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Juha Huhtakangas

THE INFLUENCE OF MEDICATION ON THE INCIDENCE, OUTCOME, AND RECURRENCE OF PRIMARY INTRACEREBRAL HEMORRHAGE

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
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INSTITUTE OF CLINICAL MEDICINE,
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Abstract

Intracerebral hemorrhage (ICH) is the most pernicious form of stroke, with high mortality. Warfarin-associated ICH (WA-ICH) carries an even higher mortality rate. The major reason for the high mortality is explained by early hematoma growth. Warfarin use has rapidly increased with the aging of the population.

We investigated temporal trends in the incidence and outcome of WA-ICHs. We found that although the proportion of warfarin users almost quadrupled in our population, the annual incidence and case fatality of WA-ICHs decreased.

Management of ICH is mostly supportive. Prevention of associated complications is the issue in improving outcome. Hypertension is the most important modifiable risk factor for primary ICH, but little is known of the effect of preceding hypertension on outcome. Aggressive lowering of blood pressure is suggested to be a feasible treatment option. Reversal of warfarin anticoagulation with prothrombin complex concentrate (PCC) has been implemented as an acute treatment option for patients with WA-ICH.

We found that the survival of WA-ICH subjects among our population improved after implementation of reversal of warfarin anticoagulation with PCC, likely because of the introduction of PCC.

Because high mean arterial blood pressure (BP) at admission is an independent predictor of early death in patients with ICH, we explored its role in survival and poor outcome separately in normotensive subjects and subjects with treated and untreated hypertension. We found that despite their higher BP values at admission, subjects with untreated hypertension showed better survival and more often a favorable outcome after BP-lowering therapy than other patients.

Studies on recurrent ICH are scarce. Underlying comorbidities, prior strokes, and drug-induced impaired platelet function may increase the risk for primary ICH (PICH). A lobar location of primary ICH may predict recurrent ICH. We investigated whether these factors predicted recurrence of PICH. In our study the annual incidence of recurrent ICH was 1.67%. Cumulative 5- and 10-year incidences were 9.6% and 14.2%. In multivariable analyses, prior ischemic stroke and diabetes proved to be independent predictors for recurrence. Moreover, diabetes was an independent risk factor for fatal recurrent PICH. Use of aspirin and serotonergic drugs did not significantly contribute to the risk.

Keywords: cerebral hemorrhage, hypertension, prognosis, prothrombin complex consentrate, recurrence, risk factors, warfarin

Huhtakangas, Juha, Lääkityksen vaikutus primaarin aivoverenvuodon insidenssiin, ennusteeseen ja uusiutumiseen.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Kliinisen lääketieteen laitos, Neurologia, PL 5000, 90014 Oulun yliopisto
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Tiivistelmä

Aivoverenvuoto (ICH) on aivoverenkiertohäiriöistä vakavin. Sille on tyypillistä korkea kuolleisuus erityisesti varfariinihoitoon liittyen, ja eloonjääneetkin vammautuvat usein vakavasti. Verenvuodon koon kasvu alkuvaiheessa selittänee korkean kuolleisuuden. Väestön ikääntymisen myötä varfariinin käyttö on lisääntynyt nopeasti.

Aivoverenvuodon hoito perustuu pitkälti ennusteen parantamiseen komplikaatioita estämällä. Verenpaine on tärkein hoidettavissa oleva riskitekijä, mutta tutkimustieto akuutin vaiheen verenpainetason merkityksestä ennusteeseen on vähäistä. Tehokasta verenpaineen alentamista alkuvaiheessa pidetään lupaavana hoitomenetelmänä. Vuodon koon kasvua pyritään rajoittamaan kumoamalla varfariinin antikoaguloiva vaikutus protrombiinikompleksi-konsentraatilla (PCC).

Väitöstyössäni selvitän varfariinin käyttöön liittyvien aivoverenvuotojen (WA-ICH) esiintymistiheyttä ja ennustetta ajan myötä. Tutkin myös vuodon koon kasvun rajoittamista ja alkuvaiheen korkean verenpaineen alentamista hoitomenetelminä sekä selvitän, mitkä tekijät johtavat ICH:n uusiutumiseen.

Totesimme WA-ICH:n ilmaantuvuuden ja tapauskuolleisuuden pienentyneen, vaikka varfariinin käyttö miltei nelinkertaistui väestössämme. Toisaalta WA-ICH -potilaiden kuolleisuus pieneni PCC-hoidon aloittamisen jälkeen, mahdollisesti sen ansiosta.

Tutkiessamme riippumattomasti varhaista kuolemaa ennustavan korkean tulovaiheen verenpaineen roolia normaaliverenpaineisilla, hoidettua ja hoitamatonta verenpainetautia sairastavilla totesimme hoitamattomien hypertonia-potilaiden selvinneen akuutin vaiheen lääkehoidon myötä muita useammin hengissä ja hyväkuntoisina korkeista tulovaiheen verenpainearvoista huolimatta.

Aivoverenvuodon uusiutumiseen vaikuttavista tekijöistä on vähän tutkimustietoa. Muu sairastavuus, aiemmat aivoverenkiertohäiriöt ja trombosyyttien toimintaan vaikuttavat lääkkeet saattavat lisätä ICH:n uusiutumisriskiä. Totesimme vuosittaisen uuden ICH:n esiintymistiheyden olevan 1,67 %. Aikaisempi aivoinfarkti ja diabetes osoittautuivat riippumattomiksi uusiutumista ennustaviksi riskitekijöiksi, minkä lisäksi diabetes ennusti kuolemaan johtavaa uutta ICH:a. Asetyylisalisyylihapon ja selektiivisten serotoniinin takaisinoton estäjien käyttäminen ei vaikuttanut merkittävästi uusiutumisriskiin.

Asiasanat: aivoverenvuoto, ennuste, protrombiinikompleksikonsentraatti, riskitekijät, uusiutuminen, varfariini, verenpainetauti

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Finally, I owe my loving gratitude to my wife and best friend, Jaana; thank you for your love and unconditional and unwavering support. Jaana, your infinite love keeps me alive; I love you.

Abbreviations

ADP	Adenosine diphosphate
ANOVA	Analysis of variance
ATACH	Antihypertensive Treatment of Acute Cerebral Hemorrhage trial
BP	Blood pressure
CAA	Cerebral amyloid angiopathy
CI	Confidence interval
CT	Computed tomography
EAFT	European Atrial Fibrillation Trial
FAST	the Factor Seven for Acute Hemorrhagic Stroke
FFP	Fresh frozen plasma
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
HR	Hazard ratio
ICH	Intracerebral hemorrhage
INR	International normalized ratio
INTERACT	Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial
ISH	International Society of Hypertension
IVH	Intraventricular hemorrhage
MABP	Mean arterial blood pressure
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug
PASW	Predictive Analytics Software
PCC	Prothrombin complex concentrate
PERFECT	PERFormance, Effectiveness and Cost of Treatment episodes
PICH	Primary intracerebral hemorrhage
RR	Relative risk
SNRI	Serotonin-norepinephrine reuptake inhibitor
SPIRIT	Stroke Prevention in Reversible Ischemia Trial
SPSS	Statistical Package for the Social Sciences
SRI	Serotonin reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
WA-ICH	Warfarin-associated intracerebral hemorrhage
WHO	World Health Organization

List of original articles

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

I Huhtakangas J, Tetri S, Juvela S, Saloheimo P, Bode MK & Hillbom M (2011) Effect of increased warfarin use on warfarin-related cerebral hemorrhage: A longitudinal population-based study. Stroke 42: 2431–2435.

II Huhtakangas J, Tetri S, Juvela S, Saloheimo P, Bode MK, Karttunen V, Käräjämäki A & Hillbom M (2012) Improved Survival of Patients with Warfarin-associated Intracerebral Hemorrhage: A Longitudinal Population-based Study. Int J Stroke. in press

III Tetri S, Huhtakangas J, Juvela S, Saloheimo P, Pyhtinen J & Hillbom M (2010) Better than expected survival after primary intracerebral hemorrhage in patients with untreated hypertension despite high admission blood pressures. Eur J Neurol 17: 708–714.

IV Huhtakangas J, Löppönen P, Tetri S, Juvela S, Saloheimo P, Bode MK & Hillbom M. Predictors of recurrent primary intracerebral hemorrhage: A retrospective population-based study. Manuscript

Contents

1 Introduction

Intracerebral hemorrhage (ICH) is the most pernicious form of stroke, with mortality ranging from 30% to 55% and severe disability in the majority of survivors (Brott *et al.* 1997, Rosand *et al.* 2004). In a recent Finnish study, 14% of all stroke patients had an ICH as their initial stroke (Meretoja *et al.* 2010). The annual incidence of ICH in Finland (23–31/100,000) is similar to that in most Western countries (Fogelholm *et al.* 1992, Numminen *et al.* 1996). Much higher incidence rates have been reported in Japan (Inagawa *et al.* 2003).

Patients with an intracranial hematoma have symptoms like sensory-motor deficits, aphasia, neglect, gaze deviation, hemianopia, ataxia, nystagmus, dysmetria, abnormalities of gaze, and cranial-nerve abnormalities (Ott *et al.* 1974, Tanaka *et al.* 1996). Especially patients with a large hematoma may have a decreased level of consciousness (Mohr *et al.* 1978). Anyhow, an ischemic stroke can include similar symptoms. That is why neuroimaging is essential for a diagnosis.

Management of ICH, if not surgical, is mostly supportive. Prevention of associated complications is the issue in improving outcome. As to treatment of ICH, in my thesis I focus on restriction of hematoma growth and treatment of high blood pressure.

Warfarin-associated ICH (WA-ICH) carries a very high mortality rate (Cucchiara *et al.* 2008, Hart *et al.* 1995, Rosand *et al.* 2004, Saloheimo *et al.* 2006). The major reason for the high mortality of patients with WA-ICH is explained by early hematoma growth (Cucchiara *et al.* 2008, Flaherty *et al.* 2008, Toyoda *et al.* 2009). In the presence of an anticoagulant effect, bleeding continues and the hematoma grows for several hours, leading to neurological deterioration (Brott *et al.* 1997, Kazui *et al.* 1996). Hematoma enlargement in warfarin-associated ICH is observed to occur over a longer period of time than in ICHs unrelated to anticoagulant treatment (Flibotte *et al.* 2004, Yasaka *et al.* 2003). Admission hematoma volume is the strongest predictor of neurological deterioration, functional outcome, and mortality of spontaneous supratentorial ICHs and WA-ICHs (Berwaerts *et al.* 2000, Broderick *et al.* 1993). Warfarin therapy appears to be an independent predictor of hematoma enlargement (Kuwashiro *et al.* 2010). The intensity of anticoagulation has also been found to be an independent predictor of three-month mortality (Rosand *et al.* 2004). A rapid increase in the use of warfarin has occurred with the aging of the population

(Lakshminarayan *et al.* 2008, Nutescu *et al.* 2004), and this may result in an increase of the number of fatal ICHs.

To give a prognosis for patients with ICH, the ICH score is a fast and simple grading scale (Hemphill *et al.* 2001). It includes a Glasgow Coma Scale score (Teasdale & Jennett 1974), age over 80 years, ICH volume over 30 cm^3, presence of infratentorial origin, and intraventricular hemorrhage.

A low GCS score, a large hematoma volume, intraventricular bleeding, use of anticoagulants, and high blood pressure on admission are well-known predictors of early death after ICH (Broderick *et al.* 1993, Daverat *et al.* 1991, Hardemark *et al.* 1999, Juvela 1995, Qureshi *et al.* 1995, Tuhrim *et al.* 1991). Atrial fibrillation on admission and ischemic heart disease are significant and independent predictors of death (Tetri *et al.* 2008). Use of warfarin is assuredly a significant predictor of death only within the first two days after the onset of ICH (Tetri *et al.* 2008).

We are still missing effective treatments for ICH. Even large clinical trials of surgical hematoma evacuation and ultra-early hemostatic therapy have not demonstrated improved outcomes (Mayer *et al.* 2008, Mendelow *et al.* 2005). In the FAST trial, hemostatic therapy with activated recombinant factor VII reduced growth of the hematoma but did not improve survival or functional outcome after intracerebral hemorrhage (Mayer *et al.* 2008).

High blood pressure is usually present at the onset of an ICH. Some studies suggest that aggressive lowering of blood pressure is a feasible and safe first aid treatment option (Nishiyama *et al.* 2000, Qureshi *et al.* 2005, Qureshi *et al.* 2006, Qureshi 2007). Theoretically, lowering blood pressure may prevent hematoma growth. However, we still lack proof that this really will take place. Lowering blood pressure might also decrease tissue edema and intracranial hypertension during the acute phase.

Studies on recurrent ICHs are scarce. The risk of recurrence varies widely (0–24%) (Hanger *et al.* 2007). Age has been found to be an independent risk factor for recurrent ICHs (Zia *et al.* 2009). The annual recurrence rate of hypertensive ICHs (Arakawa *et al.* 1998, O'Donnell *et al.* 2000) is much lower (2%) than that of amyloid angiopathy-related ICHs (10%). Use of an antiplatelet agent following a lobar ICH may also increase the risk of recurrence (Biffi *et al.* 2010). It has been reported that the use of SSRIs (selective serotonin reuptake inhibitors) might increase the risk of ICH (Smoller *et al.* 2009, Verdel *et al.* 2011).

2 Review of the literature

2.1 Subtypes of intracerebral hemorrhage

Non-traumatic hemorrhage into the brain parenchyma is called spontaneous ICH (Caplan 1992). Depending on the underlying cause of bleeding, spontaneous ICH is classified as either primary or secondary (Qureshi *et al.* 2001). Primary intracerebral hemorrhage (PICH) is a spontaneous ICH without any radiologically defined secondary cause (Qureshi *et al.* 2001). If an ICH is a consequence of trauma, it is classified as a traumatic hemorrhage (Siddique *et al.* 2002).

2.1.1 Primary intracerebral hemorrhage

Bleeding of the small penetrating arteries which are damaged by chronic hypertension, cerebral amyloid angiopathy, or other causative factors underlie PICH (Qureshi *et al.* 2001). Cerebral amyloid angiopathy (CAA) is an important cause of lobar hemorrhage among elderly people, accounting for about 10% of all types of PICHs (Ishii *et al.* 1984).

Microbleeds are suggested to represent hemorrhage-prone microangiopathy (Sueda *et al.* 2010). A correspondence ratio to prior locations of microbleeds is higher in deep ICHs than in lobar ICHs, and this may be attributable to their different pathogeneses (Sueda *et al.* 2010). Secondary causes, such as structural and vascular abnormalities, should always be considered in appropriate circumstances (Qureshi *et al.* 2001). Of all ICH cases, 78 to 88 percent are classified as primary ICHs (Qureshi *et al.* 2001).

2.1.2 Secondary intracerebral hemorrhage

Secondary ICHs account for 12 to 22 percent of all cases with an ICH. Vascular abnormalities are the most important etiologies of secondary ICHs. They should always be considered because of the high risk of recurrent hemorrhage and available treatment options (Qureshi *et al.* 2001). The other possible causes of secondary ICH include dural venous sinus thrombosis, intracranial neoplasm, coagulopathies, vasculitides, and hemorrhagic ischemic stroke (Qureshi *et al.* 2001).

Ruptures of arteriovenous malformations cause two percent of all strokes (Gross *et al.* 1984). They are a complex tangle of abnormal arteries and veins linked by one or more fistulas (The Arteriovenous Malformation Study Group 1999) (Anonymous 1999). The estimated annual rate of first hemorrhages is two to four percent (Ondra *et al.* 1990). The high annual risk of recurrent bleeding (18%) can be reduced by endovascular occlusion, surgical excision, and radiosurgery (Anonymous 1999).

Cavernous angiomas are abnormal capillary-like vessels with intermingled connective tissue (Qureshi *et al.* 2001). They also carry a relatively high (4.5%) annual risk of recurrent hemorrhage (Kondziolka *et al.* 1995), which can be reduced by surgical excision or radiosurgery (Qureshi *et al.* 2001). Venous angiomas show a very low annual risk of recurrent bleeding (Naff *et al.* 1998). Sometimes bleeding from a ruptured intracranial arterial aneurysm causes ICH or a combination of ICH and subarachnoidal hemorrhage (Griffiths *et al.* 1997).

Impaired coagulation accounts for a considerable share of secondary ICHs. ICH is a major killer in patients with congenital hemostatic defects such as factor XIII deficiency, factor X deficiency; factor V deficiency, and von Willebrand factor deficiency (Mishra *et al.* 2008). Hemophiliacs have a 10- to 20-fold higher incidence of ICH than the general population (Stieltjes *et al.* 2005). Trauma is responsible for bleeding in hemophiliacs in a high proportion of cases (57–66%) (Mishra *et al.* 2008, Stieltjes *et al.* 2005). Replacement therapy has dramatically improved the clinical outcome of ICH in this group (de Tezanos Pinto *et al.* 1992).

2.1.3 Traumatic intracerebral hemorrhage

Traumatic ICH is supposed to have almost the same pathophysiological process as a cerebral contusion. Patients with a traumatic ICH tend to be younger than patients with a primary ICH (Siddique *et al.* 2002). On the other hand, elderly people are likely to get a traumatic ICH more easily than younger people. Perhaps a traumatic ICH develops more easily in mildly atrophic brains without a tamponading effect (Siddique *et al.* 2002).

2.2 Incidence of intracerebral hemorrhage

Intracerebral hemorrhage is the second most common cause of stroke (Feigin *et al.* 2009). According to a recent meta-analysis, overall ICH incidence was 24.6 per 100,000 person-years (van Asch *et al.* 2010). In Finland, more than 1,400 new

cases of spontaneous ICH are recorded every year (Meretoja *et al.* 2010). However, incidence varies widely between different populations (van Asch *et al.* 2010). Environmental factors are suggested to influence the incidence of ICH (van Asch *et al.* 2010). Fogelholm *et al.* found an annual incidence of 31/100,000 in Central Finland (Fogelholm *et al.* 1992). Later on, the PERFECT Stroke database, which includes 94,316 incident-stroke patients, found the annual incidence of ICH to be 27.7/100,000 in Finland (from January 1, 1999 to December 31, 2007). Of all stroke patients, 14% had ICH as their initial stroke diagnosis, but these figures include all subgroups of ICH (Meretoja *et al.* 2010).

Although the incidence of ischemic stroke had declined from 1988 to 1997 in the Kuopio and Turku area, the incidence of ICH had remained stable (Sivenius *et al.* 2004). Worldwide, no substantial decrease in the incidence of ICH has been observed during the three most recent decades (van Asch *et al.* 2010).

The incidence of ICH increases with age (Fogelholm *et al.* 1992, van Asch *et al.* 2010), and men have a higher incidence than women (van Asch *et al.* 2010). This also holds true in Finland, where the reported incidence of ICH per 100,000 was 32 for men and 15 for women, while the total incidence was 23 per 100,000 (Numminen *et al.* 1996).

2.3 Pathophysiology of intracerebral hemorrhage

Rapid bleeding within the brain parenchyma causes disruption of the normal anatomy of the brain and increased intracranial pressure. The growth of a hematoma leads to damage of brain tissue via a mass effect within minutes to hours from the onset of bleeding (Qureshi *et al.* 2009). Hematoma enlargement takes place in about a third of patients (Broderick *et al.* 1990, Fujii *et al.* 1998). Mechanical disruption of the neurons and glia is the primary damage induced by hematoma growth (Qureshi *et al.* 2001). The perihematoma region is characterized by edema, apoptosis and necrosis, and inflammatory cells (Qureshi *et al.* 2003), and there is secondary tissue damage. This secondary damage occurs because of the presence of intraparenchymal blood and may be dependent on the initial hematoma volume, age, or ventricular volume (Qureshi *et al.* 2009). Secondary damage may occur through many parallel pathological pathways like the cytotoxicity of blood (Xi *et al.* 2006), hypermetabolism (Ardizzone *et al.* 2004), excitotoxicity (Qureshi *et al.* 2003), spreading depression (Mun-Bryce *et al.* 2001), and oxidative stress and inflammation (Xi *et al.* 2006). All this leads to irreversible disruption of the components of the neurovascular unit, consisting of

gray and white matter, and is followed by blood-brain barrier disruption and brain edema with massive brain cell death (Aronowski & Zhao 2011, Xi *et al.* 2006).

2.4 Symptoms and diagnosis of intracerebral hemorrhage

Patients with a large hematoma usually have a decreased level of consciousness (Mohr *et al.* 1978). Supratentorial ICH involving the thalamus, putamen, or caudate causes contralateral sensory-motor deficits. Abnormalities indicative of higher-level cortical dysfunction, like aphasia, neglect, gaze deviation, and hemianopia, may occur as a result of a disruption of connecting fibers in the subcortical white matter and functional suppression of the overlying cortex (Tanaka *et al.* 1996). An infratentorial ICH involving the cerebellum is characterized by ataxia, nystagmus, vomiting, and dysmetria (Ott *et al.* 1974). Brain-stem hemorrhages include abnormalities of gaze, cranial-nerve abnormalities, and contralateral motor deficits (Ott *et al.* 1974). Increased intracranial pressure and meningismus resulting from blood in the ventricles commonly cause headache and vomiting (Mohr *et al.* 1978).

Neuroimaging with computed tomography (CT) of the brain is needed to differentiate between ICH and ischemic stroke. CT scanning is the first-line diagnostic approach, but magnetic resonance imaging (MRI) with a gradient echo can detect acute ICHs with equal sensitivity and overall accuracy (Fiebach *et al.* 2004, Kidwell *et al.* 2004). Cerebral angiography is the most reliable method for diagnosing secondary causes of ICH (Broderick *et al.* 1999, Qureshi *et al.* 2001). Magnetic-resonance angiography and MRI can also identify secondary causes of ICH (Broderick *et al.* 1999), although their sensitivity is not well established (Qureshi *et al.* 2009).

2.5 Risk factors for primary intracerebral hemorrhage

The best documented modifiable risk factor for ICH is arterial hypertension (Caplan 1992, Thrift *et al.* 1996). Improved control of hypertension seems to reduce the incidence of ICH (Furlan *et al.* 1979). Anticoagulant medication and heavy drinking of alcohol are other well-known risk factors for ICH (Juvela *et al.* 1995, Qureshi *et al.* 2001, Steiner *et al.* 2006). Particularly, recent drug use (Caplan *et al.* 1982) and recent heavy alcohol use (Juvela *et al.* 1995) have been reported to be independent risk factors for intracerebral hemorrhage. A low serum cholesterol level is a less well established risk factor (Iso *et al.* 1989). The use of

antiplatelet medication like aspirin has been found to be a risk factor for ICH in many studies (Bhatt *et al.* 2006, He *et al.* 1998, Saloheimo *et al.* 2001, Thrift *et al.* 1999).

Other known risk factors for ICH include increasing age, amyloid angiopathy, and prior ischemic stroke (Hanger *et al.* 2007). Particularly, cerebral amyloid angiopathy (CAA) associated with ε2 and ε4 alleles of apolipoprotein E seem to cause an elevated risk for recurrent lobar hemorrhage (O'Donnell *et al.* 2000). Data from the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) and the European Atrial Fibrillation Trial (EAFT) indicate that patients with a primary underlying cerebrovascular disease have a remarkably higher risk of ICH related to oral anticoagulant treatment (Anonymous 1997, Gorter 1999).

Studies have also suggested that the presence of white matter lesions, so-called "leukoaraiosis," is an independent predictor of spontaneous ICH (Smith *et al.* 2002). On the other hand, microbleeds are suggested to represent hemorrhage-prone microangiopathy (Sueda *et al.* 2010). A correspondence ratio to prior locations of microbleeds is higher in deep ICHs than in lobar ICHs, and this may be attributable to their different pathogeneses (Biffi *et al.* 2010).

2.6 Medication and intracerebral hemorrhage

2.6.1 Role of warfarin

Warfarin is the most commonly used anticoagulant. Warfarin is used to prevent a cardioembolism resulting from atrial fibrillation and mechanical heart valves as well as for primary prevention and treatment of deep venous thrombosis and a pulmonary embolism. Vitamin K antagonists like warfarin act by inhibiting the vitamin K epoxide reductase, thereby reducing the activation of vitamin K-dependent coagulation factors, resulting in *in vivo* depletion of clotting factors II, VII, IX, and X, and proteins C and S (Hirsh *et al.* 2003). It is possible that the deficiency of these clotting factors facilitates bleeding from pathological and ruptured blood vessels (Anonymous 1997, Gorter 1999). The intensity of anticoagulation is assessed by measuring the International Normalized Ratio (Hirsh *et al.* 2003).

Anticoagulant medication is a well-known risk factor for ICH (Juvela *et al.* 1995, Qureshi *et al.* 2001, Steiner *et al.* 2006), and its use is frequently associated with the onset of ICH (Aguilar *et al.* 2007). Giving high-intensity anticoagulants

to patients with a prior brain infarction will increase their risk for hemorrhagic stroke (Ariesen *et al.* 2004). It has been hypothesized that antithrombotic agents unmask pre-existing subclinical intracerebral bleeding, which occurs with increasing frequency in the elderly population, especially in individuals with hypertension and cerebrovascular disease (Hart *et al.* 1995, Hart 2000).

A recent study from the United States showed a marked increase in the incidence of ICH concomitant with an increase in oral anticoagulant use (Flaherty *et al.* 2007). The use of warfarin has rapidly increased with the aging of the population (Quintero-Gonzalez 2010, Virjo *et al.* 2010). The age-adjusted prevalence of warfarin-treated patients with atrial fibrillation was 0.30% in seven Finnish communes in 1999 (Viitaniemi *et al.* 1999)**.** The prevalence of atrial fibrillation in Finland was estimated to be 1750/100,000 in 2009, and in a cohort of 708 patients, 60% were on warfarin (Lehto M *et al.* 2011). These patients were collected among patients with disturbing symptoms of atrial fibrillation and that is why that information cannot be used to extract the real prevalence of warfarin-treated patients with atrial fibrillation (Lehto M *et al.* 2011).

Amyloid angiopathy may contribute to warfarin-associated lobar ICH (Rosand *et al.* 2000). All combination therapies of warfarin, aspirin, and clopidogrel are associated with an increased risk of fatal and nonfatal bleeding in patients with atrial fibrillation, and dual warfarin and clopidogrel therapy and triple therapy were found to carry a more than threefold higher risk than warfarin monotherapy (Hansen *et al.* 2010).

Intracerebral hemorrhage carries a prospect of a very poor outcome if associated with anticoagulant use. Reported mortality rates vary from 46% to 73% (Cucchiara *et al.* 2008, Hart *et al.* 1995, Rosand *et al.* 2004, Saloheimo *et al.* 2006). In the presence of anticoagulant treatment, the hematoma often expands to a lethal size within 24 hours after the onset of bleeding (Hart *et al.* 1995). Patients suffering from ICH during warfarin treatment have larger hematoma volumes on admission and their final hematoma volumes are larger than those of other patients suffering from ICH (Kuwashiro *et al.* 2010). Warfarin-associated hematomas continue to enlarge over a longer period of time than hematomas unrelated to anticoagulant treatment (Flibotte *et al.* 2004, Yasaka *et al.* 2003). Although ICH is the most serious complication of anticoagulant medication, we still lack standardized treatment guidelines (Steiner *et al.* 2006).

2.6.2 Role of aspirin and other nonsteroidal anti-inflammatory drugs

Antiplatelet therapy may increase the risk of ICH, but this has not been established. An aspirin-clopidogrel combination compared with aspirin alone did not increase the rate of ICHs in a large prospective, randomized study (Bhatt *et al.* 2006). An earlier meta-analysis suggested that a high dose of aspirin (>100 mg) may contribute to increased occurrence of hemorrhagic stroke (Serebruany *et al.* 2004). Use of aspirin carries an increased risk for mortality from ICH (Lacut *et al.* 2007, Roquer *et al.* 2005, Saloheimo *et al.* 2006, Toyoda *et al.* 2009). A warning sign suggesting risk for ICH while on aspirin may be a history of epistaxis (Saloheimo *et al.* 2001). The relationship between non-aspirin nonsteroidal anti-inflammatory drugs (NSAID) and ICH is unclear; some case-control studies show no association between the use of non-aspirin NSAIDs and hemorrhagic stroke (Bak *et al.* 2003, Choi *et al.* 2008, Johnsen *et al.* 2003, Thrift *et al.* 1999).

Survivors of ICH show a greater risk for recurrent ICH than for ischemic stroke, and this has implications for the use of antithrombotic agents in these patients (Bailey *et al.* 2001). However, antiplatelet agent use is relatively common following ICH, but does not seem to be associated with a markedly increased risk of ICH recurrence (Viswanathan *et al.* 2006). It has been found that antithrombotic therapy may be independently associated with thalamic, cerebellar, and lobar hemorrhage (Itabashi *et al.* 2009). Use of an antiplatelet agent following an amyloid angiopathy-related lobar ICH may increase the risk for recurrence (Biffi *et al.* 2010).

The use of aspirin is a predictor of death within the first three months after an ICH and it is also associated with hematoma growth (Saloheimo *et al.* 2006). On the other hand, Flibotte *et al.* (Flibotte *et al.* 2004) did not find hematoma expansion to be associated with the use of antiplatelet agents. Stead (Stead *et al.* 2010) did not find any significant relationship between the use of anticoagulants, antiplatelets, or both and a bad functional outcome.

2.6.3 Role of serotonin reuptake inhibitors

The use of SSRIs (selective serotonin reuptake inhibitors) may increase the risk of ICH (Smoller *et al.* 2009, Verdel *et al.* 2011). On the other hand, four reports did not observe this type of risk (Bak *et al.* 2002, Chen *et al.* 2009, de Abajo *et al.* 2000, Kharofa *et al.* 2007). In a recent study, use of SSRI drugs with any type of antiplatelet therapy (aspirin or clopidogrel, or both) was associated with an

increased risk of bleeding among patients following acute myocardial infarction, beyond the risk associated with antiplatelet therapy alone (Labos *et al*. 2011). To date we have too limited data to allow interpretations regarding the influence of SSRIs on hemorrhagic stroke (Chittaranjan.A. *et al.* 2010). Simultaneous use of SSRIs with warfarin or aspirin did not confer a significantly greater risk for hemorrhagic stroke than warfarin or aspirin alone (Kharofa *et al.* 2007).

Most of the effects of SSRIs are linked to their inhibitory action on the serotonin reuptake transporter, which mechanism has been discovered in platelets (Berger *et al.* 2009). Paroxetine is found to produce a forceful decrease of over 80% in platelet serotonin content after two weeks of paroxetine treatment (Hergovich *et al.* 2000). Serotonin manifests powerful vasoactive effects through direct action on serotonin receptors and through nitric oxide production (Berger *et al.* 2009). Almost all serotonin existing in blood is transported in dense granules by platelets (Skop & Brown 1996). Serotonin stored in platelets may have a stake in hemostasis. SSRIs impair both the secretory response of platelets and platelet aggregation induced by ADP, collagen, and thrombin, causing an inhibition of platelet plug formation, as reflected by a significant prolongation of the closure time measured with a platelet function analyzer (Halperin.D. & Reber.G. 2007).

It is supposed that predominantly noradrenergic serotonin reuptake inhibitors like mirtazapine are likely to be safe in patients at risk of abnormal bleeding (Chittaranjan.A. *et al.* 2010). This assumption is based on several studies (Dall *et al.* 2009, Dalton *et al.* 2003, de Abajo *et al.* 1999, Meijer *et al.* 2004, Opatrny *et al.* 2008). On the other hand, bleeding associated with serotonin-norepinephrine reuptake inhibitors (SNRIs) like venlafaxine and duloxetine has been reported (Abajo 2011).

2.7 Outcome after primary intracerebral hemorrhage

The mortality of ICH patients varies between 30% and 55%, and ICH causes severe disability for the majority of survivors (Brott *et al.* 1997, Rosand *et al.* 2004). The median case fatality rate at one month was found to be 40.4% in a recent meta-analysis (van Asch *et al.* 2010). The same meta-analysis did not observe any significant change in case fatality over time during 1983–2006.

Spontaneous ICH is a serious disease with high mortality and morbidity. Before 2001, outcome was determined mainly by the severity of bleeding (Fujitsu *et al.* 1990, Juvela *et al.* 1989, Ojemann & Heros 1983, Waga *et al.* 1986). Level of consciousness, volume of the hematoma, and presence of intraventricular blood

were found to be independent predictors of death and a poor outcome in short-term outcome studies (Broderick *et al.* 1993, Daverat *et al.* 1991, Franke *et al.* 1992, Portenoy *et al.* 1987, Tuhrim *et al.* 1991). Age was found to be an independent predictor of recovery, too (Daverat *et al.* 1991, Franke *et al.* 1992). Furthermore, a high blood glucose level on admission and previous antiplatelet treatment have been found to be independent predictors of 30-day outcome after first-ever PICH (Roquer *et al.* 2005).

In 2001 Hemphill and coworkers developed an outcome risk stratification scale (the ICH Score) from a logistic regression model for all ICH patients (Hemphill *et al.* 2001). The five characteristics determined to be independent predictors of 30-day mortality were each assigned points on the basis of the strength of their association with outcome. The total ICH Score is the sum of the points of the various characteristics**.** Table 1 indicates the specific point assignments used in calculating the ICH Score.

Table 1. Determination of the ICH Score (Hemphill *et al*. 2001)

Component	ICH Score Points
GCS score	
3–4	2
5–12	1
13–15	0
ICH volume, cm^3	
≥30	1
<30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age, y	
≥80	1
<80	0
Total ICH Score	0–6

GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using the ABC/2 method; and IVH, presence of any IVH on initial CT.

The severity and location of the hemorrhage, the age of the patient, and the amount of alcohol consumed within one week before the stroke were found to be independent determinants of outcome after intracerebral hemorrhage among Finnish patients (Juvela 1995). Binge drinking has been found to have a harmful effect on hemorrhagic stroke in Korean men, too (Sull *et al.* 2009). Patients with subcortical, caudate, and cerebellar hematomas had the best prognosis, while patients with a combined ganglionic or pontine hemorrhage had the worst outcome (Juvela 1995).

Warfarin treatment increases hematoma growth in ICH patients. Among warfarin users we see larger final hematoma volumes compared with those seen in patients without anticoagulation (Kuwashiro *et al.* 2010). Intracerebral hemorrhage associated with anticoagulant use carries a prospect of a very poor outcome. As mentioned before, mortality rates are very high, varying from 46% to 73% (Cucchiara *et al.* 2008, Hart *et al.* 1995, Rosand *et al.* 2004, Saloheimo *et al.* 2006).

2.7.1 Prevention of hematoma growth

As said before, management of ICH is largely supportive. Prevention of associated complications is still the best way to improve the outcome of an ICH patient. ICH complications include hematoma expansion, perihematomal edema, and ventricular extension of the hemorrhage with hydrocephalus, seizures, venous thromboembolic events, hyperglycemia, increased blood pressure, fever, and infections. Hematoma expansion is one of the major predictors of increased early mortality and adverse outcome of ICH (Brott *et al.* 1997).

Hematoma expansion is defined as an increase in volume of 33–50% or an absolute change in hematoma volume of 12.5–20 ml on repeat CT (Anderson *et al.* 2008, Fujitsu *et al.* 1990). More than 70% of patients develop at least some increase in their bleed volume within the first day after onset (Davis *et al.* 2006). Within 24 hours from symptom onset, 38% of patients had >33% enlargement in hematoma volume (Brott *et al.* 1997); in two-thirds of these patients with a significant hematoma enlargement, hematoma growth occurred already within the first hour after the baseline CT, which was taken immediately on admission. An additional 12% of the patients developed >33% hematoma growth later on, i.e. within 24 hours after symptom onset. Patients who are on warfarin at the onset of an ICH may develop both early and delayed hematoma expansion (Cucchiara *et*

al. 2008, Flibotte *et al.* 2004, Huttner *et al.* 2006). Hematoma expansion is associated with high mortality (Flibotte *et al.* 2004, Rosand *et al.* 2004).

Hemostatic therapy, cautious lowering of high blood pressure, quick reversal of prior anticoagulation, and surgical evacuation are the suggested interventions to restrict hematoma expansion (Morgenstern *et al.* 2010).

2.7.2 Treatment of high blood pressure

Hypertension is the most important modifiable risk factor for ICH (Brott *et al.* 1986). Improved control of hypertension appears to decrease the incidence of ICH (Furlan *et al.* 1979). Previous hypertension has not been reported to be a significant predictor of a poor short-term outcome or early death after ICH (Juvela 1995, Nilsson *et al.* 2002, Saloheimo *et al.* 2006, Tetri *et al.* 2009). We still do not know how preceding hypertension, whether treated or untreated, influences long-term outcome after ICH.

High admission blood pressure has been reported to be associated with a poor short-term outcome in some but not all studies (Davis *et al.* 2006, Tetri *et al.* 2009, Tuhrim *et al.* 1991). More than two-thirds of patients show increased blood pressure during the acute phase of ICH (Qureshi 2008). The mechanism for an acute increase in blood pressure, even in the absence of a previous history of hypertension after ICH, is unknown. Elevated admission blood pressure (BP) has been shown to be a risk factor for hematoma enlargement (Broderick *et al.* 1990, Ohwaki *et al.* 2004), but the effect of preceding hypertension on hematoma growth is still unclear.

Several studies suggest that acute hypertension, particularly high systolic BP on admission, predicts high mortality and a poor neurological outcome after ICH (Dandapani *et al.* 1995, Leira *et al.* 2004, Willmot *et al.* 2004). Elevated BP has been found to increase the risk for hematoma enlargement (Broderick *et al.* 1990, Ohwaki *et al.* 2004), which leads to a higher death rate (Fujii *et al.* 1998) and early neurological deterioration (Brott *et al.* 1997) after ICH. On the other hand, some studies do not agree with these findings. A meta-analysis of patients with spontaneous ICH did not confirm that elevated BP predicts a poor outcome (Davis *et al.* 2006), and a recent study did not find any association between BP and hematoma growth (Marti-Fabregas *et al.* 2008). Furthermore, a rapid decline in BP within the first 24 hours after the onset of ICH has been reported to be associated with increased mortality (Qureshi *et al.* 1999). This may be due to the

so-called Cushing reflex, i.e. a rapid decline in blood pressure after intracranial pressure has reached too high a level (Fodstad *et al.* 2006).

Both American Stroke Association (Broderick *et al.* 2007) and European Stroke Initiative (European Stroke Initiative Writing Committee *et al.* 2006) guidelines have recommended lowering blood pressure in patients with an ICH to maintain systolic blood pressure below 180 mmHG. Both guidelines still acknowledge that there may be some patients who can tolerate more aggressive blood pressure reduction, such as those without chronic hypertension or those with a good neurological status.

The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial (Qureshi 2007) and the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) reported that aggressive reduction of systolic blood pressure to less than 140 mmHG probably decreases the rate of substantial hematoma enlargement (Anderson *et al.* 2008) without increasing adverse events (Qureshi *et al.* 2009). No differences were observed in the rates of death and disability at three months between patients treated with aggressive and conservative lowering of blood pressure in the ATACH or INTERACT studies. However, patients recruited within three hours and those with initial systolic blood pressure of 181 mmHg or more seemed to benefit most from aggressive lowering of blood pressure, as suggested by subgroup analyses from the INTERACT study (Anderson *et al.* 2008).

2.7.3 Reversal of anticoagulation

Warfarin is the most commonly used anticoagulant and its use is frequently associated with the onset of intracerebral hemorrhage, and that is why researchers have tried to counteract the effect of warfarin in patients with ICH using several methods. One possibility is to stop warfarin and give vitamin K, but this does not reverse the anticoagulant effect of warfarin rapidly enough. In fact, the International Normalized Ratio (INR) cannot be rapidly lowered simply by stopping warfarin (Goldstein *et al.* 2008). Lowering the INR may take four hours even after intravenous injection of vitamin K. Therefore, these methods are not adequate for emergency reversal of warfarin anticoagulation. Fresh frozen plasma (FFP) has largely been used in the USA, but reversal of warfarin anticoagulation by FFP may take as long as seven hours (Goldstein *et al.* 2008). More promising antidotes are prothrombin complex concentrate (PCC) and Factor VIIa concentrate, which both reverse the anticoagulant effect of warfarin within

minutes to one hour (Aguilar *et al.* 2007). All the above methods have been tested in small patient series. The use of PCC has shown the most favorable effects (Boulis *et al.* 1999, Cartmill *et al.* 2000, Chong *et al.* 2010, Fredriksson *et al.* 1992, Huttner *et al.* 2006, Kuwashiro *et al.* 2011, Siddiq *et al.* 2008, Yasaka *et al.* 2003, Zubkov *et al.* 2008). In a cohort in which warfarin was reversed with heterogeneous therapies, fresh frozen plasma being the most commonly used agent, normalization of the INR did not influence mortality or functional outcome (Stead *et al.* 2010). However, there are no controlled clinical trials on which to base a recommendation, and the outcome of treated patients has remained unclear.

A difficult dilemma is whether or when to resume anticoagulation after ICH in patients with a cardiac disease associated with a high embolization risk. The American Heart Association and American Stroke Association guidelines suggest restarting warfarin 7–10 days after ICH in patients with a very high risk of a thromboembolism (Broderick *et al.* 2007). On the other hand, in a recent study Majeed and coworkers found the optimal timing for resumption of warfarin therapy to be between 10 and 30 weeks after warfarin-related ICH (Majeed *et al.* 2010). But, an even more difficult question is how to manage patients with thromboembolic complications after ICH.

2.7.4 Recurrent ICH

The risk of recurrent ICH varies widely (0–24%) (Hanger *et al.* 2007). The risk of recurrent ICH is greater than the risk of ischemic stroke, and this has implications for the use of antithrombotic agents after ICH (Bailey *et al.* 2001). Hanger and coworkers found that the risk of ICH recurrence in survivors of an ICH is highest in the first year, being 2.1/100/year, but after that the overall rate is 1.2/100/year and is comparable with the risk of an ischemic stroke (1.3/100/year) (Hanger *et al.* 2007). In a large Swedish cohort, Zia *et al*. found that 12% (5.1 per 100 person-years) of the patients had a recurrent stroke event, either a new PICH (2.3 per 100 person-years) or a cerebral infarction (2.8 per 100 person-years) within three years after the PICH event. After adjustment for sex, age, and location of the first PICH, only age was an independent risk factor for recurrence of either PICH or cerebral infarction (Zia *et al.* 2009). The dominant location of the index bleed varies from mostly deep to mostly lobar (Maruishi *et al.* 1995, Neau *et al.* 1997). Use of an antiplatelet agent was not found to be associated with a large increase in the risk of PICH recurrence (Viswanathan *et al.* 2006). After adjustment for sex, age, and location of the first PICH, only age was an independent risk factor for

recurrence of either PICH or cerebral infarction (Zia *et al.* 2009). However, it was found that patients with a lobar PICH had a higher rate of recurrent ICH than those with a deep PICH (Bailey *et al.* 2001, Viswanathan *et al.* 2006). Recurrence of a lobar PICH is associated with previous microbleeds or macrobleeds and posterior CT white matter hypodensity, which may be markers of severity of underlying cerebral amyloid angiopathy (Biffi *et al.* 2010). Use of an antiplatelet agent following a lobar PICH may also increase the risk of recurrence (Biffi *et al.* 2010).

In a Korean study, microbleeds were found to predict recurrent ICH (Jeon *et al.* 2007). In a European cohort, microbleeds indicated a higher risk of recurrent stroke but did not signal a very high risk of ICH, because most recurrences were ischemic in nature (Thijs *et al.* 2010). Lobar microbleeds or the simultaneous presence of microbleeds in the lobar and in the deep region might indicate a particularly high risk of recurrent stroke (Thijs *et al.* 2010).

3 Aims of the research

The present series of studies focuses on the impact of medication on the incidence, outcome, and recurrence of primary intracerebral hemorrhage. I wanted to know whether the increasing use of warfarin had affected the mortality and morbidity of ICH among the population of Northern Ostrobothnia. I also wanted to explore whether the clinical outcome of patients suffering from warfarin-associated primary ICH had improved after implementation of PCC treatment. In addition, I explored the role of high admission blood pressure and preceding antiplatelet medication on outcome after ICH and the risk factors for recurrent bleeding.

The aims of the present study were:

1. to explore the association between warfarin use and the occurrence of warfarin-associated ICH in the population of Northern Ostrobothnia (I),
2. to explore whether the clinical outcome of patients with a primary ICH had improved among the population of Northern Ostrobothnia after starting PCC treatment (II),
3. to demonstrate the short-term outcome after ICH in subjects having untreated hypertension compared with those who have treated hypertension and those who do not have hypertension at all, and how admission blood pressure influences short-term outcome in these patient groups (III),
4. to find out the predictors of recurrent primary intracerebral hemorrhage, and whether the use of antiplatelet medication increases the risk for recurrent ICH (IV).

4 Subjects and methods

4.1 Subjects

For *study I* we identified all subjects with ICH associated with the use of oral anticoagulants from January 1, 1993 through December 31, 2008 among the population of Northern Ostrobothnia, Finland. The study included all patients admitted to Oulu University Hospital, which is the only hospital in the area (population in 1993–2008: 356,026–389,671) that treats acute stroke patients. ICH was verified by a head CT scan on admission in all cases. We excluded patients not living in the catchment area of the hospital, those who had a brain tumor, aneurysm, vascular malformation, hematologic malignancy, hemophilia, or head trauma, and those who had been using an anticoagulant other than warfarin. We included only patients who had a primary intracerebral hemorrhage while on warfarin therapy. We also identified seven subjects who had died from ICH without being admitted to our hospital by collecting data from death records obtained from the Causes of Death Register (Statistics Finland). The register collects death certificates from all subjects in Finland by using personal social security numbers. The data also included the subjects' use of anticoagulants at the moment of death. All except one of the seven subjects who had succumbed on the scene because of a primary ICH had been investigated by forensic autopsy. The subject who had not been autopsied had ICH as the immediate cause of death in the clinical death certificate.

Annual numbers of warfarin users among all the subjects living in Northern Ostrobothnia and the whole Finnish population were obtained from the national register of prescribed medicines kept by the Social Insurance Institution of Finland.

Study II included the same subjects as *study I* except for one subject with WA-ICH who did not have autopsy or head CT verification of the diagnosis and another one who had a brain tumor possibly underlying the bleeding (found after the first study was published).

Study III was comprised of all patients with a primary ICH admitted between January 1993 and January 2004 to the Stroke Unit of the Department of Neurology, Oulu University Hospital. We excluded patients not residing in the hospital's catchment area, those with bleeding caused by a brain tumor, aneurysm, vascular malformation, hematological malignancy, coagulation disorder, or head

trauma, and those in need of immediate surgery. Altogether 453 ICH patients were admitted during the study period. Most of the patients had a primary ICH.

For *study IV* we identified all subjects with a primary ICH from January 1, 1993 through December 31, 2008 among the population of Northern Ostrobothnia, Finland. Because the study explored the effects of risk factors and medication on long-term outcome, we first excluded those who died within 30 days after the onset of ICH. After checking the available data, we had to exclude 21 additional patients because they had a history of intracranial bleeding before 1993. As shown in the flow chart, we were left with 680 ICH patients with first-ever ICH. During the follow-up period of 10 years, 58 of them suffered altogether 68 recurrent ICHs, whereas 622 patients did not get a recurrence.

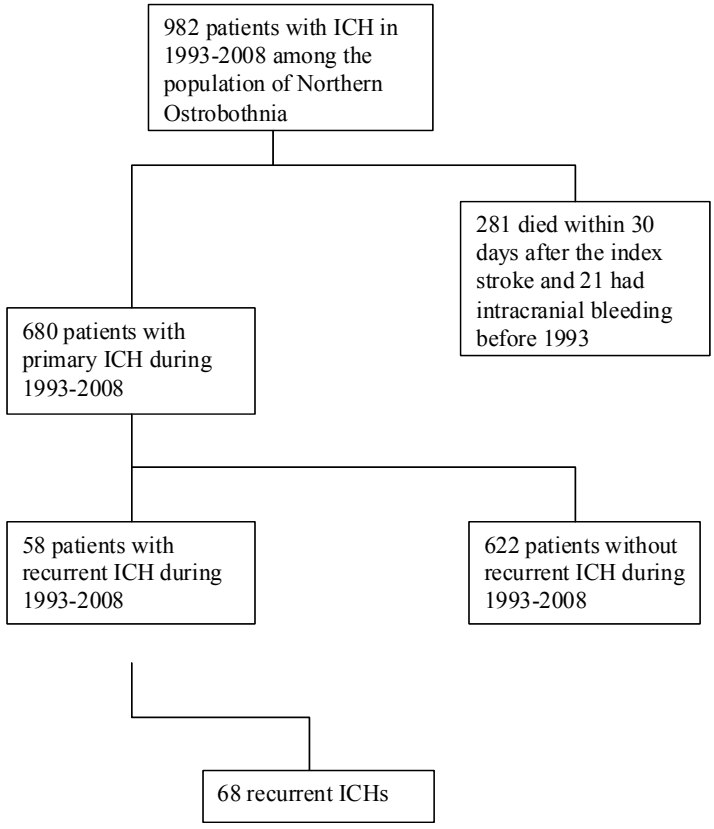

Fig. 1. Flow chart showing the composition of the material.

4.2 Ethics

The study protocols of all the studies were approved by the ethics committee of the Northern Ostrobothnia Hospital District. Permission to use the death records and to review the autopsy reports was given by Statistics Finland and the Oulu Provincial Government, respectively.

4.3 Clinical data

For *study I*, annual numbers of warfarin users among all the subjects living in Northern Ostrobothnia and the whole Finnish population were obtained from the national register of prescribed medicines kept by the Social Insurance Institution of Finland. We calculated the annual prevalences of warfarin users in Northern Ostrobothnia, the annual numbers of warfarin-associated new ICH cases per 1,000 warfarin users, and the annual death rates due to primary bleeding among these subjects.

The information for all the studies was gathered by using a structured questionnaire. Information about previous diseases, blood pressure values, and use of anticoagulants and other medication was extracted from the hospital records, as were the data on major medical complications during hospitalization after the onset of the index stroke. Delays from symptom onset to emergency room admission were also recorded. For *study IV* we gathered data on all medication prescribed for the patients from hospital records. The use of selective and non-selective serotonin reuptake inhibitors and clopidogrel were double-checked by using purchase data obtained from the national register of prescribed medicines kept by the Social Insurance Institution of Finland. Data were gathered from the forensic autopsy charts of those who had succumbed on the scene.

The subjects were considered hypertensive if their blood pressure readings preceding the index stroke 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. The patients were recorded as having diabetes mellitus if they used oral hypoglycemic agents or insulin. Previous hemorrhagic and ischemic strokes were recorded, as well as cardiac diseases, including myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation. Congestive heart failure, renal failure, liver failure, cancer, and dementia were also recorded. Other previous instances of bleeding like epistaxis and

gastrointestinal bleeding were recorded as was information about pulmonary embolisms and venous thrombosis. Information about current or former tobacco smoking and heavy drinking was collected if it was available.

The patient's clinical condition on admission was assessed using the GCS score (Teasdale & Jennett 1974). The severity of bleeding was determined by using the ICH score (Hemphill *et al.* 2001). The score takes into account the GCS score, hematoma volume and location, ventricular extension of the hematoma, and the patient's age. Functional outcome at three months was assessed according to the Glasgow Outcome Scale (GOS) (Jennett & Bond 1975). Those who showed good recovery at discharge were assumed to maintain this state for three months if they had not been readmitted. The patients' survival during the follow-up period—until December 31st, 2008—after the onset of ICH was checked from hospital records and death records. If there was no satisfactory information about the patient's outcome, I called the patient or a relative to find out the GOS score.

4.4 Radiological methods

All head CT scans were analyzed and the locations and volumes of hematomas were measured by an experienced neuroradiologist blinded to the case history of each patient, except for the time of surgery. Hematomas were divided into categories based on their location in the subcortex, basal ganglia (putamen, nucleus caudatus, and combined, extending into the thalamus and subcortical white matter), thalamus, pons, or cerebellum. They were divided into supra- and infratentorial categories, too. The presence of intraventricular bleeding was recorded.

Because this project was an ongoing process, two different methods were used to measure ICH volume over the years. The majority were measured using an accurate planimetric method (Broderick *et al.* 1993, Kothari *et al.* 1996, Saloheimo *et al.* 2005), but a minority (a small part of those from 2004 on) were measured with the ABC/2 method, which offers a reasonable approximation of hematoma volume in warfarin-associated ICH and other ICH (Sheth *et al.* 2010). Secondary structural abnormalities were searched for immediately or by follow-up brain imaging (CT or MRI) 2–3 months after the bleed. Angiography was performed if aneurysmal bleeding was suspected.

4.5 Treatment

Considering *study II* from the year 2004 onwards, PCC (COFACT^{R}, Sanquin Blood Supply Foundation) was used in our hospital to counteract the anticoagulant effect of warfarin in patients who had an ICH while on warfarin. An institutional protocol for warfarin reversal with PCC for patients with a WA-ICH included instructions on how to administer PCC according to the initial INR value and the patient's weight. To reach the target INR (≤1.5), the dose ranged from 12.5 to 30 IU per kg of body weight. The patients were also immediately given intravenous vitamin K (10 mg) to stimulate their own synthesis of coagulants. The INR was measured immediately before and 12 h after the administration of PCC and vitamin K. A second INR value was also measured from the subjects who received only vitamin K, but this was usually done ≥24 hours after the initial measurement. The decision to administer PCC and vitamin K was always based on the duty physician's assessment and was not influenced by the investigators. According to the protocol, treatment should be instituted if the patient is conscious, hematoma volume does not exceed 50 ml, and the delay from the onset of symptoms is ≤24 h.

In *study III*, blood pressure levels were monitored constantly in the emergency ward and the stroke unit. Mean arterial blood pressure (MABP) was calculated by adding 1/3 of the pulse pressure (systolic minus diastolic) to the diastolic pressure. Most of the patients (77%) with admission hypertension >180/100 mmHg, i.e. MABP >127 mmHg, received aggressive BP-lowering therapy to reach a target level of MABP <120 mmHg. Among the agents used were labetalol hydrochloride, clonidine hydrochloride, nifedipine, furosemide, and metoprolol. Some patients received more than one agent. Intracranial pressure monitoring and mannitol were not used in our stroke unit.

4.6 Statistical methods

The data for all the studies were analyzed with SPSS/PASW for Windows (release 12.0.1.2003, SPSS Inc.).

In *study I* categorical variables were compared using the Pearson Chi-square test. Spearman's rank correlation coefficients (rs) were calculated for multiple comparisons. For life table analysis, each patient was followed up until death or until one year after the ICH. Cumulative survival rates were estimated using the Kaplan-Meier product-limit method, and the curves of the different groups were

compared using the log-rank test. Analyses of variance and covariance were used to explore interactions between age, use of warfarin, and year of stroke onset. Logistic regression analysis was used to determine ORs and 95% CIs of significance of variables in predicting case fatality. The following variables were tested using the forward stepwise method: age; sex; and history of hypertension, cardiac disease, diabetes, and use of warfarin. The test for significance was based on changes in log (partial) likelihood. A two-tailed p value less than 0.05 was considered statistically significant.

In *study II* we compared the three-month functional outcomes and one-year survival rates of subjects admitted during 1993–2003 and 2004–2008. We also explored the predictors of one-year survival of the WA-ICH patients. Categorical variables were compared using Fisher's exact two-tailed test and the Pearson Chi-square test. Spearman's rank correlation coefficients (rs), t-tests, or Mann-Whitney U tests were used for comparisons of continuous variables. For life table analysis, each patient was followed up until death or until one year after the ICH. Cumulative survival rates were estimated with the Kaplan-Meier product-limit method, and the curves of the different groups were compared using the log-rank test. Cox proportional hazards models were used to determine hazard ratios (HR) and 95% confidence intervals (CI) of variables that predict survival within one year after WA-ICH. The following variables were included in the final model: age; sex; history of hypertension, cardiac disease, and diabetes; admission GCS score; size, location, and ventricular extension of the hematoma; and treatment with PCC. The test for significance was based on changes in log (partial) likelihood. A two-tailed p value less than 0.05 was considered statistically significant.

In *study III*, for univariate statistics, conventional statistical tests were used, including analysis of variance (ANOVA) with the Bonferroni method adjustment for multiple pairwise comparisons. For life table analysis and the Cox proportional hazards regression model, each patient was followed up until death or for three months after the ICH. Cumulative survival rates were estimated with the Kaplan-Meier product-limit method, and the curves of the different groups were compared using the log-rank test. The Cox proportional hazards model with a forward stepwise regression procedure was used to determine the significance of several variables in predicting relative risks (RR) with 95% CI for death. The following variables, which were known at the beginning of the follow-up, were analyzed: age, gender, history of hypertension, previous ischemic stroke, previous hemorrhagic stroke, cardiac disease, diabetes, cancer, hematoma size, location of the hematoma, presence of an intraventricular hematoma (IVH), warfarin

treatment, regular aspirin use, Glasgow Coma Scale (GCS) score on admission, current smoking and recent heavy drinking, plasma glucose on admission, and blood pressure on admission. The assumption of proportionality was checked. The test for significance was based on changes in log (partial) likelihood. A two-tailed probability value less than 0.05 was considered statistically significant.

In *study IV* the categorical variables were compared using Fisher's exact two-tailed test and the Pearson Chi-square test. Spearman's rank correlation coefficients (r_s), t-tests or Mann-Whitney U tests were used for comparisons of continuous variables. Cumulative rates of recurrent intracerebral hemorrhage were estimated with the Kaplan-Meier product-limit method, and the curves of the different groups were compared using the log-rank test. The Cox proportional hazards model was used to determine hazard ratios (HR) and 95% confidence intervals (CI) of variables that predict recurrent ICH. The following variables were included in the final model: aspirin, diabetes mellitus, untreated hypertension, treated hypertension, age, anticoagulation, prior ischemic stroke, interaction between aspirin and prior ischemic stroke, interaction between aspirin and diabetes, lobar ICH, NSSRI, high-affinity SSRI, and intermediate SSRI. The test for significance was based on changes in log (partial) likelihood. A two-tailed p value less than 0.05 was considered statistically significant.

5 Results

5.1 Increasing use of warfarin has had no untoward effect

The main finding of *study 1* was the absence of any untoward effect of increasing use of warfarin on the occurrence of WA-ICHs.

Among 982 subjects with a primary ICH we identified 182 (18.5%) who were on warfarin therapy at the onset of their stroke. One hundred and seventy-five were admitted to our hospital and seven died on the scene. These subjects were significantly older than the 800 who were not on warfarin (mean age difference 6.6 years, 95% CI 5.0–8.1, $p < 0.001$). They also more frequently had cardiac disease and diabetes and showed larger hematomas on admission than non-users. We did not observe significant differences in GCS scores or previous history of hypertension. Indications for warfarin use among the patients with ICH were atrial fibrillation (60%), cerebral infarction (14%), former thromboembolism (11%), cardiac disease (6%), prosthetic valve (5%), and other or unknown reasons (4%).

Patients not on warfarin had a significantly ($p < 0.001$) better one-year survival rate (67.9% vs. 35.2%) than warfarin users (Fig. 2). The case fatality rates of WA-ICHs were 54.4, 61.1, and 64.8% for the first 28, 90, and 365 days. The case fatality rates of ICHs unrelated to warfarin use were 23.4, 27.6, and 32.1%. The 28-day case fatality of warfarin users (54.4%) was significantly higher ($p < 0.001$) than that of non-users (23.4%). An apparent difference between the death rates developed already during the first week after stroke onset. After the first week the curves were parallel, showing no further increase in the death rate of warfarin users compared with non-users.

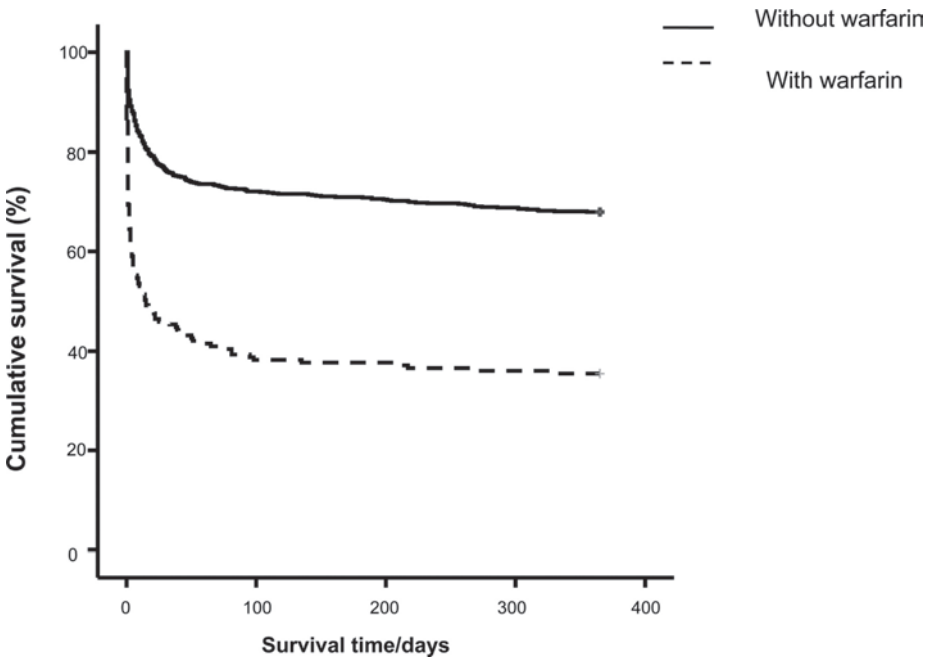

Fig. 2. Survival of subjects with ICH while on warfarin therapy (n = 182) compared with those not on warfarin (n = 800). There is a significant difference between the survival curves (p < 0.001, log-rank test). (Huhtakangas *et al*, 2011, published by permission of Wolters Kluwer Health)

The number of subjects using warfarin increased year by year among the population of Northern Ostrobothnia. As a consequence, the number of warfarin users was almost fourfold in 2008 compared with 1993. A similar increase took place among the whole Finnish population during these years, and the prevalence of warfarin users in Northern Ostrobothnia followed that development. However, we found that the number of WA-ICHs did not increase. Instead, a modest decrease was observed, whereas the incidence of ICHs not related to warfarin use remained constant. The annual 28-day case fatality rates also seemed to decrease among warfarin users, while remaining constant among non-users (Fig.3).

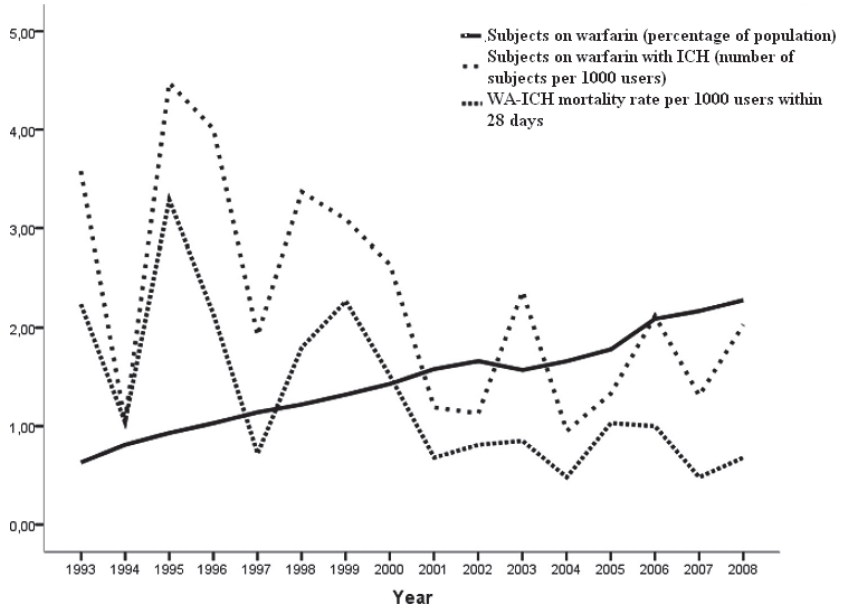

Fig. 3. Annual increase in warfarin use in relation to the incidence of WA-ICHs and the annual 28-day mortality rates due to WA-ICHs. (Huhtakangas *et al*, 2011, published by permission of Wolters Kluwer Health)

We found a negative correlation (rs = -0.477; p = 0.062) between the annual prevalence of warfarin use and the incidence of WA-ICHs during the observation period, and a significant (p = 0.041) linear-by-linear association between the increase in the prevalence of warfarin use and the decrease in WA-ICH incidence. In other words, the incidence of WA-ICHs did not follow the annual prevalence of warfarin use in Northern Ostrobothnia. We also found a significant negative correlation between the annual 28-day mortality rates of WA-ICHs and the annual prevalence of warfarin use (rs = -0.779; p = 0.002), and a significant (p = 0.012) linear-by-linear association between the increase in the prevalence of warfarin use and the decrease in WA-ICH mortality. Similar findings were observed if deaths from primary bleeding were compared with the annual prevalence of warfarin use (rs = -0.799; p < 0.001).

We explored whether age, hematoma volume, and the international normalized ratio on admission (INR) were factors which explained the lower occurrence and improved outcome of WA-ICHs. The subjects with and without a WA-ICH were older year after year (rs = 0.079; p = 0.013) and the increase in age was slightly steeper among patients with a WA-ICH. Hence, age was not likely to

contribute to the improved outcome. Hematomas were also slightly smaller towards the end of the observation period, but there was no difference between the groups. After dichotomizing the INR values into those which were within the therapeutic range (2.0–3.0) and those above the range, we observed fewer INR values above the therapeutic range at the end of the observation period compared with the early years ($p = 0.043$). This suggested improved control of anticoagulant therapy over time (improved coagulation monitoring). Among those who had an INR higher than 3.0 on admission, the 28-day case fatality rate was 61.3%, whereas the rate was 45.6% among those with an INR below 3.0 ($p = 0.051$).

5.2 Improved outcome of patients on warfarin

The main finding of *study II* was decreased case fatality among subjects with a WA-ICH after the implementation of PCC treatment.

During 1993–2008 we found altogether 181 subjects among the population of Northern Ostrobothnia who were on warfarin while being stricken by a primary ICH, 121 during 1993–2003 (i.e. before the implementation of PCC treatment), and 60 during 2004–2008. Six of these patients died outside the hospital (all before 2004). Of the 175 admitted to the hospital, 41 received PCC and vitamin K, and they were all admitted after 2003. Among the patients who did not receive PCC treatment, 38 received fresh frozen plasma and/or vitamin K, and 96 did not receive any drug to counteract the anticoagulant effect. The proportion of patients receiving PCC together with vitamin K increased year after year. It was small during 2004–2005 (27%) but increased thereafter, being 59% in 2006, 91% in 2007, and 94% in 2008. Overall, subjects who received PCC treatment showed lower mortality and a better outcome than those who did not receive the treatment.

The proportion of WA-ICH patients during 1993–2003 (19%) and 2004–2008 (18%) was similar. However, their median GCS score was found to be significantly lower before 2004 and their mean ICH volume was greater, but these differences were not statistically significant. Patients admitted before 2004 had a significantly ($p = 0.017$) higher mean INR and the proportion of patients with INR values >3 on admission was also higher (45% vs. 25%, $p = 0.014$) than that of patients admitted during 2004–2008. This suggests that INR monitoring had been more careful after 2003. The delay from symptom onset to admission did not differ between the groups ($p = 0.22$). The delay from onset to admission was less than 24 hours in 74% of the cases during 1993–2003 and in 75% during 2004–2008.

We observed a non-significant ($p = 0.079$) trend of better overall outcome among the users of warfarin during 2004–2008 when PCC treatment had been implemented. This trend was due to a lower case fatality during the latter period. The functional outcome of survivors did not differ between the treatment periods. Patients given PCC and vitamin K after WA-ICH showed a higher survival rate (56.1%) than those who were untreated (29.1%) ($p < 0.001$, log-rank test). However, this difference was influenced by selection bias, because the patients who were in poor condition had received PCC more seldom than those who were in better condition on admission.

Thromboembolic complications were not significantly more frequent among those who received PCC treatment than among those who did not receive it. Two survivors who received PCC had deep vein thrombosis, one of whom also had a pulmonary embolism. An autopsy-verified pulmonary embolism was the primary cause of death of one patient without PCC treatment. Two patients with PCC treatment and three without suffered myocardial infarction during hospital care.

Figure 4 shows that WA-ICH patients admitted during 2004–2008 had significantly ($p = 0.031$) higher one-year survival (43.3%) than patients admitted during 1993–2003 (30.6%). We also compared the one-year survival rates of those diseased during 1993–2005 and 2006–2008, because over 50% of WA-ICH patients received PCC treatment only from 2006 on. In this analysis the survival rates were 28.9% and 52.2%.

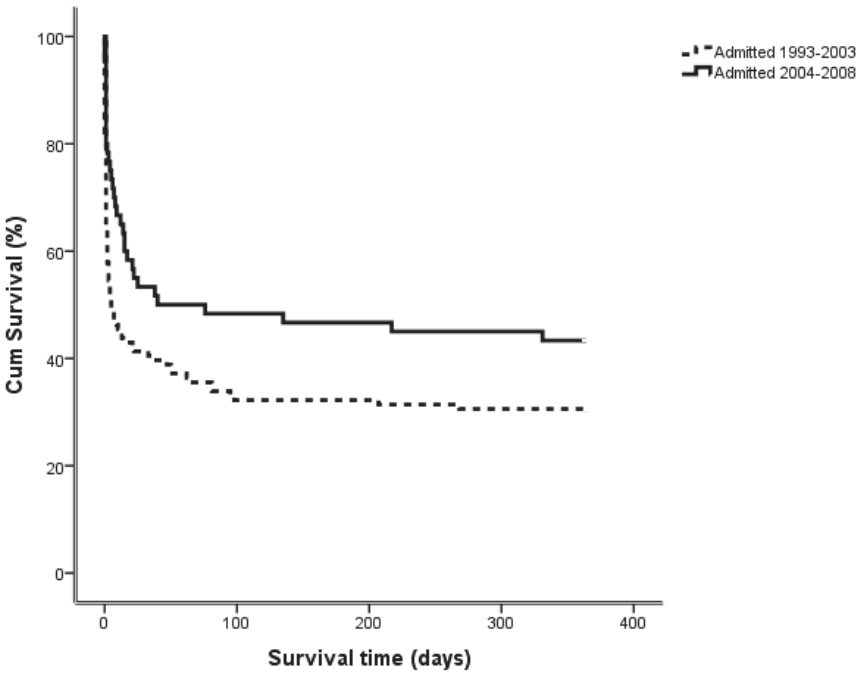

Fig. 4. One-year survival of ICH patients on warfarin. There is a significant difference (p = 0.031, log-rank test) between those admitted before 2004 (n = 121) and during 2004–2008 (n = 60). (Huhtakangas *et al*, in press, published by permission of Health Sciences - Medicine|Wiley-Blackwell)

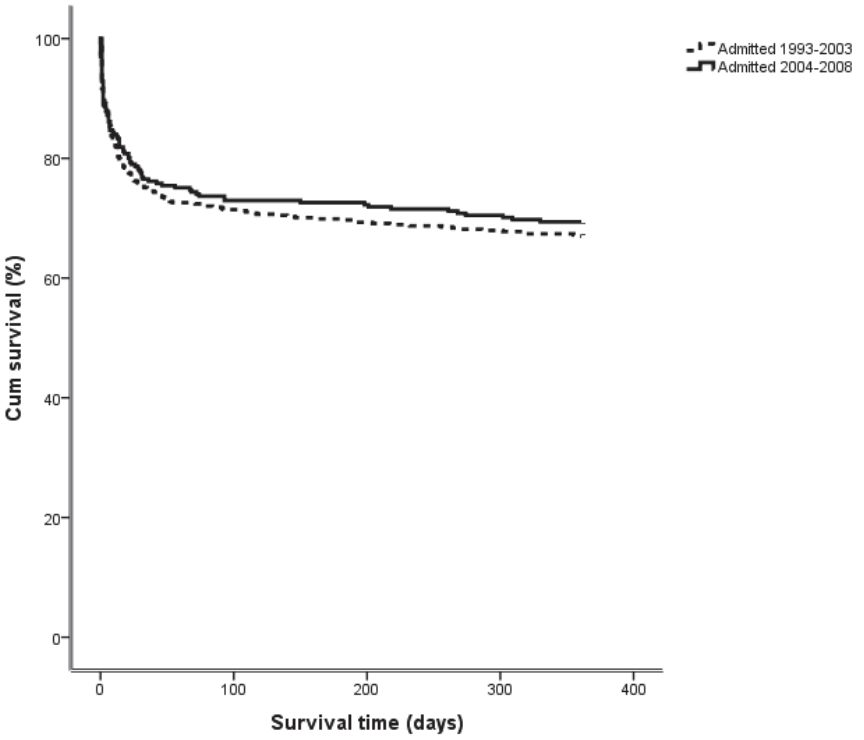

Fig. 5. One-year survival of patients not on warfarin. The difference between those admitted before 2004 (n = 518) and during 2004–2008 (n = 281) 2004 is not significant. (Huhtakangas *et al*, in press, published by permission of Health Sciences - Medicine|Wiley-Blackwell)

We did not observe a significant difference in the one-year survival rates of patients who were not on warfarin. The survival rates were 67.0% before and 69.4% after 2004. This indicates that treatment of ICH patients who were not on warfarin had not resulted in significantly improved survival during 2004–2008 compared with 1993–2003.

There was a significant correlation between the INR values of WA-ICH patients on admission (rs = 0.202; p = 0.009) and outcome. The lower the admission INR, the better the outcome at three months. We observed a favorable functional outcome at three months (normal, minimal, or moderate disability according to the GOS) in 74% of those who survived for one year if their INR on admission was below 3, whereas the corresponding rate for those having an INR

≥ 3 was 62%. Delay from symptom onset to admission was found to be associated with outcome. Those admitted >48 hours after stroke onset showed better one-year ($p = 0.006$) survival than those admitted within 48 hours. Patients admitted over 48 hours after onset also showed smaller hematomas (median 16 ml) than those admitted within 48 hours (22 ml).

Finally, we analyzed predictors of one-year survival after WA-ICH by using the Cox proportional hazards model. For the final model we excluded those with an INR < 2 on admission because they were not under the influence of an efficient anticoagulant. Those admitted more than 48 h after stroke onset were also excluded because their bleeding probably had already stabilized and their hematoma had stopped enlarging. Accordingly, we included 138 patients in the final analysis. Among these 138 subjects we found age, hematoma size, and cardiac disease to be significant independent predictors of death. As expected, a high GCS score on admission was the most significant predictor of survival. PCC treatment and female sex also improved survival independently of confounding factors.

5.3 Admission blood pressure and short-term outcome

The main finding of *study III* was that subjects with untreated hypertension had a better-than-expected short-term outcome after ICH.

The patients were divided into those with untreated hypertension, those with treated hypertension, and those without hypertension. The patients with untreated hypertension were younger than those with treated hypertension or those without hypertension. Histories of cardiac disease and diabetes as well as current use of aspirin and warfarin were more frequent among those with treated hypertension than among those with untreated hypertension. Diabetes was least frequent among those with untreated hypertension. On the other hand, patients with untreated hypertension most frequently were current heavy drinkers.

Mean arterial blood pressure (MABP) was significantly higher on admission among those with untreated hypertension than that seen among those without hypertension ($p < 0.01$) and those with treated hypertension ($p < 0.05$). However, hematoma growth correlated with admission MABP values ($r_s = 0.247$; $p < 0.05$) among those with a repeated head CT scan obtained within a week after the onset of bleeding (n = 288).

We found a significant difference in outcome ($p < 0.001$) between the groups. Patients with untreated hypertension showed the best outcome; only 4 (6%) of them died within the first three months (Fig 6).

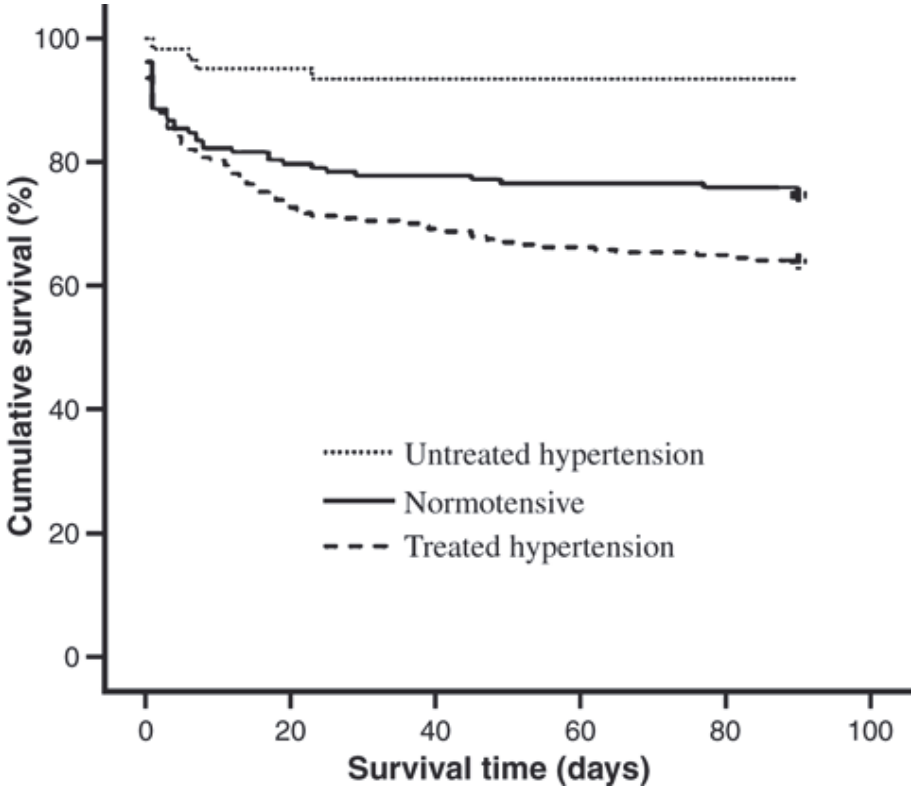

Fig. 6. Three-month survival of patients with intracerebral hemorrhage. The log-rank test revealed a significantly higher survival rate for those with untreated hypertension compared with those with treated hypertension ($P < 0.001$) and those without hypertension ($P < 0.01$), whereas the subjects without hypertension also showed better survival than those with treated hypertension ($p < 0.05$). (Tetri *et al.* 2010, published by permission of John Wiley & Sons Ltd.)

Independent predictors of death within three months were a low GCS score on admission, hematoma size, and cardiac disease in both normotensive subjects and those with treated hypertension. In addition, in those with treated hypertension, intraventricular hemorrhage, high admission MABP, age, and preceding use of warfarin or aspirin predicted death. Independent predictors of death for those with

untreated hypertension could not be analyzed, because only four subjects died within three months in this group.

Age, a low GCS score on admission, intraventricular extension and size of the hematoma, and cardiac disease significantly predicted a poor outcome among those with treated hypertension, whereas the same factors except GCS score and cardiac disease were independent predictors of a poor outcome in normotensive patients. Those who had high admission MABP (>127 mmHg) more frequently had a favorable outcome ($p = 0.058$) if they belonged to the group with untreated hypertension (25/41, 61%) compared with those who had treated hypertension (47/116, 41%) or who were normotensive (22/55, 40%). Among those who received aggressive BP-lowering treatment within 24 hours after admission, the corresponding figures were similar: i.e. those with untreated hypertension, 18/34 (53%); treated hypertension, 39/93 (42%); and normotensives, 14/37 (38%).

We observed both treated (standardized regression coefficient, $\beta = 0.197$, $p < 0.001$) and untreated ($\beta = 0.260$, $p < 0.001$) hypertension as well as a low GCS score ($\beta = –0.104$, $p < 0.05$) to be significant predictors of high admission MABP. Younger subjects more frequently had untreated hypertension, and their admission MABP values were higher than those of older subjects. High age was independently associated with low admission MABP ($\beta = –0.120$, $p < 0.05$).

We found significant associations between high admission MABP (>127 mmHg) and death within the first two days in both normotensive subjects ($p < 0.05$) and those on antihypertensive medication ($p < 0.01$). In the subjects with treated hypertension, high admission MABP was also associated with the presence of intraventricular hemorrhage ($p < 0.001$) but not with hematoma growth. We found, unexpectedly, that high admission MABP was significantly ($p < 0.001$) associated with small (< 30 ml) hematomas in those who had untreated hypertension. High admission MABP was not significantly associated with hematoma growth in these subjects.

5.4 Predictors of recurrence

The main findings of *study IV* were that both prior ischemic stroke and diabetes independent of aspirin use predicted recurrence of primary ICH and that diabetes independently and significantly predicted fatal recurrent ICH.

Among 961 subjects who had their first-ever primary ICH during the period from January 1, 1993 to December 31, 2008, 58 had at least one recurrent ICH during that time. Seven subjects had two recurrent instances of bleeding and three

even had three. The total follow-up time of the 981 subjects was 3481 person-years. The annual risk of recurrent ICH was 1.67% (Fig. 7). The 5- and 10-year cumulative incidences of recurrence were 9.6% (95% CI 6.9–12.3) and 14.2% (10.3–18.1).

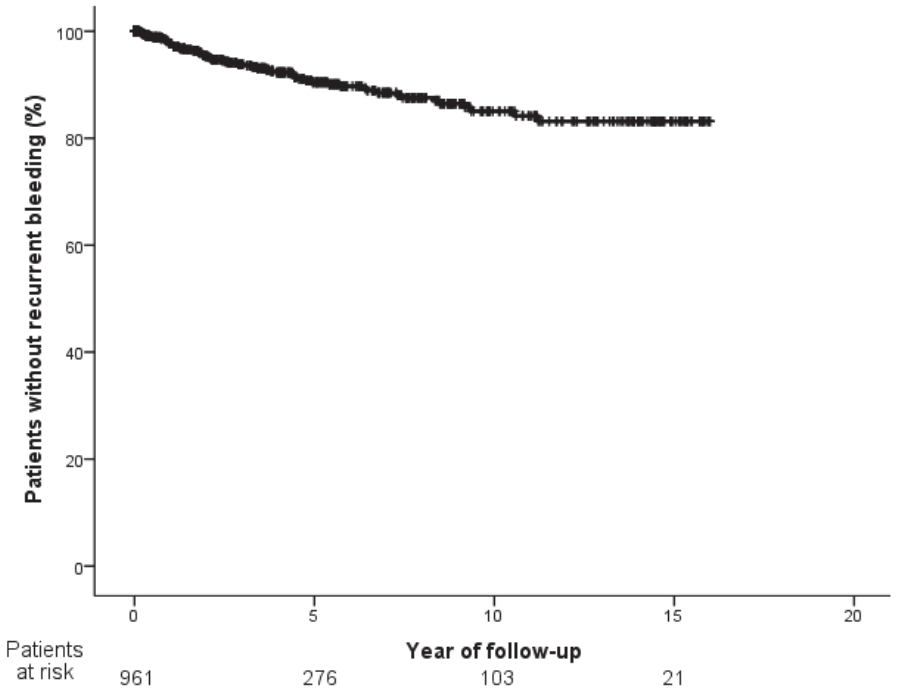

Fig. 7. Kaplan-Meier curve showing the cumulative rate of recurrent PICH for all patients. Markers on the curves indicate censored cases.

Recurrent PICHs were larger and associated with lower GCS scores on admission than first-ever PICHs (Table 1, *study IV*). Patients with a recurrent PICH significantly ($p = 0.006$) more often had a history of ischemic stroke before their first-ever ICH than subjects without a recurrent PICH. They also tended to have diabetes more often in their prestroke history, but the difference was not statistically significant.

Life table analyses using the Kaplan-Meier method suggested that history of ischemic stroke ($p = 0.001$), diabetes ($p = 0.026$), and aspirin use ($p = 0.021$) predisposed to recurrent bleeding (Figs. 8–10). Diabetics had their recurrent

instances of bleeding sooner after their first-ever bleeding (already within five years) than those with ischemic stroke and/or aspirin use.

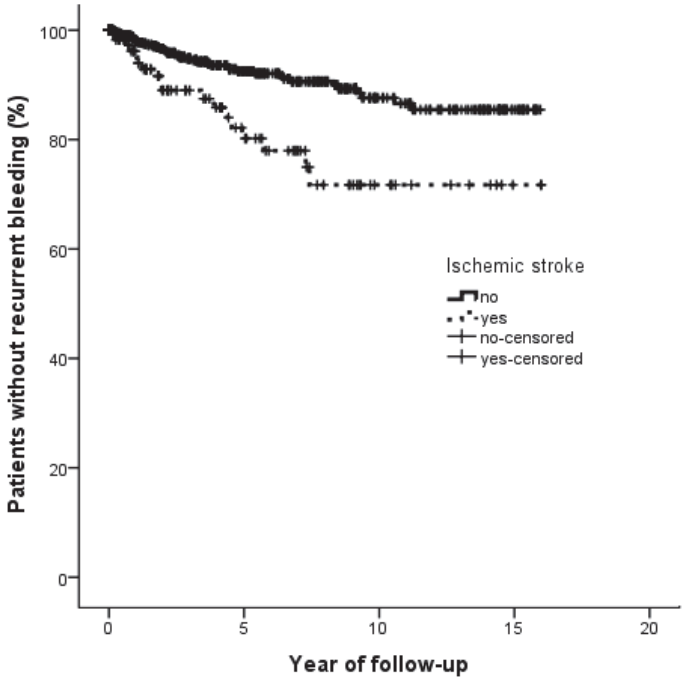

Fig. 8. Kaplan-Meier curves depicting cumulative rates of recurrent PICH show a significant difference according to history of ischemic stroke (p = 0.001). Markers on the curves indicate censored cases.

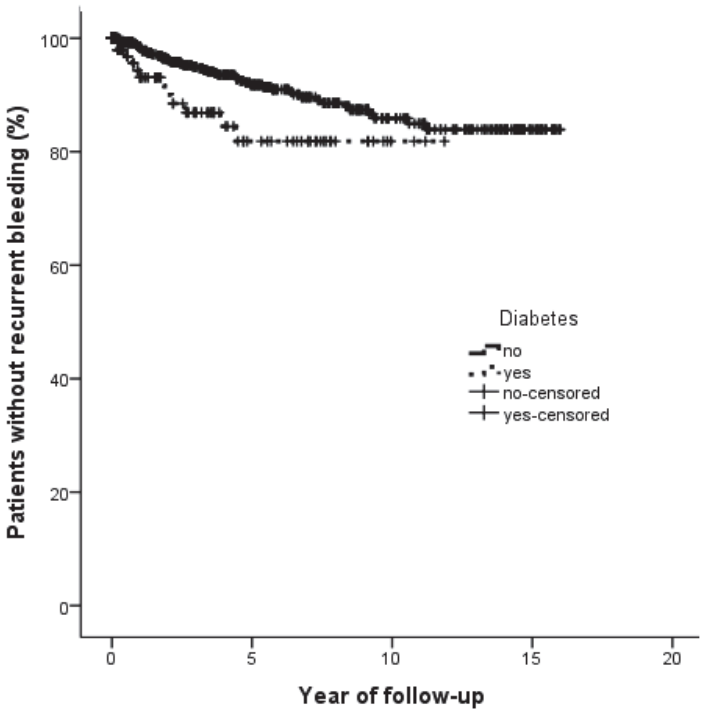

Fig. 9. Kaplan-Meier curves depicting cumulative rates of recurrent PICH show a significant difference according to history of diabetes mellitus (p = 0.026). Markers on the curves indicate censored cases.

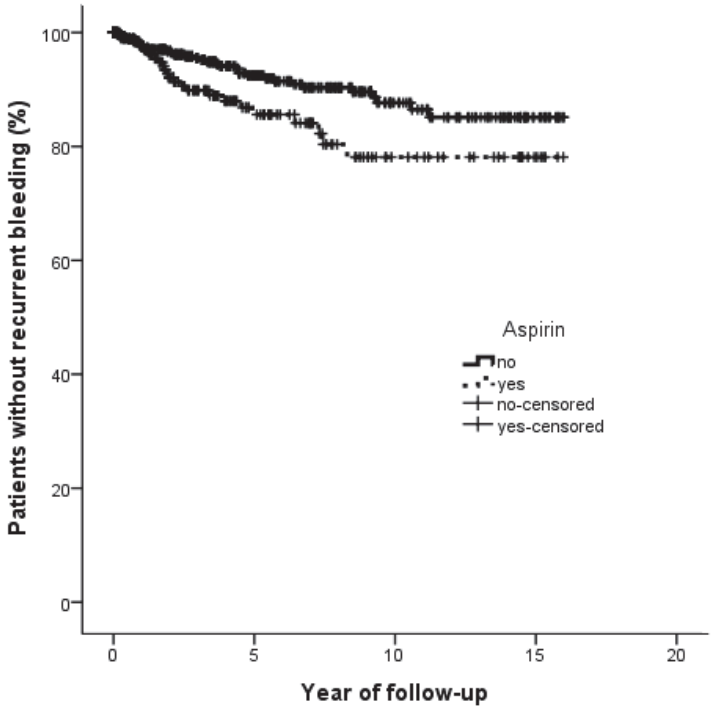

Fig. 10. Kaplan-Meier curves depicting cumulative rates of recurrent PICH show a significant difference according to use of aspirin (p = 0.021). Markers on the curves indicate censored cases.

Significant and independent predictors of recurrence were previous ischemic stroke (p = 0.001) and diabetes (p = 0.042). This was shown with a stepwise backward Cox proportional hazards model where 12 different parameters were initially included. It is noteworthy that use of aspirin and NSSRI/SSRI drugs did not appear to contribute significantly to recurrence. We did not observe any significant interaction between use of aspirin and history of ischemic stroke or diabetes in predicting recurrence. Transient ischemic attack in the patient's history was not a significant predictor, whereas brain infarction was. Finally, diabetes appeared to be the only significant and independent predictor of fatal recurrent bleeding.

The locations of the first instances of bleeding among subjects having recurrence were: deep i.e. basal ganglionic (putamen, thalamus, caudate nucleus)

in 28 patients (48.3%), lobar in 19 (32.8%), cerebellar in 9 (15.5%), and brainstem in 2 (3.4%). The most frequent patterns of recurrence were ganglionic-ganglionic (n = 24, 41.4%) and lobar-lobar (n = 13, 24.1%).

Because lobar PICHs are associated with amyloid angiopathy (Ishii *et al.* 1984), we investigated if the subcortical location predicts recurrent ICH, but there was no significant difference in terms of lobar location. Aspirin users were more frequent among those with a lobar PICH than among those with a basal ganglionic PICH, but the difference was not statistically significant (57.9 vs. 39.3% for first-ever ICH and 61.1 vs. 42.9% for first recurrent PICH).

Data on medication use before and after the index PICH were available for all patients with recurrence and for most (n = 618) of the patients without recurrence. The only significant difference in the use of drugs after the index stroke between patients with and without recurrence was observed in the use of high-affinity SSRIs. Those with a recurrence had used these drugs more frequently (p = 0.026). No significant differences were observed in the use of any drug between the patient groups during the period of onset of the index (first-ever) PICH, although aspirin use was more common among those having a recurrence. On the other hand, patients with recurrence showed significant (p = 0.046) heterogeneity according to treatment of hypertension. At the time of their first-ever bleeding their hypertension was more frequently untreated than at the time of recurrent bleeding. We did not find any differences in the use of dipyridamol, clopidogrel, nonsteroidal anti-inflammatory drugs, or selective cyclooxygenase-2 nonsteroidal anti-inflammatory drugs between the groups.

6 Discussion

6.1 Main findings

Despite the increasing use of warfarin, WA-ICHs did not increase among the population of Northern Ostrobothnia. Furthermore, the outcome of patients with a WA-ICH seemed to have improved after the implementation of PCC treatment at our hospital. Counteracting the influence of warfarin with PCC and vitamin K as soon as possible whenever the INR on admission was ≥2.0 and the ICH patient was admitted within 48 h after the onset of bleeding tended to result in lower mortality among WA-ICH patients. During the most recent years we reached mortality as low (35%) as that reported earlier in Malmö Hospital in Southern Sweden (Zia *et al.* 2009).

ICH patients with untreated hypertension and high admission MABP (>127 mmHg) frequently had small (<30 ml) hematomas and a good outcome. Among them, small ICHs occurred as warning bleeding due to high untreated blood pressure. This subgroup of ICH patients apparently needs careful counseling on blood pressure treatment to prevent further bleeding and also to prevent other complications of high blood pressure.

Predictors of recurrent primary ICH were histories of brain infraction and diabetes, and diabetes also predicted fatal recurrence independent of the use of aspirin and serotonine reuptake inhibitors, which are known to influence platelet function. On the other hand, careful treatment of hypertension seemed to prevent recurrent bleeding.

6.2 The effect of increased warfarin use

Among our population we found a fourfold increase in warfarin use during the observation period. However, the amount of ICHs among the users became less frequent. While the use of warfarin almost quadrupled from 1993 to 2008, the annual number of deaths due to primary bleeding among the users did not increase. Perhaps selection of patients for warfarin therapy was more careful, as perhaps was monitoring of the therapy. On the other hand, a recent study from the United States observed that a marked increase in the incidence of ICHs related to oral anticoagulant therapy had occurred concomitant to increased use of warfarin (Flaherty *et al.* 2007). The authors speculated that their observation may be due to

a disproportionate increase in warfarin use among elderly patients at high risk for bleeding. There are methodological differences between the two studies. In our study we used a known annual number of warfarin users, while Flaherty *et al*. had used counting units. On the other hand, Flaherty *et al*. might have missed cases in 1988, while our study was population-based. However, I think these small methodological differences do not explain the difference in observations.

The proportion of WA-ICHs was initially rather high (18.5%) in our population but tended to decrease year by year. Other authors have reported lower rates (Cordonnier *et al.* 2009, Flaherty *et al.* 2007, Jeffree *et al.* 2009, Lawrentschuk *et al.* 2003). Our patients had less INR values above the therapeutic range at the end of the observation period compared with the early years. These observations allow us to believe that selection of patients for warfarin therapy and monitoring of warfarin treatment were not optimal in our country during the early part of the study period, but subsequently improved. Management of warfarin treatment among elderly patients is hampered by drug interactions and the need for scrupulous dose adjustment to maintain the desired INR value (Gasse *et al.* 2005).

The case fatality rate of warfarin-associated ICH seems to be related to the intensity of warfarin effect as measured by the INR (Flaherty *et al.* 2008, Rosand *et al.* 2004). It seems that patients with an INR > 3.0 have a greater hematoma volume and mortality than others (Flaherty *et al.* 2008). Patients taking warfarin showed higher mortality rates the higher the INRs they had (Rosand *et al.* 2004). It seems that increasing the intensity of warfarin therapy to an INR greater than 3.0 is associated with increased mortality (Rosand *et al.* 2004). We observed a slightly decreased functional outcome among patients having an INR of 3 or more. However, there is a study claiming that neither functional outcome nor in-hospital mortality is strongly dependent on the INR measured on admission (Berwaerts *et al.* 2000). Case fatality rates among warfarin users were twofold compared with non-users, the difference being mainly due to the larger hematomas of warfarin users already on admission. In our study the increased intensity of warfarin therapy was not an independent predictor of death within the first three months. Stead *et al.* found that patients who died within 30 days had a higher INR at arrival than patients who survived (Stead *et al.* 2010). Subjects with a good outcome were found to have a lower initial INR value than patients with a poor outcome (Stead *et al.* 2010). Our study found that a low GCS score, hematoma size, and cardiac disease, including previous myocardial infarction, coronary

artery disease, heart failure, and atrial fibrillation, were significant predictors of death.

It might be that a WA-ICH is more likely to expand and expands for a longer period of time than an ICH without coagulopathy (Flibotte *et al.* 2004, Yasaka *et al.* 2003). That is why ultra-early hemostatic therapy and rapid reversal of anticoagulation are attractive targets in improving the outcome of these patients. It may also be that rapid reversal of the INR with PCC and vitamin K is effective when the INR on admission is above 2.0. Hemostatic treatment does improve the outcome of such patients with a WA-ICH (Fredriksson *et al.* 1992, Yasaka *et al.* 2003).

In March 2005 we established an institutional protocol for reversing the INR by administering a combination of prothrombin complex concentrate and vitamin K to patients with a WA-ICH. This may have diminished case fatality but does not explain the decreased incidence of WA-ICHs over time. Neither did surgical treatment. The number of patients operated on showed neither an increasing nor decreasing trend during the observation period. Operations were performed with similar frequency on those with and without warfarin at the onset of the stroke. Moreover, prevention and treatment of complications such as a thromboembolism and cardiac problems have advanced in the beginning of the 21st century in parallel with the increase in warfarin use. In our study, mortality was decreased in the PCC- and vitamin K-treated group, but treatment with PCC was not an independent predictor of survival. Patients treated with PCC were selected clinically, so we did not so often treat moribund patients who had a GCS score lower than 10 with PCC. That caused biased selection. On the other hand, there were very few patients who were treated within six hours after the onset of symptoms. Perhaps many patients were treated with PCC too late.

In conclusion, we found that, despite the increasing use of warfarin, the annual risk of users suffering a fatal ICH did not increase among the population of Northern Ostrobothnia—instead it decreased. We need controlled trials to demonstrate whether rapid reversal of the INR with PCC and vitamin K results in a better outcome for patients with a WA-ICH. As far as we know, our study is the first in Europe to describe associations between warfarin use and morbidity and mortality from ICH in a defined population over time.

6.3 Improved outcome of patients on warfarin

In our *study II*, one-year survival of subjects with a WA-ICH admitted during 2004–2008 was significantly higher than of those admitted during 1993–2003 (43.3% vs. 30.6%), whereas survival of those not on warfarin showed a negligible difference (69.4% vs. 67.0%). PCC treatment may be responsible for the improved survival of PICH patients among the population of Northern Ostrobothnia (64.8% vs. 59.9%) since it significantly improved the one-year survival of patients admitted early after the onset of bleeding and with INR levels of 2 and over. The improved survival was mainly due to the increased survival of patients with a WA-ICH.

We observed several possible reasons for the decreased mortality of subjects with a WA-ICH. These were the implementation of PCC treatment, better monitoring of the INR during warfarin treatment, and more careful selection of patients for warfarin treatment. Patients admitted before 2004 more frequently had a high INR value on admission, indicating poor control of anticoagulant treatment, and they more often suffered from cardiac diseases. Among WA-ICH patients, GCS scores were lower and hematoma volumes greater on admission before 2004 than thereafter. In addition to the implementation of PCC treatment, the stricter selection of patients for warfarin treatment and more careful monitoring of the INR may be other reasons for the decreased mortality. There was no difference in delay from symptom onset to admission by year among the patients.

It was an unexpected finding to observe that a delay of over 48 hours from symptom onset to admission was associated with better survival among WA-ICH patients. There is a possibility that the bleeding in these subjects had spontaneously stabilized before reaching a lethal size. Patients who survived outside the hospital for more than 48 h after the onset of symptoms had less severe bleeding, as shown by smaller hematoma volumes. Better survival among those with a delay from stroke onset to admission has also been reported among patients with subarachnoid hemorrhage (Kassell *et al.* 1981).

Hematoma volumes tend to be greater in patients with a WA-ICH than in patients not on anticoagulant treatment (Cucchiara *et al.* 2008, Flaherty *et al.* 2008, Kuwashiro *et al.* 2010, Saloheimo *et al.* 2006). Furthermore, hematoma growth is an independent determinant of both mortality and functional outcome (Davis *et al.* 2006). Accordingly, it is crucial to stop the bleeding as soon as possible with a suitable antidote to prevent hematoma growth and consequent

poor outcome. There is a hurry to transport a patient with a possible WA-ICH to the hospital in order to enable rapid reversal of anticoagulation. WA-ICHs are more likely to expand (Kuwashiro *et al.* 2010, Yasaka *et al.* 2003), and they continue to expand for a longer time than ICHs unrelated to anticoagulant use (Flibotte *et al.* 2004), providing time for reversal of the anticoagulant effect. Reversal of the anticoagulant effect of warfarin should be instituted even for patients with a small hematoma. The time window for this therapy has not been settled. We recommend reversal with PCC whenever the INR on admission is ≥2.0.

In conclusion, reversal of warfarin with PCC and vitamin K should be instituted as soon as possible if the patient is admitted within 48 h after the onset of bleeding. However, controlled trials may still be needed to demonstrate the efficacy and safety of the therapy (Steiner *et al.* 2006).

6.4 Outcome of patients with untreated hypertension

In most previous studies, all hypertensive patients, regardless of whether or not they have been on hypertensive medication, have been analyzed together. Our *study III* is the first to look separately at the outcomes of hypertensive patients who were on medication and those who were not. The main finding of our *study III* was a favorable outcome after ICH among subjects with untreated hypertension. Although they had high blood pressure on admission, they showed the lowest mortality (6%). In addition, high admission MABP (>127 mmHg) was associated with small (<30 ml) hematomas among them.

Ischemic heart disease, atrial fibrillation, and diabetes were previously shown to shorten survival after ICH (Tetri *et al.* 2008, Tetri *et al.* 2009). High admission MABP has also been shown to be associated with increased mortality after ICH (Fogelholm *et al.* 1997, Terayama *et al.* 1997, Tetri *et al.* 2008, Tetri *et al.* 2009). However, that was not the case among our patients with untreated hypertension. The explanation for the better outcome might be that the patients with untreated hypertension were younger than those with treated hypertension and they less frequently had comorbidities and associated medications such as warfarin and aspirin in addition to their intracranial bleeding.

A rapid decline in BP within the first 24 hours after ICH onset has been reported to be associated with increased mortality (Qureshi *et al.* 1999, Qureshi *et al.* 2009). Acute hypertension, particularly high systolic BP at admission, is found to predict high mortality and poor neurological outcome after ICH (Dandapani *et*

al. 1995, Leira *et al.* 2004, Willmot *et al.* 2004). Elevated BP has been shown to increase the risk for hematoma enlargement (Broderick *et al.* 1990, Ohwaki *et al.* 2004) and furthermore, to increase the death rate (Willmot *et al.* 2004) and early neurological deterioration (Brott *et al.* 1997) after ICH. However, a meta-analysis of patients with a spontaneous ICH did not confirm the predictive association between elevated BP and poor outcome (Davis *et al.* 2006), and no association was found between BP and hematoma growth in a recent study (Marti-Fabregas *et al.* 2008). Being aware of these conflicting observations, we decided to investigate different subgroups with spontaneous ICHs separately.

Factors which may contribute to the better outcome of subjects with untreated hypertension were considered. Young persons have a relatively small intracranial reserve space. Accordingly, an increase in intracranial pressure after the onset of bleeding may be more prominent among young patients. The inverse correlation of age with MABP may reflect this and the strength of the Cushing reflex (Leira *et al.* 2004), i.e. the increase in BP by increased intracranial pressure. In suffering from a hemorrhage of similar size and location, elderly people have a larger intracranial reserve space than young people. This and concomitant antihypertensive medication could decrease a rise in their BP. On the other hand, they certainly also have more fragile cerebral arteries, promoting enlargement of hematomas. Due to long-lasting hypertension, their autoregulation curve is shifted toward higher pressures (Paulson *et al.* 1990), and hence they are more vulnerable to brain ischemia after a lowering of blood pressure (Tietjen *et al.* 1996). Younger patients with untreated hypertension may have less impaired autoregulation of cerebral blood flow than elderly people.

We found that patients with untreated hypertension had the best outcomes, although they had the highest admission MABP values. High MABP was not associated with high mortality among them, but it was associated with small (<30 ml) hematomas. To preserve adequate perfusion pressure, aggressive lowering of BP is not recommended for ICH patients with high intracranial pressure (Broderick *et al.* 2007). It should also be kept in mind that aggressive treatment of BP may not help those who already have a large hematoma. Subjects may react differently to treatment of BP, depending on their hypertensive status and clinical condition.

I suppose that aggressive treatment of increased blood pressure might have a different influence on the outcome of ICH patients in different subgroups of subjects with a spontaneous ICH. The American guideline for treatment of ICH suggests BP of 160/90 mmHg or MABP of 110 mmHg as the target levels for BP

lowering (Morgenstern *et al.* 2010). Ongoing trials to reduce high BP in unselected patients with an ICH will hopefully resolve this issue.

6.5 Factors influencing recurrence

In *study IV* we found prior ischemic stroke and diabetes to be independent predictors of recurrent ICH. Moreover, diabetes was found to be an independent predictor of fatal recurrent ICH. However, in a study including 768 index ICHs, these factors were not investigated (Hanger *et al.* 2007). On the other hand, we did not find increased age to be a risk factor, contrary to the observations of other investigators (Hanger *et al.* 2007). Some previous studies have reported that patients with a primary lobar ICH have a higher rate of recurrent ICH than those with a deep, hemispheric ICH (Bailey *et al.* 2001, Viswanathan *et al.* 2006), but some others do not confirm this (Gonzalez-Duarte *et al.* 1998, Hanger *et al.* 2007). Our study did not find lobar location to predict recurrence among an unselected population. Lobar location predicts recurrence among selected subjects with CAA (Biffi *et al.* 2010).

The finding that prior ischemic stroke and diabetes predict recurrent PICH is important, since antiplatelet therapy is usually considered after PICH to prevent ischemic stroke and myocardial infarction. It is interesting to note that a novel antiplatelet agent, vorapaxar, increases the risk of ICH in patients with a history of stroke (Morrow *et al.* 2012). In our cohort, aspirin did not prove to be a significant predictor of PICH recurrence among patients with prior ischemic brain infarction, but our material was too small to exclude a deleterious interaction between aspirin and other drugs in this respect. The dilemma is that patients often have histories of both ischemic and hemorrhagic stroke (Bailey *et al.* 2001, Chapman *et al.* 2004). Clinicians have to evaluate the risks of recurrence for both ICH and ischemic strokes (Hanger *et al.* 2007) when considering preventive medicine.

We did not observe any differences in the use of dipyridamol, clopidogrel, nonsteroidal anti-inflammatory drugs, or selective cyclooxygenase-2 nonsteroidal anti-inflammatory drugs between subjects with and without recurrent bleeding. Warfarin medication was usually avoided after the index bleeding. Those who used warfarin before the index bleeding infrequently restarted the treatment, which policy seemed to be reflected as a slight but insignificant protective effect of prior warfarin use against recurrent ICH. This suggests that there was careful selection of medication after the index bleeding.

Cerebrovascular hypertensive vasculopathy and cerebral amyloid angiopathy (CAA) are the main underlying diseases leading to ICH. Hemorrhage due to CAA is most commonly of the lobar type (Ishii *et al.* 1984). Antithrombotic therapy may be independently associated with thalamic, cerebellar, and lobar hemorrhage (Itabashi *et al.* 2009), but SSRIs also influence platelet function. This raises the question whether SSRIs alone or combined with aspirin or other antiplatelet agents increase the risk for ICH among subjects with CAA and hypertensive cerebral vasculopathy.

CAA and hypertensive vasculopathy may show typical localization of bleeding. Ganglionic bleeding is likely the result of hypertensive vasculopathy, whereas lobar bleeding frequently results from CAA (Gonzalez-Duarte *et al.* 1998, Neau *et al.* 1997). In our population-based material, less than one-third of the instances of bleeding were lobar, whereas a bit more than half were cases of ganglionic bleeding. We found the prevalent pattern of recurrence to be ganglionic-ganglionic and the second most frequent pattern was lobar-lobar. Our findings are comparable with some earlier observations (Gonzalez-Duarte *et al.* 1998). The etiologies of lobar and ganglionic ICHs might be different, as speculated before (Gonzalez-Duarte *et al.* 1998, Neau *et al.* 1997). Furthermore, the risk factors of recurrent bleeding might be different between these groups, and this should be taken into account when choosing medication after ICH.

Our findings do not suggest that the use of SSRIs is associated with an increased risk of recurrent PICH. However, there was one patient who was using aspirin together with a high-affinity SSRI drug while he developed fatal recurrent bleeding. To date, two investigations have reported an increased risk of PICH to be associated with SSRI use (Smoller *et al.* 2009, Verdel *et al.* 2011). Four other investigations did not observe this kind of risk (Bak *et al.* 2002, Chen *et al.* 2009, de Abajo *et al.* 2000, Kharofa *et al.* 2007). The available data may still be too limited to allow a firm conclusion to be drawn either for or against a deleterious effect of SSRIs in recurrence of hemorrhagic stroke (Chittaranjan.A. *et al.* 2010). However, the combined use of SSRIs with warfarin or aspirin was not found to confer a significantly greater risk of hemorrhagic stroke than warfarin or aspirin alone (Kharofa *et al.* 2007).

Almost all serotonin existing in blood is transported in dense granules by platelets (Skop & Brown 1996). Serotonin exhibits powerful vasoactive effects through direct action on serotonin receptors and through nitric oxide production (Berger *et al.* 2009). Depletion of serotonin stored in platelets may promote bleeding (Chittaranjan.A. *et al.* 2010). SSRIs impair both platelet secretory

response and platelet aggregation induced by ADP, collagen, and thrombin, causing an inhibition of platelet plug formation, as reflected by a significant prolongation of the closure time measured by a platelet function analyzer (Halperin.D. & Reber.G. 2007).

It is supposed that predominantly noradrenergic serotonin reuptake inhibitors like mirtazapine and mianserin are likely to be safe in patients at risk of abnormal bleeding (Chittaranjan.A. *et al.* 2010). This assumption is based on several studies (Dall *et al.* 2009, Dalton *et al.* 2003, de Abajo *et al.* 1999, Meijer *et al.* 2004, Opatrny *et al.* 2008). On the other hand, bleeding associated with serotonin-norepinephrine reuptake inhibitors (SNRIs) has also been reported (Abajo 2011). As said before, in our study only one patient using high-affinity SSRI and aspirin together had a fatal recurrence; otherwise we did not find any statistically significant differences in recurrent ICH between patients using NSSRIs, high-affinity SSRIs, or intermediate-affinity SSRIs, either. On the other hand, depression itself has been implicated as a risk factor for stroke (Merikangas *et al.* 2007). We did not extract information about possible depression.

We observed the annual incidence of recurrent ICHs to be 1.67%. Incidence was higher during the first year after the stroke but decreased thereafter. Our observations are comparable with those of other investigators (Hanger *et al.* 2007, Passero *et al.* 1995, Yokota *et al.* 2004) and also with the only former Finnish population-based study in which 23 of 411 ICH patients had 27 recurrent instances of bleeding (Fogelholm *et al.* 2005). We observed the cumulative incidence of recurrence to be 9.6% at 5 years and 14.2% at 10 years. The risk of recurrence is greater during the first five years after the index PICH than after that period. This may have considerable clinical significance for clinicians who are considering when to start antithrombotic or anticoagulant medication again after ICH.

6.6 Strengths and limitations of the study

All of our studies were limited by their retrospective nature, but most of them were population-based and, therefore, avoided selection bias. We tried to take into account most of the well-known potential risk factors for early death and adjusted for them in our analyses. The strengths of our studies also include the reliable radiological analysis, ruling out secondary abnormalities.

Study I investigated the effect of increasing use of warfarin on PICH occurrence among a defined population. Annual numbers of warfarin users were

very confidently ascertained. Case ascertainment was even strengthened by the statutory registration of death certificates in Finland. Limitations of the study include the following. First, patients who died before a follow-up radiological examination was scheduled to be performed may have had undetected structural abnormalities contributing to their stroke, because autopsies were not done in all of these cases. Moreover, one of the cases who succumbed on the scene was not autopsied. Second, the statistics kept by the Social Insurance Institution of Finland were not quite complete for the first two years of the study period, which may have caused underestimation of warfarin use. Third, it is not known whether all those subjects reported by the Social Insurance Institution of Finland as warfarin users had really used the medicine for a whole year or only for a shorter period.

Good case ascertainment was also a major strength of *study II*. The annual numbers of warfarin users were accurately known and many risk factors for early death were taken into account in the analyses. The limitations include an obvious selection bias. Patients with smaller hematomas and higher GCS scores were selected for PCC treatment, whereas moribund patients remained untreated. Hematoma growth assessments were not systematically performed. Delay from the onset of symptoms to emergency room admission was not always recorded on an hourly basis.

The strength of *study III* was the strict inclusion criteria. The presence of a primary ICH was confirmed by follow-up brain imaging to exclude secondary ICH. By not including patients who were primarily treated in neurosurgical or intensive care units, we got a homogenous patient population. We thereby avoided confounding due to early surgery or ICU treatment. Among the limitations is the fact that the patients were not randomized to be treated or not treated for elevated blood pressure. All patients were treated if their BP was high enough according to our institutional protocol. It would have been unethical to leave patients without treatment. That is why we do not know if aggressive treatment of BP influenced the outcome of our subjects, but this is possible. Another limitation was that we did not systematically search for hematoma growth by means of follow-up CT scans.

The prime strength of our study *IV* was the population-based case ascertainment which should exclude selection bias. To get as reliable a cohort as possible, we ruled out 281 subjects because they died within 30 days after the index stroke and 21 subjects who had intracranial bleeding before 1993. The rather long follow-up period let us determine accurate figures for cumulative

incidence. We took into account as many of the well-known risk factors for ICH as possible and adjusted our analyses for those factors. We obtained very reliable purchase data on the use of anticoagulants, SRI medication, and antiplatelet agents from the national register of prescribed medicine and we also checked drug use from our hospital charts after the index bleeding. Accordingly, we used a double check method for drug exposure. Finally, we were able to include only verified cases of PICH. We had reliable data on head CT scans taken on admission from all the subjects who were admitted to the hospital, and most of them were also investigated later on to exclude structural causes of ICH. Those who succumbed on the scene had an autopsy-verified PICH. There are several limitations in this retrospective study. First, aspirin exposure was based only on hospital chart data, because it is available without a prescription in Finland. However, regular use of aspirin was always recorded, whereas over-the-counter use may remain unrecorded in hospital charts. On the other hand, although antihypertensive medication was recorded, we were not able to know how good our patients' adherence to medication was, i.e. did they take their prescribed medication or not at the time of stroke recurrence. Accordingly, there is a strong possibility that our study underestimates the role of poorly treated hypertension. We lacked data on some important risk factors. Information on smoking and alcohol intake was deficient. Furthermore, only bleeding events leading to either hospitalization or death were taken into account. However, even subjects with minor strokes are currently admitted to our hospital, provided that they have clear clinical signs and symptoms. We were not able to evaluate the impact of drug doses and duration of drug treatment on the risk of recurrence. We did not know whether our subjects had depression leading to the onset of stroke recurrence. Depression itself has been implicated as a risk factor for stroke and is supposed to even counteract the antiplatelet effects of some drugs (Merikangas *et al.* 2007).

7 Conclusions

Our observation that the increasing use of warfarin was not followed by an increasing amount of WA-ICHs and that instead the annual incidence of WA-ICHs decreased suggests that by optimizing the selection of patients for warfarin therapy and using accurate monitoring of warfarin treatment, warfarin is still justified as the first drug of choice when an oral anticoagulant is needed. In addition, rapid reversal of the anticoagulant effect of warfarin by means of a prothrombin complex concentrate and vitamin K is a well-supported treatment of small WA-ICHs, as suggested by several investigations, including our data from *study II* (Boulis *et al.* 1999, Cartmill *et al.* 2000, Chong *et al.* 2010, Fredriksson *et al.* 1992, Huttner *et al.* 2006, Kuwashiro *et al.* 2011, Siddiq *et al.* 2008, Yasaka *et al.* 2003, Zubkov *et al.* 2008). However, we still need controlled clinical trials on which to base a recommendation.

Despite a recent study (Tetri *et al.* 2009) which concluded that high admission blood pressure predicts early death after ICH, we found that patients with untreated hypertension have better survival despite high admission blood pressures than patients with treated hypertension after blood-pressure-lowering therapy. They even more frequently had a favorable outcome than patients without hypertension at all. However, these patients were younger and less frequently had cardiac disease, diabetes mellitus, and/or warfarin or aspirin medications. This reinforces the estimation in both the American Stroke Association's (Broderick *et al.* 2007) and the European Stroke Initiative's (European Stroke Initiative Writing Committee *et al.* 2006) guidelines and suggests that patients without chronic hypertension and those with a good neurological status may tolerate aggressive blood pressure reduction better than others. Although advances have been made in the safety of early blood pressure lowering in ICHs in the ATACH (Qureshi 2007) and INTERACT trials (Anderson *et al.* 2008) without increasing adverse events (Qureshi *et al.* 2009), the data are still insufficient for recommending a definitive policy (Morgenstern *et al.* 2010).

The crucial strategy of ICH treatment is to restrict hematoma expansion as soon as possible. This can be achieved by cautious lowering of high blood pressure, quick reversal of prior anticoagulation, and surgical evacuation (Morgenstern *et al.* 2010). The establishment of the European Research Network on Intracerebral Hemorrhage EURONICH gives us hope that we can identify ways to reduce the burden of ICH-related death and disability (Steiner *et al.* 2011).

In the future we may have more devices for recognizing patients who are at great risk of recurrent bleeding. Prior ischemic stroke and diabetes were independent risk factors for recurrent ICH in our study, suggesting the role of small vessel disease as an underlying cause. We also found diabetes to be an independent risk factor for fatal recurrent PICH. Factors responsible for this association remain to be resolved.

Increased age has been found to be a risk factor for PICH and recurrent PICH by several studies (Vermeer *et al.* 2002, Zia *et al.* 2009). This risk is apparently linked to the risk caused by CAA (Hanger *et al.* 2007). There are observations that patients with a lobar PICH have a higher rate of recurrent PICH than those with a deep, hemispheric PICH (Bailey *et al.* 2001, Viswanathan *et al.* 2006).

All risk factors should be considered carefully before restarting drugs after a PICH. In our study, warfarin was rarely started and aspirin and SRRIs were frequently started after a PICH. Aspirin showed a slight but insignificant trend of enhancing the risk for recurrent bleeding. No significant effects of combined treatments were observed. However, considerable risks may appear if several drugs are combined, i.e. warfarin with antiplatelet drugs and SSRIs. Particularly, subjects with a lobar location of hemorrhage may carry higher risks than others, due to a possible underlying CAA. Ischemic stroke, diabetes, and a lobar location of PICH should be considered as warning signs, and the presence of all three of these risk factors may warrant extra careful consideration of future therapies. Furthermore, the timing of starting treatment should take into account the fact that the risk for recurrence is highest during the first year after the index stroke.

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I Huhtakangas J, Tetri S, Juvela S, Saloheimo P, Bode MK & Hillbom M (2011) Effect of increased warfarin use on warfarin-related cerebral hemorrhage: A longitudinal population-based study. Stroke 42: 2431–2435.

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IV Huhtakangas J, Löppönen P, Tetri S, Juvela S, Saloheimo P, Bode MK & Hillbom M. Predictors of recurrent primary intracerebral hemorrhage: A retrospective population-based study. Manuscript

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