– Not a permanent resident in Finland (for Finnish patients) or not a permanent resident in Region Stockholm (Swedish patients).
– Women of childbearing potential

■ Potential harmful effects of medication

Informed consent

The treating physician will provide the patients with detailed written and oral information on the trial, including its nature, objectives, benefits, risks, expected duration, alternative treatments, and the right to withdraw, and ask patients to sign an informed consent form within 4 days of the surgery. Withdrawal from the study is possible at any time, without affecting the course of conventional treatment, in accordance with the latest version of the Declaration of Helsinki 2024 [51]. Due to the nature of CSDH (mass effect on the brain causing confusion and disorientation, lowered level of consciousness, neurological disability), some patients will not be able to give written consent Prior to randomization. Based on our previous study, approximately 20% of patients may have a reduced capacity of giving informed consent after the surgery [52]. In these cases, written informed consent will be obtained from a legally authorized representative (LAR), such as the patient's next-of-kin or legal guardian, before randomization into the trial. If a patient regains the capacity to provide consent after randomization, the treating physician will provide the patient with the same detailed written and oral information about the trial and request their written informed consent at the earliest feasible opportunity. The patient, or their LAR if the patient remains incapacitated, retains the right to withdraw consent at any time without any impact on the patient's conventional treatment or care. The original Swedish model consent form and a full English translation are available in the Online Material.

Collected data

We will document data in the electronic case report form (eCRF) on admission, intraoperatively, and at 90 days after surgery (see Table 1 for participant timeline). To preserve confidentiality, all participants are allocated a unique study identifier during the recruitment process, which is used on all data collection forms. All study documentation is held in secure offices, and the study researchers operate according to a signed code

Table 1 Participant timeline

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT	**Admission (presurgery)**	**Days ≤4**	***Day 5***	***Day 30***	***90 days (±14 days)***
ENROLMENT:					
Eligibility screen	X	X			
Informed consent		X			
ALLOCATION:					
Randomization		X			
INTERVENTIONS:					
Early resumption			X ◆—	—	— ◆
Late resumption				X ◆—	— ◆
ASSESSMENTS:					
Baseline data	X				
Surgical details		X			
Modified Rankin Scale	X	X			X
Primary outcome					X
Secondary outcomes					X
Adverse events		X	X	X	X

*TIMEPOINT refers to the number of days relative to the index CSDH surgery (Day 0)

of confidentiality. All data are entered into a password-secured database by the data managers.

Surgical technique

The standard surgical management of patients with CSDH in the study centers involves single burr-hole surgery under local anesthesia, followed by subdural irrigation [7] at body temperature [23] and generally subdural or subgaleal drain placement. All burr-hole evacuations will be performed by neurosurgical residents or board-certified neurosurgeons, reflecting the standard of care within the participating university hospitals. To ensure the pragmatic design and generalizability of the trial results, we will allow for variations in surgical technique (e.g., one vs. two burr-holes) and postoperative drainage (e.g., no drain, subdural vs. subgaleal) [8, 9, 22, 53]. The variation in surgical technique may affect some secondary outcome measures (e.g., reoperations) but it is

implausible that it would influence the components of the primary composite outcome measure [7, 9, 23, 54].

Middle meningeal artery embolization

We will allow for additional MMA embolization during the hospital stay as an adjunct to burr-hole surgery. The performance of MMA embolization during the index hospitalization will be recorded in the CRF. MMA embolizations performed after the index hospitalization due to a recurrent ipsilateral CSDH (on the same side as the surgery) will be recorded as reoperations. MMA embolizations performed after the index hospitalization due to the occurrence or growth of a new symptomatic contralateral CSDH will be recorded as a hemorrhagic complication. MMA embolizations performed as sole therapy for a CSDH not treated with burr-hole surgery during the index hospitalization, if a contralateral CSDH was operated on, will not be recorded.

Other treatment

Other medical treatments for CSDH, such as dexamethasone, tranexamic acid, angiotensin-converting enzyme inhibitors, or statins are not routinely used in the trial. The use of low-molecular heparin (LMWH) for venous thrombosis prophylaxis is permitted and will be recorded in the CRF [55].

Randomization

Patients will be randomized in a 1:1 allocation ratio stratified by study center. We will use a random block randomization technique, with a random block size of 4, 6, or 8. A member of the RELACS study group will carry out randomization perioperatively, either before or after the surgery but latest within 4 days of the surgery. The randomization is a built-in property in the online eCRF system used in the trial (provided by REDCap) [56, 57].

Intervention

Early anticoagulation resumption

Oral anticoagulation medication will be resumed 5 days after the CSDH surgery. The 5-day interval is based on the following considerations:

- Retrospective studies suggest that anticoagulation resumption after CSDH surgery may be safe as soon as 3 days after the surgery [12, 30, 58].
- Resumption of direct oral anticoagulants (DOACs) and warfarin 2–3 days after high-bleed risk surgery is safe in patients with AF [59–61]. The PAUSE trial showed that resuming DOACs 2–3 days (48–72 h) postoperatively in patients with AF undergoing major surgery or high bleeding risk surgery (including neurosurgery), has a low risk (0.9–1.9%) of major postoperative bleeding and a low risk of thromboembolism (0.2–0.6%) [62]. Further, most of major postoperative bleedings occur within 5 days of the surgery, which would make the patient ineligible for this trial [62, 63].
- To account for the potential bleeding pathogenesis of CSDH, anticoagulants will be resumed 5 days, instead of 2–3 days, after the surgery. As a safeguard mechanism, intraoperative hemorrhagic complication is an exclusion criterion for enrolment into the study. DOACs and warfarin (the patient's preoperative anticoagulation medication) will both be started on the 5th postoperative day. Since it is anticipated that the time to reach the full anticoagulative effect of warfarin will be delayed compared to DOACs [64, 65], a predefined subgroup analysis comparing those on DOACs versus warfarin is planned.

Late anticoagulation resumption

Oral anticoagulation medication will be resumed 30 days after the CSDH surgery. The 30-day interval is based on the following considerations:

- We conducted a rapid systematic review of published RCTs in CSDH from January 1, 1990, to July 27, 2024, that showed that the mean time to resume anticoagulation medication after surgery for CSDH was 4 weeks (Online Material, p6).
- In a meta-analysis of 13 studies that included timing of oral anticoagulation medication resumption after intracranial hemorrhage, the mean time to resume anticoagulation medication was 31 days [66].
- Resumption of oral anticoagulants after 30 days is the conventional care in the participating sites. Thus, to adhere to the pragmatic design of the trial, the late group was set to resume the anticoagulation medication after 30 days.

Blinding

This is an open-label trial with blinded endpoint assessment. Due to the nature of the intervention, which involves a specific medication schedule, trial participants and their treating clinicians (care providers) will not be blinded to the treatment allocation. To minimize potential bias, the following roles will be blinded: outcome assessors (the primary and secondary endpoints will be collected via a structured telephone interview conducted by a trained assessor who is unaware of the patient's treatment allocation), Data and Safety Monitoring Board (DSMB, the DSMB will only review blinded data during interim analyses), Data Interpretation Committee (a

blinded committee will interpret the final study results before the randomization code is broken [67]).

Adherence with trial intervention

In Finland, adherence to DOACs is generally high [68, 69]. However, to further ensure protocol adherence, research personnel will contact patients by telephone either 1 day before or on the day they are scheduled to begin anticoagulation medication, serving as a reminder. Patients who are discharged with a neurological status sufficient to maintain a medication diary will be provided with one, and these diaries will be collected at the end of the follow-up period. For patients who are transferred to further care or are deemed unable to reliably complete a medication diary, adherence to anticoagulation medication will be monitored by reviewing patient records and medication logs. It is important to note that all healthcare units in Finland and Sweden utilize electronic health records, facilitating accurate tracking of medication adherence. This approach aligns with the strategy used in the Dex-CSDH trial [6].

For subjects who receive warfarin, monitoring the international normalised ratio (INR) is a more appropriate measure of adherence than direct questioning. Overall percentage of time in a defined therapeutic range (usually INR 2–3) will be derived by using a linear interpolation method described by Rosendaal and colleagues, which assumes that the INR value between two measurements increases or decreases linearly from the first value to the second value [70]. Accordingly, we will impute daily INR values between two consecutive measurements, which assumes a linear increase or decrease between the two values [71–74].

Adherence with trial protocol

The final decision to initiate, delay, or discontinue oral anticoagulation for any patient will ultimately rest with the treating clinician, based on their assessment of the patient's clinical status and safety. This principle applies in all circumstances, including but not limited to the occurrence of a new thromboembolic or bleeding event prior to the scheduled resumption of anticoagulation or a patient's request to alter the timing of their medication. All instances of deviation from the assigned intervention schedule, along with the clinical reasoning, will be documented in the eCRF. For the primary analysis, all patients will be analyzed according to the intention-to-treat principle, as part of their original randomized group.

Primary outcome measure

The primary outcome is the composite of thromboembolic events (ischemic stroke, systemic embolism), hemorrhagic events (intracranial hemorrhage, major extracranial bleeding) and vascular death within 90 days of the index CSDH surgery [75–77].

Ischemic stroke is defined as:

- New sudden focal neurological deficit of presumed cerebrovascular etiology, occurring > 24 h after the index surgery, that either [78]:
  - ○ Is confirmed by brain imaging (CT/MRI) showing evidence of cerebral infarction; or
  - ○ Persists over 24 h with other potential etiologies excluded

Note that transient ischemic attacks (TIA) will not be classified as a new ischemic stroke but will be recorded as an adverse event.

Systemic embolism includes arterial thromboembolic events:

- Myocardial infarction is defined as clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin values with at least 1 value above the 99th percentile upper reference limit and at least one of the following: (1) symptoms of myocardial ischemia, (2) new ischemic ECG changes, (3) development of pathological Q waves, (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, (5) identification of a coronary thrombus by angiography or autopsy [79].
- Systemic embolism is defined as an abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion of an extremity or organ in the absence of another likely mechanism (e.g., atherosclerosis, instrumentation, or trauma). In the presence of peripheral artery disease, diagnosis of embolism to the lower extremities requires angiographic demonstration of acute arterial occlusion [80]. For example, lower limb ischemia, upper limb ischemia or mesenteric ischemia due to vascular occlusion.

Intracranial hemorrhage is defined as:

- New contralateral CSDH or growth of contralateral CSDH that requires surgery or MMA-embolization (ipsilateral CSDH recurrence defined as a separate secondary outcome) based upon radiological investigations.
- Spontaneous intracranial hemorrhage is defined as any new findings of spontaneous non-traumatic

intracranial hemorrhage based upon radiological investigations.
- New traumatic intracranial hemorrhage is defined as any new findings of traumatic intracranial hemorrhage based upon radiological investigations.
    - Rationale: Patients with CSDH may have a lowered functional capacity after the surgery and may be at heightened risk of falling. Thus, traumatic intracranial hemorrhage constitutes a relevant safety outcome measure.

Major extracranial hemorrhage [81] is defined as:

- Fatal bleeding and/or
- Decrease in hemoglobin of ≥ 20 g/L over a 24-h period or transfusion of ≥ 2 units of packed red blood cells and/or
- Symptomatic bleeding in a critical area or organ, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome. Note that intracranial hemorrhages are recorded separately and not included here.

Vascular death is defined as any death that is due to a vascular cause.

- Defined as a cause of death ICD-10 diagnosis of I00–I99 according to National Cause of Death Registers in Finland and Sweden. In Finland, Statistics Finland have has upheld a classification of causes of death since 1969, and in Sweden, The National Board of Health and Welfare has upheld a classification of causes of death since 1952 [82].

Secondary outcome measures

The study is not powered for secondary outcome measure comparisons and these outcomes (analyses) will be considered exploratory. The secondary outcomes are:

- Separation of the components of the primary composite outcome: thromboembolic events, hemorrhagic events and vascular deaths (time frame: 90 days)
- Separation of different etiologies of hemorrhagic complications (time frame: 90 days)
- Composite outcome using all-cause mortality instead of vascular death (time frame: 90 days)
- All-cause mortality and vascular deaths (time frame: 90 days and 12 months)
- Sliding modified Rankin Scale (time frame: 90 days)
    - Adjusting for baseline mRS, preoperative mRS and randomization (postoperative) mRS
- Modified Rankin Scale 0–3 vs. 4–6 (time frame: 90 days)
- Modified Rankin Scale 0–4 vs. 5–6 (time frame: 90 days)
- Reoperation of ipsilateral hematoma (time frame: 90 days)
    - MMA embolizations are also recorded
    - The decision to proceed to reoperation is made by the treating neurosurgeon and will be made by the same indications as the primary operation (i.e., symptom recurrence or insufficient resolution of clinical symptoms correlating to imaging findings (CT or MRI) of CSDH).
- Number and type of unscheduled emergency radiological examinations (time frame: 90 days)
- Number of emergency department visits (time frame: 90 days)
- Postoperative total hospitalization days, counted from the day of surgery (time frame: 90 days)

Safety endpoints

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment [83]. A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Events included in the primary composite outcome (thromboembolic events, hemorrhagic events, and vascular death) will be recorded and analyzed separately but are not classified as AEs or SAEs for reporting purposes as they constitute the primary outcome measure.

AEs will be collected from the time of randomization until the end of follow-up. Data on AEs will be collected via direct questioning during the 90-day follow-up interview and by systematically reviewing participants' comprehensive electronic health records. The local investigator will assess the causal relationship of each AE to the intervention.

Investigators at each site are required to report all SAEs to the sponsor-investigator (coordinating center)

within 24 h of becoming aware of the event. The sponsor-investigator is responsible for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) to the relevant regulatory authorities within the legally mandated timeframes (7 days for fatal/life-threatening events; 15 days for all others). The authorized Summary of Product Characteristics (SmPCs) for each anticoagulant will serve as the Reference Safety Information (RSI) for the trial.

Follow-up

The primary and secondary outcomes are assessed at 90 ± 14 days after CSDH surgery by a structured telephone interview or clinical visit (according to the telephone interview instructions) by trained personnel, who is not aware of the treatment allocation. The components of the outcome measures will be verified by trained research personnel following the structured, blinded telephone interview. Verification will be conducted using Finland's statutory nationwide centralized electronic health records database—which includes comprehensive data on all healthcare visits, diagnoses, surgeries, prescriptions, laboratory investigations, and radiological examinations—and, for Swedish patients, the equally comprehensive regional electronic health records database in Stockholm [84]. The date and causes of death will be obtained from the statutory Finnish Official Cause-of-Death Statistics (covering all residents in Finland) and the statutory Swedish National Cause of Death Register (covering all residents in Sweden) [85, 86]. Thus, follow-up in terms of the primary outcome is expected to be 100%. A detailed description of the death registers in Finland and Sweden is provided in the Online Material, p9.

Sample size

We estimated the incidence of the primary composite outcome to be 19% among patients in the late resumption group and 8% among those in the early resumption group.

The estimate for the late resumption group was based on a posthoc analysis of the FINISH trial, where the composite outcome of arterial thromboembolic events, hemorrhagic events and vascular death was 19% [28].

The estimate for the early resumption group was based on results from the ELAN trial for stroke [75], where the composite outcome—including ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial bleeding, or vascular death—was 2.9% for the early resumption group (resumption within 48 h for minor and moderate stroke, and at 6–7 days for major stroke). Similarly, in the PAUSE study [62], the incidence of thromboembolism, major bleeding, or death was 2.0% among patients with AF undergoing elective surgery, with anticoagulant resumption at 1 day after low bleeding-risk procedures and 2–3 days after high bleeding-risk surgeries. However, since the context of CSDH, which often requires emergency surgery, differs from that of elective surgery (PAUSE study [62]) and acute stroke (ELAN study [75]), the steering committee decided to set an estimated rate of 8% for the early resumption group for this trial [87].

Accordingly, using the error-spending O'Brien–Fleming method, we calculated that 302 patients would be needed for the trial to show superiority of early versus late anticoagulation resumption with 80% power and a two-sided alpha of 0.05 for the primary outcome [88–90]. The error-spending O'Brien–Fleming method was chosen for its conservative early boundaries for the interim analysis, while providing final critical values similar to a fixed study design [88–90]. Accounting for a 10% dropout rate, the final recruitment target is set at 332 patients (166 patients per group).

Data management

All study data will be stored in an eCRF provided by REDCap on a server upheld by Helsinki University Hospital [56, 57]. Data are entered locally by the local research team. On receipt of the data, the RELACS personnel, blinded to the group allocation, will make a visual check of the data and query all missing, implausible and inconsistent data. Hospital patient records will also be used to collect missing data and to interpret inconsistent or implausible data. Participant files will be maintained in storage (both in electronic and paper format) at the coordinating center for a period of 25 years after completion of the study and medical files in accordance with national laws in Finland and Sweden.

Data sharing

Researcher-initiated data sharing is not possible due to the Finnish Secondary Use Act (552/2019). Thus, all requests to process data for purposes permitted by the Secondary Use Act are given based on an official decision made by FINDATA (https://findata.fi/en/).

Statistical analysis

We will have three analysis populations: intention-to-treat (ITT), per-protocol (PP) and as-treated (AT). In the ITT analysis, all patients will be analyzed according to their randomized group assignments, with exclusions only for cases of missing information. The criteria for the PP and AT (cross-over) analysis populations are described below.

Per protocol

Early resumption group:

- Resumed anticoagulation within 7 days of the index surgery.
- If a 1 st reoperation occurs, resumed anticoagulation 5 days (latest 7 days) after the 1 st reoperation.
- If a 2nd reoperation occurs, resumed anticoagulation 30 days (± 5 days) after the 2nd reoperation (standard of care).

Late resumption group:

- Resumed anticoagulation within 30 ± 5 days of the index surgery.
- If a reoperation occurs, resumed anticoagulation 30 days after each reoperation (standard of care).

Table 2 Criteria for per-protocol and intention-to-treat in case of reoperation during the follow-up period

Reoperation number	Randomized group	
	Early resumption	Late resumption
First reoperation	Resume anticoagulation medication 5 days after the 1 st reoperation	Resume antiocoagulation medication 30 days after the 1 st reoperation
Second reoperation	Resume anticoagulation medication 30 days after the 2nd reoperation	Resume antiocoagulation medication 30 days after the 2nd reoperation

Reoperation defined as reoperation of an ipsilateral CSDH within 90 days of the index surgery

Abbreviations: *CSDH* chronic subdural hematoma

Cross-overs (as-treated)

Patients randomized to early resumption:

- Resumes within 7 days of index surgery: Not a cross-over.
- Resumes 8–24 days after index surgery: Not a cross-over.
- Resumes 30 ± 5 days (25–35 days) after index surgery: Cross-over to late resumption group.

Patients Randomized to Late Resumption:

- Resumes within 7 days of index surgery: Cross-over to early resumption group.
- Resumes 8–24 days after index surgery: Not a cross-over.

The effect of reoperations and anticoagulation medication resumption after reoperation

It can be assumed that approximately 10–15% of patients will undergo reoperation due to ipsilateral CSDH recurrence, directly influencing the management of anticoagulation re-pausing and reinitiation [7, 23]. In the FINISH trial, the median time to reoperation was 34 days (IQR 19–48 days), with only 3 out of 91 reoperations (3.3%) occurring beyond 90 days. Therefore, reoperations are highly likely to occur within the planned 90-day follow-up period in this study. If a reoperation is necessary during the follow-up period (ipsilateral reoperation or contralateral first operation), the protocol outlined in Table 2 is implemented. Given the uncertainty surrounding the optimal timing for anticoagulation medication resumption and the potential risk of early resumption increasing the risk of recurrences, we have determined it necessary to resume anticoagulation therapy 30 days following a second reoperation. This approach is intended to minimize the risk of recurrent reoperations while safeguarding patient outcomes.

Blinded data interpretation

As in previous studies [7, 91, 92], the results of this trial will be interpreted using a blinded data interpretation (BDI) scheme [93]. In brief, the trial PI, along with the site PIs, is responsible for developing the BDI plan. This plan is then presented to the trial statistician for review and approval before being submitted to the entire Writing Committee for final approval and signatures. Once approved, the trial statistician will first present the Writing Committee with blinded results labeled as group A and group B. Then, the Writing Committee will contemplate the interpretation of the results until a consensus is reached, and alternative interpretations of the findings are agreed upon in writing. Once a consensus is reached, the minute ("statement of interpretation") of the meeting is recorded and signed by all members of Writing Committee. Only after reaching common consensus and agreement regarding the blinded trial results, will the statistician break the randomization code. A manuscript will then be prepared and finalized for the publication of the results. Detailed minutes of BDI meetings will be provided as a supplement to the trial manuscript.

Primary analysis

We will carry out statistical analyses according to the ITT principle. We will perform the ITT analysis using the full analysis set, defined as all randomized patients in the groups allocated to by the randomization. No exclusions other than caused by missing information will be made. No imputation will take place, as we anticipate minimal to no missing data for the primary outcome.

The primary analysis (according to the ITT principle) estimates the percentage point difference in the primary

composite outcome between the groups. The percentage point difference is calculated for the effect of early versus late anticoagulation resumption using marginal effects after fitting a logistic regression model adjusting for study site. Study site adjustment will not be done in case of 0 events in one of the two groups at a study site to avoid sparse data bias. Given the sequential design using the error-spending O'Brien–Fleming method, we will consider the primary analysis to support superiority if the incidence of the primary composite outcome is significantly lower in the early resumption group compared to the late resumption group. Superiority will be indicated by a p-value < 0.0490 after full patient recruitment or a p-value < 0.0031 at 50% recruitment (Table 3).

Secondary analyses

In addition to the primary ITT analysis, we will perform the PP and AT analyses on the subset of the full analysis set for patients that strictly adhered to the treatment protocol (PP) and for patients according to actual received treatment (AT), using the same statistical principles as the primary analysis.

Secondary outcomes will be analyzed using repeated measures ordinal logistic, ordinal logistic, logistic and linear regression models, adjusting for study site (no study site adjustment if one of the groups has 0 events at a study site). Subgroups will be analyzed using repeated measures ordinal logistic, ordinal logistic, logistic and linear regression, including an interaction term between treatment-group and the subgroups of interest, adjusted for study site. Subgroup differences (with 95% CI) will be obtained using pairwise comparisons of predictive margins.

All secondary outcomes and subgroup analyses are prespecified as exploratory and will be assessed using a superiority framework. A detailed list of the predefined subgroups is given in the Online Material, p5.

Interim analyses

An interim analysis focusing on trial participant safety will compare between-group differences in the incidences of the composite outcome and its components. The interim analysis will be performed after half of the targeted sample size (152 patients) have completed their 90 days follow-up (Table 3). Based on the O'Brien–Fleming method, the between group difference in the primary composite outcome should reach a p-value of 0.0031 to indicate early termination of the trial due to efficacy [88–90].

The results of the interim analysis will be reported to the DMSB, which will discuss the results and recommend whether the trial should continue. The DMSB's role is to advise the trial investigators and may recommend stopping the trial early under the following conditions:

- For Efficacy: If the interim analysis shows a statistically significant difference between the groups in the primary composite outcome that meets the efficacy threshold set by the O'Brien–Fleming method ($p \leq 0.0031$), indicating that the treatment is clearly beneficial.
- For Safety or Futility: If the O'Brien–Fleming efficacy threshold is not met, but there are statistically significant ($p \leq 0.05$) differences in 3-month functional outcome (measured by the mRS) or 3-month mortality, that suggest potential harm to participants.

In both cases, the DMSB's recommendation will be based on a thorough review of the data to ensure participant safety and the trial's scientific integrity.

If there is a non-statistically significant trend ($p > 0.05$) indicating increased harm in one of the groups, the DSMB may mandate additional interim analyses to evaluate the safety of continuing the trial. If the DSMB requests an additional interim analysis, we will apply the error-spending O'Brien–Fleming method, impacting the sample size and statistical parameters in Table 3. Only blinded data will be presented for the interim analysis. Unblinding is only possible if the DSMB advises the trial investigators to halt recruitment.

We will perform a review of the dropout rate after recruiting 80% of patients to verify that the sample size calculation remains valid. This review is not an interim analysis for efficacy or safety but a check to ensure that the number of evaluable patients is sufficient to meet the trial's objectives. If the review indicates that the sample size needs to be increased to maintain the planned number of evaluable patients (initially 332), a substantial

Table 3 Critical values, p-values, and sample sizes for an error-spending O'Brien–Fleming sequential design

Information fraction	Lower efficacy*	Upper efficacy*	Approximated CI	p-value	Group A, n	Group B, n	Total, N
50% (interim analysis)	−2.962	2.9626	99.7%	0.0031	76	76	152
100% (complete study set)	−1.968	1.9686	95.1%	0.0490	151	151	302

A 10% dropout rate will be added to the final sample size of 302, giving a total sample size of 332 patients (166 patients per group)

Abbreviations: *CI*, confidence interval

* z statistics

modification application will be submitted to the regulatory authorities for approval. The sample size will not be increased to detect a smaller effect size than originally planned, and sample size re-estimation for this purpose is not planned for this trial. Separately, the trial may be stopped early for efficacy if the interim analysis demonstrates a statistically significant difference in the primary composite outcome, as determined by the error-spending O'Brien–Fleming method ($p \leq 0.0031$), indicating a larger-than-expected effect size.

Study monitoring and data safety and monitoring board

Study monitoring is provided by the Clinical Research Institute of Helsinki University Hospital, who will ensure the quality of data collection and trial integrity. The monitoring is performed in accordance with currently valid rules and regulations, Good Clinical Practice (ICH-GCP) and the standardized instructions of the Clinical Research Institute Helsinki University Hospital.

An independent DSMB has been established to protect the interests of trial participants and ensure the trial's scientific integrity. The DSMB consists of experts who are independent of the sponsor and have no competing interests. The DSMB's primary role is to monitor participant safety by reviewing accumulating data from the trial, including the pre-planned interim analysis. The DSMB reports its findings and recommendations in writing to the trial's Principal Investigator (PI). The committee operates according to a formal, detailed charter that outlines its full responsibilities, procedures, and decision-making rules. This charter is available in its entirety as an Online Supplement, p12.

The trial may be subject to inspection by relevant regulatory authorities. However, beyond the routine monitoring described above, no additional independent audits are planned.

Ethics and regulatory considerations

This clinical trial will be conducted in strict compliance with this protocol, the EU Clinical Trial Regulation (CTR) 536/2014, and the principles of Good Clinical Practice (GCP) as outlined in the International Council for Harmonisation (ICH) E6 guideline.

The study received ethical and regulatory approval in accordance with the EU Clinical Trials Regulation via CTIS. Finland served as the Reporting Member State, with Part I approved by the Finnish Medicines Agency (FIMEA/2025/003237) and Part II by the National Committee on Medical Research Ethics (Tukija, T/32/2025). The Swedish Medical Products Agency (2025-521179-29-00) approved Part II for Sweden as a participating Member State. Local institutional research approvals will be obtained by all participating centers.

Recruitment and timetable

The feasibility of recruiting 332 patients is supported by data from the preceding FINISH trial, which screened 1644 patients over a 24-month period at the participating Finnish centers [7]. This suggests a screening rate of approximately 60 patients per month in Finland. With the inclusion of Karolinska University Hospital, we anticipate a total screening rate of approximately 90 patients per month across all sites [23]. Based on previous studies, an estimated 25% of CSDH patients are on anticoagulants for atrial fibrillation [7, 8, 20]. This translates to an estimated 22–23 eligible patients per month, making the target recruitment of 332 patients achievable within an estimated 14–15 months. Recruitment progress will be monitored by the Steering Committee. If enrolment is slower than anticipated, additional international sites may be invited to join the trial to ensure the target sample size is met.

Dissemination plan

The results of this trial will be submitted for publication in an international, peer-reviewed journal, regardless of the outcome or statistical significance of the findings. The final trial report will be prepared in accordance with the CONSORT (Consolidated Standards of Reporting Trials). Findings will also be presented at national and international scientific congresses. Upon completion of the trial, a summary of the main results will be made available to trial participants in an accessible, lay-friendly format. In accordance with the trial's data sharing plan, anonymized data may be made available to other researchers upon reasonable request via FINDATA, subject to a data access agreement.

Patient and public involvement

Patients and members of the public were not involved in the planning, design, or development of this trial.

Protocol version

Protocol version 1.2 (May 4, 2025, EU-CT 2025-521179-29-00).

Protocol amendments

Any important modifications to the protocol, including changes to eligibility criteria, outcomes, or analyses, will require approval from the Steering Committee. Once approved, the lead Principal Investigator will be responsible for communicating these amendments to all relevant parties. A copy of the revised protocol will be sent to all site investigators, and a new version

number will be assigned. All necessary documentation will be submitted to the relevant ethics committees (National Committee on Medical Research Ethics, Tukija) and regulatory authorities (Finnish Medicines Agency, Swedish Medical Products Agency) for approval prior to implementation. The trial registration at the EU Clinical Trials Register will also be updated accordingly. Trial participants will be informed of any changes that directly affect their participation, and a new consent form will be administered if necessary.

Ancillary care and compensation

No special ancillary or post-trial care is planned beyond the standard clinical management of the patient, as determined by their treating physician. For compensation in the event of trial-related harm, all participants in Finland are covered by statutory patient insurance through the Finnish Mutual Patient Insurance Company. Participants in Sweden are covered by the Swedish Patient Injury Insurance (LÖF) and the Pharmaceutical Insurance (Läkemedelsförsäkringen).

Discussion

To the best of our knowledge, this is the first large-scale multicenter RCT comparing early versus late anticoagulation medication resumption in patients having AF undergoing CSDH surgery.

Our pragmatic trial is designed to detect the straight downstream biological effect of anticoagulation resumption over indirect effects. Thus, the primary outcome is a composite outcome of arterial thromboembolic events, hemorrhagic events and vascular deaths, instead of for example functional outcome. However, the effect of the functional outcome cannot be neglected and, thus, it is a key secondary outcome measure of this trial. In fact, estimating the needed sample size to detect a 1.75 odds difference in the shift of the ordinal mRS favoring early resumption would need a total of 330 patients (Online Material, p11), giving this study the power to detect such a difference.

To our knowledge, there is a pilot trial planned aiming to compare anticoagulation resumption after 30 days versus 90 days in patients on oral anticoagulation medication due to AF, with mRS as the intended primary outcome [94]. The major differences in protocol are timing of early resumption (5 days in our trials versus 30 days in the other trial) and primary outcome (composite outcome of thromboembolic events, hemorrhagic events and vascular deaths in our trial versus the modified Rankin Scale in the other trial).

Currently, there is a major lack of evidence guiding clinical decision-making for when to resume anticoagulation medication after CSDH surgery. This constitutes a daily clinical dilemma for neurosurgeons and other involved physicians, balancing the perceived risk of hemorrhagic complications versus thromboembolic complications. A multicenter RCT that could show a decrease in thromboembolic events and vascular deaths without increasing the risk for hemorrhagic complications would influence the treatment of these patients all over the world. This would not only benefit the individual patient but also health care systems all over the world, considering the sharply increasing incidence of anticoagulation use and CSDH [1, 2, 10, 11].

Early anticoagulation resumption (at 5 days postoperatively) is anticipated to reduce the risk of thromboembolic events, which are associated with very poor outcomes [28]. Although postoperative anticoagulation is traditionally delayed to avoid potential risks, such as intracranial hemorrhage or hematoma recurrence, recent evidence indicates that resuming anticoagulation early does not increase the incidence of intracranial bleeding [29] or elevate CSDH recurrence rates [33]. Moreover, even when a recurrence occurs, it is treatable condition that does not adversely affect long-term clinical or functional outcomes [95, 96]. Thus, the potential benefits of reducing thromboembolic events greatly outweigh the minimal hemorrhagic risk, supporting the safety and feasibility of early anticoagulation resumption.

A major strength of the study is that the five Finnish participating centers cover 100% of the Finnish population and the Swedish center covers approximately 25% of the Swedish population in terms of provision of neurosurgical care. In both Finland and Sweden, the surgical treatment of CSDH is exclusively carried out in university hospitals, meaning that the follow-up regarding the primary endpoint (recurrence) should be 100%. Also, in highly digitalized healthcare systems (nationwide in Finland and region-wide in Sweden) where every citizen has a unique personal identification number, the chances for successful follow-up regarding other endpoints are extremely high.

Some limitations are that the pragmatic study design allows varying types of oral anticoagulation medication, and although subgroup analyses are planned, the use of different anticoagulation medications may have different effect on the outcome. Further, patients and treating physicians are not blinded to treatment allocation; however, this is mitigated by using blinded assessors for outcome evaluation and the preplanned BDI [67].

Trial status

The study is being conducted under protocol version 1.2 (May 4, 2025). Recruitment began on July 6, 2025, and is expected to be completed by the end of 2027.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-09133-w.

Supplementary Material 1. Online material SPIRIT Checklist.

Trial governance and oversight

Steering Committee

The Steering Committee (SC) is responsible for the overall supervision of the trial and for ensuring it is conducted according to the protocol and Good Clinical Practice (GCP) standards. Key responsibilities include approving protocol amendments, monitoring trial progress, and reviewing recommendations from the DSMC. The SC convenes after each interim analysis and as otherwise required. The members are: Rahul Raj (chair), Jarno Satopää, Riku Kivisaari, Pihla Tommiska, Teemu Luostarinen, Jyri Virta, Miikka Korja, Teemu Luoto, Jussi P. Posti, Nils Danner, Timo Koivisto, Ville Leinonen, Oula Knuutinen, Simo Taimela, Teppo LN Järvinen, and Jiri Bartek.

Coordinating centre

The Coordinating Centre at Helsinki University Hospital is responsible for the central coordination and day-to-day management of the trial. It is led by the Principal Investigator (PI) and co-PI, supported by a research coordinator and data management staff.

Data and safety monitoring board

An independent DSMB, consisting of independent external clinical experts, has been established to protect the interests of trial participants by periodically reviewing accumulating safety and efficacy data. The DSMB will oversee the interim analysis, which aims to monitor participant safety. The committee operates according to a formal charter and provides recommendations to the Steering Committee regarding the continuation or modification of the trial. The members are:

– Martin Lehecka, MD, PhD, A. Prof, Helsinki University Hospital, Finland
– Frederick A. Zeiler, MD, PhD, A. Prof, Rady Faculty of Health Sciences, University of Manitoba, Canada
– Eric Thelin, MD, PhD, A. Prof, Karolinska University Hospital, Stockholm, Sweden

Writing committee

The Writing Committee is responsible for preparing the primary manuscript for publication. The committee is chaired by the lead PI, who will lead the drafting of the manuscript. All members are responsible for critically revising the manuscript for important intellectual content, providing final approval of the version to be published, and ensuring adherence to authorship guidelines. The members of the Writing Committee are: Rahul Raj (chair), Jarno Satopää, Miikka Korja, Pihla Tommiska, Teemu Luoto, Jussi P. Posti, Nils Danner, Oula Knuutinen, Simo Taimela, Teppo LN Järvinen, Jiri Bartek, Mika Niemelä.

Trial sponsor center

Helsinki University Hospital

– Contact: Rahul Raj, rahul.raj@hus.fi, +358504272517, Haartmaninkatu 4, PB 320, 00029 HUS, Finland.

Authors' contributions

Rahul Raj, Miikka Korja, Nils Danner, Jiri Bartek, Oula Knuutinen, Jussi P. Posti, Teemu Luoto and Jarno Satopää designed the trial. Pihla Tommiska, Riku Kivisaari, Teemu Luostarinen, Jyri J Virta, Simo Taimela, Teppo LN Järvinen, Mika Niemelä, Timo Koivisto, Ville Leinonen, Bjartur Saemundsson, Alexander Fletcher-Sandersjöö, Tommi Korhonen, Sami Tetri, Minna Rauhala, Dan Laukka, and Tomasz Czuba provided intellectual feedback for planning the trial and helping in drafting the manuscript. Rahul Raj drafted the manuscript. All authors have been involved in critically revising the manuscript for intellectual content. All authors read and approved the final manuscript.

Funding

Open Access funding provided by University of Helsinki (including Helsinki University Central Hospital). This study is supported by the State funding for university-level health research (Helsinki University Hospitals), Finska Läkaresällskapet, Medicinska Understödsföreningen Liv & Hälsa, Svenska Kulturfonden and Maire Taponen Foundation. The funding sources will have no role in the collection, analysis and interpretation of data; in the writing of the report and in the decision to submit the article for publication.

Data availability

Data generated by our study will be made available as soon as possible and will be available on reasonable request complying to the Act on the Secondary Use of Health and Social Data (https://findata.fi/en/). Data access requests will be reviewed by the RELACS steering group. Requestors will be required to sign a data access agreement. Only anonymized data can be shared via FINDATA.

Declarations

Consent for publication

Not required.

Competing interests

None.

Author details

[1]Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [2]Anesthesiology and Intensive Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [3]Finnish Centre for Evidence-Based Orthopedics (FICEBO), University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [4]Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [5]Department of Neurosurgery, Kuopio University Hospitaland, University of Eastern Finland, Kuopio, Finland. [6]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. [7]Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden. [8]University of Oulu and Medical Research Center, Unit of Clinical Neuroscience, Neurosurgery, Oulu, Finland. [9]Department of Neurosurgery, Tampere University Hospital and Tampere University, Tampere, Finland. [10]Department of Neurosurgery and Turku Brain Injury Center, Turku University Hospital and University of Turku, Turku, Finland. [11]Division of Clinical Neurosciences, Neurosurgery, University of Turku, Turku, Finland. [12]Department of Molecular and Clinical Medicine/The Wallenberg Laboratory, Institute of Medicine, Gothenburg University and the Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden. [13]Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden.

Received: 13 June 2025 Accepted: 5 September 2025
Published online: 17 November 2025

References

1. Balser D, Farooq S, Mehmood T, Reyes M, Samadani U. Actual and projected incidence rates for chronic subdural hematomas in United States veterans administration and civilian populations. J Neurosurg. 2015;123:1209–15.
2. Rauhala M, Luoto TM, Huhtala H, Iverson GL, Niskakangas T, Öhman J, et al. The incidence of chronic subdural hematomas from 1990 to 2015 in a defined Finnish population. J Neurosurg. 2019;132:1147–57
3. Tommiska P, Luostarinen T, Kaprio J, Korja M, Lönnrot K, Kivisaari R, et al. Incidence of surgery for chronic subdural hematoma in Finland during 1997–2014: a nationwide study. J Neurosurg. 2021;136:1886–93.
4. Gaist D, García Rodríguez LA, Hellfritzsch M, Poulsen FR, Halle B, Hallas J, et al. Association of antithrombotic drug use with subdural hematoma risk. JAMA. 2017;317:836–46.
5. Miah IP, Holl DC, Blaauw J, Lingsma HF, den Hertog HM, Jacobs B, et al. Dexamethasone versus surgery for chronic subdural hematoma. N Engl J Med. 2023;388:2230–40.
6. Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N, et al. Trial of dexamethasone for chronic subdural hematoma. N Engl J Med. 2020;383:2616–27.
7. Raj R, Tommiska P, Koivisto T, Leinonen V, Danner N, Posti JP, et al. Burr-hole drainage with or without irrigation for chronic subdural

haematoma (FINISH): a Finnish, nationwide, parallel-group, multicentre, randomised, controlled, non-inferiority trial. Lancet Lond Engl. 2024;S0140–6736(24)00686-X.
8. Grønhøj MH, Jensen TSR, Miscov R, Sindby AK, Debrabant B, Hundsholt T, et al. Optimal drainage time after evacuation of chronic subdural haematoma (DRAIN TIME 2): a multicentre, randomised, multiarm and multistage non-inferiority trial in Denmark. Lancet Neurol. 2024;0. Available from: https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(24)00175-3/abstract. Cited 16 Jun 2024.
9. Soleman J, Lutz K, Schaedelin S, Kamenova M, Guzman R, Mariani L, et al. Subperiosteal vs subdural drain after burr-hole drainage of chronic subdural hematoma: a randomized clinical trial (cSDH-drain-trial). Neurosurgery. 2019;85:E825–34.
10. Krijthe B, Kunst A, Benjamin E, Lip G, Franco F, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013;34. Available from: https://pubmed.ncbi.nlm.nih.gov/23900699/. Cited 16 Jun 2024.
11. Miyasaka Y, Barnes M, Gersh B, Cha S, Bailey K, Abhayaratna W, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114. Available from: https://pubmed.ncbi.nlm.nih.gov/16818816/. Cited 16 Jun 2024.
12. Guha D, Coyne S, Macdonald RL. Timing of the resumption of antithrombotic agents following surgical evacuation of chronic subdural hematomas: a retrospective cohort study. J Neurosurg. 2016;124:750–9.
13. Chari A, Clemente Morgado T, Rigamonti D. Recommencement of anticoagulation in chronic subdural haematoma: a systematic review and meta-analysis. Br J Neurosurg. 2014;28:2–7.
14. Amano T, Takahara K, Maehara N, Shimogawa T, Mukae N, Sayama T, et al. Optimal perioperative management of antithrombotic agents in patients with chronic subdural hematoma. Clin Neurol Neurosurg. 2016;151:43–50.
15. Kerttula S, Huttunen J, Leinonen V, Kämäräinen O-P, Danner N. The effect of antithrombotic therapy on the recurrence and outcome of chronic subdural hematoma after burr-hole craniostomy in a population-based cohort. Acta Neurochir (Wien). 2022;164:2699–708.
16. Mirzayan MJ, Calvelli K, Capelle H-H, Weigand J, Krauss JK. Subdural hematoma and oral anticoagulation: a therapeutic dilemma from the neurosurgical point of view. J Neurol Surg Part Cent Eur Neurosurg. 2016;77:31–5.
17. Kamenova M, Nevzati E, Lutz K, Dolp A, Fandino J, Mariani L, et al. Burr-hole drainage for chronic subdural hematoma under low-dose acetylsalicylic acid: a comparative risk analysis study. World Neurosurg. 2017;100:594–600.
18. Kamenova M, Lutz K, Schaedelin S, Fandino J, Mariani L, Soleman J. Does early resumption of low-dose aspirin after evacuation of chronic subdural hematoma with burr-hole drainage lead to higher recurrence rates? Neurosurgery. 2016;79:715–21.
19. Fornebo I, Sjåvik K, Alibeck M, Kristiansson H, Ståhl F, Förander P, et al. Role of antithrombotic therapy in the risk of hematoma recurrence and thromboembolism after chronic subdural hematoma evacuation: a population-based consecutive cohort study. Acta Neurochir (Wien). 2017;159:2045–52.
20. Schucht P, Fischer U, Fung C, Bernasconi C, Fichtner J, Vulcu S, et al. Follow-up computed tomography after evacuation of chronic subdural hematoma. N Engl J Med. 2019;380:1186–7.
21. Duerinck J, Van Der Veken J, Schuind S, Van Calenbergh F, van Loon J, Du Four S, et al. Randomized trial comparing burr hole craniostomy, minicraniotomy, and twist drill craniostomy for treatment of chronic subdural hematoma. Neurosurgery. 2022. https://doi.org/10.1227/neu.0000000000001997.
22. Santarius T, Kirkpatrick PJ, Ganesan D, Chia HL, Jalloh I, Smielewski P, et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. Lancet. 2009;374:1067–73.
23. Bartley A, Bartek J Jr, Jakola AS, Sundblom J, Fält M, Förander P, et al. Effect of irrigation fluid temperature on recurrence in the evacuation of chronic subdural hematoma: a randomized clinical trial. JAMA Neurol. 2023;80:58–63.
24. Nathan S, Goodarzi Z, Jette N, Gallagher C, Holroyd-Leduc J. Anticoagulant and antiplatelet use in seniors with chronic subdural hematoma: systematic review. Neurology. 2017;88:1889–93.
25. Prior A, Fiaschi P, Iaccarino C, Stefini R, Battaglini D, Balestrino A, et al. How do you manage ANTICOagulant therapy in neurosurgery? The ANTICO survey of the Italian Society of Neurosurgery (SINCH). BMC Neurol. 2021;21:98.
26. Wang H, Zhang M, Zheng H, Xia X, Luo K, Guo F, et al. The effects of antithrombotic drugs on the recurrence and mortality in patients with chronic subdural hematoma: A meta-analysis. Medicine (Baltimore). 2019;98:e13972.
27. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol. 2007;6:182–7.
28. Tommiska P, Knuutinen O, Lönnrot K, Kivisaari R, Raj R, FINISH Investigators. Association between postoperative thromboembolic and hemorrhagic complications and clinical outcomes after surgery for chronic subdural hematoma in patients with anticoagulation therapy for atrial fibrillation. Acta Neurochir (Wien). 2025;167:17.
29. Phan K, Abi-Hanna D, Kerferd J, Lu VM, Dmytriw AA, Ho Y-T, et al. Resumption of antithrombotic agents in chronic subdural hematoma: a systematic review and meta-analysis. World Neurosurg. 2018;109:e792–9.
30. Yeon JY, Kong D-S, Hong S-C. Safety of early warfarin resumption following burr hole drainage for warfarin-associated subacute or chronic subdural hemorrhage. J Neurotrauma. 2012;29:1334–41.
31. Bartek J, Sjåvik K, Kristiansson H, Ståhl F, Fornebo I, Förander P, et al. Predictors of recurrence and complications after chronic subdural hematoma surgery: a population-based study. World Neurosurg. 2017;106:609–14.
32. Gonugunta V, Buxton N. Warfarin and chronic subdural haematomas. Br J Neurosurg. 2001;15:514–7.
33. Zhang JJY, Aw NMY, Tan CH, Lee KS, Chen VHE, Wang S, et al. Impact of time to resumption of antithrombotic therapy on outcomes after surgical evacuation of chronic subdural hematoma: a multicenter cohort study. J Clin Neurosci. 2021;89:389–96.
34. Aspegren OP, Åstrand R, Lundgren MI, Romner B. Anticoagulation therapy a risk factor for the development of chronic subdural hematoma. Clin Neurol Neurosurg. 2013;115:981–4.
35. Ohba S, Kinoshita Y, Nakagawa T, Murakami H. The risk factors for recurrence of chronic subdural hematoma. Neurosurg Rev. 2013;36:145–9; discussion 149–150.
36. Brennan PM, Kolias AG, Joannides AJ, Shapey J, Marcus HJ, Gregson BA, et al. The management and outcome for patients with chronic subdural hematoma: a prospective, multicenter, observational cohort study in the United Kingdom. J Neurosurg. 2017;127:732–9.
37. Leroy H-A, Aboukaïs R, Reyns N, Bourgeois P, Labreuche J, Duhamel A, et al. Predictors of functional outcomes and recurrence of chronic subdural hematomas. J Clin Neurosci. 2015;22:1895–900.
38. Honda Y, Sorimachi T, Momose H, Takizawa K, Inokuchi S, Matsumae M. Chronic subdural haematoma associated with disturbance of consciousness: significance of acute-on-chronic subdural haematoma. Neurol Res. 2015;37:985–92.
39. Chon K-H, Lee J-M, Koh E-J, Choi H-Y. Independent predictors for recurrence of chronic subdural hematoma. Acta Neurochir (Wien). 2012;154:1541–8.
40. Choi J, Pyen J, Cho S, Kim J, Koo Y, Whang K. Influence of antithrombotic medication on the risk of chronic subdural hematoma recurrence after burr-hole surgery. J Korean Neurosurg Soc. 2020;63:513–8.
41. Ro HW, Park SK, Jang DK, Yoon WS, Jang KS, Han YM. Preoperative predictive factors for surgical and functional outcomes in chronic subdural hematoma. Acta Neurochir (Wien). 2016;158:135–9.
42. Yu X, Wu L, Ou Y, Xu L, Guo X, Yang C, et al. Clinical characteristics and outcomes of chronic subdural hematoma in patients with a history of antiplatelet therapy. Clin Neurol Neurosurg. 2021;208:106817.
43. René O, Martin H, Pavol S, Kristián V, Tomáš F, Branislav K. Factors influencing the results of surgical therapy of non-acute subdural haematomas. Eur J Trauma Emerg Surg. 2021;47:1649–55.
44. Shimizu K, Sadatomo T, Hara T, Onishi S, Yuki K, Kurisu K. Importance of frailty evaluation in the prediction of the prognosis of patients with chronic subdural hematoma. Geriatr Gerontol Int. 2018;18:1173–6.
45. Hounkpatin S, Stierer M, Frechon P, Rault F, Kelani A, Emery E, et al. Comparative analysis of surgical techniques in the management of chronic subdural hematomas and risk factors for poor outcomes. Neurosurg Rev. 2024;47:254.

46. Liu J, Ni W, Zuo Q, Yang H, Peng Y, Lin Z, et al. Middle meningeal artery embolization for nonacute subdural hematoma. N Engl J Med. 2024;391:1901–12.
47. Fiorella D, Monteith SJ, Hanel R, Atchie B, Boo S, McTaggart RA, et al. Embolization of the Middle Meningeal Artery for Chronic Subdural Hematoma. N Engl J Med. 2024;391. Available from: https://www.nejm.org/doi/doi/full/10.1056/NEJMoa2409845. Cited 21 Nov 2024.
48. Davies JM, Knopman J, Mokin M, Hassan AE, Harbaugh RE, Khalessi A, et al. Adjunctive middle meningeal artery embolization for subdural hematoma. N Engl J Med. 2024;391:1890–900.
49. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586
50. Chen A, Stecker EA, Warden B. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. J Am Heart Assoc. 2020;9:e017559.
51. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human participants. JAMA. 2025;333:71–4.
52. Raj R, Tommiska P, Luoto T, Leinonen V, Koivisto T, Tetri S, et al. Failure to improve-identifying risk factors for poor functional recovery following chronic subdural hematoma surgery. Age Ageing. 2025;54:afaf056.
53. Jensen TSR, Haldrup M, Grønhøj MH, Miscov R, Larsen CC, Debrabant B, et al. National randomized clinical trial on subdural drainage time after chronic subdural hematoma evacuation. J Neurosurg. 2021;137:799–806.
54. Sale D. Single versus double burr hole for drainage of chronic subdural hematoma: randomized controlled study. World Neurosurg. 2021;146:e565–7.
55. Pinggera D, Unterhofer C, Görtz P, Thomé C, Ortler M. Postoperative thromboembolic prophylaxis with low-molecular-weight heparin and risk of rebleeding in patients with chronic subdural hematomas: a comparative retrospective cohort study. World Neurosurg. 2017;104:284–90.
56. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
57. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81.
58. Ryu SM, Yeon JY, Kong D-S, Hong S-C. Risk of recurrent chronic subdural hematoma associated with early warfarin resumption: a matched cohort study. World Neurosurg. 2018;120:e855–62.
59. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Ortel TL, Saxonhouse SJ, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69:871–98.
60. Douketis JD, Spyropoulos AC, Murad MH, Arcelus JI, Dager WE, Dunn AS, et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. Chest. 2022;162:e207–43.
61. Douketis JD, Spyropoulos AC. Perioperative management of anticoagulant and antiplatelet therapy. NEJM Evid. 2023;2:EVIDra2200322.
62. Douketis JD, Spyropoulos AC, Duncan J, Carrier M, Le Gal G, Tafur AJ, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. JAMA Intern Med. 2019;179:1469–78.
63. Halme ALE, Roshanov PS, Tornberg SV, Lavikainen LI, Devereaux PJ, Tikkinen KAO, et al. Timing of Major Postoperative Bleeding Among Patients Undergoing Surgery. JAMA Netw Open. 2024;7:e244581.
64. Schulman S, Hwang H-G, Eikelboom JW, Kearon C, Pai M, Delaney J. Loading dose vs. maintenance dose of warfarin for reinitiation after invasive procedures: a randomized trial. J Thromb Haemost. 2014;12:1254–9.
65. Bungard TJ, Mutch J, Ritchie B. A randomized trial of restarting warfarin at maintenance versus loading doses following an elective procedure. J Thromb Thrombolysis. 2017;44:507–15.
66. El Naamani K, Abbas R, Ghanem M, Mounzer M, Tjoumakaris SI, Gooch MR, et al. Resuming anticoagulants in patients with intracranial hemorrhage: a meta-analysis and literature review. Neurosurgery. 2024;94:14–9.
67. Järvinen TLN, Sihvonen R, Bhandari M, Sprague S, Malmivaara A, Paavola M, et al. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. J Clin Epidemiol. 2014;67(7):769–72.
68. Teppo K, Jaakkola J, Airaksinen KEJ, Biancari F, Halminen O, Putaala J, et al. Mental health conditions and adherence to direct oral anticoagulants in patients with incident atrial fibrillation: a nationwide cohort study. Gen Hosp Psychiatry. 2022;74:88–93.
69. Teppo K, Jaakkola J, Biancari F, Halminen O, Linna M, Haukka J, et al. Association of income and educational levels with adherence to direct oral anticoagulant therapy in patients with incident atrial fibrillation: a Finnish nationwide cohort study. Pharmacol Res Perspect. 2022;10:e00961.
70. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69:236–9.
71. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
72. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
73. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
74. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
75. Fischer U, Koga M, Strbian D, Branca M, Abend S, Trelle S, et al. Early versus later anticoagulation for stroke with atrial fibrillation. N Engl J Med. 2023;388:2411–21.
76. European Medicines Agency. ICH Topic 9: Statistical Principles for Clinical Trials. 2006;1998:37.
77. Montori VM, Permanyer-Miralda G, Ferreira-González I, Busse JW, Pacheco-Huergo V, Bryant D, et al. Validity of composite end points in clinical trials. BMJ. 2005;330:594–6.
78. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJB, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064–89.
79. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol. 2018;72(18):2231–64.
80. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. Am Heart J. 2010;159:340-347.e1.
81. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3:692–4.
82. Socialstyrelsen D of R and S. Statistical register's production and quality National Cause of Death Register. 2022. Report No.: Item no.: 2022–5–7909. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/ovrigt/production-and-quality-dors.pdf.
83. European Medicines Agency. ICH Topic E 2 A. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. 1995. Available from: https://www.ema.europa.eu/en/ich-e2a-clinical-safety-data-management-definitions-standards-expedited-reporting-scientific-guideline#:~:text=01/06/1995-,View,-Related%20content.
84. Jormanainen V. Large-scale implementation and adoption of the Finnish national Kanta services in 2010–2017: a prospective, longitudinal, indicator-based study. Finn J eHealth eWelfare. 2018;10:381–95.
85. Statistics Finland. Official Statistics of Finland (OSF): Causes of death [online publication]. 2022. Available from: https://stat.fi/en/statistics/ksyyt.
86. Socialstyrelsen. National Cause of Death Register. 2024. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-cause-of-death--register/.
87. Douketis JD, Healey JS, Brueckmann M, Fraessdorf M, Spyropoulos AC, Wallentin L, et al. Urgent surgery or procedures in patients taking dabigatran or warfarin: analysis of perioperative outcomes from the RE-LY trial. Thromb Res. 2016;139:77–81.
88. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549–56.

89. StataCorp. Adaptive Designs: Group Sequential Trials Reference Manual, Release 18. Stata Press; 2023. Available from: https://www.stata.com/bookstore/adaptive-designs-reference-manual/. Cited 4 Oct 2024.
90. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659–63.
91. Sihvonen R, Paavola M, Malmivaara A, Itala A, Joukainen A, Nurmi H, et al. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. N Engl J Med. 2013;369:2515–24.
92. Paavola M, Malmivaara A, Taimela S, Kanto K, Inkinen J, Kalske J, et al. Subacromial decompression versus diagnostic arthroscopy for shoulder impingement: randomised, placebo surgery controlled clinical trial. BMJ. 2018;362:k2860.
93. Jarvinen TLN, Sihvonen R, Bhandari M, Sprague S, Malmivaara A, Paavola M, et al. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. J Clin Epidemiol. 2014;67(7):769–72.
94. Mansouri A, Nassiri F, Scales D, Pirouzmand F. Anticoagulation therapy timing in patients with atrial fibrillation after acute and chronic subdural haematoma (ATTAACH): a pilot randomised controlled trial. BMJ Open. 2024;14:e090224.
95. Rauhala M, Helén P, Seppä K, Huhtala H, Iverson GL, Niskakangas T, et al. Long-term excess mortality after chronic subdural hematoma. Acta Neurochir (Wien). 2020;162:1467–78.
96. Pang CH, Lee SE, Kim CH, Kim JE, Kang H-S, Park C-K, et al. Acute intracranial bleeding and recurrence after bur hole craniostomy for chronic subdural hematoma. J Neurosurg. 2015;123:65–74.

Publisher's Note