Chronic Subdural Hematoma: Epidemiology, Mortality and Risk of Recurrence

Pihla Tommiska

Department of Neurosurgery
Helsinki University Hospital
University of Helsinki
Finland

and

Faculty of Medicine
Doctoral Program in Clinical Research
University of Helsinki
Finland

Doctoral Dissertation

To be presented for public discussion with the permission
of the Faculty of Medicine, University of Helsinki,
In the Lecture hall 1 in the Töölö Hospital,
Topeliuksenkatu 5, Helsinki
On the 28th of October 2022, at noon.

Contact information:
Pihla Tommiska, MD
Department of Neurosurgery
Helsinki University Hospital
Topeliuksenkatu 5
00260 Helsinki
Finland

mobile: +358405690294
e-mail: pihla.tommiska@helsinki.fi

The Faculty of Medicine uses the Urkund system
(plagiarism recognition) to examine all doctoral dissertations.

ISBN 978-951-51-8684-3 (paperback)
ISBN 978-951-51-8685-0 (PDF)

Unigrafia
Helsinki 2022

Supervised by
Kimmo Lönnrot, MD, PhD
Department of Neurosurgery
Helsinki University Hospital and University of Helsinki
Helsinki, Finland

Associate Professor **Rahul Raj**, MD, PhD
Department of Neurosurgery
Helsinki University Hospital and University of Helsinki
Helsinki, Finland

Associate Professor **Riku Kivisaari**, MD, PhD
Department of Neurosurgery
Helsinki University Hospital and University of Helsinki
Helsinki, Finland

Reviewed by
Professor **Mikael von und zu Fraunberg**, MD, PhD
Department of Neurosurgery
Oulu University Hospital
Oulu, Finland

Associate Professor **Joonas Haapasalo**, MD, PhD
Department of Neurosurgery
Tampere University Hospital
Tampere, Finland

To be discussed with
Professor **Isabelle M. Germano**, MD, MBA
Department of Neurosurgery
Icahn School of Medicine at Mount Sinai Hospital
New York City, USA

To Nonna and Ukki

Table of contents

List of original publications

This thesis is based on the following publications:

I TOMMISKA P, LÖNNROT K, RAJ R, LUOSTARINEN T, KIVISAARI R: *Transition of a Clinical Practice to Use of Subdural Drains after Burr Hole Evacuation of Chronic Subdural Hematoma: The Helsinki Experience.* World Neurosurgery. 2019;129:e614-e626.

II TOMMISKA P, KORJA M, SIIRONEN J, KAPRIO J, RAJ R: *Mortality of older patients with dementia after surgery for chronic subdural hematoma: a nationwide study*. Age and Ageing. 2021;50(3):815-821.

III TOMMISKA P, LUOSTARINEN T, KAPRIO J, KORJA M, LÖNNROT K, KIVISAARI R, RAJ R: *Incidence of surgery for chronic subdural hematoma in Finland during 1997-2014: a nationwide study*. Journal of Neurosurgery. 2021;136(4):1186-1193.

IV/ Study protocol TOMMISKA P*, RAJ R*, SCHWARTZ C, KIVISAARI R, LUOSTARINEN T, SATOPÄÄ J, TAIMELA S, JÄRVINEN TLN, RANSTAM J, FRANTZÉN J, POSTI JP, LUOTO TM, LEINONEN V, TETRI S, KOIVISTO T, LÖNNROT K: *Finnish study of intraoperative irrigation versus drain alone after evacuation of chronic subdural haematoma (FINISH): a study protocol for a multicentre randomized controlled trial*. BMJ Open. 2020;10(6):e038275.

* Contributed equally

The original publications are reproduced here with the permission of the copyright holders. The studies I–III are referred to in the text using Roman numerals. Publication IV is referred to as study protocol.

Abbreviations

ACE .... Angiotensin-converting enzyme
AE .... Adverse event
ASDH.......... Acute subdural hematoma
BADL.......... Basic activities of daily living
BHC .... Burr-hole craniostomy
CI .... Confidence interval
CSDH.......... Chronic subdural hematoma
CSF .... Cerebrospinal fluid
CT .... Computed tomography
DOAC .... Direct oral anticoagulant
eCRF........... Electronic case report form
ESP .... European Standard Population
EUPATI...... European Patients' Academy on Therapeutic Innovation
GCS............. Glasgow Coma Scale
GOS .... Glasgow Outcome Scale
HR............... Hazard ratio
HU............... Hounsfield unit
IADL........... Instrumental activities of daily living
ICD .... International Statistical Classification of Diseases and Related Health Problems
IQR .... Interquartile range
IRR .... Incidence rate ratio
ITT.............. Intention-to-treat
LMWH .... Low-molecular-weight heparin
MAE .... Minor adverse event
MGS............ Markwalder Grading Scale
MMA .... Middle meningeal artery
MRI............. Magnetic resonance imaging
mRS .... Modified Rankin Scale
NCSP-F....... NOMESCO (Nordic Medico-Statistical Committee) Classification of Surgical Procedures Finland
OR............... Odds ratio
PCC............. Prothrombin complex concentrate
PP................ Per-protocol
PRAE.......... Procedure-related adverse event
RCT .... Randomized controlled trial
SAE............. Severe adverse event
SDH............. Subdural hematoma
SIH.............. Spontaneous intracranial hypotension
TDC .... Twist-drill craniostomy
TXA .... Tranexamic acid

VEGF .... Vascular endothelial growth factor
VKA .... Vitamin K antagonist

Abstract

Introduction
Chronic subdural hematoma (CSDH) is a common neurosurgically treated disorder. Use of a subdural drain has been reported to reduce recurrence rates. Yet, few studies dispute routine placement of subdural drains. We aimed to assess whether the change in clinical practice to incorporate the use of subdural drains had resulted in a lower need for reoperation (study I).

Previously no study has focused on the relationship between age, dementia, and outcome after CSDH surgery. We aimed to assess the one-year case-fatality after CSDH surgery in older patients with and without a pre-existing diagnosis of dementia (study II). Although the incidence of CSDH has been noted to increase, no nationwide studies have been published about the change. We assessed the incidence of CSDH surgeries in adult patients in Finland during 1997–2014 (study III).

The mainstay of the current surgical technique includes intracranial irrigation. However, the impact of irrigation on recurrence rates has not been studied in a randomized controlled setting. We aim to assess if irrigation is a necessary phase in burr-hole craniostomy (BHC) for CSDH. We have planned and started a study assessing the role of irrigation with primary respect to recurrence rates (study protocol).

Patients and methods
Study I is a retrospective observational study in which we compared the outcomes between two time periods. During the first time period (July–December 2015) subdural drain placement was arbitrary, and during the second time period (July–December 2017) drain placement was routine. The primary outcome was CSDH recurrences requiring reoperation within 6 months. Secondary outcomes were functional outcome and complications.

Studies II and III are nationwide register-based analyses. For study II, we included all older patients (over 60 years) and for study III all adult patients undergoing surgery for CSDH during 1997–2014 (referred to as cases). We searched controls matched for age, sex, and year of first hospitalization with a new dementia diagnosis, who did not have a diagnosis of CSDH. We defined a pre-existing diagnosis of dementia as the exposure. The outcome was 12-month mortality which we compared in case-only and case-control analyses. For study III, we calculated the incidences of CSDH surgery per 100,000 person-years in different age groups and sexes. We performed age standardization with the 2013 European Standard Population weights for those older than 20 years. We used negative binomial regression models to evaluate changes in incidence rate ratios (IRRs).

Study protocol is a description of a randomized, controlled, non-inferiority multicenter trial in which we compare BHC with irrigation and BHC without irrigation. The primary outcome is recurrent CSDH requiring reoperation within 6 months. Secondary outcomes include functional outcome, mortality, duration of operation, and adverse events.

Results

Study I comprised 161 patients, of which 44% (71/161) were in the drain group and 56% (90/161) in the non-drain group. In the non-drain group recurrence occurred in 18% of patients within 6 months, whereas in the drain group in 6% of patients (odds ratio [OR] 0.28, 95% confidence interval [CI] 0.09–0.87, p=0.028). The groups did not differ in neurologic outcome or complications.

Study II included 7,621 cases, of which 12% (885/7,621) had a pre-existing diagnosis of dementia. The proportion of cases with dementia increased from 9.7% to 12.2% between 1997–2002 and 2012–2014 (p=0.038). Dementia was independently associated with one-year case-fatality (OR for dementia vs. no dementia 1.50, 95% CI 1.26–1.78). The association was strongest for 60–69-year-olds (OR 3.21, 95% CI 1.59–6.47). One-year mortality was 26% for those undergoing CSDH surgery with pre-existing dementia, whereas mortality was 16% for those having dementia but no CSDH (p<0.001).

Study III included 9,280 cases. The age-standardized incidence of CSDH surgery increased from 12.2. to 16.5 per 100,000 person-years from 1997 to 2014. The age- and sex-adjusted incidence of CSDH surgery increased by 30% (IRR 1.30, 95% CI 1.20–1.41). The incidence increased more in the older age groups and did not increase for those aged 18–59 years.

Conclusions

The incorporation of subdural drain use after BHC for CSDH resulted in lower 6-month recurrence rates with no difference in functional outcome or complications. For older patients, dementia is a risk factor for one-year mortality after CSDH surgery. The proportion of older patients undergoing CSDH and having a dementia diagnosis has increased, and thus we need more evidence and research on the benefits and indications of CSDH evacuation among the frail aged. The age- and sex-adjusted incidence of CSDH surgery increased significantly in Finland during the past two decades. Major increases occurred for those aged 60 years and older. We expect the increase to continue as the population ages.

We planned and executed a national multicenter randomized controlled trial (RCT), in which the recruitment was finished in August 2022. The results will be published in 2023.

Tiivistelmä (abstract in Finnish)

Johdanto
Krooninen subduraalihematooma on yleinen neurokirurgisesti hoidettava sairaus. Subduraalidreenin käytön on todettu vähentävän vuodon uusiutumista. Osa tutkimuksista kyseenalaistaa silti dreenin rutiininomaisen käytön. Osatyössä I tutkimme, kuinka subduraalidreenin kliininen käyttö oli vaikuttanut uusintaleikkausten määrään.

Iän, dementian ja kuolleisuuden välistä yhteyttä kroonisen subduraalihematooman leikkaushoidon jälkeen ei ole tutkittu. Osatyössä II tutkimme kuolleisuutta leikkauksen jälkeen iäkkäillä potilailla, joilla on dementia. Vaikka kroonisen subduraalihematooman ilmaantuvuuden on havaittu kasvaneen, kansallisia tutkimuksia ilmaantuvuuden muutoksista ei ole julkaistu. Osatyössä III tutkimme kroonisen subduraalihematooman leikkauksen ilmaantuvuutta Suomessa vuosina 1997–2014.

Nykyiseen leikkausmenetelmään kuuluu kallonsisäinen huuhtelu, vaikka huuhtelun tarpeellisuutta ei ole osoitettu satunnaistetuissa yhdenveroisuustutkimuksissa. Suunnittelimme ja aloitimme tutkimuksen, jossa arvioimme huuhtelun vaikutusta uusintaleikkausten määrään (tutkimusprotokolla).

Metodit
Osatyö I on takautuva havaintotutkimus, jossa vertasimme uusintaleikkausten määrää potilailla, jotka oli hoidettu subduraalidreenin kanssa ja ilman dreeniä. Osatyöt II ja III ovat kansallisia rekisteriperustaisia tutkimuksia. Osatyössä II valitsimme tapauksiksi yli 60-vuotiaat ja osatyössä III yli 18-vuotiaat potilaat, jotka oli hoidettu leikkauksella vuosina 1997–2014. Haimme dementiaa sairastaville tapauksille kaltaistetut verrokit, joilla ei ollut kroonista subduraalihematoomaa. Osatyössä II vertasimme yhden vuoden kuolleisuutta tapauksiin rajoittuvissa ja tapaus-verrokkianalyyseissä. Määritimme leikkauksen ilmaantuvuudet 100 000 henkilövuotta kohden osatyössä III. Teimme ikävakioinnin Euroopan standardiväestön perusteella. Vertasimme ilmaantumistiheyksien suhteita negatiivisten binomiregressiomallien avulla.

Tutkimusprotokolla kuvaa viiden keskuksen satunnaistetun yhdenveroisuustutkimuksen suunnitelmaa. Tutkimuksessa vertaamme uusintaleikkausten tarvetta huuhteluleikkauksen ja ilman huuhtelua suoritettavan leikkauksen jälkeen.

Tulokset
Osatyössä I ilman dreeniä hoidettaessa uusintaleikkaukseen joutui 18 % potilaista, kun taas dreeniä käytettäessä uusiutumisia oli 6 %. Toimintakyvyssä tai komplikaatioissa ei ollut eroja.

Osatyössä II dementiaa sairastavien potilaiden osuus nousi 9,7 %:sta 12,2 %:iin 1997–2002 ja 2012–2014 välillä. Dementia oli itsenäisesti yhteydessä yhden vuoden kuolleisuuteen, ja yhteys oli vahvin 60–69-vuotiailla. Yhden vuoden kuolleisuus oli 26 % niillä kroonisen subduraalihematooman vuoksi leikatuilla potilailla, joilla oli aikaisempi dementiadiagnoosi. Kaltaistettujen verrokkien kuolleisuus oli 16 %.

Osatyössä III kroonisen subduraalihematooman leikkauksen ikävakioitu ilmaantuvuus nousi 12,2:sta 16,5:een 100 000 henkilövuotta kohden vuosien 1997–2014 aikana. Ikä- ja sukupuolivakioitu ilmaantuvuus nousi 30 % ja ilmaantuvuus nousi enemmän iäkkäimmillä potilailla.

Johtopäätökset
Subduraalidreenin käyttöönotto johti uusintaleikkausten määrän vähenemiseen, mutta ei vaikuttanut toimintakykyyn tai komplikaatioihin. Dementia on iäkkäillä potilailla riskitekijä kuolleisuudelle kroonisen subduraalihematooman leikkaushoidon jälkeen. Dementiaa ja kroonista subduraalihematoomaa sairastavia potilaita on yhä enemmän, joten iäkkäisiin potilaisiin keskittyviä tutkimuksia tarvitaan lisää. Kroonisen subduraalihematooman leikkauksen ikä- ja sukupuolivakioitu ilmaantuvuus nousi Suomessa viimeisten kahden vuosikymmenen aikana. Väestön ikääntyessä odotamme taudin ilmaantuvuuden kasvavan edelleen.

Suunnittelimme ja toteutimme kansallisen viiden keskuksen satunnaistetun yhdenveroisuustutkimuksen. Tutkimuksen rekrytointi päättyi elokuussa 2022 ja julkaisemme tulokset vuonna 2023.

Introduction

Chronic subdural hematoma (CSDH) is a common neurosurgically treated disorder, especially prevalent among the elderly population.[1] CSDH is typically initiated by a minor head trauma a few weeks before the symptoms arise.[2] Risk factors for the condition include high age[3], male sex[4], alcohol abuse[5], antithrombotic medication[6], and brain atrophy[7]. Surgery is the treatment of choice in case a CSDH is causing symptoms or significant mass effect.[8] Approximately 85% of patients with a CSDH diagnosis undergo operation[1]. Thus far, there is no consensus regarding the optimal surgical technique. Worldwide, burr-hole craniostomy (BHC) has become the most practiced method.[9,10] Other surgical techniques include the use of two burr-holes, twist-drill craniostomy (TDC) and even craniotomy in selected patient populations.[11]

The current reoperation rate is approximately 10–20%[12,13] and depends on treatment- and patient-related factors but also on the definition of recurrence in the study. Use of a subdural drain has been reported to effectively reduce recurrence rates.[14–17] Yet, few studies dispute routine placement of subdural drains.[18]

At the Department of Neurosurgery of Helsinki University Hospital, use of a subdural drain was established in routine practice on April 1, 2017. Study I aimed to assess whether the change in clinical practice to incorporate the use of subdural drains had resulted in a lower need for reoperation. Primarily, we compared reoperation rates of patients treated with postoperative drains during the drain era (2017) with reoperation rates of patients who did not receive drains during the pre-drain era (2015). Secondarily, we compared complications, functional outcome, and the changes in hematoma size between the two groups.

BHC is most commonly performed with intracranial saline irrigation to wash out the hematoma.[12] The recurrence rate after CSDH treatment with irrigation and insertion of a subdural drain is approximately 10%.[13] However, there is little data available to confirm the impact of intraoperative irrigation on recurrence rates.[19–27] There are no published randomized controlled trials (RCTs) comparing irrigation with no irrigation in BHC with drainage. In retrospective analyses the results have been contradictory. Some reports even suggest that there might be an increased risk of complications related to irrigation, such as irrigation-induced intracerebral and subarachnoid hemorrhage[28] or postoperative pneumocephalus[19,20,29].

After publishing study I, we wanted to start up an RCT. In study IV we aim to assess if intraoperative irrigation is a necessary phase in BHC for CSDH. We compare the use of intraoperative irrigation with no intraoperative irrigation with primary respect to recurrence rates. Secondary interests include complications, functional outcome, and mortality. If there is no difference in recurrence rates between irrigation and no irrigation, surgery times could be shortened by omitting the phase of irrigation.

Driven by the worldwide patterns of population aging and increasing use of antithrombotic medication, the incidence of CSDH has increased during the past decades.[1,6,30–32] The incidence estimates of CSDH vary from 29 to 64 per 100,000 among persons aged over 65 years.[1,33,34] Moreover, the aging trend has led to a growing number of people with dementing disorders, and the prevalence of dementia is expected to triple by 2050.[35] The societal burden will be inevitable as dementia is a major contributor to dependence[36] and institutionalization[37].

Few studies have examined older patients treated for CSDH and as high as 32% one-year mortality rates have been detected after diagnosis of CSDH.[38] However, no study has focused on the relationship between age, dementia and outcome after CSDH surgery. In study II, we assessed the incidence of CSDH surgery in older patients (over 60 years) and one-year case-fatality after CSDH surgery in patients with and without a pre-existing diagnosis of dementia from 1997 to 2014. Our hypotheses included that the proportion of patients with a pre-existing diagnosis of dementia had increased and that one-year case-fatality would be higher for those with pre-existing dementia. We also hypothesized that patients with dementia and undergoing CSDH surgery would have higher one-year case-fatality than their matched controls with dementia but without a diagnosis of CSDH.

Although the incidence of CSDH has been noted to increase, no nationwide studies have been published about the change. We assessed the incidence of CSDH surgeries in Finland during an 18-year time period (1997–2014) in study III. Our hypothesis was that the incidence of CSDH surgery has continued to increase and particularly in the older age groups. If a remarkable nationwide increase was detected, this would accentuate the need for preventive measures.

This thesis deals with CSDH in adults. Pediatric CSDH is a separate disease entity and is not discussed in this thesis.

Review of the literature

Historical aspects

Johannes Wepfer was the first to report CSDH in 1657.[39] He found a large cyst filled with blood beneath the dura mater at an autopsy. The patient had died of an "apopleptic stroke" with aphasia and hemiplegia.[40] A similar autopsy finding was reported in 1747 by Giovanni Morgagni. In 1817 Houssard described the clot and enveloping membrane structures and attempted to explain formation of the hematoma. Rudolf Virchow proposed in 1857 that the hematoma was caused by a chronic inflammatory reaction in the dura mater, and thus called the condition "pachymeningitis haemorrhagica interna". He suggested that the chronic inflammation in the dura was followed by fibrin formation and proliferation of capillaries from the dura.[39] Jacob Kremiansky supported the theory and noted alcoholism as an etiological factor in his autopsy studies 1868.[41] The inflammation theory was widely accepted until Wilfred Trotter presented the traumatic etiology in 1914.[2] He suggested that a minor injury ("so trivial as to escape attention") caused tearing of a vein leading to a subdural bleeding. Trotter was also the first to suggest the currently used term "chronic subdural hemorrhage".

Trephination was already performed in the Neolithic era (10,000–4,500 before the common era [BCE]) for a variety of conditions.[41] Favorable outcomes for CSDH must have encouraged the surgeons at the time to continue operating. Thus, the current preferred method of surgery was performed for CSDH long before the condition and its pathophysiology were known. In Finland, the first reported successful neurosurgical procedure involving trephination was performed by Carl Daniel von Haartman in the city of Turku in 1817.[42,43] Successful neurosurgical treatment for CSDH was first reported by Hulke in Lancet in 1883.[44] Tracy Jackson Putnam and Harvey Cushing published a review in 1925, in which they concluded that surgery was the preferred treatment for CSDH and advocated also early diagnosis.[41] However, based on merely clinical signs without radiological imaging, diagnosis was impossible to make since the disorder can present with a variety of symptoms – many of which are quite unspecific.

In 1918, "pneumoencephalography" was introduced by Walter E. Dandy.[45] This invasive method included injection of air into the brain ventricles which enabled ventricles to be more defined on an X-ray image. In 1927, Egas Moniz introduced "arterial encephalography" – the early version of cerebral angiography.[41,46] Only indirect signs of intracranial lesions could be detected with these imaging modalities. However, CSDHs were diagnosed earlier and outcomes after surgery improved after adoption of these imaging techniques.[41] The first head computed tomography (CT) was installed in London in 1971, and thereafter a new era of imaging-based diagnosis began.[47]

Definition and structure

CSDH is an encapsulated old collection of blood and blood degradation products. The hematoma is accumulated in the subdural space between the two outer cerebral meninges, the dura mater and arachnoid mater. Thus, the bleeding locates intracranial but not intracerebral. Subdural hematomas are classified as acute within 3 days of trauma, subacute 4–20 days after trauma and chronic after 21 days.[48] Cases with no history of trauma can be classified based on the duration of symptoms.[48] Recurrent head trauma may induce acute bleeding over a CSDH resulting in an acute-on-chronic subdural hematoma.[49] CSDHs present most often unilaterally, and approximately one fifth of the cases are bilateral.[1,50,51]

The capsule surrounding the CSDH consists of a thick external membrane right beneath the dura mater and a thin internal membrane above the arachnoid mater. (**Figure 1**) The external membrane includes collagen fibrils, fibroblasts, mast cells, erythrocytes, and blood vessels with weak walls and high permeability which enables the leakage of blood and hematoma enlargement.[52] The thinner internal avascular membrane consists of collagen fibrils and fibroblasts.[52] The external membrane is also called parietal and the inner membrane is called visceral. However, as surgeons have observed, CSDHs present with a great variety regarding both subdural fluid and membranes. At times, the CSDH is covered by a thick membrane, whereas in other cases the membrane is hardly visible. The subdural fluid type varies from red fresh blood-colored hematoma to older engine oil-colored hematoma, to serous fluid.

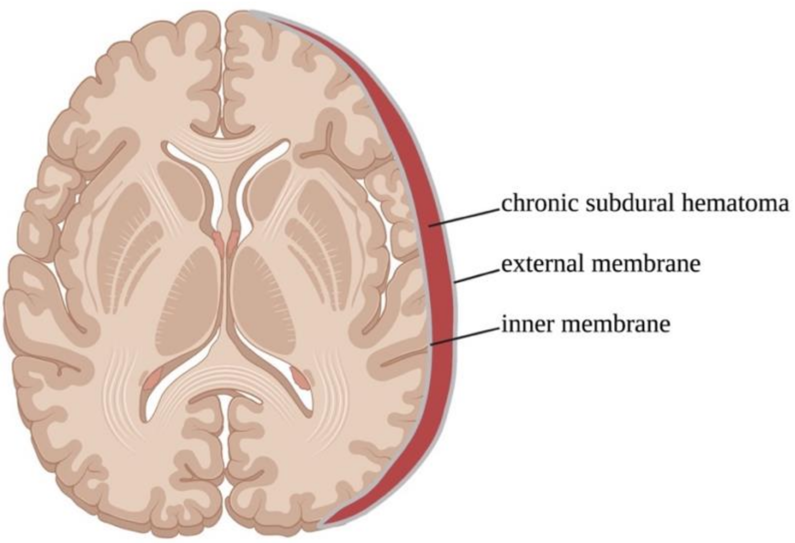


Figure 1 Schematic drawing of a chronic subdural hematoma, axial view. The hematoma is surrounded by a thick external membrane and a thin internal membrane. Created with BioRender.com. © Pihla Tommiska

Etiology and pathogenesis

The etiology of CSDH is not completely understood. There are several inconsistencies which is why researchers have questioned the traumatic etiology presented by Trotter in 1914. First, if a slow venous hemorrhage was the only cause, a symptomatic hematoma would expect to evolve within days. However, the progression of the condition takes several weeks by definition. Second, it has been observed that head imaging at the time of acute trauma can be normal and the patient may still develop a CSDH weeks later. Third, although some patients present with mixed density hematomas where acute hemorrhage is visible, the majority present with homogenous hypodense hematomas i.e. a collection entirely comprised of old blood. Still, the collection enlarges over time which questions if acute hemorrhage is the sole source of growth.

The current conception of the etiology combines certain elements of the previous theories. The condition is believed to be a result of a complex process involving inflammation, membrane formation, angiogenesis, and fibrinolysis.[53] Normally, the subdural space is non-existent and the dura mater and the arachnoid mater close together. Beneath the two layers of the dura (periosteal and meningeal dura) adjacent to the arachnoid mater is located a layer of specialized connective tissue.[54] This layer is called the dural border cell layer, and the pathologic subdural space can potentially form within it. Characteristic to the dural border cell layer is large extracellular space containing nonfilamentous material and the scarcity of tight junctions.[55,56] This layer does not endure major stretching. Veins traversing the dural border cell layer are not firmly attached to it. If a person has brain atrophy, the arachnoid mater is drawn towards the center. Still, the dura is attached to the cranium which causes stretching to the dural border cell layer and the veins traversing it. These veins are susceptible to shear if a minor force is added.[56,57]

Minor or moderate head trauma is believed to injure the dural border cell layer and veins traversing it leading to a cascade of inflammatory reactions.[53] In an attempt to repair the dural border cell tear, the inflammatory cells proliferate which results in the formation of new membranes.[53] The characteristic membrane, particularly the external membrane seems to be the source of fluid exudation and hematoma growth.[52,53] Angiogenic factors are released and this promotes the formation of delicate neovessels within the membranes. These fragile vessels are prone to leak through fluid and blood.[52,53] Microhemorrhage promotes inflammatory response which again leads to membrane formation. The pathophysiological process and continuous CSDH cycle are depicted in **Figure 2**. This hypothesis was originally presented by Edlmann et al.[53] Especially in young and healthy persons with nonatrophic brain, the process is likely to result in full absorption of the hematoma as neomembranes become mature and neovessels stabilize.[58] However, if microhemorrhage exceeds absorption CSDH persists.[56,58]

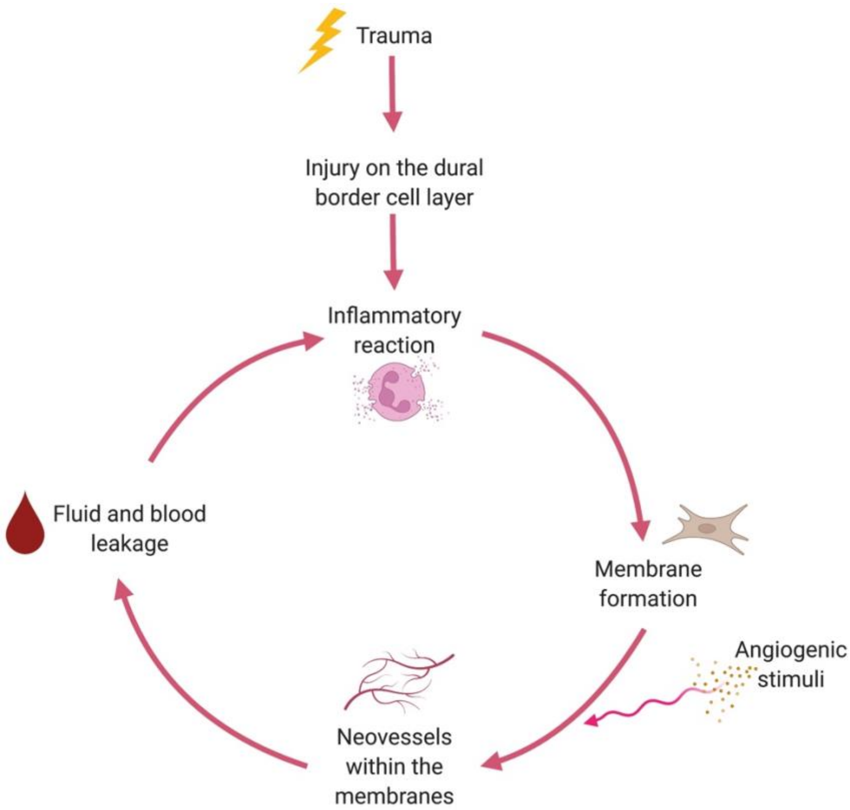


Figure 2 The pathophysiological process behind the formation of a chronic subdural hematoma. Created with BioRender.com. © Pihla Tommiska

Two different etiologies have been presented. CSDH may evolve from a traumatic acute subdural hematoma (ASDH) as often seen in clinical practice.[59] Trauma results in tearing of a bridging vein, or less commonly, tearing of a cortical arteries or veins.[60] Fibrinolysis results in the liquefaction of the acute hematoma clot.[61,62] The growing subdural collection launches an inflammatory reaction and the CSDH cycle.[61] Alternatively, CSDH may evolve from a collection of cerebrospinal fluid (CSF), also called a subdural hygroma.[59] Especially promoted by cerebral atrophy, a subdural hygroma may develop at the site of lowest pressure in the cranium.[59] Injury on the dural border cell layer triggers the CSDH cycle leading to microhemorrhage.[56] It was suggested by Lee et al. that half of CSDHs develop through an ASDH and half through a subdural hygroma[59], although disputed by others[63]. In a small study (n=27) by Ahmed et al.[64], 15% of initially conservatively treated ASDHs later required operative treatment for CSDH.

Epidemiology

The earliest and the latest epidemiological population-based reports on the incidence of CSDH found in PubMed (searched in May 2022) are both from Finland. According to a study by Fogelholm and Waltimo[3], during 1967–1973 the overall annual incidence of CSDH was 1.7/100,000, reaching 6.4/100,000 for those aged over 80 years.[3] According to Rauhala et al.[1], during 2011–2015 the overall annual incidence was 17.6/100,000 and 129.5/100,000 for those aged over 80 years.[1] Thus, the overall incidence has increased tenfold during the last 50 years in Finland. Age of patients with CSDH has also increased.[1] In the 1970s, only half of patients were older than 60 years[3], whereas in 2010s the median age was 79 years[1]. The incidence of CSDH is predicted to continue to increase in the future.[65]

One probable reason behind the increased number of CSDHs is the growing use of antithrombotic medication.[1,6] Better access to imaging also may have contributed to the higher incidence.[11,56] In Finland CT scanning was introduced in the late 1970s, and before that 38% of cases were found on autopsies[3], whereas in the recent decades the number has been 2%[1]. Other speculated reasons include improved awareness about the condition among the medical profession[11,56], more active aging population[56], and advances in imaging techniques[11]. Also, it may be that the wide availability of CT scanners has led to a lower threshold to control a head CT for patients with recurrent falls, specific, and unspecific neurological symptoms.[34]

Risk factors

Advancing age and brain atrophy

Age is a major risk factor for CSDH.[51] In a large Japanese CSDH study[66] including over 63,000 cases during 2010–2013, the mean age of patients with newly diagnosed CSDH was 76 years. In low-and-middle-income countries, the mean age is around 60 years.[60] The age of patients with CSDH has increased during the last decades, and even patients over the age of 90 can be successfully treated with minimally invasive surgical procedures.[67] However, CSDH can also be interpreted as a sentinel health event for aged people with high mortality rates.[38,68]

Cerebral atrophy has anecdotally been presented as the reason why CSDHs more often occur in the elderly.[7] Atrophy also plays an important role in the pathogenesis of the condition, resulting more easily in shearing of the dural border cell layer. In a study by Yang et al.[7], the degree of atrophy was higher in patients who developed later a CSDH compared to their age-matched controls who did not develop a CSDH. The association between atrophy and development of CSDH was greater in younger patients (65 year-olds).[7] However, causal relationship between atrophy and CSDH has not been shown. Some researchers have raised the question whether atrophy causes CSDH or CSDH causes atrophy. In a study by Bin Zahid et al.[69], CSDH was associated with a significant increase in brain atrophy which develops after the CSDH diagnosis. However, before the development of a CSDH, the atrophy rates were similar to patients without dementia. Thus, this study suggests that brain atrophy develops after rather than before CSDH development.

Other reasons why CSDHs occur more often in the elderly, might be their predisposition to falls and use of antithrombotic medication.[51]

History of trauma

History of trauma is present in 50–80% of CSDH cases.[1,5,51,56,70,71] However, the trauma can be so minor that the patient does not recall it at the time of the diagnosis. In a large population-based Finnish study[1], 59% of the patients had a preceding head trauma. The most common type of trauma was ground level fall accounting 77%, followed by bicycle accident (3%) and fall from a height of over 1 meter (3%). Ground level fall was related to the CSDH in 54% of patients aged over 80 years, but only 31% of patients younger than 60 years.[1] According to a large Japanese epidemiological study[72], ground level fall is the most common cause of trauma among the elderly, whereas traffic accident is the most common cause among the younger patients. A Brazilian study had similar findings regarding the types of trauma and age groups.[71] It may be that older patients have a longer time period from trauma to operation compared to younger.[73] The ratio between traumatic and atraumatic CSDHs has remained stable during the last few decades.[1] Polypharmacy and chronic diseases may predispose to falls in the elderly,[74,75] resulting later in a CSDH.

Male sex

CSDH presents more commonly in men.[1,3,30,33,51,71,72,76] The male/female ratio of CSDH patients varies depending on the country and era. The reported male/female ratio ranges from 1.7:1 to 4.8:1 depending on the country (**Table 1**). Few studies have reported that male predominance diminishes with age.[51] Studies suggest that the percentage of male patients is decreasing and the percentage of female patients increasing.[5,66] This may be due to the aging trend as women have a higher life expectancy.

Reasons for this long observed male preponderance remain unknown. Explanations such as differences in use of alcohol and susceptibility to trauma have been speculated, however no study has validated this.[4] Researchers have also tried to explain the male predominance by differences in the degree of brain atrophy between the sexes, initially caused by anatomical difference in the cranium.[77] A small Australian study (n=155) compared the risk factors between men and women, and no significant difference in history of trauma, cerebral atrophy or alcohol abuse was detected.[4] Paradoxically, use of antithrombotic medication was more prevalent in women in this study.[4]

Table 1. *The male to female ratio of chronic subdural hematoma patients in different countries.*

Country	Male to female ratio
Spain[78]	1.7 / 1
Switzerland[51]	1.8 / 1
Finland[1]	2 / 1
Japan[66]	2.2 / 1
the United Kingdom[70]	2.9 / 1
Brazil[71]	4.8 / 1

Alcohol

CSDHs are known to be more prevalent in persons with alcohol abuse. Alcohol consumption contributes to brain atrophy[79] and hepatogenic coagulopathy, but also increases the risk of trauma. Chronic alcohol abusers are overrepresented among younger CSDH patients. In a Finnish epidemiological study, 44% of patients under 60 years were chronic alcohol abusers, whereas the percentage was only 0.3% among those aged 80 or older.[1] In Finland, chronic alcohol overuse among CSDH patients was also more common in men compared with women (14% vs. 6%)[1], although no gender difference was detected in the previously mentioned Australian study[4]. The proportion of alcohol-related CSDH cases has decreased during the last decades.[1]

Use of antithrombotic medication and coagulopathy

Antithrombotic medication is widely used and especially in the multimorbid population that most often contracts CSDH. In a Finnish population-based study[1], 49% of patients with CSDH were on antithrombotic medication during 2011–2015. Because of the extensive use, a precise risk quantification is difficult. In a nationwide Danish case-control study by Gaist et al.[6], use of antithrombotic medication was associated with higher risk for subdural hematoma (SDH), with highest risk when combining vitamin K antagonists (VKA) and antiplatelets. Of the SDHs in the study, 55% were classified as subacute or chronic and 45% were acute. Use of VKA was associated with a significantly higher risk of subacute or chronic SDH. According to Gaist et al., use of low-dose aspirin was not associated with risk for subacute or chronic SDH.

In another case-control study by De Bonis et al.[80], an increased risk for subacute or chronic SDH was found among those using anticoagulants. According to their study also use of antiplatelet medication increased the risk of subacute or chronic SDHs.[80]

In a randomized placebo-controlled trial involving healthy older persons, use of primary preventive low-dose aspirin resulted in significantly higher risk of subdural or extradural hemorrhage and did not reduce the risk of cardiovascular disease significantly in comparison to placebo.[81]

Use of antithrombotic medication seems to be more prevalent among older CSDH patients and those who do not have a history of trauma.[1,82,83] In the study by Rauhala et al.[1], 10% were using antithrombotic medication among those 18–59 years, whereas 57% were using antithrombotic medication among those 80 years or older. In a study by Aspegren et al.[82], significantly more patients with atraumatic CSDH were using antithrombotic medication compared with patients who had a history of trauma (63% vs. 42%).

Increasing incidence of CSDH has been associated with increased use of antithrombotic medication. The percentage of CSDH patients on antithrombotic medication increased from 27% to 49% during 1990–2015 in the study by Rauhala et al.[1] The use of direct oral anticoagulants (DOACs) in clinical practice has grown since their introduction, and use of warfarin has declined.[84] In a large meta-analysis comparing warfarin and DOAC in patients with atrial fibrillation, overall intracranial hemorrhage (including subdural and epidural hematomas, hemorrhagic stroke, and subarachnoid hemorrhage) was reduced by half when using DOAC.[85] As antithrombotic medications have been shown to predispose to CSDH, indications for these agents should be carefully and individually evaluated regularly especially for elderly patients at risk for falls.[51]

Coagulation disorders should be suspected in CSDH patients younger than 65 years without risk factors as such disorders may be overrepresented in this population.[86,87] In a small study assessing patients under 65 years operated for CSDH, 38% had an undiagnosed factor VII deficiency.[86] Also all recurrences occurred in patients with factor VII deficiency in this study.[86]

Low intracranial pressure states

Low or fluctuating intracranial pressure may cause stretching of delicate vasculature and predispose to CSDHs. Atraumatic subdural hematoma is a well-known possible complication of overdrainage after ventricular shunt surgery.[88] Treatment may include adjustment in the drainage speed or surgical evacuation of the hematoma. CSDH has been reported to develop as a rare complication after endoscopic III ventriculostomy[89], spinal anesthesia[90], lumbar puncture[91], and microdiscectomy[92]. In a retrospective analysis assessing all neurosurgical procedures conducted from January 1987 to July 2001, the incidence of CSDH after neurosurgery was 0.8%.[93] The incidence was highest at 7.5% after arachnoid cyst opening and/or shunting, followed by 2.4% after aneurysm clipping surgery.[93] The incidence of CSDH after brain tumor surgery was 0.4%.[93] Subdural hygromas are also sometimes seen on postoperative imaging after craniotomies or other neurosurgical interventions. However, postoperative hygromas usually gradually absorb by themselves without surgical treatment.

Subdural fluid collection is a common secondary entity in spontaneous intracranial hypotension (SIH).[94] Differentiation between SIH induced subdural collection and primary CSDH may be difficult, and it is known that SIH is sometimes misdiagnosed as CSDH. Classically, patients with SIH present with orthostatic headache and bilateral hygromas.[95] SIH is caused by spinal outflow of CSF which may lead to sagging of the brain.[94] This stretches the bridging veins and can result in a subdural collection. Primary treatment options for SIH consist of conservative therapy (bedrest, hydration, and oral caffeine administration) and epidural blood patch.[96]

It has been suggested that CSF leakage can cause (in addition to SIH) also CSDH, especially among young patients. In a small prospective study by Beck et al.[97], 26% of younger patients (≤ 60 years old) with a CSDH diagnosis had a proven spinal CSF leakage on imaging. The study suggests that spinal CSF leak may be unexpectedly common cause of CSDH among younger patients.[97] Whether patients in this study actually suffered from SIH remains unclear. However, in conclusion patients with certain risk factors (e.g. young age, early or multiple recurrence, unrelieved symptoms, bilateral CSDH, and orthostatic headache) might benefit from screening for spinal CSF leaks.[95,97]

Long-term dialysis

The incidence of subdural hematomas (SDHs) is much greater in patients on long-term dialysis compared with general population for all age groups.[98,99] In a study by Sood et al.[98], the incidence of SDH was ten times higher among long-term dialysis patients than that of the general population. The higher incidence may be due to coagulation abnormalities, venous hypertension and increased bleeding tendency in uremia.[98,99] Moreover, low-molecular-weight heparins (LMWHs) are used during the dialysis procedure which may predispose to the formation of a SDH.[99]

Arachnoid cyst

Arachnoid cysts are CSF filled sacs that are often congenital but may develop after head trauma.[100] Intracranial arachnoid cysts are a relatively common incidental finding on imaging with a reported prevalence of 1.4%.[101] However, intracranial arachnoid cyst has been reported as a risk factor for CSDH in juveniles after mild head trauma.[102,103] Mori et al.[102] reported 12 cases of CSDH with associated arachnoid cysts. The prevalence of arachnoid cysts in patients with CSDH was 2.2%.[102] The patients were significantly younger (mean age 28 ± 20 years) and 5 of the 12 were under 15 years old.[102] The patients presented with symptoms of increased intracranial pressure (headache and nausea).[102]

Clinical signs and symptoms

The clinical progression involves three phases: initial head trauma, latency period, and clinical presentation.[104] By definition the hematoma is classified as chronic when 21 days has elapsed since trauma.[48] However, the duration of the latency period may vary and no universal definition of when a SDH becomes chronic exists. Mean interval from injury to diagnosis has been described 52 days.[59] Commonly the symptoms develop rather acutely and drive the patient to seek medical help. The clinical signs and symptoms may result from increased intracranial pressure or direct compression of neurologic structures. The symptoms include gait disturbance, falls, limb weakness, headache, dizziness, cognitive decline, speech impairment, somnolence, nausea, and epileptic seizures.[1,50,70] Patients often present with multiple symptoms.[1,50,70]

Patients with bilateral hematomas are more likely to experience nausea or vomiting, symptoms of increased intracranial pressure.[105] Headache is the most frequent symptom among younger patients whereas elderly patients more often present with limb weakness.[71,73,78,97,106] Also it seems that disturbance of consciousness is a more common symptom among elderly patients[66] and these patients have a more severe neurological condition on admission[72]. In a large Japanese retrospective study, more than half of patients 70 years or older presented with lowered consciousness on admission.[66] It may be due to that older patients are more often diagnosed with larger hematomas when the condition has progressed further. Older patients also more frequently present with altered mental state or confusion.[71,76,78]

The patients generally have a stable condition at admission. However, if a large hematoma is left untreated the condition may deteriorate and ultimately lead to death. Especially patients with large bilateral CSDHs or patients younger than 65 years presenting with headaches but without neurologic deficits should be observed closely as their need for surgical evacuation may quickly become vital.[12]

Diagnosis

Because of the wide variety of symptoms, some of which are rather unspecific, the patient's comorbidities, and often minor or forgotten trauma, CSDH can be a diagnostic challenge for the medical staff. CSDH is suspected based on head trauma history and neurological symptoms. The definite diagnosis requires head imaging. Most often a non-contrasted head CT scan is taken where the CSDH appears as a crescent-shaped, typically hypodense (<30 Hounsfield units [HU]) hemispheric collection[107] (**Figure 3**). The age of hemoglobin breakdown affects the radiographic characterization.[108] Because of the location between the dura and the arachnoid mater, CSDH typically crosses suture lines unlike epidural hematomas.[109] Differential diagnoses include subdural empyema and hygroma. CT scan is cost-effective, rapid, and easily accessible but the internal anatomy of a CSDH may be more detectable on magnetic resonance imaging (MRI). However, the availability and logistics of MRI limits its use as the first line radiological imaging study and is currently most often performed when other diagnoses are initially suspected.

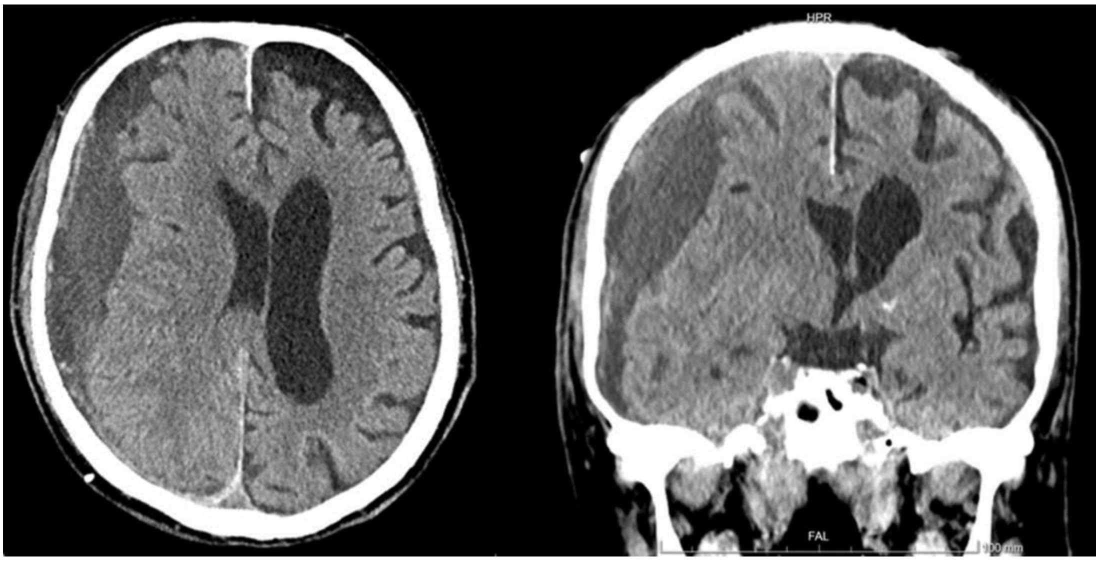


Figure 3 A hypodense chronic subdural hematoma on the right hemisphere on a CT scan in axial view (left) and coronal view (right). The hematoma has mass effect and forces the midline structures to the left causing subfalcine herniation.

The hematoma width and midline shift are measured to help assess the mass effect. A CSDH can be unilateral or bilateral. Bilateral CSDHs often have lesser degree of midline shift on imaging.[105] The lacking of midline shift is due to opposite, equal forces on both hemispheres. Thus, although minimal midline shift, bilateral CSDHs may still cause significant mass effect and consequently symptoms of increased intracranial pressure as mentioned earlier.[105] In case of bilateral CSDHs with no midline shift, assessing the indirect allusive radiographic signs such as the effacement of the cortical sulci, openness of the basal cisterns, and compression of ventricles, is important.[109]

CSDHs may have isodense (30–60 HU) or hyperdense (>60 HU) components.[107] As the hematoma matures, a transition through isodensity to hypodensity occurs.[109] However, the age of the SDH cannot be accurately determined based on hematoma density on a CT scan.[110] An isodense hematoma has the same density as the adjacent brain parenchyma which can make it difficult to detect the lesion.[109] Especially in the subacute phase the subdural hematoma may appear isodense on CT. MRI may be helpful then as the high signal intensity on T1 weighted image (caused by methemoglobin) clearly distinguishes a subdural hematoma from most non-hemorrhagic fluid collections.[109] As the CSDH ages, T2 signal typically increases and the T1 signal gradually decreases on MRI.[109]

CSDHs can be classified based on the internal architecture and density. Nakaguchi et al. originally proposed four types of CSDHs: homogenous, laminar, separated, and trabecular[111] (**Figure 4**). The authors suspected that these types possibly represent different stages during the natural history of the disease process. A CSDH initially develops as the homogenous type and sometimes progresses to the laminar type.[111] As the hematoma matures, it may appear separated on imaging. Finally the hematoma absorbs through the trabecular stage.[111]

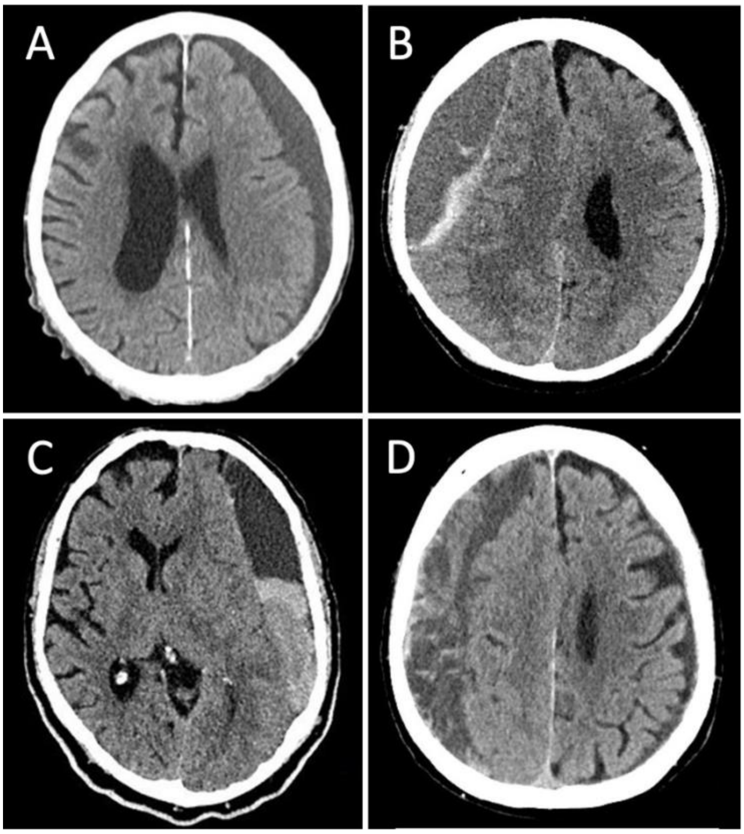


Figure 4 The Nakaguchi classification[111] of chronic subdural hematomas according to their internal architecture. **A)** Homogenous type. **B)** Laminar type. This type of hematoma is characterized by a high-density layer running along the inner membrane. **C)** Separated type. The hematoma has separated into two components of different densities with the lower density component lying above the higher density component. **D)** Trabecular type. The hematoma is characterized by inhomogeneous contents, and numerous septations are visible within the subdural space.

The International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10) diagnostic codes for the condition include S06.5 traumatic subdural hemorrhage and I62.0 nontraumatic subdural hemorrhage (ICD-10 has been in use in Finland since 1996). Thus, a SDH is either classified as traumatic or nontraumatic according to the diagnostic coding. A proposal has been made to the Classification and Statistics Advisory Committee of the World Health Organization to update the coding for SDHs in the ICD-11 classification to improve registry research and classification.[112]

Management

Reversal of anticoagulation and antiplatelet agents

Many of the multimorbid patients are on antithrombotic medication before the diagnosis of a CSDH. Antithrombotic medication is used to reduce the risk of venous and arterial thromboembolic events in patients with for example atrial fibrillation, ischemic heart disease, prosthetic heart valve, peripheral arteriosclerosis, or cerebrovascular accident. The medication is discontinued at the time of the diagnosis to prevent further expansion of the hematoma. Correction of drug-induced coagulopathy and thrombopathy is extremely important in reducing the risks of bleeding during surgical treatment and recurrence. In case immediate surgery is needed, rapid reversal of anticoagulation is performed. Warfarin can be counteracted by vitamin K or prothrombin complex concentrate (PCC), LMWH by protamine sulphate, and antiplatelet medication by platelet transfusion and/or desmopressin.[113] DOACs can be counteracted by PCC or specific antidotes idarucizumab and andexanet alfa.[114]

Surgical and endovascular treatment

Symptomatic CSDHs or hematomas with significant mass effect are generally operated on unless the patient is moribund and deemed not to benefit from surgery. The aim of surgery is to alleviate symptoms and improve functional ability. Three primary surgical techniques are used: TDC, BHC, and craniotomy. TDC involves a small opening (<10 mm) made with a twist-drill, BHC an opening of between 10–30 mm, and a craniotomy comprehends larger openings. All three surgical techniques are currently in use, and within each category variations in the operative details exist. BHC seems to be the most popular method worldwide.[9,10,12] In case of a CSDH with multiple membranes or loculations, the chosen operative technique may be craniotomy instead of a BHC or TDC.[107] However, if the patient's poor condition does not tolerate craniotomy, TDC or BHC are preferred. Thus, the operative technique should be chosen individually.[107]

Twist-drill craniostomy

Twist-drill craniostomy (TDC) is performed bedside with a hand-held manual twist-drill under local anesthesia. There is variation regarding the operative details of the procedure. The original method, first published in 1977 by Tabaddor and Shulman[115], includes a twist-drill hole placed at the rostral part of the hematoma. A 1 cm incision is made, and the twist-drill hole is aimed at a 45° angle to the surface of the bone. A large cannula is then inserted in the subdural cavity, and the drain originally kept in place for about 24 hours. A newer method involves a hollow screw, which is threaded through a twist-drill hole and connected to a closed drainage system.[116] This technique is modified from the original TDC. Distinctively the hollow screw technique does not require insertion of a subdural catheter.

An advantage of TDC is that it can be performed under local anesthesia and therefore is suitable for patients who will not tolerate general anesthesia. Also, the procedure is inexpensive in comparison to the more invasive techniques as TDC can be performed bedside and may result in shorter length of hospital stay.[117] However, TDC has been noticed to result in recurrences more often.[117]

According to a meta-analysis by Ducruet et al.[61], complication rate after TDC is 0–18% and mortality rate 5–8%. CSDH recurred in 3–33% of patients and required reoperation in 8–26% of patients. Two meta-analyses by Ducruet et al.[61] and Almenawer et al.[11] demonstrated that TDC results in non-inferior outcome in terms of morbidity, mortality and recurrence rates.

Burr-hole craniostomy

Burr-hole craniostomy (BHC) is currently the most popular technique for primary CSDH in most reporting countries.[9,10] In a Canadian survey study published in 2005, 85% of neurosurgeons preferred single or double BHCs to other surgical techniques.[9] In the United Kingdom and Ireland a survey published in 2008 revealed that 92% of neurosurgeons preferred BHC over other surgical techniques.[10] However, variations exist also within this technique regarding e.g. type of anesthesia and number of burr-holes. The procedure can be performed under local or general anesthesia, and the decision may depend on the surgeon’s preference and the patient’s comorbidities. Preoperative dose of antibiotics is given at the induction of anesthesia.

The surgeon usually drills one or two 14-mm burr-holes over the maximum convexity of the CSDH. If the procedure is performed with two burr-holes, they are drilled approximately 7 cm apart, most often one frontal and one parietal, but the exact location depends on the CT scan. The dura is opened sharply with cruciate incision and coagulated with bipolar forceps. The hematoma classically erupts at this point, and if irrigation is used, the subdural cavity is irrigated with saline solution until the fluid runs clear. Easily accessible membrane loculations can be punctured and coagulated if deemed safe. However, these loculations may be difficult to distinct from the cerebral cortex and sometimes surgical microscope is used in determining this. In some countries intraoperative irrigation is used and in others not. After that, a drain is inserted either in the subdural space or subgaleally above the burr-hole. The drain is tunneled about 5 cm away from the scalp incision. The head is tilted so that the burr-hole is at the highest point (anterior burr-hole if two) to minimize postoperative pneumocephalus. Some surgeons place an absorbable sponge (e.g. Spongostan ®, Tachosil ®) on the burr-hole to promote hemostasis. The drain is connected to a soft collection bag and kept in place most often 48 hours.[107]

The number of burr-holes used in BHC varies. In the United Kingdom and Canada most surgeons prefer two burr-holes.[9,118] However, in Finland the procedure is performed using a single burr-hole. No class I evidence exists if one method is better than the other. A meta-analysis by Wan et al.[119], found no difference between single and double BHC regarding recurrences, complications or morbidity.

Craniotomy

As less invasive craniostomies (BHC or TDC) are sufficient for most patients, craniotomies are nowadays rarely performed for primary CSDHs. However, craniotomy may be indicated for recurrences, hematomas with abundant acute, solid component, or hematomas with multiple loculations.[120] In craniotomy the incision is made in the coronal plane in a linear or curvilinear manner over the largest extent of the hematoma. One or two burr-holes are drilled, and the dura is stripped from the inner surface of the bone using a Penfield dissector. A bone flap of about 5 cm in diameter is raised. The dura mater is sharply opened in a cruciate or stellate manner. The hematoma is irrigated with saline solution, and membrane loculations coagulated with bipolar forceps and sometimes dissected. If a drain is used, it is placed into the rostral part of the cavity and tunneled 5 cm away from the scalp incision. The dura mater is closed, and the bone flap secured with a fixation system. The drain is usually removed after 48 hours.[107]

Comparison of the surgical techniques

Three large meta-analyses have compared the three surgical techniques and the consensus in these was that craniotomy is associated with lower recurrence rate than BHC or TDC but higher mortality and morbidity.[11,61,121] Complication rates are significantly higher after craniotomy (12%) compared with TDC (3%) and BHC (4%).[121] Patients treated with TDC have lowest mortality and morbidity, however, highest rate of recurrence.[121] Thus, it seems that BHC has the best cure to complication ratio.[121,122]

Irrigation

The current gold standard of treatment in most countries includes BHC with intracranial irrigation followed by subdural drainage.[12] The role of irrigation has however not been established. Nine retrospective studies have previously assessed the effect of intraoperative irrigation in BHC with drainage. The studies are presented in **Table 2**. Sample sizes in these studies ranged between 56–186 patients. Most commonly the outcome of interest was the rate of recurrence. In two studies, intraoperative irrigation was found to be associated with significantly lower recurrence rate compared with no intraoperative irrigation.[21,22] In five studies the authors found no difference in recurrences whether irrigation was used or not.[19,23–26] According to two studies no intraoperative irrigation was associated with significantly lower recurrence compared with irrigation.[20,27] Thus, the previous studies have had contradictory results and the sample sizes have been small. Some studies have reported irrigation-related complications, e.g. pneumocephalus[19,20,29] and intracerebral and subarachnoid hemorrhage[28]. An ongoing Swedish RCT is comparing intraoperative irrigation with body temperature and room temperature fluid.[123]

Table 2. *Summary of previous studies assessing intraoperative irrigation in burr-hole craniostomy with drainage for chronic subdural hematomas.*

Study	Number of patients	Methods/ Aims	Outcome	Complications/ Mortality	Conclusion
Suzuki et al., 1998[25]	Overall: 186 Burr-hole drainage without irrigation: 119 Burr-hole drainage with irrigation: 67	Retrospective analysis on recurrence rates (no irrigation 1988–1993; irrigation 1986–1988)	There was no significant difference in recurrence between the cohorts (3.36% vs. 2.99%).	Mortality: 0.54%	The recurrence of chronic subdural hematoma is not influenced by irrigation.
Kuroki et al., 2001[27]	Overall: 101 Burr-hole drainage without irrigation: 56 Burr-hole drainage with irrigation: 45	Comparative analysis on recurrence rates	The rate of recurrence was significantly lower for the no irrigation cohort ($p<0.05$; 1 vs. 5). Irrigation led to intracranial air.	No postoperative complications	Burr-hole drainage without irrigation is a simple, less invasive procedure. The prevention of intracapsular air intrusion during surgery might help prevent recurrence.
Zakaraia et al., 2008[26]	Overall: 82 Burr-hole drainage without irrigation: 42 Burr-hole drainage with irrigation: 40	Cross-sectional study of recurrence rate	No significant difference in the recurrence rate (14.3% in the drainage group vs. 10% in the irrigation group). There was no difference in outcomes between the operative methods.	Complication rate 6.1%; no mortality.	Neurosurgeons may choose not to irrigate the chronic subdural space.
Ishibashi et al., 2011[24]	Overall: 92 Burr-hole drainage with irrigation: 34 Burr-hole drainage: 58	Retrospective analysis on recurrence rates and mortality	The recurrence rate was higher in the burr-hole drainage cohort (10.3 vs. 2.9%). No significant differences between groups regarding good outcome and deaths, but poor outcome was more frequent in the burr-hole drainage group ($p=0.009$).	No treatment-associated mortality	Burr-hole drainage with irrigation is the more effective method for treatment of patients with chronic subdural hematomas.

Kim et al., 2014[20]	Overall: 152 Burr-hole drainage without irrigation: 38 Burr-hole drainage with irrigation: 114	Retrospective analysis on recurrence rates	The recurrence rate was 19.1% (n=29). The recurrence rate was significantly higher in the irrigation group (p=0.003; 1 vs. 28). Pneumocephalus more common in irrigation group (p=0.02).	No catastrophic complications were found in postoperative course (only except urinary tract infection, delirium and pulmonary edema)	No difference in clinical outcome in the groups. The recurrence rate was, however, higher in irrigation group. Irrigation should be reserved only for selected cases.
Jang et al., 2015[22]	Overall: 93 Single burr-hole drainage without irrigation: 31 Double burr-hole drainage without irrigation: 32 Double burr-hole drainage with irrigation: 30	Retrospective analysis on recurrence rates	The double burr-hole drainage with irrigation cohort showed the most effective resolution of hematoma and midline shift (p<0.05) as well as lowest recurrence rate (p<0.05).	Overall mortality 5/93; no significant difference between cohorts	Double burr-hole drainage with irrigation is the most effective method of treatment.
Lee et al., 2015[21]	Overall: 100 Burr-hole drainage without irrigation: 32 Burr-hole drainage with irrigation: 68	Retrospective analysis on recurrence rates	Recurrence rate was 8.8% in the irrigation group and 28.1% in the no-irrigation group (p=0.017).	Complications or mortality not reported.	Burr-hole drainage with irrigation may reduce the recurrence rate.
Iftikhar et al., 2016[23] (only abstract available)	Overall: 56 Burr-hole drainage without irrigation: 22 Burr-hole drainage with irrigation: 34	Retrospective analysis on recurrence rates	Recurrence rate was 17.6% in the irrigation group and 9.1% in the no-irrigation group (p=0.46).	The irrigation group had a mortality rate of 5.9% compared with 4.5% in the no-irrigation group (p=0.66).	No statistically significant difference in recurrence or mortality.
Wang et al., 2017[19]	Overall: 151 Burr-hole drainage without irrigation: 63 Burr-hole drainage with irrigation: 88	Retrospective analysis on recurrence rates	Patients in the irrigation group had more pneumocrania (p<0.05). No significant differences in rates of rebleeding, recurrence, infection, and other complications (p>0.05).	Overall complication rates: rebleeding 8.6%, epilepsy 3.3%, wound infection 1.3%. Mortality not reported.	Irrigation had no improvement in the long-term curative effect, but it increased the risk of short-term complication in terms of pneumocrania.

Drainage

The benefit of subdural drain use has been established in a high-quality RCT[50] and two meta-analyses[124,125]. Use of a subdural drain is an effective method to reduce symptomatic recurrences and need for reoperation. It has also been associated with improvements in short- and long-term functional outcome[125] and reduced mortality[50]. The drain is most often kept in place for approximately 48 hours, but a recent randomized study suggests that 24 hours may be sufficient[126]. The purpose is to give the brain time to expand but minimize the risk of infection related to the presence of the drain. The duration of drainage may be individually shortened in case of no efflux or lengthened in case of fluid efflux is continuous at 48 hours. In the surgery, if the brain re-expands immediately into the opening, the drain can be inserted in a subgaleal position just above the burr-hole.[127]

Nakaguchi et al.[128] conducted a small prospective study (n=63) regarding the relationship between drain tip location and postoperative recurrence after BHC. Subdural drain tip located in the frontal region resulted in the lowest recurrence rate in comparison to other directions (frontal 5%, parietal 38%, occipital 36%, temporal 33%). Subdural air was detected significantly less when placing the tip of the drain in fontal direction in comparison to all other directions. The study concluded that placing the tip of the subdural drain in the frontal convexity to remove subdural air is an effective method for preventing postoperative recurrences.

There has been some controversy around the position of the drain. Some centers prefer subgaleal location (also referred as subperiosteal) over subdural location. A Swiss RCT found a lower recurrence rate in the subgaleal drain group than in the subdural drain group (8.3% vs. 12%).[127] Although the noninferiority criteria were not met in the trial, the authors suggested that subgaleal drain position may be warranted in routine clinical practice as it was associated to lower recurrence rates, fewer surgical infections, and lower drain misplacement rates. However, the study had a substantially high misplacement rate in the subdural drain group. Three meta-analyses comparing subdural and subgaleal drains all supported the use of subgaleal drain as it seems more efficient and safe method.[129–131] More high-quality RCTs are needed to provide class I evidence.

Perioperative treatment

The choice of anesthesia depends on the choice of surgical method. TDC is usually performed in local anesthesia and craniotomy in general anesthesia.[60] However, BHC may be performed either under local or general anesthesia. General anesthesia is associated with higher medical risks and longer hospital stays.[132] However, local anesthesia may be experienced as uncomfortable for the patient although this can be alleviated with benzodiazepine sedation. Also, in case the patient has acute confusion or agitation as symptoms caused by the hematoma, the procedure is sometimes technically challenging to perform under local anesthesia and movement of patient during surgery may increase the chance of surgical complications. Only limited studies comparing anesthesia modalities exist. There is one ongoing RCT comparing general and local anesthesia during surgery.[133] According to a large prospective multicenter study from the United Kingdom[118], 93% of operations were performed under general anesthesia. In this study BHC was the most common procedure (89%) followed by craniotomy (9%).[118]

Whether postoperative bed rest should be prescribed remains controversial. According to two questionnaires conducted in the United Kingdom and Ireland[134] and in Canada[9], about half of neurosurgeons prescribe postoperative bed rest. The length of bed rest was most often 1–2 days.[9,134] Postoperative bed rest is thought to promote brain re-expansion and thus reduce recurrences[60], and one study even found lower recurrences with three days supine position[135]. However, bed rest may associate with immobility, thromboembolic complications, and infections. According to a retrospective analysis by Kurabe et al.[136], early mobilization was associated with reduced postoperative complications in comparison to delayed mobilization after surgery for elderly CSDH patients. In Finland, early mobilization is actively encouraged in the neurosurgical ward with physiotherapist's assistance if needed.

Middle meningeal artery embolization

Recently, there has been a growing interest in a new minimally invasive technique to treat CSDH, middle meningeal artery (MMA) embolization. The purpose is to prevent microhemorrhage by embolizing the MMA. The neovessels in the CSDH membranes derive from the dura mater and are mainly perfused by branches of the MMA.[137] Cessation of arterial flow to the dura may result in resolution of the CSDH as absorption exceeds microhemorrhage.[138]

The current data only includes case series and non-randomized small studies.[139] According to a recent prospective multicenter analysis (n=154) by Kan et al.[140], MMA embolization effectively reduced the hematoma volume and prevented its growth. The authors concluded that MMA embolization may provide a safe and efficacious alternative both as primary and secondary treatment for recurrences after surgery.[140] A recent meta-analysis had a similar conclusion and stated that MMA embolization may be associated with a lower recurrence rate and comparable complication rates.[141] There are several ongoing RCTs assessing the efficacy of MMA embolization.[142–148] Hopefully these studies will shed light on if this technique could be adopted to broader clinical practice and which patients will benefit from the treatment.

Pharmaceutical treatment

Corticosteroids

Corticosteroids have been used in the treatment of CSDHs for a long time[149], and dexamethasone primarily has still been used recently in some countries. A systematic review published in 2019 concluded that addition of corticosteroids used as adjunct to surgery may be effective.[150] However, the risk of bias in this meta-analysis was generally high and the authors warranted interpretation of results with caution. Before 2020 the efficacy and safety of these agents had not been studied in a randomized controlled setting. Also, the true mechanism of action of corticosteroids in CSDH has remained unknown. Their anti-inflammatory and antiangiogenic functions have been believed to be beneficial.[56]

In 2020 a large, multicenter, placebo-controlled RCT was published in the New England Journal of Medicine.[70] The study compared 2-week tapering course of dexamethasone with placebo. The decision to surgically evacuate was left to the treating physician, and 94% of patients underwent surgery. Dexamethasone treatment resulted in fewer favorable functional outcome (84% vs. 90%) which was the primary outcome and more adverse events (AEs). However, the need for reoperation was significantly lower (2% vs. 7%). Based on this trial, use of dexamethasone is not recommended when used adjunct to surgery. Definitive conclusions whether dexamethasone could be valid as primary conservative intent, cannot be drawn. However, the DECSA trial[151] specifically assessing the role of dexamethasone as an alternative to surgery was recently terminated early due to significant differences in the treatment arms on safety parameters.[152] The final results have not been published yet, but the researchers concluded in their conference presentation that dexamethasone therapy is not indicated over surgery.[152]

Tranexamic acid

Tranexamic acid (TXA) is an antifibrinolytic medication. It is believed that by the fibrinolysis preventing function TXA could inhibit the hyperfibrinolytic activity and continuous bleeding from the outer membrane of the CSDH.[53,112] To date there is no high-quality evidence on the efficacy of TXA use. In a small retrospective analysis, all CSDHs treated with TXA alone (n=18) resolved.[153] Several ongoing RCTs are assessing the role of TXA both as a conservative treatment and adjunct to surgery.[154–157]

Antiepileptic medication

The incidence of posttraumatic epileptic seizures in patients with CSDHs is 5–10%.[158–160] Risk factors for epileptic seizures include alcohol abuse, change in mental status, previous stroke and mixed density hematoma.[158,159] Routine use of prophylactic antiepileptic medication is not recommended but instead the decision should be made individually.[160–163] Prophylactic use may be beneficial for patients with multiple risk factors.[158,160] Phenytoin and levetiracetam have similar efficacy but treatment with levetiracetam may result in fewer AEs.[158]

Other pharmaceuticals

Atorvastatin is a less researched pharmaceutical than corticosteroids or TXA. Statins have been reported to reduce inflammation in vessel walls and induce vascular repairment[164,165], which is why these pharmaceuticals have been of interest in CSDH research. ATOCH is a placebo-controlled phase II RCT[166] assessing the safety and efficacy of atorvastatin as conservative treatment for mild to moderate CSDHs. The study discovered that patients taking atorvastatin had 12 mL more CSDH volume reduction at 8 weeks compared to those in the placebo group. Thus, there was only a minor difference between the groups, and it seems that the CSDHs included in trial were small as only 17% of patients required surgical intervention. Interestingly, two prospective studies were later retracted by the authors due to various errors and misleading results.[167,168] Currently there is one ongoing RCT assessing the efficacy of atorvastatin as conservative treatment and also adjunct to surgery.[169]

Another pharmaceutical of interest has been angiotensin-converting enzyme (ACE) inhibitors. The exact mechanism is unknown but ACE inhibitors may reduce neovascularization in the CSDH membranes by reducing the production of vascular endothelial growth factors (VEGFs) which are potent angiogenic factors.[170] In a retrospective analysis, those using ACE inhibitors had a significantly lower recurrence rate than those without medication (5% vs. 18%).[170] A small placebo controlled RCT assessed the effect of postoperative 5 mg of perindopril on recurrences after BHC with drainage for CSDH. [171] However, the trial was terminated early since no difference was detected between perindopril and placebo. Notably, no recurrences occurred among the randomized patients but 18% of the excluded patients had a hematoma recurrence. This suggests that the patients with highest risk of recurrence may have been excluded.

Resumption of antithrombotic medication

Neurosurgeons are daily confronted with the complex dilemma of when to restart antithrombotic medication, particularly after surgical evacuation of CSDH. Early restart poses a risk of hemorrhage and recurrent CSDH. However, prolonged discontinuation exposes the multimorbid patients to thromboembolic complications which may be fatal. Definite recommendations are currently missing.

In clinical practice, generally resumption of thromboembolism prophylactic dose of LMWH is regarded as appropriate 12–24 hours after surgical evacuation of CSDH if needed (i.e. for high-risk patients). A postoperative follow-up scan may help in the decision to restart the anticoagulative medication. When it comes to the resumption of full-dose anticoagulants, the risk-benefit ratio is considered individually for each patient. This analysis includes weighing the patient's indication for anticoagulation, history of thrombosis, coagulation function according to laboratory tests, possibly a control head CT scan, and clinical examination. The operating surgeon also assesses the hemostatic function during the operation and makes their recommendation on the earliest possible resumption. A large prospective trial would be needed to make an evidence-based guideline on the optimal time to restart full-dose anticoagulation after CSDH surgery.

Follow-up

CSDH patients are discharged from the neurosurgical unit when mobile. Some patients may need further rehabilitation at a regional hospital. In Finland early postoperative CT scans are not performed in routine but based on clinical need if symptoms persist, the patient deteriorates, or if in the operation the volume of the erupted hematoma is small. An RCT published in the New England Journal of Medicine in 2019 found no benefit in routine follow-up CT and patients followed clinically without routine CT scans had fewer reoperations.[172] This finding and no benefit of routine scanning is supported by other studies as well.[173–175] The risk in routine follow-up head CT is that it may reveal a recurrent hematoma in clinically asymptomatic patient and lead to a decision to reoperate. According to a Finnish retrospective study, 18% of patients reoperated were in fact asymptomatic but reoperated due to a large CSDH on the follow-up CT.[173] However, a follow-up CT scan may help with the decision to restart antithrombotic medication and is taken in Finland for patients with premorbid antithrombotic medication before the follow-up visit at about 6 weeks after surgery. There are currently no official guidelines on how and when patients should be followed up after CSDH and practices differ between countries.[175]

Conservative treatment

The pathogenetic process of CSDH development may result in full absorption of the subdural collection without surgery, particularly in previously healthy persons without severe brain atrophy.[58] The absorption occurs following the maturation of neomembranes and stabilization of neovessels.[58] However, in older multimorbid patients microhemorrhage may exceed absorption and result in a persistent CSDH and neurologic symptoms.[56,58] Currently, no universal recommendations exist on when a CSDH should be operatively managed and in which case conservative approach would be advisable. The decision is based on the clinician's judgement. In general, patients in whom the surgical risks are calculated to outweigh the benefits of operation are conservatively managed. This includes asymptomatic small CSDHs and moribund patients with poor prognosis. Patients with small CSDHs can have a clinical and radiologic follow-up at an outpatient clinic to check that the hematoma is not expanding. Antithrombotic medications are paused at the time of diagnosis and may be restarted if the CSDH has resorbed in the follow-up CT scan. Alternatively, the patient can be advised to seek medical help if any typical symptoms arise.

In the Finnish population-based study by Rauhala et al.[1], 15% of patients with a CSDH diagnosis were conservatively treated and 85% operatively treated. In a study from the United States by Balser et al.[65] assessing veteran population, only 29% were operatively treated. The variation may for example depend on different thresholds to take head CT scans.

Outcomes and complications

Hematoma recurrence

Hematoma recurrence requiring reoperation is probably the most important complication after CSDH surgery. The recurrence rate depends on the surgical technique, and after BHC for CSDH with drainage recurrence rate is approximately 10%.[13] Most recurrences requiring reoperation occur within one month of the index operation.[173]

Some factors that have been associated with a CSDH recurrence are bilaterality[176–178], visible thick hematoma membrane during surgery[179], and presence of postoperative midline shift[180]. Patients with insufficient brain re-expansion during surgery seem to experience a recurrence more often.[179,181] Some factors correlating with poor brain re-expansion may be older age, persistent post-operative subdural air (pneumocephalus), and pre-existing cerebral infarction.[181] Pneumocephalus has been associated with recurrence in other studies as well.[182]

Nakaguchi et al. introduced a classification of CSDHs based on the internal architecture in 2001 and suggested that this classification may help predict hematoma recurrence.[111] They found that the recurrence rate of the separated type of CSDH was high, whereas the recurrence of the trabecular type was low.[111] The association between the separated internal architecture and hematoma recurrence has been supported by other studies as well.[180,182,183] Nevertheless, the Nakaguchi classification has not led to any wider use to predict recurrence in clinical practice.

Anticoagulant therapy has been associated with recurrence[180], but also contradictory findings exist[184]. According to a Swedish population based study[185], there was no difference in recurrence rates of patients with antithrombotic medication at the time of diagnosis and no antithrombotic medication. Early resumption also did not associate with more recurrence but with lower thromboembolic complications.[185]

Functional outcome and mortality

The modified Rankin Scale (mRS)[186] is a commonly used measure of neurological outcome in CSDH studies. (**Table 3**) The mRS describes the patient's physical disability and need for assistance but also considers ability to perform instrumental activities of daily living (IADL, such as meal preparation, shopping, handling financials) and basic ADLs (BADL, such as walking, dressing, showering). In CSDH studies, the mRS is sometimes dichotomized to favorable functional outcome (mRS 0–3) and unfavorable (mRS 4–6) outcome. Dichotomization to favourable mRS 0–2 and unfavourable mRS 3–6 is also sometimes used but more rarely among CSDH studies.[66]

Table 3. *Modified Rankin Scale score and description*

mRS score	Description
0	**No symptoms** at all
1	**No significant disability**: despite symptoms, able to carry out all usual duties and activities
2	**Slight disability**: unable to perform all previous activities but able to look after own affairs without assistance
3	**Moderate disability**: requiring some help but able to walk without assistance
4	**Moderately severe disability**: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	**Severe disability**: bedridden, incontinent and requiring constant nursing care and attention
6	**Death**

Another measure of outcome is the Glasgow Outcome Scale (GOS)[187]. (**Table 4**) However, GOS has been criticized for being insufficiently sensitive to functionally disturbing deficits in cognition, behavior, and mood.[188] GOS can likewise be further dichotomized to favorable outcome (GOS 4–5) and unfavorable outcome (1–3).

The Markwalder Grading Scale (MGS)[189] has been used in many studies. (**Table 5**) It is also used for classifying the neurological status of patients on admission along with the Glasgow Coma Scale (GCS) score.[190] MGS utilizes descriptive terms about the level of consciousness which is probably one reason why some researchers prefer the GCS score.

Table 4. *Glasgow Outcome Scale score and description*

GOS score	Description
5	**Good recovery**. Able to return to normal functional level and employment.
4	**Moderate disability (disabled but independent).** Minor neurological deficits, still independent in daily living.
3	**Severe disability (conscious but disabled).** Need of assistance, significant neurological deficit that interferes with daily activities and prevents return to employment.
2	**Persistent vegetative state.** Coma, minimal responsiveness. Patient totally dependent of others.
1	**Death**.

Table 5. *Markwalder Grading Scale score and description*

MGS score	Description
0	Patient neurologically normal
1	Patient alert and oriented; mild symptoms such as headache; absent or mild neurological deficit, such as reflex asymmetry
2	Patient drowsy or disoriented with variable neurological deficit, such as hemiparesis
3	Patient stuporous but responding appropriately to noxious stimuli; severe focal signs, such as hemiplegia
4	Patient comatose with absent motor responses to painful stimuli; decerebrate or decorticate posturing

Outcomes after surgical evacuation of CSDH have been generally perceived as favorable, with good functional outcome achieved in over 80% of patients.[50] It seems that younger patients have better outcomes compared to the elderly.[66,106,179] It may be that younger patients often have better neurological condition on admission compared to the older generation[72] which partly explains the better outcomes. Poor neurological condition on admission[50,78] and postoperative complications, such as infections and thromboembolic events[106], are associated with poor outcome. In a large study by Toi et al.[66], older age groups had more often disturbance of consciousness on admission. The percentage of poor outcome (defined as a mRS score of 3–6 in this study) was 12% of patients under 70 years of age and 57% of those over 90 years of age.[66] However in a large population-based Scandinavian study, patients older than 90 years had similar rates of recurrence, morbidity, and mortality as younger patients.[67] This study along with others suggests that age alone should not be a contraindication for surgery.[67,191]

The mortality rates of CSDH patients vary widely in different studies depending on the study population, treatment, duration of follow-up and country. One-year mortality up to 32% has been reported.[38] In the RCT by Santarius et al.[50], mortality rate was 9% at 6 months after treatment with BHC and subdural drainage.[50] At 5 years postoperatively 34% of patients had died, and the patients treated with subdural drains still had significantly lower mortality than those treated without drains.[192] The long-term survival of patients treated with subdural drain was however not different from the general population in this study.[192] Factors associated with higher mortality include old age[38,179,193], poor neurological condition on admission[38,179,193,194], postoperative complications[106], and comorbidities such as cardiac and renal failure[179,193].

Other complications

In addition to CSDH recurrence requiring reoperation, other potentially severe procedure-related complications include ASDH, intracerebral hemorrhage, seizure, wound infection, subdural empyema, and tension pneumocephalus.[122] In a large Japanese retrospective study including 500 patients treated with BHC and closed system drainage, 5% suffered a postoperative complication.[181] The most common surgery-related complications were ASDH due to insufficient wound hemostasis (2.6%) and tension pneumocephalus (0.8%). According to a Finnish large retrospective analysis, the most common postoperative surgery-related complication was seizure (5%) followed by ASDH (1%) and intracerebral hemorrhage (0.6%).[173] Lowered GCS on admission may be predictive of seizures as a complication.[159] In a study by Huang et al., a decrease of one mean GCS increased seizures by 22%, most of which occurred within three months after CSDH.[159] Postoperative hospital-acquired infections, such as pneumonia and thromboembolic complications, are also common especially among the elderly patients and may sometimes be fatal.[78,173] Patients who experience complications more often have unfavorable outcomes.[106]

Dementia and mortality

The population aging has led to a growing number of people with dementia.[35] For those older than 65 years, the worldwide incidence is 4.2 per 100,000.[195] The worldwide prevalence is alarmingly expected to triple by 2050[35], although some evidence suggests that the incidence might not increase in high-income contries.[196,197] The proportionate increases in the number of people with dementia are predicted to be more radical in low- and middle-income countries than in high-income countries.[35] In Finland the number of new diagnoses of dementia per year is 14,500 among those aged older than 64 years.[198] In 2013 the number of persons with moderate or severe dementia in Finland was 93,000 and by 2060 the prevalence of dementia is expected grow to 240,000.[198]

Dementia is associated with significant mortality.[199,200] The median survival after a diagnosis of dementia is estimated between 3.2 and 6.6. years.[199] High age weakens the prognosis and it seems that male gender might also be a predictor of mortality.[199,201] The type, severity and symptoms of dementia as well as other comorbidities affect the life expectancy.[198,201,202]

Interestingly, according to a study by Bin Zahid et al.[69], development of a CSDH increases the atrophy rate to more than twice the speed of patients with dementia. The results suggest that CSDH has neurotoxic consequences. The association between dementia and CSDH is however not well known nor studied.

Aims of the study

1. To confirm whether in clinical practice patients treated with postoperative subdural drains had lower recurrence rates compared with those who were treated without drains. (Study I)

2. To assess the association between dementia and one-year case-fatality in older persons undergoing CSDH surgery. (Study II)

3. To estimate the national incidence of surgeries for CSDH in Finland. (Study III)

4. To plan and start a multicenter RCT to study whether no intraoperative irrigation and subdural drainage results in non-inferior outcome compared with intraoperative irrigation and subdural drainage after burr-hole craniostomy of CSDH. (Study protocol)

Methods and materials

Study population

The summary of the materials and methods of studies I–III and study protocol are shown in **Table 6**. In study I, the study population consisted of patients treated in the pre-drain era and patients treated in the drain era. The patients in the pre-drain era underwent a BHC for CSDH between July and December in 2015 and in the drain era patients were operated on between July and December in 2017. All patients operated for a CSDH at the Department of Neurosurgery of Helsinki University Hospital were assessed for eligibility. We excluded patients treated with a drain in the pre-drain era and patients treated without a drain in the drain era. Other exclusion criteria included a history of intracranial surgery, shunt for CSF diversion, or if the patient was treated with other methods (subgaleal drain, IRRAflow catheter).

In studies II and III, we used the nationwide Finnish Care Register for Health Care which contains data on all persons treated in a hospital in Finland. The database includes all persons hospitalized for CSDH surgery, as in Finland intracranial surgeries are only performed in public hospitals – mainly university hospitals but also regional central hospitals. We identified all persons undergoing primary surgery for CSDH during 1997–2014. We defined CSDH surgery as an ICD-10 diagnosis code of S06.5 or I62.0 combined with a NOMESCO (Nordic Medico-Statistical Committee) Classification of Surgical Procedures Finland (NCSP-F) code of AAD10 ("evacuation of chronic subdural hematoma").

We excluded those under the age of 60 years in study II. We defined cases as persons over the age of 60 years with a primary CSDH surgery during 1997–2014. We defined exposure as a person having a pre-existing diagnosis of dementia or receiving the diagnosis within one-year of the CSDH surgery. We searched for patients hospitalized for any reason with a diagnosis of dementia (ICD-9: 290, 331, 791; ICD-10: G30, F00, F01, F02, F03) during 1987–2014. We defined persons who underwent CSDH evacuation with a diagnosis of dementia as exposed cases. We defined persons who underwent CSDH evacuation without a diagnosis of dementia as non-exposed cases. We defined persons with dementia but no hospitalization due to head trauma as exposed controls. We searched four exposed controls to match with the controls based on age, sex, and year of first hospitalization with a new dementia diagnosis.

We excluded persons under the age of 18 for study III. Thus, the study population in study III included all adults undergoing surgery for CSDH during 1997–2014. We did a registry validation for the Finnish Care Register for Health Care regarding operated CSDH and found a high accuracy of 92%.

Table 6. *The methods in the studies I–III and the study protocol*

	Study I	Study II	Study III	Study protocol
Study aim	To confirm whether in clinical practice patients treated with postoperative subdural drains had lower recurrence rates compared with those who were treated without drains.	To assess the association between dementia and one-year case-fatality in older persons undergoing CSDH surgery.	To estimate the national incidence of surgeries for CSDH in Finland during 1997–2014.	To study whether no intraoperative irrigation and subdural drainage results in non-inferior outcome compared with intraoperative irrigation and subdural drainage after burr-hole craniostomy of CSDH
Patient source or registry	Data collection concerning medical history, imaging, and treatment from the Helsinki University Hospital's electronic health record.	Nationwide Finnish Care Register for Health Care that comprehensively includes patients hospitalized for CSDH evacuation.	Nationwide Finnish Care Register for Health Care that comprehensively includes patients hospitalized for CSDH evacuation.	Prospective recruitment and randomization.
Study time	July–December 2015 (pre-drain era) and July–December 2017 (drain era). Patients were followed up 6 months postoperatively.	From January 1997 to December 2014. Patients were followed up from operation until death or end of 2017.	From January 1997 to December 2014. Patients were followed up from operation until death or end of 2017.	From January 2020 to August 2022. Patients will be followed up 6 months postoperatively.
Inclusion criteria	Patients undergoing burr-hole craniostomy for CSDH.	Cases: Patients undergoing surgery for CSDH (ICD-10 S06.5 and I62.0 combined with NCSP-F AAD10). Controls: matched for age, sex and year of dementia diagnosis, without a CSDH diagnosis.	Patients undergoing surgery for CSDH (ICD-10 S06.5 and I62.0 combined with NCSP-F AAD10).	- age over 18 years - hypodense or isodense hematoma on CT - correlating clinical symptoms - in bilateral cases both hematomas treated according to the protocol
Exclusion criteria	- previous intracranial surgery - cerebrospinal fluid shunt - treatment with other types of drains	Age under 60 years.	Age under 18 years.	- other surgical method required - cerebrospinal fluid shunt - history of intracranial surgery - GCS<9 - condition not suitable for drain treatment - hematologic or intracranial malignancy - acute infection - high risk of thrombosis
Outcome	Primary outcome: CSDH reoperation within 6 months. Secondary outcome: Functional outcome within 7 days and at 6 months, 30-day and 6-month mortality, length of stay, infections, and other complications.	One-year mortality compared in case-only and case-control analyses.	Incidence rate of CSDH surgery in Finland and the change in the incidence rate.	Primary outcome: CSDH reoperation within 6 months. Secondary outcome: functional outcome at 6 months, mortality within 6 months, duration of the operation, length of stay, CSDH volume reduction, and AEs.

Statistical analyses	Chi square test for categorical variables, Fisher's exact test when appropriate, Shapiro-Wilk test to evaluate normality, Mann-Whitney U test to compare continuous data, t-test to compare normally distributed data, binary logistic regression analysis to assess associations between variables and recurrences, Kaplan-Meier curves to show time to recurrence.	We used binary logistic regression adjusting for variables that differed between dementia and non-dementia patients and one-year survivors and non-survivors. We assessed the association between dementia and mortality using Cox proportional Hazards models. We compared one-year mortality in the case-control analysis using Chi square test.	We calculated the incidence rates of CSDH evacuation per 100,000 person-years separately in each age group and sex. We performed age standardization with weights from the 2013 European Standard Population. We used negative binomial regression to assess age- and sex-adjusted changes in the incidence rate ratios (IRRs).	To declare non-inferiority, both the ITT and PP analyses must support the conclusion. The non-inferiority margin is set at 7.5%. We assess the secondary outcomes using a Chi square test or logistic regression. We analyze continuous outcomes using a t-test or analysis of covariance. We include the effect of potential confounding factors in the statistical models.

Study variables

In study I, we retrospectively obtained the data regarding the patient's medical history, imaging, and treatment from the Helsinki University Hospital's electronic health record. We collected patient's baseline and follow-up data on residence, mobility, medical history, history of head trauma, main symptom, mRS score, and presence of hemiparesis or dysphasia. We analyzed all pre- and postoperative imaging data. We measured the midline shift, hematoma width and calculated the volume by using the ABC/2 formula[203]. We determined the reduction of the CSDH volume after operation. We recorded the color and pressure of the hematoma in the operation.

For studies II and III, we gathered dates of birth, dates of index surgeries, dates of possible reoperation, sex, and treatment hospitals from the Finnish Care Register for Health Care. We extracted population size data broken down by sex, age groups, and calendar years from the Sotkanet Indicator Bank[204] for incidence rate calculations. We defined reoperation as a second CSDH evacuation within one year after the index CSDH surgery. We received dates of death from the Finnish Official Cause-of-Death Statistics from Statistics Finland.

Outcomes

In study I, our primary outcome was recurrent CSDH necessitating reoperation within 6 months of the primary operation. Because Helsinki University Hospital is the only institution in the catchment area performing neurosurgery, all patients are referred to this hospital and thus, we were able to get information regarding all occurred reoperations. Our secondary outcomes included functional outcome (measured by mRS score) within 7 days and at 6 months, 30-day and 6-month mortality, length of stay in the neurosurgical unit, and complications. We collected the dates of death through the Finnish Population Registry which includes up-to-date data of all Finnish citizens.

In study II, the primary outcome was one-year mortality in case-only and case-control analyses. We received the vital status data from the Population Register Centre. Secondarily, we assessed the percentage of patients with a pre-existing dementia diagnosis undergoing CSDH evacuation. In study III, the primary outcome of interest was the incidence rate of CSDH surgery in Finland and the change in the incidence rates during 1997–2014. We followed up the study population from CSDH evacuation until death or end of 2017 in studies II and III.

Statistical analyses

In study I, we used Chi square test to compare categorical variables, adjusting the Bonferroni method and used Fisher's exact test when appropriate. We evaluated continuous variables for normality with the Shapiro-Wilk test and used the Mann-Whitney U test to compare nonparametric data. We compared normally distributed data with the t-test. We assessed if there were any differences in the baseline patient characteristics between the drain and non-drain groups. We used binary logistic regression to study associations between variables and risk of recurrence. We adjusted for differences in baseline characteristics and reported the odds ratios (ORs) and 95% confidence intervals (CIs). We illustrated the difference in time to recurrence between the subdural drain and non-drain groups with Kaplan-Meier curves (without significance testing). We considered a p-value less than 0.05 statistically significant.

For studies II and III, we divided the patients into four as equally sized as possible treatment quartiles according to the year of surgery (1997–2002, 2003–2007, 2008–2011, 2012–2014). The age groups were 18–59, 60–69, 70–79, 80–89 and 90+ in both studies, however, excluding the youngest age group (under 60-year-olds) in study II. We calculated the incidence rates of CSDH surgery per 100,000 person-years separately in each age group and in study III also for men and women. In study III we applied age standardization for those older than 20 years with weights from the 2013 European Standard Population (ESP)[205]. We presented patient characteristics and outcomes as frequencies, percentages, medians, and interquartile ranges (IQRs).

In study II we used Chi square test to compare categorical data and Mann-Whitney U or Kruskal-Wallis H test to compare continuous data. We used binary logistic regression adjusting for certain variables that differed between dementia and non-dementia patients and one-year survivors and non-survivors. We assessed the association between dementia and mortality and used Cox proportional Hazards models to estimate hazard ratio (HR) for one-year mortality. We compared one-year mortality in the case-control analysis using a Chi square test.

In study III we showed one-year case fatality rates and 95% CIs after CSDH surgery in different age groups and sexes in Kaplan-Meier curves. The Poisson regression model showed overdispersion and thus, we used negative binomial regression instead to assess age- and sex-adjusted changes in the incidence rate ratios (IRRs).

Methods in the FINISH trial

Study design and setting

Finnish study of intraoperative irrigation versus drain alone after evacuation of chronic subdural haematoma (FINISH) is a prospective, randomized, controlled, parallel group, non-inferiority multicenter trial. We wanted to compare single BHC of CSDH with intraoperative irrigation and BHC of CSDH without irrigation. A passive subdural drain was used for 48 hours in both groups. Our hypothesis was that no irrigation results in non-inferior outcome in comparison with irrigation with primary respect to recurrences. All five neurosurgical departments in Finland, 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) participated in the study. These neurosurgical units are the only units performing neurosurgery in Finland.

Participants

In the five neurosurgical units, all patients referred for CSDH surgery were screened for eligibility. A preoperative clinical examination and a head CT or MRI scan were performed. If the clinical and imaging findings were consistent with a diagnosis of symptomatic CSDH and a BHC with drainage was deemed appropriate, the patient's interest to take part in the trial was inquired. The inclusion criteria included age over 18 years, a primarily hypodense or isodense hematoma on CT (or alternatively chronic hematoma on MRI) with correlating clinical symptoms. Patients with operatively managed bilateral CSDHs were analyzed as a single participant and treated according to the protocol on both sides.

Exclusion criteria included CSDH requiring other surgical method than BHC, patients with CSF shunt, any prior intracranial surgery, GCS<9 and rapid surgery required, patient's postoperative condition expected to be insufficient for drain treatment (i.e. disoriented patient), active treatment for a hematologic malignancy during the previous 5 years, patients with a central nervous system malignancy, acute infection requiring antibiotic treatment, high risk of life-threatening thrombosis (e.g. recent coronary stent, intracranial stent) and cessation of antithrombotic medication not recommended.

Ethics, public involvement and informed consent

The institutional review board of the Helsinki and Uusimaa Hospital District approved the study (HUS/3035/2019 §238). We registered the study at ClinicalTrials.gov. All centers received local institutional research approvals for the consent form and the electronic case report form (eCRF) which we used for data collection.

We designed the study in collaboration with patient organization experts from the European Patients' Academy on Therapeutic Innovation (EUPATI Finland, https://fi.eupati.eu/). It was agreed upon that after completion of the trial, public data sharing and spreading would be jointly discussed.

At admission, the attending neurosurgeon provided the patient with detailed written and oral information on the trial and requested the patient's written consent to take part. In case the patient due to their poor condition was not able to provide written consent before randomization, delayed consent was requested from the patient after surgery. In these cases, pre-randomization oral consent was inquired from the patient's next of kin. Withdrawal from the study was permitted at any phase.

Data collection

We documented the data in the eCRF. Data were collected preoperatively, intraoperatively, within 48–72 hours postoperatively, at 6 weeks (±2 weeks), and at 6 months. The preoperative and postoperative head CT and MRI scans were sent and stored in the Picture Archiving and Communication System of Helsinki University Hospital. Independent assessors blinded to other patient information analyzed the images. All study participants were given a unique study identifier number, which was used for pseudonymization. We did not disclose the group assignment in the patient records to preserve blinding. However, the surgeon obviously was aware of the randomization group. All researchers signed a code of confidentiality, and all information was stored in secure offices or password-secured databases.

Surgical technique

Currently in Finland, the mainstay of operative management has included single BHC with intraoperative irrigation and passive subdural drainage. We performed BHCs under local anesthesia, often combined with sedation with benzodiazepines and/or opioids. We only performed the procedure under general anesthesia if local anesthesia was considered unsafe. We gave preoperative antibiotics according to local protocols (usually a second-generation cephalosporin 30–60 min before incision). In a typical procedure, the neurosurgeon drilled one 14 mm burr-hole over the estimated maximum convexity of the hematoma. Bilateral CSDHs were treated similarly on both sides. In case irrigation was used, after incision of the dura mater, the neurosurgeon irrigated the subdural space with body temperature Ringer's lactate saline solution until rinsing appeared clear. As a minimum 200 mL of irrigation per side was required (i.e. for bilateral CSDHs a minimum of 400 mL in total).

Thereafter the surgeon inserted a subdural drain 3–5 cm deep, parallel to the cranium. The position of the drain (frontal, occipital) was decided by the operating surgeon. The distal end of the drain was tunneled under the subgalea approximately 4–5 cm from the incision and connected to a passive drainage bag. All centers used 10F drains. We did not routinely use burr-hole covers (e.g. Spongostan® or Tachosil®). The surgeon closed the skin in two layers and fixed the drain to the skin. The different steps of the procedure are shown in **Figure 5**. The drainage bag was kept at bed level for 48 hours (±12 hours).[50,206] We allowed patient mobilization during drainage.

We randomized patients in a 1:1 allocation ratio stratified by study center. We used block randomization with a random block size of 4, 6 or 8. The randomization happened in the operating room through the online eCRF system (Granitics, Espoo, Finland) right before the skin incision. If the participant was randomized to the irrigation group, the operation was performed as previously described i.e. with irrigation. Also, a 10 mL subdural fluid sample was taken after opening the dura. If the participant was randomized to the no-irrigation group, after taking the subdural fluid sample, a subdural drain was inserted. Thus, the step of irrigation was omitted but otherwise the surgeon performed the procedure as usual. We recorded the volume of irrigation fluid and duration of surgery.

Outcomes and follow-up

The primary outcome was symptomatic ipsilateral recurrence of CSDH requiring reoperation within 6 months of the index surgery. The treating neurosurgeon made the decision to proceed to reoperation based on the same indications as for the primary surgery. All recurrences were operated according to the current operative standard i.e. BHC with irrigation and postoperative subdural drainage.

Secondary outcomes included functional outcome (measured by mRS score) at 6 months, mortality within 6 months, duration of surgery, length of hospital stay, and change in volume of CSDH at 2 months after surgery. Our safety outcomes included the number and severity of AEs and procedure-related AEs (PRAEs). We categorized AEs as severe AEs (SAEs) and minor AEs (MAEs). An SAE was any inappropriate medical event that resulted in death, disability, or incapacity, required or prolonged hospitalization, or was life-threatening. MAEs were mild medical events such as local infections manageable with oral antibiotics. MAEs were more easily tolerated by the patient and not life-threatening.

We followed the patients up for 6 months. The patient had a routine head CT scan and follow-up visit at an outpatient clinic at 4–8 weeks postoperatively. We recorded all recurrences leading to reoperation and all AEs within 6 months. We assessed the functional outcome (mRS) at 6 months through a phone interview. We obtained the dates and causes of death within 6 months through the Finnish Official Cause-of-Death Statistics. This statutory register includes data on every deceased Finnish citizen.

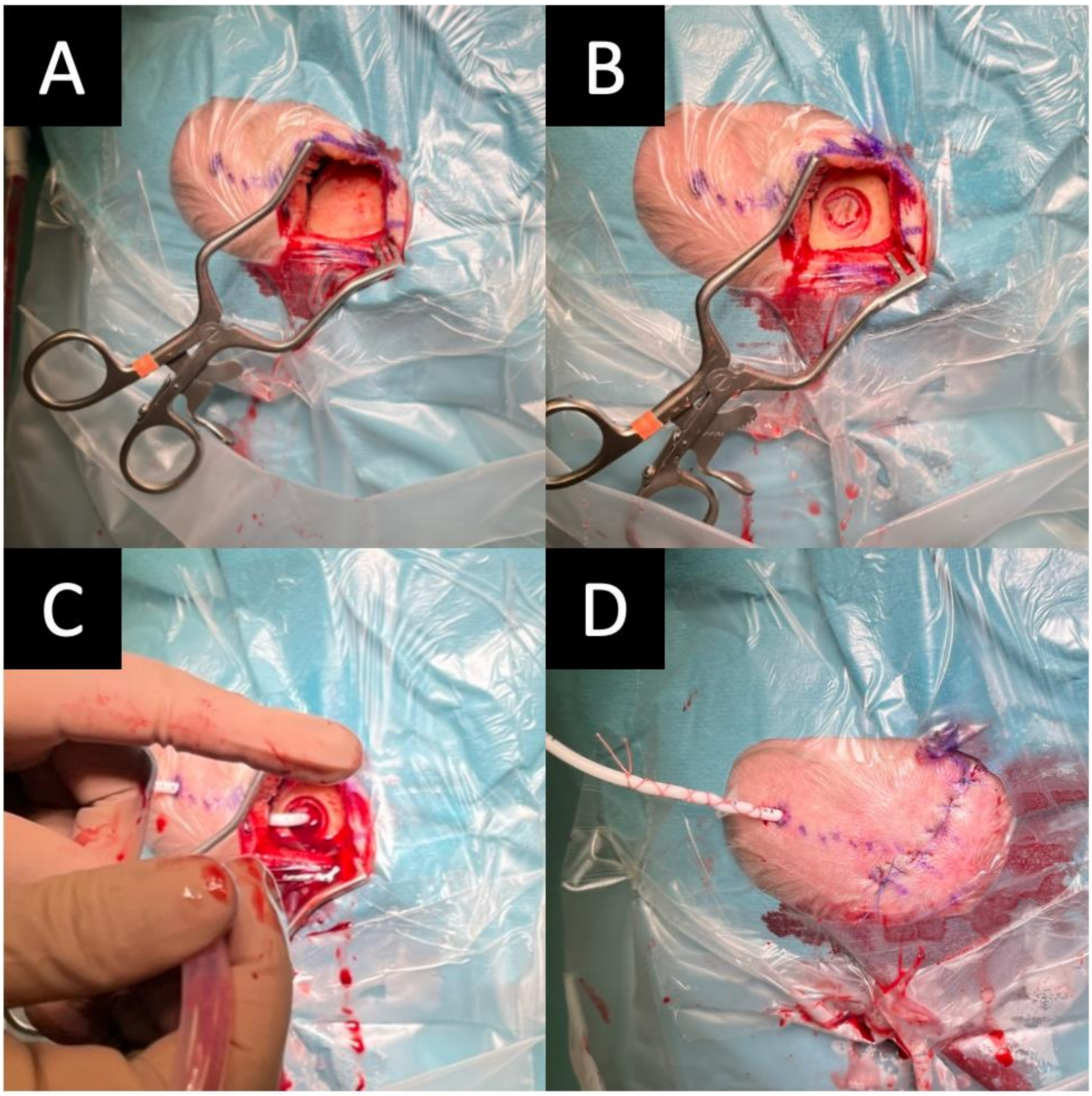


Figure 5 Burr-hole craniostomy for a chronic subdural hematoma on the right side. **A)** The opening of the skin. Cranium is visible in the opening. **B)** A 14-mm burr-hole with the dura mater visible in the opening. **C)** The insertion of the drain in the subdural space in the frontal direction. **D)** The subdural drain tunneled under the subgalea and secured to the skin with Roman sandal sutures.

Sample size and statistical analyses

We predefined the non-inferiority margin for the primary outcome as 7.5%. Given a 2.5% level of significance, 80% power, and 10% non-adherence and cross-over rate, the randomization target was set at 270 participants per group i.e. total study population of 540 participants. However, a higher-than-expected non-adherence rate was detected during an interim analysis, and the updated sample size calculations yielded a total study population of 578 participants.

We will perform the statistical analyses on both the intention-to-treat (ITT) and per-protocol (PP) participant groups. We will only assert non-inferiority of single BHC without irrigation and subdural drainage whether both the ITT and PP analyses support this conclusion. We will include all randomized participants in the ITT analysis. We include all participants that have been managed according to the protocol, have available measurements and with no major protocol violations nor inclusion or exclusion criteria violations in the PP analysis.

We will present continuous variables as mean with standard deviation or median with IQR and categorical variables as frequencies with percentages. We will interpret the statistical analysis to support non-inferiority if a 95% two-sided CI excludes a difference in the primary outcome in favor of irrigation of more than 7.5% (the predefined non-inferiority margin). We will assess the secondary outcomes using a Chi square test or logistic regression. We will analyze continuous outcomes using a t-test or analysis of covariance. We will include the effect of potential confounding factors in the statistical models. We will keep the treatment groups blinded during the statistical analyses.

Results

Patients and characteristics

Summary of patient characteristics and outcomes are shown in **Table 7**. Study I comprised 161 patients and the register-based studies II and III were larger with sample sizes of 7,621 and 9,280, respectively. Study II only included patients older than 60 years, which explains the higher median age of patients compared with study III. In study I the age of patients was higher than in study III (77 years vs. 74 years). Study I included patients from years 2015 and 2017, whereas patients in study III were operated during 1997–2014.

The percentage of female patients was the same in all studies. The prevalence of dementia was markedly higher in study I than in studies II and III. We found a lower reoperation rate within 6 months in study I compared to studies II and III, but the 6-month mortality did not differ in the three studies (11–13%). The age and sex distribution of patients undergoing surgery for CSDH in Finland during 1997–2014 is depicted in **Figure 6**. The age group with the highest number of patients was 70–79-year-olds and the male predominance diminished with age as visible in **Figure 6**.

Table 7. *Summary of patient characteristics and outcomes in studies I–III*

	Study I	Study II	Study III
Number of patients/cases	161	7,621	9,280
Median age (IQR)	77 (69–84)	77 (70–83)	74 (64–82)
Female sex	32%	34%	33%
Prevalence of dementia	22%	12%	10%
Reoperations			
within 6 months	12%	19.8%	18.7%
within 12 months	*na*	20.0%	18.9%
Mortality			
at 6 months	13%	12%	11%
at 12 months	*na*	16%	15%

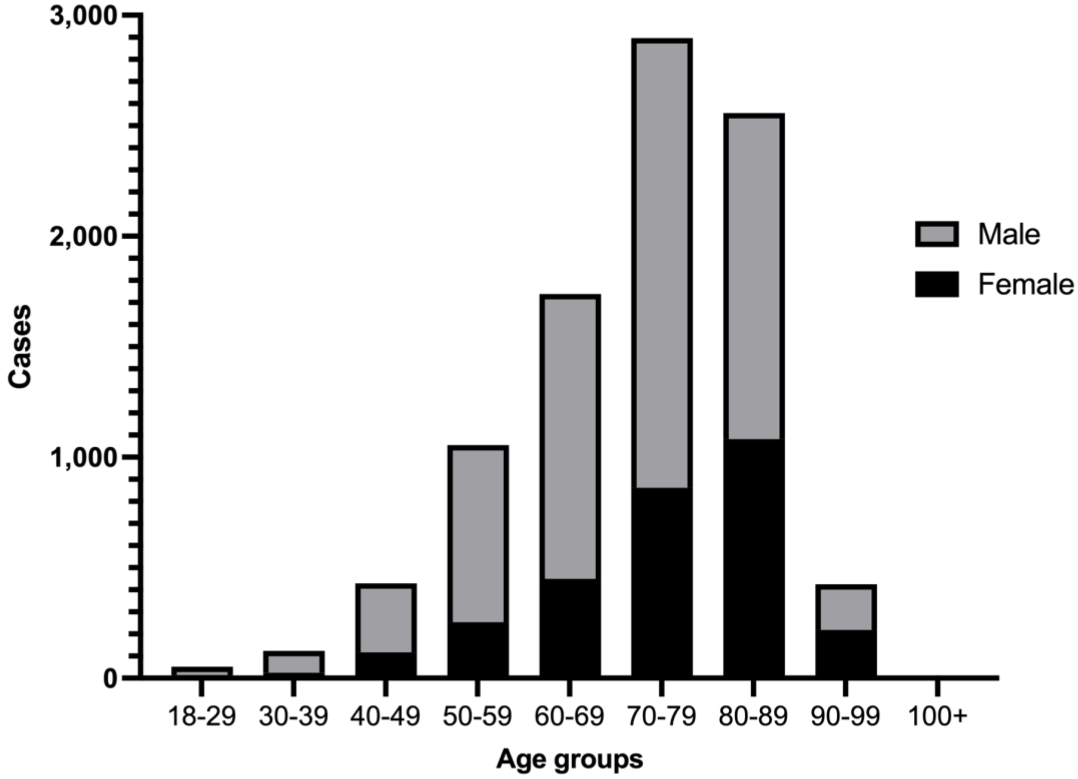


Figure 6 Age and sex distribution of patients undergoing surgery for a chronic subdural hematoma during 1997–2014 in Finland. Data from study III. Tommiska et al. unpublished results.

Association between subdural drain and recurrence

Of the 161 patients in study I, 71 (44%) were in the subdural drain group and 90 (56%) in the non-drain group. We found no major differences in baseline characteristics between the two groups apart from that the hematomas in the subdural drain group were thicker than in the non-drain group (median, 23 mm vs. 20 mm, p=0.007). However, the total volume of CSDH did not differ between the groups. The number of patients preoperatively suffering from hemiparesis or dysphasia were 78 (48%) and 52 (33%), respectively. The most common symptoms were gait disturbance or falls and limb weakness and 81% of patients had a recent history of head trauma.

We found a 6-month recurrence rate of 6% (4/71) in the subdural drain group and 18% (16/90) in the non-drain group (p=0.028). In a univariable logistic regression analysis, the use of a subdural drain was associated with an OR of 0.28 (95% CI 0.09–0.87) for recurrence within 6 months in comparison to treatment without drain. In patients with unilateral CSDHs, the recurrence rate was 5% (3/55) in the drain group and 17% (12/72) in the non-drain group (p=0.06). In patients with bilateral CSDHs, the recurrences were 6% (1/16) in the drain group and 22% (4/18) in the non-drain group (p=0.22). The risk for recurrence was highest during 30 days following surgery and remained low after that. Also in study III, the median time to surgery was 30 days and this remained stable during the whole study period from 1997–2014.

We did not find any other factors associated with 6-month recurrence apart from the use of subdural drain in study I. Drain use was also independently associated with reduced risk of 6-month recurrence in a post hoc logistic regression analysis adjusting for age, sex, preoperative neurologic deficit, and history of antithrombotic medication (OR 0.27, 95% CI 0.08–0.85, p=0.025).

The only secondary outcome that differed between the two groups was hematoma volume reduction. The mean volume reduction was 70% in the subdural drain group and 50% in the non-drain group (p=0.005). We did not find any significant differences in immediate or 6-month neurological outcome (p=0.85 and 0.72), 30-day and 6-month mortality (p=0.14 and 0.55), hospital length of stay (p=0.17), need for further care (p=0.56), infections within 30 days (p=0.85) or 6 months (p=0.96), or any other complications (p=0.20). The complications were diagnosed within 7 days of the primary surgery. In our patient population, no patient experienced a wound infection, intracranial empyema, or other intracranial infection.

The rate of reoperation within 6 months was lower in study I than in studies II and III (**Figure 7**). Reoperations within 6 months occurred in 12% of patients in study I, whereas the percentages were 20% in study II and 19% in study III. In study III, the one-year reoperation rate did not change between 1997 and 2014. In study III, the patients undergoing reoperation were slightly older (median age 75 vs. 74 years), were more often men (76% vs. 65%), and had a lower one-year mortality rate (11% vs. 16%).

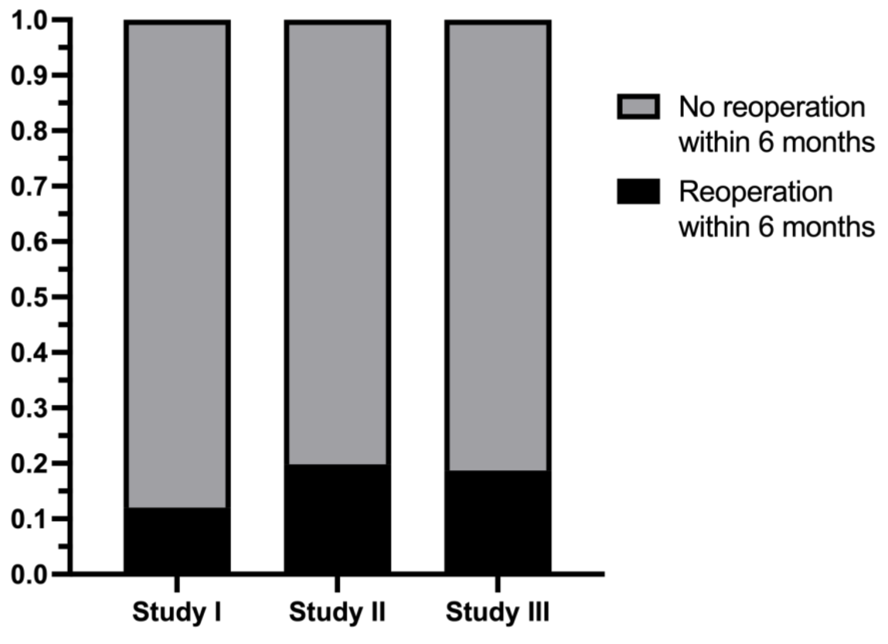


Figure 7 Reoperation rate within 6 months of the primary chronic subdural hematoma evacuation in studies I–III.

Mortality after chronic subdural hematoma surgery

In study II, the total follow-up time from primary CSDH surgery to death or end of 2017 was 43,210 patient-years, and the median follow-up time was 4.8 years (IQR 2.2–8.2 years). During the total follow-up 65% (4,916/7,621) of cases died. In study III, the total follow-up time with the same criteria was 58,497 patient-years, and the median follow-up was slightly longer 5.3 years (IQR 2.5–9.2 years). During the total follow up 59% (5,509/9,280) of cases died.

In study II, the one-year case-fatality after CSDH surgery was 16%. One-year non-survivors were older than survivors (82 years vs. 76 years) and more often treated in a central hospital (13% vs. 10%) than in a university hospital. The non-survivors also had fewer reoperations (15% vs. 21%) and more often had a diagnosis of dementia (19% vs. 10%) compared with one-year survivors. The one-year case-fatality was similarly 15% in study III, and it remained stable during the study period 1997–2014.

Mortality rates at 6 months after surgery for CSDH in studies I–III are shown in **Figure 8**. Six-month mortalities were approximately the same: 13% in study I, 12% in study II, and 11% in study III. We also reported one-month mortality in study I, which was 5%.

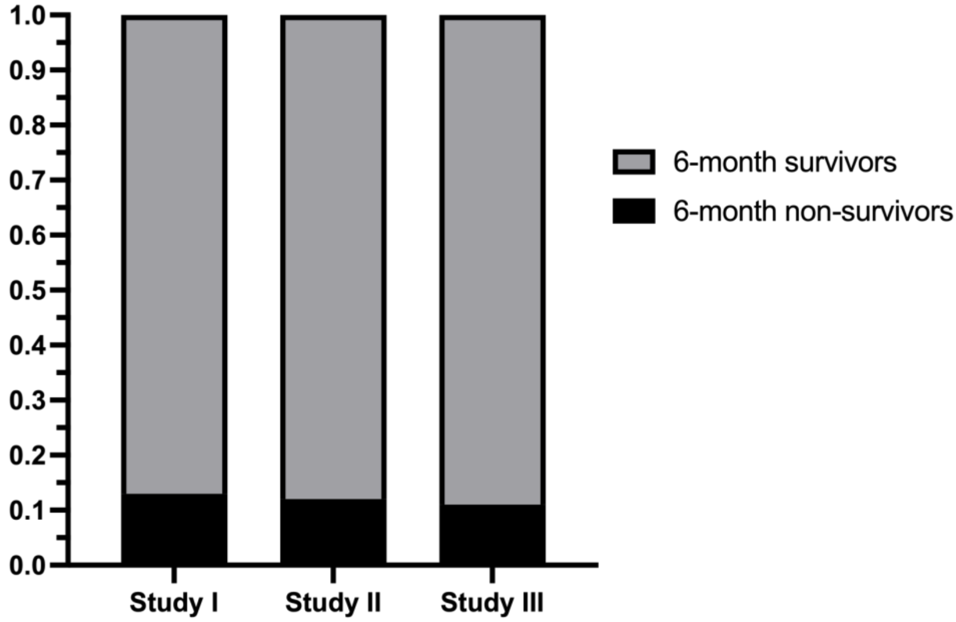


Figure 8 Mortality rate at 6 months after chronic subdural hematoma surgery in studies I–III.

Association between dementia and mortality

Among the 7,621 cases in study II, 885 (12%) had a diagnosis of dementia (exposed cases) and 6,736 did not have dementia (non-exposed cases). The proportion of exposed cases increased during the study period (9.7% in 1997–2002 vs. 12.2% in 2012–2014, p for trend=0.038). During the total follow-up of 43,210 patient-years, 61% of non-exposed cases died, whereas 88% of the exposed cases died (p<0.001). There were more female patients among the exposed cases (48% vs. 33%, p<0.001) and they were older (median age 82 years vs. 76 years, p<0.001). The exposed cases were more often operated in a central hospital (13% vs. 10%, p=0.005) than in a university hospital, and the exposed had fewer reoperations (17% vs. 20%, p=0.038).

We found a significantly higher one-year case fatality among the exposed cases compared to non-exposed cases (26% vs. 15%, p<0.001). A pre-existing diagnosis of dementia was associated with an increased risk of one-year case-fatality with an OR of 1.50 (95% CI 1.26–1.78, p<0.001). Higher age associated with an increased risk of one-year case-fatality (OR 1.08, 95% CI 1.06–1.08). Female sex (OR 0.81, 95% CI 0.71–0.92), reoperation within one-year (OR 0.67, 95% CI 0.56–0.79), and a recent year of CSDH surgery associated with a lower risk of one-year case-fatality. The association between dementia and one-year case-fatality was strongest among those aged 60–69 years (OR 3.21, 95% CI 1.59–6.47, p=0.001). The association became weaker in higher age groups and no association was found between dementia and death after CSDH surgery for those older than 90 years (OR 1.20, p=0.47). The ORs with 95% CIs in different age groups are shown in **Figure 9**.

In the Cox proportional Hazards model adjusted for age, sex, hospital level of care, reoperation, and index operation year, dementia was associated with one-year case-fatality with an HR of 1.38 (95% CI 1.20–1.60, p<0.001).

We identified 832 (94%) sets with at least one matched exposed control for the 885 exposed cases. The exposed controls were matched for age, sex, and year of first hospitalization with a new dementia diagnosis. In total there were 2,933 exposed controls. The one-year mortality was significantly higher in the exposed case group than in the exposed controls, 26% vs. 16% (p<0.001).

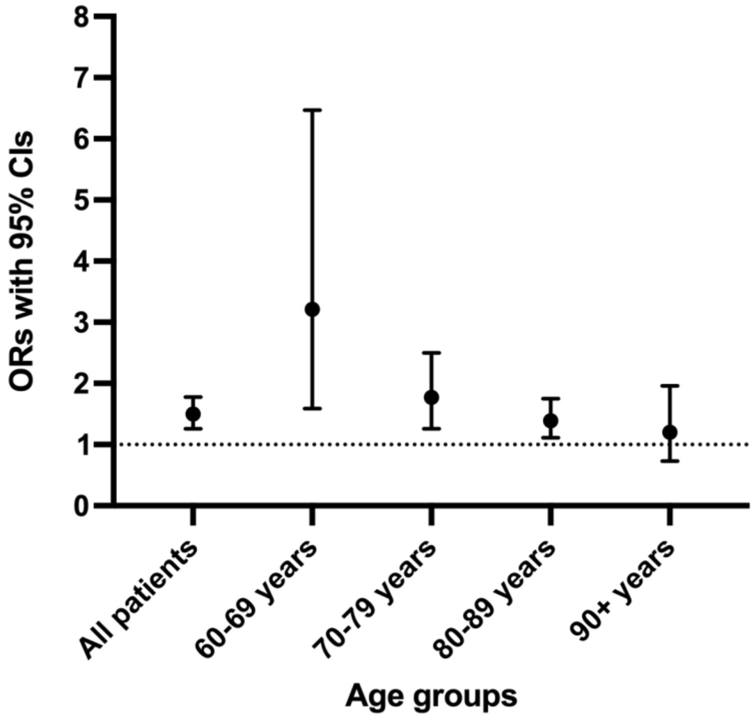


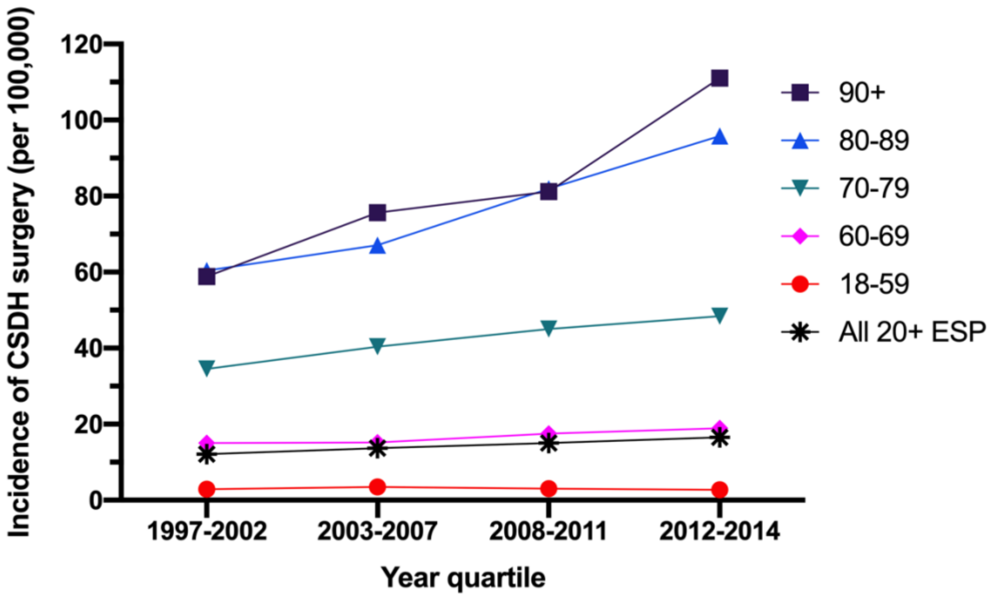
Figure 9 Case-mix adjusted association between dementia and one-year case-fatality among cases of different age groups in study II. The association between dementia and one-year case fatality was strongest among those aged 60–69 years, followed by those aged 70–79 years. The logistic regression analyses were adjusted for age, sex, year of primary operation, reoperation, and hospital level of care. OR=odds ratio, CI=confidence interval.

Incidence of surgery for chronic subdural hematoma in Finland

Among the identified 9,280 patients in study III, the median age increased from 73 years to 76 years during 1997–2014. Of the study population 67% were men and the male to female ratio of 2:1 remained stable. We saw an increase in the proportion of patients undergoing surgery at a university level hospital (83% in 1997–2002 vs. 95% in 2012–2014). The median age of women, 78 years, was higher than for men which was 73 years. We found no difference in hospital level of care or case-fatality between men and women.

The incidences of CSDH surgery in different age groups are shown in **Figure 10**. There was a 36% increase in the age-standardized incidence of CSDH surgery from 12.1 to 16.5 per 100,000 person-years between 1997–2002 and 2012–2014. The increases were largest for those 80–89 and over 90 years. For those older than 90 years, the age-group specific incidence almost doubled from 58.8 to 111 per 100,000 person-years between 1997–2002 and 2012–2014. For those 80–89 years, the incidence increased from 60.4 to 95.8 per 100,000 person-years.

During 1997–2011, the age-standardized incidence of surgery for CSDH was about threefold in men compared to women. During 2012–2014 the sex difference levelled out as the incidence in men was only 1.4 times higher. For both men and women, the increases in incidence were more evident in the two oldest age groups.



	1997-2002	2003-2007	2008-2011	2012-2014
18-59	2.9	3.5	3.0	2.7
60-69	15.0	15.2	17.5	18.9
70-79	34.5	40.4	45.0	48.4
80-89	60.4	67.1	81.9	95.8
90+	58.8	75.6	81.2	111.0
All 20+ ESP	12.1	13.7	15.0	16.5

Figure 10 The incidence of chronic subdural hematoma surgery (n/100,000 person-years) in age groups during 1997–2014. Age-specific incidence was based on the total population of the same age at the same time period in Finland. We applied age standardization for those aged 20 years and older with weights from the 2013 ESP. Reproduced with permission from the Journal of Neurosurgery. Original article by Tommiska et al.[207] CSDH=chronic subdural hematoma, ESP=European Standard Population.

The age- and sex-adjusted incidence of CSDH surgery increased by 30% (IRR 1.30, 95% CI 1.20–1.41) from 1997–2002 to 2012–2014. The age- and sex-adjusted changes in IRRs with 95% CIs of CSDH surgery from 1997–2002 (reference) to 2012–2014 are shown in **Figure 11**. The incidence did not increase among 18–59-year-olds. The increase was higher the older the age group. The incidence increased with an IRR of 1.24 among 60–69-years-olds, increased with an IRR of 1.32 among 70–79-years-olds, increased with an IRR of 1.46 among 80–89-years-olds, and increased with an IRR of 1.85 among the over 90-year-olds.

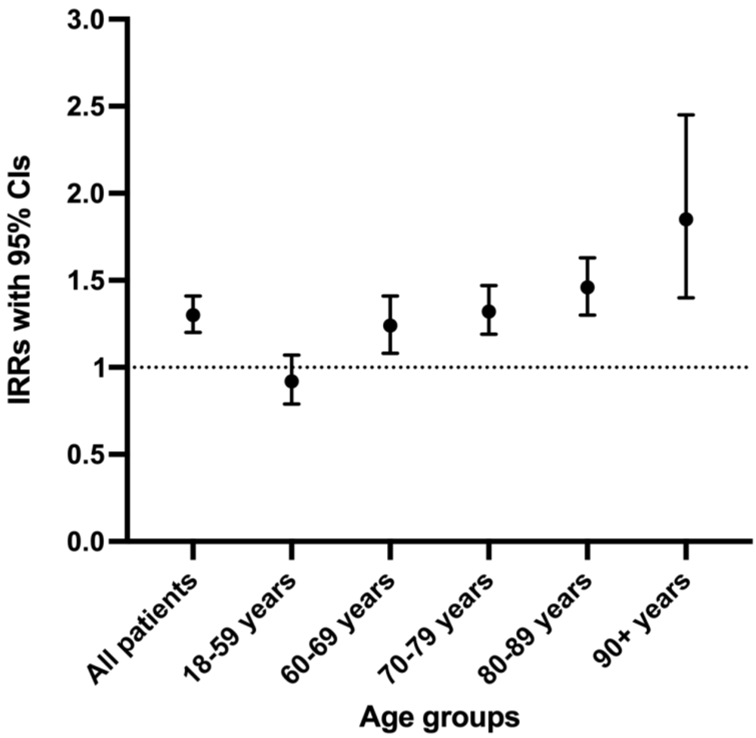


Figure 11 Age- and sex-adjusted changes in incidence rate ratios with 95% confidence intervals of chronic subdural hematoma surgery from 1997–2002 (reference) to 2012–2014. The incidence increased the most in the oldest age groups. CI=confidence interval, IRR=incidence rate ratio.

FINISH trial recruitment

We started recruiting participants for the FINISH trial in January 2020 at Helsinki University Hospital. Up until June 2020 Helsinki University Hospital was the only center recruiting patients. In July 2020 Oulu University Hospital started recruiting, and Kuopio University Hospital joined in August 2020. Turku and Tampere University Hospitals started recruiting during October 2020. The five specific catchment areas and their corresponding university hospital in Finland are presented in **Figure 12**. We reached the target sample size of 578 participants and stopped recruitment in August 2022. The cumulative number of patients recruited during each month is shown in **Figure 13**. The 6-month follow-up period continues until February 2023.

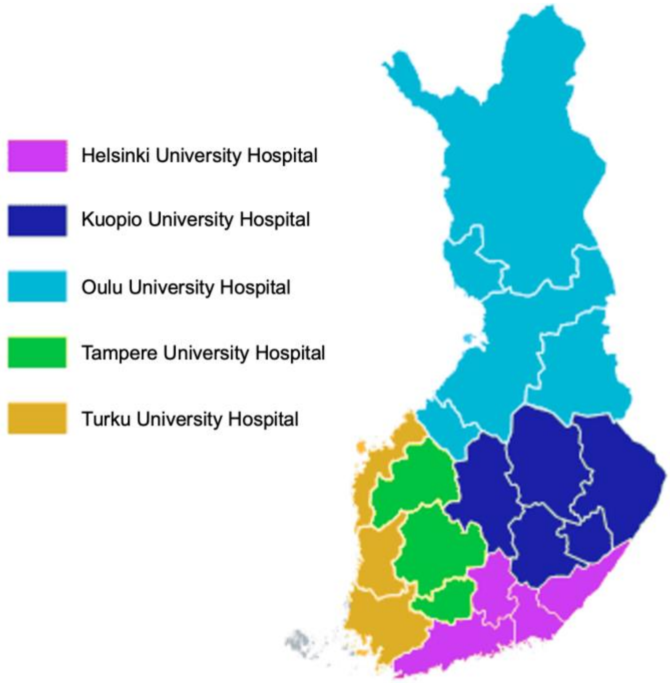


Figure 12 The specific catchment areas and their corresponding university hospital in Finland.

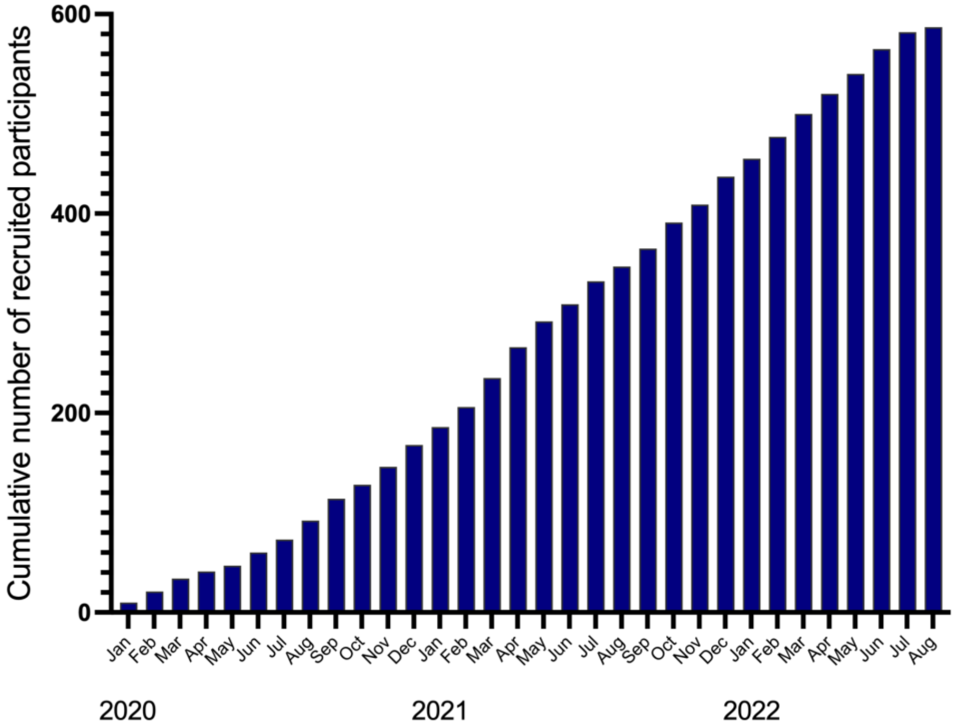


Figure 13 Cumulative number of recruited participants in the FINISH trial. The recruitment started in January 2020 and finished in August 2022. Tommiska et al. unpublished results.

Discussion

Key findings

We showed in study I that the change in clinical practice to routine use of subdural drains after BHC for CSDH reduced the 6-month recurrences from 18% to 6% without any effect on postoperative infections or complications. Subdural drain use resulted in a remarkable CSDH volume reduction. In study II we found that dementia is an independent risk factor for one-year mortality in older patients undergoing surgery for CSDH. We identified the strongest association for those aged 60–69 years. Our case-control analysis showed that patients with dementia undergoing surgery for CSDH had a higher risk of death compared with patients with dementia but no diagnosis of CSDH. The age- and sex-adjusted incidence of CSDH surgery has grown by 30% during 1997–2014 as shown in study III. The increases were largest in the oldest age groups. The male to female ratio of 2:1 remained stable.

The role of subdural drainage

We found a significantly reduced rate of recurrences in patients treated with subdural drains, which is in line with reports of numerous RCTs[15–17,50]. In an RCT by Santarius et al.[50], subdural drain use reduced recurrences from 24% to 9.3%, and the trial was stopped early because of a significant benefit was detected. In a prospective study by Singh et al.[15], subdural drain use reduced recurrences from 26% to 9% (p=0.002). In a Japanese prospective randomized study by Tsutsumi et al.[16], the authors found a reduction in recurrences from 17% when treating with burr-hole irrigation alone to 3.1% when closed system subdural drainage was used. The reduction detected in study I from 18% to 6% is in concordance with these previous studies. The pre-drain era (2015) reoperation rate of 18% in study I is comparable to the reoperation rate of 19% during 1997–2014 derived in study III.

In the study by Santarius et al.[50], subdural drain use also significantly reduced 6-month mortality from 18.1% to 8.6%. In study I, the use of subdural drain did not affect mortality as has also been found in other studies[15]. In our study only 64% of patients had a favorable functional outcome (mRS 0–3) at 6 months, whereas according to Santarius et al.[50] 84% of patients recovered to a favorable functional outcome. This may be due to that the patients were slightly older in our study. Also, in our patient population before CSDH diagnosis fewer patients were independent regarding mobility and residence compared with their study. In our study 22% of patients had pre-existing dementia, whereas in their study the percentage was only 3%. As known, dementia is a major contributor to dependence[36], and brain atrophy may progress further after CSDH as suggested by Bin Zahid et al.[69]

Study I was conducted at Helsinki University Hospital, and within the Helsinki catchment area, all patients needing reoperation are sent here for surgery as it is the only institution performing intracranial surgery. Thus, we reached a 100% follow-up rate regarding reoperations. Our follow-up completion rate regarding data on functional outcome was 79%, on mobility 76%, and on infections 75%.

Dementia and chronic subdural hematoma

There is a lack of studies assessing the relationship between dementia and outcome after surgery for CSDH. In our literature review, we found one study in which the authors did not find dementia and poor postoperative functional outcome to be associated.[208] Outcome in the elderly after surgery for CSDH has been studied. Some studies have reported higher morbidity and mortality in the elderly compared with young patients.[38,179,209–211] Nevertheless, other studies have reported no independent association between high age and outcome.[67,212,213]

In study II, we found a significant difference in the mortality of patients undergoing surgery for CSDH with and without dementia. Patients with dementia undergoing surgery for CSDH had a one-year mortality of 26% which is approximately the overall one-year mortality of older hip fracture patients (27%).[214] In older patients CSDH may, as well as hip fracture, be perceived as a sentinel health event and an manifestation of a deterioration in health.[215,216] Dementing disorders have long been recognized as a major predictor of death in the elderly and truly malignant.[217–219] A study by Baldereschi et al.[218] reported that dementia constitutes a higher mortality risk than neoplastic disease or heart failure. Thus, the results of study II are expected.

Our case-control analysis demonstrated that patients with dementia undergoing CSDH surgery had higher one-year mortality compared with patients with dementia but without a CSDH. There may still be other underlying diseases contributing to the higher mortality of patients with CSDHs. Miranda et al.[38] discussed that CSDH may unmask and even aggravate underlying pathologies. Also, it is possible that patients with dementia receive their diagnosis of CSDH later as the symptoms may be even more difficult to detect. It has been previously presented that delayed diagnosis and worse functional status at admission is associated with unfavorable outcome and mortality after surgery for CSDH.[50]

We found the proportion of patients with dementia increasing which in concordance with previous research. According to Rauhala et al.[1], the proportion of patients with dementia and a diagnosis of CSDH increased from 3% to 13% during 1990–2015. However, the exact numbers are not comparable as study II only included patients older than 60 years and undergoing surgery for CSDH.

Study II is a nationwide hospital-based analysis in which we have used validated and high-quality Finnish registers.[220,221] The findings are strengthened by the matched case-control analysis. We found at least one exposed control for 94% of exposed cases and the total number of cases and controls was as high as 10,554. In Finland the neurosurgical hospital care is tax-funded, and insurances or socioeconomic factors do not influence accessibility of health services. Therefore, study II covers the entire patient population hospitalized for CSDH in Finland.

Incidence of chronic subdural hematoma

One presumable reason for the increased incidence of CSDH surgery is the rise in life expectancy. During the study period from 1997 to 2014, the average life expectancy in Finland increased from 81 to 84 years for women and 73 to 78 years for men.[222] At the same time, the aging population is more active and considered to tolerate surgery due to their better condition. Although doubted by some[1], availability of CT may have resulted in better detection of CSDHs[11,56]. For example between 2000 and 2018, the number of performed head CT scans increased by 85%.[223,224] We find it possible that an easier access to imaging has influenced the incidence of surgically treated CSDHs as the condition often presents with ambiguous symptoms[225]. However, as in Finland the indication for surgery is unequivocally a CSDH with correlating symptoms, we find it unlikely that a lower threshold to operate could explain the observed increasing incidence of CSDH surgery. The use of antithrombotic medication became also widespread during the study period and may explain in part the results.[1,6] The percentage of the adult Finnish population using antithrombotic medication increased from 5.8% to 8.3% from 2009 to 2017.[226,227]

Two studies have previously assessed the change in the incidence of CSDH or the incidence of CSDH surgery. Other studies have assessed incidences during time periods of a few years but not the time trends and changes in incidences of CSDH. During a 25-year period from 1969 to 1993 in Lund, Sweden, the unadjusted incidence of CSDH surgery increased from 2 to 5.3 per 100,000 person-years.[30] During 26 years from 1990 to 2015 in Pirkanmaa, Finland, the unadjusted incidence of CSDH increased from 8.2 to 17.6 per 100,000 person-years.[1] In our study III, the age-standardized incidence of CSDH surgery was 16.5 per 100,000 person-years during 2012–2014, i.e. slightly lower. One reason may be that we only included CSDHs treated with surgery, and the study conducted in Pirkanmaa included also conservatively treated cases.

Our finding that the incidence is higher in older age groups is in concordance with several previous reports.[1,3,34,65,72] The patient median age has also been reported to have increased. In a study conducted during 1967–1973, only half of the patients with CSDH were over 60 years old.[3] In the study from Pirkanmaa, Finland, the authors reported the median age rising from 73 to 79 years during a 26-year time period, 1990–

2015.[1] In our study, the patient median age increased from 73 to 76 years during an 18-year time period, 1997–2014. Concomitantly, the expected lifespan in Finland increased by 4 years, from 77 to 81 years.[204]

We found in studies II and III that those not undergoing reoperations had a higher one-year mortality. However, the reason behind this supposed association may be that reoperation is not indicated and offered for patients who are not expected to benefit from the procedure or those who are too ill to undergo surgery. Therefore, we advise to interpret this finding with caution.

Study III, as study II, includes the whole population hospitalized for CSDH in Finland. We assessed the capturing of surgically treated CSDH cases by the Finnish Care Register for Health Care and found a high accuracy percentage of 92% in study III. We evaluate the true incidence of surgically treated CSDH cases to be 8.7% higher than the reported incidence. The longer study period than in most previous studies and a large nationwide sample size of 9,280 cases are strengths in study III.

The role of intraoperative irrigation

The FINISH study is the first multicenter nationwide pragmatic RCT assessing the role of intraoperative irrigation in BHC followed by subdural drainage for CSDH. The incidence of CSDH is increasing and reducing the risk of recurrence is crucial to prevent hospitalization of the fragile elderly. If non-inferiority of treatment without intraoperative irrigation is claimed in a large multicenter RCT, it may possibly change the gold standard of operative technique of CSDHs. Omitting the phase of irrigation could result in shortened operation times and perhaps even fewer complications. As the procedure is performed under local anesthesia, shortened operation time may reduce patient stress. The non-inferiority of no irrigation may also open new opportunities to develop minimally invasive surgical methods in the future. Given the increasing incidence, we expect benefits for healthcare systems worldwide.

In Finland, CSDH surgery is exclusively centralized in the five neurosurgical departments which are involved in the trial. Thus, we expect a 100% follow-up rate regarding the primary outcome. Also, our healthcare systems are highly digitalized and thus, we expect high follow-up rates regarding secondary outcomes.

Future research areas

The prevalence of dementia is expected to increase, particularly in low- and middle-income countries.[35] As the incidence of CSDH continues to increase, we will probably have more patients with dementia undergoing surgery for CSDH in the future. In Finland, surgeries for CSDH are performed routinely in local anesthesia to inhibit any complications associated with general anesthesia.[228,229] The frail elderly patients with multiple comorbidities are especially susceptible to such complications. We need more research focusing on older patients with dementia and CSDH. Despite the high mortality, there is an indication for surgery if severe neurological symptoms can be alleviated and the patient is estimated to tolerate an intracranial procedure.

The expeditiously growing incidence of CSDH especially among the elderly, highlights the need for intensified prevention. Reducing the risk of falls and weighing the risk-benefit ratio of antithrombotic medication become more and more important in the future. Also, as surgery and hospitalization are serious exertions to the frail elderly, we need new minimally invasive techniques to assure patient safety. It remains to be seen if for example MMA embolization or omitting the step of irrigation in BHC will open such possibilities.

As the pathophysiology of CSDH is a complex combination of inflammation, membrane formation, angiogenesis, and fibrinolysis, and the clinical presentation, imaging and surgical findings vary widely, it is unlikely that a one-for-all management strategy would apply in this pathology. In the future the aim is to develop different treatment algorithms with optimal surgical or endovascular technique and adjuvant therapies based on the individual risk of recurrence and thrombotic complications to attain best possible outcomes.

Limitations

The studies include limitations to be mentioned. Study I is a retrospective analysis, and the results should therefore be interpreted with caution. It may be that other factors not considered in the study (e.g. the duration of drainage and amount of intraoperative irrigation) also affect the risk of recurrence.

Study II and III are register-based analyses, and all registries include some miscoding and diagnostic imprecisions. In both studies we only assessed associations but cannot conclude any causalities. Confounding variables may be present among the cases and controls and explain the observed differences in mortalities in study II and the increasing incidence of CSDH surgery in study III. Nevertheless, we tried to minimize such risk by the employment of nationwide coverage. Data on the surgical method to evacuate CSDH (e.g. number of burr-holes, drain usage, duration of drainage) are missing from the studies. Neither did we have information if the reoperations were performed because of an actual recurring ipsilateral hematoma or if a new incident CSDH or a complication had developed to the patient.

Also, the register that we used (Care Register for Health Care) only includes patients that have been hospitalized with a discharge diagnosis of dementia. Thus, it is possible that patients diagnosed and treated in an outpatient clinic are missing from the registry.

We believe that the true prevalence of dementia is higher than reported in study II. In study I, 22% of patients had a diagnosis of dementia mentioned in their medical charts (**Table 7**) and this study even included patients younger than 60 years. It is possible that the dementia diagnosis is not always registered during discharge, and we have missed these cases when searching for dementia diagnoses in the Care Register for Health Care. These patients have been identified as non-exposed cases. However, the mortality of exposed cases was still markedly higher. Therefore, the difference in mortalities may be even larger in reality.

Also, conservatively treated patients and autopsies are not included in studies II and III. Therefore, we expect the overall incidence of CSDH to be higher than the incidence of CSDH surgery which we have reported in study III.

Conclusion

1. We found that the use of subdural drain after BHC for CSDH effectively reduced the risk of 6-month recurrence without any effect on functional outcome, infections, or complications.

2. We showed that dementia is an independent significant risk factor for one-year mortality after surgery for CSDH in older persons.

3. We found that the age- and sex-adjusted incidence of CSDH surgery has increased, with largest increases for those 60 years and older.

4. We planned and executed a national multicenter RCT, in which the recruitment was finished in August 2022. The results will be published in 2023.

Acknowledgements

This thesis was carried out at the Department of Neurosurgery at the Helsinki University Hospital between the years 2018 and 2022. The research was financially supported by grants from the Finnish Medical Foundation, Orion Research Foundation sr, Maire Taponen Foundation, Maud Kuistila Memorial Foundation, Aarne Koskelo Foundation, Päivikki and Sakari Sohlberg Foundation, Uulo Arhio Foundation, Biomedicum Helsinki Foundation, Alfred Kordelin Foundation, Aarne and Aili Turunen Foundation, and Finska Läkaresällskapet.

Thank you to my opponent, Professor Isabelle M. Germano from the Department of Neurosurgery at Mount Sinai Hospital, New York. I am truly honored for your agreement as my opponent in the public defense. I also wish to express my gratitude to Professor and Head of the Department Mika Niemelä for being the custodian in the defense.

I am grateful to my three outstanding supervisors, Kimmo Lönnrot, Rahul Raj, and Riku Kivisaari. Thank you, Kimmo, for first introducing me to neurosurgery and research. On our first ever meeting you made me understand how important research is in medicine. You taught me a lot about medicine in general during the data collection of the first study which was before my clinical studies had even begun. I am grateful for your support, patience, encouragement, and trust in me. Rahul, it is a privilege to work with someone as brilliant as you. Thank you for the countless hours you spent with statistics, analyzing data and writing with me. Your work ethic and passion for research is inspirational, and from the first day I have felt extremely lucky to have you as my supervisor. Thank you, Riku, for being the “spiritual leader” of our research group. Your encouragement has meant a lot to me, and I really look up to you as a leader, researcher, and neurosurgeon. Fortunately, I know the cooperation with my supervisors will continue in the future.

Thank you to the reviewers of this thesis, Mikael von und zu Fraunberg and Joonas Haapasalo. Your excellent comments improved my thesis. I am grateful to my thesis committee members Anna Östberg and Antti Lindgren for involvement. I also thank the co-authors of the original publications included in this thesis for all their valuable contributions. Thank you Teemu Luostarinen, Miikka Korja, Jari Siironen, Jaakko Kaprio, Christoph Schwartz, Jarno Satopää, Simo Taimela, Teppo Järvinen, Jonas Ranstam, Janek Frantzén, Jussi Posti, Teemu Luoto, Ville Leinonen, Sami Tetri, and Timo Koivisto. Our irreplaceable research nurse, Maarit Tuomisto, deserves a special mention and commendation.

Thank you to the departments of neurosurgery at Helsinki University Hospital, Kuopio University Hospital, Tampere University Hospital, Turku University Hospital, and Oulu University Hospital for being involved in the FINISH trial. I also want to thank the physicians, nurses, and other staff at Töölö Hospital for being supportive when I first started working at the department.

Lastly, I want to thank my family and friends for your support and love. You are too many to mention here but I want you to know you mean everything to me. My grandparents have been a major inspiration behind this research, and their support is invaluable. This thesis is dedicated to my dear *Nonna* and *Ukki*.

In Helsinki,
October 2022

Literature

1. Rauhala, M. *et al.* The incidence of chronic subdural hematomas from 1990 to 2015 in a defined Finnish population. *J. Neurosurg.* **132**, 1147–1157 (2019).
2. Trotter, W. Chronic subdural haemorrhage of traumatic origin, and its relation to pachymeningitis haemorrhagica interna. *Br J Surg* **2**, 271–291 (1914).
3. Fogelholm, R. & Waltimo, O. Epidemiology of chronic subdural haematoma. *Acta Neurochir. (Wien).* **32**, 247–250 (1975).
4. Marshman, L. A. G., Manickam, A. & Carter, D. Risk factors for chronic subdural haematoma formation do not account for the established male bias. *Clin. Neurol. Neurosurg.* **131**, 1–4 (2015).
5. Sim, Y. W., Min, K. S., Lee, M. S., Kim, Y. G. & Kim, D. H. Recent Changes in risk factors of chronic subdural hematoma. *Journal of Korean Neurosurgical Society* **52**, 234–239 (2012).
6. Gaist, D. *et al.* Association of Antithrombotic Drug Use With Subdural Hematoma Risk. *JAMA* **317**, 836 (2017).
7. Yang, A. Il *et al.* Cerebral atrophy is associated with development of chronic subdural haematoma. *Brain Inj.* **26**, 1731–6 (2012).
8. Fomchenko, E. I., Gilmore, E. J., Matouk, C. C., Gerrard, J. L. & Sheth, K. N. Management of Subdural Hematomas: Part II. Surgical Management of Subdural Hematomas. *Curr. Treat. Options Neurol.* **20**, 1–20 (2018).
9. Cenic, A., Bhandari, M. & Ready, K. Management of chronic subdural hematoma: a national survey and literature review. *Can. J. Neurol. Sci.* **32**, 501–506 (2005).
10. Santarius, T., Lawton, R., Kirkpatrick, P. J. & Hutchinson, P. J. The management of primary chronic subdural haematoma: A questionnaire survey of practice in the United Kingdom and the Republic of Ireland. *Br. J. Neurosurg.* **22**, 529–534 (2008).
11. Almenawer, S. A. *et al.* Chronic subdural hematoma management: A systematic review and meta-analysis of 34829 patients. *Ann. Surg.* **259**, 449–457 (2014).
12. Kolias, A. G., Chari, A., Santarius, T. & Hutchinson, P. J. Chronic subdural haematoma: modern management and emerging therapies. *Nat. Rev. Neurol.* **10**, 570–578 (2014).
13. Peng, D. & Zhu, Y. External drains versus no drains after burr-hole evacuation for the treatment of chronic subdural haematoma in adults. *Cochrane Database Syst. Rev.* (2016). doi:10.1002/14651858.CD011402.PUB2
14. Santarius, T. *et al.* Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. *Lancet* **374**, 1067–1073 (2009).
15. Singh, A. K. *et al.* A prospective randomized study of use of drain versus no drain after burr-hole evacuation of chronic subdural hematoma. *Neurol. India* **62**, 169–174 (2014).
16. Tsutsumi, K. *et al.* The relationship of preoperative magnetic resonance imaging findings and closed system drainage in the recurrence of chronic subdural hematoma. *J. Neurosurg.* **87**, 870–875 (1997).
17. Wakai, S. *et al.* Efficacy of closed-system drainage in treating chronic subdural

hematoma: A prospective comparative study. *Neurosurgery* **26**, 771–773 (1990).

18. Sivaraju, L., Moorthy, R. K., Jeyaseelan, V. & Rajshekhar, V. Routine placement of subdural drain after burr hole evacuation of chronic and subacute subdural hematoma: a contrarian evidence based approach. *Neurosurg. Rev.* **41**, 165–171 (2018).
19. Wang, Q.-P., Yuan, Y., Guan, J.-W. & Jiang, X.-B. A comparative study of irrigation versus no irrigation during burr hole craniostomy to treat chronic subdural hematoma. *BMC Surg.* **17**, 99 (2017).
20. Kim, D. H. *et al.* Recurrence of the Chronic Subdural Hematoma after Burr-Hole Drainage with or without Intraoperative Saline Irrigation. *Korean J. neurotrauma* **10**, 101–5 (2014).
21. Lee, C. *et al.* Effect of Intra-operative Saline Irrigation during Burr Hole Surgery on the Recurrence for Chronic Subdural Hematomas. *The Nerve* **1**, 26–29 (2015).
22. Jang, K.-M., Kwon, J.-T., Hwang, S.-N., Park, Y.-S. & Nam, T.-K. Comparison of the Outcomes and Recurrence with Three Surgical Techniques for Chronic Subdural Hematoma: Single, Double Burr Hole, and Double Burr Hole Drainage with Irrigation. *Korean J. neurotrauma* **11**, 75–80 (2015).
23. Iftikhar, M., Siddiqui, U. T., Rauf, M. Y., Malik, A. O. & Javed, G. Comparison of Irrigation versus No Irrigation during Burr Hole Evacuation of Chronic Subdural Hematoma. *J. Neurol. Surg. A. Cent. Eur. Neurosurg.* **77**, 416–21 (2016).
24. Ishibashi, A., Yokokura, Y. & Adachi, H. A Comparative Study of Treatments for Chronic Subdural Hematoma: Burr Hole Drainage versus Burr Hole Drainage with Irrigation. *Kurume Med. J.* **58**, 35–39 (2011).
25. Suzuki, K. *et al.* Treatment of chronic subdural hematoma by closed-system drainage without irrigation. *Surg. Neurol.* **50**, 231–234 (1998).
26. Zakaraia, A. M., Adnan, J. S., Haspani, M. S. M., Naing, N. N. & Abdullah, J. M. Outcome of 2 different types of operative techniques practiced for chronic subdural hematoma in Malaysia: an analysis. *Surg. Neurol.* **69**, 608–615 (2008).
27. Kuroki, T. *et al.* Strict closed-system drainage for treating chronic subdural haematoma. *Acta Neurochir. (Wien).* **143**, 1041–1044 (2001).
28. Seung, W.-B. & Jeong, J. H. Postoperative Subarachnoid Hemorrhage and Multipunctate Intracerebral Hemorrhages Following Evacuation of Bilateral Chronic Subdural Hematomas. *Korean J. neurotrauma* **13**, 149–152 (2017).
29. Ihab, Z. Pneumocephalus after surgical evacuation of chronic subdural hematoma: Is it a serious complication? *Asian J. Neurosurg.* **7**, 66–74 (2012).
30. Mellergård, P. & Wisten, O. Operations and re-operations for chronic subdural haematomas during a 25-year period in a well defined population. *Acta Neurochir. (Wien).* **138**, 708–713 (1996).
31. Adelborg, K., Grove, E. L., Sundbøll, J., Laursen, M. & Schmidt, M. Sixteen-year nationwide trends in antithrombotic drug use in Denmark and its correlation with landmark studies. *Heart* **102**, 1883–1889 (2016).
32. Connolly, B. J., Pearce, L. A. & Hart, R. G. Vitamin K Antagonists and Risk of Subdural Hematoma. *Stroke* **45**, 1672–1678 (2014).
33. Hiroshi, K., Keiichi, K., Ichirou, I., Hideki, S. & Norihiko, T. Chronic Subdural Hematoma in Elderly People: Present Status on Awaji Island and Epidemiological Prospect. *Neurol. Med. Chir. (Tokyo).* **32**, 207–209 (1992).

34. Adhiyaman, V., Chattopadhyay, I., Irshad, F., Curran, D. & Abraham, S. Increasing incidence of chronic subdural haematoma in the elderly. *QJM* **110**, 375–378 (2017).
35. Prince, M. *et al.* The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimer's Dement.* **9**, 63-75.e2 (2013).
36. Sousa, R. M. *et al.* The contribution of chronic diseases to the prevalence of dependence among older people in Latin America, China and India: A 10/66 Dementia Research Group population-based survey. *BMC Geriatr.* **10**, 1–12 (2010).
37. Joling, K. J. *et al.* Time from diagnosis to institutionalization and death in people with dementia. *Alzheimer's Dement.* **16**, 662–671 (2020).
38. Miranda, L. B., Braxton, E., Hobbs, J. & Quigley, M. R. Chronic subdural hematoma in the elderly: not a benign disease. *J. Neurosurg.* **114**, 72–76 (2011).
39. D'Errico, A. P. & German, W. J. *Chronic Subdural Hematoma*. *Yale J Biol Med* **3**, (1930).
40. Hoessly, G. F. Intracranial Hemorrhage in the Seventeenth Century: A Reappraisal of Johann Jacob Wepfer's Contribution Regarding Subdural Hematoma. *J. Neurosurg.* **24**, 493–496 (1966).
41. Weigel, R., Krauss, J. K. & Schmiedek, P. Concepts of neurosurgical management of chronic subdural haematoma: historical perspectives. *Br. J. Neurosurg.* **18**, 8–18 (2004).
42. Nyström, S. *Neurokirurgia*. (Gummerus, 1988).
43. Klossner, A. R. *Turun lääninsairaalan vaiheita 1756-1856 : ensimmäiset 100 vuotta ; Turun lääninsairaalan vaiheita 1857-1957 : toiset sata vuotta.* (Turun yliopistollisen keskussairaalan liittohallitus, 1956).
44. Hulke. Middlesex hospital: Severe blow on the right temple, followed by right hemiplegia and coma, and then by spastic rigidity of the left arm; Trephining; Evacuation of inflammatory fluid by incision through dura mater; Quick disappearance of cerebral symtoms; *Lancet* **122**, 814–815 (1883).
45. Dandy, W. E. Ventriculography following the injection of air into the cerebral ventricles. *Ann. Surg.* **68**, 5 (1918).
46. Artico, M. *et al.* Egas Moniz: 90 Years (1927–2017) from Cerebral Angiography. *Front. Neuroanat.* **11**, 81 (2017).
47. Castillo, M. History and evolution of brain tumor imaging: insights through radiology. *Radiology* **273**, S111–S125 (2014).
48. Mckissock, W., Richardson, A. & Bloom, W. H. Subdural haematoma. A review of 389 cases. *Lancet* **275**, 1365–1369 (1960).
49. Lee, K. S. *et al.* Acute-on-Chronic Subdural Hematoma: Not Uncommon Events. *J. Korean Neurosurg. Soc.* **50**, 512 (2011).
50. Santarius, T. *et al.* Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. *Lancet* **374**, 1067–1073 (2009).
51. Baechli, H., Nordmann, A., Bucher, H. C. & Gratzl, O. Demographics and prevalent risk factors of chronic subdural haematoma: Results of a large single-center cohort study. *Neurosurg. Rev.* **27**, 263–266 (2004).
52. Sato, S. & Suzuki, J. Ultrastructural observations of the capsule of chronic subdural hematoma in various clinical stages. *J. Neurosurg.* **43**, 569–578 (1975).
53. Edlmann, E., Giorgi-Coll, S., Whitfield, P. C., Carpenter, K. L. H. &

Hutchinson, P. J. Pathophysiology of chronic subdural haematoma: inflammation, angiogenesis and implications for pharmacotherapy. *J. Neuroinflammation* **14**, 108 (2017).
54. Inglis, K. Subdural haemorrhage, cysts and false membranes; illustrating the influence of intrinsic factors in disease when development of the body is normal. *Brain* **69**, 157–194 (1946).
55. Nabeshima, S., Reese, T. S., Landis, D. M. D. & Brightman, M. W. Junctions in the meninges and marginal glia. *J. Comp. Neurol.* **164**, 127–169 (1975).
56. Santarius, T., Kirkpatrick, P. J., Kolias, A. G. & Hutchinson, P. J. Working toward rational and evidence-based treatment of chronic subdural hematoma. *Clin. Neurosurg.* **57**, 112–22 (2010).
57. Yamashima, T. & Friede, R. L. Why do bridging veins rupture into the virtual subdural space? *Neurosurgery, and Psychiatry* **47**, 121–127 (1984).
58. Lee, K. S. Natural history of chronic subdural haematoma. *Brain Inj.* **18**, 351–358 (2004).
59. Lee, K. S., Doh, J. W., Bae, H. G. & Yun, I. G. Relations among traumatic subdural lesions. *J. Korean Med. Sci.* **11**, 55–63 (1996).
60. Winn, H. Youmans and Winn Neurological Surgery - 8th Edition. **1**, 260–261 (2022).
61. Ducruet, A. F. *et al.* The surgical management of chronic subdural hematoma. *Neurosurg. Rev.* **35**, 155–169 (2012).
62. Y, K., M, C., T, T. & Y, S. Coagulation and fibrinolysis in chronic subdural hematoma. *Neurosurgery* **25**, 25 (1989).
63. Komiyama, K. *et al.* Computed tomography findings after head injury preceding chronic subdural hematoma. *Neurosurg. Focus* **47**, (2019).
64. Ahmed, E. *et al.* Frequency of conservatively managed traumatic acute subdural haematoma changing into chronic subdural haematoma. *J. Ayub Med. Coll. Abbottabad* **24**, 71–74 (2012).
65. 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.* **123**, 1209–1215 (2015).
66. Toi, H. *et al.* Present epidemiology of chronic subdural hematoma in Japan: analysis of 63,358 cases recorded in a national administrative database. *J. Neurosurg.* **128**, 222–228 (2017).
67. Bartek, J. *et al.* Surgery for chronic subdural hematoma in nonagenarians: A Scandinavian population-based multicenter study. *Acta Neurol. Scand.* **136**, 516–520 (2017).
68. Stippler, M. *et al.* Chronic subdural hematoma patients aged 90 years and older. *Neurol. Res.* **35**, 243–246 (2013).
69. Zahid, A. Bin *et al.* Increase in brain atrophy after subdural hematoma to rates greater than associated with dementia. *J. Neurosurg.* **129**, 1579–1587 (2018).
70. Hutchinson, P. J. *et al.* Trial of Dexamethasone for Chronic Subdural Hematoma. *N. Engl. J. Med.* **383**, NEJMoa2020473 (2020).
71. Sousa, E. B. *et al.* Epidemiological characteristics of 778 patients who underwent surgical drainage of chronic subdural hematomas in Brasília, Brazil. *BMC Surg.* **13**, 5 (2013).
72. Karibe, H. *et al.* Epidemiology of chronic subdural hematoma. *Neurol. Surg.* **39**, 1149–1153 (2011).

73. Fogelholm, R., Heiskanen, O. & Waltimo, O. Chronic subdural hematoma in adults: Influence of patient's age on symptoms, signs, and thickness of hematoma. *J. Neurosurg.* **42**, 43–46 (1975).
74. Kojima, T. *et al.* Polypharmacy as a risk for fall occurrence in geriatric outpatients. *Geriatr. Gerontol. Int.* **12**, 425–430 (2012).
75. Helgadóttir, B., Laflamme, L., Monárrez-Espino, J. & Möller, J. Medication and fall injury in the elderly population; Do individual demographics, health status and lifestyle matter? *BMC Geriatr.* **14**, 1–8 (2014).
76. Asghar, M., Adhiyaman, V., Greenway, M. W., Bhowmick, B. K. & Bates, A. Chronic subdural haematoma in the elderly--a North Wales experience. *J. R. Soc. Med.* **95**, 290–2 (2002).
77. Lee, K. S. Chronic Subdural Hematoma in the Aged, Trauma or Degeneration? *J. Korean Neurosurg. Soc.* **59**, 1–5 (2016).
78. Gelabert-González, M., Iglesias-Pais, M., García-Allut, A. & Martínez-Rumbo, R. Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. *Clin. Neurol. Neurosurg.* **107**, 223–229 (2005).
79. Paul, C. A. *et al.* Association of Alcohol Consumption With Brain Volume in the Framingham Study. *Arch. Neurol.* **65**, 1363–1367 (2008).
80. De Bonis, P. *et al.* Antiplatelet/Anticoagulant Agents and Chronic Subdural Hematoma in the Elderly. *PLoS One* **8**, e68732 (2013).
81. McNeil, J. J. *et al.* Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *N. Engl. J. Med.* **379**, 1509–1518 (2018).
82. Aspegren, O. P., Åstrand, R., Lundgren, M. I. & Romner, B. Anticoagulation therapy a risk factor for the development of chronic subdural hematoma. *Clin. Neurol. Neurosurg.* **115**, 981–984 (2013).
83. Lindvall, P. & Koskinen, L. O. D. Anticoagulants and antiplatelet agents and the risk of development and recurrence of chronic subdural haematomas. *J. Clin. Neurosci.* **16**, 1287–1290 (2009).
84. Olesen, J. B. *et al.* Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. *Europace* **17**, 187–193 (2015).
85. Ruff, C. T. *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* **383**, 955–962 (2014).
86. Dobran, M. *et al.* Spontaneous chronic subdural hematoma in young adult: the role of missing coagulation factors. *G. Chir.* **38**, 66 (2017).
87. Albanese, A. *et al.* Spontaneous chronic subdural hematomas in young adults with a deficiency in coagulation factor XIII. Report of three cases. *J. Neurosurg.* **102**, 1130–1132 (2005).
88. Merkler, A. E., Ch'ang, J., Parker, W. E., Murthy, S. B. & Kamel, H. The Rate of Complications after Ventriculoperitoneal Shunt Surgery. *World Neurosurg.* **98**, 654–658 (2017).
89. Beni-Adani, L., Siomin, V., Segev, Y., Beni, S. & Constantini, S. Increasing chronic subdural hematoma after endoscopic III ventriculostomy. *Childs. Nerv. Syst.* **16**, 402–5 (2000).
90. Acharya, R. Chronic subdural haematoma complicating spinal anaesthesia. *Neurol. Sci.* **25**, 348–350 (2005).
91. Lavie, F. *et al.* Bilateral intracranial subdural hematoma following lumbar puncture: report of a case. *Rev Neurol* **154**, 703–5 (1998).

92. Beier, A. D., Soo, T. M. & Claybrooks, R. Subdural hematoma after microdiscectomy: a case report and review of the literature. *Spine J.* **9**, (2009).
93. Mori, K., Maeda, M., Maas, A. & Dunn, L. Risk factors for the occurrence of chronic subdural haematomas after neurosurgical procedures. *Acta Neurochir. 2003 1457* **145**, 533–540 (2003).
94. Schievink, W. I., Maya, M. M., Moser, F. G. & Tourje, J. Spectrum of subdural fluid collections in spontaneous intracranial hypotension. *J. Neurosurg.* **103**, 608–613 (2005).
95. Takahashi, K., Mima, T. & Akiba, Y. Chronic Subdural Hematoma Associated with Spontaneous Intracranial Hypotension: Therapeutic Strategies and Outcomes of 55 Cases. *Neurol. Med. Chir. (Tokyo).* **56**, 69 (2016).
96. Kranz, P. G., Gray, L., Malinzak, M. D. & Amrhein, T. J. Spontaneous Intracranial Hypotension: Pathogenesis, Diagnosis, and Treatment. *Neuroimaging Clin. N. Am.* **29**, 581–594 (2019).
97. Beck, J. *et al.* Spinal cerebrospinal fluid leak as the cause of chronic subdural hematomas in nongeriatric patients. *J. Neurosurg.* **121**, 1380–1387 (2014).
98. Sood, P., Sinson, G. P. & Cohen, E. P. Subdural Hematomas in Chronic Dialysis Patients: Significant and Increasing. *Clin. J. Am. Soc. Nephrol.* **2**, 956–959 (2007).
99. Fayed, A. *et al.* Retrospective analysis of nontraumatic subdural hematoma incidence and outcomes in Egyptian patients with end-stage renal disease on hemodialysis. *Ren. Fail.* **43**, 1322–1328 (2021).
100. Arachnoid Cysts | Johns Hopkins Medicine. Available at: https://www.hopkinsmedicine.org/health/conditions-and-diseases/arachnoid-cysts. (Accessed: 19th April 2022)
101. Al-Holou, W. N. *et al.* Prevalence and natural history of arachnoid cysts in adults. *J. Neurosurg.* **118**, 222–231 (2013).
102. Mori, K., Yamamoto, T., Horinaka, N. & Maeda, M. Arachnoid cyst is a risk factor for chronic subdural hematoma in juveniles: twelve cases of chronic subdural hematoma associated with arachnoid cyst. *J. Neurotrauma* **19**, 1017–1027 (2002).
103. Wu, X. *et al.* Arachnoid Cyst-Associated Chronic Subdural Hematoma: Report of 14 Cases and a Systematic Literature Review. *World Neurosurg.* **109**, e118–e130 (2018).
104. Iliescu, I. A. & Constantinescu, A. I. Clinical evolutional aspects of chronic subdural haematomas – literature review. *J. Med. Life* **8**, 26 (2015).
105. Hsieh, C. T. *et al.* Chronic subdural hematoma: Differences between unilateral and bilateral occurrence. *J. Clin. Neurosci.* **34**, 252–258 (2016).
106. Ou, Y. *et al.* A comparative study of chronic subdural hematoma in three age ranges: Below 40 years, 41-79 years, and 80 years and older. *Clin. Neurol. Neurosurg.* **178**, 63–69 (2019).
107. Quiñones-Hinojosa, A. & Schmidek, H. H. *Schmidek & Sweet operative neurosurgical techniques : indications, methods, and results*. (Elsevier, 2022).
108. Huisman, T. A. G. M. Intracranial hemorrhage: ultrasound, CT and MRI findings. *Eur. Radiol.* **15**, 434–440 (2005).
109. Klein, J. S., Brant, W. E., Helms, C. A. & Vinson, E. N. *Brant and Helms' fundamentals of diagnostic radiology*. (Philadelphia : Wolters Kluwer, 2019).
110. Sieswerda-Hoogendoorn, T., Postema, F. A. M., Verbaan, D., Majoie, C. B. & Van Rijn, R. R. Age determination of subdural hematomas with CT and MRI:

A systematic review. *Eur. J. Radiol.* **83**, 1257–1268 (2014).
111. Nakaguchi, H., Tanishima, T. & Yoshimasu, N. Factors in the natural history of chronic subdural hematomas that influence their postoperative recurrence. *J. Neurosurg.* **95**, 256–262 (2001).
112. Iorio-Morin, C. *et al.* Chronic Subdural Hematoma: Toward a New Management Paradigm for an Increasingly Complex Population. *J. Neurotrauma* **35**, 1882–1885 (2018).
113. Levi, M., Eerenberg, E. & Kamphuisen, P. W. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. *J. Thromb. Haemost.* **9**, 1705–1712 (2011).
114. Ilmakunnas, M. Antitromboottisen lääkityksen kumoaminen päivystysleikkauksissa – HUS ATEK Leikkaussalit. (2020).
115. Tabaddor, K. & Shulman, K. Definitive treatment of chronic subdural hematoma by twist-drill craniostomy and closed-system drainage. *J. Neurosurg.* **46**, 220–226 (1977).
116. Emonds, N. & Hassler, W. E. New device to treat chronic subdural hematoma--hollow screw. *Neurol. Res.* **21**, 77–78 (1999).
117. Balser, D. *et al.* Evolving Management of Symptomatic Chronic Subdural Hematoma: Experience of a Single Institution and Review of the Literature. *Neurol. Res.* **35**, 233 (2013).
118. Brennan, P. M. *et al.* The management and outcome for patients with chronic subdural hematoma: a prospective, multicenter, observational cohort study in the United Kingdom. *J. Neurosurg.* **127**, 732–739 (2017).
119. Wan, Y. *et al.* Single Versus Double Burr Hole Craniostomy in Surgical Treatment of Chronic Subdural Hematoma: A Meta-Analysis. *World Neurosurg.* **131**, e149–e154 (2019).
120. Markwalder, T. M. Chronic subdural hematomas: A review. *Journal of Neurosurgery* **54**, 637–645 (1981).
121. Weigel, R., Schmiedek, P. & Krauss, J. K. Outcome of contemporary surgery for chronic subdural haematoma: evidence based review. *J. Neurol. Neurosurg. Psychiatry* **74**, 937–943 (2003).
122. Lega, B. C., Danish, S. F., Malhotra, N. R., Sonnad, S. S. & Stein, S. C. Choosing the best operation for chronic subdural hematoma: a decision analysis. *J. Neurosurg.* **113**, 615–621 (2010).
123. Bartley, A. *et al.* The Swedish study of Irrigation-fluid temperature in the evacuation of Chronic subdural hematoma (SIC!): study protocol for a multicenter randomized controlled trial. *Trials* **18**, (2017).
124. Liu, W., Bakker, N. A. & Groen, R. J. M. Chronic subdural hematoma: a systematic review and meta-analysis of surgical procedures. *J. Neurosurg.* **121**, 665–673 (2014).
125. Alcalá-Cerra, G., Young, A. M. H., Moscote-Salazar, L. R. & Paternina-Caicedo, Á. Efficacy and safety of subdural drains after burr-hole evacuation of chronic subdural hematomas: systematic review and meta-analysis of randomized controlled trials. *World Neurosurg.* **82**, 1148–1157 (2014).
126. Søren, T. *et al.* National randomized clinical trial on subdural drainage time after chronic subdural hematoma evacuation. *J. Neurosurg.* **1**, 1–8 (2021).
127. Soleman, J. *et al.* Subperiosteal vs Subdural Drain After Burr-Hole Drainage of Chronic Subdural Hematoma: A Randomized Clinical Trial (cSDH-Drain-Trial). *Neurosurgery* **85**, E825–E834 (2019).

128. Nakaguchi, H., Tanishima, T. & Yoshimasu, N. Relationship between drainage catheter location and postoperative recurrence of chronic subdural hematoma after burr-hole irrigation and closed-system drainage. *J. Neurosurg.* **93**, 791–795 (2000).
129. Greuter, L., Nader, H. & Soleman, J. Type of Drain in Chronic Subdural Hematoma-A Systematic Review and Meta-Analysis. *Front. Neurol.* **11**, (2020).
130. Ding, H., Liu, S., Quan, X., Liao, S. & Liu, L. Subperiosteal versus Subdural Drain After Burr Hole Drainage for Chronic Subdural Hematomas: A Systematic Review and Meta-Analysis. *World Neurosurg.* **136**, 90–100 (2020).
131. Xie, Y. *et al.* A Comparison of Subperiosteal or Subgaleal Drainage with Subdural Drainage on the Outcomes of Chronic Subdural Hematoma: A Meta-Analysis. *World Neurosurg.* **135**, e723–e730 (2020).
132. Blaauw, J. *et al.* Neurosurgical and Perioperative Management of Chronic Subdural Hematoma. *Front. Neurol.* **11**, (2020).
133. General Anesthesia Versus Locoregional Anesthesia for Evacuation of Chronic Subdural Hematoma - Full Text View - ClinicalTrials.gov. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03666949?term=neuranesth&cond=Chronic+Subdural+Hematoma&draw=2&rank=1. (Accessed: 12th May 2022)
134. Santarius, T., Lawton, R., Kirkpatrick, P. J. & Hutchinson, P. J. The management of primary chronic subdural haematoma: a questionnaire survey of practice in the United Kingdom and the Republic of Ireland. *Br. J. Neurosurg.* **22**, 529–534 (2008).
135. Abouzari, M. *et al.* The role of postoperative patient posture in the recurrence of traumatic chronic subdural hematoma after burr-hole surgery. *Neurosurgery* **61**, 794–797 (2007).
136. Kurabe, S., Ozawa, T., Watanabe, T. & Aiba, T. Efficacy and safety of postoperative early mobilization for chronic subdural hematoma in elderly patients. *Acta Neurochir. (Wien).* **152**, 1171–1174 (2010).
137. Court, J. *et al.* Embolization of the Middle meningeal artery in chronic subdural hematoma — A systematic review. *Clin. Neurol. Neurosurg.* **186**, (2019).
138. Moshayedi, P. & Liebeskind, D. S. Middle Meningeal Artery Embolization in Chronic Subdural Hematoma: Implications of Pathophysiology in Trial Design. *Front. Neurol.* **11**, (2020).
139. Waqas, M. *et al.* Safety and Effectiveness of Embolization for Chronic Subdural Hematoma: Systematic Review and Case Series. *World Neurosurg.* **126**, 228–236 (2019).
140. Kan, P. *et al.* Middle Meningeal Artery Embolization for Chronic Subdural Hematoma: A Multi-Center Experience of 154 Consecutive Embolizations. *Neurosurgery* **88**, 268–277 (2021).
141. Ironside, N. *et al.* Middle meningeal artery embolization for chronic subdural hematoma: a systematic review and meta-analysis. *J. Neurointerv. Surg.* **13**, 951–957 (2021).
142. Swedish Trial on Embolization of Middle Meningeal Artery Versus Surgical Evacuation in Chronic Subdural Hematoma - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT05267184?term=middle+meningeal&cond=Chronic+Subdural+Hematoma&draw=2&rank=3. (Accessed: 11th May

2022)
143. Middle Meningeal Artery Embolization With Liquid Embolic Agent for Treatment of Chronic Subdural Hematoma - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04574843?term=middle+meningeal&cond=Chronic+Subdural+Hematoma&draw=2&rank=6. (Accessed: 11th May 2022)
144. Middle Meningeal Artery Embolization for Treatment of Chronic Subdural Hematoma - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03307395?term=middle+meningeal&cond=Chronic+Subdural+Hematoma&draw=2&rank=2. (Accessed: 11th May 2022)
145. Dartmouth Middle Meningeal Embolization Trial (DaMMET) - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04270955?term=middle+meningeal&cond=Chronic+Subdural+Hematoma&draw=2&rank=10. (Accessed: 11th May 2022)
146. Embolization of the Middle Meningeal Artery for the Prevention of Chronic Subdural Hematoma Recurrence in High Risk Patients (EMPROTECT) - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04372147?term=middle+meningeal&cond=Chronic+Subdural+Hematoma&draw=3&rank=11. (Accessed: 11th May 2022)
147. The SQUID Trial for the Embolization of the Middle Meningeal Artery for Treatment of Chronic Subdural Hematoma (STEM) - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04410146?term=middle+meningeal&cond=Chronic+Subdural+Hematoma&draw=3&rank=14. (Accessed: 11th May 2022)
148. Embolization of Middle Meningeal Artery for Subdural Hematoma in Canada (EMMA Can) - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04923984?term=middle+meningeal&cond=Chronic+Subdural+Hematoma&draw=3&rank=18. (Accessed: 11th May 2022)
149. Bender, M. B. & Christoff, N. Nonsurgical Treatment of Subdural Hematomas. *Arch. Neurol.* **31**, 73–79 (1974).
150. Holl, D. C. *et al.* Corticosteroid treatment compared with surgery in chronic subdural hematoma: a systematic review and meta-analysis. *Acta Neurochir. (Wien).* **161**, 1231–1242 (2019).
151. Miah, I. P. *et al.* Dexamethasone therapy versus surgery for chronic subdural haematoma (DECSA trial): study protocol for a randomised controlled trial. *Trials* **19**, (2018).
152. EAN 2021: Dexamethasone Does Not Match Surgery for Chronic Subdural Hematoma in Randomized Trial | PracticeUpdate. *Neurology* (2021). Available at: https://www.practiceupdate.com/content/ean-2021-dexamethasone-does-not-match-surgery-for-chronic-subdural-hematoma-in-randomized-trial/120314. (Accessed: 11th May 2022)
153. Kageyama, H., Toyooka, T., Tsuzuki, N. & Oka, K. Nonsurgical treatment of chronic subdural hematoma with tranexamic acid. *J. Neurosurg.* **119**, 332–337

(2013).
154. Iorio-Morin, C., Blanchard, J., Richer, M. & Mathieu, D. Tranexamic Acid in Chronic Subdural Hematomas (TRACS): Study protocol for a randomized controlled trial. *Trials* **17**, (2016).
155. A Study on the Safety of Tranexamic Acid for the Chronic Subdural Hematoma Population - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02618382. (Accessed: 10th May 2022)
156. Immenga, S. *et al.* Tranexamic acid to prevent operation in chronic subdural haematoma (TORCH): study protocol for a randomised placebo-controlled clinical trial. *Trials* **23**, (2022).
157. Tranexamic Acid in the Treatment of Residual Chronic Subdural Hematoma - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03280212. (Accessed: 10th May 2022)
158. Won, S.-Y. *et al.* A systematic review of epileptic seizures in adults with subdural haematomas. (2017). doi:10.1016/j.seizure.2016.11.017
159. Huang, Y. H. *et al.* Risk factors and outcome of seizures after chronic subdural hematoma. *Neurocrit. Care* **14**, 253–259 (2011).
160. Sundaram Nachiappan, D. & Garg, K. Role of prophylactic antiepileptic drugs in chronic subdural hematoma-a systematic review and meta-analysis. doi:10.1007/s10143-020-01388-y/Published
161. Ratilal, B. O., Pappamikail, L., Costa, J. & Sampaio, C. Anticonvulsants for preventing seizures in patients with chronic subdural haematoma. *Cochrane Database Syst. Rev.* **2013**, (2013).
162. Rubin, G. & Rappaport, Z. H. Epilepsy in chronic subdural haematoma. *Acta Neurochir. (Wien).* **123**, 39–42 (1993).
163. Ohno, K. *et al.* Low incidence of seizures in patients with chronic subdural haematoma. *JNeurol Neurosurg Psychiatry* **56**, 1231–1233 (1993).
164. Potey, C. *et al.* Early treatment with atorvastatin exerts parenchymal and vascular protective effects in experimental cerebral ischaemia. *Br. J. Pharmacol.* **172**, 5188–5198 (2015).
165. Liu, Y., Wei, J., Hu, S. & Hu, L. Beneficial Effects of Statins on Endothelial Progenitor Cells. *Am J Med Sci* **344**, 220–226 (2012).
166. Jiang, R. *et al.* Safety and Efficacy of Atorvastatin for Chronic Subdural Hematoma in Chinese Patients: A Randomized ClinicalTrial. *JAMA Neurol.* **75**, 1338–1346 (2018).
167. Office, F. E. Retraction: Atorvastatin may attenuate recurrence of chronic subdural hematoma [Front. Neurosci., 10, 303, (2016)] doi: 10.3389/fnins.2016.00303. *Front. Neurosci.* **10**, 465 (2016).
168. Liu, H. Retraction: Effect of atorvastatin on resolution of chronic subdural hematoma: a prospective observational study. *J. Neurosurg.* **126**, 651–651 (2017).
169. Efficacy of Atorvastatin in Chronic Subdural Haematoma - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03956368. (Accessed: 10th May 2022)
170. Weigel, R., Hohenstein, A., Schlickum, L., Weiss, C. & Schilling, L. Angiotensin converting enzyme inhibition for arterial hypertension reduces the risk of recurrence in patients with chronic subdural hematoma possibly by an antiangiogenic mechanism. *Neurosurgery* **61**, 788–792 (2007).

171. Poulsen, F. R., Munthe, S., Søe, M. & Halle, B. Perindopril and residual chronic subdural hematoma volumes six weeks after burr hole surgery: a randomized trial. *Clin. Neurol. Neurosurg.* **123**, 4–8 (2014).
172. Schucht, P. *et al.* Follow-up Computed Tomography after Evacuation of Chronic Subdural Hematoma. *N. Engl. J. Med.* **380**, 1186–1187 (2019).
173. Rauhala, M. *et al.* Chronic subdural hematoma-incidence, complications, and financial impact. *Acta Neurochir. (Wien).* **162**, 2033–2043 (2020).
174. Pedersen, C., Sundbye, F. & Poulsen, F. No Value of Routine Brain Computed Tomography 6 Weeks after Evacuation of Chronic Subdural Hematoma. *Surg. J. (New York, N.Y.)* **3**, e174–e176 (2017).
175. Hulsbergen, A. F. C. *et al.* International practice variation in postoperative imaging of chronic subdural hematoma patients. *J. Neurosurg.* **131**, 1912–1919 (2018).
176. Han, M. H. *et al.* Predictive factors for recurrence and clinical outcomes in patients with chronic subdural hematoma. *J. Neurosurg.* **127**, 1117–1125 (2016).
177. Torihashi, K. *et al.* Independent predictors for recurrence of chronic subdural hematoma: a review of 343 consecutive surgical cases. *Neurosurgery* **63**, 1125–1129 (2008).
178. Bartek, J. *et al.* Predictors of Recurrence and Complications After Chronic Subdural Hematoma Surgery: A Population-Based Study. *World Neurosurg.* **106**, 609–614 (2017).
179. Ramachandran, R. & Hegde, T. Chronic subdural hematomas—causes of morbidity and mortality. *Surg. Neurol.* **67**, 367–372 (2007).
180. Chon, K. H., Lee, J. M., Koh, E. J. & Choi, H. Y. Independent predictors for recurrence of chronic subdural hematoma. *Acta Neurochir. (Wien).* **154**, 1541–1548 (2012).
181. Mori, K. & Maeda, M. Surgical treatment of chronic subdural hematoma in 500 consecutive cases: clinical characteristics, surgical outcome, complications, and recurrence rate. *Neurol. Med. Chir. (Tokyo).* **41**, 371–381 (2001).
182. Ohba, S., Kinoshita, Y., Nakagawa, T. & Murakami, H. The risk factors for recurrence of chronic subdural hematoma. *Neurosurg. Rev.* **36**, 145–150 (2013).
183. Miah, I. P. *et al.* Radiological prognostic factors of chronic subdural hematoma recurrence: a systematic review and meta-analysis. *Neuroradiology* **63**, 27–40 (2021).
184. Nathan, S., Goodarzi, Z., Jette, N., Gallagher, C. & Holroyd-Leduc, J. Anticoagulant and antiplatelet use in seniors with chronic subdural hematoma. *Neurology* **88**, 1889–1893 (2017).
185. Fornebo, I. *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).* **159**, 2045–2052 (2017).
186. Banks, J. L. & Marotta, C. A. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke* **38**, 1091–6 (2007).
187. Jennett, B. & Bond, M. Assessment of outcome after severe brain damage: A practical scale. *Lancet* **305**, 480–484 (1975).
188. Shukla, D., Devi, B. I. & Agrawal, A. Outcome measures for traumatic brain

injury. *Clin. Neurol. Neurosurg.* **113**, 435–441 (2011).
189. Markwalder, T. M., Steinsiepe, K. F., Rohner, M., Reichenbach, W. & Markwalder, H. The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. *J. Neurosurg.* **55**, 390–396 (1981).
190. Chari, A. *et al.* Core Outcomes and Common Data Elements in Chronic Subdural Hematoma: A Systematic Review of the Literature Focusing on Reported Outcomes. *J. Neurotrauma* **33**, 1212 (2016).
191. Munoz-Bendix, C. *et al.* Outcome following surgical treatment of chronic subdural hematoma in the oldest-old population. *Neurosurg. Rev.* **40**, 461–468 (2017).
192. Guilfoyle, M. R., Hutchinson, P. J. A. & Santarius, T. Improved long-term survival with subdural drains following evacuation of chronic subdural haematoma. *Acta Neurochir. (Wien).* **159**, 903–905 (2017).
193. Rauhala, M. *et al.* Long-term excess mortality after chronic subdural hematoma. *Acta Neurochir. (Wien).* **162**, 1467–1478 (2020).
194. Wang, S. *et al.* Risk factors of hospital mortality in chronic subdural hematoma: A retrospective analysis of 1117 patients, a single institute experience. *J. Clin. Neurosci.* **67**, 46–51 (2019).
195. Pringsheim, T., Fiest, K. & Jette, N. The international incidence and prevalence of neurologic conditions: how common are they? *Neurology* **83**, 1661–4 (2014).
196. Derby, C. A., Katz, M. J., Lipton, R. B. & Hall, C. B. Trends in Dementia Incidence in a Birth Cohort Analysis of the Einstein Aging Study. *JAMA Neurol.* **74**, 1345–1351 (2017).
197. Langa, K. M. Is the risk of Alzheimer's disease and dementia declining? *Alzheimers. Res. Ther.* **7**, 34 (2015).
198. Erkinjuntti, T., Remes, A., Rinne, J. & Soininen, H. *Muistisairaudet*. (Kustannus oy Duodecim, 2015).
199. Todd, S., Barr, S., Roberts, M. & Passmore, A. P. Survival in dementia and predictors of mortality: a review. *Int. J. Geriatr. Psychiatry* **28**, 1109–1124 (2013).
200. Guehne, U., Riedel-Heller, S. & Angermeyer, M. C. Mortality in Dementia. *Neuroepidemiology* **25**, 153–162 (2005).
201. Connors, M. H. *et al.* Predictors of Mortality in Dementia: The PRIME Study. *J. Alzheimers. Dis.* **52**, 967–974 (2016).
202. Bränsvik, V., Granvik, E., Minthon, L., Nordström, P. & Nägga, K. Mortality in patients with behavioural and psychological symptoms of dementia: a registry-based study. *Aging Ment. Health* **25**, 1101–1109 (2021).
203. Gebel, J. M. *et al.* Comparison of the ABC/2 Estimation Technique to Computer-Assisted Volumetric Analysis of Intraparenchymal and Subdural Hematomas Complicating the GUSTO-1 Trial. *Stroke* **29**, 1799–1801 (1998).
204. Sotkanet.fi Statistical information on welfare and health in Finland. Available at: https://sotkanet.fi/sotkanet/en/index? (Accessed: 3rd July 2020)
205. *Revision of the European Standard Population - Report of Eurostat's task force, 2013 edition*. (2013). doi:10.2785/11470
206. Glancz, L. J. *et al.* Does Drain Position and Duration Influence Outcomes in Patients Undergoing Burr-Hole Evacuation of Chronic Subdural Hematoma? Lessons from a UK Multicenter Prospective Cohort Study. *Neurosurgery* **85**, 486–493 (2018).
207. Tommiska, P. *et al.* Incidence of surgery for chronic subdural hematoma in

Finland during 1997–2014: a nationwide study. *J. Neurosurg.* **136**, 1186–1193 (2021).
208. Abe, Y. *et al.* Outcomes of chronic subdural hematoma with preexisting comorbidities causing disturbed consciousness. *J. Neurosurg.* **126**, 1042–1046 (2017).
209. Christopher, E. *et al.* Outcomes following surgery in subgroups of comatose and very elderly patients with chronic subdural hematoma. *Neurosurg. Rev.* **42**, 427–431 (2019).
210. Kwon, C.-S., Al-Awar, O., Richards, O., Izu, A. & Lengvenis, G. Predicting Prognosis of Patients with Chronic Subdural Hematoma: A New Scoring System. *World Neurosurg.* **109**, e707–e714 (2018).
211. Shimizu, K. *et al.* Importance of frailty evaluation in the prediction of the prognosis of patients with chronic subdural hematoma. *Geriatr Gerontol Int* **18**, 1173–1176 (2018).
212. De Bonis, P. *et al.* Chronic subdural hematoma in patients aged 80 years and older: A two-centre study. *Clin. Neurol. Neurosurg.* **170**, 88–92 (2018).
213. Dobran, M. *et al.* Clinical Outcome of Patients Over 90 Years of Age Treated for Chronic Subdural Hematoma. *J. Korean Neurosurg. Soc.* (2019). doi:10.3340/jkns.2018.0011
214. Panula, J. *et al.* Mortality and cause of death in hip fracture patients aged 65 or older: a population-based study. *BMC Musculoskelet. Disord.* **12**, 105 (2011).
215. Diehr, P., Williamson, J., Patrick, D. L., Bild, D. E. & Burke, G. L. *Patterns of Self-Rated Health in Older Adults Before and After Sentinel Health Events*. *JAGS* **49**, (2001).
216. Dumont, T. M., Rughani, A. I., Goeckes, T. & Tranmer, B. I. Chronic Subdural Hematoma: A Sentinel Health Event. *World Neurosurg.* **80**, 889–892 (2013).
217. Qiu, C., Bäckman, L., Winblad, B., Agüero-Torres, H. & Fratiglioni, L. The influence of education on clinically diagnosed dementia incidence and mortality data from the Kungsholmen Project. *Arch. Neurol.* **58**, 2034–9 (2001).
218. Baldereschi, M. *et al.* Dementia is a major predictor of death among the Italian elderly. ILSA Working Group. Italian Longitudinal Study on Aging. *Neurology* **52**, 709–13 (1999).
219. Katzman, R. *et al.* The malignancy of dementia. Predictors of mortality in clinically diagnosed dementia in a population survey of Shanghai, China. *Arch. Neurol.* **51**, 1220–5 (1994).
220. Keskimäki, I. & Aro, S. Accuracy of data on diagnoses, procedures and accidents in the Finnish Hospital Discharge Register. *Int Jx Heal Sci* **2**, 15–21 (1991).
221. Sund, R. Quality of the Finnish Hospital Discharge Register: A systematic review. *Scand. J. Public Health* **40**, 505–515 (2012).
222. Life expectancy, table | Findicator.fi. Available at: https://findikaattori.fi/en/table/46. (Accessed: 3rd November 2020)
223. Hakanen, A. *Radiologisten tutkimusten ja toimenpiteiden määrät vuonna 2000*. (2002).
224. Ruonala, V. *Radiologisten tutkimusten ja toimenpiteiden määrät vuonna 2018*. *STUK-B 242* (2019).
225. Tommiska, P., Lönnrot, K., Raj, R., Luostarinen, T. & Kivisaari, R. Transition of a Clinical Practice to Use of Subdural Drains after Burr Hole Evacuation of Chronic Subdural Hematoma: The Helsinki Experience. *World Neurosurg.* **129**,

e614–e626 (2019).
226. Finnish Medicines Agency Fimea Institution & Social Insurance Institution. *Suomen lääketilasto - Finnish Statistics on Medicines 2009*. (2010).
227. Finnish Medicines Agency Fimea & Institution and Social Insurance Institution. *Suomen lääketilasto - Finnish Statistics on Medicines 2017*. (2018).
228. Kim, S. O., Jung, S. Il, Won, Y. S., Choi, C. S. & Yang, J. Y. A Comparative Study of Local versus General Anesthesia for Chronic Subdural Hematoma in Elderly Patients Over 60 Years. *Korean J. Neurotrauma* **9**, 47 (2013).
229. Surve, R. M., Bansal, S., Reddy, M. & Philip, M. Use of Dexmedetomidine Along With Local Infiltration Versus General Anesthesia for Burr Hole and Evacuation of Chronic Subdural Hematoma (CSDH). *J. Neurosurg. Anesthesiol.* **29**, 274–280 (2017).