OULU 2016
D 1346

ACTA UNIVERSITATIS OULUENSIS

Pekka Löppönen

PRECEDING MEDICATION, INFLAMMATION, AND HEMATOMA EVACUATION PREDICT OUTCOME OF INTRACEREBRAL HEMORRHAGE

A POPULATION BASED STUDY

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
OULU UNIVERSITY HOSPITAL;
MEDICAL RESEARCH CENTER OULU

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Academic Dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 1 of Oulu University Hospital, on 4 May 2016, at 12 noon

UNIVERSITY OF OULU, OULU 2016

Acta Univ. Oul. D 1346, 2016

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ISBN 978-952-62-1127-5 (Paperback)
ISBN 978-952-62-1128-2 (PDF)

ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)

Cover Design
Raimo Ahonen

JUVENES PRINT
TAMPERE 2016

Löppönen, Pekka, Preceding medication, inflammation, and hematoma evacuation predict outcome of intracerebral hemorrhage. A population based study

University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Oulu University Hospital; Medical Research Center Oulu

Acta Univ. Oul. D 1346, 2016

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Abstract

Primary intracerebral hemorrhage (pICH) is a severe, suddenly occurring disease involving high mortality and poor functional outcome. In the absence of curative treatment patient management is mainly supportive with the emphasis on preventing hematoma enlargement and complications. Better understanding of the factors predicting outcome are needed to define effective treatments.

An unselected population-based registry study of 982 pICH patients admitted to Oulu University Hospital during the years 1993 to 2008 was conducted

The study revealed that concomitant use of warfarin and serotonin-modulating antidepressants at the time of pICH increases the case fatality rate compared to patients with warfarin alone.

An elevated C-reactive protein value on admission was an independent predictor of unfavorable outcome after pICH. This association was not explained by pre-existing heart disease, diabetes, severity of the bleeding, or infections.

Patients undergoing surgical hematoma evacuation were observed to have improved 3-month survival compared to conservatively treated patients. Improved survival was noticed especially in patients with ≤70 years of age with ≥30ml supratentorial ICHs. Hematoma evacuation did not improve functional outcome.

Earlier ischemic stroke was found to be an independent predictor of recurrent pICH. Diabetes seemed to increase and treated hypertension decrease the risk for fatal recurrence. Aspirin or serotonin-modulating antidepressants did not seem to increase the risk of recurrence.

Keywords: C-reactive protein, hematoma evacuation, intracerebral hemorrhage, outcome, recurrence, serotonin-modulating antidepressants, warfarin

Löppönen, Pekka, Edeltävän lääkityksen, tulehduksen ja leikkaushoidon vaikutus aivoverenvuodon ennusteeseen. Väestöpohjainen tutkimus
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Oulun yliopistollinen sairaala; Medical Research Center Oulu
Acta Univ. Oul. D 1346, 2016
Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Primääri aivoverenvuoto (pICH) on vakava, yhtäkkisesti alkava sairaus, johon liittyy korkea kuolleisuus ja vaikea vammautuminen. Parantavan hoidon puuttuessa on hoito lähinnä elintoimintoja tukevaa vuodon laajenemisen ja komplikaatioiden estämistä. Ennusteeseen vaikuttavien tekijöiden parempi tunteminen on ehto tehokkaiden hoitojen löytämiseksi.

Väitöskirjatutkimustani varten kerättiin Oulun yliopistollisen sairaalan alueelta vuosien 1993-2008 aikana 982 aivoverenvuotoon sairastuneen potilaan väestöpohjainen aineisto.

Tutkimus osoitti, että varfariinin ja selektiivisen serotoniinin takaisinoton estäjän (SSRI) yhteiskäyttö aivoverenvuodon aikana lisäsi kuolevuutta pelkkään varfariiniin nähden.

Alkuvaiheen koholla oleva C-reaktiivinen proteiini oli itsenäinen aivoverenvuodon jälkeistä vammautuneisuutta ennustava tekijä. Yhteys ei selittynyt olemassa olevalla sydänsairaudella, diabeteksella, aivoverenvuodon vaikeudella tai infektioilla.

Kirurginen aivoverenvuodon poistoleikkaus paransi kolmen kuukauden ennustetta verrattuna potilaisiin ilman leikkausta. Erityisesti leikkaus auttoi alle 70-vuotiaita potilaita, joilla oli yli 30 millilitran kokoinen pinnallisempi vuoto. Leikkaus ei parantanut fyysistä kuntoutumista.

Aiempi sairastettu aivoinfarkti oli itsenäinen aivoverenvuodon uusiutumista ennustava tekijä. Diabetes saattaa lisätä ja hoidossa oleva verenpainetauti laskea riskiä tappavaan uusintavuotoon. Aspiriinin tai SSRI:n käyttö eivät lisänneet uusintavuodon riskiä.

Asiasanat: aivoverenvuoto, C-reaktiivinen proteiini, ennuste, leikkaushoito, SSRI-lääkkeet, uusiutuminen, varfariini

Acknowledgements

This study was carried out in the Department of Neurosurgery, Oulu University Hospital.

I wish to show my greatest gratitude to Professor Sami Tetri, MD, PhD, for his guidance and supervision. He first introduced me to the clinical work of neurosurgery but quite early on also to the field of research. His never-ending enthusiasm and critical point-of-view make him not only a productive researcher but an excellent supervisor as well. He advised me both in science and in life during these years and for this I am forever grateful.

I also wish to thank Professor Emeritus Matti Hillbom, MD, PhD, for his supervision. He is an experienced scientist with a comprehensive vision of neurological literature thus giving start to this whole project. His wisdom and expertise made these publications possible.

I want to warmly thank my research group. Docent Seppo Juvela, MD, PhD, showed remarkable understanding in neurosurgical science and in bioanalytics and was always eager to help me in times of trouble. I thank Juha Huhtakangas, MD, PhD, Pertti Saloheimo, MD, PhD, Michaela K. Bode, MD, PhD, and Cheng Qian, MD, for their collaboration in this project, too.

I show my gratitude for my follow-up group Professor John Koivukangas, MD, PhD, Docent Timo Kumpulainen, MD, PhD, and Tarja Haapaniemi, MD, PhD, for their co-operation.

I wish to thank my colleagues at Oulu University Hospital Department of Neurosurgery for their support at the beginning of my clinical and academic career.

I want to thank secretaries Mirja Karppinen and Mirja Kouvala for their help during these years.

The official reviewers of this thesis Docent Juhana Frösen, MD, PhD, and Docent Mikael von and zu Fraunberg, MD, PhD, are gratefully acknowledged for their constructive comments. I also wish to thank Tarja Manninen, MA, for revising the English language.

My parents and colleagues Professor Heikki Löppönen, MD, PhD, and Docent Tuija Löppönen, MD, PhD, deserve great gratitude. After these 32 years they still remain as parental and professional role models for me. I thank warmly also my brother Juha and my sister Anni for giving me perspective for what is actually important in life.

Finally I wish to express my dearest gratitude to my beloved wife Maija for all her patience, support, and help that has made this work possible, and my daughter Leona for cheering me with her heart-melting laughter. I eagerly wait to spend my spare time again with you. “I love you. That is all.”

This study was financially supported by Oulu University Hospital, Suomen Lääketieteen Säätiö, and Pohjois-Suomen Terveydenhuollon Tukisäätiö who are gratefully acknowledged.

Seinäjoki, February 2016 Pekka Löppönen

Abbreviations

AHA	American Heart Association
APOE	Apolipoprotein E
ASA	American Stroke Association
CAA	Cerebral amyloid angiopathy
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
EVD	External ventricular drainage
FFP	Fresh frozen plasma
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
HR	Hazard ratio
ICH	Intracerebral hemorrhage
ICP	Intracerebral pressure
INR	International normalized ratio
IVH	Intraventricular hemorrhage
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
pICH	Primary intracerebral hemorrhage
PIT	Platelet infusion therapy
PTCC	Prothrombin complex concentrate
rVIIa	Recombinant factor VIIa
SAH	Subarachnoid hemorrhage
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
WA-(p)ICH	Warfarin-associated (primary) intracerebral hemorrhage

List of original publications

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I Löppönen P, Tetri S, Juvela S, Huhtakangas J, Saloheimo P, Bode MK & Hillbom M (2014) Association between warfarin combined with serotonin-modulating antidepressants and increased case fatality in primary intracerebral hemorrhage: a population-based study. J Neurosurg 120: 1358–1363.

II Löppönen P, Qian C, Tetri S, Juvela S, Huhtakangas J, Bode MK & Hillbom M (2014) Predictive value of C-reactive protein for the outcome after primary intracerebral hemorrhage. J Neurosurg 121: 1374–1379.

III Löppönen P, Tetri S, Juvela S, Huhtakangas J, Saloheimo P, Bode MK, Koivukangas J & Hillbom M (2013) A population based study of outcomes after evacuation of primary supratentorial intracerebral hemorrhage. Clin Neurol Neurosurg 115: 1350–1355.

IV Huhtakangas J, Löppönen P, Tetri S, Juvela S, Saloheimo P, Bode MK & Hillbom M (2013) Predictors for recurrent primary intracerebral hemorrhage: a retrospective population-based study. Stroke 44: 585–590.

Contents

1 Introduction

Intracerebral hemorrhage (ICH) occurs when a blood vessel within the brain ruptures thus causing the blood to leak inside the brain tissue. In primary intracerebral hemorrhage (pICH) bleeding occurs spontaneously without a secondary cause for the hemorrhage. Bleeding increases intracranial pressure and causes damage to the brain cells. The symptoms of ICH are usually progressing neurological deficits depending on the location and volume of the hematoma (Ropper & Davis 1980). ICH can lead to impaired consciousness, coma, or even death. Yet, no curative treatment has been found and several questions still remain concerning the optimal treatment of these patients.

In the absence of curative treatment patient management is mainly supportive with the emphasis on preventing hematoma enlargement and complications. Better understanding of all the factors predicting outcome are needed to define more effective treatments.

The use of warfarin (Garcia-Rodriguez *et al.* 2013) and aspirin (He *et al.* 1998) are associated with an increased risk of ICH. Due to antithrombotic effects serotonergic antidepressants are also associated with intracerebral bleeding (Shin *et al.* 2014). Warfarin and antidepressants are widely used drugs with interactions predisposing to severe bleeding (Hackam & Mrkobrada 2012).

Difficulties in inventing better treatments and predicting patient outcome after ICH have raised interest in patients' biomarkers such as C-reactive protein (CRP). The association between CRP and patient outcome has not yet been conclusively determined (Hasan *et al.* 2012).

Surgical hematoma evacuation is thought to reduce intracranial pressure and increase brain perfusion (Fernandes *et al.* 2000b). Potential risks include additional damage to the viable brain tissue, infections, and re-bleeding complications. The role of surgical treatment is controversial but some patients might benefit from hematoma evacuation (Mendelow *et al.* 2013).

Despite proper initial management, up to 4 percent of patients suffer a recurrent ICH (Hanger *et al.* 2007). Concerning risks for a recurrence such factors as medication, genetics, and patient history have been suggested but not all causes have been defined properly.

This study was designed to investigate case fatality among ICH patients using warfarin and serotonergic antidepressants. The predictive value of CRP concerning outcome is also clarified. Patient groups who might benefit from

surgical hematoma evacuation are explored. In addition, factors leading to a recurrence of ICH are investigated.

2 Review of the literature

2.1 Definition of ICH

Intracerebral hemorrhage can be categorized into spontaneous ICH and traumatic ICH. Spontaneous ICH is classified as primary intracerebral hemorrhage (pICH) when no secondary cause for bleeding such as arteriovenous malformations, aneurysms, tumors, or cavernous angiomas can be found. Generally speaking ICH usually refers to primary intracerebral hemorrhage.

2.2 Epidemiology

The overall global incidence of pICH is 24.6 per 100 000 person years and increases with age (van Asch *et al.* 2010). Incidence has not been reported to significantly change from 1980 to 2006. There is a trend towards lower incidence in women than men though this difference is not statistically significant. Incidence varies between different regions and in Asia it is almost twofold compared to elsewhere. The incidence of pICH in Northern Ostrobothnia is 17 per 100 000 person years (Huhtakangas *et al.* 2011) and is comparable to observations of the whole Finland (Meretoja *et al.* 2010).

2.3 Risk factors for ICH

Studies indicate that hypertension is the single most important risk factor with at least a 9-fold increased risk of ICH (O'Donnell *et al.* 2010). Other significant risk factors include age, smoking, obesity, unhealthy cardiovascular diet, diabetes, and alcohol intake (Emerging Risk Factors Collaboration *et al.* 2010b, O'Donnell *et al.* 2010). Cerebral amyloid angiopathy (CAA) that is a vascular, degenerative disease also causes an increased ICH risk (Viswanathan & Greenberg 2011). Familial screenings to prevent intracranial aneurysm ruptures have been successful (Ronkainen *et al.* 1998) but models to find patients with an increased familial risk for ICH are still underway (Lindgren 2014).

2.4 Clinical presentation

Clinical symptoms usually include progressing neurological defects depending on the location of the hematoma. Symptoms tend to proceed during minutes or hours (Brott *et al.* 1997). In comparison, ischemic attacks or subarachnoid hemorrhages tend to begin abruptly. If bleeding continues to a larger hematoma vomiting and headache can occur due to increased intracranial pressure. About 14 % of patients present seizures within the week after the ICH (De Herdt *et al.* 2011).

2.5 Treatment

The updated treatment guidelines by the American Heart Association and the American Stroke Association (AHA/ASA) (Hemphill *et al.* 2015) recommend rapid diagnosis confirmation with radiological brain imaging, usually by a head CT (computed tomography) scan. Defects in coagulation factors or thrombocytes should be treated. Further, thromboembolisms should be prevented carefully. Blood pressure and blood glucose levels should be tested and treated if abnormal. Patient management and monitoring should happen in intensive care unit. Multidisciplinary rehabilitation is recommended.

The size of a hematoma is a strong predictor of outcome (Broderick *et al.* 1993) and surgery is a way to decrease that volume. Surgery might also prevent re-bleeding and hematoma growth when performed early (Gregson *et al.* 2012). Many clinical studies have demonstrated a possible benefit from surgery but larger randomized controlled trials have not confirmed this gain (Mendelow *et al.* 2013). Surgical hematoma evacuation might show evidence of benefit on certain patients but definitive guidelines are still needed.

2.6 Mortality and outcome

The global median case fatality at 1 month is 40.4% (van Asch *et al.* 2010). Less than half of patients survive 1 year and less than one third survive 5 years (Poon *et al.* 2014). The independency rate after pICH has been estimated to vary from 12% to 39% (van Asch *et al.* 2010).

Generally reported factors affecting mortality after ICH are a low level of consciousness, age, the infratentorial location of hematoma, hematoma size, and the presence of intraventricular hemorrhage (Hemphill *et al.* 2001). Regardless of the hematoma size, hematoma growth has also been found to be an independent

determinant of mortality and functional outcome (Davis *et al.* 2006). The use of anticoagulants at the time of ICH is an independent predictor of death (Cucchiara *et al.* 2008a, Huhtakangas *et al.* 2011). Antiplatelet use increases mortality as well (Saloheimo *et al.* 2006, Thompson *et al.* 2010).

2.7 Effect of medication on the ICH outcome

The effectiveness of oral anticoagulants has been proved clearly in several diseases although they increase the risk of bleeding (Hirsh *et al.* 2003). Besides, oral anticoagulants are among the drugs with most interactions with other drugs. Warfarin has interactions with several foods and drugs including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs) (Hirsh *et al.* 2003, Holbrook *et al.* 2005). The concomitant use of warfarin with interacting drugs is associated with a 3- to 4.5-fold risk of serious bleeding (Gasse *et al.* 2005). Several different mechanisms for interactions are possible. The most important medical interaction is caused by inhibiting CYP2C9 enzyme that increases warfarin concentration leading to improved anticoagulation (Cervera *et al.* 2012). The risk of bleeding can also be increased indirectly by inhibiting platelet function with another drug.

2.7.1 Anticoagulants

Warfarin

Warfarin is a common anticoagulant used in prevention of thromboembolism in atrial fibrillation and artificial heart valves. It is also used in treating deep vein thrombosis and pulmonary embolism. Warfarin decreases blood coagulation by inhibiting vitamin K epoxide reductase thus preventing the formation of different clotting factors. The level of anticoagulation is usually assessed by the International Normalized Ratio (INR). The desired INR value is usually 2.0 to 3.0 (Goldstein *et al.* 2011).

Intracerebral hemorrhage is the most devastating risk of anticoagulant therapy (Franke *et al.* 1990). The risk of ICH has been reported to be 2- to 5-fold in warfarin-users compared to non-users (Garcia-Rodriguez *et al.* 2013, Steiner *et al.* 2006). The risk of bleeding is elevated despite appropriate INR monitoring (Jeffree *et al.* 2009). Patients treated with warfarin have a 0.2–1.0% annual risk of

warfarin-associated ICH (WA-ICH) (Aguilar *et al.* 2007, Flaherty 2010). Predictors for WA-ICH are advancing age, prior ischemic stroke, hypertension, leukoaraiosis, earlier use of warfarin, high intensity of anticoagulation, and concomitant antiplatelet use (Flaherty 2010).

In the USA the incidence of warfarin-associated ICH quintupled in the 1990s due to the increased use of warfarin (Flaherty *et al.* 2007). In Northern Ostrobothnia the use of warfarin increased from 1993 to 2008, however, the incidence of warfarin-associated ICHs remained constant (Huhtakangas *et al.* 2011). WA-ICHs account for up to 20% of all ICHs (Flaherty 2010).

Oral anticoagulant use is associated with greater hematoma volume and hematoma expansion (Cucchiara *et al.* 2008b, Franke *et al.* 1990, Radberg *et al.* 1991). Bleeding seems to continue longer in WA-ICH compared to non-WA-ICH creating hematoma expansion (Flibotte *et al.* 2004). Inappropriately high INR values are associated with larger hematomas (Flaherty *et al.* 2008), early hematoma growth (Huttner *et al.* 2006) and an increased risk of death (Koo *et al.* 2004, Rosand *et al.* 2004).

Warfarin use is associated with an elevated risk of intraventricular hemorrhage (IVH) and also the expansion of deep hematomas into the ventricles (Biffi *et al.* 2011). Oral anticoagulation use is associated with an increased risk of lobar hematoma location compared to that of deep hematoma location (Pezzini *et al.* 2014).

The 30-day mortality rate after WA-ICH has been reported to be from 45 to 67% (Aguilar *et al.* 2007, Franke *et al.* 1990, Zubkov *et al.* 2007). In Northern Ostrobothnia the one-year survival of WA-ICH patients was 43.3% and was significantly improved by the introduction of prothrombin complex concentrate (PTCC) treatment (Huhtakangas *et al.* 2012). Warfarin-use at the time of ICH significantly and independently of confounding factors increases the risk of death (Cucchiara *et al.* 2008b, Flibotte *et al.* 2004, Huhtakangas *et al.* 2011, Rosand *et al.* 2004, Saloheimo *et al.* 2006).

Reversal of anticoagulation

In non-emergency situations when immediate reversal of anticoagulation is not mandatory, the reversal of anticoagulation is done by discontinuing the use of warfarin and giving vitamin K. However, this natural reversal of anticoagulation is mediated by a synthesis of new coagulation factors and therefore it takes several days. In case of WA-ICH, additional coagulation factors are needed

promptly after the bleeding is diagnosed, in order to reverse anticoagulation immediately and reduce the imminent risk of hematoma growth. The use of fresh frozen plasma (FFP) and prothrombin complex concentrate (PTCC) have been found efficient (Goldstein *et al.* 2008, Huhtakangas *et al.* 2012). The introduction of PTCC treatment significantly improved survival of WA-ICH patients in Northern Ostrobothnia (Huhtakangas *et al.* 2012). Recombinant factor VIIa (rVIIa) does not improve survival after WA-ICH and it is generally not recommended (Mayer *et al.* 2008, Yuan *et al.* 2010).

New oral anticoagulants

Several new anticoagulants have been marketed lately. These drugs alter different parts of the coagulation cascade reducing fibrin formation (Figure 1). Benefits include more predictable anticoagulation, less interactions and no need for routine blood samples. Direct thrombin inhibitor dabigatran was shown at least equal in stroke prevention in atrial fibrillation (AF) compared to warfarin with less hemorrhagic events (Connolly *et al.* 2009). Rivaroxaban and apixaban are factor Xa inhibitors. Rivaroxaban was shown to be as efficient as warfarin in preventing ischemic events in AF with significantly less ICH (Patel *et al.* 2011). Also, in patients with AF apixaban reduced the risk of ischemic stroke compared to aspirin (Connolly *et al.* 2011) and warfarin (Granger *et al.* 2011) with a lower risk of intracranial hemorrhage. A recent meta-analysis states that dabigatran, rivaroxaban, and apixaban seem equally effective compared to warfarin in preventing ischemic strokes and are generally associated with a lower risk of intracranial bleeding (Gomez-Outes *et al.* 2013). Dabigatran, rivaroxaban and apixaban are approved for stroke prophylaxis in atrial fibrillation.

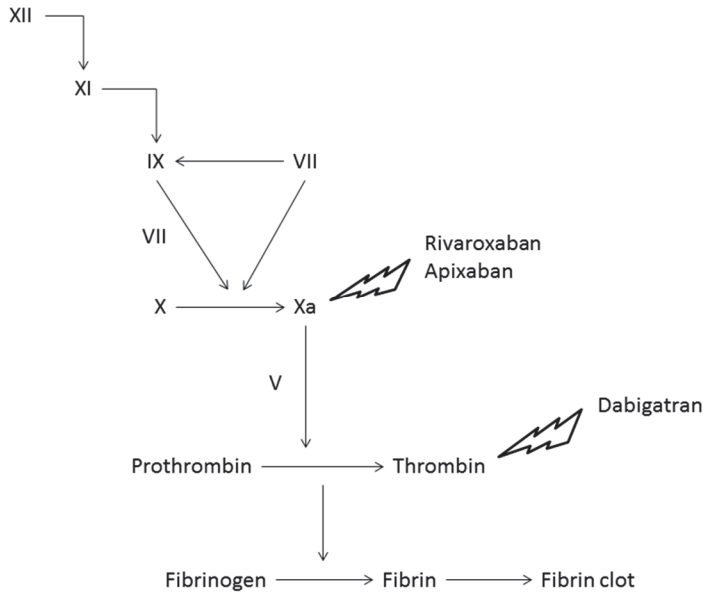

Fig. 1. Coagulation cascade.

The biggest concern with these new anticoagulants has been the lack of specific antidotes. In case of ICH clotting factors are usually restored with PTCC (Suryanarayan & Schulman 2014). PTCC can completely reverse the anticoagulation effect of rivaroxaban but not that of dabigatran (Eerenberg *et al.* 2011). Dabigatran is cleared by renal excretion so optimizing renal function is essential and even hemodialysis can be considered in some cases (James *et al.* 2013). New antidotes are already under investigation and clinical trials are ongoing (Suryanarayan & Schulman 2014). The first results from studies of an antidote to reverse the anticoagulant effects of dabigatran have already been published (Pollack *et al.* 2015) and a new antidote is marketed.

2.7.2 Antiplatelets

Aspirin

Aspirin is often used as an anti-platelet drug preventing heart-attacks and strokes but is also used as an anti-inflammatory drug. Aspirin irreversibly inactivates cyclooxygenase enzyme that blocks thromboxane A_2 production in platelets leading to lower platelet aggregation. Since cyclooxygenase inactivation is irreversible it takes time for platelet aggregation to normalize.

It is estimated that up to 30% of ICH patients are using antiplatelets at the time of ictus (Stead *et al.* 2010) and an early meta-analysis from 1998 showed that the use of aspirin use increases the risk of hemorrhagic stroke (He *et al.* 1998).

However, studies examining the risk of aspirin use have been contradictory. It has been stated that the use of antiplatelet medication at the onset of ICH does not increase hematoma volume or hematoma expansion (Moussouttas *et al.* 2010, Sansing *et al.* 2009). Yet, antiplatelet treatment has also been found to independently predict larger hematoma volume in lobar hematomas (Falcone *et al.* 2013) and it was shown to be associated significantly with hematoma growth (Kuramatsu *et al.* 2012, Saloheimo *et al.* 2006).

Earlier studies also stated that the use of aspirin at the time of ICH is an independent predictor of death (Roquer *et al.* 2005, Saloheimo *et al.* 2006). However, the effect on increased mortality has been questioned (Chen *et al.* 2013) and many studies also report that the use of antiplatelets would not affect functional outcome (Creutzfeldt *et al.* 2009, Foerch *et al.* 2006, Sansing *et al.* 2009, Stead *et al.* 2010).

A recent systematic review screening 2,873 studies states that antiplatelet therapy at the time of ICH is independently associated with increased mortality but not with impaired functional outcome (Thompson *et al.* 2010).

Clopidogrel

Clopidogrel is an adenosine diphosphate receptor antagonist preventing platelet aggregation. It is used for prevention of stroke and myocardial infarction but adverse effects include an increased risk of bleeding. Compared to the use of aspirin, the use of clopidogrel is associated with an enlargement of intracerebral

hematoma size but also elevated in-hospital mortality has been noticed (Campbell *et al.* 2011, Ducruet *et al.* 2010).

It has also been speculated that the mortality rate after ICH is higher among patients with clopidogrel and aspirin dual therapy compared to aspirin alone due to an increased risk of bleeding and hematoma enlargement (Campbell *et al.* 2011). Still, a recent systematic review and meta-analysis states that dual antiplatelet therapy with aspirin combined with clopidogrel does not increase the risk of ICH compared to aspirin monotherapy but effectively decreases the risk of ischemic stroke (Gouya *et al.* 2014).

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) reversibly inhibit cyclooxygenase enzymes and thereby the synthesis of prostaglandins and thromboxanes. This leads to anti-inflammatory response but also increases the risk of bleeding. The effects of NSAIDs on the risk of intracerebral hemorrhage have not been thoroughly studied. Problems with the study protocols include vast over-the-counter sale enabling bias. Earlier studies found no increased risk (Bak *et al.* 2003, Choi *et al.* 2008, Johnsen *et al.* 2003, Thrift *et al.* 1999). A later study suggested that the use of NSAID is associated with an increased risk of hemorrhagic stroke (Chang *et al.* 2010).

Platelet infusion therapy

In order to improve the outcome of ICH patients using antiplatelets the effect of platelet infusion therapy (PIT) is studied. Earlier studies failed to show any benefit from PIT on mortality or outcome (Creutzfeldt *et al.* 2009, Ducruet *et al.* 2010). Minor but promising results have also been reported as results have shown improved platelet activity after PIT but this success has not lead to improved outcome (Naidech *et al.* 2012). A meta-analysis with 6 suitable studies including patients with spontaneous or traumatic ICHs showed no clear benefit from platelet infusion therapy (Batchelor & Grayson 2012). At the moment, a larger multicenter randomized controlled trial called Platelet Transfusion in Acute Intracerebral Hemorrhage is underway (ClinicalTrials.gov Identifier: NCT00699621). This study was initiated by Oulu University Hospital.

2.7.3 Serotonin-modulating antidepressants

Serotonin-modulating antidepressants are a group of medication generally used to treat depression and other mental disorders. Most common drugs are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Inhibiting reuptake increases serotonin level in the synaptic cleft between neurons enabling efficient binding to the postsynaptic receptor. SSRI/SNRIs reduce platelet serotonin level and doing so impair platelet aggregation and platelet secretory response (de Abajo 2011). This leads to an impaired hemostasis. Increasing the use of SSRIs eventually led to a suspicion of increased bleeding (de Abajo *et al.* 1999, Skop & Brown 1996, Verdel *et al.* 2011). Still, in 2012 a Cochrane analysis questioned the excess bleeding risk of SSRIs due to inadequate data from randomized controlled trials (Mead *et al.* 2012).

Moreover, early studies did not find SSRI/SNRIs increasing the risk of ICH (Bak *et al.* 2002, de Abajo *et al.* 2000, Kharofa *et al.* 2007). Nonetheless, in a study from 2009 the use of SSRIs was associated with an increased risk of hemorrhagic stroke and fatal stroke (Smoller *et al.* 2009). Later the use of SSRIs showed an association with the risk of intracranial bleeding (Verdel *et al.* 2011). A meta-analysis was conducted to reveal that the use of SSRIs is associated with an increased risk of intracerebral hemorrhage but also with that of ischemic stroke (Shin *et al.* 2014).

Concomitant use of warfarin and SSRIs has been noticed to increase the risk of bleeding (Cochran *et al.* 2011, Schelleman *et al.* 2011, Wallerstedt *et al.* 2009). It has been speculated that the risk could be increased regardless of the patient's INR value (Wallerstedt *et al.* 2009). The combined use of SSRI/SNRIs with warfarin did not reveal a higher intracerebral bleeding risk in earlier studies (Kharofa *et al.* 2007). However, in 2012 in an epidemiological meta-analysis of over 500 000 patients the use of SSRIs was associated with an increased risk of ICH in mono-therapy but also when combined with oral anticoagulants compared to oral anticoagulants alone (Hackam & Mrkobrada 2012).

Because serotonin-modulating antidepressants reduce platelet aggregation it has been suspected that concomitant use with antiplatelets might increase the bleeding risk. This view is supported by the observation that patients taking SSRI with aspirin after acute myocardial infarction were at an increased risk of gastrointestinal bleeding, hemorrhagic stroke or other bleeding requiring hospitalization (Labos *et al.* 2011). Concomitant use of SSRIs and aspirin with

the increased risk of gastrointestinal bleeding is well documented (Dall *et al.* 2009, Masclee *et al.* 2014). In turn, the use of SSRIs combined with aspirin and the risk of ICH has not been so clear (Kharofa *et al.* 2007).

Serotonergic drugs are categorized as high-, intermediate- and low-affinity SSRIs by their affinity for the serotonin transporter. It has been stated that an increased risk of abnormal bleeding is associated with the degree of serotonin reuptake inhibition (Meijer *et al.* 2004, van Walraven *et al.* 2001). Still, to date studies have not found clear correlation between the drug affinity for the serotonin transporter and the risk of hemorrhagic stroke (Chen *et al.* 2009, Schelleman *et al.* 2011, Verdel *et al.* 2011).

2.8 Effect of laboratory markers on outcome

In ICH the hemorrhage causes direct mechanical damage to brain tissue and increases intracranial pressure leading to reduced tissue perfusion. It has been noticed that in ICH the blood leaking to brain tissue also leads to secondary damage due to inflammation, red cell lysis, and thrombin production. Within hours or days these cascades cause disruption of the blood-brain-barrier, perihematomal edema, and death of brain parenchymal cells (Ziai 2013). In order to reduce or even prevent secondary damage a better comprehension of these reactions is required.

Different biomarkers are investigated to understand physiological and pathological changes in ICH patients. They could be used to measure the difficulty of the bleeding but also the state of recovery. At best they could direct the treatments.

C-reactive protein (CRP) is a sensitive but nonspecific marker of inflammation. Serum CRP level is widely used as a diagnostic test for infections and tissue damage in clinical medicine. In acute infection or trauma CRP can increase up to 1000-fold in hours (Nordestgaard & Zacho 2009). CRP elevation reaches its peak in 48 hours after the initial stimulus and normalizes within 7–14 days if the stimulus ends (Nordestgaard & Zacho 2009).

Elevated CRP levels have been found in patients with hypertension, cardiac disease, diabetes, and smoking (Elkind *et al.* 2009). Elevated CRP levels were noticed to predict an increased risk of myocardial infarction (Buckley *et al.* 2009, Ridker *et al.* 1998). CRP levels have also been found to predict poor outcome after aneurysmal subarachnoid hemorrhage (SAH) (Juvela *et al.* 2012) and ischemic stroke (Elkind *et al.* 2009). An increasing number of studies reveal that

elevated CRP levels are also associated with higher all-cause mortality (Emerging Risk Factors Collaboration *et al.* 2010a, Marsik *et al.* 2008).

A relatively small review and meta-analysis of different biomarkers on hemorrhagic stroke and ischemic stroke patients found no prognostic value of CRP after ICH (Hasan *et al.* 2012). A population-based registry of 152 ICH patients in Germany found no predictive value on admission CRP for 1-year survival or functional outcome (Palm *et al.* 2013). However, there is some evidence of CRP predicting short-term mortality after ICH (Alexandrova & Danovska 2011, Di Napoli *et al.* 2011). CRP levels measured after 48 hours of ICH have been proposed to predict mortality and poor outcome better than admission levels (Di Napoli *et al.* 2012).

ICH often leads to severe disability with impaired mobility and prolonged hospitalization. Infections due to these defects are frequent complications and they worsen the outcome (Diedler *et al.* 2009). However, infections increase the CRP level and could therefore hinder the prognostic value of CRP.

2.9 Operative treatment

In general, surgery could theoretically prevent brain herniation, lower intracerebral pressure (ICP), decrease the mass effect, and remove toxic hematoma dissolution products. These potentially beneficial means were brought down when the first prospective trial published in 1961 found surgery to worsen the outcome after spontaneous ICH compared to conservative treatment (McKissock *et al.* 1961). Since then other small studies have shown contradictory results of the benefit of surgery leaving the question open (Auer *et al.* 1989, Juvela *et al.* 1989). Meta-analysis of the first 7 trials in 2000 remained with no solid conclusions but with a need for new trials (Fernandes *et al.* 2000a).

In 2005 the STICH trial, a large modern prospective study of 1033 patients with spontaneous supratentorial ICH, showed no overall benefit from surgical hematoma evacuation compared to conservative treatment (Mendelow *et al.* 2005). However, some of the results could be biased. Patients were selected only when the benefit from surgery was uncertain and 26% of the patients selected to conservative treatment were later operated on because of clinical deterioration. These factors could have influenced the outcome. Still, some differences between the groups appeared when comparing hematoma size, location, operative technique and level of consciousness but the differences were statistically insignificant.

A Cochrane review of surgery on primary supratentorial ICH was compiled in 2008 (Prasad *et al.* 2008). The results from accepted trials showed that surgery significantly decreased the odds of being dead or dependent after ICH. The authors notified that patient loss and the inadequate quality of most studies included may cause review results to be subject to bias.

In 2012 a meta-analysis was published consisting data of 2186 patients in 8 earlier prospective studies (Gregson *et al.* 2012). This meta-analysis collected raw patient data to find individual groups that might benefit from surgery. The meta-analysis indicated improved outcome after surgery if undertaken within 8 hours after bleeding, or the hematoma size was 20 to 50 ml, or GCS was between 9 and 12, or the patient's age was between 50 and 69 years. There was also a statistically insignificant trend suggesting that surgery might benefit patients with superficial hematomas without IVH.

The latest extensive randomized trial STICH II was published in 2013 (Mendelow *et al.* 2013) based on the results of a subgroup analysis from the first STICH study (Mendelow *et al.* 2005). The patients selected for randomization had a spontaneous ICH $\leq$1 cm from cortex with volume of 10 to 100 ml, no IVH, had arrived within 48h of ictus and were conscious on arrival. A total of 601 patients were recruited. 59% of the surgically treated and 62% of the conservatively treated patients had unfavorable outcome after the 6-month follow-up but the difference was statistically insignificant. The authors interpret that early surgery might have a small but relevant impact on this patient group.

The data from earlier meta-analyses were updated with the STICH II patient data thus combining 15 randomized controlled trials comparing surgical and conservative treatments (Mendelow *et al.* 2013). The results from altogether 3366 patients showed significant advantage from surgical hematoma evacuation in general but also showed significant heterogeneity between studies. This suggests that surgery has a role in treating ICH but some uncertainty remains in patient selection. Still, patients with lobar hematomas without intraventricular bleeding did not benefit from surgery.

The latest guidelines for treating spontaneous ICH were given in 2015 by the American Heart Association and the American Stroke Association (Hemphill *et al.* 2015). Evidence-based recommendations included both the classification of recommendations and level of evidence (Table 1). The only class I recommendation suggests that early hematoma evacuation should be performed on patients with cerebellar hemorrhage and concern of brainstem compression or

hydrocephalus, especially on those hematomas > 3 cm in diameter. In other cases surgery cannot be recommended but may still benefit in life-saving situations.

Table 1. 2015 AHA/ASA guidelines for surgical treatment of ICH.

Recommendations	Class/Level of Evidence
Patients with cerebellar hemorrhage who are deteriorating or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo hematoma evacuation as soon as possible.	Class I, Level B
Patients with cerebellar hemorrhage who are deteriorating or who have brainstem compression and/or hydrocephalus from ventricular obstruction should not be treated with intraventricular drainage.	Class III, Level C
The usefulness of surgery after ICH is uncertain for most patients.	Class IIb, Level A
Early hematoma evacuation is not clearly beneficial compared with hematoma evacuation when patients deteriorate.	Class IIb, Level A
Evacuation of supratentorial hematoma in deteriorating patients might be considered as a life-saving procedure.	Class IIb, Level C
Decompressive craniectomy with or without hematoma evacuation might reduce mortality for patients with supratentorial ICH who are in a coma, have large hematomas with significant midline shift, or have elevated ICP refractory to medical management	Class IIb, Level C
The effectiveness of minimally invasive clot evacuation with stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain	Class IIb, Level B

2.10 Predictors of recurrence

Those surviving ICH are in an increased risk of recurrence. Annual recurrence rates after ICH vary but the latest review and meta-analysis from 2014 (Poon *et al.* 2014) reported the annual risk of recurrence from 1.3% to 7.4%.

To date not much is still known about the risk factors affecting recurrence. Hypertension and higher age have been associated with recurrent ICH (Hanger *et al.* 2007, Vermeer *et al.* 2002). Lobar location also appears to be associated with

recurrence (Hanger *et al.* 2007). Recurrent ICH also appears to be associated with apolipoprotein E (APOE) ε2 or ε4 alleles (Tzourio *et al.* 2008). Anticoagulant medication is an important risk factor for index ICH but naturally also for the recurrent ICH (Kennedy *et al.* 2005). A recent meta-analysis states that out of all eligible studies with multivariable analyses two reported lobar ICH location, two prior ICH and one study reported APOE genotype as independent risk factors for ICH recurrence (Poon *et al.* 2014).

Generally ICH location is thought to reveal underlying causes for bleeding. Deep ICHs are usually considered to occur due to hypertensive vasculopathy and lobar ICHs due to cerebral amyloid angiopathy (CAA) (Bailey *et al.* 2001, Vermeer *et al.* 2002). According to a review in 2001 recurrence after lobar ICH is higher compared to deep ICH (4.4% vs 2.1% per person-years) (Bailey *et al.* 2001). This result of a higher recurrence rate after lobar ICH is also reinforced by other studies suspecting the role of CAA (Hill *et al.* 2000, Viswanathan *et al.* 2006, Weimar *et al.* 2011).

The increasing use of brain imaging such as MRI has found new patient groups in a risk of recurrence. In addition to earlier ICHs also undetected subclinical brain microbleeds appear to increase the risk of ICH (Greenberg *et al.* 2004, Lovelock *et al.* 2010). The risk is higher especially in patients with antithrombotic or anticoagulant medication (Lovelock *et al.* 2010).

The cardiovascular risk factors for ICH and ischemic stroke have similarities. Yet, a systematic review from 2001 reported that the survivors of ICH have a higher risk of a recurrent ICH than those of ischemic stroke (Bailey *et al.* 2001). Since then many observational studies have also stated that the risk for ischemic stroke is higher compared to a recurrent ICH (Flynn *et al.* 2010b, Fogelholm *et al.* 2005, Hill *et al.* 2000, Vermeer *et al.* 2002). Nonetheless, Hanger *et al.* reported that the ICH recurrence rate was 2.1/100/year for the first year and after the first year of the index ICH the risk for recurrent ICH and ischemic stroke were similar (1.2/100/year vs 1.3/100/year) (Hanger *et al.* 2007). Still, a novel population-based study from Sweden noticed that after the index ICH 63% of stroke recurrences were ischemic (Pennlert *et al.* 2014). These conflicting results induce difficulties in determining the risk-benefit ratio for the use of antiplatelets and anticoagulants after ICH.

In addition to previous ischemic events, some evidence has been presented that the risk of ICH might be higher in patients with earlier lacunar infarct compared to non-lacunar infarct (Azarpazhooh *et al.* 2008).

Although antiplatelet use is associated with an increased risk of index ICH the use of antiplatelets has not been found to increase the risk of recurrence (Viswanathan *et al.* 2006, Weimar *et al.* 2011). Also, the use of serotonergic antidepressants is associated with an increased risk of ICH (Hackam & Mrkobrada 2012) but the association with ICH recurrence has not yet been studied.

There are suggestions to avoid statin use after ICH (Westover *et al.* 2011). Current evidence from meta-analysis with 31 trials had no significant correlation with statin use and ICHs. In contrary, statin use seems to decrease the risk of stroke and mortality (McKinney & Kostis 2012).

3 Aims of the research

The series of the studies focused on medications predisposing to ICH, laboratory markers predicting outcome, surgical treatment, and recurrence of ICH in a population based setting. The following questions were addressed:

1. Does concurrent use of serotonin-modulating antidepressants and warfarin increase the case fatality of patients with ICH? (I)
2. Does the admission CRP value predict outcome after ICH? (II)
3. Does surgical hematoma evacuation improve short-term survival or outcome after ICH? Are there specific patient groups that might benefit from hematoma evacuation? (III)
4. What are the independent predictors for recurrent ICH? (IV)

4 Subjects and methods

4.1 Ethics

The study protocol was approved by the Regional Ethics Committee of the Northern Ostrobothnia Hospital District.

4.2 Patients

For the *studies I–IV* a population based registry from 1 January 1993 to 31 December 2008 was retrospectively collected. Altogether 982 patients with pICH were identified in the population of Northern Ostrobothnia Finland. Oulu University Hospital is the only hospital in the area treating acute ICH patients. Only the patients living in the area at the time of the ICH were included. The patients with a secondary cause for the ICH e.g. head trauma, brain tumor, aneurysm, vascular malformation, hematologic malignancy, or hemophilia were excluded. All of the patients fulfilling these inclusion criteria were included. Six of these 982 patients died outside the hospital and were identified by the Causes of Death Register of Statistics Finland. Their ICH was verified by autopsy. The autopsy records included the data on the use of medication at the time of death. Out of 982 patients with pICH, 21 (2%) had to be excluded later because they had already had an intracranial bleeding of some kind before 1993. Earlier hospital records than 1993 were rarely available for thorough examination so a decision was made to exclude them. Unfortunately, unclear intracranial bleeding histories of these 21 patients were not noticed before the submission of *the study III.* Altogether 961 patients had a confirmed first-ever pICH during the years 1993–2008. The population included in the studies presented in this thesis is shown in Table 2.

The study I included 176 patients with first-ever warfarin-associated pICH (WA-pICH).

The study II included 961 first-ever pICH patients. 813 (85%) of 961 patients had their C-reactive protein levels on admission available.

The study III included 982 patients with pICH. Of these 127 (13%) underwent surgical hematoma evacuation and 855 (87%) had conservative treatment.

The study IV included 961 patients with first-ever pICH. 281 (29%) patients were excluded because they had died within 30 days of index bleeding. Altogether 680 patients were included. 58 of 680 patients had a recurrent pICH during the follow-up. Altogether these 58 patients had 68 recurrent pICHs.

Table 2. Characteristics and outcome of 982 patients with primary ICH included in the study population.

Characteristics	Total (n=982)
Men, n (%)	528 (54)
Mean age, yr (SD)	69 (12)
Previous diseases, n (%)	
Hypertension	613 (62)
Cardiac disease	384 (39)
Diabetes	171 (17)
Warfarin use, n (%)	182 (19)
Median GCS score (25^{th} and 75^{th} percentiles)	14 (10, 15)
Mean hematoma volume, ml (SD)	33 (42)
Hematoma volume ≥30 ml, n (%)	348 (35)
Location of the hematoma	
Subcortical	294 (30)
Thalamic	165 (17)
Ganglionic	348 (35)
Infratentorial	129 (13)
Primary intraventricular, multiple and other	46 (5)
Intraventricular extension, n (%)	431 (44)
GOS at 3 months, n (%)	
Favorable	421 (43)
Poor	561 (57)
Died within 7 days, n (%)	151 (15)
Died within 30 days, n (%)	288 (29)
Died within 90 days, n (%)	330 (34)

4.3 Clinical data

Information about the previous diseases and medical history were extracted from the hospital records. This includes current and earlier periods of treatment in Oulu University Hospital. No additional information was needed from the Care Register for Health Care maintained by the National Institute for Health and Welfare. Cardiac disease was considered as earlier myocardial infarction, coronary artery disease, heart failure, or atrial fibrillation. Patients were considered diabetic if they used

hypoglycemic medication or insulin. Patients were considered hypertensive if their blood pressure readings preceding the pICH had repeatedly exceeded 160/90 mmHg in accordance with the WHO/ISH statement (Whitworth & World Health Organization, International Society of Hypertension Writing Group 2003) or if they were taking antihypertensive medication. Information about earlier hypertension was based on patient records and the patients' blood pressure at admission was recorded as another factor. Also the information about dementia, hemorrhagic and ischemic strokes, thrombosis, hematologic malignancy, cancer, liver, or kidney failure was recorded. Ischemic stroke was categorized apart from transient ischemic events and ischemic strokes were diagnosed by head CT examination. The information about increased bleeding tendency i.e. earlier epitaxis, hematuria, or gastrointestinal bleeding was gathered. Current lifestyle matters such as smoking and alcohol drinking were recorded as dichotomized variables according to the data available in the patient records. The patients' height and weight were recorded as well if they were available.

The information about drug use was obtained from the hospital records and double-checked from the national register of prescribed medicines kept by the Social Insurance Institution of Finland. This data includes all drug purchases by individuals linked to their social security numbers. However, the use of aspirin is not all registered because it is also available without prescription in Finland.

The patients' clinical condition was assessed by Glasgow Coma Scale (GCS) (Teasdale & Jennett 1974) on arrival. The blood pressure management, thromboprophylaxis, and the reversal of warfarin treatment were accomplished according to the institution and hospital treatment protocols (Huhtakangas *et al.* 2012, Morgenstern *et al.* 2010, Tetri *et al.* 2008a). The patients who had been on warfarin were immediately given either fresh frozen plasma (FFP) or prothrombin complex concentrate (PTCC) together with vitamin K to restore coagulation factors and to lower the international normalized ratio (INR). This treatment was not given to subjects who were moribund on admission.

4.4 Radiological data

pICH was verified by a brain CT scan on admission. All available CT scans and other imaging examinations were analyzed and the locations and volumes of the hematomas measured by experienced neuroradiologists blinded to the case history of each subject. Two different methods were used to measure hematoma volumes during the study. Most of the scans were analyzed with a planimetric method (Broderick *et al.*

1993) and a small part using the ABC/2 method (Kothari *et al.* 1996). On the basis of their locations the hematomas were classified into subcortical, thalamic, ganglionic (including extension of putaminal hematoma into thalamus and/or subcortical white matter), infratentorial (cerebellum and/or pons) hematomas, and other (primary intraventricular, multiple etc.) hematomas. Subcortical, thalamic, and ganglionic hematomas were categorized as supratentorial. Thalamic and ganglionic hematomas were categorized as deep supratentorial. If aneurysms and arteriovenous malformations were suspected CT, MRI, or digital subtraction angiography was performed immediately. Most survivors were checked for other structural abnormalities by follow-up brain imaging (CT or MRI) 2–3 months after the bleeding.

4.5 Laboratory markers

The blood samples for CRP analysis were obtained at the emergency or the next morning on the ward (<24 hours on admission). The CRP was analyzed with a turbidimetric method (normal values <10 mg/l, coefficient of variation <6%, Siemens Activa).

4.6 Surgical treatment

The hematomas were evacuated by standard craniotomy or through a burr hole. Data on additional need for external ventricular drainage (EVD) was collected. Those undergoing only EVD were classified in the group of conservatively treated patients.

4.7 Outcome statistics

The death records were obtained from the Causes of Death Register for the whole study population. The patients were followed up for 3 months after the ICH at the neurosurgical or neurological outpatient clinic or in the rehabilitation ward of our hospital with the exception of those who showed good recovery at discharge. The latter were assumed to have maintained this state for 3 months unless they had been readmitted. The outcome was assessed according to the Glasgow Outcome Scale (GOS) (Jennett & Bond 1975). For *the studies I, III and IV* the patients with GOS scores of 4–5 (moderate disability or good recovery) were considered to have a favorable outcome, whereas the patients with scores of 1–3 (death, persistent vegetative state or severe disability) were considered to have a poor outcome.

For *the study II* complications during the hospitalization such as infections, thromboembolic complication, cardiac infarctions or bleedings were recorded. The patients with minimal or no disability (GOS 5) were considered to have a favorable outcome, whereas the patients with moderate disability or worse (GOS 1–4) were considered to have an unfavorable outcome.

4.8 Statistical analyses

The data were analyzed with SPSS for Windows (release 20.0.0). The categorical variables were compared by conventional statistical methods such as Fisher's exact two-tailed test and the Pearson Chi-square test. T-tests, Mann-Whitney U-test, a 1-way ANOVA, and/or the Kruskal-Wallis test for nonparametric ANOVA were used for comparisons of the continuous variables. Spearman's rank correlation coefficients (r_s) were used to test univariable associations between the continuous variables. For the life table analysis, each subject was followed up until death or until three months after pICH. Predictors for outcome at 3 months were searched for using unconditional logistic regression. The cumulative risk of death was estimated by the Kaplan-Meier product-limit method, and the curves for the various groups were compared using the log-rank test. Cox proportional-hazards regression analysis was performed to determine the hazard ratios (HR) and 95% confidence intervals (CI). The proportionality assumption was checked. The test for significance was based on changes in log (partial) likelihood. A two-tailed P value of less than 0.05 was considered to be statistically significant.

5 Results

5.1 Concurrent use of serotonin-modulating antidepressants with warfarin increases mortality

The main finding in *the study I* was the increased case fatality after ICH in patients who had received SSRI/SNRIs with warfarin compared to patients with warfarin alone.

Eligible data was available of 176 patients with WA-ICH. The characteristics are presented in *the study I* (appendix). Of these 140 (79.5%) had received warfarin alone, 17 (9.6%) had warfarin combined with aspirin (ASA group), and 19 (10.8%) had warfarin combined with SSRI/SNRI (SSRI/SNRI group). No significant differences in the baseline characteristics or treatments were found between the groups. The 30-day case fatality between the groups was also insignificant (p=0.063).

Survival among the groups is presented in Figure 2. The 30-day case fatality rates were 50.7% for warfarin alone, 58.8% for the ASA group, and 78.9% for the SSRI/SNRI group (p=0.033 SSRI/SNRI group compared to warfarin alone). Three patients in the SSRI/SNRI group had used both aspirin and SSRI/SNRI with warfarin. After excluding these patients the difference between the SSRI/SNRI group and the warfarin group alone remained even more significant (87.5% vs 50.7%, p=0.006).

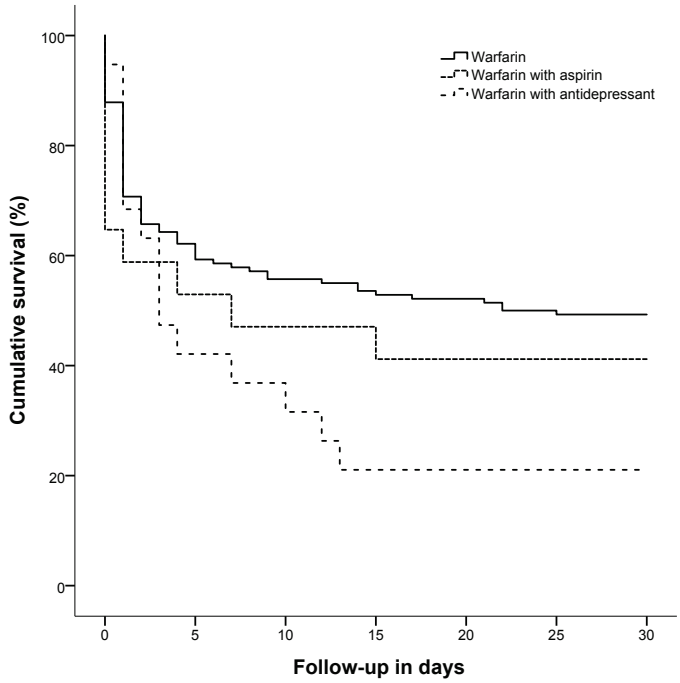

Fig. 2. Cumulative case fatality of plCH patients by medication. Log-rank test showed significant difference between patients with warfarin combined with SSRI/SNRI compared to patients with warfarin alone (p=0.033). (Löppönen *et al*, 2014, published by permission of American Association of Neurological Surgeons).

In univariable analysis the independent predictors of death within 30 days were a low GCS score, a large hematoma size, intraventricular hemorrhage, a high INR value, and SSRI/SNRI combined with warfarin, whereas the PTCC treatment showed a protective effect. In multivariable analysis a low GSC score, the large hematoma size, and SSRI/SNRI combined with warfarin (adjusted HR 2.10, 95% CI 1.13–3.92, p=0.019) significantly and independently predicted 30-day case fatality (Table 3).

Table 3. Predictors of Case Fatality at 30 Days after pICH.

Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)
Medication		
Warfarin with aspirin	1.35 (0.70–2.63)	2.20 (0.86–5.64)
Warfarin with SSRI/SNRI	1.76 (1.00–3.08)*	2.10 (1.13–3.92)†
Age (per year)	1.01 (0.98–1.03)	1.02 (0.99–1.05)
Cardiac disease	1.45 (0.88–2.37)	1.63 (0.92–2.90)
Diabetes	0.94 (0.59–1.49)	1.03 (0.61–1.74)
Hematoma size (per 10 ml)	1.11 (1.08–1.13)‡	1.05 (1.02–1.09)‡
GCS on admission (per unit)	0.82 (0.78–0.86)‡	0.85 (0.79–0.90)‡
Intraventricular hemorrhage	2.56 (1.66–3.94)‡	1.21 (0.73–2.00)
INR on admission	1.23 (1.05–1.45)‡	1.06 (0.87–1.30)
PTCC treatment	0.38 (0.21–0.70)‡	0.55 (0.29–1.07)
Hematoma evacuated	0.90 (0.53–1.77)	0.72 (0.36–1.43)

In multivariable analysis the hazard ratios were also adjusted for sex.

*p=0.048, †p=0.019, ‡p<0.01

5.2 CRP as a predictor of unfavorable outcome after pICH

The main finding in *the study II* was that the elevated CRP level measured within 24 hours of ictus is an independent predictor of unfavorable outcome.

Of 961 patients 192 (24%) had a favorable and 615 (76%) an unfavorable outcome within 3 months. The baseline and clinical characteristics are presented in Table 4. The patients with unfavorable outcome were significantly more often older ones and women. They also had more often diabetes, cardiac disease, warfarin medication, a lower level of consciousness, a larger hematoma, intraventricular bleeding, hematoma evacuation, infectious complications, and a higher level of CRP on admission. Urinary tract infection was observed in 8 (4%) of 192 patients with favorable outcome and in 80 (13%) of 615 patients with unfavorable outcome ($p<0.001$). Three (2%) of the patients with favorable outcome and 125 (20%) of the patients with unfavorable outcome were diagnosed with pneumonia ($p<0.001$).

Table 4. Baseline and clinical characteristics of the patients with pICH, according to outcome.

Variable	Favorable Outcome (n=192)	Unfavorable Outcome (n=615)	Total (n=807)	p value
Mean age, yr±SD	64±11	71±12	69±12	<0.001
Men, n (%)	116 (60)	320 (52)	436 (54)	0.042
Previous diseases, n (%)				
Hypertension	124 (65)	390 (63)	514 (64)	0.769
Diabetes	20 (10)	125 (20)	145 (18)	0.002
Cardiac disease	52 (27)	257 (42)	309 (38)	<0.001
Warfarin medication	19 (10)	128 (21)	147 (18)	<0.001
Mean INR on arrival, unit±SD	1,2±0,6	1,6±1,1	1,5±1,0	<0.001
Mean CRP value, per mg/l±SD	7,3±5,5	12,6±26,0	11,3±23,0	0.005
Median GCS (25 & 75 percentiles)	15 (14,15)	13 (6,15)	14 (10,15)	<0.001
Mean hematoma volume, ml±SD	12±16	41±45	34±42	<0.001
Intraventricular hemorrhage, n (%)	31 (16)	339 (55)	370 (46)	<0.001
Subcortical hematoma, n (%)	64 (33)	173 (28)	237 (29)	0.167
Hematoma evacuation, n (%)	11 (6)	98 (16)	109 (14)	<0.001
Infectious complications, n (%)				
Urinary tract	8 (4)	80 (13)	88 (11)	<0.001
Pneumonia	3 (2)	125 (20)	128 (16)	<0.001
Dead within 3 months, n (%)	0 (0)	280 (46)	280 (35)	<0.001

The admission CRP values were significantly higher in patients with diabetes, cardiac disease, warfarin medication, and impaired outcome at 3 months. The admission CRP values are presented in *the study II* (appendix). A threshold in CRP value was noticed between good recovery and unfavorable outcome (mean, per mg/l±SD, 7.3±5.5 vs 12.6±26.0, $p<0.005$). The hematoma size correlated with the admission CRP levels ($r_s=0.084$, $p=0.018$). The GSC score on arrival showed significant correlation with the CRP values after 24 hours of ictus but not with the admission CRP values (at admission: $r_s=0.067$, $p=0.060$, after 24 hours: $r_s=0.237$, $p<0.001$). The CRP value on admission did not correlate with diagnosed infections but repeated CRP values taken later during the hospitalization showed a correlation with clinical infections ($p<0.01$).

In multivariable analysis the significant predictors of unfavorable outcome were older age, diabetes, low GCS on arrival, hematoma size, intraventricular bleeding, non-subcortical location, and elevated CRP level on admission. The risk

for an unfavorable outcome increased 1.4-fold every 10-mg/l increase in CRP level (OR 1.41 per 10mg/l [95% CI 1.09–1.81], p<0.001) (Table 5).

The patients who later developed pneumonia (n=128) had their CRP levels rising higher compared to those without pneumonia (47.9±68.0 vs 21.5±35.8 within 48 hours and 67.3±59.1 vs 25.5±42.5 within 96 hours, p<0.001 for both). After excluding the patients who developed pneumonia and repeating the multivariable analysis the high CRP level on admission still predicted an unfavorable outcome (OR 1.45 per 10mg/l [95% CI 1.10–1.90], p<0.01).

Table 5. Predictors of an unfavorable outcome after pICH.

Variable	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age (per year)	1.05 (1.04–1.06)*	1.06 (1.04–1.08)*
Cardiac disease	1.93 (1.35–2.76)*	0.96 (0.60–1.53)
Diabetes	2.19 (1.33–3.63)†	1.99 (1.09–3.64)†
GCS (per unit)	0.65 (0.58–0.73)*	0.75 (0.67–0.84)*
Hematoma size (per ml)	1.05 (1.04–1.07)*	1.05 (1.03–1.07)*
Intraventricular hemorrhage	6.40 (4.22–9.71)*	2.70 (1.66–4.38)*
Subcortical hematoma location	0.78 (0.55–1.11)	0.33 (0.20–0.54)*
CRP on admission (per 10mg/l)	1.37 (1.10–1.70)‡	1.41 (1.09–1.81)‡

The odds ratios in the multivariable analysis were also adjusted for sex.

*p<0.001, †p<0.05, ‡p<0.01

5.3 Surgical hematoma evacuation improves survival

The main finding in *the study III* was improved 3-month survival of ICH patients who underwent surgical hematoma evacuation compared to those with conservative treatment and especially of patients with ≤70 years of age with ≥30 ml supratentorial ICHs. Hematoma evacuation did not improve functional outcome at 3 months.

Of 982 patients with pICH altogether 127 (13%) underwent surgical hematoma evacuation. Those 855 patients without hematoma evacuation (87%) were considered as conservatively treated patients. The surgically treated patients were significantly younger than those without operation (mean age, 63 vs 70, p<0.001). The patients with hematoma evacuation had significantly larger hematomas (66 ml vs 28 ml, p<0.001) and significantly lower GCS scores (median GCS, 11 vs 14, p<0.001). Craniotomy was used on 62% and trepanation on 38% on hematoma evacuation. Subcortical hematoma location was significantly more often found in the surgically treated patients (68% vs 24%, p<0.001). No significant differences were found in cumulative mortality at 7, 30,

or 90 days between the patients who were selected to surgery compared to the patients treated conservatively. Furthermore, the patients ending up in the surgical group still showed poorer functional outcome at 3 months (72% vs 55%, $p<0.001$) (Table 6).

However, the multivariable analysis showed hematoma evacuation independently of confounding factors to lower mortality at 7, 30, and 90 days ($p<0.03$). Other significant predictors of death at 90 days were larger hematoma size, low GSC score, presence of intraventricular hemorrhage, infratentorial location, warfarin use, and older age. The multivariable analysis is presented in *the study III* (appendix).

Table 6. Characteristics and outcome of 982 patients with primary ICH.

Characteristics	Hematoma evacuation (n=127)	Conservative treatment (n=855)	Total (n=982)
Men, n (%)	63 (50)	465 (54)	528 (54)
Mean age, yr (SD)	63 (11.2)*	70 (12.2)	69 (12.3)
Previous diseases, n (%)			
Hypertension	79 (62)	534 (62)	613 (62)
Cardiac disease†	53 (42)	331 (39)	384 (39)
Diabetes	22 (17)	149 (17)	171 (17)
Warfarin use, n (%)	20 (16)	162 (19)	182 (19)
Median GCS score (25^{th} and 75^{th} percentiles)	11 (6, 14)*	14 (10, 15)	14 (10, 15)
Mean hematoma volume, ml (SD)	66 (36)*	28 (40)	33 (42)
Hematoma volume ≥30 ml, n (%)	111 (87)*	237 (28)	348 (35)
Location of the hematoma			
Subcortical	86 (68)*	208 (24)	294 (30)
Thalamic	4 (3)	161 (19)	165 (17)
Ganglionic‡	29 (23)	319 (37)	348 (35)
Infratentorial§	8 (6)	121 (14)	129 (13)
Primary intraventricular, multiple and other	0 (0)	46 (5)	46 (5)
Intraventricular extension, n (%)	77 (61)*	354 (41)	431 (44)
GOS at 3 months, n (%)			
Favorable	36 (28)*	385 (45)	421 (43)
Poor	91 (72)*	470 (55)	561 (57)
Died within 7 days, n (%)	22 (15)	129 (17)	151 (15)
Died within 30 days, n (%)	43 (34)	245 (29)	288 (29)
Died within 90 days, n (%)	47 (37)	283 (33)	330 (34)

*p<0.001 for difference between hematoma evacuation group and conservatively treated group

†includes previous myocardial infarction, coronary artery disease, hearth failure and atrial fibrillation

‡includes putamen, basal ganglia and extension of putaminal hematoma into thalamus and/or subcortical white matter

§includes cerebellum and pons

Because of the variation in hematoma size and patient age between the groups subgroup analyses were also made with younger age and larger hematomas. There were altogether 154 patients with ≤70 years of age and ≥30 ml hematomas. There were 78 (51%) surgically treated and 76 (49%) conservatively treated patients in these subgroups. Warfarin use and deep supratentorial hematomas were less common and subcortical hematomas were more general in the surgical group. Mortality at 90 days was significantly higher in the conservatively treated group ($p<0.05$).

Of these 154 patients 138 had supratentorial (66 subcortical and 72 deep) hematomas. In multivariable analysis of the patients with supratentorial hematomas (138) the independent predictors of death at 90 days were low GCS on admission ($p<0.001$), hematoma size ($p<0.02$), and IVH ($p<0.01$). Hematoma evacuation independently lowered ($p<0.001$) mortality at 90 days. For the patients with subcortical hematomas (66) the hematoma size increased ($p<0.01$) and the hematoma evacuation lowered ($p<0.02$) mortality at 90 days. Also, for the patients with deep supratentorial hematomas (72) the low GCS on admission increased ($p<0.001$) and the hematoma evacuation lowered ($p<0.02$) mortality at 90 days (Table 7).

The cumulative survival at 90 days among these 138 patients with ≤70 years of age and ≥30 ml supratentorial hematomas was significantly better when the hematoma was evacuated compared to conservative treatment ($p=0.031$) (Figure 3). The functional outcome at 90 days was not improved by surgery among these patient groups.

Table 7. Predictors for 90-day mortality in 138 patients ≤70 years of age with ≥30 ml supratentorial ICH obtained by multivariable Cox regression analyses.

Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)
Supratentorial location (n=138)		
Hematoma size (per 10 ml)	1.15 (1.10–1.20)*	1.07 (1.01–1.13)‡
GCS on admission (per unit)	0.80 (0.74–0.85)*	0.83 (0.76–0.90)*
Intraventricular hemorrhage	9.88 (3.58–27.31)*	6.33 (2.15–18.58)†
Warfarin use	2.76 (1.56–4.87)*	1.47 (0.75–2.88)
Age (per year)	1.03 (1.00–1.07)#	1.04 (1.00–1.08)
Hematoma evacuation	0.58 (0.35–0.97)§	0.26 (0.14–0.49)*
Subcortical location (n=66)		
Hematoma size (per 10 ml)	1.31 (1.19–1.43)*	1.34 (1.13–1.56)†
GCS on admission (per unit)	0.81 (0.71–0.93)†	0.92 (0.79–1.08)
Intraventricular hemorrhage	17.08 (2.27–128.56)†	5.86 (0.54–63.62)
Use of warfarin	2.11 (069–6.48)	3.78 (0.94–15.14)
Age (per year)	1.01 (0.95–1.07)	1.02 (0.95–1.10)
Hematoma evacuation	0.88 (0.31–2.47)	0.15 (0.04–0.68)‡
Deep supratentorial location (n=72)		
Hematoma size (per 10 ml)	1.11 (1.05–1.17)*	1.06 (1.00–1.13)
GCS on admission (per unit)	0.79 (0.72–0.86)*	0.80 (0.72–0.90)*
Intraventricular hemorrhage	6.04 (1.85–19.68)†	3.28 (0.91–11.88)
Warfarin use	3.73 (1.84–7.78)*	1.46 (0.60–3.60)
Age (per year)	1.05 (1.01–1.10)‡	1.04 (0.99–1.09)
Hematoma evacuation	0.78 (0.40–1.50)	0.37 (0.17–0.82)‡

In multivariable analysis HRs have been adjusted for sex and variables listed in the table. The HRs of categorical variables represent comparisons with patients with no risk factor.

*p<0.001, †p<0.01, ‡p<0.02, §p<0.05, #p=0.050

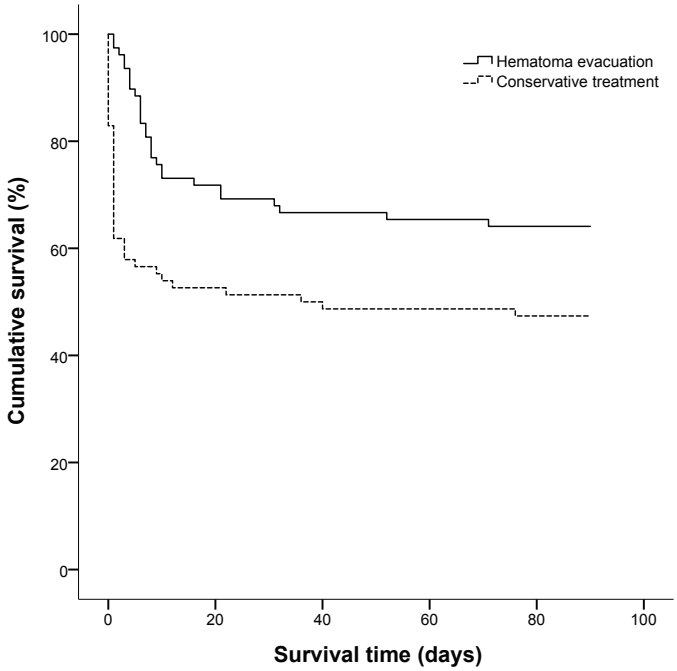

Fig. 3. 3-month survival of patients ≤70 years of age with ≥30 ml supratentorial ICHs according to hematoma evacuation or conservative treatment. The log-rank test revealed a significant difference between the survival curves (p=0.031). (Löppönen *et al*, 2013, published by permission of Elsevier).

5.4 Prior ischemic stroke predicts recurrence of pICH

The main finding in *the study IV* was that prior ischemic stroke is an independent predictor of recurrent ICH.

Of 680 patients with first-ever ICH included in the study 58 had a recurrent ICH. Of these 58, 3 patients had 3 recurrent ICHs and 4 patients had 2 recurrences. Altogether these 58 patients had 68 recurrent ICHs. The baseline characteristics are presented in Table 8. The mean follow-up time was 3.62 years and a total follow-up time was 3481 person-years.

The admission GCS scores were significantly lower ($p<0.001$) and hematoma sizes significantly larger ($p=0.003$) at recurrent ICHs. The hematoma location did not differ between the first and recurrent ICH. Significant heterogeneity was

observed among those 58 patients with later recurrences. Untreated hypertension was more frequent at the time of the first-ever bleeding than at the time of recurrence (p=0.046). There were no significant differences in drug use. None of the patients were using warfarin at the time of the recurrent ICH.

The patients with recurrent ICH had more often used high-affinity SSRIs at the time of the recurrent bleeding compared to those without recurrence (p=0.026). They had also used more aspirin and SNRIs and also less often intermediate-affinity SSRIs though these were not statistically significant differences.

The location of first-ever ICH among 58 patients who had recurrences later was ganglionic in 28 (48.3%), lobar in 19 (32.8%), cerebellar in 9 (15.5%), and brain stem in 2 (3.4%) patients. The locations patterns for the first and recurrent ICHs were most often ganglionic-ganglionic (n=24, 41.4%) and lobar-lobar (n=13, 24.1%). There was a non-significant trend in aspirin use between the lobar and ganglionic ICHs (57.9% vs 39.3% for first-ever and 61.1% vs 42.9% for first recurrence).

The annual average incidence for recurrence was 1.67%. The cumulative incidence for recurrence at 5 years was 9.6% (95% CI 6.9–12.3) and at 10 years 14.2% (10.3–18.1).

The average annual recurrence rate was higher in patients with a previous ischemic stroke (3.52% vs 1.35%), diabetes (3.34% vs 1.47%), and aspirin use (2.54% vs 1.34%). The cumulative rate of recurrence was higher among those with a previous ischemic stroke (19.8% vs 7.5% at 5 years and 28.3% vs 12.4% at 10 years) (Figure 4). Higher cumulative recurrence rates were detected also in patients with diabetes or the use of aspirin.

Table 8. Characteristics of the Patients before First-Ever and Recurrent Bleeds.

Variable	Subjects with recurrence			Without recurrence
	First bleeding (n=58)	First recurrent (n=58)	Fatal recurrent (n=30)	(n=622)
Sex, men, n (%)	32 (55.2)	32 (55.2)	16 (53.3)	337 (54.2)
Age (mean±SD)	65.36±10.78	68.79±10.80	70.31±11.78	67.51±12.39
GCS (mean±SD)	14.25±1.97	10.84±4.48	7.10±3.45	13.21±2.78
Volume (mean±SD)	18.59±26.0	30.81±43.21	52.60±53.67	20.09±22.41
Lobar pICH, n (%)	19 (32.8)	18/57 (31.6)	12 (40.0)	199/608 (32.7)
Preceding diseases, n (%)				
Hypertension treated	25 (43.1)	37 (63.8)	18 (60.0)	296/620 (47.7)
Hypertension untreated	9 (15.5)	3 (5.2)	0	102/620 (16.5)
Ischemic stroke	18 (31.0)	23 (39.7)	13 (43.3)	103/620 (16.6)
Diabetes	12 (20.7)	14 (24.1)	9 (30.0)	88/620 (14.2)
Preceding drug use, n (%)				
Warfarin	2 (3.4)	0	0	79 (12.7)
Aspirin	24 (41.4)	27 (46.6)	17 (56.7)	189/620 (30.5)
SSRI/SNRI	2 (3.4)	6 (10.3)	3 (10.0)	8/618 (1.3)

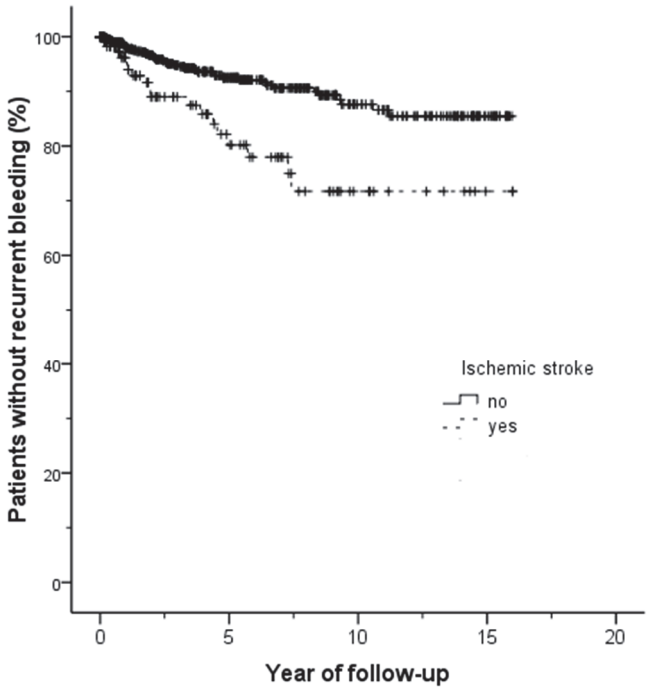

Fig. 4. Kaplan-Meier curve shows a significant difference (p=0.01) in cumulative rates of recurrent primary ICH among subjects with and without previous ischemic stroke. Censored cases are indicated by markers. (Huhtakangas *et al*, 2013, published by permission of Wolters Kluwer Health).

In univariable analysis diabetes and aspirin use were associated with an increased ICH recurrence. In multivariable analysis only the previous ischemic stroke significantly and independently of confounding factors predicted recurrent ICH (adjusted hazard ratio 2.22, 95% confidence interval 1.22–14.05, p=0.009) (Table 9). The use of SSRI/SNRIs did not increase the risk for recurrence. Diabetes tended to increase (adjusted HR 2.38, 95% CI 0.98–5.80, p=0.056) and treated hypertension tended to decrease (adjusted HR 0.45, 95% CI 0.20–1.01, p=0.054) the risk for fatal recurrence.

Table 9. Risk Factors for First Recurrent Hemorrhage According to Variables Known at the Beginning of Follow-Up.

Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age, person–year	1.00 (0.98–1.02)	0.99 (0.97–1.02)
Women	0.87 (0.52–1.46)	0.94(0.56–11.59)
Prior ischemic stroke	2.54 (1.46–14.44)†	2.22(1.22–14.05)†
Diabetes mellitus	2.04 (1.08–13.86)*	1.76 (0.92–13.39)
Untreated hypertension	0.74 (0.34–11.58)	
Treated hypertension	0.82 (0.47–11.43)	
Subcortical location	1.03 (0.60–11.78)	
Warfarin	0.38 (0.92–11.55)	
Aspirin	1.83 (1.09–13.09)*	1.41 (0.79–12.52)
SSRI/SNRI	2.09 (0.75–15.79)	
Interaction between aspirin and prior ischemic stroke	0.95 (0.29–13.14)	
Interaction between aspirin and diabetes mellitus	0.50 (0.14–11.81)	

*p<0.05,†p<0.01

6 Discussion

6.1 Main findings

The use of serotonin-modulating antidepressants with warfarin, compared with warfarin alone, is associated with increased case fatality after ICH. The hematoma volume and impaired level of consciousness on admission were also significant predictors of case fatality.

The elevated CRP level observed within 24 hours after ICH independently of confounding factors predicted an unfavorable outcome. This correlation could not be explained by preexisting diabetes, heart disease, severity of the bleeding, or infections.

Surgical hematoma evacuation improved 3-month survival relative to conservative treatment particularly in patients aged ≤70 years with ≥30 ml supratentorial hematomas. Hematoma evacuation did not improve functional outcome.

Prior ischemic stroke independently increased the risk of recurrent ICH. The use of aspirin or serotonergic drugs did not increase the risk of recurrence.

6.2 Use of serotonin-modulating antidepressants with warfarin

The study I is the first to report higher case fatality after ICH among patients with the concomitant use of SSRI/SNRIs and warfarin compared to warfarin alone. This result remained significant even when analyzed with all the known confounding factors such as patient characteristics, medications, and treatments.
It is known that the use of SSRIs increases the risk of bleeding. In fact, two recent meta-analyses state that serotonergic antidepressants increase the risk of intracerebral hemorrhage (Hackam & Mrkobrada 2012, Shin *et al.* 2014). This increased risk is most likely due to impaired platelet function (de Abajo 2011).

The most likely cause for higher case fatality is the rapid enlargement of the hematoma on SSRI/SNRI patients. Hematoma growth is a well-known determinant of mortality and poor outcome (Davis *et al.* 2006). In *the study I* the data on the average hematoma size and other risk factors did not differ between the different groups on arrival but repeated head CT scans were unfortunately seldom available. Due to an increased bleeding risk hematoma enlargement seems

to be the most probable reason for increased mortality, but this still remains hypothetical.

It has been noticed that depression itself increases the risk of stroke and hemorrhagic stroke (Pan *et al.* 2011). This could have confused the interpretation of the results in *the study I* where depression itself could not be specified clearly apart from the SSRI/SNRI use. However, in recent meta-analysis where the confounding factor of depression was considered, the risk of ICH was higher in the SSRI users than in the non-users (Shin *et al.* 2014). This finding notably strengthens and justifies the results in *the study I.*

Another surprising finding was the higher mortality of the patients with the use of SSRI/SNRI and warfarin compared to the patients with the use of aspirin and warfarin. This finding has not yet been confirmed by other studies. Still, both SSRIs and aspirin affect primary hemostasis thus increasing the bleeding risk in a similar way. In *the study I* different SSRI/SNRIs with varying doses combined in the same group might have caused this finding. The unobserved over-the-counter sale of aspirin in Finland could also have had an unnoticed effect in results.

The study I presented patients with different types of antidepressants. There seemed to be a trend in the patients with high-affinity SSRIs and larger hematomas while the patients with low-affinity SSRI/SNRIs showed smaller hematomas. This trend was statistically insignificant due to the small number of patients and these groups with different affinity drugs had to be combined.

According to *the study I* it appears that SSRI/SNRIs carry an increased risk of case fatality after WA-ICH. However, in general it has been estimated that SSRIs might cause 1 additional ICH per 10 000 persons (0.01%) treated for 1 year thus making the absolute risk of ICH relatively low (Hackam & Mrkobrada 2012, Hankey 2014, van Asch *et al.* 2010). The use of SSRIs is most likely safe but when combined with warfarin an increased risk of case fatality after ICH is involved. This increased risk must be considered especially when surgical interventions are planned.

6.3 Predictive value of CRP

The study II showed that the elevated CRP level within 24 hours of ICH is an independent predictor of unfavorable outcome. This effect was not explained by preexisting diseases, hematoma size, level of consciousness, or infections. Well known risk factors for mortality after ICH include a low level of consciousness, high age, infratentorial hematoma location, hematoma size, and intraventricular

hemorrhage (Hemphill *et al.* 2001). All the known confounding factors were included in multivariable analysis with the admission CRP levels. Regardless of the confounding factors the elevated CRP level still remained an independent predictor of unfavorable outcome.

The results from *the study II* are supported by some of the earlier findings (Alexandrova & Danovska 2011, Di Napoli *et al.* 2011). An unfavorable outcome after ICH also seems to be associated with an increase in CRP values during the next few days (Di Napoli *et al.* 2012). This increase could be speculated to result from increasing primary damage such as re-bleeding and hematoma size increase, secondary brain tissue damage due to inflammatory reactions, or infections such as pneumonia.

There was a correlation between the high admission CRP level and the hematoma volume in *the study II*, however, in the multivariable analysis the high CRP level still remained as an independent predictor of unfavorable outcome regardless of the hematoma volume. Results about CRP elevation and hematoma growth after ICH have been published lately. The admission CRP level >10mg/l was found to independently predict early hematoma growth and early worsening of patient consciousness, both of which are associated with higher case fatality (Di Napoli *et al.* 2014). Unfortunately, in *the study II* the hematoma growth was seldom controlled with repeated head CTs so this hypothesis remains obscure.

These *study II* findings about CRP being an independent predictor of an unfavorable outcome are in line with the hypothesis of the secondary brain damage after ICH. This secondary damage is thought to be caused by inflammation, red cell lysis, and thrombin production (Ziai 2013). This secondary damage to the brain could explain the elevating CRP values even without increasing primary damage such as hematoma growth (Castillo *et al.* 2002).

In *the study II* cardiac disease and diabetes were significantly associated with elevated admission CRP values. Both cardiac disease and diabetes have been found to independently increase CRP levels (Elkind *et al.* 2009). Cardiac disease and diabetes are also independent predictors of death after ICH (Tetri *et al.* 2008b, Tetri *et al.* 2009). Nonetheless, when all these confounding factors were compared in multivariable analysis cardiac disease was not a predictor of unfavorable outcome. This suggests that ICH itself affects the CRP level more than cardiac disease. In other words, the predictive value of CRP was not disturbed by the already chronically risen CRP value in the patients with cardiac disease.

After excluding the patients with later diagnosed pneumonia the multivariable analysis still revealed an elevated CRP value on admission independently predicting unfavorable outcome. The conclusion drawn from this is that the elevation of CRP values comes from the severity of ICH itself, not from clinical infections. Most clinical infections are likely to be noticed during hospitalization and in these cases an increase in the CRP value was generally associated with pneumonia. Of course some infections might have been left unidentified and this could interfere with the predictive value of CRP. The retrospective study design places its restrictions on the interpretation of the results and these results should be later confirmed with prospective series.

It appears that the elevated CRP level indicates an increased risk of cardiovascular mortality and might result in a poor outcome after ICH. Even though the high CRP value on admission may predict worse outcome after ICH it cannot yet be used as a proper prognostic factor because it still remains to be seen what clinical relevance can be obtained from this. Whether the high CRP value truly predicts secondary brain damage or hematoma enlargement cannot be confirmed by this study.

6.4 Role of surgery

The study III showed that on a population basis, the patients with ICH who had their hematoma evacuated had significantly lower mortality at 90 days compared to the patients with conservative treatment independent of confounding factors. This benefit was also shown in a subgroup of patients who were ≤70 years of age with ≥30 ml supratentorial ICHs. Hematoma evacuation did not improve functional outcome at 90 days.

Of all the 982 patients with ICH altogether 13% had their hematoma evacuated. The patients that had been selected for surgical intervention differed from those that had been treated conservatively. It is obvious that patient selection during years must have been considered as a lifesaving procedure for those of younger age with larger hematomas because both of these factors were over-represented in the surgical group. Still, in multivariable analyses surgical hematoma evacuation improved mortality at 7, 30, and 90 days independent of known confounding factors. Other independent predictors of death at 90 days were hematoma size, low GCS on admission, intraventricular hemorrhage, infratentorial location of hematoma, warfarin use, and high age, all of which are well-known factors of mortality (Hemphill *et al.* 2001).

The patients treated conservatively had significantly more often infratentorial hemorrhages. According to current knowledge larger cerebellar hemorrhages causing ventricular compression should undergo hematoma evacuation and should not be treated with intraventricular drainage (Hemphill *et al.* 2015). This conclusion is also strengthened by the study results as the infratentorial hematoma location was an independent predictor of death at 90 days for the whole population. Perhaps some patients with infratentorial ICH treated conservatively might have benefited from hematoma evacuation but this conclusion cannot be confirmed by this study.

As surgery seemed to have been considered for younger patients with larger hematomas analyses of subgroups were conducted in order to gain more selectively defined groups that might benefit from surgery. All the patients who were ≤70 years of age and had a ≥30 ml supratentorial hematoma were selected. In multivariable analyses among these patients the 90-day mortality was lowered by hematoma evacuation. Surgical hematoma evacuation independently benefited patients with supratentorial, subcortical, or deep supratentorial hematomas. These finding are in line with the meta-analysis of individual patient data on the benefit of surgery (Gregson *et al.* 2012).

The results in *the study III* demonstrate that without hematoma evacuation more patients would have died. This appears to be the conclusion in the current literature too. The latest meta-analysis including STICH II data with 3366 patients (Mendelow *et al.* 2013) concludes that there is a role for hematoma evacuation but at the moment we do not know the exact patient selection. The selection criteria used in the analyses of *the study III* subgroup showed improved mortality but unfortunately surgery did not improve functional outcome. More lives were saved at the cost of more neurological disability that perhaps should not be the goal.

Probably one problem in determining the right patients for surgery lies in the inclusion criteria of STICH studies. The first STICH study included ICH patients whose neurosurgeon was uncertain whether patients should be operated on and then randomized to treatment groups. Young patients with larger lobar hematomas might have been initially more easily operated on for life-saving reasons. This would have excluded these young patients from randomization and the study. Also, 26% of patients randomized to conservative treatment in STICH and 21% of patients in STICH II were later surgically operated on when their consciousness deteriorated. Statistically these patients had larger hematomas and lower GCS scores. Due to intention-to-treat protocol these initially conservatively treated patients probably benefited from surgery thus improving survival in the

medical group. Without cross-over the results might have showed significant differences.

The European Stroke Organisation (ESO) guidelines do not support surgical hematoma evacuation on a routine basis but give a weak recommendation when considering operation for patients with supratentorial hematoma and GCS score 9 to 12 (Steiner *et al.* 2014). Altogether the AHA/ASA guidelines state that surgical hematoma evacuation should only be used on patients with cerebellar hemorrhage who are deteriorating or on patients with brainstem compression and hydrocephalus. To current knowledge hematoma evacuation can also be used as a life-saving treatment for those deteriorating patients with large supratentorial hematomas and elevated ICP without a response to medical treatment (Hemphill *et al.* 2015).

6.5 Preventing recurrence

The study IV showed that a previous ischemic stroke is an independent predictor of recurrent ICH. Diabetes and aspirin use showed significance for recurrence in univariable analysis. Diabetes may also increase the risk of fatal recurrent ICH and the treatment of hypertension may reduce the risk. The patients with index lobar ICH were not more likely to have a recurrent ICH compared to those with index deep ICH.

The previous ischemic stroke as a risk factor for ICH has raised concern in an earlier study but there was no significant correlation (Passero *et al.* 1995). A recent population-based study also suggested an earlier ischemic stroke to be a risk factor for recurrence after WA-ICH, though the small statistical power of the study failed again to show significance (Poli *et al.* 2014). According to these findings it could be theorized that earlier ischemic events might locally weaken the vessel walls thus increasing the risk of rupture. In turn, ischemic history might also be a signal of generalized degenerative arteriosclerosis in brain.

Antiplatelet use itself did not independently increase the risk of recurrent ICH in *the study IV*. This result is in line with the current knowledge that the use of antiplatelets does not increase the risk of recurrent ICH (Viswanathan *et al.* 2006, Weimar *et al.* 2011). Yet, antiplatelet use at the onset of ICH has been reported to increase the risk of mortality (Saloheimo *et al.* 2006, Thompson *et al.* 2010). Still, according to the current AHA/ASA guideline aspirin use might be continued after ICH if risks for ischemic events are high. Aspirin use could probably be restarted

in a few days after ICH (Hemphill *et al.* 2015). According to *the study IV* the risk of recurrent ICH after ischemic stroke is elevated regardless of aspirin use.

The use of warfarin did not show a predictive value for recurrent ICH. The reason for this is obvious because none of the patients with recurrence were on warfarin. According to the AHA/ASA guidelines treatment of non-valvular atrial fibrillation with warfarin after lobar WA-ICH should be avoided. Anticoagulants after non-lobar ICH could be considered, if indications are strong. Optimal timing to resume these medications is uncertain but oral anticoagulants should usually be avoided for 4 weeks. The recurrence risk of novel oral anticoagulants remains uncertain (Hemphill *et al.* 2015).

Earlier studies have indicated lobar location to increase the risk of re-bleeding (Hanger *et al.* 2007, Neau *et al.* 1997, Vermeer *et al.* 2002). In *the study IV* the lobar location of index bleeding was not a predictor of recurrence. This could be due to underpowered study population but there could also be other factors involved. These earlier studies were not population-based and also missed to find ischemic stroke as a predictor for recurrence.

Diabetes and treated hypertension had borderline significances in increasing and decreasing the risk for fatal recurrence. Though statistically insignificant these results are credible because diabetes and high blood pressure on arrival have been shown to predict death after ICH (Tetri *et al.* 2009). Also, these findings of diabetes and hypertension support the hypothesis of ICH being a manifestation of atherosclerosis in cerebral vessels. Perhaps ICH recurrence after ischemic events results most likely from generalized degeneration rather than focal ischemic arterial weakening. In any case, the AHA/ASA recommendations for preventing ICH recurrence state that blood pressure should be treated aggressively and long-term goals should be <130 mmHg in systolic and 80 mmHg in diastolic blood pressure (Hemphill *et al.* 2015).

6.6 Strengths and limitations of the study

All studies are based on the data that is one of the largest population-based ICH registries in the world. The data was gathered with strict inclusion criteria. All well-known risk factors and confounding factors were carefully taken into account. Radiological analyses were made carefully by neuroradiologists blinded to the case. The retrospective study design limits the conclusions but only slightly since the population-based data of all the ICH patients from Northern

Ostrobothnia includes also the autopsy data of the patients who died before reaching hospital.

In *the study I* a major strength is double-checking of medications from the national registry. Even so, it was a minor limitation that aspirin use could not be examined in the same way due to the national sales practice. Yet, hospital records were thoroughly examined for aspirin use. Another limitation was that because of the small patient population all of the SSRI/SNRI patients had to be combined in the same group and no sub-group analyses were possible. Thirdly, there were three patients using warfarin, aspirin, and SSRI/SNRI simultaneously perhaps influencing the results. Fourthly, the bleeding tendency could not be examined beyond regular tests. Finally, the increased case fatality rate was hypothesized to result from rapid hematoma enlargement but repeated head CT scans were seldom available to confirm this.

In *the study II* a limitation was that 16% of patients had to be excluded from the analyses because of the lack of the admission CRP values. However, the excluded patients had the same hematoma size on admission as those included so this could be considered only a minor limitation. One of the strengths of the study is that the population was large enough to clearly identify the association of CRP value on unfavorable outcome after ICH. This association was strong even when the patients with clinical pneumonia were excluded in another analysis. Of course, there might have been unnoticed subclinical infections or hematoma growth that could have influenced the CRP values.

The main limitation in *the study III* was the retrospective point of view on the treatment efficiency. Definitive conclusions about treatments cannot be done on the basis of the results, the study being retrospective. Without pre-defined patient randomization patient selection to operative and conservative treatments are different. It can be presumed that moribund patients are less likely to be operated on whereas younger patients are aggressively operated on for life-saving reasons. This possible bias was taken into account as well as possible with thorough identification of all other known predictors of outcome. However, a population-based study setting has its clear strengths. The patient population is unselected when all ICH patients in the area are included. The use of death records in Finland allows inclusion of all the ICH patients, even those without reaching hospital. Also, death as a primary end point is by definition a certain variable certifying epidemiological results. The main strength of a population-based study setting is the ability to screen and find new hypotheses. Yet again, treatment guidelines are best formed by prospective randomized trials.

In *the study IV* some limitations should be notified. All the data about the previous diseases is based on hospital records. Information about earlier diseases such as hypertension and ischemic strokes could be considered as reliable information. Of course, a bias of earlier undetected low-symptomatic ischemic events is still possible but this should be considered only a minor issue. The data on aspirin use could be marginally biased due to non-prescribed use described earlier. The definitive effect of antihypertensive treatment cannot be certainly verified and some patients might still have had poorly treated hypertension. Accurate data on alcohol intake and smoking were not available, either. One of the limitations could also be that the presence of depression itself was not recorded. Depression has been associated as a risk factor for stroke.

6.7 Future research aspects on studying ICH

Different types of antidepressants were presented in *the study I*. A trend was noticed with high-affinity SSRIs and larger hematomas in contrast to low-affinity SSRI/SNRIs with smaller hematomas but this trend was statistically insignificant. However, there is evidence supporting a correlation between drugs with higher serotonin receptor affinity and a higher risk of upper gastrointestinal bleeding (de Abajo *et al.* 2006). This raises a question if there could also be a correlation between the degree of serotonin transporter affinity and the risk of ICH or a higher case fatality rate after ICH. The study population was too small to reveal any correlation. The current evidence presented in the literature states the same problem, but not enough data is available and further studies are still required (Shin *et al.* 2014).

The study II presented statistically significant association with the elevated CRP value on arrival and the unfavorable outcome after ICH. It is understandable that many biomarkers including CRP carry hopes of an easy and efficient tool to better understand the biochemical factors in ICH and to offer a way to assess patient outcome (Brunswick *et al.* 2012). Perhaps secondary brain damage could be reduced in future by efficient ways to treat inflammatory reaction after ICH (Castillo *et al.* 2002). In order to achieve greater benefit from CRP and other biomarkers larger prospective studies should be organized.

The results from *the study III* revealed that hematoma evacuation might be beneficial especially for younger patients with larger supratentorial hematomas. However, definitive guidelines cannot yet be drawn, the current literature showing uncertain results (Mendelow *et al.* 2013). As surgical interventions are

not showing solid benefit several suggestions have been made in behalf of decompressive craniectomy with or without hematoma evacuation. In fact, a systematic review presents some evidence suggesting improved outcome (Takeuchi *et al.* 2013). Minimally invasive methods for hematoma evacuation could also have an aspect in treatment (Longatti & Basaldella 2013, Mould *et al.* 2013). Yet, evidence is scarce and new trials are expected to solve the role of surgery.

The study IV showed earlier ischemic stroke to be a risk factor for recurrent ICH. This leads to difficulties in medical balancing between the risk for ischemic and bleeding complications. The most important question whether or not to start anticoagulation therapy after ICH still remains a question without definitive answers (Flynn *et al.* 2010a, Goldstein & Greenberg 2010, Hemphill *et al.* 2015). Fortunately, to date at least one randomized controlled study is initiated and the results are eagerly awaited (RESTART trial, www.RESTARTtrial.com). Also, serotonergic antidepressants have been shown to increase the risk of initial ICH and in *the study IV* the patients with recurrent ICH had more often used high-affinity SSRIs at the time of the recurrent bleeding compared to those without recurrence. However, in multivariable analysis the risk was insignificant. The re-bleeding risk caused by serotonergic antidepressants remains to be evaluated by larger studies.

7 Conclusions

1. The concurrent use of serotonin-modulating antidepressants with warfarin increases the case fatality rate after ICH compared to warfarin alone. Larger studies are required to confirm this finding. In general, SSRI/SNRI use seems to increase the risk of ICH only slightly. Still, careful consideration should be paid when combining SSRI/SNRIs to patients taking warfarin.
2. The elevated admission CRP value is a statistically independent risk factor of unfavorable outcome after ICH. This association is not explained by preexisting diabetes, heart disease, severity of the bleeding, or infections. However, the predictive value of CRP at the moment comes with preconditions because substantial clinical implications still go short. More research is needed to obtain relevance to clinicians on duty.
3. Surgical hematoma evacuation compared to conservative treatment showed improved 3-month survival. This improvement was noticed especially among patients with ≤70 years of age with ≥30 ml supratentorial ICHs. Hematoma evacuation did not improve functional outcome at 3 months. These findings support current guidelines stating that certain subgroups might benefit from hematoma evacuation but in general the role of surgery is still unresolved.
4. Previous ischemic stroke is an independent risk factor for a recurrent ICH. Moreover, diabetes seems to increase and treated hypertension decrease the risk for fatal recurrence. Aspirin or SSRI/SNRIs do not seem to increase recurrence risk. These findings should encourage treating hypertension, diabetes, and cardiovascular risk factors well. Definitive guidelines for restarting anticoagulant medication after ICH ought to be confirmed with larger studies.

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I Löppönen P, Tetri S, Juvela S, Huhtakangas J, Saloheimo P, Bode MK & Hillbom M (2014) Association between warfarin combined with serotonin-modulating antidepressants and increased case fatality in primary intracerebral hemorrhage: a population-based study. J Neurosurg 120: 1358–1363.

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ISBN 978-952-62-1127-5 (Paperback)
ISBN 978-952-62-1128-2 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)