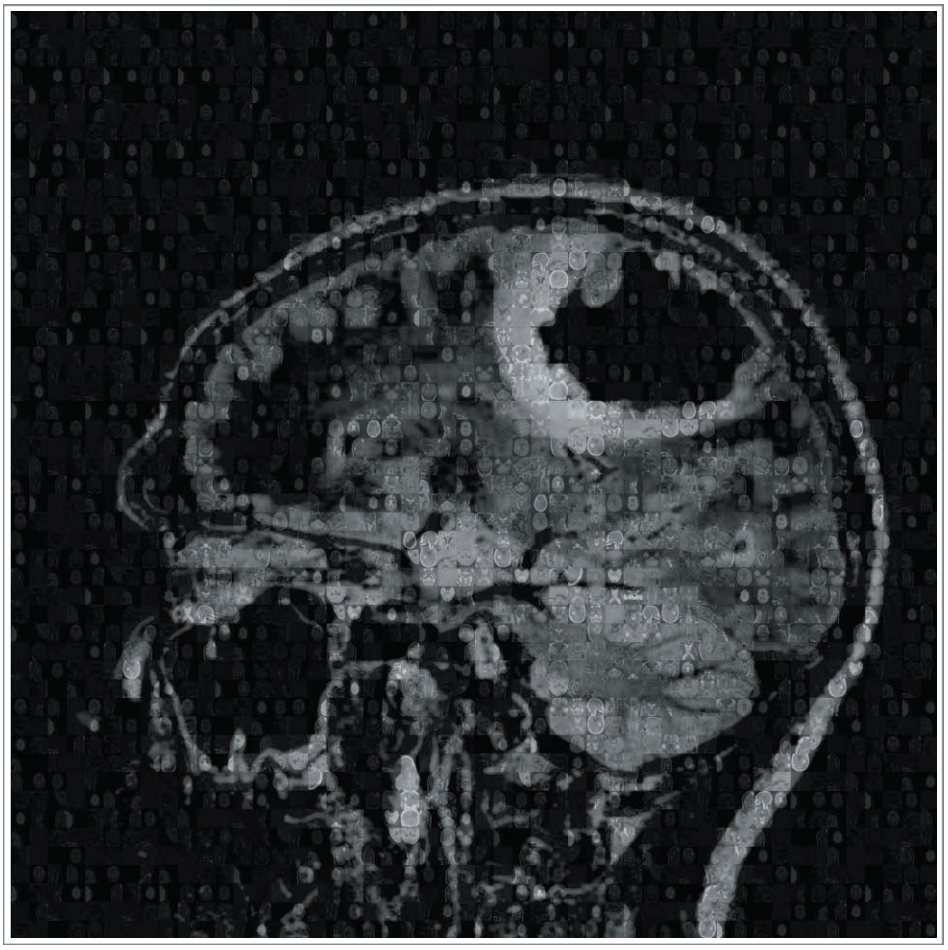

New insights into intracerebral hemorrhage

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NEW INSIGHTS INTO INTRACEREBRAL HEMORRHAGE

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Abstract

Non-traumatic intracerebral hemorrhage (ICH) is caused by a rupture of a brain artery leading to blood penetration into brain parenchyma. The incidence of ICH is 10–22 per 100 000 persons per year worldwide. The prognosis is poor, with approximately 40% of the patients dying within one month, and a large number of the survivors remaining with major disabilities. There is no proven effective medical or surgical treatment option, treatment being mainly supportive in nature, with management in dedicated stroke units reducing mortality and morbidity.

Major risk factors for ICH include hypertension and older age. Hypertension is a well-known risk factor for ICH, shown in several case-control studies. On many of the other potential risk factors, such as smoking, diabetes, and alcohol intake, the results have been conflicting. In addition to the chronic risk factors above, certain preceding triggering events may temporally predispose individuals to ICH. However, data on such triggers in ICH are virtually lacking.

Factors that take part in hemostasis and coagulation affect the prognosis of ICH patients. Calcium plays an important role in coagulation, and hypocalcemia has been associated with larger ICH volumes, severity of symptoms, ICH expansion, whereas elevated calcium levels with better outcomes, regardless of similar ICH volumes between hypo-, normo- and hypercalcemic patients. However, there are some contradictions in the results between different studies.

Older age, longer hospital stay, poorer motor function at discharge, severity of the neurological deficits, use of antithrombotic medication, larger and deep ICH, and intraventricular extension of ICH have all been reported to associate with worse health-related quality of life (HRQoL) after ICH. These parameters are mainly associated with the severity of the index ICH, and little is known about the effect of other components of quality of life, such as mood and anxiety.

We aimed to assess factors in our population-based cohort of ICH patients that have been less studied, and gained less attention in earlier studies, taking into consideration novel factors such as feelings of depression and fatigue prior to the index ICH. We wanted to assess whether triggering factors predisposing

to the event exist in ICH. We also studied the effect of hypocalcemia on ICH volume and mortality. In addition to traditional prognostic measures, we attempted to assess quality of life and depression after ICH. We further determined how occipital location, the rarest single-lobe location, affects the outcome of the patients.

The prospective part of the study included patients admitted to the Helsinki University Hospital between May 2014 and December 2016. An informed written consent was needed to participate (patient/proxy). Hemorrhages related to tumor, trauma, ischemic stroke, vascular malformations, and other structural abnormalities were excluded. The patients were interviewed during hospital stay, and given structured questionnaires. HRQoL at 3 months after ICH was measured using the European Quality of Life Scale (EQ-5D-5L), and the 15D scale. The recovery was evaluated by a combination of revisiting the electronic medical records and a telephone call. Controls were matched by age and sex, and randomly selected from the participants of the FINRISK study, a large Finnish population survey on risk factors of chronic non-communicable diseases. Ages were matched in 5-year age bands. However, as the oldest FINRISK participants were 74-year-olds, controls for the age group 75-84 were selected from the age group of 70-74 years, and patients aged ≥85 years were excluded. The retrospective part included a registry of 1013 consecutive ICH patients admitted to the Helsinki University Hospital between January 2005 and March 2010, and the substudy on hypocalcemia included 447 of the patients that had computed tomography (CT) of the brain and serum/plasma ionized calcium taken within 72 hours of symptom onset and within 12 hours of each other.

A total of 277 primary ICH patients were recruited to the prospective part of the study, of which 250 could be included in the risk factor analysis, 97 were able to provide consistent answers on the trigger questions, and 124 returned the quality of life questionnaire. In the case-control study, the cases had more often hypertension, history of heart attack, lipid-lowering medication, and reported more frequently fatigue prior to ICH. In persons aged <70 years, hypertension and fatigue were more common among cases. In persons aged ≥70 years, the factors associating with the risk of ICH were premorbid fatigue, use of lipid-lowering medication, and overweight. None of the studied possible triggers alone was more frequent during the hazard period compared to the

control period. However, when all physical triggers were combined, there was an association with the triggering event and onset of ICH (risk ratio 1.32, 95% confidence interval 1.01-1.73). Predictors for lower HRQoL by both EQ-5D-5L and 15D scales were higher NIHSS, older age, and chronic heart failure. Feeling sad/depressed for more than 2 weeks during the year prior to ICH was a predictor for lower EQ-5D-5L, and history of ICH for lower 15D utility indexes. Prior feelings of sadness/depression were associated with depression/anxiety at 3 months after ICH.

In our study, we found that ICH patients had more often fatigue prior to their ICH than the controls of similar sex and age. Hypertension was associated with risk of ICH, as expected. Of the triggering factors present immediately prior to the onset of ICH, physical triggers as a group were associated with the onset time. Hypocalcemic ICH patients had larger ICH volumes than normocalcemic patients. Their higher mortality rate is likely mediated through larger ICH volumes. HRQoL after ICH was associated with the severity of the stroke, comorbidities, and age. However, in our study, feelings of depression before ICH had stronger influence on reporting depression/anxiety after ICH than stroke severity-related and outcome parameters. Few were diagnosed with depression, or had antidepressant medication. This information could be used to identify patients at risk for post-ICH depression. Compared to other ICH patients, occipital ICH patients were younger, had milder neurological deficits, smaller ICH volumes, more often structural etiology, and better outcomes. The risk for epilepsy was similar with other ICH patients. Our studies brought novel insights in lesser studied aspects of ICH.

Tiivistelmä

Ei-traumaattinen aivoverenvuoto aiheutuu aivovaltimon seinämän rikkoontumisesta, mikä johtaa veren purkautumiseen aivokudokseen. Aivoverenvuodon maailmanlaajuinen ilmaantuvuus on 10-22 100 000 henkilöä kohti vuodessa. Sairastuneiden toipumisennuste on heikko. Noin 40% sairastuneista menehtyy kuukauden kuluessa, ja suuri osa selviytyvistä vammautuu. Hoitokeinot ovat pääosin elintoimintoja tukevia, eikä tehokkaaksi osoitettua lääkkeellistä tai kirurgista hoitoa ole keksitty. Hoito aivohalvausyksiköissä kuitenkin vähentää kuolleisuutta.

Verenpainetauti ja korkea ikä kuuluvat aivoverenvuodon merkittäviin riskitekijöihin, ja verenpainetaudin merkitys on osoitettu useissa tapausverrokkitutkimuksissa. Monien muiden mahdollisten riskitekijöiden, kuten tupakoinnin, diabeteksen ja alkoholin, osalta tuloksissa on ristiriitaisuutta. Pitkäaikaisten riskitekijöiden ohella myös ns. trigger-tekijät, jotka vaikuttavat tapahtumaa edeltävästi esimerkiksi verenpainetta nostamalla, voivat mahdollisesti altistaa aivoverenvuodolle. Tällaisia laukaisevia tekijöitä ei ole aivoverenvuotopotilailla juuri tutkittu.

Veren hyytymiseen vaikuttavilla tekijöillä on yhteys aivoverenvuotopotilaan ennusteeseen. Veren kalsiumilla on merkittävä rooli veren hyytymisessä, ja hypokalsemian onkin esitetty vaikuttavan aivoverenvuodon kokoon ja kasvuun sekä oireiden vaikeuteen.

Korkeampi ikä, pidempi sairaalahoito, huonompi liikuntakyky, vaikeampi neurologinen oireisto, antitromboottinen lääkitys, kookas ja syvä aivoverenvuoto ja verenvuodon purkautuminen aivokammioihin on yhdistetty huonompaan elämänlaatuun aivoverenvuodon jälkeen. Tiedetään kuitenkin vain vähän muista sairastumisen jälkeisistä elämänlaatuun vaikuttavista osasista, kuten mielialatekijöistä.

Tavoitteemme oli tarkastella vähemmän tutkittuja aivoverenvuodon riskiin, toipumiseen ja elämänlaatuun liittyviä tekijöitä, ottaen huomioon myös ennen sairastumista koetut mielialatekijät ja uupumus, sekä sairastumishetkelle mahdollisesti altistavia trigger-tekijöitä. Halusimme selvittää, miten hypokalsemia vaikuttaa aivoverenvuodon kokoon ja kuolleisuuteen. Tutkimme, miten aivoverenvuodon sijainti takaraivolohkossa vaikuttaa potilaiden toipumiseen.

Tutkimuksen prospektiiviseen osaan rekrytoitiin Helsingin yliopistollisessa sairaalassa aikavälillä 5/2014-12/2016 hoidettuja potilaita, jotka antoivat kirjallisen suostumuksen (potilas/omainen). Aivoverenvuodot, jotka liittyivät aivokasvaimeen, traumaan, aivoinfarktiin, vaskulaariseen malformaatioon tai muuhun rakenteelliseen poikkeavuuteen jäivät tutkimuksen ulkopuolelle. Potilaat haastateltiin sairaalassa oloaikana, ja he saivat kyselylomakkeet täytettävikseen. Elämänlaatu kolmen kuukauden kohdalla sairastumisesta selvitettiin EQ-5D-5L- ja 15D-lomakkein. Toipumista arvioitiin sairauskertomusmerkinnöistä ja puhelinsoitolla. Kontrollihenkilöt valikoitiin sattumanvaraisesti iän ja sukupuolen perusteella FINRISKI-tutkimuksesta. FINRISKI on laaja väestötutkimus kroonisten tarttumattomien tautien riski- ja suojatekijöistä suomalaisessa väestössä. Iät sovitettiin viiden vuoden ikäjaksoin. Koska FINRISKIN vanhimmat osallistujat ovat 74-vuotiaita, valittiin 75-84-vuotiaiden kontrollihenkilöt ikäryhmästä 70-74. Iältään ≥85-vuotiaat potilaat jätettiin tutkimuksen ulkopuolelle. Retrospektiivisessä osiossa käytettiin jo olemassa olevaa 1013 potilaan aineistoa, johon on koottu kaikki Helsingin yliopistollisessa sairaalassa aikavälillä 1/2005-3/2010 hoidetut aivoverenvuotopotilaat. Ne 447 potilasta, joilta oli otettu pään viipaletutkimus ja seerumin/plasman ionisoitu kalsium 72 tunnin kuluessa oireiden alkamisesta ja ko. tutkimukset 12 tunnin sisällä toisistaan, osallistuivat hypokalsemia-tutkimukseen.

Rekrytoimme tutkimukseen 277 aivoverenvuotopotilasta. Potilaista 250 voitiin sisällyttää tapaus-verrokkitutkimukseen, 97 potilasta pystyivät vastaamaan luotettavasti trigger-kysymyksiin, ja 124 potilasta palautti elämänlaatukyselylomakkeet. Aivoverenvuotopotilailla oli verrokkejaan useammin verenpainetauti, sairastettu sydäninfarkti ja/tai kolesterolilääkitys, ja suurempi osa heistä raportoi uupumusta ennen sairastumistaan. Alle 70-vuotiailla potilailla oli verrokkejaan useammin verenpainetauti ja uupumusta ennen aivoverenvuotoa. Vähintään 70-vuotiaiden ikäryhmässä uupumus ennen sairastumista, kolesterolilääkitys ja ylipaino lisäsivät riskiä sairastua aivoverenvuotoon. Yksikään tutkituista trigger-tekijöistä ei yksinään ollut yleisempi aivoverenvuotoa edeltävinä kahtena tuntina verrattuna vastaavaan ajankohtaan edellisenä päivänä. Fysikaaliset triggerit yhdistettynä assosioituivat kuitenkin sairastumishetkeen riskisuhteella 1.32 (95% luottamusväli 1.01-1.73). Molemmilla tutkituilla mittareilla oireiston vaikeusaste, korkea ikä

ja sydämen vajaatoiminta ennustivat huonompaa elämänlaatua kolmen kuukauden kohdalla sairastumisesta. Aiempi aivoverenvuoto ennusti huonompaa elämänlaatua 15D-asteikolla, ja sairastumista edeltävän vuoden aikana koettu vähintään kahden viikon kestoinen masentuneisuus EQ-5D-5L-asteikolla. Aiempi masentuneisuus assosioitui myös sairastumisen jälkeiseen masennuksen ja/tai ahdistuksen tunteisiin.

Tutkimuksessa siis havaitsimme, että aivoverenvuotopotilaat kärsivät saman ikäisiä ja sukupuolisia verrokkejaan enemmän uupumuksesta jo ennen sairastumistaan. Oletetusti verenpainetauti assosioitui aivoverenvuodon riskiin, ja fysikaaliset triggerit ryhmänä assosioituivat aivoverenvuodon tapahtumahetkeen. Hypokalseemisten potilaiden aivoverenvuodot olivat suurempia kuin normokalseemisilla, ja kuolleisuus suurempaa, mikä todennäköisesti johtui kookkaammista vuodoista. Aivoverenvuodon jälkeinen elämänlaatu assosioitui aivohalvausoireiston vakavuuteen, taustasairauksiin ja ikään. Tutkimuksessamme merkittävimpänä tekijänä aivoverenvuodon jälkeisiin mielialaoireisiin olivat kuitenkin mielialaoireet jo ennen sairastumista. Vain harvalla oli tiedossa oleva masennusdiagnoosi tai -lääkitys. Tätä tietoa voitaisiin hyödyntää, jotta potilaat, jotka ovat riskissä sairastua aivoverenvuodon jälkeiseen masennukseen löydettäisiin. Verrattuna muihin aivoverenvuotopotilaisiin, takaraivolohkon aivoverenvuotoon sairastuneet olivat nuorempia, lievempioireisia, ja heidän aivoverenvuodot olivat pienempiä, ja vuodon etiologiana useammin rakenteellinen poikkeavuus. Riski sairastua epilepsiaan oli verrannollinen muihin potilaisiin. Tutkimuksemme toi uusia näkökulmia aivoverenvuodon vähemmän tutkittuihin puoliin.

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List of original publications

This thesis is based on the following publications referred to in the text by their Roman numerals:

I Sallinen H, Pietilä A, Salomaa V, Strbian D. Risk Factors of Intracerebral Hemorrhage: A Case-Control Study. J Stroke Cerebrovasc Dis. 2020;29:104630.

II Sallinen H, Putaala J, Strbian D. Triggering factors in non-traumatic intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2020;29:104921.

III Sallinen H, Wu TY, Meretoja A, Putaala J, Tatlisumak T, Strbian D. Effect of baseline hypocalcaemia on volume of intracerebral haemorrhage in patients presenting within 72 hours from symptom onset. J Neurol Sci. 2019;403:24–29.

IV Sallinen H, Sairanen T, Strbian D. Quality of life and depression 3 months after intracerebral hemorrhage. Brain Behav. 2019;e01270.

V Räty S, Sallinen H, Virtanen P, Haapaniemi E, Wu TY, Putaala J, Meretoja A, Tatlisumak T, Strbian D. Occipital intracerebral haemorrhage – clinical characteristics, outcome, and post-ICH epilepsy. Acta Neurol Scand. 2020;10.1111/ane.13303. doi:10.1111/ane.13303.

Abbreviations

ADP	adenosine diphosphate
AF	atrial fibrillation
AHA/ASA	American Heart Association/American Stroke Association
APC	activated protein C
APOE	apolipoprotein E
AVM	arteriovenous malformation
BI	Barthel Index
BBB	blood-brain barrier
BP	blood pressure
CAA	cerebral amyloid angiopathy
CI	confidence interval
CMB	cerebral microbleed
CSF	cerebrospinal fluid
CT	computed tomography
CTA	computed tomography angiography
DOAC	direct oral anticoagulant
DSA	digital subtraction angiography
DWMH	deep white matter hyperintense signals
ESO	European Stroke Organisation
FLAIR	fluid-attenuated inversion recovery
GCS	Glasgow Coma Scale
GWAS	genome-wide association study
HA	hypertensive arteriopathy
Hb	hemoglobin
HICHS	Helsinki Intracerebral Hemorrhage Study
HICHS-2	Helsinki Intracerebral Hemorrhage Study-2
HMWK	high molecular weight kininogen
HO-1	heme oxygenase 1
Hp	haptoglobin
HRQoL	Health-related quality of life
ICH	intracerebral hemorrhage
ICP	intracranial pressure
IL	interleukin

INR	international normalized ratio
IQR	interquartile range
IVH	intraventricular hemorrhage
LDL	low-density lipoprotein
LMWH	low molecular weight heparin
LPR1	low-density lipoprotein receptor-related protein-1
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
OAC	oral anticoagulation
OR	odds ratio
PCC	prothrombin concentrates
PL	phospholipid
PVH	periventricular hyperintensity
QoL	quality of life
RCVS	reversible cerebral vasoconstriction syndrome
rFVIIa	recombinant activated factor VIIa
RR	relative risk
SAH	subarachnoid hemorrhage
SE	standard error
SVD	small vessel disease
TF	tissue factor
TIA	transient ischemic attack
TLR4	toll like receptor 4
TNF-α	tumor necrosis factor alpha
TXA2	thromboxane A2
VFD	visual field defect
VKA	vitamin K antagonist
VWF	von Willebrand factor
WMH	white matter hyperintensities
WML	white matter lesion

1 Introduction

Non-traumatic intracerebral hemorrhage (ICH) is caused by a rupture of a brain artery leading to blood penetration into brain parenchyma. The incidence of ICH is 10-22 per 100 000 persons per year worldwide, with a higher incidence in low to middle income countries, compared to high income countries[1]. The prognosis is poor, with approximately 40% of the patients dying within one month, and a large number of the survivors remaining with major disabilities[2]. There is no proven effective medical or surgical treatment option, treatment being mainly supportive in nature. However, management in dedicated stroke units reduces mortality and morbidity[3].

Major risk factors for ICH include hypertension and older age. Hypertension is a well-known risk factor for ICH, shown in several case-control studies[4,5]. On many of the other potential risk factors, such as smoking, diabetes, and alcohol intake, the results have been conflicting. In addition to chronic risk factors, certain preceding triggering events may temporally predispose individuals to stroke[6,7]. However, data on such triggers in ICH are virtually lacking.

Factors affecting the prognosis of the patients include older age, lower baseline Glasgow Coma Scale (GCS), higher National Institutes of Health Stroke Scale (NIHSS) score, infratentorial location, ICH and intraventricular hemorrhage (IVH) volumes and their growth, edema, hyperglycemia, hydrocephalus, herniation, anticoagulation, and multiple hemorrhages[8–13]. Factors that take part in hemostasis and coagulation affect the prognosis of ICH patients[14]. Calcium plays an important role in coagulation[15–17], and hypocalcemia has been reported to associate with larger ICH volumes, severity of symptoms[18], ICH expansion[19], and elevated calcium levels with better outcomes, regardless of similar ICH volumes between hypo-, normo- and hypercalcemic patients[20]. However, between the studies are some differences on how calcium affects the ICH volume and outcome.

Older age, longer hospital stay, poorer motor function at discharge, severity of the neurological deficits by baseline NIHSS, use of antithrombotic medication, large and deep ICH, intraventricular extension of ICH, and early worsening of the neurological deficit have all been reported to associate with worse health-related quality of life (HRQoL) after ICH[21,22]. These

parameters are mainly associated with the severity of the index ICH, and little is known about the effect of other components of quality of life, such as mood and anxiety.

In this study, we wanted to address ICH in a wide spectrum, taking into account risk factors, triggering factors, parameters associated with hematoma growth in the acute setting, as well as factors affecting the prognosis and post-stroke quality of life in a prospective cohort of ICH patients in a single center (one substudy also included retrospective patients to gain a larger number of patients, and another substudy included only retrospective patients).

We aimed to analyze factors in a population-based cohort of ICH patients, that have been less studied, and gained less attention in earlier studies, taking into consideration novel factors such as feelings of depression and fatigue prior to the index ICH. We also wanted to find out whether triggering factors predisposing to the event exist in ICH. As results between earlier studies on the association between hypocalcemia and ICH volume are somewhat conflicting, we wanted to examine the effect of hypocalcemia in ICH volume and mortality in a large consecutive cohort of non-traumatic ICH patients. In addition to traditional prognostic measures, we wanted to assess quality of life and depression after ICH, and addressed such factors affecting the subjective quality of life that are not included in traditional outcome measures.

Gaining new insights on the risk factors, and factors affecting prognosis - both physical and mental - will likely help in both preventing ICH as well as offering the patients better treatment.

2 Review of the literature

2.1 Definition, incidence, and pathophysiology of ICH

ICH literally means hemorrhage in the brain, and results from rupture of an intracerebral artery when bleeding occurs into the brain parenchyma leading to a hematoma. Additionally, the bleeding can rupture into the ventricles, causing intraventricular hemorrhage. Of all strokes, approximately 10-15% are caused by intracerebral hemorrhage[1].

ICH can be classified as primary or secondary. Non-traumatic ICH occurs without a predisposing head trauma. Primary ICH originates from a spontaneous rupture of small brain arteries, whereas in secondary ICH, there is an underlying structural cause, such as a vascular malformation[23]. The term spontaneous ICH is sometimes used, when no other cause apart from hypertension is found[24]. However, the classification of ICH is confusing, as often times the knowledge on the underlying pathology and exact source of bleeding is unknown[24]. Thus, in different sources, the definitions somewhat vary, and classifying the non-traumatic ICH as structural (ICH caused by an underlying structural source) and non-structural may be convenient.

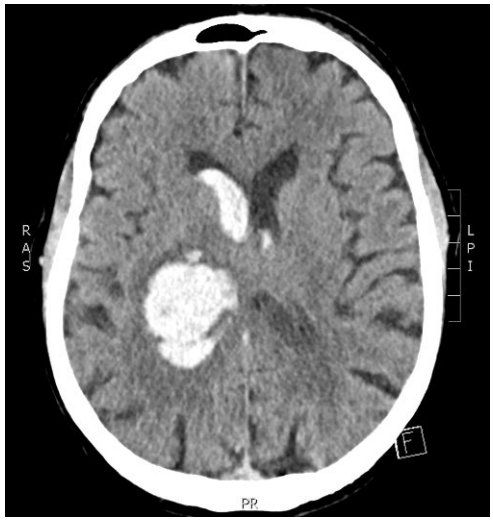

Figure 1. Example of a deep ICH in right hemisphere, with intraventricular extension.

Johann Jakob Wepfer based in Germany and Switzerland in the 17th century was the first to make note that stroke can be caused by either hemorrhage or clotting[25]. In the next century, Italian Morgagni of Padua, worked on postmortem studies and linked them with different clinical stroke subtypes[25,26].

Huge progress has been made in the diagnosis and management of stroke in the past few decades. As recently as just almost fifty years ago, the standard procedure to differentiate brain hemorrhage from ischemic stroke was a lumbar puncture to detect blood in the cerebrospinal fluid. In later years, midline echogram (transcranial sonography i.e. ultrasound-based imaging technique) could be used to detect a displacement of the midline structures due to unilateral lesion in the brain. Afterwards, the diagnostics of ICH were revolutionized by advanced imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), which in addition to showing the hematoma itself, may help in deciphering the etiology of the bleeding[25,27,28].

However, the advancement for specific stroke therapies concerns ischemic stroke, and not ICH, with proven efficacy of drugs for secondary prevention of ischemic stroke such as aspirin and anticoagulants, and intravenous tissue plasminogen activator to lyse the intra-arterial clot in the brain artery, as well as more recently proven efficacy of thrombectomy to remove the intra-arterial clot[29].

ICH remains a devastating condition, and early mortality rates are approximately 40%, with many of the survivors remaining disabled[2]. The incidence of ICH is 10-22 per 100 000 persons worldwide annually, with a higher incidence in low to middle income countries, compared to high income countries[1]. The incidence differs between ethnicities; in a meta-analysis and systematic review, the incidence was comparable for white, black, Hispanic, Indian, and Maori people, but two times higher for east and southeast Asian people (51.8 per 100 000 person-years). The incidence is higher among males, and increases with older age. In some regions, the incidence has been reported to decrease between years 1980 and 2008, possibly due to change in environmental factors, such as better blood pressure control[2].

Processes leading to ICH include amyloid angiopathy, structural vascular malformations such as cavernomas, arteriovenous malformations (AVM), cerebral venous thrombosis, vasculitis, ruptured aneurysms, ischemia with hemorrhagic transformation, and trauma[14,30].

Table 1 depicts an example of classification by underlying ICH etiology.

Table 1. Classification of non-traumatic ICH by underlying etiology. Adapted from Textbook of Stroke Medicine (M. Brainin et al, 3rd Edition, Cambridge University Press, 2019, p.214).

Arterial disease	Small-vessel disease	Acquired small-vessel disease Amyloid angiopathy Genetic small-vessel disease
	Large-vessel disease	Intracranial aneurysm Moyamoya Vasculitis Reversible cerebral vasoconstriction syndrome Secondary hemorrhagic transformation of brain infarct
Venous disease	Acute intracerebral venous and/or sinus thrombosis	
Vascular malformation	Arteriovenous malformation Dural arteriovenous fistula Cerebral cavernous malformation	
Hemostatic disorder	Hematologic disease	Congenital factor VII deficiency, hemophilia, thrombocytopenia, etc.
	Iatrogenic disorders	Vitamin K antagonists, FX-inhibitors, F-II-inhibitors, anti-platelet agents, thrombolysis with recombinant tissue plasminogen activator, etc.
ICH in the context of other disease and condition	Substance abuse Infective endocarditis Neoplasms	
Cryptogenic	Cause suspected but not detectable with currently available diagnostic tests	

There are two types of vessel pathologies accounting for most primary intracerebral hemorrhages: deep perforator arteriopathy (hypertensive arteriopathy) and cerebral amyloid angiopathy (CAA)[31]. CAA is caused by ß-amyloid deposits within cortical and leptomeningeal arteries[32]. Hypertensive arteriolopathy is characterized by loss of smooth muscle cells from the tunica media, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall; additionally, microatheromas and microaneurysms are possible[33]. ICH caused by hypertensive arteriopathy predominantly occurs in deep structures such as thalamus and basal ganglia (nonlobar ICH), whereas CAA causes lobar cortical or subcortical hemorrhages[34] as CAA affects cortical and leptomeningeal vessels[35]. More than 50% of primary ICH are thought to relate to hypertension, whereas CAA accounts for approximately 30% of the cases[28]. However, patients may have both pathologies co-existing; one study demonstrated that of patients with

lobar hemorrhages, only 16% had solely CAA, whereas 42% of the patients had both CAA and hypertensive arteriopathy[35].

Of the secondary causes of ICH, the most common structural etiologies leading to ICH include vascular malformations, neoplasms, and hemorrhagic infarction[36]. The prevalence of AVM – abnormal connection between arterial and venous systems without the normal capillary bed - is approximately 0.2% in adults, and the annual risk of hemorrhage in unruptured AVM is approximately 2%. The prevalence of cavernomas (cluster of thin-walled vessels without elastic fibers or smooth muscle, commonly surrounded by a rim of hemosiderin-laden gliotic tissue) is slightly higher than AVM, approximated 0.3-0.6%, but the risk of first bleeding is lower, around 0.4-0.6% per year[36].

Expansion of the hematoma is common, occurring in up to one third of ICH patients, and most commonly during the first 24 hours[30]. Risk factors for hematoma expansion include anticoagulation treatment, spot sign in computed tomography angiography (CTA) suggesting on-going bleeding (Figure 2.), shorter time from ICH onset to computed tomography (CT), and larger hematoma size[37].

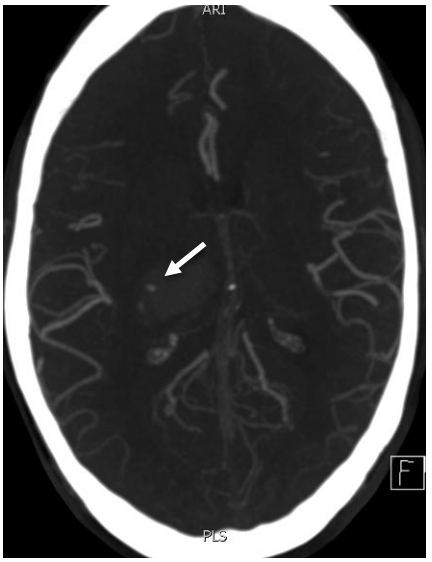

Figure 2. Brain CTA shows spot signs (arrow) indicating ongoing bleeding

Following the primary injury caused by the mass effect, secondary injury to the neurons is caused by edema surrounding the hematoma, inflammation, and toxic biochemical and metabolic effects of the components of the clot and its degradation[38]. Upon occurrence of ICH, microglia/macrophages are rapidly activated. The microglia and macrophages are essential in phagocytizing and clean-up of the hematoma[39]. However, by releasing inflammatory factors and inducing a cascade of inflammatory reactions, they contribute to the pathological changes in the blood-brain barrier (BBB), edema and cell death. Activated microglia/macrophages appear in classically activated M1 and alternative activated M2 phenotypes. Early after ICH several blood components activate the microglia/macrophages into M1 phenotype. They express receptors such as toll like receptor 4 (TLR4) and heme oxygenase 1 (HO-1) which help in clearing the hematoma. Additionally, they produce proinflammatory mediators such as various interleukins (IL), tumor necrosis factor alpha (TNF-α), oxidative metabolites and iron content, which all exacerbate brain damage. In contrast, M2 may improve brain recovery by secreting factors that help in reducing inflammation, clearing cell debris and tissue remodeling. Thus, inhibiting M1 and promoting M2 would be useful for post-ICH recovery. TLR4 associates with inflammation, leukocyte infiltration, and cytokine and chemokine production in the setting of ICH. TNF-α and IL-1β are essential mediators of the neuronal damage after ICH[40]. The reactive microglia persist for 4 weeks, peaking at 3 to 7 days after ICH[41].

Additionally, oxidative stress – a condition with overproduction of free radicals, essentially reactive oxygen species – plays an important role in secondary brain injury after ICH, causing damage to the cells. Reactive oxygen species and nitric oxide are released as neutrophils are activated within the inflammatory response. To eliminate free radicals, superoxide dismutase is used, which causes redundant lipid peroxidation, and this in turn changes the physical properties of cellular membranes, and alters proteins and nucleic acids, resulting in brain damage. Free radicals are also formed by blood cell degradation products such as iron ions. Hemoglobin and iron released from the red blood cells within the hematoma play an important role in neuronal damage after ICH. The mechanisms of neuronal injury are considered inflammation, oxidation, nitric oxide scavenging, and

edema. Thrombin, an important mediator in blood clotting, may also participate in attracting inflammatory cells into the damaged area, and promote edema formation[40].

Neutrophils infiltrate the site of the hemorrhage within 4 to 5 hours after ICH, peaking at 3 days. In addition to producing reactive oxygen species, they release proinflammatory proteases, and thus affect the BBB permeability and promote damage to the neurons. Apoptosis of the leukocytes within 2 days after arriving at the site of the hemorrhage further activates microglia and macrophages[41].

Inflammation, red cell lysis, and thrombin production lead to BBB disruption, and thus edema formation[41]. In experimental ICH models, edema surrounding the hematoma has been found to develop in three steps. First, within as early as the first hour after ICH, clot retraction, hydrostatic pressure and plasma proteins cause edema, as serum moves from the hematoma to the surrounding tissue. The second stage associates with thrombin production via the clotting cascade, cytokines, matrix metalloproteinases, reactive oxygen species, and complement mediators, and the third stage with erythrocyte lysis and hemoglobin toxicity[41,42]. The first stage is known as ionic edema, and the second and third are characterized by vasogenic edema. The final stage is resolution of the edema[42]. Perihematomal volume has been shown to increase fastest during the first 2 days after ICH, and to peak toward the end of the second week[43], and the extent of the edema to correlate with ICH volume[44]. However, the correlation with edema has been proposed to associate especially with the surface of ICH, rather than volume itself, thus playing a relatively larger role in irregularly shaped and smaller hematomas[45]. Edema surrounding the ICH causes compression of the adjacent structures and may increase intracranial pressure (ICP), and thus lead to hydrocephalus, or brain herniation[44].

The hematoma dissolves within months. The microglia/macrophages recognize the erythrocytes and their degradation products by their surface receptors, such as CD163 and CD47. Haptoglobin (Hp), present in human plasma, binds to hemoglobin, forming a Hb-Hp complex recognized by CD163, expressed on monocyte-macrophage system, and thus leading to endocytosis of the complex. Hp and CD163 are upregulated by excessive Hb. Free heme

released from ferric Hb under oxidative conditions, is toxic to the tissues. Hemopexin (a heme scavenger protein) is able to bind to heme, and sequester it to inactive form, to be catabolized in liver. The heme-hemopexin complex can also be endocytosed and degraded by lysosomal activity by cells that express low-density lipoprotein receptor-related protein-1 (LPR1), which appears on the surface of various cells including macrophages, astrocytes, neurons, hepatocytes and vascular endothelial cells. These two pathways have been considered the most important endogenous scavenging pathways in clearance of the hematoma following ICH[39].

The different components of secondary brain injury after ICH serve as potential targets for drugs to mitigate the brain damage caused by ICH.

2.2 Classification

ICH is often classified by location as either lobar, nonlobar, infratentorial or mixed. Other classification by location is division to deep or lobar. Deep ICH comprises ICH stemming from basal ganglia, thalamus, internal capsule, cerebellum or brain stem[28]. The typical etiologies and risk factors differ between different locations[46]. However, the information on the actual bleeding source derived from the classification by location is limited[47].

SMASH-U is an ICH classification system developed in our center[14]. According to the classification, the ICHs are classified as Non-stroke (e.g. trauma); Stroke, non-ICH (e.g. ischemic stroke with hemorrhagic transformation); Structural lesion (structural vascular malformation at ICH site); Medication; Amyloid angiopathy (lobar, cortical or corticosubcortical hemorrhage in a patient 55 years of age or older); Systemic/other disease (e.g. liver cirrhosis); Hypertension, and Undetermined when the hematoma does not apply to any of the other classes.

H-ATOMIC, another classification of ICH, includes 7 categories: hypertension, cerebral amyloid angiopathy, tumor, oral anticoagulants, vascular malformation, infrequent causes and cryptogenic, and takes additionally into account the level of certainty of each category as possible, probable, and definite[48].

2.3 Different risk factors and etiologies

Hypertension, smoking, excessive alcohol consumption, decreased low-density lipoprotein cholesterol (LDL), low triglycerides, medication (including anticoagulants, antiplatelets, selective serotonin reuptake medication, and sympathomimetic drugs), old age, male sex, Asian ethnicity, CAA, cerebral microbleeds, and chronic kidney disease have been claimed risk factors for ICH[34,49]. However, the results between studies on risk factors have been partly conflicting. A systematic review that comprised of 14 case-control studies and 11 cohort studies stated age, male sex, hypertension, and high alcohol intake as risk factors for ICH[4]. In the INTERSTROKE study, a large international case-control study on risk factors of stroke with 3059 ICH cases, hypertension, regular physical activity, diet, waist-to-hip ratio, psychosocial factors, cardiac causes, and alcohol consumption were associated with ICH, whereas current smoking, diabetes, and apolipoproteins were not[5].

In a prospective cohort study of almost 40 000 women, smokers had a relative ICH risk of 2.15 (individuals smoking less than 15 cigarettes a day) and 2.67 (individuals smoking 15 or more cigarettes a day) compared to nonsmokers[50]. In a prospective cohort study of male physicians, the relative risk for ICH was 2.06 for participants smoking daily 20 cigarettes or more, compared to non-smokers[51].

The role of hypertension and usefulness of antihypertensive treatment is outlined by the PROGRESS trial, which demonstrated a 76% reduction of relative risk of ICH in individuals treated with antihypertensive medication, compared to placebo in a follow-up time of 5 years[52]. Inadequate blood pressure control has also been shown to increase risk for ICH recurrence[53]. In an Italian case-control study with 3173 ICH patients aged 55 years and older, and 3155 controls, heavy alcohol intake associated with the risk of deep ICH, but not with lobar ICH[54].

Of the anticoagulant agents, the newer direct oral anticoagulants (DOACs) have been proven as efficacious as warfarin in the prevention of ischemic stroke in patients with atrial fibrillation, but to harbor a smaller risk for major bleeding[55–58].

The role of statins and very low cholesterol levels as risk factors for ICH have been under debate during the past years. The SPARCL study with 4731

patients demonstrated a reduction of overall stroke incidence among TIA and ischemic stroke patients treated with high dose atorvastatin compared to placebo. However, there was a small increase in the incidence of ICH in the statin group[59]. In an analysis of 672 consecutive ICH patients, higher LDL-levels were associated with lower likelihood of hematoma expansion and decreased in-hospital mortality among ICH patients[60]. In a meta-analysis from 2012, there was no significant increase in ICH among statin users, and ICH risk was not associated with the achieved LDL levels or the degree of LDL reduction. Total stroke risk was reduced in the statin treatment group[61]. In a recent meta-analysis of 39 studies and almost 300 000 patients, lipid-lowering therapy was not significantly associated with increased ICH risk when primary and secondary prevention were combined[62]. In secondary prevention trials, lipid lowering was associated with an increased ICH risk with an odds ratio (OR) of 1.12 (95% CI 1.00-1.38). However, the estimated benefits in lowering the risk for ischemic stroke were evaluated to greatly exceed the risk for ICH[62]. Statins have even been considered possibly having neuroprotective effects in ICH by targeting secondary brain injury pathways in the surrounding brain tissue[63].

As ICH is not just one entity, but has different underlying vessel pathologies, the risk factors in those different underlying pathologies also differ. Martini et al. studied risk factors according to the location of ICH: APOE (apolipoprotein E) e2 or e4 genotype was associated with lobar ICH, whereas hypertension was associated specifically with nonlobar ICH[46].

Knowledge on the genetic contributors of ICH is still limited. Incidence of ICH differs between ethnicities[64]. A genetic association study with 2189 ICH cases and 4041 controls estimated heritability of 45% for ICH, 70% for the CAA-related ICH, and 35% for the hypertension-related ICH. Also in that study, APOE e2 or e4 genotype was shown to associate with CAA-related ICH[65]. A systematic review on risk genes for ICH including 64 articles, identified 38 genetic loci variously associated with risk of ICH, hematoma volume, and outcome. Only 8 of the studies had used genome-wide association studies (GWAS), the others were candidate gene studies[66]. Additionally, there are some monogenic or familial diseases caused by rare mutations, manifesting clinically as ICH, such as familial CAA, where usually

the APP (the beta-amyloid precursor protein gene) is mutated, causing ICH at a younger age[67].

2.3.1 ICH and coagulation

Factors that are involved in hemostasis markedly affect the prognosis of ICH patients[14]. Disorders of coagulation, including anticoagulation drugs, associate with larger hematomas, and promote ICH expansion, thus worsening the prognosis of the patients. Reduced platelet activity has also been found to associate with ICH growth and worse outcome[68].

In primary hemostasis, platelets adhere to endothelial proteins at the site of injury, and themselves, and form a platelet plug, which is followed by formation of an insoluble fibrin mesh that attaches into and around the platelet plug, created by the proteolytic coagulation cascade (secondary hemostasis). Additionally, the fibrinolysis pathway and downregulation of the cascade are essential, preventing excess thrombus formation[69,70].

The damaged vessel wall – as in the context of ICH - lets platelets adhere to components of the extracellular matrix by their surface receptors, which causes them to activate, thus beginning the cascade of primary hemostasis. Activated platelets release agonists, which lead to activation of nearby thrombocytes. This complex cascade leads to adhesion and aggregation of platelets, and plug formation[70]. Also calcium plays an important role in primary hemostasis. Various platelet activation agonists (e.g. subendothelial collagen and adenosine diphosphate (ADP)), and thrombin cause a rise of intracellular Ca^{2+} as a result of the activated signaling cascades. The rise of cytosolic calcium helps in further activation of the platelets and clot formation[15,16].

Secondary hemostasis leads to cleavage of soluble fibrinogen to insoluble fibrin by thrombin, a result of a cascade of activated serine proteases. In healthy blood vessels, the cascade is inhibited. The secondary hemostasis begins in two separate, but intertwined pathways, termed intrinsic and extrinsic pathways. When blood gets in contact with exposed extravascular tissues rich in tissue factor (such as fibroblasts), a complex of tissue factor and factor VIIa leads to activation of factors X and IX, and finally, Xa, in the presence of its cofactor Va, activates prothrombin to generate thrombin[70]. Calcium also has an important role in this

extracellular coagulation cascade, and activates various coagulation factors to their active forms[17].

Thrombin acts in many important ways in the coagulation cascade. In addition to cleaving fibrinogen to generate insoluble fibrin, it activates platelets via cleavage of PAR1 and PAR4, activates factor IX, which then activates factor XI, and activates cofactors VIII and V. The cascades work together, forming positive feedback loops, and thus amplifying the reactions[70].

Contributors of primary and secondary hemostasis are depicted in Figures 3 and 4.

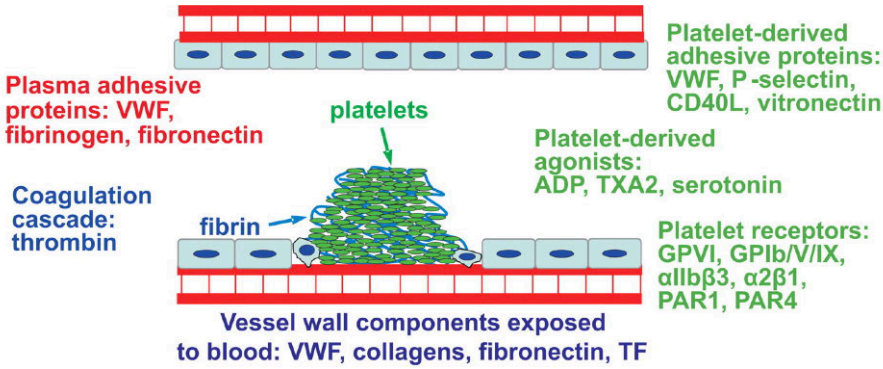

Figure 3. Primary hemostasis; the platelet response. Platelet aggregation at the site of injury is mediated by platelet receptors, platelet-derived agonists, platelet-derived adhesive proteins, and plasma-derived adhesive proteins. Fibrin deposition around the resulting platelet plug is generated by the coagulation cascade. ADP = adenosine diphosphate; TXA2 = thromboxane A2; VWF = von Willebrand factor. Reprinted from Gale, A. J. Continuing education course #2: current understanding of hemostasis. Toxicol Pathol **39**, 273-280 (2011) with permission from SAGE Publications.

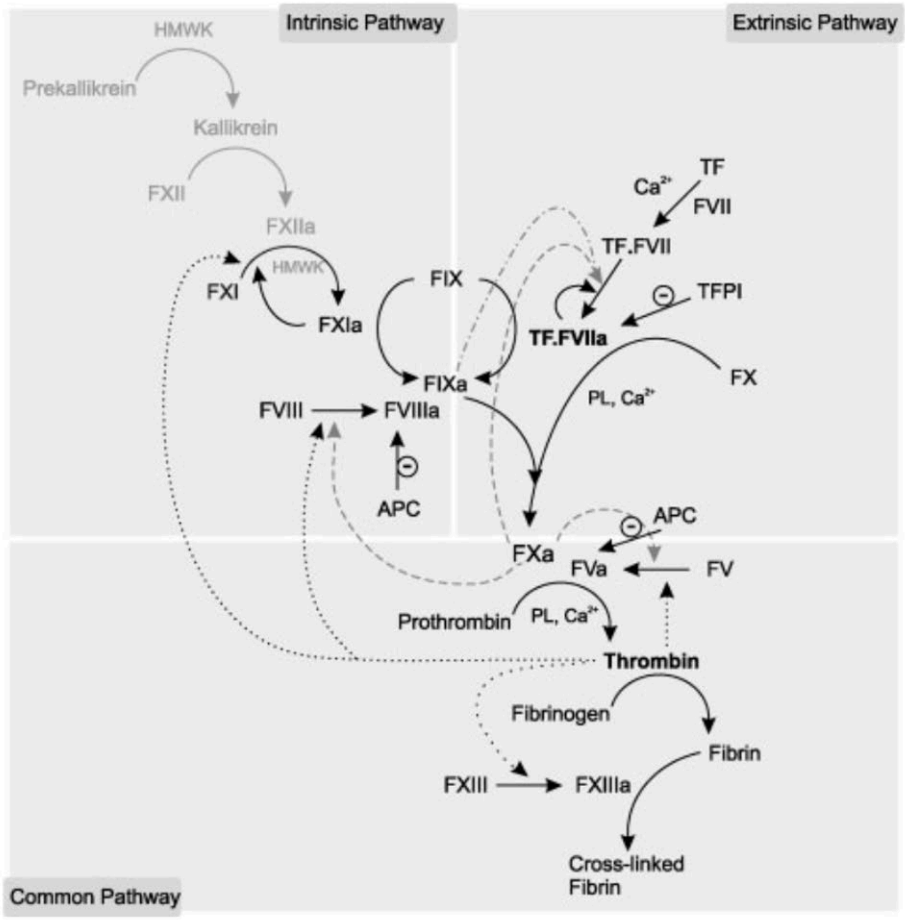

Figure 4. Schematic overview of the blood coagulation cascade. The model is divided in the intrinsic, extrinsic, and common pathway. F###: blood coagulation factors denoted in Roman numerals. Active forms are denoted by a small 'a' added to the Roman number. TF, tissue factor: PL, phospholipid; HMWK, high molecular weight kininogen. Positive feedback loops by thrombin (dotted lines), FIXa (dashed dotted line), and FXa (dashed line) are indicated in grey. O indicates inhibition by activated protein C (APC) and tissue factor pathway inhibitor. Reproduced from Spronk H, Govers-Riemslag JW, ten Cate H. The blood coagulation system as a molecular machine. Bioessays. 2003;25:1220-1228 with permission from Wiley.

2.3.2 White matter lesions

The two most common types of small vessel pathology behind spontaneous ICH – CAA and HA – have characteristic markers in neuroimaging, such as cerebral microbleeds (CMB), white matter hyperintensities (WMH), and enlarged perivascular spaces[32]. Other features related to cerebral small

vessel disease (SVD) are small subcortical infarcts, lacunes, and brain atrophy[71].

WMH) – also known as white matter lesions (WML) or leukoaraiosis – imply to the bilateral, and either patchy or confluent abnormalities seen in the white matter of the brain in neuroimaging, either as areas of hypodensity in CT or hyperintensity in T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI sequences[72–74].

As discussed earlier, CAA typically associates with lobar macro- and microbleeds, whereas HA with deep bleeds[75]. Post mortem studies have shown that the histopathology behind WML changes is heterogeneous, and the exact pathogenesis of the changes is not known. Damage to the tissue may include myelin and axonal loss, astrocytic reactions, microglial responses, lipohyalinosis, arteriosclerosis, vessel wall leakage, and collagen deposition in venular walls, presumably caused by ischemia/hypoxia, hypoperfusion, leakage in blood-brain barrier, inflammation, degeneration, and amyloid angiopathy[76].

Charidimou et al. discovered that the WMH were common in both CAA and HA. The distribution patterns differed between the two etiologies of SVD. Multiple punctate subcortical FLAIR hyperintensities (multiple spots) were more common in CAA-assumed pathology, whereas WMH around the basal ganglia were more typical in HA[32].

WMH changes associate with cognitive decline, dementia, and risk for both ischemic and hemorrhagic stroke[74,77]. Additionally, they have been associated with mood, gait, and urinary problems[33]. The severity of WMH is known to associate with worse outcome after stroke. After ischemic stroke, WMH changes are associated with an increased risk for dementia, functional impairment, stroke recurrence, and mortality[73]. After ICH, leukoaraiosis has been demonstrated to associate with death and worse functional outcome, however, there is some controversy between studies regarding functional outcome, but it is noteworthy that the follow-up times are quite short, ranging from 28 to 90 days[78,79]. Accordingly, the possible associations between ICH volume and growth, and the degree of WMH changes have been controversial between studies[80–83].

WMH can be seen as a rim of periventricular hyperintensity, periventricular hyperintensity extending into the deep white matter, or deep

WMH separated from periventricular signal changes in brain MRI, and as hypointensity in brain CT[84]. The WMH can be graded in brain MRI or CT, and different grading scales have been developed. The Fazekas scale is widely used to grade the extent of WMH in brain MRI imaging. Fazekas graded the periventricular hyperintensity (PVH) and deep white matter hyperintense signals (DWMH) separately. PVH was graded as 0 = absence, 1 = "caps" or pencil-thin lining, 2 = smooth "halo", 3 = irregular PVH extending into the deep white matter. DWMH was graded as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent areas[85]. FLAIR or T2 sequences are best for analyzing WMH in MRI[86]. MRI is considered superior to CT in detecting small WML, however, in detecting large lesions, it performs equally[84].

There are a number of conditions that may mimic the WMH changes of vascular origin in MRI, including multiple sclerosis and inflammatory causes. Patterns of white matter disease, patient's age, history and symptoms should be considered when evaluating the changes[86].

There are several WML grading classifications in CT images. Van Swieten classification takes into account 3 different planes (through the choroid plexus of the posterior horns, through the sella media, and through the centrum semiovale). The WML severity is scored from 0 to 2, and anterior and posterior parts are graded individually, severity being scored on the more affected side. The score yields to an overall value of 0-4[87]. Modified van Swieten score yields a total score of 0-8, as right and left sides are evaluated separately[88]. The Blennow score takes into account the extension (scoring 0-3) and intensity (scoring 0-3) of the WML[89].

Cortical microbleeds (CMB) are small foci of chronic blood products within the brain tissue. They are detected in MRI imaging, using special MRI sequences (such as T2*) that are sensitive in detecting the hemosiderin deposits, showing CMB as black or hypointense lesions, or signal voids[75].

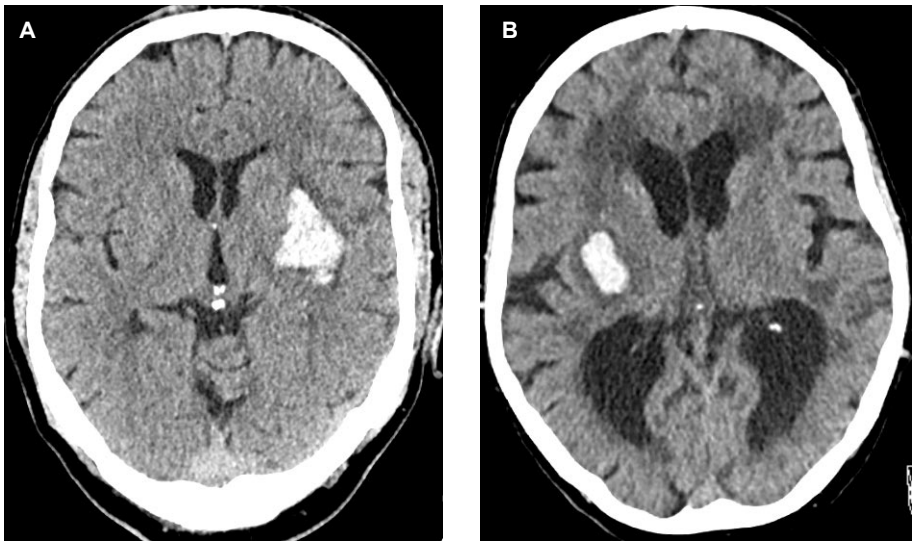

Figure 5. Examples of brain CT scans from patients with ICH with **A)** minor WML changes (modified van Swieten 2), and **B)** extensive WML changes (modified van Swieten 8).

2.4 Triggering factors

Case-crossover design – closely related to case-control design - can be used to study temporal association between a certain event and its possible triggering factors. In this type of study, each person serves as her/his own control. Control periods can be multiple, or single, e.g. the same time point on the previous day. The possible studied triggering factor should be transient, and the event itself have an abrupt onset[90].

In an observational study on 848 ICH patients, in 30% of the patients the symptoms began at rest, in 50% during light exertion, and in 20% during moderate to vigorous exertion. In 27% of the patients, the researchers identified a potential triggering event, such as strenuous exercise or sudden transition from the supine to the erect position on awakening. However, there was no comparison with other time points or controls. The study also included different etiologies, including brain tumors and vascular malformations[91].

In addition to chronic risk factors, preceding triggering events causing a temporal predisposition to stroke have been identified. In a study on SAH patients, drinking coffee or cola, vigorous physical exercise, nose blowing, straining for defecation, being startled, anger, and sexual intercourse before the rupture of an aneurysm occurred with increased relative risk compared to

the patients' usual frequency of exposure, and were considered as trigger factors to the event. The effect of the association was considered to be through the events leading to rapid rise in blood pressure, and thus predisposing to SAH[6,92]. In another cohort using case-crossover design, during the 2-hours following moderate to extreme physical exertion, the risk for aneurysm rupture was increased to 2.7-fold[93].

Sexual activity, exertion, coughing, sneezing, and straining at stool have been found to associate with the timing of reversible cerebral vasoconstriction syndrome (RCVS)[94]. Among ischemic stroke patients, moderate to vigorous physical activity increased the risk of stroke to 2.3 fold within 1 hour of the physical activity[7], whereas in another study, negative emotions were the most common trigger during the 2-hour period before stroke onset (14.5% of the 200 patients). Also anger and sudden posture change due to startling associated with the onset time, whereas temperature change, positive emotions, heavy eating, and physical exercise did not[95].

Many of the studied triggers are events that cause a rise in blood pressure[96–98].

Other mechanisms considered in the setting of cardiovascular events and triggering factors have been their physiological effect on blood pressure, heart rate, and myocardial oxygen demand, which are at least in part mediated by catecholamine secretion[99,100].

Data on triggering factors of ICH are virtually lacking. As the mechanisms of ICH and ischemic stroke differ, ICH caused by a rupture of a brain vessel, and ischemic stroke by an occlusion, the possible triggering factors and their mechanisms are likely different.

2.5 Diagnosis and patient evaluation

The symptoms of ICH depend on the location and size of the hemorrhage. Typical clinical presentation is an abrupt onset of neurological deficit[101] such as left- or right-sided hemiparesis. Hemorrhagic and ischemic stroke cannot be differentiated by clinical presentation. However, decreased level of consciousness, vomiting, headache, seizures, and very high blood pressure early in the course of the disease might imply to ICH[101]. Supratentorial hemorrhages involving the putamen, caudate, and thalamus present with contralateral sensory-motor deficits. The severity of the deficit associates with

involvement of the internal capsule. Aphasia, neglect, and hemianopia indicate dysfunction of the higher-level cortical structures. Clinical signs of brainstem dysfunction in the setting of infratentorial hemorrhages include abnormalities of gaze, cranial nerve abnormalities, and contralateral motor deficits. Ataxia, nystagmus, and dysmetria may be present in cerebellar hemorrhages[23].

The mass effect caused by the bleeding in the brain parenchyma causes damage by compressing local structures, and leading to increased ICP[38,101]. Increase of global ICP can cause herniation, and cause compression of the arteries, leading to secondary ischemia[38]. In posterior fossa hemorrhages the local compression can lead to obstruction of the aqueduct, leading to obstructive hydrocephalus[38].

When suspected by symptoms, the diagnosis of ICH relies on rapid neuroimaging with either CT or MRI[3,101].

CT is widely available, and fast to perform. In addition to ICH detection, it provides information on possible intraventricular extension, edema surrounding the hematoma, and midline shift with possible herniation or brainstem compression[101]. CTA can be used to detect vascular abnormalities[101] such as arteriovenous malformations or aneurysms. A spot sign, i.e. enhancing focus or foci within the hematoma in the CTA source images, is a predictor of hematoma expansion[102], and worse prognosis[103].

Size of the hematoma can be calculated in the CT images using the ABC/2 method, where A is the largest hemorrhage diameter, B the diameter at 90° to A, and C the approximate number of CT slices with hemorrhage, multiplied by slice thickness[104]. Alternatively, computer-based automated software such as Analyze or Osirix can be used for hematoma volume calculation, however, the volumes by the semiautomated measurement are a little smaller[105]. As ABC/2 assumes ICH as an ellipse, in irregular shaped hematomas, ABC/2.4 formula has been proposed[106].

With suspicion of vascular malformations, digital subtraction angiography (DSA) remains the gold standard, with sensitivity and specificity exceeding 99% in detecting vascular abnormalities. However, as an invasive method not so readily available, it is largely replaced by CTA and magnetic resonance angiography (MRA)[107].

MRI is equivalent to non-contrast CT in the diagnosis of ICH[101], however, it is not as readily available, requires a longer in-bore time, and is more sensitive to movement, which can be a problem with patients having

altered consciousness or restlessness. MRI can aid in detecting underlying causes such as tumor or hemorrhagic transformation of ischemic stroke[28,101]. MRI performs better in detecting chronic hemorrhage[108].

Suspected stroke, including ICH patients, requires rapid transfer to hospital that is prepared to treat stroke patients, and perform rapid neuroimaging[3]. Level of consciousness (GCS), and baseline severity score should be evaluated. NIHSS, commonly used in the evaluation of acute ischemic stroke, may be useful also in ICH, though a decreased level of consciousness more commonly present in ICH patients may lessen its usefulness[3]. GCS is commonly used for evaluating ICH patients in the acute phase, informing about possible deteriorations.

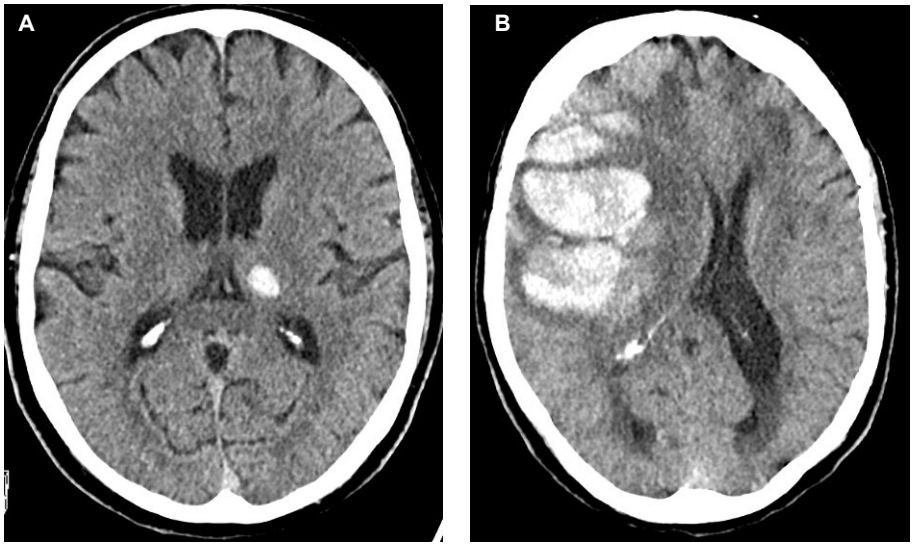

Figure 6. Examples of **A)** a small deep left-sided hemispheric ICH, and **B)** a large right-sided lobar ICH.

2.6 Treatment

2.6.1 Prevention of hematoma growth and rebleeding

There are few proven effective acute or preventive treatments for ICH[31]. Most ICH patients have elevated blood pressure (BP) in the acute stage[101]. Elevated BP has been shown to correlate with the risk of hematoma expansion and poor outcome[109]. Therefore, reducing arterial blood pressure in the

hyperacute phase was suggested and tested in randomized controlled trials. There is, however, controversy in the targeted blood pressure. The INTERACT-2 trial, randomizing almost 2800 patients to target systolic groups of BP < 140 or < 180 mmHg, found no difference in death or severe disability at 90 days, but patients in the lower blood pressure target group had better functional outcomes[110]. The ATACH-2 study then randomized 1000 patients out of the planned 1280 to the same blood pressure targets. The study was terminated early after an interim analysis showing no difference in death or severe disability or outcome by mRS at 90 days, but showed increase in renal adverse events in the intensively treated group[111]. In ATACH-2, the BP lowering was fast and marked; average systolic BP over the 24 hours being 120-130 mmHg in ATACH-2, and 135-145 mmHg in INTERACT-2. The studies did not find reduction in hematoma expansion among the more actively treated groups. Thus, the optimal BP target is still unknown. The American Heart Association/American Stroke Association (AHA/ASA) guideline from 2015 comments systolic BP target < 140 mmHg as being safe[3], and the European Stroke Organisation (ESO) guideline from 2014 states the same target as safe, and possibly superior to the target of < 180 mmHg[112].

Complete blood count, electrolytes, liver tests, creatinine, glucose, and coagulation studies should be obtained[101], and severe coagulation factor deficiencies or severe thrombocytopenia should receive appropriate replacements[3]. If the patient is using oral anticoagulants (vitamin K antagonist i.e. warfarin, or DOACs), their effect should be reversed. Prothrombin concentrates (PCC) along with vitamin K are suggested for the reversal of vitamin K antagonists. Antagonists for DOACs have been developed[113]. Recombinant activated factor VIIa (rFVIIa), used to treat hemophilia patients and congenital FVII deficiency, can normalize international normalized ratio (INR) rapidly, but does not substitute all vitamin K-dependent factors, and is thus not recommended to be used routinely in the setting of vitamin K antagonist (VKA) related ICH[3]. rFVIIa has also been tested in spot-sign positive (indicating on-going bleeding) non-anticoagulant related ICH patients. However, it did not improve radiological or clinical outcomes[114]. PCC have some reversal effect on DOACs, and they are recommended to reverse the Xa inhibitor group of DOACs in major bleeding such as ICH, if a specific antidote is not available[113,115]. Protamine sulfate is recommended for patients with ICH

occurring under heparin infusion or low molecular weight heparin (LMWH)[3,116]. In a randomized controlled multicenter trial of ICH patients having been using antiplatelet therapy before their ICH, where 97 patients received platelet transfusion, and 93 patients standard care, platelet transfusion increased the odds for death and disability[117], and cannot be recommended in treatment of ICH. Tranexamic acid is used to reduce post-operative and traumatic bleeding. This far, randomized controlled ICH-trials have not managed to show efficacy in improving outcome after non-traumatic ICH, although observational studies have signaled smaller hematoma growth with tranexamic acid. There are still ongoing randomized controlled studies on testing the efficacy of tranexamic acid on ICH patients[118,119].

2.6.2 General management of the patient

Hyperglycemia and hypoglycemia should be avoided, and seizures treated with antiepileptic agents[3]. High blood glucose levels within 72 hours from admission have been shown to independently correlate with worse functional outcome[120]. Temperature management seems reasonable, but the target is unclear. Intensive care or stroke units are recommended for initial treatment and monitoring of acute ICH patients. The patients should be screened for dysphagia, and intermittent pneumatic compression is recommended for prevention of venous thromboembolism[3]. In a meta-analysis of 1000 ICH patients, early (from 1 to 6 days after admission) enoxaparin/heparin treatment was associated with a reduction of pulmonary embolism rates, and a non-significant reduction in mortality. No association was found with deep venous thrombosis[121]. AHA/ASA guidelines recommend to consider low-dose subcutaneous LMWH treatment after day 1 to 4 to prevent venous thromboembolism, after cessation of bleeding has been documented[3]. In SAH patients, a randomized single-center study comparing enoxaparine to placebo, no beneficial effect on neurological outcome was seen in patients receiving enoxaparine, but the rate of intracranial bleeding was higher in the patients treated with enoxaparine[122].

2.6.3 Surgical treatment and combating the mass effect

There are ongoing trials on surgical treatment for ICH. At the moment, the role of surgery is not clear[31], and the results whether surgery is beneficial or not,

differ between studies[115]. A meta-analysis of 4 observational ICH studies with 6580 patients, of which 578 patients with cerebellar hemorrhage, surgical hematoma evacuation of a cerebellar ICH was not associated with better functional outcome, but was associated with better survival, compared to conservative treatment. Among patients with hematoma size of 12mL or smaller, it was harmful[123]. A meta-analysis of 3 studies analyzing the efficacy of neuroendoscopic surgery versus craniotomy in patients with hypertensive supratentorial ICH showed that neuroendoscopic surgery was associated with decreased mortality and tendency toward lower complication rate compared to craniotomy[124]. As large randomized trials failed to show beneficial effect of open surgical evacuation in supratentorial ICH[125,126], MISTIE III trial tested the efficacy of minimally invasive catheter evacuation followed by thrombolysis for improving the outcome of ICH patients with supratentorial hemorrhages. However, the trial did not improve the proportion of patients with good outcome[127]. A randomized trial comparing medical management and surgery among 119 patients, of which 72 (60.5%) received surgery, and the rest the best medical treatment, surgery was associated with better survival, but not with better functional outcome[128]. Hemicraniectomy is another surgical approach targeting to reduce the mass effect of the hemorrhage, and there is an ongoing randomized multicenter study (SWITCH) with the aim of testing the usefulness of the operation[115].

IVH can cause blockage of the cerebrospinal fluid (CSF) circulation, and lead to hydrocephalus, which may necessitate treatment with an external ventricular drain, possibly accompanied with clot lysis by intraventricular rt-PA injection[115].

The most common causes for elevated ICP in the context of ICH are the mass effect caused by the hematoma and IVH. Guidelines recommend ICP monitoring with an intraparenchymal or ventricular device in patients with coma, significant IVH and hydrocephalus, and evidence of transtentorial herniation, targeting cerebral perfusion pressure of 50-70 mmHg. Conservative measures to reduce the ICP are elevation of the head to 30^{0}, adequate sedation, and avoiding hyponatremia. Hyperosmolar therapy (mannitol or hypertonic saline) may be considered when there is a risk of transtentorial herniation[3,101].

2.6.4 Treatment for the secondary changes

Extravascular blood and its degradation products trigger processes that lead to further brain injury. These elements include calcium released from the cells, thrombin-mediated activation of protease-activated receptors, fibrinogen, heme and microglia activating transcription factors and proinflammatory cytokines, the cascades leading to entry of systemic immune cells such as neutrophils, macrophages and lymphocytes[115]. At present, there are studies assessing usefulness of substances that would reduce the toxic effects of hemoglobin (chelating agents), hemoglobin scavenging agents (such as haptoglobin), and anti-inflammatory agents[31]. A recently published multicenter futility-design randomized placebo-controlled phase 2 trial on iron chelator deferoxamine mesylate in ICH patients concluded that deferoxamine mesylate was safe, but treatment was not sufficiently promising to support phase 3 trial[129]. Regarding secondary injury, the polarization of microglia to the pro-inflammatory type M1 and anti-inflammatory M2 types has been considered essential[130]. No proven therapy to reduce edema and improve patient's outcome exists yet[30].

2.7 Outcome, mortality and recovery

Approximately 40% of ICH patients die within the first months after ICH, and many of the survivors have disabilities[2]. Compared to ischemic stroke, ICH patients have been shown to have less favorable outcome and more severe disabilities[130]. Older age, lower GCS, higher NIHSS, infratentorial location, ICH and IVH volumes and their growth, edema, hyperglycemia, hydrocephalus, herniation, anticoagulation, and multiple hemorrhages are predictors of mortality after ICH[8,9,10,12,13]. Higher NIHSS predicts worse functional outcome[131]. Functional dependence is shown to associate with age, lower GCS, larger baseline ICH volume, hematoma expansion, and IVH[132].

There are altogether 19 published scores to predict prognosis after ICH (mortality and/or functional outcome)[133]. The ICH Score is considered most widely used and best validated[3]. The ICH Score takes into account five characteristics: GCS, ICH volume with a cut point of 30 mL, age with the cut point of 80 years, presence of IVH, and infratentorial origin of ICH, infratentorial location having a worse prognosis. Total score ranges from 0 to 6 points. The ICH Score can be used to predict 30-day mortality, each increase

in points associating with progressive increase in mortality[8]. A single-center study comparing all those scores found that ICH-FOS, taking into account age, NIHSS, GCS, ICH volume, intraventricular extension, glucose and ICH location, performed only slightly better than admission NIHSS in predicting 3-month and 12-month mortality[133].

A systematic review and meta-analysis of 122 longitudinal population-based cohort studies that reported long-term (>30 days) outcome after spontaneous ICH, found 1-year survival to be 46% and 5-year survival 29%. The recurrence rate for survivors ranged between 1.3-7.4% per year (average follow-up period was 1-7 years). The four studies that reported the risks for recurrent ICH and ischemic stroke after ICH found the risks of ICH and ischemic stroke similar[134]. In a Danish registry study of 15 270 ICH patients between 1996 and 2011, ICH recurrence rate was observed as 8.9% within one year and 13.7% within 5 years. Surgical treatment and renal insufficiency were associated with increased recurrence rate, whereas antihypertensive medication associated with decreased recurrence rate[135]. In a cohort study identifying almost 6000 ICH patients in a population of more than 1.7 million U.S. Medicare beneficiaries, the 1-year cumulative incidence of arterial ischemic events (including a composite of ischemic stroke and myocardial infarction) was 5.7% for ICH patients and 1.8% for patients without ICH, and remained high with a hazard ratio of 6.7 after adjusting for confounders. In their secondary analysis the risk for ischemic stroke was higher after ICH during a follow-up time of 6 months, but the risk for myocardial infarction was not[136]. In a French cohort of 310 ICH patients alive at 30 days after ICH, 20.0% had a major vascular event during a follow-up period of 5 years. Ischemic events (including intra- and extracerebral events) were more frequent than hemorrhagic events, but there was a difference according to ICH location – deep ICH associated with future ischemic events (ischemic events being 6 times higher compared to hemorrhagic events) and lobar ICH with future hemorrhagic events[137].

When evaluating long-term outcome, in addition to mortality and functional outcome, patient's self-assessed quality of life, possible cognitive impairment, psychiatric disorders, epileptic seizures, ICH recurrence and thromboembolic events should be considered[132].

Most studies use the 7-stage modified Rankin Scale (mRS) as a measure of functional outcome, a favorable outcome usually defined as mRS ≤ 2 or ≤3[132]. There are few population-based studies on functional outcome after ICH. A systematic review on outcome after ICH reported 32.8-42.4% of all patients (53.7-83.7% of survivors) at 6 months, and 16.7-24.6% of patients (53.8-57.1% of survivors) at 1 year to be independent (mRS ≤ 2)[134]. The patients are at risk of ICH recurrence as well as other vascular events[137], and new events are likely to affect the functional capacity of the patients.

Obviously, mortality and functional outcome have many predictors in common[132]. In a cohort of 3255 Chinese patients, predictors for poor functional outcome (mRS ≥ 3) were older age, admission NIHSS and GCS, blood glucose, infratentorial location, ICH volume, and intraventricular extension of the hemorrhage[138]. Lower scores measured by Barthel Index (BI), indicating greater functional dependence had an association with older age, lower GCS, baseline ICH volume, change of the ICH volume at 24 hours, and IVH[139]. Patients with lobar hemorrhages have been observed to have a better functional outcome in comparison to deep/non-lobar hemorrhages, whereas no difference in relation to hemorrhage laterality was noted[140]. In a study of long-term functional outcome of 131 young (< 50 years old) ICH survivors, 25% of the patients had poor functional outcome (mRS 3-5). Almost half of the 131 patients (42.0 %) reported some level of one-sided motor dysfunction, and 39.7% one-sided sensory dysfunction, 20.6% difficulties in understanding or producing speech, 27.5% spasticity, 16.0% visual field impairment, and 10.7% diplopia[141].

Studies reporting return to work after ICH are scarce[132]. A Danish register study on returning to work after stroke reported that 43.0% of 2272 ICH survivors were gainfully occupied two years after ICH occurrence. After ischemic stroke, returning to work was more likely[142]. A Japanese study reported only 12.6% of 119 ICH survivors having returned fully to work at 1 year after ICH[143].

In a prospective study of 173 ICH patients, the mRS scores showed significant improvement between discharge and 3 months after ICH, but did not differ between follow-up times at 6 and 12 months after ICH, compared to 3 months. However, the BI kept improving up to the end of the follow-up time of 12 months[144].

Cognitive impairment in ICH patients have been thought to have multiple mechanisms. It can be related to the underlying pathology causing ICH, arise as a direct consequence to the brain lesion, and be associated with psychiatric manifestations and other comorbidities[132]. In different cohorts of ICH patients, cognitive impairment prior to ICH has been fairly frequent. A French study on 417 ICH patients reported 29% of the patients cognitively impaired prior to their ICH, 16% fulfilling criteria for dementia[145]. Another study reported 24.7% of the 166 patients cognitively impaired before ICH[146]. CAA and lobar ICH location associated with cognitive impairment in both studies. A study investigating the incidence of and risk factors for early and delayed dementia after ICH identified the incidence of dementia to be 19% 6 months after ICH and 5.8% per year afterwards in a cohort of 738 patients without pre-ICH dementia. Risk factors for early dementia were larger hematoma size and lobar location, whereas lower educational level, incident mood symptoms, increasing white matter disease severity, increasing lobar CMB burden and the APOE ε4 variant associated with delayed dementia. Only older age was a risk factor for both early and delayed dementia[147].

Seizures in the acute setting (within 7 days of stroke onset) are more prevalent after ICH compared to ischemic stroke[148]. Different studies demonstrated around one in seven to ten of ICH patients to have seizures in the acute setting[148–150]. In a Finnish cohort of 615 ICH patients surviving longer than 3 months, 13.5% developed post-stroke epilepsy. New-onset epilepsy had the highest incidence during the first year after ICH. Onset of epilepsy associated with subcortical ICH location and early seizures[151].

2.8 Secondary prevention

After ischemic stroke, there are several means of secondary prevention such as anticoagulant therapy, and statins[152,153]. The most important etiologic factor to control after ICH is hypertension, however, no ICH specific secondary preventive medications exist[115].

A large proportion of ICH patients are using, or have an indication to antiplatelet or anticoagulants drugs[115]. On top of recurrent ICH, ICH survivors also have a risk for thrombotic events, such as ischemic stroke and myocardial infarction, which raises concerns for the benefits and risks of secondary prevention, such as antiplatelet therapy[134,154]. Especially

patients with deep ICH have been noted to have a high risk for future ischemic events[137], as well as older patients[136]. There are currently no randomized controlled trials on resumption of OAC after ICH, however, several large observational studies and meta-analyses exist[155,156]. A meta-analysis of ICH patients with atrial fibrillation (AF) showed that the rate of ischemic stroke exceeded the rate of recurrent ICH, and anticoagulation reduced the rate of thromboembolic complications and mortality, without causing an increase in recurrent ICH rates[157]. In a study observing patients with or without resumption of antiplatelets after mild or moderate ICH, there was no significant difference in functional outcome or health-related quality of life at 90 days[158]. In light of current evidence, OAC resumption is considered beneficial in decreasing thromboembolic complications and mortality. The resumption may be safer in non-lobar than lobar ICH, and should be combined with strict blood pressure control, and decided individually weighing potential risks and benefits[155].

A meta-analysis of 8 studies with 6259 patients demonstrated an overrepresentation of cerebellar ICH and IVH among OAC-treated ICH patients, and the authors conclude, that the mechanisms behind the underlying arteriopathy, pathophysiology, and bleeding pattern of OAC-related ICH should be investigated more thoroughly[159].

2.9 Measuring quality of life

Defining quality of life (QoL) as a comparable measure is not easy. QoL has been defined for example as of need satisfaction, health-related subjective experiences, or psychosocial and physical well-being. As measuring QoL is complex, a multidimensional approach is essential. According to a consensus, at least physical, functional, psychological, and social health dimensions should be included in QoL assessment[160].

There are several scales to measure quality of life; few of them are stroke-specific[160,161]. EQ-5D-5L[162] and 15D questionnaires are developed to measure HRQoL, and they have been validated, and used in cohorts with stroke patients[163–167]. EQ-5D-5L is developed by EuroQol Group (www.euroqol.org), and it defines health in terms of 5 dimensions: Mobility, Self- Care, Usual Activities, Pain/Discomfort, and Anxiety/ Depression, each of them with five response levels (no problems, slight, moderate, severe, and

extreme problems). The EQ-5D-5L utility score is an index, which combines those five dimensions into one score, which is calculated using population-based preference weights. 1 represents perfect health, 0 death, and a negative value health states is considered worse than death.

15D is a 15-dimension (Mobility, Vision, Hearing, Breathing, Sleeping, Eating, Speech, Excretion, Usual activities, Mental function, Discomfort and symptoms, Depression, Distress, Vitality, Sex) health state descriptive questionnaire with five levels for each question, 5 being the worst and 1 the best possible. 15D results in a single index (15D score) on a 0-1 scale, representing the overall HRQoL. The index is calculated using a set of population-based utility weights[166].

2.10 Quality of life and depression after ICH

Several studies assessed HRQoL after stroke[168–170], but few focused on ICH patients. Also stroke patients with no or limited disabilities can experience reduced QoL[160,171,172]. Stroke patients may have difficulties in social relations and mental functions, and experience poor quality of life, even when they recover fully physically[173]. A Singaporean study found that stroke survivors had lower HRQoL than the general population even before the stroke, and as expected the HRQoL further decreased after stroke[174].

Age, length of hospital stay, and motor function at discharge have been shown to predict HRQoL at six months after stroke[168]. In another study, the strongest association with poor HRQoL three months after ICH was baseline NIHSS $\geq$ 14 vs. < 14[21]. Additionally, older age, use of antithrombotics, larger and deep ICH, IVH, early worsening of the neurological deficit, and completion of the questionnaire by proxy responder associated with worse HRQoL[22]. After adjustment for disability and other relevant clinical factors, patient-reported outcomes (including physical functioning, satisfaction with social roles, pain interference, fatigue, anxiety, and sleep disturbance) have been reported to be similar between different subtypes of stroke (ischemic stroke, ICH, and SAH)[175].

Stroke and depression have a two-sided relation: risk of depression is increased after stroke, and on the other hand, depression is a risk factor for stroke[176]. Depression after ICH has been demonstrated to have a negative effect on outcome unrelated to the severity of the initial symptoms[177].

Psychiatric symptoms after ICH are less studied than after ischemic stroke[132]. The most prevalent psychiatric manifestation in ICH-survivors able to communicate was anxiety (prevalence 22% at three months, and 40% in a different cohort with median follow-up of 10 years)[134,178]. In different studies, the prevalence of depression has been found to be approximately a fifth of the ICH-survivors, ranging between 20.1% at three months[179], 15% at one year[177], and 23.1% at a median follow-up of 10 years[178].

3 Aims of the study

We aimed to analyze factors in a population-based cohort of ICH patients, that have been less studied, and gained less attention in earlier studies, taking into consideration novel factors such as feelings of depression and fatigue prior to the index ICH. We also wanted to find out whether triggering factors predisposing to the event exist in ICH. As results between earlier studies on the association between hypocalcemia and ICH volume are somewhat conflicting, we wanted to examine the effect of hypocalcemia in ICH volume and mortality in a large consecutive cohort of non-traumatic ICH patients. In addition to traditional prognostic measures, we attempted to assess quality of life and depression after ICH. We further determined how occipital location, the rarest single-lobe location, affects the outcome of the patients.

4 Patients and methods

The study was conducted at the Helsinki University Hospital, which is an academic teaching hospital and the only neurological emergency department with 24/7 service in Southern Finland, with a catchment area of 1.5 million inhabitants.

4.1 Publications I, II, and IV

In publications I, II and IV, the patient cohort is a part of the Helsinki Intracerebral Hemorrhage Study-2 (HICHS-2), a study focusing on genetic and environmental risk factors for ICH. The study began in 2014, and is still ongoing. However, the substudy that included the more extensive interview, questionnaires, and follow-up of the patients was terminated 31-DEC-2016.

We aimed to recruit all consecutive patients treated in our hospital, presenting with possible spontaneous intracerebral hemorrhage immediately after first imaging. Hemorrhages, which related clearly to tumors, trauma, ischemic stroke, vascular malformations, or other structural abnormalities were excluded, and if one of those would be likely, further imaging was awaited before recruiting the patient. If later studies disclosed a tumor, trauma, ischemic stroke, vascular malformations, and other structural abnormalities behind the ICH, a recruited patient was subsequently excluded from the analyses.

To participate, the patient had to give an informed signed consent. If the patient was able to give an informed consent but could not write due to for example dominant hand paresis, the consent could be signed by a witness, who was not related to the study. If the patient was not able to express his/her opinion on participation, the consent could be given by his/her proxy.

The patients were interviewed using structured questionnaires, and additional questionnaires were given upon recruitment. The interview included questions on potential trigger factors, which were actions causing Valsalva (lifting an object weighing over 20 kg, having to strain when defecating/urinating, vomiting, coughing, sneezing, squatting for a long period of time), abrupt change in position, heavy physical exertion, a heavy meal, a sudden change in temperature, exposure to a traffic jam, and sexual activity. The questionnaires included questions on lifestyle and possible risk factors

such as medical history, social matters, profession, feelings of depression, smoking, and alcohol consumption before ICH. If the questionnaire was not returned during the hospital stay period, it was sent to the patient's home address. Medical history was obtained using a combination of questionnaires and medical records. The severity of the symptoms was graded by using NIHSS and GCS scores on admission. The size of the hematoma was calculated by the ABC/2 method, where A, B and C are the largest perpendicular measures of the hematoma on CT images. The hematomas were classified using the etiologic SMASH-U classification[14].

The patients were followed-up at three months and at one year after ICH. At that time point, living and working status, mRS, and Barthel Index were evaluated by a combination of revisiting the electronic medical charts and a telephone interview. At three months after ICH, the patients were sent 15D and EQ-5D-5L questionnaires.

The controls (Publication I) were frequency-matched to cases by sex and age, and randomly selected among the participants with no history of transient ischemic attack (TIA) or stroke of the FINRISK study (collections from years 2002 and 2007). FINRISK is a large Finnish population survey on risk factors of chronic non-communicable diseases, conducted by National Institute for Health and Welfare of Finland[180,181]. The ages were matched in 5-year age bands. As the oldest participants in the FINRISK study were 74-year-olds, the controls for ICH patients aged between 75 and 84 years were selected from the age group of 70-74 years. Patients aged 85 years and older (N=27) were excluded from the analyses. Three control persons were selected for each ICH patient. The control participants had filled in structured questionnaires including medical history, health-related lifestyle habits, and socio-economic status.

This study has been approved by the institutional review board and local ethical committee of the Helsinki University Hospital (11.12.2013 311/13/03/01/2013 and 12.10.2016 HUS/1662/2016).

4.2 Publications III and V

4.2.1 Patient selection

Publications III and V were retrospective analyses of the Helsinki ICH study (HICHS), which consists of 1013 consecutive ICH patients treated in the Helsinki University Hospital between January 2005 and March 2010. Patients having ICH caused by tumor or trauma were excluded. Medical records were used to obtain information on comorbidities, medication, and clinical status of the patients. NIHSS and GCS were used to assess the severity of the symptoms. The Population Registry Centre provided the data on all-cause mortality (last updated in November 2014). Foreign residents were lost to follow-up.

To be included in the analysis (publication III), ionized plasma/serum calcium and admission CT of the brain had to be taken within 72 hours of symptom onset, the two taken within 12 hours of each other. For wake-up strokes, and if the symptom onset time was unclear, we used the time when the patient was last known to be well as symptom onset time. Pure intraventricular hemorrhages were few (n=5), and they were excluded.

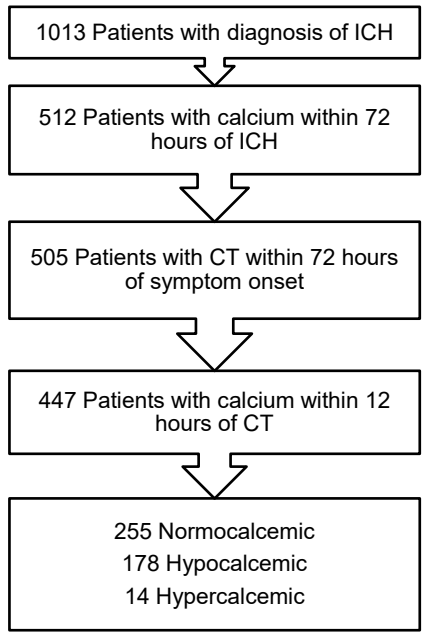

Figure 7. Cohort selection flow chart (Publication III). Permission to reproduce received from Elsevier. Abbreviations: ICH: intracerebral hemorrhage; CT: computed tomography

For Publication V, the medical files of patients with occipital ICH were further retrospectively analyzed on visual symptoms, rehabilitation, residual visual function, vision-related disability, habitation, return to work, and ability to drive a car, based on data reported in neurological, neurosurgical, or ophthalmological outpatient appointments and from physiotherapists', occupational therapists', and neuropsychologists' evaluations, as well as from the contacts to other specialties or to primary care. Visual field defect (VFD) was evaluated with confrontation perimetry on admission, and residual defect with standard automated perimetry after the acute phase or confrontation perimetry at discharge or at follow-up visits. The mRS could be categorized to 0-2 and 3-6 based on the retrospective data. We excluded patients with pre-ICH epilepsy from the analysis of the incidence of post-ICH epilepsy. This study was an observational registry study, approved by the institutional review board.

4.2.2 Neuroradiological data and analysis

Brain CT or MRI was used to detect ICH. ICH volumes were measured using semi-automated planimetry (Analyze 12.0 software)[11,105]. The hematomas were classified using the SMASH-U classification developed in our center[14]. Hemorrhage location was evaluated from the primary brain CT or MRI. The affected anatomical structures were classified as 'supratentorial lobar', 'supratentorial deep', 'infratentorial', or 'IVH'. If both deep and cortical structures were affected, a neuroradiologist evaluated the assumed origin of the ICH. If the origin could not be identified, the ICH was classified as 'mixed'. In the case of multifocal hemorrhages, the ICH was classified as lobar only if all hemorrhages were lobar. The locations were determined by a neuroradiologist on the basis of established anatomical landmarks. To be classified as occipital, the hemorrhage had to be limited to the occipital lobe.

4.3 Statistical analyses (all publications)

Statistical analyses were conducted using SPSS v.22, 24 or 25 (IBM, Armonk, NY). In the analyses, two-sided probability (P) value < 0.05 was considered significant. We expressed categorical variables as counts and percents (%), continuous variables with normal distribution as mean and standard error

(SE), and continuous variables not normally distributed as median and interquartile range (IQR) values. The differences between the groups were calculated using the $\chi 2$ test, the t test, or the Mann-Whitney U test as appropriate.

For the trigger study (Publication II), case-crossover design was used, each case serving as its own control, closely analogous to a matched pair case-control design[90]. We used a single control period, as opposed to multiple controls periods[182]. The hazard period for the triggers was defined as 0-2 hours prior to the ictus, and the control period was the previous day between the same time points. The ratio of the reported potential trigger factor during the hazard period, compared to the same period on the previous day, was used to calculate the relative risks (RR) for each factor.

For publication IV (QoL), the multivariable analysis for depression/anxiety was made using R Package 'brglm' to be able to handle the situation with no cases in one group.

5 Results

5.1 Publication I

Two-hundred and fifty patients of our study population fulfilled the study criteria. Thus we selected 750 controls from the FINRISK study population. Approximately half of the participants (128 cases; 51.2%) were under 70 years of age.

Multivariable analysis for risk factors of ICH is shown in Table 2. The cases had more frequently history of hypertension, heart attack, fatigue, lipid-lowering medication, and higher education than their controls, when all age groups were analyzed together. Overweight was more frequent among controls. In the younger cohort (<70-year-olds) – with the cases more accurately age-matched – hypertension, higher education, and fatigue were significantly more common among cases. In the older cohort, the ICH cases had higher education, more fatigue prior to ICH, use of lipid-lowering medication, and were overweight. We also tested the same potential risk factors including age as a continuous variable in the model for the older age group. Overweight was the only parameter which did not significantly differ between patients and controls. Fatigue was not associated with heavy exercise among cases or controls in any of the age groups. There was no association between fatigue and ICH location.

Table 2. Multivariable analysis for risk factors of ICH. Reprinted from Publication I. Permission to reproduce received from Elsevier.

Variable	OR (95% CI)	P value
Overweight (BMI >25)		
All	0.42 (0.27, 0.66)	0.0002
Age < 70 years	NA	NA
Age ≥ 70 years	0.30 (0.16, 0.56)	0.0002
Underweight (BMI <18.5)		
All	NA	NA
Age < 70 years	NA	NA
Age ≥ 70 years	2.59 (0.15, 43.71)	0.510
Hypertension		
All	1.60 (1.01, 2.54)	0.047
Age < 70 years	2.01 (1.07, 3.77)	0.029
Age ≥ 70 years	1.36 (0.70, 2.65)	0.369
History of heart attack		
All	3.64 (1.03, 12.91)	0.046
Age < 70 years	7.64 (0.88, 65.97)	0.065
Age ≥ 70 years	3.91 (0.78, 19.54)	0.097
Lipid-lowering medication		
All	2.08 (1.27, 3.39)	0.004
Age < 70 years	NA	NA
Age ≥ 70 years	2.05 (1.08, 3.90)	0.029
History of smoking (current or previous)		
All		
Age < 70 years	NA	NA
Age ≥ 70 years	NA	NA
	1.45 (0.78, 2.71)	0.240
High education (Bachelor/Master) vs. lower education (primary school/high school/vocational school)		
All	2.96 (1.78, 4.93)	<0.0001
Age < 70 years	3.60 (1.79, 7.25)	0.0003
Age ≥ 70 years	2.13 (1.01, 4.49)	0.047
Fatigue often (vs. no/seldom; for cases prior to ICH)		
All	4.54 (2.59, 7.95)	<0.0001
Age < 70 years	3.50 (1.65, 7.42)	0.001
Age ≥ 70 years	6.07 (2.49, 14.80)	<0.0001
Sad or depressed for more than 2 weeks during the prior 12 months		
All	1.59 (0.89, 2.83)	0.116
Age < 70 years	1.52 (0.72, 3.21)	0.267
Age ≥ 70 years	1.86 (0.73, 4.72)	0.191

ICH: intracerebral hemorrhage; OR: odds ratio; CI: confidence interval; BMI: body mass index

5.2 Publication II

Ninety-seven patients (35.0% of our cohort of 277 ICH patients) were able to provide consistent answers on the trigger questions, and thus eligible for the analyses. The median delay between ICH onset and interview was 2 days (IQR 1-3), ranging from 0 to 14 days; for one patient the timing was not recorded.

The relative risks for the exposures of potential trigger factors during the 2-hour period preceding the ICH, compared to the same period on the day before are shown in Table 3.

None of the studied possible triggers alone could be shown to affect the onset time of ICH. However, when actions causing Valsalva, physical exercise, and sexual activity were combined as a physical trigger (i.e. factors that raise blood pressure abruptly), we found it to be associated with the onset-time of ICH (RR 1.32, 95% CI 1.01, 1.73).

Table 3. Relative risks for the exposures of potential trigger factors during the 2-hour period preceding the ICH, compared to the same period the day before. Reprinted from Publication II. Permission to reproduce received from Elsevier.

Triggering factor	Number of included patients	Exposed in the hazard period	The day of the ICH only (only in the hazard period)	The day before only	Both periods	No exposure in either time period	RR (95% CI)
Physical trigger (Valsalva, heavy exercise, sex)	96	41	17	7	24	48	1.32 (1.01, 1.73)
Valsalva	78	23	7	4	16	51	1.15 (0.85, 1.56)
Heavy exercise	95	13	6	2	7	80	1.44 (0.87, 2.41)
Sex	88	5	4	3	1	80	1.25 (0.39, 3.99)
Change in position (such as startling)	94	0	0	0	0	94	NA
Heavy meal	93	2	2	4	0	87	0.50 (0.092, 2.73)
Change in temperature	94	4	2	4	2	86	0.67 (0.25, 1.78)
Exposure to traffic	95	5	3	4	2	86	0.83 (0.32, 2.15)

5.3 Publication III

In total, 178 hypocalcemic and 255 normocalcemic patients were included in the analyses. Hypercalcemic patients were few, and comprised only 3.1% of the patients (n=14). Their median ICH volume was 6.5 mL (IQR 3.1-34.6 mL).

As shown in Table 4, in comparison to normocalcemic patients, hypocalcemic patients had ($P<0.05$) larger ICH and IVH volumes, were more often male, less often had dyslipidemia, had higher admission NIHSS scores

and lower GCS scores, higher white cell count, C-reactive protein (CRP), and glucose on admission or in ambulance, and lower potassium, sodium, and creatinine values.

Table 4. Characteristics of the patients and comparison of the radiological parameters, laboratory test results, and outcome parameters that differed (P<0.05) between the hypocalcemic and normocalcemic patients. Modified from Publication III. Permission to reproduce received from Elsevier.

Variable	Hypocalcemic patients (n=178)	Normocalcemic patients (n=255)	P value	Missing values hypocalcemia / normocalcemia
Male	119 (66.9)	145 (56.9)	**0.04**	0/0
Dyslipidemia	23 (13.3)	55 (21.7)	**0.03**	5/1
Clinical admission parameters				
NIHSS	19.0 (10.0-34.0)	12.0 (6.0-21.0)	**<0.001**	0/0
GCS	10.0 (4.0-14.0)	14.0 (10.0-15.0)	**<0.001**	0/0
Radiological parameters on admission CT				
ICH volume, mL	30.2 (11.4-58.7)	16.8 (7.4-44.2)	**<0.001**	0/0
IVH volume, mL	2.9 (0.0-22.5)	0.0 (0.0-8.7)	**<0.001**	0/0
Admission laboratory results				
White cell count, 10^9/L	9.7 (7.2-12.0)	8.0 (6.4-10.4)	**<0.001**	2/3
CRP, mg/dL	5.0 (3.0-7.0)	4.0 (3.0-6.0)	**0.017**	2/2
Glucose on admission or in ambulance, mmol/L	8.4 (6.9-10.8)	7.5 (6.3-9.5)	**<0.001**	1/1
Potassium, mmol/L	3.7 (3.3-4.0)	3.8 (3.5-4.1)	**0.018**	6/5
Sodium, mmol/L	137.0 (135.0-139.0)	138.0 (136.0-140.0)	**0.046**	5/5
Creatinine, μmol/L	63.0 (54.0-82.5)	69.0 (58.0-85.8)	**0.040**	9/7
90-d-Mortality	93 (53.1)	87 (34.5)	**<0.001**	3/3

ICH: intracerebral hemorrhage; NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow Coma Scale; CT: computed tomography; IVH: intraventricular hemorrhage; CRP: C-reactive protein

Data are presented as number of patients with percentages in parentheses, median with interquartile ranges in parentheses, and mean with standard error in parentheses.

Admission hypocalcemia was strongly associated with larger hematoma volume (β =11.77, 95% CI 4.66-18.87, P = 0.001) in the multivariable logistic regression model, as depicted in Table 5. Additionally, only older age had an independent association with ICH volume.

Table 5. Multivariable linear regression analysis for ICH volume predictors. Modified from Publication III. Permission to reproduce received from Elsevier.

Variable	β (95% CI)	SE	P value	Missing data
Hypocalcemia	11.77 (4.66-18.87)	3.62	**0.001**	0
Age (per year)	0.45 (0.16-0.74)	0.15	**0.002**	0
Use of statin prior to ICH	9.55 (-0.80-19.90)	5.26	0.070	11
Antiplatelet medication prior to ICH	3.93 (-5.46-13.31)	4.77	0.41	1
Use of oral anticoagulant (warfarin) prior to ICH	8.79 (-2.53-20.10)	5.76	0.13	0
Antihypertensive medication prior to ICH	3.41 (-4.51-11.33)	4.03	0.40	0

CI: confidence interval; SE: standard error; ICH: intracerebral hemorrhage

Hypocalcemic patients had higher three-month mortality in comparison to normocalcemic patients (53.1% vs. 34.5%; P < 0.001) in the unadjusted analysis. However, as depicted in Table 6, hypocalcemia did not have an association with mortality in the multivariable logistic regression model after adjusting for known predictors of mortality (OR 0.69, 95% CI 3.58-12.96, P=0.13).

Table 6. Multivariable analysis for predictors of mortality at 90 days (n=427)**.** Modified from Publication III. Permission to reproduce received from Elsevier.

Variable	OR	95% confidence interval	P value	Missing data
Age, per year	1.04	1.02-1.06	**<0.001**	0
Volume of ICH, mL	1.03	1.02-1.04	**<0.001**	0
Volume of IVH, mL	1.04	1.03-1.06	**<0.001**	0
Infratentorial location of ICH	6.81	3.58-12.96	**<0.001**	0
Hypocalcemia	0.69	0.42-1.12	0.13	0
Anticoagulant medication (warfarin) prior to ICH	1.08	0.49-2.39	0.85	0
Multiple ICHs on imaging	1.72	0.59-5.04)	0.32	0

OR: odds ratio; ICH: intracerebral hemorrhage; IVH, intraventricular hemorrhage

5.4 Publication IV

Four hundred and fifty-six patients with ICH were treated in our hospital during the study period. Of those patients, 291 (63.8%) gave their consent for participation in our study. Of the consented patients, 277 did not turn out to have an exclusive secondary cause for ICH during the follow-up period. Fifty-six patients (20.2%) died in the follow-up time of 3 months. We lost one foreign patient to follow-up. Median age of the patients included in the analyses was 70.5

years (IQR 62.0-78.0 years), median NIHSS 5.0 (IQR 2.3-11.0), median GCS 15 (IQR 14.0-15.0), and the median ICH volume 8.9 mL (IQR 2.6-19.0 mL). The questionnaire was returned by124 patients (56.4% of the survived patients).

The non-responders had more severe strokes by NIHSS (median 7.8; IQR 3.0-14.8 vs. median 5.0; IQR 2.3-11.0; P = 0.018), as well as worse outcome at three months: a larger proportion of the patients had mRS 3-5 (59.4% vs. 44.4%; P = 0.030), lower BI (median 95.0; IQR 35.0-100.0 vs. median 100.0; IQR 85.0-100.0; P = 0.013), and they were less likely to live at home (54.7% vs. 77.4%; P < 0.001). In regard to the other parameters the groups were similar.

In our cohort, the median EQ-5D-5L utility index was 0.590. Seven (5.6%) patients had incomplete answers, and thus the index was incalculable. The EQ-5D index values vary from 0.909 (age group 25-34) to 0.583 (age group 75+), and the average value is 0.800 in the general Finnish population[183]. Our cohort had a median 15D utility index value of 0.817. Sixteen (12.9%) patients had incomplete answers, and incalculable index values.

The distribution of the EQ-5D-5L and 15D utility index values are depicted in Figure 8.

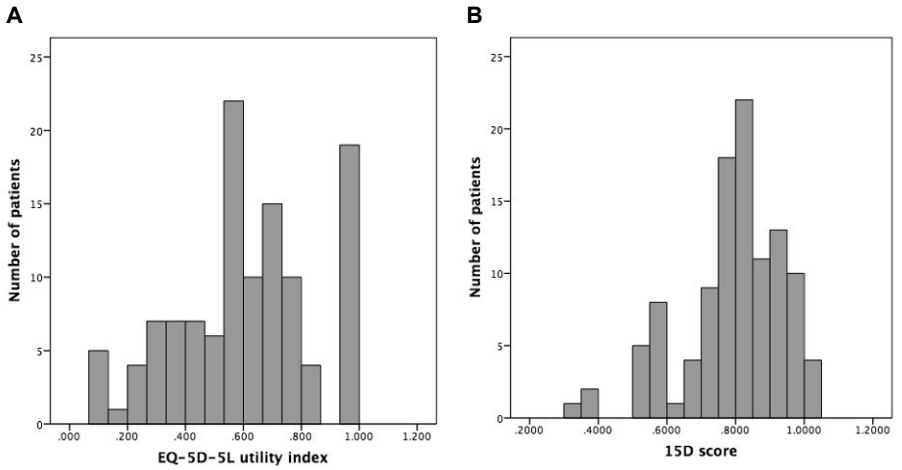

Figure 8. The distribution of the **A)** EQ-5D-5L (n=117), and **B)** 15D (n=108) utility index values at 3 months after ICH. Reprinted from Publication IV. Permission to reproduce granted by publishing terms by Wiley.

As shown in Table 7, among the 117 patients with calculable utility indexes by EQ-5D-5L, lower HRQoL (≤ 0.590) was associated (P<0.05) with consent given by patient's proxy, history of chronic obstructive pulmonary disease or

asthma, frequently felt home-related stress, lower education level, higher NIHSS and lower GCS scores on admission, higher baseline ICH volumes, deep ICH location, DNR orders during hospital stay, lower BI, higher mRS, and the patients were less likely to live at home at 3 months and 1 year. Higher HRQoL had an association with cancer, including curatively treated forms. The detailed values including the parameters with no significant difference between the groups are represented in Table 1 of Publication IV.

Table 7. Comparison of the patients with low and high EQ-5D-5L utility index (n=117) † Parameters with significant difference (P<0.05) in univariate and/or multivariable analyses are shown. Reprinted from Publication IV. Permission to reproduce granted by publishing terms by Wiley.

Variable	Low (≤ 0.590) n= 59	High (> 0.590) n= 58	P value
Age, y	70.0 (62.0-80.0)	70.5 (61.8-75.0)	0.195
Agreement by proxy	25 (42.4)	8 (13.8)	**0.001**
COPD/asthma	9 (15.3)	2 (3.4)	**0.029**
Chronic heart failure	7 (11.9)	1 (1.7)	0.061
History of cancer	9 (15.3)	18 (31.0)	**0.043**
No or little stress at home‡	39 (72.2)	47 (90.4)	**0.017**
Sad or depressed for more than 2 weeks during the year prior to ICH‡	14 (30.4)	6 (11.1)	0.160
High education (Master or Bachelor's degree) ‡	10 (17.9)	20 (35.1)	**0.038**
NIHSS on admission	10.0 (3.0-15.0)	4.0 (2.0-6.0)	**<0.001**
GCS on admission	15.0 (13.0-15.0)	15.0 (14.0-15.0)	**<0.001**
Baseline ICH volume, mL	10.9 (4.5-23.0)	7.2 (1.9-16.2)	**0.037**
ICH location			**0.001**
ICH location, lobar	8 (13.6)	24 (41.4)	
ICH location, deep supratentorial	48 (81.4)	30 (51.7)	
ICH location, infratentorial	3 (5.1)	4 (6.9)	
DNR orders in hospital	12 (20.3)	3 (5.2)	**0.014**
mRS at 3 months			**<0.001**
mRS 0	0 (0.0)	5 (8.6)	
mRS 1	2 (3.4)	11 (19.0)	
mRS 2	16 (27.1)	34 (58.6)	
mRS 3	15 (25.4)	5 (8.6)	
mRS 4	16 (27.1)	3 (5.2)	
mRS 5	10 (16.9)	0 (0.0)	
Barthel Index at 3 months	90.0 (55.0-100.0)	100.0 (100.0-100.0)	**<0.001**
Living at home at 3 months	36 (61.0)	55 (94.8)	**<0.001**

Data are n (%), mean (SE), or median (IQR)
Abbreviations: mRS, modified Rankin Scale; ICH, intracerebral hemorrhage; COPD, chronic obstructive pulmonary disease; NIHSS, the National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; DNR, do not resuscitate
† n=7 exclusion due to incomplete answers
‡ Missing data for sad or depressed for more than two weeks in 17 patients (14.5%), no or little stress at home in 11 patients (9.4%), high education in 4 patients (3.4%)

Among the 108 patients with calculable 15D indexes, the lower scores associated (P<0.05) with older age, antihypertensive medication, lower education level, higher NIHSS, lower GCS, larger baseline ICH volumes, DNR orders in hospital, higher mRS, and lower BI at 3 months, consent given by proxy, and the patients having lower scores were less likely to live at home at 3 months and 1 year. The parameters with significant differences in either univariate or multivariate analyses are depicted in Table 8.

Table 8. Comparison of the patients with low and high 15D score (n=108) †. The parameters with significant differences in univariate and/or multivariable analyses are shown. Reprinted from Publication IV. Permission to reproduce granted by publishing terms by Wiley.

Variable	Low (≤ 0.817) n=54	High (> 0.817) n=54	P value
Age, y	72.0 (62.8-80.0)	68.0 (60.5-75.0)	**0.035**
Agreement by proxy	27 (50.0)	6 (11.1)	**<0.001**
History of any ICH	6 (11.1)	1 (1.9)	0.113
Chronic heart failure	6 (11.1)	1 (1.9)	0.113
Antihypertensive medication	34 (63.0)	23 (42.6)	**0.034**
High education (Master or Bachelor's degree)‡	9 (17.6)	22 (41.5)	**0.008**
NIHSS on admission	9.0 (3.8-15.5)	3.0 (2.0-5.0)	**<0.001**
GCS on admission	14.5 (13.0-15.0)	15.0 (15.0-15.0)	**<0.001**
Baseline ICH volume, mL	13.6 (6.2-24.5)	4.5 (1.7-16.0)	**0.002**
DNR orders in hospital	14 (25.9)	2 (3.7)	**0.001**
mRS at 3 months			**<0.001**
mRS 0	0 (0.0)	4 (7.4)	
mRS 1	2 (3.7)	11 (20.4)	
mRS 2	14 (25.9)	33 (61.1)	
mRS 3	15 (27.8)	4 (7.4)	
mRS 4	13 (24.1)	2 (3.7)	
mRS 5	10 (18.5)	0 (0.0)	
Barthel Index at 3 months	92.5 (53.8-100.0)	100 (100.0-100.0)	**<0.001**
Living at home at 3 months	33 (61.1)	52 (96.3)	**<0.001**

Data are n (%), mean (SE), or median (IQR).
Abbreviations: mRS, modified Rankin Scale; ICH, intracerebral hemorrhage; NIHSS, the National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; DNR, do not resuscitate
† n=16 exclusion due to incomplete answers
‡ Missing data for high education in 4 patients (3.7%),

The EQ-5D-5L and 15D utility indexes by mRS is depicted in Figure 9.

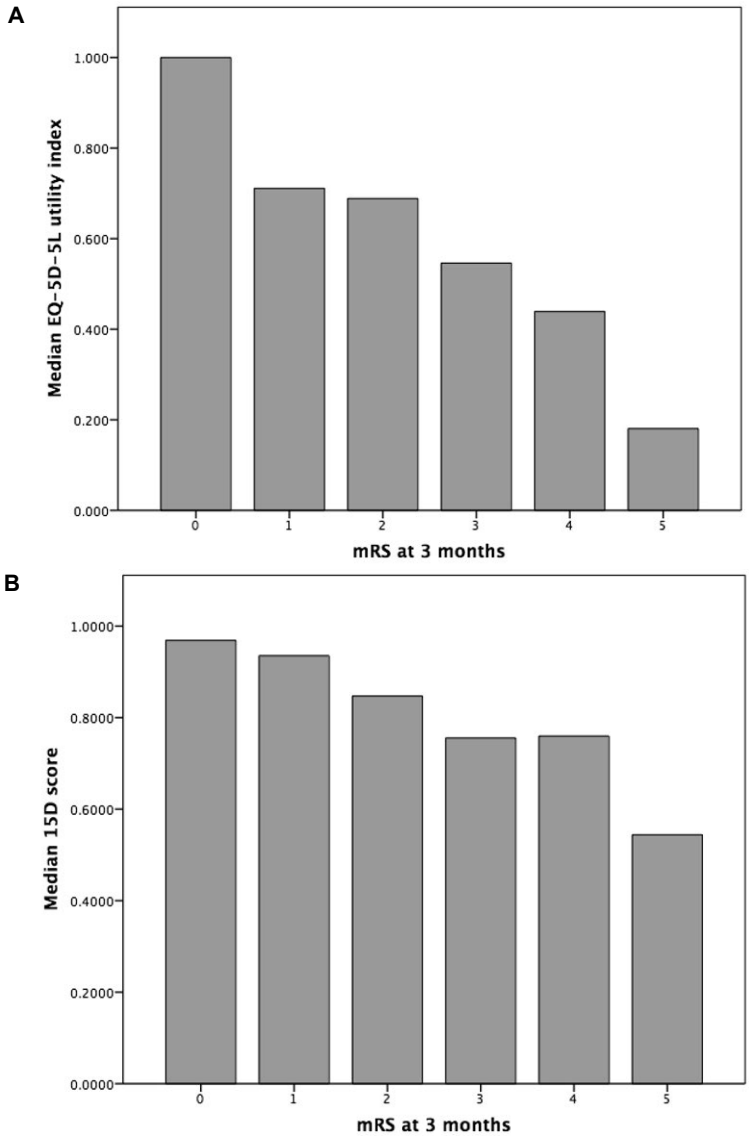

Figure 9. **A)** EQ-5D-5L (n=117), and **B)** 15D (n=108) utility indexes across mRS groups at 3 months after ICH. Reprinted from Publication IV. Permission to reproduce granted by publishing terms by Wiley.

Table 9 shows the multivariable regression analyses for lower HRQoL in both EQ-5D-5L and 15D index values. Predictors for lower HRQoL in both measures were chronic heart failure, higher NIHSS on arrival, and older age. Lower EQ-5D-5L utility index was associated with feeling sad or depressed for more than 2 weeks during the year prior to ICH. History of any ICH was associated with lower 15D index.

Table 9. Multivariable binary logistic regression analysis for predictors of decreased a) EQ-5D-5L utility index, and b) 15D score at 3 months† Reprinted from Publication IV. Permission to reproduce granted by publishing terms by Wiley.

Variable	OR (95% CI)	P value
Predictor for decreased EQ-5D-5L utility index‡		
Chronic heart failure	18.12 (1.73-189.27)	0.016
History of cancer	0.20 (0.053-0.77)	0.019
NIHSS at arrival	1.28 (1.13-1.46)	<0.001
Age per year	1.10 (1.03-1.16)	0.002
Sad or depressed for more than 2 weeks during the year prior ICH	10.64 (2.39-47.28)	0.002
Predictor for decreased 15D utility index§		
Chronic heart failure	12.84 (1.31-126.32)	0.029
NIHSS at arrival	1.28 (1.15-1.44)	<0.001
Age per year	1.09 (1.03-1.15)	0.003
History of any ICH	11.85 (1.01-138.90)	0.049

† 95 patients included in analysis due to missing data (EQ-5D-5L); 104 patients included in analysis due to missing data (15D)
‡ Adjusted for: agreement by proxy, mRS 3-5 prior to ICH, COPD/asthma, coronary artery disease, no or little stress at home, living alone, high education, GCS on admission, baseline ICH volume, ICH location, DNR orders in hospital
§ Adjusted for: agreement by proxy, antihypertensive medication, living alone, occupational status, high education, GCS on admission, baseline ICH volume, any neurosurgery, DNR orders in hospital
Abbreviations: NIHSS, the National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage

Table 10 shows comparison between the patients that reported having or not having feelings of depression/anxiety at the time point of 3 months after the hemorrhage. Feelings of depression were more common among patients with mRS 3-5 three months after ICH, dementia patients, patients with DNR orders in hospital and patients that had already felt sad or depressed during the previous year before ICH. Only patient reported depression in the year prior to ICH was an independent predictor for feelings of depression and/or anxiety at 3 months after ICH in the multivariable analysis (Table 11). Only 4 (3.7%) of the patients had had antidepressant treatment, and one (0.9%) patient psychotherapy.

Table 10. Comparison of the patients with or without reported depression and/or anxiety in EQ-5D-5L three months after ICH (n=122) †. Modified from Publication IV. Permission to reproduce granted by publishing terms by Wiley.

Variable	Not depressed/ anxiety n=68	Depressed/ anxiety n=54	P value
Age, y	69.5 (62.3-75.8)	72.5 (59.8-79.3)	0.335
Male	34 (50.0)	30 (55.6)	0.542
Agreement by proxy	18 (26.5)	18 (33.3)	0.409
mRS 3-5 prior to ICH	1 (1.5)	3 (5.6)	0.321
Diabetes	10 (14.7)	6 (11.1)	0.559
History of ischemic stroke	8 (11.8)	7 (13.0)	0.841
History of any ICH	2 (2.9)	5 (9.3)	0.239
COPD or asthma	4 (5.9)	7 (13.0)	0.212
Dementia	0 (0.0)	5 (9.3)	**0.015**
Coronary artery disease	4 (5.9)	8 (14.8)	0.100
History of atrial fibrillation	15 (22.1)	16 (29.6)	0.340
Chronic heart failure	3 (4.4)	5 (9.3)	0.464
History of cancer	15 (22.1)	13 (24.1)	0.793
Antiplatelet treatment	15 (22.1)	10 (18.5)	0.630
Anticoagulant treatment	11 (16.2)	15 (27.8)	0.120
Antihypertensive medication	35 (51.5)	29 (53.7)	0.806
Antidepressant medication	2 (2.9)	1 (1.9)	1.000
Sad or depressed for more than 2 weeks during the year prior to ICH‡	6 (10.0)	15 (33.3)	**0.003**
Alcohol use (within 1 year prior to ICH)‡	55 (83.3)	43 (81.1)	0.754
No or little stress at home‡	53 (86.9)	37 (74.0)	0.085
Living alone	23 (33.8)	16 (29.6)	0.622
Married or registered relationship) ‡	40 (59.7)	33 (63.5)	0.676
Occupational status, working	13 (19.1)	13 (24.1)	0.507
High education (Master or Bachelor's degree) ‡	21 (31.8)	10 (19.2)	0.123
NIHSS on admission	5 (2.3-9.8)	6 (2.0-13.3)	0.262
GCS on admission	15 (14.0-15.0)	15 (13.8-15.0)	0.683
Baseline ICH volume, mL	8.0 (1.9-16.4)	12.0 (4.0-21.9)	0.082
ICH location			0.555
ICH location, lobar	22 (32.4)	13 (24.1)	
ICH location, deep supratentorial	42 (61.8)	38 (70.4)	
ICH location, infratentorial	4 (5.9)	3 (5.6)	
ICH evacuation/any neurosurgery	1 (1.5)	4 (7.4)	0.169
DNR orders in hospital	4 (5.9)	12 (22.2)	**0.008**
Deterioration (increase in NIHSS at least 4 points) within 1 week of ICH	5 (7.4)	2 (3.7)	0.462
Acute myocardial infarction or heart failure within 1 week of ICH	0 (0.0)	2 (3.7)	0.194
mRS at 3 months			0.175
mRS 0	4 (5.9)	1 (1.9)	
mRS 1	10 (14.7)	3 (5.6)	
mRS 2	31 (45.6)	20 (37.0)	
mRS 3	10 (14.7)	12 (22.2)	
mRS 4	8 (11.8)	13 (24.1)	
mRS 5	5 (7.4)	5 (9.3)	
mRS 3-5 at 3 months	23 (33.8)	30 (55.6)	**0.016**
Barthel Index at 3 months	100 (91.3-100.0)	97.5 (80.0-100.0)	0.164
EQ-5D-5L utility index at 3 months‡	0.711 (0.577-1.000)	0.517 (0.341-0.588)	**<0.001**
15D score at 3 months‡	0.885 (0.769-0.941)	0.770 (0.588-0.827)	**<0.001**
Living at home at 3 months	54 (79.4)	42 (77.8)	0.827
Working at 3 months	2 (2.9)	2 (3.7)	1.000

Data are n (%), mean (SE), or median (IQR)
Abbreviations: mRS, modified Rankin Scale; ICH, intracerebral hemorrhage; COPD, chronic obstructive pulmonary disease; NIHSS, the National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; DNR, do not resuscitate
† n=2 exclusion due to incomplete answers
‡ Missing data for BMI in 5 patients (4.1%), sad or depressed for more than two weeks in 17 patients (13.9 %), alcohol use in 3 patients (2.5%), no or little stress at home in 11 patients (9.0%), marital status in 3 patients (2.5%), high education in 4 patients (3.3%), EQ-5D-5L index in 5 patients (4.1%), 15D index in 14 patients (11.5%).

Table 11. Multivariable binary logistic regression analysis for associations with depression/anxiety in EQ-5D-5L at 3 months (n=122).†. Reprinted from Publication IV. Permission to reproduce granted by publishing terms by Wiley.

Variable	OR (95% CI)	P value
Sad or depressed for more than 2 weeks during the year prior to ICH	3.62 (1.14-11.45)	**0.029**
Dementia prior to ICH	16.65 (0.50-549.45)	0.11
DNR orders in hospital	4.87(0.99-23.95)	0.051
Stress at home prior to ICH	3.01 (0.86-10.58)	0.086
Baseline ICH volume	0.99 (0.96-1.03)	0.53
mRS 3-5 at 3 months	1.90 (0.75-4.80)	0.17

Abbreviations: DNR, do not resuscitate; ICH, intracerebral hemorrhage
† 102 patients included in analysis due to missing data

5.5 Publication V

Our cohort of 1013 ICH patients included 19 patients with occipital ICH, which accounted for 5.3% of lobar and 1.9% of all ICH patients. Age was the only baseline characteristic that differed between occipital ICH patients and other ICH patients, occipital ICH patients being significantly younger with the median age of 63 years (lobar 71 years, P=0.007; all 68 years, P=0.04).

The occipital ICH patients had lower NIHSS and higher GCS than other lobar ICH patients (median NIHSS 1 vs 8, P<0.001; median GCS 15 vs 14, P<0.001) and other ICH patients (NIHSS 11, P<0.001; GCS 14, P<0.001). Visual symptoms were prevalent (74% of occipital ICH patients), and 63% had visual symptoms as their only neurological deficit. With visual field confrontation, 15 out of 18 patients had VFD. ICH volume was significantly smaller in occipital ICH patients than other lobar ICH patients (6.3mL vs. 17.7mL, P=0.008). Amyloid angiopathy (53%) and structural lesions (26%) were the most prevalent etiologies according to SMASH-U classification.

Occipital ICH patients had better outcomes than other ICH patients. The median discharge mRS was 2 (IQR 1-2), 84% of the patients having mRS of 0-2; compared to median mRS 4 (IQR 3-5), and mRS 0–2 in 24% of patients among non-occipital lobar ICH, and median mRS 5 (IQR 3-5), and mRS 0–2 in 17% of the patients among all ICH (P<0.001). Only one (5%) occipital ICH patient died during hospital stay. One occipital ICH patient was lost to follow-up, and none of the remaining 17 patients died during the follow-up time of 12 months. Thus, 3- and 12-month mortality was 6% - significantly less than among non-occipital lobar ICH patients at 12 months (34%, P=0.01) and

among all non-occipital ICH patients at 3 and 12 months (33% and 37%, P=0.02 and P=0.006). Occipital location had an independent association with mRS 0-2 at discharge even when adjusted for strong predictors of outcome (OR 11.02, 95% CI 1.55–78.20).

Eight occipital ICH patients reported residual visual impairments at follow-up, and 10 patients had automated standard perimetry done within 7 months of their ICH. Six patients had VFD, and only 2 of them had a defect that was a quadrant or larger. There were 7 patients that were not examined with standard automated perimetry, and 6 of them had normal confrontation perimetry at discharge or at follow-up visits. One year after ICH, 16 patients lived at home, and one lived in a nursing home. Two patients lost their driving license due to their neurological deficits, and 9 patients were allowed to drive a car. Five patients out of the 6 non-retired returned to work. Fourteen patients had mRS of 0-2 at 3 and 12 months. The mRS of 2 patients at 3 months and 3 patients at 12 months could not be evaluated. Two (11%) occipital ICH patients had seizures within 1 week of their ICH, whereas 20% of the non-occipital lobar (P=0.55) and 11% of the non-occipital ICH (P>0.99) patients had early seizures. Eighteen percent of the occipital ICH patients that were alive were diagnosed having epilepsy after ICH, and the incidence was comparable to that of non-occipital lobar ICH patients (16%, P=0.74), and bigger than all non-occipital ICH patients (9%), but the difference was not significant (P=0.19).

6 Discussion

6.1 Main results in the context of existing literature

In this study, we wanted to assess ICH in a wide spectrum, from risk factors to factors affecting the outcome of the patients. We wanted to find out novel predictors for the risk of ICH, as well as such factors affecting outcome that are not visible in the traditional outcome measures.

6.1.1 Risk factors of ICH (I)

We compared ICH patients to their stroke-free controls of similar age and sex. We also included assessment of fatigue and prior depressive feelings, and their role as risk factors for ICH. Association of various psychological factors with ICH risk is methodologically difficult to study, and includes a certain level of subjectivity and higher possibility of bias, which might be the main reason for the limited data on the subject. The INTERSTROKE study used a combined measure of psychosocial factors combining stress, depression and life events, and demonstrated that psychosocial factors were associated with ICH risk[5]. In our study, ICH patients reported significantly more often premorbid fatigue than their controls. Premorbid feelings of depression were more common among ICH patients than their controls, but the difference was no longer significant in the multivariable analysis.

In a Chinese cohort study, longer sleep duration, daytime napping, and poor sleep quality were associated with higher risk of incident stroke. In that study, there was no significant association with ICH and longer sleep duration (≥ 9 hours) or daytime napping, however, the number of incident ICH was much smaller than ischemic stroke, and the authors concluded that the number might be too small to reach statistical significance[184], and longer sleep duration has been found to associate with ICH[185]. One study found the association of ICH and sleep duration of 8 hours compared to 6-8 hours per night only in women[186]. In a prospective study cohort, longer sleep duration as well as a substantial increase in sleep time over the observation period were predictors for stroke[187]. Longer sleep duration has been associated with a number of conditions including inflammatory biomarkers[188], metabolic syndrome[189], and WMH volume[190]. We reasoned that the possible

mechanisms might include a combination of underlying factors causing fatigue (such as sleep apnea, other underlying diseases, and overall poor health), need for longer resting, as well as different psychosocial factors. Depressive feelings might also associate with overall poorer lifestyle factors, such as unhealthy diet and less exercise, which might increase the risk for cardiovascular disease.

As previously found out, and also verified in our study among the under 70-year-olds, hypertension is a major risk factor for ICH[5,191–193]. In our study, however, among the cohort of 70 years and older, the multivariable analysis did not show difference in hypertension between cases and controls. We were not able to evaluate the exact reason for this. An earlier study also showed differences in risk factors in different age groups, and in their study, hypertension increased the risk for ICH only among patients under 70 years old[194]. We hypothesized that possibly other causes than hypertensive angiopathy – such as amyloid angiopathy – play a larger role in the pathological mechanisms of ICH in the older age group. Presumably, duration of hypertension in years as well as severity of hypertension (the blood pressure values) have an effect on the risk of ICH. In our cohort, those parameters were not known.

We studied the possible association between alcohol consumption and risk for ICH, defined as estimated amount of alcohol consumption per week, or any alcohol use within the previous 12 months. The results between earlier studies are somewhat conflicting, as in a rather large case-control study of 2660 ICH cases and controls, up to moderate alcohol consumption reduced the risk of ICH, whereas heavy alcohol consumption increased the risk for nonlobar ICH in black and Hispanic, but not in white ICH patients[195]. Possibly, up to moderate alcohol consumption may also correlate with other healthy life-style factors. A meta-analysis including 27 studies demonstrated that alcohol consumption of up to 2 drinks/day associated with reduced risk of ischemic stroke, and no association with ICH. Heavy alcohol consumption increased the risk for both ischemic and hemorrhagic stroke[196].

As was the case with alcohol, we found no association with ICH and current smoking or history of smoking. The same result has been reported in many of the earlier studies[5,191,197,198]. However, some studies have reported smoking to increase the risk for ICH[199,200].

6.1.2 Triggering factors in ICH (II)

In this study on the possible association of triggering factors and ICH onset, we found that a combination of physical triggers associated with the onset of ICH. However, the effect was fairly small, which may correlate with the difficulties in receiving information from the acutely ill ICH patients, or reflect a truly small effect of the triggering events. To our knowledge, this type of case-crossover design has not been previously used to study if triggering factors can be associated with the timing of ICH. A retrospective case series identified 16 ICH patients with different etiologies sought to investigate temporal relationship between ICH and sexual intercourse, however no controls or case-crossover design was used[201].

Case-crossover design has been previously used to study triggering events preceding for example SAH[6,92], ischemic stroke[7,95], myocardial infarction[202], and injuries[203]. In this type of design, the studied trigger should be transient, and the onset time sudden[90]. In the setting of SAH, drinking coffee or cola, vigorous physical exercise, nose blowing, straining for defecation, being startled, anger, and sexual intercourse before the rupture of an aneurysm could be identified as trigger factors to the hemorrhage, with increased relative risk compared to the patients' usual frequency of exposure[92,93]. The effect was big enough to be identified in smaller subcohorts of as few as 50-70 patients[92]. Among ischemic stroke patients, negative emotions, anger, and sudden posture change due to startling associated with the stroke onset time, whereas temperature change, positive emotions, heavy eating, and physical exercise had no association[95].

As ICH and ischemic stroke have essentially different mechanisms (vessel rupture vs. vessel occlusion), it is likely that the mechanisms of the triggering events are different. Many of the triggering events studied are linked to abrupt elevation of blood pressure[96–98,204]. Catecholamine secretion has been suggested to be one of the mediators of the physiological effect on blood pressure, heart rate, and myocardial oxygen demand caused by the triggering event in the setting of cardiovascular events[99,100]. In our study, the actions that associated to the ICH onset time were the combination of those which lead to rapid and short-lasting rise in blood pressure. In ICH, it seems a plausible explanation, that the association is driven by abruptly increased blood pressure leading to a rupture of an already weakened vessel wall. As we could not

identify any of the triggering events alone to be associated with ICH onset time, it is likely that our sample size is too small, and possibly the effect is also smaller than for example in SAH.

6.1.3 Hypocalcemia and ICH (III)

In our retrospective study on the association of hypocalcemia, ICH volume and mortality, we showed that hypocalcemia was common (approximately 40% of ICH patients), and that hypocalcemic patients had larger admission ICH volumes and higher 90-day mortality. However, in a multivariable binary logistic regression analysis, hypocalcemia was not an independent predictor of mortality, increased mortality among the hypocalcemic patients being likely explained by the larger hematoma volumes.

Earlier studies have shown hypocalcemia to be a frequent finding in critically ill patients, and its association with higher mortality[205], and hypocalcemia has been suggested as possibly being a reflector of poor outcome. Catecholamine-mediated translocation of plasma calcium into tissues and increased fecal and/or urinary calcium excretion, and hyperadrenergic state associated with calcium derangement have been postulated as possible mechanisms[205]. In our cohort, independent association with mortality was not noted. However, as we included ICH volume, which is a strong and independent predictor for mortality, in the multivariable model, the result was not unexpected.

The association between hypocalcemia and larger ICH volumes has been reported also in previous studies[18,19]. Similarly with our study, Inoue et al. did not find a significant association between hypocalcemia and mortality, after having adjusted for hematoma volume and NIHSS[18]. Morotti et al. did not include outcome analysis[19]. In a study by You et al., however, no difference in hematoma volume was observed, but hypercalcemic patients had better outcome[20]. In a study of 1262 ICH patients, published after our study, low serum calcium associated with poor outcome, and had an inverse linear association with ICH volume[206]. Another study of 658 hypertensive ICH patients published after our study also confirmed the association of lower calcium level with larger hematoma volumes and worse outcome[207]. Taking into consideration several studies with results pointing in a similar direction, the association between calcium, and larger hematoma volumes and worse

outcome seems robust. However, whether hypocalcemia might have an independent predictive value for worse outcome, when the effect of ICH volume has been taken into account, was not shown in our study, and would warrant further research, possibly using a prospective setting, and including all possible known parameters that might affect calcium levels, such as vitamin D status and kidney function.

In addition to calcium, magnesium – another mediator in coagulation – has been shown to affect hematoma volume in ICH patients, as patients with lower magnesium levels having been shown to have larger hematoma volumes and greater hematoma expansion presumably due to coagulopathy, platelet dysfunction, higher blood pressure, and inflammatory response[208]. In the setting of ischemic stroke, a genetic study on causal association of serum magnesium and calcium concentrations with stroke risk found that genetically higher serum magnesium concentrations associated with a reduced risk of cardioembolic stroke. For calcium, there was no association[209]. The finding outlines the complexity of the matter – the complex interplay of genetic and environmental factors affecting both the risk for disease as well as the outcome.

The proposed mechanisms for hypocalcemic patients having larger hematoma volumes as most of the studies imply, have been calcium's effect on coagulation and the association with blood pressure. However, in the study of Morotti et al.[19], there was no significant difference in blood pressure between hypocalcemic and normocalcemic patients, as was the case in our study. Additionally, hypocalcemia possibly reflecting poor liver function, and thus affecting coagulation has been suggested as a possible mechanism[18]. In our study, hypocalcemic patients had not significantly more often liver disease. In the setting of bleeding patients, the alterations in hemostasis have been thought to be partly caused by hypocalcemia, and to contribute to morbidity and mortality[210]. Thus, the proposed association of hypocalcemia with coagulation and larger hematoma volumes seems reasonable.

As the calcium levels before ICH are not known, another explanation might be that the neuronal damage caused by the hematoma would lower the calcium concentration in the blood. Thus, patients with larger hematomas would have larger amount of calcium drawn from the extracellular spaces to the cells, and hypocalcemia would be rather the result of a large ICH volume than its cause. Animal studies have demonstrated that ischemia in neurons causes prolonged

calcium influx from extracellular sources to the cells[211]. An experimental ICH model in cats demonstrated a longstanding loss of calcium ions in the extracellular space, the ionic movement also taking place in the cells that were not directly damaged[212], implying to the role of endothelial dysfunction in the context of neuronal cell damage and hypocalcemia. The pathophysiology may be complex, and it is possible that alterations in blood calcium levels are secondary to dysfunction in the parathyroid hormone-vitamin D axis following acute immune response in ICH[213].

In our cohort, the median time from ICH onset time to imaging was longer in the hypocalcemic group (median 3.5 hours, IQR 1.6-9.8 vs. 2.1 hours, IQR 1.4-4.8; p=0.002). However, time did not predict independently ICH volume in linear multivariable analysis.

6.1.4 Quality of life after ICH (IV)

In our substudy on health-related quality of life, baseline stroke severity and ICH volume were strongly associated with HRQoL three months after ICH. Asthma/COPD and chronic heart failure were predictors for worse quality of life, as also earlier studies have implied[214,215]. Older age had an independent association with diminished quality of life – as also seen in the general population[183].

Twenty-one (17.2%) of the 122 patients included in the analysis on depressive symptoms after ICH reported having been feeling depressed for more than 2 weeks during the year prior to ICH. However, only 4 (3.7%) patients had been receiving antidepressant medication and only one (0.9%) patient psychotherapy, implying possibly underrecognition and undertreatment of depression. Feelings of depression as measured by the depression/anxiety domain of the EQ-5D-5L questionnaire were more frequently reported by patients with higher mRS as an indicator of worse functional outcome. However, of the tested parameters, only feeling sad or depressed before ICH predicted feelings of depression/anxiety at three months after ICH. Similarly, also among subarachnoid hemorrhage (SAH) patients, pre-SAH depression and premorbid psychosocial stress were predictors for depression at three months after SAH[216]. Among ICH patients in our cohort, marital status or living with family had no association with depression/anxiety after ICH.

In our study, patients with pre-ICH dementia were few, but all of them reported feelings of depression/anxiety after ICH. Indeed, dementia patients have been reported to frequently have depression[217]. However, as pre-ICH dementia was rare in our cohort, a significant association between dementia and depression was not noted.

A multi-center study on depression after ICH concluded that depression among ICH patients is common, but may remain underrecognized. Only less than 10% of the patients with depressive symptoms received any commonly used antidepressive medication[218]. Especially, as post-ICH depression has been shown to have a negative influence on patients' outcome that is not related to initial hemorrhage severity[177], diagnosing and treating depression could have widespread influence in patients functioning and reducing suffering after ICH. Our results imply that simple questions on premorbid feelings of depression could be one tool to help finding patients at risk for post-stroke depression.

6.1.5 Occipital ICH (V)

In our study, occipital location was rare compared to other locations, occipital ICH consisting of 5.3% of lobar and 1.9% of all ICH. The hemorrhage volumes were smaller than in other lobar locations, and structural etiology was more common. The functional status of the patients at discharge was better, and less patients died within 12 months. However, in multivariable analysis the difference in mortality was not significant, and the confidence intervals were wide, probably due to the small number of occipital ICH patients. Risk of symptomatic epilepsy was the same as for the other locations. The smaller prevalence (even when adjusted with the size of the lobes) and volume of occipital ICH, as well as least growth in the size of the hematoma have been described earlier[219]. It has been hypothesized[219] that the smaller volume and growth might be linked to higher gray/white-matter ratio[220] and lower arterial pressure gradient[221].

Visual field defect was the most prevalent symptom in the acute phase (over 80% of occipital ICH patients), which is not surprising as the cohort was limited to patients having ICH in the lobe that harbors vision-related structures. Approximately 50% continued to having residual visual symptoms. However, the symptoms may be underrecognized, as only half of the patients

were examined with standard automated perimetry, and VFD may go unrecognized by the patient as well as by medical personnel[222,223].

In our cohort of occipital ICH patients, structural etiology was more common compared to ICH in other locations, which likely correlates with the better outcome, as well as the younger age of the patients. Structural etiology (by SMASH-U classification) has been shown to have the most favorable outcome among ICH patients[14]. Previously, occipital location has been shown to predict good functional outcome at 3 months[219]. The outcome of occipital ICH patients seemed better by also robust measurements such as mortality, and return to work - as evaluation of solely mRS can lead to underestimation of visual and possibly cognitive symptoms. Studies on ischemic stroke have shown that damage to the white matter might be essential in predicting poor functional outcome after stroke[224]. Thus, if the gray/white matter ratio has a role in the interplay of hematoma location, volume and prognosis, damage to the white matter might be essential.

6.2 Strengths and limitations

The strength of our study includes a homogenous cohort, as a vast majority of the patients are ethnic Finns. For the evaluation on quality of life we used two different methods (15D and EQ-5D-5L questionnaires). Case cross-over design (Publication II) leads to no selection bias, each case serving as its own control. The patients were interviewed face-to-face, and thus we could evaluate if the patient was able to provide consistent answers, and the orientation was sufficient for the interview.

For publication III (hypocalcemia) one of the strengths is using the ionized calcium, which is better for reflecting physically active calcium[225]. Most patients were admitted shortly after stroke (within the first hours). For analyzing the most relevant values, the timing between admission, laboratory testing and imaging were relatively short and limited.

The limitations include the rather small cohort as well as the amount of missing data in the prospective part of the study. Due to the nature of the illness, many patients had aphasia, depressed level of consciousness, or confusion, and were not able to provide answers to the questions. Many of the parameters of quality of life are subjective, and difficult to measure. As expected, the patients participating in reporting and interviewing, were more

mildly affected than the non-participants. The pre-ICH feelings such as fatigue and feelings of depression could be questioned only after ICH, and thus it is possible that the present feelings affect the answers on past feelings. Obviously, a diagnosis of pre-ICH depression cannot be made by our questionnaire. In the substudy on risk factors (I), the eldest controls were 74-year-olds, and thus significantly younger than the cases. The cases and controls were compared in several age groups: all, under 70-year-olds, and 70 years and older. Thus, only in the younger age group, the ages of cases and controls were similar. The participants were mainly habitants of the Uusimaa region, whereas the control population could not be limited to the Uusimaa region to get an adequate number of controls. Unfortunately, many parameters in the questionnaires for cases and controls were not comparable and had to be left out of our study. The question on regularity of fatigue was also questioned using different terms for cases and controls, and had to be re-classified. Obviously, this might cause some unreliability in the results.

For publications III (hypocalcemia) and V (Occipital ICH) the retrospective nature of the study was a limitation. Even though the patients in the original cohort were consecutive, there was a large number of patients without calcium testing, as testing calcium routinely did not belong to the protocol in our center. It cannot be ruled out that selection bias would exist for measuring calcium for certain patients. As we had no certain time point for control imaging, and all patients did not have follow-up imaging, ICH growth could not be assessed. As functional outcome of the patients was not known, we were not able to study the effect of hypocalcemia to functional recovery.

For occipital ICH patients, the mRS was defined retrospectively, and even though the electronic medical files are extensive in Finland, the mRS needed to be grouped, and for every patient it was not possible to reconstruct the exact mRS value at a certain time point. The patients were not routinely screened for VFD by standard automated perimetry. As the number of occipital ICH patients was small, the statistical analyses are less reliable.

6.3 Implications for future research

As our cohort was rather small, it would be interesting to combine ICH patients from different parts of Finland for a risk factor analysis, and possibly with a wider set of questions that would correspond to the already-existing FINRISK

study. Also for the trigger study, a multicenter study reaching a substantially larger patient number would bring additional power to the analyses.

Interesting topic for future research would be to analyze the effect of hypocalcemia and its causes more thoroughly in a prospective setting, ideally taking into consideration the level prior to index ICH. More extensive laboratory testing in order to evaluate the causes of hypocalcemia could be done (including vitamin D as well as parathyroid hormone). The timing of the laboratory testing could be as early as possible, preferably before intravenous fluid administration, and possibly include repeated laboratory sampling to find out how time effects the calcium values. Better evaluation of functional recovery could be evaluated as well as testing if and how correction of hypocalcemia has any effect on patients' prognosis.

The relationship of depression before and after ICH would be interesting to perform in a larger cohort of ICH patients, and include more thorough testing of depression, including a structured evaluation of the symptoms, such as Beck's Depression Inventory, as well as follow-up of the patients.

7 Conclusions

Of the studied risk factors, hypertension was associated with risk of ICH among all patients and in the group of patients under 70 years of age. Fatigue prior to ICH was more common among all ICH cases, which might be linked to a combination of underlying factors causing fatigue (such as sleep apnea), need for longer resting and different psychosocial factors.

We found that physical triggers i.e. factors that raise blood pressure abruptly, associate with the timing of ICH, potentially serving as triggering factors for ICH.

Admission hypocalcemia associated with larger ICH volumes. Patients with admission hypocalcemia had a higher 90-day mortality compared to normocalcemic patients (53.1% vs. 34.5%), due to their larger ICH volumes.

Stroke severity, comorbidities and age were associated with HRQoL after ICH. Feelings of depression before ICH had a stronger influence on reporting depression/anxiety after ICH than stroke severity-related and outcome parameters. Simple questioning of premorbid feelings of depression could help identify ICH patients at risk for depression.

Compared to other ICH patients, occipital ICH was less frequent, the patients were younger, had milder neurological deficits, smaller ICH volumes, more often structural etiology, and better outcomes. The risk for epilepsy was, however, similar to other ICH patients.

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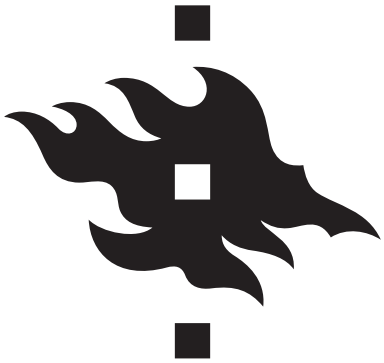

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