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FACTORS AFFECTING OUTCOME AFTER PRIMARY INTRACEREBRAL HEMORRHAGE

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Abstract

Primary intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes. ICH is the most devastating subtype of stroke with high mortality and morbidity; 35–52% of patients die during the first month after the bleeding. The most important risk factor for onset of ICH is hypertension, especially untreated hypertension, and the well-known predictors for early death after ICH are a low GCS (i.e low level of consciousness) score on admission, the size of the hematoma, and the precence of intraventricular blood. Preceeding use of anticoagulants and advanced age further impair the outcome. Thromboembolic complications after the bleed are common and difficult to prevent.

The present cohort study included all patients (n = 453) with verified primary ICH admitted to the stroke unit of Oulu University Hospital within a period of 11 years (from January 1993 to January 2004). The impacts of previous diseases, including ischemic heart disease, atrial fibrillation on admission, hypertension, and diabetes as well as of high admission blood pressure and plasma glucose levels on outcome were evaluated. The safety and efficacy of prevention of venous thromboembolism with enoxaparin, a low molecular weight heparin (LMWH), was investigated. In a population-based study covering a 3-year period, the risk factors and seasonal distribution of ICH were investigated.

Independent of the severity of bleeding and patients' age, ischemic heart disease, diabetes, and atrial fibrillation were found to be significant predictors for early death after ICH. High blood pressure on admission predicted early death, whereas elevated admission plasma glucose level was associated with the severity of bleeding but was not an independent predictor for early death. Treatment with enoxaparin (20 mg per day subcutaneously) for prevention of venous thromboembolism was not associated with increased mortality but did not seem to prevent venous thromboembolic complications. The incidence of ICH was higher during the winter among patients with untreated hypertension but not in normotensive and treated hypertensive patients.

Keywords: cardiac disease, cerebral hemorrhage, diabetes, hypertension, outcome, risk factors, season, venous thromboembolism

Acknowledgements

Abbreviations

AVM	Arteriovenous malformation
BMI	Body mass index
CAA	Cerebral amyloid angiopathy
CBF	Cerebral blood flow
CPF	Cerebral perfusion flow
CPP	Cerebral perfusion pressure (CPP = MABP-ICP)
Cl	Confidence level
CT	Computed tomography
DBP	Diastolic blood pressure
DSA	Digital subtraction angiography
DVT	Deep-vein thrombosis
GCS	Glasgow coma scale
GOS	Glasgow outcome scale
HR	Hazard ratio
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
INR	International normalized value
IVH	Intraventricular hemorrhage
LMWH	Low molecular weight heparins
MABP	Mean arterial blood pressure (MABP = DBP + 1/3 × (SBP – DBP))
MRI	Magnetic resonance imaging
OR	Odds ratio
PE	Pulmonary embolism
RR	Relative risk
SSS-PRG	Prognostic score of the Scandinavian Stroke Scale
SBP	Systolic blood pressure
VTC	Venous thromboembolic complications

List of original publications

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

I   Tetri S, Mäntymäki L, Juvela S, Saloheimo P, Pyhtinen J, Rusanen H & Hillbom M (2008) Impact of ischemic heart disease and atrial fibrillation on survival after spontaneous intracerebral hemorrhage. J Neurosurg 108: 1172–1177.
II   Tetri S, Juvela S, Saloheimo P, Pyhtinen J & Hillbom M (2009) Hypertension and diabetes as predictors for early death after spontaneous intracerebral hemorrhage. J Neurosurg 110: 403–410.
III Tetri S, Hakala J, Juvela S, Saloheimo P, Pyhtinen J, Rusanen H, Savolainen E-R & Hillbom M (2008) Safety of low-dose subcutaneous enoxaparin for the prevention of venous thromboembolism after primary intracerebral haemorrhage. Thromb Res 123: 206–212.
IV   Saloheimo P, Tetri S, Juvela S, Pyhtinen J & Hillbom M (2008) Seasonal variation of intracerebral haemorrhage in subjects with untreated hypertension. Acta Neurol Scand (In Press).

Contents

1   Introduction

Primary intracerebral hemorrhage (ICH), i.e. spontaneous extravasation of blood into the brain parenchyma, begins very suddenly and is a medical catastrophe. After the onset, bleeding may continue and the hematoma grow for several hours, leading to progressive clinical deterioration of the patient's condition (Fujii *et al.* 1994, Kazui *et al.* 1996, Brott *et al.* 1997). Computed tomography (CT) soon after the onset of symptoms is crucial for the diagnosis. Urgent emergency procedures and intensive care are often needed. Case fatality is high, as 35–52% of patients die within 30 days and half of the deaths occur in the first two days (Broderick *et al.* 1993a, Anderson *et al.* 1994, Councell *et al.* 1995). Up to 58% of survivors have been reported to be functionally independent at 1 year (Hårdemark *et al.* 1999).

The incidence of ICH varies geographically, ranging from 10 to 20/100,000 persons per year (Giroud *et al.* 1991, Broderick *et al.* 1993b). ICH incidence in Finland seems to be somewhat higher, 21 to 31/100,000 persons/year (Fogelholm *et al.* 1992a, Saloheimo *et al.* 2006). The highest incidence has been reported in Japan, 48/100,000 persons/year (Inagawa 2000).

The well-known risk factors for ICH are hypertension, heavy drinking of alcohol, and anticoagulant medication (Qureshi *et al.* 2001, Steiner *et al.* 2006a). Cold exposure during winter has also been suggested to trigger ICH (Caplan 1988). Risk factors for early death include clinical and radiological severity of the bleeding. Low GCS score (i.e. level of consciousness, Teasdale & Jennet 1974) and hematoma volume appear to be the most important predictors for early death after ICH. Moreover, intraventricular bleeding, use of anticoagulants, and high blood pressure on admission also predict early death after ICH (Daverat *et al.* 1991, Tuhrim *et al.* 1991, Broderick *et al.* 1993a, Qureshi *et al.* 1995, Juvela 1995a, Hårdemark *et al.* 1999).

Treatment of patients with ICH has turned out to be complicated in many ways. Apart from standard medical treatments, no novel specific therapies improving outcome have been introduced. Despite preventing hematoma enlargement, recombinant activated factor VII treatment showed no beneficial effect on outcome in a randomized pacebo-controlled clinical trial (Mayer *et al.* 2008). On the other hand, the benefits of surgery have been hard to assess because of the lack of appropriate randomized controlled trials without considerable selection bias and with sufficient patient populations. There are also wide variations in surgical practices between countries (Gregson & Mendelow 2003,

Mendelow *et al.* 2007). Currently, patients with large subcortical hematomas or cerebellar hematomas (> 3 cm in diameter) showing clinically deteriorating levels of consciousness should be operated on, while patients with deeply located hematomas should perhaps not.

In the absence of effective treatments, more efforts should be invested into finding out and preventing the risk factors for poor outcome. Of the several complications after ICH, the prevention and treatment of venous thromboembolic complications (VTC) are especially challenging and very inadequately studied.

The present study was designed to find out the impact of cardiac diseases, hypertension, diabetes, and clinical admission variables on survival after ICH. The safety and efficacy of preventing VTC with enoxaparin were also investigated. In addition, seasonal variation in the incidence of ICH according to the treatment status of hypertension was investigated. In the future, treatments should take into account the effects of independent predictors for early death and the use of safe prevention of VTC to improve the outcome of this devastating disease.

2 Review of the literature

2.1 Symptoms and diagnosis of intracerebral hemorrhage

The clinical presentation of ICH usually starts with a focal neurological deficit followed by progression of symptoms over minutes to hours (Ropper & Davis 1980). This symptomatic progression over hours is uncommon in patients with ischemic stroke. Another manifestation is a sudden decline in the level of consciousness. Patients who can tell about the history of onset describe symptoms resembling those of transient ischemic attack such as numbness, tingling, or weakness (Greenberg *et al.* 1993). Increased blood pressure and impaired level of consciousness are common (Goldstein & Simell 2005).

Compared to patients with ischemic stroke or subarachnoid hemorrhage, vomiting is more common in patients with ICH (Goldstein & Simell 2005). Headache is more common with ICH than with ischemic stroke but less common than with subarachnoid hemorrhage (Goldstein & Simell 2005).

Diagnosis is confirmed by brain imaging. Computed tomography (CT) and magnetic resonance imaging (MRI) show the presence of ICH equally well. CT has the advantage of demonstrating the intraventricular extension of the hemorrhage, while MRI shows better the underlying structures and perihematomal edema. CT can also easily be repeated in case of a clinical deterioration as well as to evaluate the hematoma growth rate within the first few hours after admission. CT angiography and conventional digital subtraction angiography can provide additional information of underlying vascular malformations, such as an aneurysm or arteriovenous malformation (AVM).

2.2 Subgroups of intracerebral hemorrhage

2.2.1 Primary intracerebral hemorrhage

The term 'spontaneous intracerebral hematoma' refers to non-traumatic bleeding into the brain parenchyma (Caplan 1992). 'Primary intracerebral hemorrhage' means a spontaneous hematoma without any secondary cause, such as vascular abnormality or brain tumor, which have been ruled out by radiological or pathological investigations (Qureshi *et al.* 2001). Primary intracerebral hemorrhage originates from bleeding of small arteries damaged by chronic

hypertension, cerebral amyloid angiopathy (CAA), or other causative factors (Gilbert & Vinters 1983, Qureshi *et al.* 2001). Almost two thirds of primary intracerebral hematomas are related to chronic hypertension (Brott *et al.* 1986). In these cases the hematoma is typically located deep, in the basal ganglia, thalamus, or brain stem (Caplan 1992) (Figure 1). ICHs related to CAA, on the other hand, are mainly lobar or subcortical hematomas (Gilbert & Vinters 1983) (Figure 2). Intraventricular hemorrhage requires angiography because of the probability of underlying vascular malformation (Flint *et al.* 2008), and primary intraventricular hemorrhage without any vascular malformation is a rare type of ICH (1%) usually originating from the head of the caudate nucleus (Butler *et al.* 1972, Passero *et al.* 2002) (Figure 3).

Fig. 1. Left putaminal ICH in a 60-year-old female with a history of hypertension.
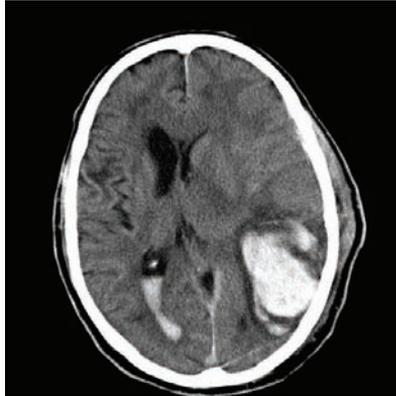
Fig. 2. Right parietal hematoma in a 57-year-old man with a history of recurrent ICH. The patient belonged to a Finnish family with cerebral amyloid angiopathy confirmed genetically and at autopsy (Rovelet-Lecrux *et al.* 2007).

Fig. 3. Midline primary intraventricular ICH in a 70-year-old male. Digital subtraction angiography (DSA) did not reveal any underlying vascular malformation.

2.2.2 Secondary intracerebral hemorrhage

Only 12–18% of all ICH cases are classifiable as the secondary type of ICH (Qureshi *et al.* 2001). The most important causes of secondary ICH are vascular abnormalities, which carry the risk of rebleeding. The most common anomalies are cerebral arterial aneurysms, arteriovenous malformations (AVM), and cavernous hemangiomas. The other etiologies include coagulopathies, systemic

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vascular diseases, and rarely brain tumors. The secondary causes of ICH are represented in Table 1.

Table 1. Secondary causes of ICH.

Causes
Vascular or structural abnormality
Aneurysm
Arteriovenous malformation
Dural arteriovenous fistula
Cavernous hemangioma
Venous angioma
Moyamoya disease
Tumor
Coagulopathy
Hematological disease (leukaemia, thrombocytopenia)
Disseminated intravascular coagulation
Alcohol-induced coagulopathy
Hepatic failure
Other
CNS vasculitis
Cerebral venous thrombosis
Reperfusion after carotid endarterectomy
After thrombolysis

Aneurysms

In a recent meta-analysis, the incidence of subarachnoid hemorrhage was 9.1 (95% CI 8.8–9.5) / 100,000/ year (de Rooij *et al.* 2007). The incidence of SAH in Finland is higher, approximately 15–17/100,000/year (Fogelhom *et al.* 1993, Numminen *et al.* 1996, de Rooij *et al.* 2007). The highest incidence rates (22.7/ 100,000/ year; 95% CI 21.9–23.5) have been reported from Japan (de Rooij *et al.* 2007).

In 85% of cases, subarachnoid hemorrhage results from a rupture of an intracranial arterial aneurysm (van Gijn & Rinkel 2001). Aneurysmal rupture may also cause ICH, mostly in cases where either a middle cerebral or a distal anterior cerebral artery aneurysm ruptures (Nowak *et al.* 1998) (figure 4). The risk of rebleeding is highest within the first 24 hours after the rupture, and 50% of patients have a rebleed within 6 months (Jane *et al.* 1985, Juvela 1989a). An aneurysm can be occluded endovascularly with platinum coils or surgically by

clipping to prevent rebleeding. Patients with a space-occupying intracerebral hematoma and impaired consciousness should be operated on as emergency cases (Heiskanen *et al.* 1988). Depending on the patient's level of consciousness and the neurosurgeon's experience, DSA, 3D-CT angiography, or no angiography are performed before emergency surgery. During the operation, the hematoma is evacuated and the aneurysm clipped.
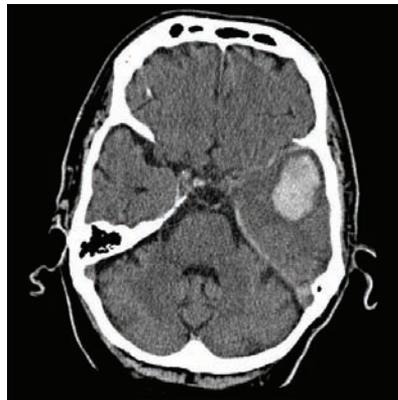
Fig. 4. Left-side temporal ICH caused by an angiographically confirmed ruptured median carotid artery aneurysm in a 53-year-old male. A very small amount of blood can be seen in the subarachnoid space.

Arteriovenous malformations (AVM)

Arteriovenous malformations (AVM) of the brain are complex vascular lesions, in which arterial blood flows directly into draining veins without an intervening capillary bed. High blood flow and direct transmission of arterial pressure to the venous structures lead to pathological dilatation and growth of vessels as well as impairment of intracranial hemodynamics. AVMs are probably congenital but not hereditary lesions, and their etiology is unknown (The Arteriovenous Study Group 1999). ICH is the most common clinical presentation of AVM (figure 5). The estimated long-term average annual rate of hemorrhage varies between 2 and 3% (Hernesniemi *et al.* 2008). The annual risk of rebleeding is highest (5–6%) during the first 5 years after the initial hemorrhage (Fults *et al.* 1984, Itoyama *et al.* 1989, Mast *et al.* 1997). AVMs are treated with stereotactic radiosurgery, endovascular embolization, microsurgery, or a combination of these treatments.

The risk of surgery can be estimated with the Spetzler-Martin grading system (Spetzler & Martin, 1986).
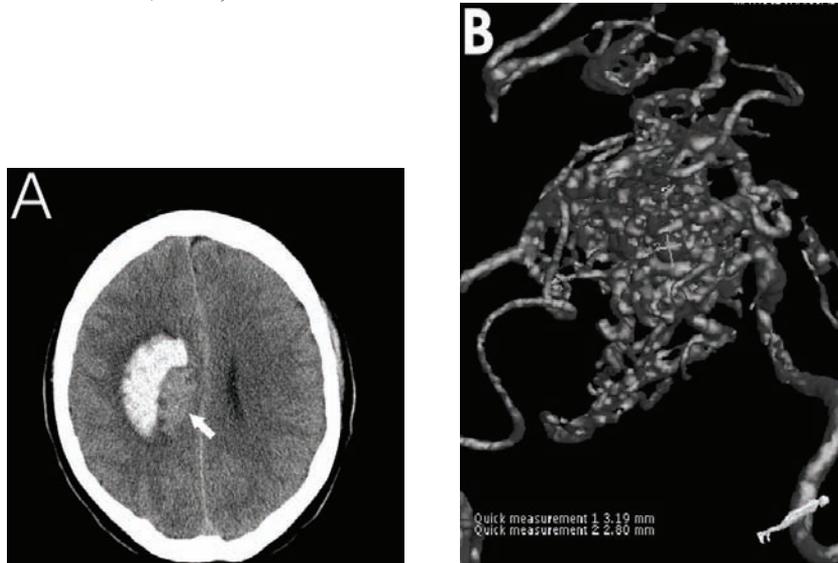
Fig. 5. A. CT scan of right-side ICH caused by AVM in a 44-year-old male. AVM is visible even in the plain CT scan (white arrow). B. 3D-DSA of the aneurysm with a small secondary aneurysm.

Cavernous hemangiomas

Cavernous hemangiomas are low-flow vascular malformations with no feeding arteries or draining veins. Modern imaging technologies help to increasingly detect asymptomatic and symptomatic cavernous hemangiomas. The usual clinical presentation is epilepsy, but the malformation also carries a 1–2% risk of ICH per year (Cantu *et al.* 2005). Symptomatic cavernous hemangiomas are considered for surgical removal (Ojemann & Ogilvy 1999).

Coagulopathy

Liver cirrhosis and other liver diseases may contribute to the risk of ICH due the impaired coagulation (Gronbaek *et al.* 2008). Heavy alcohol intake is a risk factor for liver diseases and can produce changes in the coagulation system (Gorelick 1987, Hillbom & Numminen 1998, Hillbom *et al.* 1999).

Patients with malignant hematological diseases, such as leukaemia and polycythemia vera, relatively often experience ICH. ICH that is a complication of these diseases is considered secondary ICH. Anticoagulant therapy, usually warfarin, carries an 8 to 10-fold risk of ICH (Wintzen *et al.* 1984, Franke *et al.* 1990). Antiplatelet therapy, usually aspirin, also increases the risk of ICH (Juvela *et al.* 1995b,Thrift *et al.* 1999b Saloheimo *et al.* 2001) These medications increase the risk of ICH but do not necessarily cause it. Therefore, ICH occurring during the use of these medications with no secondary structural anomaly is considered primary ICH.

2.2.3 Traumatic intracerebral hemorrhage

The prevalence of head trauma patients who develop ICH as a major CT finding amounts to 15% (Mathiesen *et al.* 1995a). The development of traumatic ICH does not correlate with the intensity of injury and may be delayed (figure 6), though it usually occurs within 48 hours of head trauma (Cooper 1992, Alvarez-Sabin *et al.* 1995). It has been suggested that traumatic ICH develops more easily in mildly atrophic brains with no tamponading effect (Siddique *et al.* 2002). Head trauma patients with ICH are usually older than those with head trauma without ICH. They are also significantly younger than patients with primary ICH (Siddique *et al.* 2002). This may be due to the more common and heavier alcohol consumption in trauma patients than in patients with primary ICH. The prognosis of patients with traumatic ICH is much better compared to patients with primary ICH (Siddique *et al.* 2002). The significance of surgery in cases of traumatic ICH is undefined. One non-randomized study found better outcomes in patients who underwent clot evacuation (Mathiesen *et al.* 1995a).
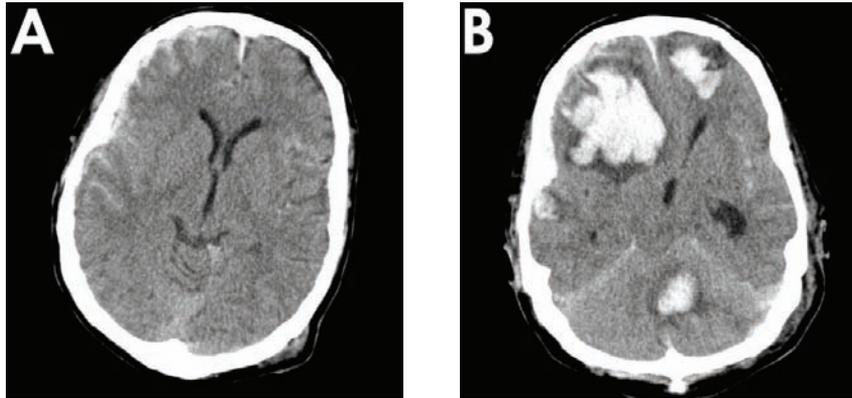
Fig. 6. A. Delayed traumatic ICH in a 51-year-old male suffering from chronic alcoholism. A CT-scan 2 hours after the injury. B. Multiple traumatic ICH in a CT scan taken 24 hours after the injury.

2.3 Risk factors of primary intracerebral hemorrhage

2.3.1 Untreated and treated hypertension

Hypertension is the most prevalent risk factor for ICH (Brott *et al.* 1986). It is considered a major risk factor in half of all patients presenting with ICH and in 75% of those with deep hematomas (Fogelholm *et al.* 1992a, Hylek & Singer 1994, Hart *et al.* 1995, Juvela *et al.* 1995b, Mathiesen *et al.* 1995b, Juvela 1996, Woo *et al.* 2002, Ariesen *et al.* 2003). A systematic review has confirmed that hypertension frequently associates with deep ICH (Jackson *et al.* 2006). The risk of ICH increases at higher blood pressure values (Suh *et al.* 2001).

The role of untreated hypertension as a risk factor for ICH is difficult to estimate. Population-based studies have reported a 17% incidence of undiagnosed hypertension (Burt *et al.* 1995, Woo *et al.* 2002). A relatively large Australian study suggested a higher risk of ICH in patients who had discontinued antihypertensive medication (Thrift *et al.* 1998). Untreated hypertension has been found to be a highly prevalent risk factor for hemorrhagic stroke (ICH and subarachnoid hemorrhage combined) (Woo *et al.* 2002 and 2004). This risk factor is treatable, and the authors estimated that one fourth of hemorrhagic strokes could be prevented if all hypertensive subjects received treatment. In case of non-lobar ICH the figure may be even higher (40–65%). Programs of active treatment

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of hypertension with antihypertensive medication have significantly reduced the risk of ICH (Hypertension Detection and Follow-up Program 1982, SHEP Cooperative Research Group 1991).

2.3.2 Diabetes

Diabetes is a well-known risk factor for ischemic stroke (Sacco 1998, Ringelstein & Nabavi 2000). On the other hand, it is less clear whether there is an association between diabetes and ICH (van Zagten *et al.* 1994). However, the incidence of diabetes was found to be significantly higher in patients with ICH compared to controls in two studies (Zodpey *et al.* 2000, Zia *et al.* 2006). A systematic review of 8 case-control studies could not confirm that diabetes predicts the risk for ICH; the overall Odds Ratio (OR) was 1.27 (95% Cl, 0.98–1.65) (Ariesen *et al.* 2003). Up till now, it has not been shown that diabetes independently predicts ICH. Meta-analyses may underestimate the role of minor risk factors for ICH as well as overestimate some risk factors highlighted by selection bias in individual studies.

2.3.3 Amyloid angiopathy and genetic factors

Cerebral amyloid angiopathy (CAA) is a major cause of lobar ICH in older patients (Qureshi *et al.* 2001, McCarron & Nicoll 2004). CAA is a degenerative process of arterial media, which mainly affects cortical and leptomeningeal vessels, predisposing to ICH. CAA is caused by the deposition of β-amyloid protein on the vessel wall (Qureshi *et al.* 2001). The prevalence of CAA rises with age, being approximately 60% among those over 90 years of age (McCarron & Nicoll 2004). The diagnosis is clinically suspected in multiple lobar bleedings with no other obvious cause of ICH in patients 55 years of age or older (Knudsen *et al.* 2001). There are currently no diagnostic tests to detect CAA, and the diagnosis is usually confirmed by neuropathological findings at autopsy (Sacco 2000).

CAA associates with the presence of the apolipoprotein ε2 and ε4 alleles of the apolipoprotein E gene in elderly ICH patients (McCarron & Nicoll 1998, McCarron *et al.* 1999). Carriers of either ε2 or ε4 alleles show a 3-fold risk for recurrent ICH (O'Donnell *et al.* 2000). The expression of these alleles seems to augment the vasculopathic effect of CAA (Qureshi *et al.* 2001). There may also be other underlying genetic factors for ICH. A recent meta-analysis of APOE genotypes and the risk of different stroke types suggested that ε4+ genotype may

increase the risk of ischemic stroke (of principally the large-artery subtype) and marginally that of subarachnoid hemorrhage, while ε2+ genotype may increase the risk for spontaneous ICH of mainly the lobar subtype (Sudlow *et al.* 2006). The risk for spontaneous ICH has traditionally been associated with low serum cholesterol levels, which correlate with the occurrence of the ε2+ genotype. However, when larger studies were included in the analysis, no association between APOE ε4+ genotype and ischemic stroke was found. The authors concluded that publication, reporting, and selection bias make studies of APOE in stroke difficult to interpret. Positive family history has been reported to be a risk factor for ICH (Woo *et al.* 2002). However, this finding is based on interview data and therefore carries the possibility of recall bias. Kubota *et al.* 1997 found positive family history to predict ICH, although it did not emerge as an independent predictor in multivariate analysis.

2.3.4 Alcohol consumption and stimulant use

The relationship between alcohol intake and increased ICH risk has been identified in many case-control studies. (Kagan *et al.* 1980, Calandre *et al.* 1986, Monforte *et al.* 1990, Juvela *et al.* 1995b, Thrift *et al.* 1996, Zodpey *et al.* 2000, Saloheimo *et al.* 2001). Short-term recent moderate or heavy binge alcohol intake within 24 hours or one week seems to be a more important risk factor for ICH than long-term habitual heavy drinking (Juvela *et al.* 1995b). In a meta-analysis of 8 studies, both moderate ($\leq$ 56 g/day alcohol) and heavy (> 56 g/day alcohol) consumption of alcohol increased the risk of ICH (Ariesen *et al.* 2003). Although heavy alcohol drinking associates with elevated blood pressure, it also increases the risk for ICH by impairing blood coagulation and affecting the integrity of cerebral blood vessels independently of hypertension (Gorelick 1987, Klatsky *et al.* 1989, Hillbom *et al.* 1999). Based on experimental studies, it has been speculated that depletion of magnesium from the brain vascular tissues initiates alcohol-induced hemorrhagic strokes (Altura & Altura 1994).

Amphetamine or cocaine use can provoke ICH. This uncommon etiology is mainly seen in young adults (Toffol *et al.* 1987). The association between amphetamine use and ICH has been known for a long time (Gericke 1945) and is nowadays increasingly recognized (Delaney & Estes 1980, Harrington 1983). Cocaine use also associates with ICH (Brust & Richter 1977, Mangiardi *et al.* 1988, Fessler *et al.* 1997), but because vascular malformations are frequently

found in stimulant users with ICH, they should be actively searched for in such patients (Selmi *et al.* 1995, McEvoy *et al.* 2000).

Cigarette smoking is a well-known predictor of ischemic stroke in both men and women (Abbott *et al.* 1986, Colditz *et al.* 1988), but its role as a risk factor for ICH is less clear. Not all studies have foud it to be an independent predictor of ICH (Fogelholm & Murros 1993, Juvela *et al.* 1995b), while two recent studies found heavy smoking ($\geq$ 20 cigarettes per day in men and $\geq$ 15 cigarettes per day in women) to independently predict ICH in both men and women (Kurth *et al.* 2003).

2.3.5 Use of anticoagulants and platelet inhibitors

Warfarin therapy carries a significant risk for ICH. The risk for ICH in warfarin users has been reported to be 8 to 10-fold (Wintzen *et al.* 1984, Franke *et al.* 1990) compared with nonusers. ICHs associated with oral anticoagulation account for a considerable proportion of all ICHs (6.9% according to Cucchiara *et al.* 2008), and mortality from such ICHs is very high, 50–67% (Rosand *et al.* 2004, Steiner *et al.* 2006a). The intensity of anticoagulation also influences the risk for ICH. Every 0.5 unit increase in INR (international normalized ratio) is followed by a 1.4-fold increase in the risk for ICH. (The Stroke Prevention In Reversible Ischemia Trial Study Group, 1997)). However, two-thirds of warfarin-associated ICHs occur at INR values 3.0 or less (Rosand *et al.* 2004).

A meta-analysis showed that aspirin use increases the risk for hemorrhagic stroke (He *et al.*1999). However, the risk of ICH seems to associate with high doses of aspirin. Aspirin monotherapy at a dose of 1300 mg or over per day associated with a 2-fold risk for ICH (Thrift *et al.* 1999b). Whether the use of clopidogrel carries a similar risk for ICH is not known. Conflicting observations have been reported concerning concomitant use of aspirin and clopidogrel. In a large study, aspirin-clopidogrel combination treatment was not associated with an additional risk for ICH compared to aspirin treatment alone (Bhatt *et al.*2006). However, another large study found that the risk of life-threatening or major bleeding increased when aspirin and clopidogrel were used simultaneously (Diener *et al*. 2004). A recent follow-up study of events in a cohort of patients with ICH did not find a significant effect of antiplatelet therapy on recurrent hemorrhage (Viswanathan *et al.* 2006).

2.3.6 Season as a risk factor

Cold temperature has been found to raise blood pressure (Brennan *et al.* 1982, Keatinge *et al.* 1984), and this cold-related elevation may be a mechanism triggering ICH (Caplan 1988). A previous study from Finland (Sotaniemi *et al.* 1972) already suggested that a cold environmental temperature may trigger the onset of cerebral hemorrhage. Some population-based studies have found a higher incidence of ICH during winter (Shinkawa *et al.* 1990, Jacovlevic *et al.* 1996, Rothwell *et al.* 1996, Inagawa *et al.* 2000, Wang *et al.* 2002), whereas other studies have not found any seasonal variation (Sobel *et al.* 1987, Giroud *et al.* 1989, Kelly-Hayes *et al.* 1995, Khan *et al.* 2005).

A recent Finnish study showed that antihypertensive medication reduces the peak blood pressure values in subjects exposed to cold (Komulainen 2007). This is naturally not the case in subjects with untreated hypertension. They may show high peak blood pressure values when exposed to cold and have even higher values than are seen in normotensive subjects (Minami *et al.* 1996). Inagawa (2003) found a significantly higher incidence of ICH in subjects with untreated hypertension during wintertime, but this has not been confirmed in other studies.

2.3.7 Other risk factors

Modern imaging methods, such as gradient-echo T2*-weighted MRI, can visualize blood breakdown products. This has led to the discovery of cerebral microbleeds (Fazekas *et al.* 1999). Microbleeds are frequent findings in patients with ICH (Greenberg *et al.* 1996, Roob *et al.* 2000) and may also predict ICH. If patients with previous ischemic stroke have microbleeds and use antithrombotic and anticoagulant drugs, they may have a greater risk for ICH (Wong *et al.* 2003) compared with those who do not have microbleeds.

Primary ICH can also develop in medical conditions that acutely raise blood pressure, such as eclampsia, acute glomerulonephritis, and pheochromocytoma (Levai *et al.* 1971, Beck & Menezes 1981, Scardigli *et al.* 1985). Strenuous physical activity has also been reported to be a risk factor for ICH (Passero *et al.* 2001, Thrift *et al.*2002a), as have acute stress and sexual intercourse (Finelli 1993, Lammie *et al.* 2000).

The risk for ICH as opposed to ischemic stroke is suggested to be lower in subjects with high cholesterol levels (Thrift *et al.* 2002b). In a large study, cholesterol lowering was associated with a significantly higher number of ICHs

(Amarenco *et al.* 2006). In a case-control study, statin therapy was not found to be a risk factor for ICH, although there was a clear association between low cholesterol and ICH (Woo *et al.* 2004).

The risk for ICH is higher among patients who have previously had an ischemic stroke. The prevalence of previous ischemic stroke in patients with ICH has been reported to be 29% (Zahuranec *et al.* 2006).

Finally, low socioeconomic status and low level of education have been shown to associate with a high incidence of stroke in general and ICH in particular (Qureshi *et al.* 1999b, Thrift *et al.* 2006). This may be related to better health habits and more efficient treatment of hypertension among those with higher socioeconomic status.

2.4   Short-term outcome after primary intracerebral hemorrhage

2.4.1 Predictors for short-term outcome

ICH is the most devastating subgroup of strokes with high mortality and morbidity. Thirty-five to 52% of patients are likely to die within the first month after the bleeding (Bramford *et al.* 1990, Fogelholm *et al.* 1992a, Broderick *et al.* 1993a, Andersson *et al.* 1994, Councell *et al.* 1995). Half of the deaths occur in the first 2 days (Broderick *et al.* 1993a). Of all patients with ICH, 20 % are functionally independent at six months (Counsell *et al.* 1995), and 58% of ICH survivors are functionally independent at 1 year (Hårdemark *et al.* 1999). The relative proportion of functionally independent patients increases over time because many severely handicapped patients die within the first year after ICH (Fogelholm *et al.* 1992a).

The well-known predictors for early death and poor functional outcome include the clinical and radiological severity of the bleeding. Level of consciousness and hematoma volume (Daverat *et al.* 1991, Tuhrim *et al.* 1991, Broderick *et al.* 1993a, Qureshi 1995, Juvela 1995a, Hårdemark *et al.* 1999) as well as the presence of intraventricular blood (Tuhrim *et al.* 1991 & 1999, Hemphill *et al.* 2001) have repeatedly been reported to independently predict death within 30 days after the bleed. Age has not been systematically reported to influence short-term outcome. However, it has been reported (Hemphill *et al.* 2001) that very old age ($\geq$ 80 years) significantly increases 30-day mortality. High

age also predicts a worse long-term outcome (Portenoy, *et al.* 1987, Daverat *et al.* 1991, Franke *et al.* 1992, Lisk *et al.* 1994).

Use of anticoagulants at the time of ICH onset clearly predicts short-term mortality (Franke et al 1990, Fogelholm *et al.* 1992b, Hart *et al.* 1995, Neau *et al.* 2001). Rosand *et al.* 2004 found that warfarin users have two-fold mortality compared to nonusers. However, in-hospital mortality is not markedly dependent on INR measured on admission (Berwaerts *et al.* 2000). Thus far, three studies have found that the use of antiplatelets also increases 30-day mortality after ICH (Roquer *et al.* 2005, Saloheimo *et al.* 2005, Lacut *et al.* 2007). A possible mechanism for the increase of acute mortality may be the effect of antiplatelet agents on hematoma enlargement (Sorimachi *et al.*2007)

High mean arterial blood pressure (MABP) on admission has been repeatedly reported to be associated with early death and poor functional outcome after ICH (Dandabani *et al.* 1995, Fogelholm *et al.* 1997, Terayama *et al.* 1997, Willmot *et al.* 2004). This may be related to the "Cushing reflex"; blood pressure is elevated concomitantly with intracranial pressure to maintain a sufficient perfusion pressure in the brain (Cushing 1903). This means that elevated MABP reflects increased intracranial pressure, which is the major contributor to poor outcome via impairment of perfusion pressure. High admission plasma glucose has also been associated with poor outcome in two studies (Passero *et al.* 2003, Fogelholm *et al.* 2005). On the other hand, the review by Capes *et al.* 2001 reported no such association.

A widely used ordinal prediction model for 30-day outcome was presented by Hemphill *et al.* 2001 (Table 2). The total ICH score is the sum of the points assigned to the characteristics mentioned in the Table 2 (0–6 points). Thirty-day mortality increases as the ICH score rises. In the cohort of patients treated in California University Hospital, ICH scores of 1, 2, 3, and 4 associated with mortality rates of 13%, 26%, 72%, and 97%, respectively. None of the patients with an ICH score of 0 died, while all the patients with an ICH score of 5 died, and none scored 6 points.

Table 2. Determinant of the practical ICH score (Hemphill *et al.* 2001)

Component	ICH score points
GCS	
3–4	2
5–12	1
13–15	0
ICH volume, cm^3	
≥ 30	1
< 30	0
IVH	
Yes	1
No	0
Infatentorial location	
Yes	1
No	0
Age, y	
≥ 80	1
< 80	0
Total ICH score	0–6

2.4.2 Cardiac diseases as predictors for outcome

In patients with ischemic stroke, previous cardiac diseases (cardiac failure, ischemic heart disease, or atrial fibrillation) have been reported to influence outcome after stroke, and cardiac complications are common (Hankey 2003). The influence of cardiac diseases on outcome in patients with ICH is less clear.

One population-based study found cardiac disease (coronary artery disease or atrial fibrillation) to be an independent predictor for 30-day mortality (Nilsson *et al.* 2002). Three hospital-based studies failed to establish ischemic heart disease as a risk factor for early death after ICH (Wong 1999, Rosand *et al.* 2004, Roquer *et al.* 2005). One study suggested that atrial fibrillation may impair the prognosis of ICH (Ostabal *et al.* 1996). Both antiplatelet agents and anticoagulants are commonly used in secondary prevention of cardiac disease. Consequently, the use of these agents may have emerged as a risk factor for early death after ICH due a proxy effect of a history of cardiac disease.

2.4.3 Hypertension and diabetes as predictors for poor outcome

Although hypertension is the most important risk factor for ICH, pre-existing hypertension has not been reported to predict early death or poor functional outcome after ICH (Juvela 1995a, Nilsson *et al.* 2002, Saloheimo *et al.* 2006). Diabetes has been reported to be an independent risk factor for early death in two studies (Arboix *et al.* 2000, Passero *et al.* 2003). The mechanism of how diabetes increases the risk for early death is unclear, although hyperglycemia may cause brain edema and perihematomal cell death after ICH according to experimental studies (Song *et al.* 2003). Diabetics may also be more frequently associated with cardiac and infectious complications.

2.5   Complications of primary intracerebral hemorrhage

2.5.1 Hematoma enlargement

In the past, ICH was believed to be a stable process with maximal volume at the onset. Enlargement of the primary ICH was first reported by Kelley *et al.* 1982 in a case series of 4 patients showing rapid hematoma enlargement between the admission CT scan and subsequent contrast-enhanced scans. Kazui *et al.* 1996 conducted a retrospective study demonstrating hematoma enlargement, which was confirmed by Brott *et al.* 1998 in a prospective study. In the latter study, 38% of patients showed substantial (> 33%) hematoma growth within the first 24 hours after symptom onset. In a meta-analysis of 3 prospective studies, 73% of patients showed some degree of hematoma enlargement (Davis *et al.* 2006).

Expansion usually progresses during the first 6 hours after the onset of stroke, and it is observed in only 5–12 % of patients scanned later than 6 hours after the onset (Fujii *et al.* 1994, Kazui *et al.* 1996, Brott *et al.* 2007) (figure 7). Enlargement of the hematoma has turned out to be a common and important-to-prevent phenomenon. The importance of hematoma growth has now been recognized, and it has been identified as an independent predictor for mortality and poor functional outcome after ICH (Davis *et al.* 2006). The factors predisposing to and predicting hematoma enlargement include heavy drinking of alcohol, irregular shape of the hematoma, disturbed level of consciousness, and low level of fibrinogen (Fujii *et al.* 1998) as well as preceding use of anticoagulant (Flaherty *et al.* 2008) and antiplatelet drugs (Sorimachi *et al.* 2007) .

Two studies have found previous antiplatelet therapy to be a predictor for hematoma enlargement (Toyoda *et al.* 2005, Sorimachi *et al.* 2007).
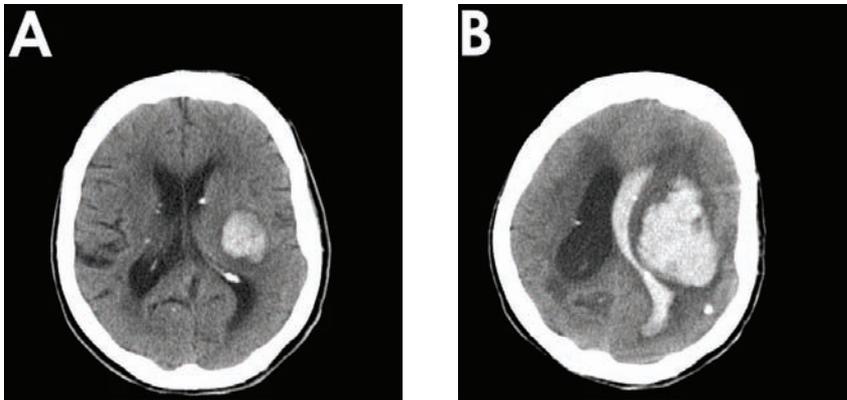
Fig. 7. A 76-year-old female with sudden right-sided hemiparesis. CT scan (A) taken 1 hour after the onset showing left thalamic ICH. The patient developed significant clinical deterioration within 6 hours after the onset, and a second CT scan (B) showed hematoma enlargement. The patient had been using aspirin.

2.5.2 Cardiac complications

The risk for cardiopulmonary instability in patients with ICH is highest during the first 24 hours after the onset (Qureshi *et al.* 2001). Increased intracranial pressure leads to severe hypertension and bradycardia, called Cushing responses (Cushing 1903). Accompanying insufficiency in the right and left ventricles of the heart may lead to neurogenic pulmonary edema (Chen 1995). Acute electrocardiographic changes are highly prevalent in patients with ICH, and they frequently seem to associate with pre-existing coronary artery disease (Khechinashvili & Asplund 2002). ICH may also provoke a phenomenon called Tako-tsubo cardiomyopathy, which manifests as reversible left ventricle hypertrophy mimicking acute myocardial infarction (Tsuchihashi *et al.* 2001, Rahimi *et al.* 2007).

2.5.3 Venous thromboembolism

Patients with ICH suffer from prolonged immobility due their impaired consciousness and/or paresis of the lower extremities. Warlow *et al.* 1975 showed that, if nothing is done to prevent deep venous thrombosis (DVT), 53% of stroke patients develop DVT and 15% develop pulmonary embolism (PE). Patients with ICH may even have a higher incidence of venous thromboembolic complications (VTC) than those with ischemic stroke (Skaf et al 2005).

The options for preventing VTCs are compression stockings, pneumatic sequential compression devices, and anticoagulant treatment (Lacut *et al.* 2005, Andre *et al.* 2007). These methods are recommended in the current American (Broderick *et al.* 2007) and European (Steiner *et al.* 2006b) guidelines. Prevention with the use of anticoagulants is problematic because of the risk of hematoma expansion, and only two studies have demonstrated their use in patients with ICH (Dickmann *et al.* 1988, Boeer *et al.* 1991). Furthermore, the safety of the treatment remains unclear.

2.5.4 Hydrocephalus

Infratentorial ICH or extension of ICH to the ventricles may lead to obstructive hydrocephalus. Both intraventricular hemorrhage and hydrocephalus in patients with ICH are associated with high mortality (Diringer *et al.* 1998, Tuhrim et al 1999). Moderate or severe hydrocephalus should be treated with external ventricular drainage, which normalizes intracranial pressure. However, the benefit of ventricular drainage has not yet been proved (Adams & Diringer 1998, Tuhrim *et al.* 1999). External ventricular drainage may also lead to an increased volume of IVH, infection, and IVH may lead the development of chronic hydrocephalus requiring a permanent shunt.

2.5.5 Surgical complications

External ventricular drainage carries risks for intracerebral hematoma, intraventricular hematoma, and infections (Lozier *et al.* 2002). The incidence of bacterial meningitis after the placement of drainage varies from 6 to 22% (Holloway *et al.* 1996, Lozier *et al.* 2002). Evacuation of the hematoma is followed by a risk for a rebleed, which seems to be higher after mini-invasive procedures compared to craniotomy (Teernstara *et al.* 2003). Surgical

complications of craniotomy include secondary trauma to normal brain tissue and infarction due to vascular injury.

2.6 Treatment of primary intracerebral hemorrhage

2.6.1 Conservative treatment

Conservative treatment of ICH covers all emergency and critical care procedures except operative treatment. In general, all patients with ICH should be admitted to a neurosurgical or neurological intensive care setting, because it reduces mortality (Diringer *et al.* 2001). Moreover, physicians should be cautious about early limitations of care because that strongly affects the prognosis of these patients (Becker *et al.* 2001, Hemphill *et al.* 2004). Recently, a do-not-resuscitate order was shown to independently predict death in patients with ICH (Zahuranec *et al.* 2007).

Securing the airways

The onset of ICH is typically followed by a rapid decline of consciousness and progression of neurological symptoms. Loss of the normal reflexes to maintain an open airway develops, which increases the risk of aspiration, hypoxemia, and hypercapnia. Cerebral vasodilatation may develop and raise ICP. To avoid this entailment, appropriate intubation and mechanical ventilation are needed (Gujjar *et al.* 1998). Sedatives (such as propofol) and non-depolarizing neuromuscular drugs (such as vecuronium) are used to facilitate the intubation procedure. However, drugs that raise ICP should be avoided (Roppolo *et al.* 2004).

Controlling blood pressure

High admission MABP has been repeatedly reported to predict early death and poor outcome after ICH (Dandabani *et al.* 1995, Fogelholm *et al.* 1997, Terayama *et al.* 1997, Willmot *et al.* 2004). Blood pressure maintains the cerebral perfusion pressure (CPP), and overaggressive lowering of blood pressure may theoretically worsen cerebral perfusion in cases with high intracranial pressure (CPP = MABP-ICP).

However, treatment of high admission blood pressure (BP) and its effect on outcome have not been thoroughly investigated. According to some reports, a controlled blood pressure reduction of 15 to 20% did not seem to have a deleterious effect on cerebral blood flow (CBF), and autoregulation of CBF was preserved (Powers *et al.* 1999 & 2001, Qureshi *et al.* 1999a). On the other hand, one retrospective study showed that aggressive treatment of high BP increased mortality (Qureshi *et al.* 1999a). In another observational prospective study, blood pressure reduction to the target level of < 160/90 was associated with neurological deterioration but, on the other hand, there was a trend toward better outcome among the patients who received blood pressure lowering medication within the first 6 hours after onset (Qureshi *et al.* 2005). Currently, there are no randomized controlled trials available to suggest whether lowering of BP in the acute phase should be recommended. However, both the European and the American guidelines give some recommendations (Steiner *et al.* 2006b, Broderick *et al.* 2007).

The main argument for the lowering of blood pressure in the acute phase after the onset of ICH is that high blood pressure can cause early hematoma expansion. Elevated systolic blood pressure (SBP) > 160 mmHg has been associated with early hematoma growth in retrospective studies but not in prospective studies (Brott *et al.* 1997, Broderick *et al.* 2007). Kazui *et al.* 1997 found no clear association between high admission blood pressure (SBP > 210mmHg) and hematoma expansion or neurological deterioration. In a pilot study of intensive blood pressure reduction, the treatment reduced the risk of hematoma growth (Andersson *et al.* 2008). Currently, the question remains unsolved and further studies are needed.

The recommendations of the European Stroke Initiative 2006 (Steiner *et al.* 2006b) and the American Stroke Association 2007 (Broderick *et al.* 2007) for the management of high blood pressure are presented in Table 3. In the European recommendations, patients are divided into two groups according to whether or not they have had previous hypertension. This is because hypertensive patients suffer from impaired autoregulation of cerebral blood flow. Their brains show better tolerance of higher levels of MABP, while they have a higher risk of hypoperfusion at low MABP levels, which are usually well tolerated by normotensives (Chillon & Baumbach 2002). The recommendations give different target levels for previously hypertensive and normotensive individuals (see Table 3). The recommendations of the American Heart Association (Broderick *et al.* 2007) divide patients into three groups. Patients with very high blood pressure

(MABP > 150mmHg) are recommended to be treated aggressively with intravenous medications to lower the pressure, while others are treated differently depending on whether they have evidence or suspicion of elevated ICP. The recommended medication for hypertension consists of intravenous 10 to 80 mg boluses of labetalol at every 10 minutes (Mayer & Rincon 2005). Sodium nitroprusside should be avoided because it raises ICP (Cottrell *et al.* 1978).

At present, the impact of the above treatment procedures on outcome remains unknown. While waiting for the results of prospective randomized controlled studies on the treatment of high arterial BP on admission in patients with ICH, the treatment should be tailored individually for each patient.

Table 3. Recommendations given by the American Heart Association (AHA) and the European Stroke Initiative (EUSI) for the treatment of acute high blood pressure in patients with ICH.

Groups	AHA recommendations			EUSI recommendations	
	Class IIb, level of evidence C			Class IV evidence	
	Very high pressure	Elevated ICP	Not elevated ICP	Hypertension	Normotensive
Treatment level	SBP > 200 or MABP > 150	SBP > 180 or MABP > 130	SBP > 180 or MAPB > 130	SBP > 180 and/or DBP > 105	SBP > 160 and/or DPB > 95
Target level	Aggressive reduction	keep CPP > 60 to 80	MABP ≤ 110	BP 170/100	BP 150/90

ICP = intracerebral pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, MABP = mean arterial blood pressure, BP = blood pressure, CPP = cerebral perfusion pressure. All values are in mmHg.

Management of increased intracranial pressure

Emergency management of elevated intracranial pressure (ICP) includes head elevation, use of mannitol, and hyperventilation even before the installation of any ICP measurement devices. The management also includes sedation, phenobarbital therapy, hypothermia, and fluid infusion according to the cerebral perfusion pressure (CPP) guided therapy (Rosner & Daughton 1990, Rosner 1995, Fernandes *et al.* 2000b, Chambers *et al.* 2001). Neurosurgical methods for lowering ICP include placement of an external ventricular catheter and decompressive craniectomy (Mitchell *et al.* 2007).

Head elevation to 30 degrees improves jugular venous outflow and reduces ICP. Before head elevation, hypovolemia should be excluded, because in hypovolemic patients the treatment likely impairs CPP. Hyperventilation is a very effective method for lowering ICP in emergency situations, but it simultaneously decreases CBF by lowering pCO_2, which may lead to secondary ischemic brain injury. The ICP-lowering effect of hyperventilation only lasts for a few hours. The target level of pCO_2 is 26–30 mmHg (The Brain Trauma Foundation 2000).

Mannitol draws fluid out of edematous and normal brain tissue and thereby decreases ICP. Mannitol as 20% solution is administered in intravenous doses of 1.0–1.5 g/kg of followed by bolus doses of 0.25–1.0g/kg as needed. Mannitol use may be complicated by hypovolemia, induction of a hyperosmotic state, renal failure, and rebound intracranial hypertension. Hypertonic saline can be used instead of mannitol (Qureshi & Suarez 2000). Based on the results of randomized trials with relatively small sample sizes, routine corticosteroid admistration is not recommended (Feigin *et al.* 2005).

Sedatives are used to keep patients relaxed and motionless. If ICP is still high after the treatments described above, barbiturate coma can be induced. High doses of barbiturate depress the metabolic activity of the brain and reduce CBF, which lead to a decrease of ICP. However, this treatment carries a significant risk of complications, most commonly hypotension, cardiovascular and respiratory depression, and prolonged coma (Schwab *et al.* 1997).

CPP is secured and optimized by fluid infusion; pressor infusion is started if CPP < 70 mmHg, or BP is reduced if CPP > 110 mmHg. The goal of CPP-guided therapy is to minimize reflex vasodilatation and ischemia in the brain (Mayer & Rincon 2005). Still, the effect of this treatment on outcome has not been proved.

Controlling body temperature

Fever has caused neuronal injury and death after ICH in experimental models (Szczudlik *et al.* 2002). Paracetamol and physical cooling are used to decrease body temperature in clinical settings, but there is not much evidence to show that lowering of the body temperature in patients with ICH will improve outcome (Mayer *et al.* 2001). There are no randomized controlled trials on additional cooling of patients. However, hypothermia (body temperature cooled to 32–33 °C) has been used to treat patients with high ICP (The Brain Trauma Foundation, 2000).

Reversal of anticoagulation

As mentioned earlier, anticoagulant treatment preceding the onset of ICH is related to high mortality and poor functional outcome compared to ICH without preceding anticoagulation (Hart *et al.* 1995, Rosand *et al.* 2004, Cucchiara *et al.* 2008). Anticoagulation should be reversed immediately to prevent further deterioration, and warfarin users should have their INR value lowered below 1.4 immediately after the diagnosis of ICH (Fredriksson *et al.* 1992). This is done by using either fresh frozen plasma or prothrombin complex concentrate together with vitamin K.

Fresh frozen plasma may cause heart failure in patients with cardiac diseases or renal failure, while prothrombin complex concentrate normalizes INR more rapidly and can be given in smaller volumes (Fredriksson *et al.* 1992). It also reduces the risk for hematoma growth more effectively (Huttner *et al.* 2006). If there is a strong indication for anticoagulation (such as a heart valve prosthesis), anticoagulation can be restarted 10–14 days after ICH (Ananthasubramaniam *et al.* 2001).

Patients with thrombocytemia or platelet dysfunction can be treated with platelet transfusion and/or desmopressin (Mannucci *et al.* 1983). There is no evidence as to whether or not this improves the outcome of patients with preceding use of aspirin or clopidogrel. If the patient has used heparin or low molecular weight heparins (LMWH) before the onset of ICH, the effect of the medication should be reversed with protamine sulfate (Wakefield & Stanley 1996).

Stopping the bleeding

Efforts to reduce early hematoma growth by hemostatic agents have been made recently. These treatments should be given at the early stage of bleeding, because hematoma growth usually occurs within 6 hours of onset (Fujii *et al.* 1994, Kazui *et al.* 1996, Broderick *et al.* 1997). Preliminary results from a large trial testing the effects of recombinant activated factor VII were promising; treatment reduced hematoma enlargement and was associated with a 38% reduction in mortality (Mayer 2008). However, the final results showed no significant differences in outcome between the study groups in spite of efficient prevention of hematoma growth with activated factor VII. The unexpected results were explained by the

higher frequency of arterial thrombotic events in the group receiving 80 μg of recombinant activated factor VII (Mayer *et al.* 2008).

2.6.2 Surgical treatment

While medical treatments of ICH have not shown any significant benefit, the impact of surgery on outcome is also uncertain because of a lack of appropriate randomized trials with sufficient sample sizes and unbiased study design. Randomized controlled trials have yielded somewhat contradictory findings. The first randomized controlled trial conducted in 1961 showed worse outcomes after operative treatment compared to conservative treatment (McKissock *et al.* 1961). In 1989, two controlled randomized studies were published showing opposite findings. Juvela *et al.* 1989b found no overall benefit from surgery, but the sample size (n = 52) was too small to detect the potential benefits of surgery. In this trial, surgery improved significantly survival in patients with GCS scores of 7 to 10, but all survivors remained severely disabled. Auer *et al.* 1989 reported a randomized study of endoscopically operated patients (n = 100) showing a significant benefit from surgery in both reduced mortality and morbidity from lobar hematomas. A meta-analysis of seven trials failed to show a clear benefit of surgery in patients with ICH (Fernandes *et al.* 2000a).

The results of the awaited large randomized controlled trial on early surgery versus initiative conservative treatment (STICH) were published in 2005 (Mendelow *et al.* 2005). The study showed no overall benefit from early surgery. However, only patients whose neurosurgeon was uncertain about the benefit of surgery were enrolled in randomization (the clinical uncertainty principle). In addition, 26% of the patients enrolled in the conservative treatment group later underwent surgical hematoma evacuation because of clinical deterioration. Therefore, there is no justification for the conclusion that surgery of ICH is useless. In this study, the patients who underwent early surgery if the hematoma was lobar and located close to the cerebral cortex (under 1 cm from the surface) showed better outcome, but the difference was not significant. On the other hand, surgery was associated with a nonsignificant trend toward worse outcome among patients with GCS scores (Glasgow Coma Scale Score, Teasdale & Jennet 1974) of 5 to 8 but improved outcome in those with GCS scores of 9 to 12. Alert and somnolent patients did not seem to benefit from surgical clot removal. These results resemble those obtained in previous smaller randomized trials. In conclusion, the STICH results do not significantly change the current practice.

Patients with a subcortical hematoma at least 3 cm in diameter and impaired consciousness should be operated on, whereas the benefits of surgery for patients with putaminal ICH in somnolent, stuporous, or "semi-comatose" state (GCS 7 to 12) are still uncertain (Broderick *et al.* 1999, Gregson & Mendelow 2003, Juvela & Kase 2005, Steiner *et al.* 2006b).

No controlled randomized trials concerning surgery of cerebellar hematomas have been done. Nevertheless, patients with large cerebellar ICHs (diameter > 3cm) and with signs of hydrocephalus or brain stem compression have a poor prognosis when treated conservatively (Da Pian *et al.* 1984). On the other hand, several reports have confirmed a good outcome in these patients when treated surgically (Ott *et al.* 1974, Firsching *et al.* 1991, van Loon *et al.* 1993, Kobyashi *et al.* 1994). Currently, surgical evacuation of cerebellar ICH (≥ 3 cm in diameter) causing impaired consciousness and external drainage in cases of hydrocephalus are generally accepted treatments (Juvela & Kase 2005).

Different techniques have been used to evacuate ICH. Endoscopic aspiration of the hematoma is considered a feasible technique for evacuating deep hematomas (Auer *et al.* 1989, Marquart *et al.* 2003). However, a Cochrane review of endoscopic evacuation did not show any benefit on outcome in patients with ICH (Prasad & Shrivastava 2000). Another minimally invasive technique is stereotactic clot aspiration enhanced by thrombolytic agents (Tzaan *et al.* 1997, Teernstara *et al.* 2003, Vespa *et al.* 2004). It provides a reduction of clot size (not total removal), but carries a high (22%) risk of rebleed (Teernstara *et al.* 2003). In cases of intraventricular hemorrhage causing moderate or severe hydrocephalus, ventricular drainage is a commonly used. Thrombolysis through a ventricular catheter has also been studied. A pilot study reported a trend toward better outcome in patients treated with thrombolysis (Naff *et al.* 2000). A subsequent controlled trial also showed an increased frequency of clot resolution (Naff *et al.* 2004). At present, hematoma evacuation by craniotomy seems to provide the best outcome in lobar hematomas (Mendelow *et al.* 2005).

The decision to operate is based on local traditions that vary from center to center. International variations in surgical practice are wide. As many as 74% of patients undergo surgery in Lithuania compared to only 2% in Hungary (Gregson & Mendelow 2003). The STICH trial suggests that lobar hematomas located near the cortex should be operated on, but these patients have a relatively good prognosis even when treated conservatively, provided they are alert or somnolent (Juvela 1995b, Hårdemark *et al.* 1999, Castellanos *et al.* 2005). In the future, minimally invasive surgery, possibly with thrombolytic therapy providing

efficient clot evacuation, may be developed to minimize the operation-related damage to brain tissue.

3   Aims of the research

The main aim of this study was to identify the impact of previous diseases, such as cardiac diseases (especially ischemic heart disease and current atrial fibrillation), hypertension, and diabetes, on outcome after primary intracerebral hemorrhage. The seasonal variation in the occurrence of ICH according to hypertensive status was explored because ICHs may occur more frequently during the cold period in subjects who are prone to cold-induced BP elevation. Finally, from a practical point of view, it was important to find out how we should prevent thromboembolic complications during the acute phase of ICH. The following questions were addressed:

1. Does a history of ischemic heart disease and myocardial infarction or current atrial fibrillation independent of the severity of bleeding impair the survival of patients with acute ICH? (I)
2. Does a history of hypertension or high mean arterial blood pressure on admission impair the survival of patients with acute ICH? (II)
3. Does a history of diabetes or high plasma glucose level on admission impair the survival of patients with acute ICH? (II)
4. Has the current treatment practice of using subcutaneous low-dose enoxaparin for the prevention of venous thromboembolism after ICH been effective and safe? (III)
5. Is there seasonal variation in the occurrence of ICH among the population of Northern Ostrobothnia, and does hypertension modify the possible seasonality of ICH? (IV)

4 Patients and methods

4.1 Subjects

The population for Study I (Impact of ischemic heart disease and atrial fibrillation on survival after spontaneous intracerebral hemorrhage) included all patients with ICH admitted to the Department of Neurology, Oulu University Hospital, Finland between January 1993 and January 2004. The hospital is the only one serving acute stroke patients in the region of Northern Ostrobothnia (population 373,868 on 31.12.2003). The Department of Neurology is the only department with a stroke unit in the hospital, and most stroke patients are hence treated there. We excluded the patients not resident 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 admitted to the other departments of the hospital. The patients admitted to the other departments had one of the above-mentioned diseases. Patients (n = 89) who needed immediate surgery were admitted to the Department of Neurosurgery and were excluded from this study. Altogether 453 non-surgical patients were included.

The final analysis for study II (Hypertension and diabetes as predictors for early death after spontaneous intracerebral hemorrhage) included a subgroup of 379 patients from the above-mentioned population. These patients had blood pressure levels and plasma glucose values available, while the 74 patients lacking this information were excluded.

The population for study III (Safety of low-dose subcutaneous enoxaparin for the prevention of venous thromboembolism after primary intracerebral haemorrhage) included all patients with ICH admitted to the Department of Neurology, Oulu University Hospital, Finland, between January 1993 and January 2004 and surviving for at least the first two days after admission. The patients who did not survive for the first two days were excluded because, according to the practice of the hospital, thromboprophylaxis is not started for patients already moribund on admission. Altogether 407 patients survived for at least 48 h after admission and were included.

Study IV (Seasonal variation of intracerebral haemorrhage in subjects with untreated hypertension) was a population-based study, which included all the patients with verified spontaneous ICH during 3 calendar years (January 1993 –

December 1995) in a defined area (Northern Ostrobothnia, Finland, population 356,026 in that study period). The exclusion criteria were the same as in study I, except that all patients admitted to departments other than the Department of Neurology department were also included, as were the surgical cases. Data were also extracted from the forensic autopsy charts of those who had succumbed on the scene. Accordingly, this study includes all the subjects with verified spontaneous ICH (n = 217) who were living in the Northern Ostrobothnia region during the 3-year study period.

4.2   Clinical data

The time of ICH onset was defined as the acute onset of headache or a neurological deficit. For all of the four studies (I–IV), information on previous diseases, blood pressure histories, medication, and health habits were extracted from the hospital records. Subjects were considered to be hypertensive if their blood pressure readings preceding ICH had exceeded 160/90 mmHg at least twice (in accordance with to the WHO/ISH statement, Whithworth 2003), or if they were taking antihypertensive medication. For study IV, patients or their relatives were also interviewed and those who had, unsupervised, terminated their antihypertensive medication were classified as having untreated hypertension.

The patients were recorded as having diabetes mellitus if they were receiving oral hypoglycemic agents or insulin. Previous hemorrhagic (ICH or subarachnoid hemorrhage) and ischemic strokes were recorded, as were cardiac diseases, including myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation. Any cases of gastrointestinal bleeding in the patients' history were also recorded. Recent heavy drinking was defined as weekly ingestion of at least 300 g of ethanol during the month preceding the stroke.

The patient's clinical condition on admission was assessed using the Glasgow Coma Scale (GCS) score (Teasdale & Jennet 1974) and the prognostic score of the Scandinavian Stroke Study Group (SSS-PRG), which includes consciousness, gaze palsy, and limb strength (Scandinavian Stroke Study Group 1985). Patients were followed up at our outpatient clinic or in the rehabilitation ward of our hospital. Outcome was assessed according to the Glasgow Outcome Scale (GOS, Jennet & Bond 1975) on scheduled follow-up visits to the hospital approximately 3 months after the ICH, except for those who showed good recovery at the time of discharge. Those patients were assumed to have maintained this state for up to

3 months, unless they had been readmitted or had deceased. These data were collected from the medical records.

For study IV, the mean monthly temperatures during the study period were obtained from the Finnish Meteorological Institute. For analyses, the year was dichotomized into a warm period (May to October; mean monthly temperatures +1.4 to +14.9 degrees Celsius) and a cold period (November to April; mean monthly temperatures −9.5 to +0.7 degrees Celsius).

4.3 Neuroradiological methods

ICH was verified by head CT scanning of all patients admitted to the hospital, and secondary structural abnormalities were searched for by follow-up brain imaging (CT or MRI) 2–3 months after the bleed. Angiography was performed if aneurysmal bleeding was suspected. A second head CT was performed during the first week after admission in cases showing significant clinical deterioration. All CT scans were examined and the locations and volumes of hematomas measured by an experienced neuroradiologist unaware of the patients' case histories. Hematomas were divided into categories based on their location.

Hematoma volumes were measured on a workstation using the method previously described (Boderick *et al.*1993a), i.e. by encircling the boundaries of each hematoma with the pointer slice by slice and thereby determining its area. The area was then multiplied by slice thickness (5 mm in the posterior fossa and 10 mm supratentorially). The total hematoma volume was obtained by using the formula of an ellipsoid ($4/3\pi$ x dimensions abc). The presence of intraventricular hematoma was also recorded. Enlargement of the hematoma was assessed if a second CT scan was obtained within two weeks after the onset of ICH. For statistical analysis, the relative volume enlargement (percentage) of each hematoma was calculated.

4.4 Laboratory procedures

For study III, the anti-factor Xa levels, which reflect the anticoagulant effect of enoxaparin (Siddiqui & Wagstaff 2005), were measured by taking serial blood samples from 49 randomly chosen patients both before and after starting enoxaparin treatment. Enoxaparin (20 mg) was injected subcutaneously once daily at 8 a.m., and the blood samples were taken 2–3 hours later (at 10–11 a.m.). Anti-factor Xa levels were measured according to the standard hospital methods

and expressed in U/ml. Samples were available from 17 patients treated with enoxaparin and 32 patients who had not received anticoagulants.

4.5   Mortality data

For studies I–IV, the patients' survival during the first 3 months after the onset of ICH was checked, and death certificates were obtained from the Causes of Death Register maintained by Statistics Finland. Autopsy records were also checked. Accordingly, we were able to confirm all the deaths and to ascertain their immediate causes.

For study IV, the fatal cases of ICH occurring in the community during the study period were identified from death records (Statistics Finland), but cases without verification of ICH at autopsy or by brain imaging were excluded.

4.6   Treatment

In study II, all patients received standardized medical treatment according to a structured institutional protocol for acute cerebrovascular diseases. Blood pressure and plasma glucose levels were monitored. Mean arterial blood pressure (MABP) was calculated by adding 1/3 of the pulse pressure value (systolic minus diastolic) to the diastolic pressure reading. Patients with admission hypertension > 180/100 mmHg, i.e. MABP > 127 mmHg, received intravenous antihypertensive drugs (usually labetalol hydrochloride) to reach a target level of MABP < 120 mmHg. Likewise, patients with admission hyperglycemia (plasma glucose > 8 mmol/l or 144 mg/dl) were given short-acting insulin to reach a target level of < 8 mmol/l.

In study III, the decision to start thromboprophylaxis was always based on the duty physicians' assessment and was not influenced by the investigators. During the whole study period, the physicians on duty followed the departmental guideline to start thromboprophylaxis with a low-dose anticoagulant after 24 hours of the onset of stroke for those patients who had a paralyzed lower limb and were not moribund. Neither compression stockings nor pneumatic sequential compression devices were used, because these were not yet available during the study period as they are nowadays.

4.7 Statistical methods

Data in all the studies were analyzed with the SPSS for Windows (release 12.0.1.2003, SPSS Inc.). For univariate statistics, conventional statistical tests were used (Fisher's exact 2-tailed test and Pearson's χ^2 test, and continuous variables by means of the Mann-Whitney U-test, Student's t test, ANOVA, and the Kruskal-Wallis test). Univariate associations of continuous variables were tested by Spearman rank (r_s) correlation coefficients.

In studies I–III, each patient was followed until death or for 3 months after their ICH. The Cox proportional-hazards model with a forward stepwise regression procedure was used to determine the significance of several variables in predicting the hazard ratio (HR with 95% CI) for death. Cumulative survival rates were estimated by the Kaplan-Meier product-limit method, and the curves of the different groups were compared by the log-rank test. The assumption of proportionality was checked. The test for significance was based on changes in log (partial) likelihood. A 2-tailed probability value of < 0.05 was considered statistically significant. In Study IV, multivariate unconditional logistic regression was used to test the associations with the occurrence of ICH during the cold period.

5 Results

5.1 Predictors for outcome

5.1.1 Ischemic heart disease and atrial fibrillation (Study I)

During the study period of 11 years, 453 patients with verified ICH were admitted to the stroke unit of the Department of Neurology. One hundred and thirty-seven patients had previous ischemic heart disease and 54 had atrial fibrillation on admission.

Three hundred and twenty-five (72%) of the 453 patients survived for three months, whereas only 79/137 (58%) patients with ischemic heart disease and 21/54 (39%) patients with atrial fibrillation on admission survived for 3 months. The differences in cumulative survival rates between the groups were significant. ($p < 0.001$ for the presence of ischemic heart disease and atrial fibrillation compared to absence, I; Fig 1&2).

Among the patients who died within 3 months, hypertension, previous ischemic stroke, diabetes, older age, and use of warfarin and aspirin were significantly more common (Table 4). Patients who had large hematomas, intraventricular or infratentorial hematomas, and low GCS scores on admission were significantly more common among the patients who died within three months (Table 5). The patients who showed hematoma enlargement also had poor outcome.

Table 4. Baseline characteristics according to outcome in 453 patients with primary ICH.

Characteristics	Died within 3 months (n = 128)	Survived for 3 moths (n = 325)	Total (n = 453)
Men, n (%)	71 (55)	170 (52)	241 (53)
Mean age (yrs ± SD)	75 ± 10*	67 ± 12	69 ± 12
Previous diseases, n (%)			
hypertension	84 (66)*	150 (46)	234 (52)
untreated hypertension	4 (3)*	57 (18)	61 (13)
ischemic heart disease†	58 (45)*	79 (24)	137 (30)
myocardial infarction	10 (8)	23 (7)	33 (7)
atrial fibrillation	33 (26)*	21 (6)	54 (12)
ischemic stroke	44 (34)*	64 (20)	108 (24)
diabetes mellitus	41 (32)*	40 (12)	81 (18)
cancer	14 (11)	32 (10)	46 (10)
hemorrhagic stroke	15 (12)	23 (7)	38 (8)
gastrointestinal bleeding	5 (4)	14 (4)	19 (4)
Current heavy drinker (%)	7 (5)	33 (10)	40 (9)
Current smoker (%)	9 (7)	30 (9)	39 (9)
Current medication (%)			
neither aspirin nor warfarin	46 (36)*	215 (66)	261 (58)
aspirin	49 (38)**	81 (25)	130 (29)
varfarin	33 (26)*	29 (9)	62 (14)

*p < 0.001 and ** p < 0.05 between patients who did or did not survive for 3 months after ICH

† Includes coronary artery disease and myocardial infarction

Table 5. Clinical characteristics according to outcome in 453 patients with primary ICH.

Characteristics	Died within 3 months (n = 128)	Survived for 3 moths (n = 325)	Total (n = 453)
Median volume of ICH (ml;25th and 75th percentiles)	30 (10, 70)*	11 (5, 22)	12 (6, 30)
Hematoma volume > 30 ml, n (%)	66 (52)*	53* (16)*	119 (26)
Presence of IVH, n (%)	87 (68)*	79 (24)	166 (37)
Location of hematoma, n (%)			
subcortex	17 (13)*	94 (29)	111 (25)
basal ganglia and combined‡	63 (49)	135 (42)	198 (44)
thalamus	19 (15)	51 (16)	70 (15)
cerebellum and pons	29 (23)**	45 (14)	74 (16)
Hematoma enlargement 33%, n (%)	12/39 (31)	15/249 (6)	27/288 (9)
Median GCS score on admission; (25th and 75th percentiles)	10 (5, 14)*	15 (14, 15)	14 (12, 15)

*p < 0.001 and ** p < 0.05 between patients who did or did not survive for 3 months after ICH

† Includes coronary artery disease and myocardial infarction.

‡ Extension of putaminal hematoma into thalamus and/or subcortical white matter.

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Multivariate analysis identified the following predictors for death within the first 2 days: use of warfarin (HR 4.08, 95% Cl 1.61–10.31), hematoma size (HR 1.11 per 10 ml, 95% Cl 1.06–1.18), infratentorial location of hematoma (HR 2.23, 95% Cl 1.11–4.47), and low GCS score (HR 0.82 per unit, 95% Cl 0.76–0.90).

Table 6 represents the significant independent predictors for death within the first 3 months. They were hematoma size, infratentorial location of hematoma, intraventricular bleed, age, low GCS score, atrial fibrillation on admission, and history of ischemic heart disease.

Table 6. Predictors for death during the first 3 months after ICH.

Variable	Univariate RR (95% Cl)	Multivariate RR (95% Cl)
Volume of ICH (per 10 ml)	1.20 (1.16–1.24)†	1.11 (1.07–1.16)†
Precence of IVH	4.85 (3.34–7.04)†	2.62 (1.71–4.02)†
Age (per year)	1.06 (1.04–1.08)†	1.04 (1.02–1.06)†
GCS score on admission (per unit)	0.77 (0.74–0.80)†	0.82 (0.79–0.87)†
Infatentorial location	2.13 (1.46–3.13)†	1.93 (1.26–2.97)†
Ischemic heart disease	2.15 (1.52–3.05)†	1.67 (1.12–2.48)§
Atrial fibrillation on admission	3.39 (2.27–5.05)†	1.79 (1.12–2.86)§
Diabetes	2.59 (1.79–3.76)†	1.44 (0.96–2.18)
Ischemic stroke	1.87 (1.30–2.69)†	1.35 (0.90–2.01)
Aspirin medication	2.42 (1.62–3.63)†	1.16 (0.73–1.85)
Warfarin medication	4.06 (2.60–6.36)†	1.58 (0.90–2.75)

In multivariate analysis the relative risks have been adjusted for sex and the variables listed in the table.

The relative risks of categorical variables represent comparisons of patients with no risk factor.

RR = relative risk, Cl = confidence level. †$p < 0.01$, § < 0.02.

Many patients with ischemic heart disease were on aspirin or, if they had atrial fibrillation, warfarin medication at the time of ICH onset. Thirty-one of those with ischemic heart disease were on warfarin, 66 were on aspirin, and 40 were using neither of these drugs on admission. Of those with ischemic heart disease and who were on warfarin, 18/31 (58%) died, whereas of those on aspirin or on neither of these drugs, 27/66 (41%) and 13/40 (33%) died, respectively. Accordingly, those who had either warfarin or aspirin on admission showed a higher mortality rate than those who had neither of these two medications (p = 0.034). Thirty of those with atrial fibrillation on admission were on warfarin and 13 on aspirin medication. Of those on warfarin, 18/30 (60%) died, whereas of those on aspirin, 11/13 (85%) died within 3 months. The latter figure was the highest mortality rate in any subgroup studied. These patients had significantly

larger hematomas already on admission compared to nonusers of aspirin and warfarin (Mann-Whitney U-test, p = 0.011).

Because both ischemic heart disease and atrial fibrillation on admission were frequently associated with the use of aspirin and warfarin, we also tested for interactions. We did not observe any significant interactions between the history of ischemic heart disease and the use of either aspirin or warfarin. Nor did we observe interactions between atrial fibrillation on admission and either aspirin or warfarin use (p values from 0.36 to 0.43). After entry of the interaction terms into the model, the significant predictors remained unchanged.

The primary bleed was the main cause of death, accounting for 97/128 deaths (76%). However, only 3 patients had their cause of death verified by autopsy. Cardiac complications were more frequent (16 % versus 9 %) in the patients with heart disease (ischemic heart disease or atrial fibrillation on admission).

5.1.2 High admission blood pressure and glucose (Study II)

Among the 453 patients with verified ICH, there were 379 patients who had admission blood glucose and blood pressure levels available. This subgroup was analyzed for the effect of these factors on outcome.

Admission glucose levels were higher for those who died within 2 days (mean ± SD, 11.1 ± 4.1 vs. 7.6 ± 3.0 mmol/l, p < 0.001) and 3 months (9.5 ± 3.8 vs. 7.4 ± 2.9, p < 0.001) than for those who survived. Likewise, admission MABPs were higher for those who died within 2 days (mean ± SD, 137 ± 22 vs. 125 ± 21 mmHg, p < 0.001) and 3 months (132 ± 21 vs. 124 ± 21, p < 0.01) than for those who survived. There was a significant correlation between admission MABP and plasma glucose values (r_s = 0.20, p < 0.001) even after the exclusion of diabetics (r_s = 0.17, p < 0.01).

The patients who belonged to the highest (75th) quartile of admission MABP (MABP > 139 mmHg, n = 104) and plasma glucose (> 8.8 mmol/l, n = 93) turned out to have significantly higher 3-month mortality rates than the patients with lower MABP and glucose on admission (p < 0.01). Many patients, i.e. 21/104 (20.2%) and 25/93 (26.9%) of those belonging to the highest quartile of admission MABP and plasma glucose, respectively, died within 2 days. They also had larger hematomas than did the others (p < 0.001). Finally, a subgroup analysis of the patients who belonged to the highest (75th) quartile of admission MABP and plasma glucose and who survived for 2 days was performed. Those with high admission plasma glucose showed significantly (p < 0.01) shorter survival within

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3 months (II; Fig 1.) than the others, while those with high admission MABP did not show any significant difference.

Multivariate analysis was done to identify independent predictors for death during the first 2 days and within the 3 months after ICH. Forty (11%) patients died within 2 days and 106 (28%) within 3 months. The significant independent predictors for death within 2 days were hematoma size (RR 1.12, 95% Cl 1.03–1.22), low GCS score (RR 0.84, 95% Cl 0.77–0.92), and preceding use of warfarin (RR 3.92, 95% Cl 1.79–8.58). The predictors for death within 3 months are shown in table 7. In addition to the predictors of death within 2 days, they included cardiac disease, IVH, high age, and high MABP on admission. High admission plasma glucose was not a significant predictor for death within either 2 days or 3 months.

Table 7. Predictors for death during the first 3 months after ICH.

Variable	Univariate RR (95% CI)	Multivariate RR (95% CI)
Admission glucose level (mmol/l)	1.13 (1.08–1.17)‡	1.04 (0.99–1.10)
Mean RR (per mmHg)	1.015 (1.01–1.02)‡	1.01 (1.00–1.02)*
Size of ICH (per 10ml)	1.24 (1.19–1.23)‡	1.09 (1.04–1.15)†
Presence of IVH	4.95 (3.26–7.50)‡	2.28 (1.44–3.63)‡
Age (per year)	1.06 (1.04–1.08)‡	1.04 (1.02–1.07)‡
GCS on admission	0.77 (0.74–0.81)‡	0.83 (0.79–0.87)‡
Basal ganglia and combined	0.40 (0.21–0.78)†	1.61 (0.87–2.97)
Thalamus	0.97 (0.58–1.60)	1.61 (0.77–3.38)
Cerebellum and pons	0.76 (0.40–1.46)	1.94 (0.96–3.94)
Cardiac disease	3.39 (2.28–5.05)‡	2.32 (1.49–3.62)‡
Use of warfarin	3.71 (2.24–6.15)‡	1.81 (1.11–2.96)*

In multivariate analysis the relative risks were adjusted for sex and the variables listed in the table. The relative risks of the categorical variables represent comparisons of patients with no risk factor.

RR = relative risk, CI = confidence level. *p < 0.05, †p < 0.01, ‡p < 0.001

Medication was given to 184 patients to lower the high BP noted on admission. This treatment was started immediately after admission. The treated patients had significantly (p < 0.001) higher MABP compared to those who remained untreated (mean ± SD, 135 ± 19 vs. 118 ± 19). However, no significant difference in either the 2-day or the 3-month survival rates emerged between the treated and untreated patients. Seventy-three non-diabetic patients had admission hyperglycemia (blood glucose > 8 mmol/l). They showed significantly shorter survival (p < 0.001) despite treatment with short-acting insulin than did those with lower admission plasma glucose levels. After exclusion of both diabetics and

those who died within the first 2 days, patients with admission hyperglycemia still showed a higher 3-month death rate (p < 0.01).

5.1.3 Hypertension and diabetes (Study II)

Among the 379 patients included in this study, 197 patients had treated hypertension, 76 had untreated hypertension, and 68 had diabetes.

Two hundred and seventy-three patients survived for 3 months (72%). The patients who died within 3 months had significantly more frequently diabetes, cardiac disease, high age, and warfarin or aspirin medication. One hundred and twenty-seven of the 197 (65%) patients with treated hypertension and 72/76 (95%) with untreated hypertension survived for 3 months, and there was a significant (p < 0.001) association between hypertensive status and case fatality (Table 8). Of the patients with diabetes, 35/68 (51%) survived for 3 months. Patients who had large hematomas, intraventricular extension of the hematoma, and low GCS scores were significantly overrepresented among the patients who died within 3 months (Table 9).

Multivariate analysis yielded the following predictors for death in 3 months were hematoma size, low GCS score , use of warfarin, cardiac disease, high age, and diabetes (RR 1.61, 95% Cl 1.03–2.53, p < 0.05). Hypertension was not an independent predictor for death in either 2 days or 3 months.

Table 8. Baseline characteristics according to outcome in 379 patients with primary ICH.

Characteristics	Died within 3 months (n = 106)	Survived for 3 moths (n = 273)	Total (n = 379)
Men, n (%)	61 (58)	148 (54)	209 (55)
Mean age, yrs ± SD	75 ± 9.7*	67 ± 12.0	69 ± 11.9
Mean BMI (kg/m^2) ± SD	26.6 ± 5.0	27.2 ± 5.2	27.1 ±5.2
Previous diseases, n (%)			
diabetes	33 (31)*	35 (13)	68 (18)
hypertension			
no	32 (30)	74 (27)	106 (28)
treated	70 (66)*	127 (47)	197 (52
untreated	4 (4)*	72 (26)	76 (20)
ischemic stroke	28 (26)	49 (18)	77 (20)
cancer	14 (13)	26 (10)	40 (11)
cardiac disease†	68 (64)*	79 (29)	145 (38)
gastrointestinal bleeding	4 (4)	8 (3)	12 (3)
Current heavy drinker (%)	7/101 (7)	28/261 (11)	35/362 (10)
Current smoker (%)	9/102 (9)	25/256 (10)	34/358 (9)
Current medication (%)			
neither aspirin nor warfarin	41 (39)*	183 (67)	224 (59)
aspirin	41 (39)*	67 (25)	108 (28)
varfarin	24 (23)*	23 (8)	47 (12)

* $p < 0.001$. † includes previous myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation. BMI = Body mass

Table 9. Clinical characteristics according to outcome in 379 patients with primary ICH.

Characteristics	Died within 3 months (n = 106)	Survived for 3 moths (n = 273)	Total (n = 379)
Median GCS score on admission (25th and 75th percentiles)	10 (5, 14)*	15 (14, 15)	14 (12, 15)
Median volume of hematoma, ml (25th and 75th percentiles)	30 (10, 66)*	11 (5, 21)	12 (6, 30)
Admission plasma glucose level > 8.0 (%)	59 (56)*	69 (25)	128 (34)
Mean admission plasma glucose level ± SD	9.5 ± 3.8*	7.4 ± 2.9	8.0 ± 3.3
Median admission plasma glucose level (25th and 75th quartiles)	8.4 (6.5, 11.1)*	6.6 (5.8, 8.2)	6.9 (6.0, 8.8)
Admission blood pressure > 180/100 (%)	62 (58)†	128 (47)	190 (50)
Mean admission MAPB ± SD	131 ± 21*	124 ± 21	126 ± 21
Median admission MABP (25th and 75th quartiles)	132 (118, 47)**	124 (110, 138)	127 (110, 140)
Presence of IVH, n (%)	74 (70)*	70 (26)	144 (38)
Location of hematoma, n (%)†			
subcortex	15 (14)	81 (30)	96 (25)
basal ganglia and combined‡	54 (51)	111 (41)	165 (44)
thalamus	16 (16)	41 (15)	57 (15)
cerebellum and pons	21 (20)	40 (15)	61 (16)

* $p < 0.001$, ** $p < 0.01$, † $p < 0.05$. ‡ Extension of putaminal hematoma into thalamus and/or subcortical white matter. MABP = mean arterial blood pressure

5.2 Season as a risk factor for ICH (Study IV)

In this population-based cohort from Northern Ostrobothnia, 217 patients with verified primary intracerebral hemorrhage during a period of 3 years were found. Five of them had succumbed on the scene and were identified from the death records. One hundred and seven patients had onset of ICH during the warm period (May to October) and 110 during the cold period (November to April).

Patients with untreated hypertension had onset of ICH more often during the cold than during the warm period of the year (IV: Table 1, $p = 0.024$). Deep hematomas (thalamic and basal ganglia) were more frequent during the cold than the warm period (IV: Table 2, $p = 0.026$). The patients with untreated hypertension were significantly younger than those with treated hypertension (mean age 62.3 vs 67.2 years ($p = 0.006$) and were more often heavy drinkers of alcohol (32.1% vs 15.4%, $p = 0.011$).

Forward stepwise logistic regression analysis yielded untreated hypertension as the only significant risk factor predicting ICH during the cold period, as shown in table 10.

Table 10. Univariate and multivariate ORs for ICH during the cold period of the year.

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)
Hypertension		
Normotension	1.0	1.0
Treated hypertension	1.23 (0.71–2.30)	1.23 (0.63–2.40)
Untreated hypertension	2.66 (1.18–6.01)*	3.60 (1.27–10.21)†
Aspirin medication	0.92 (0.48–1.77)	0.98 (0.45–2.12)
Warfarin medication	0.74 (0.32–1.68)	1.02 (0.40–2.62)
Diabetes	0.63 (0.28–1.43)	0.67 (0.25–1.81)
Current smoking	0.70 (0.29–1.70)	0.62 (0.24–1.62)
Heavy drinking	0.86 (0.39–1.89)	0.55 (0.21–1.46)

Multivariate ORs were adjusted for sex, age, and the variables listed in the table. *p = 0.019, †p = 0.016

5.3   Venous thromboembolic complications (Study III)

During the 11-year study period, physicians on duty followed the departmental guideline to start thromboprophylaxis with a low-dose anticoagulant after 24 hours of the onset of stroke for those patients who had a paralyzed lower limb and were not moribund. The use of low-dose enoxaparin for thromboprophylaxis increased throughout the study period (test for trend, $p < 0.001$).

Of the 453 patients admitted to the Department of Neurology during this period, 407 survived for at least two days. Only 6 of the 46 patients who died within the first two days received subcutaneous enoxaparin. All the patients who died within the first two days were excluded from the final analysis. Of the 407 patients who survived for at least two days, 202 were given enoxaparin once daily at a dose of 20 mg and 24 at a dose of 40 mg, while 6 patients were given some other type of LMWH. Anticoagulants were started within 48 h of admission for 61% of these patients and within 120 h for the others who were treated.

The baseline characteristics of the patients are shown in Table 11. The patients in the treatment group were significantly older ($p < 0.05$), less frequently men ($p < 0.05$), and in worse clinical condition on admission according to SSS-PRG (Scandinavian Stroke Study Group 1985) scores (mean 14 ± 5.5 vs. 17.3 ± 6.5, $p < 0.01$). On the other hand, they had less frequently cancer ($p < 0.025$) and were less often heavy drinkers ($p < 0.001$) of alcohol. The clinical

charachteristics of the patients are shown in Table 12. Hematoma volumes did not differ between the treated and untreated groups, but the patients in the treatment group had more often intraventricular ($p < 0.01$) and thalamic ($p < 0.016$) hematomas.

Table 11. Baseline characteristics of 407 subjects with primary ICH.

Characteristics	ICH with thromboprophylaxis (n = 232)	ICH with thromboprophylaxis (n = 175)	Total (n = 407)
Men, n (%)	114 (49)*	102 (58)	216 (53)
Mean age, yrs ± SD	70.0 ± 11.7*	66.2 ± 12.7	68.4 ± 12.0
Mean BMI (kg/m^2) ± SD	27.5 ± 5.1	26.9 ± 5.2	27.1 ± 5.2
Mean GCS ± SD	13.2 ± 2.6	13.2 ± 3.3	13.2 ± 2.9
Mean SSS-PRG ± SD	14.0 ± 5.5**	17.3 ± 6.5	15.4 ± 6.1
Previous diseases, n (%)			
hypertension	125 (54)	80 (46)	205 (50)
hypertension untreated	28 (12)	32 (22)	60 (15
cardiac disease	87 (38)	62 (35)	149 (37)
ischemic stroke	55 (24)	37 (21)	92 (23)
diabetes	42 (18)	22 (13)	64 (16)
cancer	17 (7)*	22 (13)	39 (10)
hemorrhagic stroke	16 (7)	14 (8)	30 (7)
gastrointestinal bleeding	9 (4)	9 (5)	18 (4)
Current smoker (%)	17 (7)	18 (10)	35 (9)
Current heavy drinker (%)	12 (5)**	26 (15)	38 (9)
Use of aspirin	73 (31)	44 (25)	117 (29)
Use of warfarin	29 (13)	15 (9)	44 (11)

* $p < 0.05$, ** $p < 0.01$

Table 12. Clinical characteristics of 407 patients with primary ICH.

Characteristics	ICH with thromboprophylaxis (n = 232)	ICH without thromboprophylaxis (n = 175)	Total (n = 407)
Median volume of ICH, ml (25th and 75th percentiles)	12 (6, 25)	9.5 (5, 22.5)	11 (5, 24)
Presence of IVH, n (%)	88 (38)*	41 (23)	129 (32)
Location of hematoma, n (%)†			
subcortex	57 (25)	50 (29)	107 (26)
putamen	27 (12)	34 (19)	61 (4)
basal ganglia and combined‡	68 (29)	40 (23)	108 (27)
thalamus	50 (22)**	17 (10)	67 (16)
cerebellum and pons	30 (13)	34 (19)	64 (16)
Enlargement of the hematoma by ≥ 33%, n (%)	15/171 (9)	8/113 (7)	23/284 (8)
Thromboembolic complication, n (%)	6 (3)	4 (2)	10 (2)
Pulmonary embolism, n (%)	2 (1)	2 (1)	4 (1)

* $p < 0.01$, ** $p < 0.05$. ‡Extension of putaminal hematoma into thalamus and/or subcortical white matter.

The outcomes (Glasgow Outcome scale, GOS, Jennet & Bond 1975) of the patients treated or untreated with thromboprophylaxis are presented in Table 13. 19.4% of the patients in the treatment group and 21.1% of the patients not treated with enoxaparin died within three months, and the difference was not statistically significant. The outcome of the survivors was worse in the treatment group, and they more often remained severely disabled ($p = 0.001$). After adjustment for age and SSS-PGR, multivariate logistic regression analysis showed that treatment did not increase the risk of survival with severe disability either among all the patients (OR 1.06, 95%Cl 0.64–1.75) or among the survivors (OR 1.38, 0.75–2.55).

Table 13. Outcome of 407 patients with primary ICH according to treatment with thromboprophylaxis.

Glasgow Outcome Scale at 3 months, n (%)	ICH with thromboprophylaxis (n = 232)	ICH without thromboprophylaxis (n = 175)	Total (n = 407)
Good recovery	48 (21)	76 (43) *	124 (30)
Moderate disability	58 (25)	36 (21)	94 (23)
Severe disability or vegetative	81 (35)	26 (15) *	107 (26
Dead	45 (19)	37 (21)	82 (20)

*$p < 0.01$

Symptomatic venous thromboembolic complications (VTC) during the acute phase of treatment were observed in 6 patients treated with enoxaparin and in 4 untreated patients (Table 12). In two patients initially treated with enoxaparin VTCs occurred after discontinuation of the treatment. Three patients died of pulmonary embolism (PE); two had not received thromboprophylaxis, and the third one had PE 13 days after discontinuation of the treatment.

6 Discussion

6.1 Main findings

Ischemic heart disease and atrial fibrillation, significantly and independently of the severity of bleeding, patients' age, and other potential confounding factors, predict death within 1 month and 3 months after ICH. These are novel findings, and neither of these factors has been listed as predictors for early death in recent reviews (Qureshi *et al.* 2001, Mayer &Rincon 2005). Diabetes was also found to be a predictor for early death, which confirms the finding of two previous studies (Arboix *et al.* 2000, Passero *et al.* 2003). Hypertension, which is the major risk factor for ICH, was not found to be a predictor for early death. This was in line with some earlier studies (Juvela 1995a, Nilsson *et al.* 2002, Saloheimo *et al.* 2006). However, high MABP on admission was an independent risk factor for early death whereas admission hyperglycemia was not. The latter clearly correlated with several factors reflecting the severity of the bleeding. The finding that patients with untreated hypertension had onset of ICH more often during the cold than during the warm period of the year confirms a similar finding from Japan (Inagawa 2003). Finally, use of low-dose enoxaparin for prevention of VTC appeared to be relatively harmless, which is a novel finding.

6.1.1 Impact on survival of ischemic heart disease, heart failure, and atrial fibrillation on admission

The untoward effects of ischemic heart disease and atrial fibrillation on survival can be observed two days after onset of ICH. The predictors for death within two days were hematoma size, low GCS score on admission, and warfarin medication. After the first two days from onset, preceding warfarin use was a minor predictor for death, mainly because the majority of patients on warfarin who did not survive died within the first two days after onset of ICH.

Both warfarin and aspirin are widely used in the secondary prevention of cardiovascular diseases. In Finland, the age-adjusted prevalence of warfarin users is 0.65% (Viitaniemi *et al.* 1999). This is a relatively high prevalence, and nearly half of the patients take warfarin for atrial fibrillation (Eskola *et al.* 1996). Being on warfarin medication is a known predictor for early death after ICH because of poor coagulation and consequent rapid enlargement of the hematoma (Kase *et al.*

1985). Aspirin use has also been reported to independently predict increased mortality (Roguer *et al.* 2005, Saloheimo *et al.* 2006, Lacut *et al.* 2007). Aspirin use may have an association with rapid hematoma enlargement (Toyoda *et al.* 2005, Sorimachi *et al.* 2007), but this finding remains to be confirmed. In this study, the highest mortality rate (85% in 3 months) was seen among those who had atrial fibrillation on admission and used aspirin. These patients also had very large hematomas already on admission.

Irrespective of medications, ischemic heart disease and atrial fibrillation independently predicted early death after ICH. The reason for this remains unknown. Warfarin and aspirin treatment are discontinued after ICH, which may predispose to cardiovascular complications. Cardiac complications were observed more often in patients with pre-existing cardiac disease (7% vs. 2%), but the difference was not significant. Some deaths may have occurred due to pulmonary embolism (PE), but we were not able to confirm this because only a few subjects were autopsied. However, hospitalized patients with heart failure have an increased risk for PE (Beemath *et al.* 2006), and sudden death is a frequent manifestation of PE (Kelly *et al.* 2001). Primary bleed was reported as an immediate cause of death in 76% of the patients, but some of these deaths may actually have been caused by PE.

6.1.2 Untreated hypertension as a risk factor and impact of hypertension and admission blood pressure on survival

Impact of hypertension on survival

In this study, patients were considered to have hypertension if they had antihypertensive medication or previously measured high BPs. Patients with untreated hypertension had much better outcome. Only 5% of the patients with untreated hypertension died within 3 months. They were younger and had no comorbidities, and ICH was in many cases the first manifestation of their disease. The outcome of ICH may be different in patients with treated and untreated hypertension, and inclusion of patients with untreated hypertension in the group of patients with hypertension may therefore dilute the effect of treated hypertension. Cardiac complications of hypertension may be a powerful factor which impairs the outcome of ICH patients who are on medication for

hypertension and have related complications such as atrial fibrillation and cardiac insufficiency.

Seasonality as a risk factor for ICH

In Northern Ostrobothnia, temperature changes are relatively wide. During the study period the mean temperature (average from 3 years) was highest in July (+14.9 °C) and lowest in February (−9.5 °C). The population is relatively homogenous and access to the public health care is equal in the area. The wide temperature changes enabled us to study the impact of the cold period on the incidence of ICH.

Patients with untreated hypertension had a higher incidence of ICH during the cold period than did patients who had treated hypertension or were normotensive. This result can be explained in many ways. The most powerful risk factor for ICH is hypertension (Brott *et al.* 1986). Cold exposure increases blood pressure by activating the sympathetic nervous system (Brennan *et al.* 1982, Keatinge *et al.* 1984). If the baseline blood pressure is lowered by antihypertensive treatment, the blood pressure peaks induced by cold exposure remain lower compared to those in patients with untreated hypertension (Komulainen 2007). This may explain why the incidence of ICH was higher in the cold period only in patients with untreated hypertension. Earlier, some observations by Minami *et al.* 1996 have suggested that seasonal variation in BP may be greater in patients with untreated hypertension. Our observation of the significantly higher frequency of deep hematomas during the cold period supports this idea. It is known that deep hematomas are mostly related to hypertension (Caplan 1992, Jackson *et al.* 2006). Thus far, only one previous study has reported an increased incidence of ICH in the winter season, particularly in subjects with untreated hypertension (Inagawa 2003).

Blood pressure

In patients with ICH, the mass effect caused by the hematoma elevates intracranial pressure (ICP) and reduces cerebral perfusion pressure (CPP). Autoregulation of cerebral blood flow (CBF) protects against an expeditious fall of blood pressure. In the case of ICH, autoregulation of CBF aims to preserve CPP by elevating BP. This systemic hypertension caused by increased ICP is called the Cushing reflex (Cushing 1903). Reduction of the high admission

MABP by drugs could, theoretically, promote hypoperfusion. However, high MABP recorded during the first 48 hours after the onset of ICH has been shown to predict poor outcome (Brott *et al.* 1997, Schwarz *et al.* 2000, Leira *et al.* 2004, Willmot *et al.* 2004). In two previous studies on selected patient populations with history of hypertension and supratentorial hemorrhage, high MABP on admission correlated with poor outcome (Dandapani *et al.* 1995, Fogelholm *et al.* 1997). High admission MABP may also predict hematoma enlargement (Broderick *et al.* 1990, Kazui *et al.* 1997, Ohwaki *et al.* 2004).

In our cohort study, high admission MABP predicted early death, but was not associated with hematoma volume. Some patients who were in a very poor clinical condition already on admission had low MABP despite their large hematoma. This agrees with the fact that, when ICP is very high, the vasomotor center fails and BP declines. In this situation, the rapid decline of BP is predictive of ensuing death. The fact that we had also patients who were in a moribund state with low initial BP explains why there was no association between hematoma volume and high MABP on admission.

It has been suggested that effective lowering of high BP on admission may improve outcome and reduce hematoma enlargement (Dandapani *et al.* 1995). This may not be true for all patients. Patients who already have a large hematoma on admission and therefore high ICP may not benefit from treatment. In fact, there is a study to show that a rapid decline of BP within the first 24 hours after the onset of ICH predicts poor outcome and early death (Qureshi *et al.* 1999a). In another study, patients with aggressive treatment of hypertension were reported to have a low rate of neurological deterioration and hematoma expansion if they survived (Qureshi *et al.* 2005), but their 1-month death rate was also high, suggesting that there are patients who will not benefit from antihypertensive treatment. We found no significant difference in mortality between those who did or did not receive medical treatment for high admission BP. Randomized controlled studies are needed to prove the benefit of aggressive treatment of admission hypertension.

6.1.3 Impact of diabetes and admission plasma glucose level on survival

Two potential risk factors that could influence the short-term outcome after ICH are diabetes and blood high glucose level on admission. The latter factor can be controlled by efficient treatment, which could improve the outcome. In our study,

high admission plasma glucose level associated with early death. Hyperglycemia correlated positively with hematoma volume particularly in non-diabetic patients. This type of association suggests that a high admission plasma glucose level is due to a stress reaction caused by severe bleeding. The acute stress reaction caused by ICH can activate the sympathetic nervous system and cause hyperglycemia. This has already been shown in patients with subarachnoid hemorrhage (Naredi *et al.* 2000). Stress-induced hyperglycemia has also been shown to predict poor outcome after ischemic stroke and subarachnoid hemorrhage (Capes *et al.* 2001, Juvela *et al.* 2005, Frontera *et al.* 2006). However, as regards patients with ICH, a meta-analysis of 4 studies did not find hyperglycemia to associate with early death after ICH (Capes *et al.* 2001). The present findings agree with the results of this meta-analysis. On the other hand, two recent studies found an association between hyperglycemia and early death in diabetic and non-diabetic patients with ICH (Passero *et al.* 2003, Fogelholm *et al.* 2005). Finally, a recent prospective observational follow-up study concluded that very early insulin therapy apparently does not improve outcome (Godoy *et al.* 2008). The insulin treatment protocol used in that study reduced mortality only for the first 12 hours but not thereafter.

Diabetes was found to be an independent predictor for death within 3 months after ICH. Patients with diabetes had a tendency to larger hematomas. Pneumonia was a common cause of immediate death after the primary bleed. The increased risk of diabetics for early death could be partly explained by exposure to cardiac and infectious complications, but we were not able to confirm this because of the low autopsy rate.

6.1.4 Low-dose enoxaparin for prevention of venous thromboembolism

Patients with ICH run a high risk for venous thromboembolic complications (VTCs) because of their prolonged immobility and paresis of the lower extremities. Deep venous thrombosis and pulmonary embolism are common autopsy findings in patients who died in hospital (Sandler & Martin 1989, Linblad *et al.* 1991). The prevention of VTCs with LMWHs or unfractioned heparin (UFH) in patients with ICH is recommended to be started at the earliest 24 hours after the onset of ICH according to the European guidelines and 72–92 hours after the onset according to the American guidelines (Steiner *et al.* 2006b, Broderick *et al.* 2007). Despite these recommendations, the safety and efficacy of such

prophylaxis has not been assessed and remains controversial. A potential risk of the treatment is neurological deterioration due to enlargement of the hematoma.

During the study period (1993–2004), LMWHs (mainly enoxaparin 20 mg daily) were used for the prevention of VTCs in patients with acute ICH having a paralyzed lower limb. Compression stockings and pneumatic sequential compression devices were not used because they were not available. The practice was not based on any evidence from controlled trials. Nowadays, both stockings and pneumatic sequential compression devices together with enoxaparin are used for this purpose, and a controlled trial to prove the efficacy and safety of this management is ongoing.

The present study was a retrospective analysis of the previous practice. The patients were not randomized for any treatment. Treatment was given if the physician on duty decided that the patient was in need for thromboprophylaxis and LMWH was not contraindicated.

The patients who received treatment were significantly older, had more often intraventricular extension of the hematoma, and were in worse clinical condition on admission according to SSS-PRG (Scandinavian Stroke Study Group 1985). Despite their worse clinical condition on admission, the patients in the treatment group had a similar death rate compared to those without thromboprophylaxis (19.4% vs. 21.1%). It appeared, however, that the functional status of the survivors was subsequently worse in the treatment group. According to multivariate analysis, the treatment did not independently predict worse outcome. Intraventricular extension of hemorrhage, which correlates with poor outcome (Juvela 1995a), was recorded more often in those who received treatment. Therefore, it seems that thromboprophylaxis did not save the lives of some patients at the cost of an increased number of disabled patients.

The dose of enoxaparin 20 mg/day may have been too low to be efficient. The half-life of enoxaparin is 4.5 hours (Siddiqui & Wagstaff 2005). We observed a significant level of anti-factor Xa activity within 2–3 hours after enoxaparin administration in patients given a single dose of 20 mg, but sufficient levels may not have lasted for 24 hours because of the short half-life. Previous studies in patients with other types of stroke have suggested that LMWH should be started with a higher dose of enoxaparin (40 mg daily or 20 mg twice daily) because a higher dose may prevent VTCs more effectively. A relatively large study comparing placebo, enoxaparin 20 mg daily, and enoxaparin 40 mg daily in acutely ill non-surgical patients found no decrease in radiologically confirmed

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VTCs in patients given 20 mg daily compared with placebo, but there was a significant decrease if enoxaparin 40 mg daily was used (Samama *et al.* 2008) .

Our study is the first to report on the safety of low-dose enoxaparin for the prevention of VTC in patients with ICH. The safety and efficacy of a higher dose of enoxaparin should be confirmed in controlled randomized trials.

6.2 Strengths and limitations of the present study

The strengths of this investigation are the strict inclusion criteria and the large and homogenous patient population. In the stroke unit, cardiac and other complications are monitored carefully. All CT scans were reanalyzed by an experienced neuroradiologist who was blind to the case histories.

In studies I–III, some selection bias is possible since the patients who underwent surgery or died on the scene were excluded. The effect of cardiac diseases on the death rate seemed to manifest mainly after the onset of ICH, and those who died on the scene may therefore not influence this finding. In study II, the patients who lacked admission plasma glucose level and blood pressure values were excluded. This lowered the 3-month death rate from 28.4% to 28.0%, which seems to be an insignificant lowering. If surgical patients were included, the overall 3-months mortality rate would rise from 28.4% to 30.0%, which also seems insignificant. The majority of surgical patients needed intensive care after surgery. ICP monitoring, use of mannitol, infections, and other factors make those treated at the intensive care unit less suitable to be analyzed together with the other patients. Moreover, the impact of surgery on survival is not clear (Juvela *et al.* 1989b, Mendelow *et al.* 2005). Therefore, by excluding surgical cases, the natural outcome of conservatively treated patients with ICH could be better assessed.

The limitation of studies I–III is the low autopsy rate. According to the death certificates issued by clinicians, the majority of deaths were caused by the primary bleeding. Some of the deaths, however, could have been due to pulmonary embolism or cardiac complications. Another limitation is the lack of systematic repeated CT scanning to detect hematoma enlargement. Therefore, it could not be verified whether, for example, the use of antithrombotic drugs resulted in rapid growth of the hematoma.

Study III was not a controlled study. Systematic verification of DVTs by imaging methods was not performed. Nor were systematic repeat CT scans obtained to detect hematoma enlargement. Therefore, no firm conclusion could be

drawn to guide the prevention of VTCs among patients with acute ICH. The study was carried out to investigate whether the current policy of using LMWHs for VTC prevention had been sufficiently safe. No increase of case fatality was found among those who had received treatment.

Study IV was a population-based one. All of the ICH patients admitted to our hospital, including those who underwent surgery as well as those who died on the scene, were included. Our hospital is the only one in the area of Northern Ostrobothnia which admits acute stroke patients. Therefore, it is likely that selection bias was avoided. The blood pressure data for this study were obtained by interviewing the patients or their proxies and by simultaneously checking the hospital records. By combining the two methods, the risk of misclassifying some hypertensive subjects as normotensives was minimized. The limitation of the study was that situational factors were not recorded. Therefore, it is not know whether the patients had been indoors or outdoors, or if they had had strenuous physical exertion or been drinking heavily at the time of the stroke onset. Another limitation was the small number of patients per month. Therefore, the year was dichotomized into a warm and a cold period, as the month-by-month analysis was not feasible. However, the temperature differences during these two periods were quite clear-cut and similar in all parts of the study area.

7   Conclusions

1. History of ischemic heart disease and/or current atrial fibrillation independently predict early death after primary ICH.
2. High admission blood pressure also predicts early death after ICH, while history of hypertension does not.
3. History of diabetes independently predicts early death after primary ICH, whereas a high admission plasma glucose level seems to result from a stress reaction and does not necessarily predict early death.
4. Patients with primary ICH treated with 20 mg of enoxaparin daily during the acute phase for prevention of venous thromboembolism did not show increased mortality.
5. Cold temperature carries an additional risk for primary ICH in subjects with untreated hypertension, probably due to the greater cold-induced elevation of BP in such subjects compared with those on medication or normotensives.

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