RISK FACTORS AND OUTCOME OF PRIMARY INTRACEREBRAL HEMORRHAGE WITH SPECIAL REFERENCE TO ASPIRIN

PERTTI SALOHEIMO

Faculty of Medicine,
Department of Neurology,
University of Oulu;
Department of Neurosurgery,
University of Helsinki

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Supervised by
Professor Matti Hillbom
Docent Seppo Juvela

Reviewed by
Professor Juhani Sivenius
Professor Heikki Vapaatalo

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Faculty of Medicine, Department of Neurology, University of Oulu, P.O.Box 5000, FIN-90014 University of Oulu, Finland; Department of Neurosurgery, University of Helsinki, P.O.Box 22, FIN-00260 Helsinki, Finland

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Abstract

Primary intracerebral hemorrhage (ICH) comprises 10–15% of all strokes. Arterial hypertension and warfarin use are well documented risk factors for ICH, but aspirin use also seems to predispose to ICH.

The annual incidence of primary ICH in western populations is 12–31 / 100,000. Mortality is high: 14–52% during the first month and 14–80% during the first year after ICH. The size and location of the hemorrhage, a midline shift in head computed tomography, intraventricular spread of the hemorrhage, level of consciousness on admission, and high blood glucose independently predict mortality.

For a risk factor study, 98 consecutive patients admitted into the Department of Neurology, Oulu University Hospital, because of ICH between January 1993 and September 1995 were compared with 206 control subjects drawn from a population register. Thromboxane and prostacyclin biosynthesis were measured from serial urine samples of 43 patients. For outcome studies, all subjects (n = 208) with incident ICH during the study period in the population of Northern Ostrobothnia, Finland, were identified.

Untreated hypertension was the main modifiable risk factor for ICH. Use of aspirin appeared to be a significant risk factor for ICH in the subjects with a history of epistaxis. Enhanced thromboxane and prostacyclin biosynthesis were observed in the acute phase and 3 months after ICH. Regular use of aspirin preceding ICH doubled the 3-month mortality rate compared with nonusers of aspirin/ warfarin. Aspirin use also associated with early hematoma growth. Patients with ICH showed increased long-term mortality up to 7 years after ICH compared to controls. No excess mortality was observed among those with good recovery at 3 months, but those who were severely disabled at 3 months after ICH showed marked excess mortality.

Keywords: aspirin, cerebral hemorrhage, mortality, outcome, prostacyclin, risk factors, thromboxanes

Besides a wife, medicine, I have a mistress, literature. But I never mention her, for those who live outside the law, shall perish outside the law.

Anton Chekhov

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Espoo, October 2005 Pertti Saloheimo

Abbreviations

AA	arachidonic acid
ADL	activities of daily living
ADP	adenosine diphosphate
ANOVA	analysis of variance
AVM	arteriovenous malformation
BMI	body mass index
BTG	beta-thromboglobulin
CAA	cerebral amyloid angiopathy
CI	confidence interval
COX	cyclooxygenase
CT	computed tomography
DVT	deep venous thrombosis
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GP	glycoprotein
ICH	intracerebral hemorrhage
INR	international normalized ratio
MRI	magnetic resonance imaging
mRNA	messenger RNA
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PE	pulmonary embolism
PG	prostaglandin
$PGF_{1\alpha}$	prostaglandin F 1 alpha
PGI_2	prostacyclin
PLA_2	phospholipase A_2
rFVII	recombinant activated clotting factor VII
RR	relative risk
r_s	Spearman's correlation coefficient
SAH	subarachnoid hemorrhage
SD	standard deviation
SSS-PRG	the prognostic score of the Scandinavian Stroke Scale
TXA_2	thromboxane A_2
TXB_2	thromboxane B_2
vVF	von Willebrand factor
±	after mean value, standard deviation

List of original publications

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

I Saloheimo P, Juvela S & Hillbom M (2001) Use of aspirin, epistaxis and untreated hypertension as risk factors for primary intracerebral hemorrhage in middle-aged and elderly people. Stroke 32:399–404.

II Saloheimo P, Juvela S, Riutta A, Pyhtinen J & Hillbom M (2005) Thromboxane and prostacyclin biosynthesis in patients with acute spontaneous intracerebral hemorrhage. Thromb Res 115:367–373.

III Saloheimo P, Ahonen M, Juvela S, Pyhtinen J, Savolainen E-R & Hillbom M (2005) Regular aspirin use preceding the onset of primary intracerebral hemorrhage is an independent predictor for death. Stroke (in press).

IV Saloheimo P, Lapp T-M, Juvela S & Hillbom M (2005) The impact of functional status at three months on long-term survival after spontaneous intracerebral hemorrhage. Submitted for publication.

Contents

1 Introduction

The World Health Organization (WHO) defines stroke as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting for more than 24 h or leading to death, with no apparent cause other than vascular origin (Aho *et al.* 1980). Stroke is the most important cause of physical disability in people over 60 years of age (Kaste *et al.* 1998).

Stroke is a consequence of various pathological mechanisms. Ischemic stroke comprises about 75–80% of all strokes in the western industrialized countries (Kaste *et al.* 1998, MacWalter *et al.* 2001), whereas spontaneous intracerebral hemorrhage (ICH) is estimated to account for 10–15% of all strokes and subarachnoid hemorrhage for the rest (Kase 1996, Kaste *et al.* 1998, MacWalter *et al.* 2001, Qureshi *et al.* 2001). In the Far East, ICH accounts for a somewhat greater portion of strokes. In China, for example, ICH accounts for almost 30% of all strokes (Zhang *et al.* 2003).

Before the era of appropriate neuroimaging, i.e. computed tomography (CT), it was not possible to reliably distinguish ICH from ischemic stroke without autopsy. At that time, the most severe strokes were commonly thought to be hemorrhagic, while the milder ones were usually clinically diagnosed as ischemic strokes. It has been estimated that 24% of ICHs in the earlier years were mislabeled as cerebral infarctions (Drury *et al.* 1984). However, the treatment and prevention strategies are different for ischemic and hemorrhagic strokes. Therefore, it is important to accurately verify the type of stroke as soon as possible.

Earlier studies on the epidemiology and risk factors of stroke addressed strokes as a homogenous group without dividing them into subtypes. CT became available in the 1970s, but even after that, some studies included high percentages of cases without a diagnosis confirmed by head CT (Reunanen *et al.* 1986, Jerntorp & Berglund 1992). In the 1980s, case ascertainment of stroke subtypes by head CT became the method of choice, and diagnosis based exclusively on clinical presentation was abandoned.

When brain imaging became widely available, the picture of ICH also cleared up. Management of ICH has long lacked innovations, whereas thrombolytic therapy has recently revolutionized the treatment of brain infarction. However, the development of stroke units and the more intensive neurological care of ischemic stroke patients have also benefited ICH patients. The general medical management of patients with ICH is in line with the treatment of ischemic stroke – appriopriate use of oxygen, intravenous saline,

and antipyretics, prompt attention to any medical complication, integrated physiotherapy, and early mobilization in the milder cases (Indredavik *et al.* 1999, MacWalter *et al.* 2001). But the prophylaxis and treatment of thrombotic complications (deep vein thrombosis and pulmonary embolism) constitute a special issue in the management of patients with ICH (Keir *et al.* 2002, Kelly *et al.* 2003).

Until this year, not much research has been dedicated to finding effective new treatments for ICH. However, Mayer at al. (2005) recently reported that treatment with recombinant activated factor VII (rFVII) within 4 hours after the onset of ICH limited the growth of the hematoma, reduced mortality, and improved functional outcome.

The role of surgical therapy for ICH is still somewhat controversial (Hankey & Hon 1997). The first adequately powered study of surgical therapy was published a short time ago, and it did not support routine surgical clot evacuation in most patients with spontaneous ICH (Mendelow *et al.* 2005). However, carefully selected patients may still benefit from surgery (Kobayashi *et al.* 1994, Gregson & Mendelow 2003).

Because the treatment of ICH is so difficult, and the outcome for many so poor, prevention assumes the greatest importance (MacWalter *et al.* 2001). Arterial hypertension and heavy alcohol consumption are important and preventable risk factors for ICH (Ariesen *et al.* 2003). Investigations aimed to identify the modifiable risk factors of ICH have revealed that not only warfarin (Hart *et al.* 1995) but also aspirin therapy (He *et al.* 1998) increases the risk for ICH. Both drugs are widely used in the primary and secondary prevention of ischemic events, and their adverse effects are, therefore, of great practical importance. The role of aspirin as a risk factor is less well-known than that of warfarin.

The saga of aspirin is probably one of the oldest in the history of medicine (Mueller & Scheidt 1994). Willow was already used as medicine by ancient Egyptians, but the origins of its use probably date back tens of thousands of years (Jeffreys 2004). The therapeutic benefits of willow bark extract and other plant sources of salicylates were also known by Hippocrates 2400 years ago (Mueller & Scheidt 1994). Willow was used as a folk medicine in parts of Europe throughout the Middle Ages and up to the Renaissance, and it was also used by native Americans and by Khoikhois in South Africa (Mueller & Scheidt 1994, Jeffreys 2004).

The modern history of salicylates began with Reverend Edward Stone in Oxfordshire, England, who reported his experiments with willow bark extract in the treatment of agues (fevers) in a letter to the president of the Royal Society in 1763. Salicin was refined from willow in 1828 by Joseph Buchner at Munich University. Italian Raffaele Piria first produced salisylic acid in 1838. In 1853, the French scientist Charles Gerhardt was the first to synthetize chemically acetylsalicylic acid. In the 1890s, Felix Hoffman developed an improved synthetic pathway to acetylsalicylic acid. Finally, acetylsalicylic acid, under the brand name Aspirin, was made a commercial product by Bayer Company in 1899 (Mueller & Scheidt 1994). Since those times, over 26,000 scientific papers have been written about aspirin (Jeffreys 2004).

This early pain-killer entered the field of cerebrovascular diseases about 50 years ago, when its ability to prevent myocardial infarction was observed (Craven 1950). However, the mechanism of action of aspirin was not discovered until 1971 (Vane 1971). Nowadays, aspirin is widely used in both primary and secondary prophylaxis of cardiovascular diseases and ischemic stroke. It has even been suggested that a small dose of aspirin along with a statin, antihypertensive drugs, and folic acid should be used by all people over 55 years of age as a ”polypill” (Wald & Law 2003).

However, since aspirin is so widely used, its adverse effects are also quite prevalent. Aspirin use is associated with various hemorrhagic adverse drug reactions, which may sometimes be fatal (Juntti-Patinen & Neuvonen 2002). The total lifetime complication rate of aspirin therapy has been estimated to be 6.79%, with a mortality rate of 0.18% (Hur *et al.* 2005). Most interest has been focused on aspirin-induced gastric ulcers and consequent gastrointestinal bleeding. It is well-known that aspirin causes peptic ulcers by reducing gastric mucosal cyclooxygenase (COX) activity and prostaglandin synthesis (Feldman *et al.* 2000). How aspirin increases the risk for intracranial bleeding is less clear.

2 Review of the literature

2.1 Subtypes of intracerebral hemorrhage

2.1.1 Primary (spontaneous) intracerebral hemorrhage

Primary or spontaneous ICH is defined as bleeding into the brain parenchyma without accompanying trauma (MacWalter *et al.* 2001). Intraparenchymal bleeding results from the rupture of any of the small penetrating arteries that originate from the basilar arteries or the anterior, middle, or posterior cerebral arteries. The bleeding may extend into the cerebral ventricles and, in rare cases, the subarachnoid space (MacWalter *et al.* 2001, Qureshi *et al.* 2001). Primary intraventricular hemorrhage is an uncommon type on spontaneous ICH (Passero *et al.* 2002). Primary intracerebral hemorrhage accounts for 78 to 88 percent of cases of intracerebral hemorrhage (Qureshi *et al.* 2001).

2.1.2 Secondary intracerebral hemorrhage

Secondary ICH accounts for a minority of cases with intracerebral bleeding. Secondary ICH occurs in association with vascular abnormalities, tumors, or impaired coagulation (Qureshi *et al.* 2001). The causes of secondary ICH are listed in Table 1.

2.1.2.1 Intracerebral hemorrhage due to vascular abnormalities

Arteriovenous malformations (AVM) are a complex tangle of abnormal arteries and veins linked by one or more fistulas, and ICH is the most common clinical presentation of AVM (The Arteriovenous Malformation Study Group 1999). These lesions are occasionally discovered angiographically in cases of ICH, but their presence is more often documented by magnetic resonance imaging (MRI) (Kase 1996). The 18% annual risk of recurrent hemorrhage can be reduced by surgical excision, endovascular occlusion, and radiotherapy (The Arteriovenous Malformation Study Group 1999).

Table 1. Causes of secondary ICH (Qureshi et al. *2001).*

Causes
Arteriovenous malformation
Cavernous angioma
Venous angioma
Intracranial aneurysm
Dural venous sinus thrombosis
Coagulopathy
Vasculitis
Intracranial neoplasm
Hemorrhagic ischemic stroke

Cavernous malformations are congenital vascular anomalies that consist of abnormal capillary-like vessels with intermingled connective tissue (Kondziolka *et al.* 1995, Qureshi *et al.* 2001). They are being increasingly recognized as causes of ICH due to the high diagnostic yield of MRI. Clinically, they present as seizures (27–70%), ICH (10–30%), or progressive neurological deficits, which actually result from recurrent small hemorrhages within and around the malformation (Kase 1996). The 4.5% annual risk of recurrent hemorrhage can be reduced by surgical excision or radiosurgery (Kondziolka *et al.* 1995, Qureshi *et al.* 2001).

Venous angiomas are abnormal dilatation of venules and carry a very low annual risk of ICH (0.15%) (Naff *et al.* 1988). They can be detected by conventional angiography or MRI (Qureshi *et al.* 2001).

The rupture of a saccular aneurysm of a medium-sized intracranial artery usually results in subarachnoid hemorrhage (SAH) (Qureshi *et al.* 2001). The bleeding may sometimes involve the brain parenchyma, causing ICH or a combination of ICH and SAH (Griffiths *et al.* 1997, Shimoda *et al.* 1997). Without surgical clipping or placement of endovascular coils, the risk of recurrent hemorrhage is 50% within the first 6 months after the bleeding (Jane *et al.* 1985).

2.1.2.2 Intracerebral hemorrhages due to other causes

Patients with hemophilia are susceptible to both spontaneous and posttraumatic ICH. The incidence of ICH in hemophilia is 2.5–3% of patients per year. However, ICH is a common cause of death in factor VIII or IX deficiency. Only very severe thrombocytopenia is associated with spontaneous hemorrhage. In idiopathic thrombocytopenic purpura, the development of spontaneous ICH is unusual, ranging within 1–3% of cases. In patients with von Willebrand's disease, spontaneous ICH is a rare complication. (Olson 1993.) In addition to primary disorders of hemostasis or coagulation, a number of rare genetic disorders are associated with an increased risk for ICH (Natowicz & Kelley 1987).

Several types of hematological malignancies, such as acute lymphocytic leukemia, acute promyelocytic leukemia and polycythemia vera can cause ICH (Kase 1996, Arboix & Besses 1997). ICHs due to intracranial neoplasm result from necrosis and bleeding within hypervascular tumors (Qureshi *et al.* 2001).

ICHs due to vasculitis result from rupture of small or medium-sized arteries with inflammation and degeneration. Vasculitis can be diagnosed by cerebral angiography, measurement of serologic and cerebrospinal fluid markers, or brain biopsy (Razumowsky *et al.* 2001, Qureshi *et al.* 2001). ICH is also known to be a complication of infective endocarditis (Masuda *et al.* 1992), and it has further been reported as a complication of bacterial meningitis (Gironell *et al.* 1995).

Dural venous sinus thrombosis causes hemorrhagic venous infarction. This cause of ICH may be detected by magnetic resonance venography or conventional angiography. Anticoagulation may improve outcome (Qureshi *et al.* 2001).

Repeat CTs have documented late ICH in regions of embolic cerebral infarcts (Cerebral Embolism Study Group 1984, Shields *et al.* 1984), and it has been suggested that 50% of brain infarcts become hemorrhagic within a week after the stroke (Bozzao *et al.* 1991). The mechanism is thought to be reperfusion of tissue whose arterioles and capillaries have been injured by ischemia (Caplan 1988). Postendarterectomy ICH is a well-documented complication of carotid surgery (Caplan *et al.* 1978). ICH may also complicate thrombolytic therapy for brain infarction (Ringleb *et al.* 2002).

2.1.3 Traumatic intracerebral hemorrhage

During 1996–2000, the annual incidence of first traumatic brain injury requiring hospitalization in Finland was 102/100,000. Cerebral contusion comprised 37.2% of these cases, giving an incidence of 37.9/100,000 for cerebral contusion (Alaranta *et al.* 2002). Cerebral contusion and traumatic cerebral hemorrhage are probably gradations of a single pathophysiological process (van Dellen 1996). Siddique *et al.* (2002) observed that 1.6% of patients included in a hospital-based head injury database had an isolated ICH as the only major abnormality detectable on CT scans (when subdural and extradural hematomas were excluded). The patients with traumatic ICH were younger than those with spontaneous ICH in the same database (median age 51 years vs. 65 years, respectively). The frontal and temporal poles are the most common locations of traumatic cerebral hematomas (van Dellen 1996).

2.2 Risk factors and etiology of primary intracerebral hemorrhage

2.2.1 Hypertensive intracerebral hemorrhage

Arterial hypertension is the best documented treatable risk factor for ICH (Caplan 1992, Thrift *et al.* 1996). Hypertension can be attributed to 37–72% of cases of ICH (Brott *et al.* 1986, Broderick *et al.* 1993a, Hsiang *et al.* 1996, Nilsson *et al.* 2000).

Untreated hypertension seems to carry a higher risk for ICH than treated hypertension (Woo *et al.* 2004, Li *et al.* 2005). Thrift *et al.* (1998) reported that the risk for ICH associated with hypertension was significantly greater among the hypertensive subjects who had stopped taking medication, supervised or unsupervised. Hsiang *et al.* (1996) observed that only 20% of the hypertensive subjects stricken by ICH had been compliant

with their antihypertensive medication. Moreover, Klungel *et al.* (1999) reported that about a quarter of all incident strokes among hypertensives were attributable to undertreatment of hypertension. Therefore, adequate control of hypertension is probably the most important prophylaxis of ICH.

Not only chronic hypertension but also a sudden rise in blood pressure may cause ICH by exposing the cerebral vasculature to acute augmentation of blood flow in regions with either normal or injured blood vessels (Caplan 1988).

2.2.2 Intracerebral hemorrhage associated with cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is characterized by the deposition of β-amyloid protein in the blood vessels of the cerebral cortex and leptomeninges (Qureshi *et al.* 2001). Because the incidence of CAA increases steadily with age, it characteristically causes ICH in the elderly (Kase 1996, McCarron & Nicoll 2004). The superficial location of the affected vessels in the cortex and leptomeninges is responsible for the predominantly lobar location of ICHs (Kase 1996, Sacco 2000). It has generally been thought that CAA is responsible for lobar ICHs in elderly nonhypertensive subjects. However, CAA and hypertensive vascular changes may coexist, as both are common in the elderly (Broderick *et al.* 1993a).

The clinical diagnosis of probable CAA is based on findings of multiple lobar hemorrhages in patients aged over 60 years, in the absence of findings that point to another explanation. A definite diagnosis of intracerebral hemorrhage related to CAA requires confirmation at autopsy of severe CAA in the presence of lobar hemorrhage, with no evidence of any other cause. The neuropathological diagnosis of probable CAA is based on the findings in a biopsy specimen or a tissue sample obtained during the evacuation of the hematoma. (Sacco 2000.)

2.2.3 Drug-related intracerebral hemorrhage

ICH may be associated with the use of various drugs. The use of warfarin or other anticoagulants has been shown to increase the risk for ICH in a number of studies (Atrial Fibrillation Investigators 1994, Hart *et al.* 1995, Juvela *et al.* 1995). Cases of ICH related to the use of oral anticoagulants (warfarin) account for 9 to 10 percent of ICHs (Kase 1996). Conventional intensities of anticoagulation increase the risk of intracerebral hemorrhage 5 to 10 times for many stroke-prone patients. Persons aged over 75 years or with a history of cerebrovascular disease will have a rate of intracerebral bleeding of about 1% per year if treated with anticoagulants to an international normalized ratio (INR) between 2 and 3. (Hart 2000.) Warfarin is widely used in Finland to prevent cardioembolic stroke in subjects with atrial fibrillation. In one study (Viitaniemi *et al.* 1999), the age-adjusted prevalence of such patients was 0.30%.

It has been postulated that antithrombotic agents unmask subclinical bleeding that occurs with increasing frequency in the elderly population, especially in individuals with

hypertension and cerebrovascular disease (Hart *et al.* 1995). Amyloid angiopathy may be an important contributor to warfarin-associated lobar hemorrhage (Rosand *et al.* 2000).

Many studies have suggested that the use of aspirin may predispose to spontaneous ICH (The Dutch TIA Trial Study Group 1991, The Swedish Aspirin Low-dose Trial Collaborative Group 1991, UK Transient Ischaemic Attack Study Group 1991, Thrift *et al.* 1999). This finding has also been confirmed in meta-analyses (He *et al.* 1998, Antithrombotic Trialists' Collaboration 2002). However, the question about the safe dose of aspirin has remained unclear (Thrift *et al.* 1999, Antithrombotic Trialists' Collaboration 2002). Aspirin use has also been found to be a risk factor for intracranial hematomas in patients with acute head injuries (Raymond *et al.* 1992).

Nonsteroidal anti-inflammatory drugs (NSAID) other than aspirin do not seem to associate with an increased risk for ICH (Thrift *et al.* 1999, Bak *et al.* 2003, Johnsen *et al.* 2003). However, in two Danish studies (Bak *et al.* 2003, Johnsen *et al.* 2003), the use of NSAIDs was assessed on the basis of a prescription database. This is an unreliable method because most NSAIDs are sold over the counter. Juvela *et al.* (1995) observed a tendency of NSAIDs to increase the risk for ICH in people of working age. However, despite the limitations of the available data, the current evidence does not support an increased risk for ICH associated with use of NSAIDs other than aspirin (Qureshi 2003).

Ticlopidine and clopidogrel are thienopyridine derivatives with antiplatelet activity (Antithrombotic Trialists' Collaboration 2002, Hankey *et al.* 2000a). They act by inhibiting the binding of adenosine diphosphate (ADP) to its platelet receptor and blocking the ADP-dependent activation of platelets. According to a systematic review, thienopyridines carry a similar risk of intracranial bleeding as aspirin (Hankey *et al.* 2000a). The clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) study showed that clopidogrel was at least equally safe as aspirin (325 mg daily) (CAPRIE Steering Committee 1996). The use of platelet glycoprotein (GP) IIb/IIIa inhibitors in patients undergoing percutaneous coronary revascularization is associated with a small risk for ICH (Blankenship 1999).

ICH has also been reported in association with the use of sympathomimetic drugs, such as amphetamines, most commonly intravenous methamphetamine (Delaney & Estes 1980), ephedrine (Yin 1990), pseudoephedrine (Loizou *et al.* 1982), and phenylpropanolamine used in nasal decongestants (Mueller 1983). These agents are known to increase heart rate and blood pressure (Caplan 1988). ICH can also occur after use of cocaine and its precipitate form, called "crack" (Kase 1996). The cocaine-associated hemorrhages have occurred within minutes to a few hours after drug use, and they probably result from cocaine-induced hypertension or arterial spasm followed by reperfusion or, rarely, as a consequence of drug-induced cerebral vasculitis (Kase 1996, Green *et al.* 1990). However, recent evidence suggests that illicit drug-related ICH often seems to be related to underlying vascular malformation (McEvoy *et al.* 2000).

2.2.4 Lifestyle risk factors of primary intracerebral hemorrhage

Excessive alcohol use has been observed to associate with increased risk for ICH in several case-control (Calandre *et al.* 1986, Monforte *et al.* 1990, Gill *et al.* 1991, Juvela *et al.* 1995, Woo *et al.* 2002) and cohort studies (Iso *et al.* 1995, Kiyohara *et al.* 1995), and the finding was confirmed in a recent systematic review (Ariesen *et al.* 2003). The lowest

observed threshold of daily alcohol consumption for an increased risk for ICH is > 36 g (Kubota *et al.* 1997). High daily alcohol intake increases the risk for ICH independent of hypertension, but a combination of heavy drinking and hypertension may further increase the risk (Hillbom *et al.* 1999).

Alcohol impairs the hemostatic mechanism by inhibiting platelet aggregation and thromboxane A_2 (TXA_2) formation. In addition, alcohol enhances prostacyclin (PGI_2) production and potentiates the inhibitory effects of PGI_2 on platelet aggregation (Renaud & Ruf 1996). On the other hand, a transient increase in platelet reactivity and TXB_2 formation has been observed in the recovery phase after prolonged heavy drinking of alcohol (Hillbom *et al.* 1985a, Hillbom *et al.* 1985b). Alcohol also prolongs bleeding time and inhibits thrombopoiesis, and heavy drinking may lead to thrombocytopenia (Rubin & Rand 1994). Alcoholic liver disease may alter platelet function as well (Rubin & Rand 1994), and liver dysfunction may contribute to the development of ICH (Fujii *et al.* 1994). Alcohol also potentiates the aspirin-induced prolongation of bleeding time (Deykin *et al.* 1982, James & Walsh 1985).

Smoking is associated with a moderately increased risk for ICH (Hankey 1999, Ariesen *et al.* 2003). There is also a dose-dependent relationship between the number of cigarettes smoked and the risk for ICH (Hankey 1999, Kurth *et al.* 2003). Ex-smokers have relative risks for stroke and its subtypes that are intermediate between those of non-smokers and current smokers. Smoking may predispose individuals to intracranial arterial disease by accelerating atherogenesis and may cause atheromatous small intracranial arteries or aneurysms to rupture by causing an acute rise in blood pressure (Hankey 1999).

A U-shaped relationship between stroke incidence and the degree of physical activity has been observed. Moderate physical activity (2000 to 2999 kcal/wk in Lee & Paffenbarger 1998) was protective against stroke when compared to light physical activity, but more strenuous physical activity was less protective (Menotti & Seccareccia 1985, Lindsted *et al.* 1991, Lee & Paffenbarger 1998). However, the subtypes of stroke have been inaccurately differentiated in these studies. Nakayama *et al.* (1997) observed that heavy physical activity increased the risk for all strokes in middle-aged and elderly men, whereas avoidance of physical exercise increased the risk for ICH in women.

2.2.5 Genetic factors

Woo *et al.* (2002) observed in their recent case-control study that the presence of the ε2 or ε4 allele of apolipoprotein E is a significant risk factor for lobar ICH. They estimated that one third of all cases of lobar ICH are attributable to the possession of these alleles. It has previously been reported that the presence of the ε2 and ε4 alleles of the apolipoprotein E gene triplicates the risk of recurrent hemorrhage among survivors of lobar intracerebral hemorrhage related to amyloid angiopathy (O'Donnell *et al.* 2000). These alleles are associated with increased deposition of β-amyloid protein (by ε4) (Greenberg *et al.* 1995) and degenerative changes, such as fibrinoid necrosis, in the vessel wall (by ε2) (Greenberg *et al.* 1998).

Hereditary cerebral hemorrhage with amyloidosis–Dutch type is an autosomal dominant disease caused by deposition of β-amyloid in the leptomeningeal arteries and cortical arterioles. The disease is due to a point mutation in the amyloid precursor protein gene at chromosome 21, and it is clinically characterized by recurrent strokes and

dementia. (Bornebroek *et al.* 1996.) Supratentorial microbleeds have been found to occur independently of the presence of hypertension in patients with this disorder (van den Boom *et al.* 2005).

Woo *et al.* (2002) also observed that having a first-degree relative with ICH was a significant risk factor for ICH, suggesting that genetic risk factors other than apolipoprotein E alleles may be important in the incidence of ICH. However, the accuracy with which a subject can recall whether a relative's stroke was ischemic, ICH, or SAH is questionable. In a Japanese study, family history of stroke appeared to be significantly related to ICH (Okada *et al.* 1976).

2.2.6 Other etiologies and risk factors

Diabetes mellitus has been reported to be a significant risk factor for ICH in two studies (Leppälä *et al.* 1999, Zopdey *et al.* 2000). Juvela (1996) found diabetes to be significantly more common in patients with ICH than in those with subarachnoid hemorrhage. Although many other studies have failed to establish diabetes as a significant risk factor (Inzitari *et al.* 1990, Woo *et al.* 1992, Giroud *et al.* 1995, Thrift *et al.* 1996, Kubota *et al.* 1997), a recent systematic review concluded that diabetes is associated with a slightly elevated risk for ICH (Ariesen *et al.* 2003).

Higher serum cholesterol levels seem to associate with a lower risk for ICH (Ariesen *et al.* 2003, Thrift *et al.* 1996) but a higher risk for ischemic stroke (Tirschwell *et al.* 2004). Actually, an increased risk for ICH has been observed with low cholesterol (Segal *et al.* 1999, Tirschwell *et al.* 2004), and a threshold in this relation has been suggested, with the highest risk in subjects with serum cholesterol below 4.1 mmol/l (Yano *et al.* 1989).

Prior cerebral infarction seems to associate with an increased risk for ICH (Okada *et al.* 1976, Brott *et al.* 1986, Woo *et al.* 2002). Ischemic lacunar infarctions and deep intracerebral hemorrhages are both complications of small-vessel disease due to hypertension (Cole & Yates 1967, Caplan 1988). The finding also raises the possibility that ischemic damage may lead to changes in the brain parenchyma or vasculature that increase the susceptibility to developing hemorrhage (Rosand & Greenberg 2002).

It has been suggested that hepatic disease associates with the risk for ICH independent of alcohol use (Boudouresques *et al.* 1980, Calandre *et al.* 1986). Patients with hemorrhagic stroke have been found to have relatively higher body mass indexes (BMI), blood pressures, and leptin levels (Söderberg *et al.* 1999). Whether obesity in the absence of hypertension is associated with ICH is less certain (DiPietro *et al.* 1994).

ICH has been described in medical conditions characterized by acute hypertension, such as acute glomerulonephritis, eclampsia, and pheochromocytoma, (Caplan 1988). In a registry of 900 consecutive cases of hemorrhagic stroke, 8 cases of ICH associated with polycystic kidney disease were found. In these cases, hypertension had been inadequately treated or undetected (Ryu 1990). Albuminuria has also been reported to predispose to ICH (Okada *et al.* 1976).

A transient rise in blood pressure has probably been the cause of ICH in the cases reported after painful dental intervention (Barbas *et al.* 1987) and after trigeminal nerve decompression for trigeminal neuralgia (Haines *et al.* 1978). Cases of ICH have been reported in association with exposure to extremely cold weather (Caplan *et al.* 1984). A

wintertime peak in the incidence of ICH has been reported in Japan (Inagawa *et al.* 2000a).

Cases of ICH that developed during migraine attacks have also been reported (Cole & Aube 1987). During vasoconstriction, ischemia and even infarction may develop. When vasoconstriction improved, local blood flow increased, and the zone containing ischemic capillaries was reperfused and bled (Caplan 1988).

2.3 Incidence of primary intracerebral hemorrhage

The incidence of ICH varies in different populations. The lowest figures, based on a study with CT confirmation in 80% of stroke cases, have been reported in Libya, where the crude annual incidence of ICH was 9/100,000 during the years 1983–84 (Ashok *et al.* 1986). Fogelholm *et al.* (1992) reported a crude annual incidence of 31/100,000 in Central Finland during 1985–89. The highest incidence rate has been reported in Japan, 48/100,000 (Inagawa *et al.* 2000a) (Table 2).

The discrepancies between the earlier and more recent studies reflect the revolutionary impact of CT on the accurate diagnosis of ICH. Many smaller ICHs, which were diagnosed clinically as cerebral infarcts in the pre-CT era, are now easily identified by CT. Conversely, some large cerebral infarcts that produced early changes in the patient's level of consciousness were previously misclassified as ICH (Broderick *et al.* 1993b).

ICH is more common in men than in women. Nilsson *et al.* (2000) reported adjusted incidence rates per 100,000 population of 32.2 for men and 24.7 for women in southern Sweden. In Japan, the corresponding figures were 59 and 37 (Inagawa *et al.* 2000a). A population-based stroke register from four separate districts in Finland showed an ICH incidence of 32.1 for men and 15.1 for women during the years 1989–1991 (total incidence 23.4) (Numminen *et al.* 1996). However, Fogelholm *et al.* (1992) did not find any sex difference in the incidence of ICH (32/100,000 for men and 31/100,000 for women).

Table 2. Incidence rate of ICH per 100,000 population based on studies with CT confirmation in ≥ 80% of stroke cases.

Location	Incidence rate / 100,000	Reference
South Alabama, USA	23	Gross *et al.* 1984
Benghazi, Libya	9	Ashok *et al.* 1986
Rochester, Minnesota, USA	15*	Broderick *et al.* 1989
Oxfordshire, England	14	Bamford *et al.* 1990
Dijon, France	12*	Giroud *et al.* 1991
Central Finland	31	Fogelholm *et al.* 1992
Greater Cincinnati, Ohio, USA	15*	Broderick *et al.* 1993b
Southern Sweden	28*	Nilsson *et al.* 2000
Izumo City, Japan	48*	Inagawa *et al.* 2000a

*Adjusted for age and sex

The incidence of ICH increases with age. Fogelholm *et al.* (1992) reported an incidence of only 2/100,000 in subjects < 40 years of age but 320/100,000 in the age group of 70–79 years. The incidence rates for different age groups also reported by Nilsson *et al.* (2000), Giroud *et al.* (1991) and Inagawa *et al.* (2000a) are in accordance with the Finnish observations.

2.4 Outcome after primary intracerebral hemorrhage

2.4.1 Mortality

The mass effect resulting from the hematoma volume, the edematous tissue surrounding the hematoma, and obstructive hydrocephalus with subsequent herniation is the chief secondary cause of death in the first few days after ICH (Qureshi *et al.* 2001).

Deep venous thrombosis (DVT) is a rather common complication of immobility after stroke. DVT predisposes patients to the risk of pulmonary embolism (PE), which may be fatal. In a Swedish study with the causes of death verified by autopsy, 3% of stroke patients succumbed to PE within 3 months (Viitanen *et al.* 1987). Another potentially fatal complication after stroke is pneumonia, which was, after the primary bleed, the second most common cause of death within 1 month after ICH in the Oxfordshire Community Stroke Project (Counsell *et al.* 1995). After 30 days had elapsed, pneumonia was the commonest killer of ICH patients.

Warfarin use impairs the outcome after ICH, approximately doubling mortality (Rosand 2004). Warfarin use has been shown to increase the risk for in-hospital hematoma expansion, which probably mediates part of warfarin's effect on ICH mortality (Flibotte *et al.* 2004).

Mortality during the first month after ICH is 14–52% (Fogelholm *et al.* 1992, Broderick *et al.* 1994, Counsell *et al.* 1995, Inagawa *et al.* 2000b, Nilsson *et al.* 2002, Kiyohara *et al.* 2003) (Table 3). The majority of deaths occur in the early phase after ICH, up to 27% during the first 24 hours (Fogelholm *et al.* 1992). Juvela (1995) reported that 11% of patients died during the first 24 hours after hemorrhage, 19% within 3 days, and 33% within 2 weeks. In the Oxfordshire Community Stroke Project, 24% of the patients with ICH died within the first 24 h and 39% within the first week (Counsell *et al.* 1995). In a Swedish population-based study, 18% of the patients with ICH died within the first 2 days (Nilsson *et al.* 2002), and Franke *et al.* (1992) reported a 2-day mortality of 24%.

Table 3. Mortality after ICH in population-based studies.

Reference	Time	1 month	1 year	2 years	5 years
Kiyohara *et al.* 2003	1961–1987		80%		
Counsell *et al.* 1995	1981–1986	52%			68%
Fogelholm *et al.* 1992	1985–1989	50%			65%*
Broderick *et al.* 1994	1988	43%			
Inagawa *et al.* 2000b	1991–1996	14%		27%	
Nilsson *et al.* 2002	1996	36%	47%		

* Mean follow-up 2.7 years

Independent predictors of short-term mortality (30 days) include the size and location of the hemorrhage, a midline shift in head computed tomography (CT), intraventricular spread of the hemorrhage, low Glasgow Coma Scale (GCS) score on admission, and high blood glucose on admission (Daverat *et al.* 1991, Tuhrim *et al.* 1991, Broderick *et al.* 1993c, Inagawa *et al.* 2000b, Fogelholm *et al.* 2004).

The relative risk of death for those who survive beyond 30 days after stroke (ischemic and hemorrhagic combined) is > 2-fold compared to that in the general population (Hankey *et al.* 2000b). Previous studies on long-term outcome after ICH have reported a wide range of 1-year mortality from 14 to 80% (Francke *et al.* 1992, Juvela 1995, Hårdemark *et al.* 1999, Nilsson *et al.* 2002, Kiyohara *et al.* 2003). Two-year mortality rates from 27 to 61% have been reported (Giroud *et al.* 1991, Rosenow *et al.* 1997, Inagawa *et al.* 2000b). Fogelholm *et al.* (1992) reported that 65% of patients with ICH died within a median follow-up time of 32 months. Chambers *et al.* (1987) reported a 5-year survival rate of 21% for patients with supratentorial hemorrhage and 22% for those with infratentorial hemorrhage. However, only 31% of all strokes in their study were diagnosed with CT.

The predictors for long-term (> 6 months) survival after primary ICH include the initial level of consciousness, the severity of handicap caused by the stroke in the early phase, the patient's age, and the volume and location of the hematoma (Franke *et al.* 1992, Juvela 1995, Hårdemark *et al.* 1999, Inagawa *et al.* 2000b, Nilsson *et al.* 2002).

2.4.2 Functional outcome

The Modified Rankin Scale, the Oxford Handicap Scale, and the Glasgow Outcome Scale (GOS) provide the most practical instruments for outcome evaluation after stroke (Kaste *et al.* 1998). The Modified Rankin scale uses a 0–5 point scale (0 = no symptoms, 5 = severe disability, requires constant attention) (van Swieten *et al.* 1988). The Oxford Handicap Scale has been derived from the Modified Rankin Scale (Kaste *et al.* 1998). The Glasgow Outcome Scale consists of five well-defined outcomes: death, persistent vegetative state, severe disability, moderate disability, and good recovery (Jennett & Bond 1975). The Barthel Index (Mahoney & Barthel 1965) is a widely used ADL (activities of daily living) scale that measures the ability of a stroke patient to take care of his/her life independently and reflects the need for help that either the family or society has to provide (Lyden & Lau 1991, Kaste *et al.* 1998).

Daverat *et al.* (1991) and Dixon *et al.* (1985) reported that 73–78% of the patients who survived for at least 6 months after ICH were functionally independent (good recovery and moderate disability according to GOS; moderately disabled, able to take care of themselves at home, move outdoors, do shopping, and use public transportation), while 22–27% were dependent (severe disability and vegetative state; severely disabled persons need assistance for some ADL every day). Juvela (1995) assessed the 1-year outcome after ICH and reported that 65% of the survivors were independent and 35% dependent. Hårdemark *et al.* (1999) reported that, 1 year after ICH, 58% of the survivors had a modified Rankin score of 0–3 (the patient is no more than moderately disabled, with some need for help but able to walk without assistance). Poor outcome was observed in 42% of the survivors. After a mean follow-up of 32 months, Fogelholm *et al.* (1992) observed 78% of the survivors to be in the categories I–III on the Rankin scale (Rankin 1957) and

22% to be in the categories IV–V. They reported that most of the severely handicapped patients had died by the end of the follow-up, which explained the small final percentage of patients with poor functional outcome.

The size, location, and intraventricular extension of the hemorrhage, the GCS score, limb paresis, communication disorders, age, and alcohol consumed within a week before the hemorrhage have been identified as independent predictors for poor functional outcome after ICH (Dixon *et al.* 1985, Portenoy *et al.* 1987, Daverat *et al.* 1991, Fogelholm *et al.* 1992, Anderson *et al.* 1994, Lisk *et al.* 1994, Juvela 1995, Lampl *et al.* 1995, Hårdemark *et al.* 1999, Flemming *et al.* 2001). Lobar hematomas have usually been associated with better outcome than deep hematomas (Juvela 1995, Hårdemark *et al.* 1999).

2.5 Pathophysiological and clinical features of intracerebral hemorrhage

2.5.1 Vascular changes

Chronic hypertension causes degenerative changes in the penetrating arteries in the brain. These changes may lead to leakage of blood (hemorrhage) or to interruption of blood flow (infarction) (Caplan 1988). The degenerative changes consist of fatty deposition and fibrinoid necrosis with local thinning of the vessels (MacWalter *et al.* 2001). They reduce the compliance of the vessel wall and increase the likelihood of spontaneous rupture (MacWalter *et al.* 2001, Qureshi *et al.* 2001). In 1868, Charcot and Bouchard attributed intracerebral bleeding to rupture at points of dilatation in the walls of small arterioles (microaneurysms) (Cole & Yates 1967). These are, in fact, pseudoaneurysms, i.e. small collections of extravasated blood with a fibrin capsule. They are thought to result from the aforementioned degenerative changes. (MacWalter *et al.* 2001.)

On the other hand, there is *in vitro* evidence suggesting that amyloid-β deposition in cortical blood vessels may lead to changes in the proteolytic environment within the vessel wall, which may then predispose to ICH. Fibrillar amyloid-β may cause cellular degeneration, promote anticoagulation, stimulate tissue plasminogen activator, and lead to degradation of extracellular matrix and endothelial damage. (McCarron & Nicoll 2004.)

In the recent years, studies with gradient-echo T2-weighted MRI have demonstrated cerebral microbleeds in patients with ICH in various parts of the brain, with preference for the cortical-subcortical regions and the basal ganglia/thalami (Roob *et al.* 2000), but also in patients with ischemic stroke (Kwa *et al.* 1998). These microbleeds are considered indicative of bleeding-prone cerebral small-vessel disease (Kwa *et al.* 1998, Roob *et al.* 2000). They are associated with chronic hypertension, cerebral amyloid angiopathy, old age, ICH, lacunar infarcts, and low serum cholesterol (Kwa *et al.* 1998, Greenberg 1998, Roob *et al.* 2000, Lee *et al.* 2004). In addition, these microbleeds have been found to constitute a risk factor for aspirin-associated ICH (Wong *et al.* 2003) and subsequent ICH among patients with ischemic stroke (Fan *et al.* 2003). It has been proposed that the rupture of a single small artery may cause damage and rupture of other vessels and, in

patients with impaired hemostatic mechanisms, may snowball to become a large symptomatic hematoma (Wong *et al.* 2003).

It has been suggested that lobar microbleeds result from previous minor bleeds originating from amyloid angiopathy (Greenberg 1998). The pathology of microbleeds in the deep brain structures (basal ganglia and thalamus) remains uncertain, but an association with Charcot-Bouchard aneurysms has been suggested (Wong *et al.* 2003).

2.5.2 Progression of hematoma and secondary neurologic deterioration

After the rupture of an intracerebral vessel, the expanding hematoma penetrates through the surrounding brain tissue, until the increase of tissue pressure slows down and eventually stops the bleeding (MacWalter *et al.* 2001). It has been shown that, in 38% of patients admitted within 3 hours after the onset of ICH, hematomas continue to enlarge during the first 24 hours (Brott *et al.* 1997). Fujii *et al.* (1998) observed that hematomas grew in 14% of the patients admitted within 24 hours after the onset of ICH, but the incidence of hematoma enlargement was 21.4% in the patients admitted within 1 hour after the onset of ICH.

Hematoma enlargement has been shown to significantly associate with clinical deterioration and increased mortality (Brott *et al.* 1997, Fujii *et al.* 1998). An increased risk for hematoma enlargement has been observed in association with heavy drinking of alcohol, disturbed consciousness, decreased blood coagulability, increased blood pressure, liver disease, thrombocytopenia, insufficient thrombin generation, and elevated INR value (Caplan 1992, Kazui *et al.* 1997, Fujii *et al.* 1998, Takahashi *et al.* 1998, Oppenheim-Eden *et al.* 1999, Yasaka *et al.* 2003, Willmot *et al.* 2004, Fang *et al.* 2005). It has been suggested that ongoing enlargement of ICH might be detected on the basis of extravasation of radiographic contrast into the hematoma after CT angiography (Becker *et al.* 1999).

Among patients with anticoagulant-related ICH, immediate normalization of coagulation to prevent subsequent hematoma enlargement ought to be a major target for therapy. Treatment with prothrombin complex concentrate seems to be the most effective alternative (Fredriksson *et al.* 1992, Yasaka *et al.* 2003). In cases of life-threatening ICH associated with idiopathic thrombocytopenic purpura, platelet transfusion is recommended (Olson 1993). Use of recombinant activated factor VII (rFVII) to prevent ICH enlargement has recently been investigated (Mayer at al. 2005). Treatment with rFVII within 4 hours after the onset of ICH limited the growth of the hematoma, reduced mortality, and improved functional outcome at 90 days, but resulted in increased frequency of thromboembolic adverse events.

Expansion of the hematoma is the most common cause of underlying neurologic deterioration within the first few hours after the onset of ICH, but progressive cerebral edema is also implicated in neurologic deterioration that occurs > 12 hours after the onset of ICH (Flemming *et al.* 1999, Qureshi *et al.* 2001). Deterioration may be recognized clinically based on worsening deficit, new deficit, or declining level of consciousness (Flemming *et al.* 1999).

Neurologic deterioration after admission has been observed in 23–33% of patients with ICH (Mayer *et al.* 1994, Qureshi *et al.* 1995, Flemming *et al.* 1999). The risk of deterioration is highest on the first in-patient day and declines on the subsequent days (Mayer *et al.* 1994). The presence of a large hematoma and ventricular blood increases the risk of subsequent deterioration and death (Mayer *et al.* 1994, Qureshi *et al.* 1995).

2.6 Prevention of intracerebral hemorrhage

Because the outcome after ICH is so poor, primary prevention is of supreme importance. Prevention and treatment of hypertension would probably be the most effective measures for reducing the incidence of ICH. Lifestyle modifications include dietary change and promotion of physical activity to avoid obesity and to prevent hypertension (MacWalter *et al.* 2001). Decreasing sodium chloride intake has been shown to reduce blood pressure (Midgley *et al.* 1996). Excessive alcohol use (Juvela *et al.* 1995, Gill *et al.* 1991, Calandre *et al.* 1986, Monforte *et al.* 1990, Iso *et al.* 1995, Kiyohara *et al.* 1995, Hillbom *et al.* 1999) and smoking (Thrift et al 1998, Qureshi *et al.* 1997, Hankey 1999, Kurth *et al.* 2003) should be avoided and probably also coffee drinking, although the data on the effect of coffee are less conclusive (Costa 2002).

When patients take warfarin, it is important to strive for good control of INR to minimize the risk of hemorrhagic complications, including ICH. When prescribing warfarin or aspirin as well as other antiplatelet agents, it is good practice also to treat possible concurrent hypertension. (MacWalter *et al.* 2001.)

Effective control of hypertension is especially important after ICH, to prevent re-bleeding (MacWalter *et al.* 2001). Inadequate control of hypertension is a major risk factor for recurrent ICH, and outcome after recurrent ICH has been shown to be worse than after the primary bleed (Passero *et al.* 1995, Gonzáles-Duarte *et al.* 1998).

2.7 Role of aspirin in intracerebral hemorrhage

Aspirin (acetylsalicylic acid) and other NSAIDs act by blocking prostaglandin (PG) synthesis. The subsequent reduced formation of various eicosanoids (thromboxane A_2, PGE_2, and prostacyclin) in different tissues accounts for the variety of pharmacological effects of aspirin (Patrono 1994). Thromboxane A_2 (TXA_2) is mainly synthetized in platelets and promotes platelet activation and vasoconstriction. Its effects are antagonized by platelet-inhibitory and vasodilatory prostacyclin (PGI_2), which is produced in endothelial cells (Schafer 1996).

2.7.1 Mechanism of platelet activation

Thromboxane biosynthesis in platelets is induced by platelet activation. Normally, a monolayer of endothelial cells lines the intima of the entire circulatory tree and secretes potent, locally acting platelet-inhibitory products, e.g. PGI_2 and nitric oxide (NO). These compounds also relax the smooth muscle in the vessel wall. (see Schafer 1996.)

At a site of vascular injury, thromboresistant endothelium is disrupted and prothrombotic subendothelial vessel wall constituents (e.g. collagen) are exposed to blood. Two adhesion receptors on platelet membrane, glycoprotein (GP) Ib-IX-V and GPVI, that bind von Willebrand factor (vWf) and collagen, respectively, are primarily responsible for regulating platelet adhesion to the vessel wall. Other platelet activators can simultaneously bind to their specific platelet surface receptors. (Schafer 1996, Andrews & Berndt 2004.)

Following adhesion, rapid signal transduction leads to platelet activation, cytoskeletal changes associated with shape change, and activation of platelet integrins. The major platelet integrin αIIbβ3 (GPIIb-IIIa) binds vWF or fibrinogen to mediate platelet aggregation. Platelet activation involving GPIb-IX-V or GPVI also leads to secretion of preformed platelet agonists (e.g. ADP) from intracellular storage granules. Platelet activation also induces phospholipase A_2 (PLA_2) -mediated release of free arachidonic acid from membrane phospholipoid pools, which initiates biosynthesis of TXA_2. Released ADP and TXA_2 bind to their respective platelet receptors to further amplify the platelet activation process. (Schafer 1996, Andrews & Berndt 2004.)

Finally, the activated and degranulated platelets attach to each other in the process of aggregation to form an occlusive thrombus at the site of vascular damage. The thrombus accelerates the coagulation cascade, leading to stabilization of the clot by fibrin and αIIbβ3-dependent contraction. (see Schafer 1996, Andrews & Berndt 2004.)

In endothelial cells, enhanced PGI_2 production is induced as a compensatory mechanism for increased TXA_2 production in platelets (Catella-Lawson 2001). PGI_2 released from endothelial cells binds to its receptors on platelet membrane and mediates its inhibitory effect by raising intraplatelet cyclic adenosine monophosphate (cAMP) level. (Schafer 1996.)

2.7.2 Prostaglandin biosynthesis

The steps of PG synthesis in platelets and endothelial cells are shown in Figure 1: First, free arachidonic acid (AA) is hydrolyzed from cell membrane phospholipid pools by PLA_2. AA is converted by cyclooxygenases (COX-1 in platelets and COX-2 in endothelial cells) to PG endoperoxidases, PGG_2, and PGH_2. These endoperoxidases are metabolized to thromboxane A_2 (TXA_2) by thromboxane synthase in platelets and to prostacyclin (PGI_2) by prostacyclin synthase in endothelial cells. Finally, TXA_2 and PGI_2 break down to inactive metabolites thromboxane B_2 (TXB_2) and 6-ketoprostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$). (Samuelsson *et al.* 1975, Roth & Calverley 1994, Schafer 1996, Catella-Lawson 2001.) Two major metabolic pathways of TXA_2 are dehydrogenation to 11-dehydrothromboxane B_2 (11-dehydro-TXB_2) and β-oxidation to 2,3-dinor-TXB_2 (Roberts *et al.* 1981). 6-keto-$PGF_{1\alpha}$ is metabolized to 2,3-dinor-6-keto-$PGF_{1\alpha}$. (Brash *et al.* 1983.)

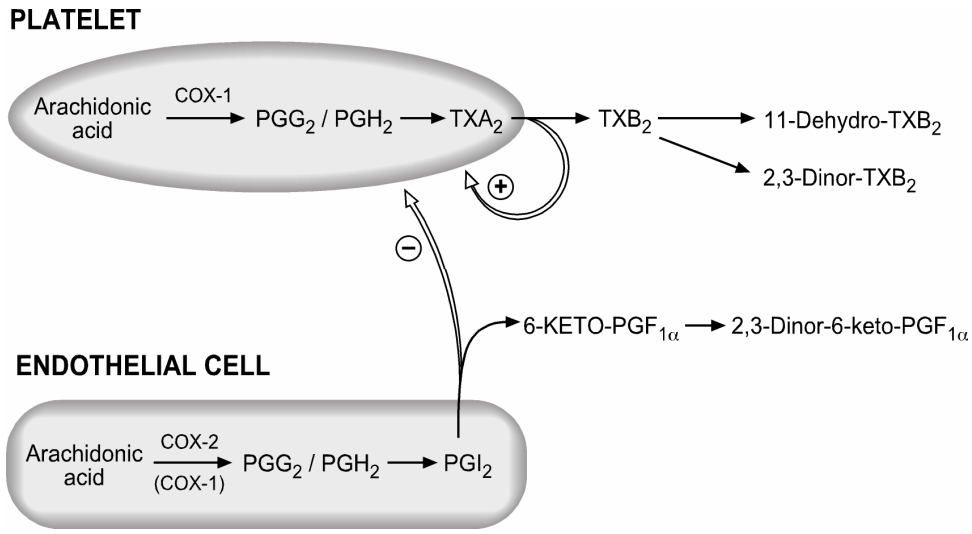

Fig. 1. Prostaglandin biosynthesis in platelets and endothelial cells, the effects of TXA_2 and PGI_2 on platelet activation, and their metabolism. TXA_2 enhances (+) and PGI_2 inhibits (-) platelet activation. (FitzGerald *et al.* 1983, Patrono *et al.* 1990, Schafer 1996, Catella-Lawson 2001.)

2.7.3 Mechanism of the antithrombotic effect of aspirin

Aspirin blocks PG biosynthesis by irreversibly acetylating the COX enzyme. Aspirin has a high affinity to the single serine residue at position 530 within the active site of COX. The hydroxyl group of the serine residue is acetylated through transfer of aspirin's acetyl group ($COCH_3$), and aspirin itself is converted to salicylic acid (Figure 2). (Roth & Carverley 1994, Patrono 1994, Catella-Lawson 2001.) This process of acetylation produces a covalent O-acetyl bond that resists hydrolysis under intracellular conditions and results in irreversible inactivation of platelet COX (Roth & Carverley 1994).

In contrast, NSAIDs other than aspirin bind reversibly at the active site of the COX enzyme and exert a short-lived effect on platelets (Roth & Calverley 1994, Catella-Lawson 2001). Selective COX-2 inhibitors suppress PGI_2 formation without concomitant inhibition of TXA_2 biosynthesis (Catella-Lawson 2001). Experimental research suggests that these drugs may contribute to the prothrombotic state, and they have actually been observed to increase the risk of serious cardiovascular events (Bresalier *et al.* 2005, Solomon *et al.* 2005).

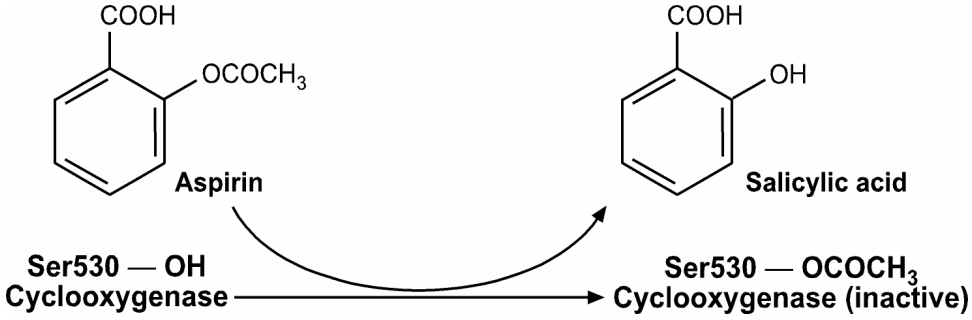

Fig. 2. Aspirin acetylates the hydroxyl group of a serine residue at position 530 in the polypeptide chain of human cyclooxygenase and inactivates the enzyme. Aspirin itself is converted to salicylic acid. (Modified from Patrono 1994.)

As fragments of the cytoplasm of bone marrow megakaryocytes, blood platelets lack a nucleus and are unable to synthesize new mRNA. Therefore, the inactivation of COX by aspirin cannot be repaired during the life-span of platelets (approximately 8–10 days). Consequently, after the withdrawal of aspirin treatment, COX activity recovers slowly as a function of platelet turnover. (Burch *et al.* 1978, Patrono 1994, Roth & Carverley 1994.)

However, the inhibitory effect of aspirin on platelet TXA_2 production is very rapid, with maximal effects attained within 15–30 minutes (Dabaghi *et al.* 1994). It has been suggested that the interaction of platelets and aspirin takes place in portal circulation. Apparently, orally taken aspirin enters portal blood at about the same rate as do platelets from preportal circulation, and during about 30 minutes after aspirin ingestion, the entire mass of platelets of the treated individual is exposed to aspirin being absorbed from the upper gastrointestinal tract. Actually, access to platelets in portal rather than extraportal blood may be an important aspect of aspirin's antiplatelet effect because the drug is partially deacetylated, and thus inactivated, during its subsequent passage through the liver. (Pedersen & FitzGerald 1984, Roth & Carverley 1994.) Aspirin has a half-life of only 20 minutes in systemic circulation (Schafer 1996).

Aspirin also blocks the production of PGI_2, which is the major COX metabolite of AA in vascular endothelial cells (see Schafer 1996). Although platelet and endothelial COX are equally sensitive to aspirin, under *in vivo* conditions platelet PG synthesis is much more sensitive to orally administered aspirin than the synthesis in other cells. Direct studies of patients show that inhibition of PGI_2 synthesis in endothelial cells requires higher doses of aspirin than does blockade of TXA_2 formation in platelets (FitzGerald *et al.* 1983a). However, considerable overlap exists between the two effects, and no dose of aspirin will block TXA_2 formation completely without affecting PGI_2 production (Roth & Carverley 1994). It has been shown that daily use of 40 mg of aspirin for one week is able to inhibit a large proportion of maximum TXA_2 release, with PGI_2 synthesis being scantly affected (Tohgi *et al.* 1992). In this study, PGI_2 production decreased significantly after aspirin doses of 320 or 1,280 mg/day.

There has been a downward trend in the recommended daily dose of aspirin for the prevention of arterial thromboembolism, and a dose of 75–160 mg is currently considered sufficient in all high-risk situations (Patrono 1994, Catella-Lawson 2001).

An important distinction between PGI_2 and TXA_2 production with regard to aspirin-dependent inhibition is the ability of endothelial cells to replace inactive COX by protein

synthesis (Roth & Carverley 1994). Accordingly, the production of PGI_2 in endothelial cells recovers more quickly after discontinuation of aspirin treatment than does TXA_2 production by platelets.

2.7.4 Measurement of platelet function

Measurement of bleeding time (Ivy *et al.* 1941) is a simple test of platelet function. Standardized bleeding time reflects the overall hemostatic role of platelets *in vivo* (Harker & Slichter 1972). Aspirin ingestion has been shown to significantly prolong the mean bleeding time in normal subjects (Mielke *et al.* 1969).

Evidence of increased *in vivo* platelet activation can also be attained by the detection of elevated plasma levels of beta-thromboglobulin (BTG). BTG is released into circulation by the α-granules of platelets upon activation, and it is a reliable marker of *in vivo* platelet activation. (Fisher *et al.* 1982.)

Platelet function can be measured *in vitro* by evaluating platelet aggregation in relation to endogenously formed compounds (ADP, adrenaline, collagen and thrombin) that affect platelet function. Thromboxane release associated with platelet aggregation can be used as another measure of platelet function. (Siess *et al.* 1981.)

Measurement of TXA_2 *in vivo* is complicated due to its very short half-life, and its more stable metabolite TXB_2 also disappears rapidly from human circulation. Furthermore, AA release from biological membranes (and thus the synthesis of TXA_2 and PGI_2) is likely to be phasic rather than continuous. The third problem is that the measurement of these products is highly liable to artifacts when samples (e.g. plasma) are obtained by invasive techniques, which inevitably promotes *ex vivo* platelet activation. (FitzGerald *et al.* 1983b, Patrono *et al.* 1990.)

One method of circumventing problems of sampling-induced artifacts and *ex vivo* prostaglandin formation is the measurement of metabolites that have an extended half-life. The only noninvasive approach to the quantification of endogenous TXA_2 and PGI_2 biosynthesis is the measurement of their metabolites in urine (FitzGerald *et al.* 1983b). TXB_2, the inactive metabolite of TXA_2, undergoes two major pathways of metabolism resulting in the formation of 11-dehydro-TXB_2 and 2,3-dinor-TXB_2 (Patrono *et al.* 1990). The most abundant metabolite of PGI_2 in urine is 2,3-dinor-$PGF_{1\alpha}$ (FitzGerald *et al.* 1983b). These urinary metabolites can be determined by radioimmunoassay (Riutta *et al.* 1992, Riutta *et al.* 1994, Numminen *et al.* 2000) or enzyme immunoassay (Bruno *et al.* 2002).

2.7.5 Platelet function in vascular diseases

Increased platelet activation has been observed in numerous vascular diseases, including unstable angina, myocardial infarction, severe peripheral atherosclerosis, transient ischemic attack, and ischemic and hemorrhagic stroke (Numano *et al.* 1981, Catella & FitzGerald 1987, Patrono *et al.* 1990, van Wersch & Franke 1993, Koudstaal *et al.* 1993, Liu *et al.* 1994, van Kooten *et al.* 1994, van Kooten *et al.* 1999). Increased platelet activation has also been shown in patients with non-insulin-dependent diabetes mellitus or

type IIa hypercholesterolemia and in current smokers (Patrono *et al.* 1990, Rångemark *et al.* 1992).

2.7.5.1 Platelet function and aspirin effects in ischemic stroke

van Wersch and Franke (1993) observed unphysiologically enhanced ADP-induced platelet activation in 68% of their patients with cerebral infarction who were not aspirin users. Elevated BTG as a marker of platelet activation has also been observed in cerebrovascular disease (Fisher *et al.* 1982, Liu *et al.* 1994).

Koudstaal *et al.* (1993) demonstrated increased urinary excretion of 11-dehydro-TXB_2 in 51% of their patients with ischemic stroke. They also observed that 50 mg of aspirin per day for 7 days was followed by an average reduction of 85% in thromboxane biosynthesis. Somewhat later they reported, on the basis of consecutive urine samples obtained during the first 48 hours after onset of ischemic stroke, that patients with enhanced thromboxane biosynthesis showed peak values of 11-dehydro-TXB_2 excretion at different time points, suggesting episodic platelet activation in acute ischemic stroke (van Kooten *et al.* 1994). They also observed that repeatedly increased 11-dehydro-TXB_2 levels were related to the severity of stroke on admission (van Kooten *et al.* 1997).

Increased urinary excretion of 11-dehydro-TXB_2 in acute ischemic stroke has also been observed by other investigators (McConnell *et al.* 2001). Cherian *et al.* (2003) recorded increased blood concentrations of soluble P-selectin and platelet-derived microvesicles as markers of platelet activation within 7 days after acute ischemic stroke.

Increased excretion of 11-dehydro-TXB_2 has also been reported 1–4 (Bruno *et al.* 2002) and 3–9 months after ischemic stroke (van Kooten *et al.* 1999). In the latter study, a significant association between poor stroke outcome and increased urinary 11-dehydro-TXB_2 excretion was observed. These observations, together with those of increased 11-dehydro-TXB_2 excretion in such a chronic condition as atherosclerosis (Catella & FitzGerald 1987), raise the possibility that thromboxane biosynthesis may be chronically enhanced due to generalized vascular disease in patients at risk for myocardial infarction, stroke, etc.

2.7.5.2 Platelet function in intracerebral hemorrhage

Platelet function has been investigated in only a few studies involving ICH patients. van Wersch and Franke (1993) observed enhanced platelet aggregation in 9/24 (37.5%) of patients with ICH. Liu *et al.* (1994) reported elevated plasma BTG concentrations in both acute non-hemorrhagic and hemorrhagic strokes. Their study included 21 patients with hemorrhagic stroke.

Urinary excretion of 11-dehydro-TXB_2 has been found to be increased in only one study including 11 patients with ICH (van Kooten *et al.* 1999). In this study, 11-dehydro-TXB_2 excretion was determined in the late phase (3 to 9 months) after ICH. Altogether, these 3 studies have included only 56 patients with ICH.

3 Aims of the research

For effective prevention of ICH, it is important to recognize the modifiable risk factors, such as lifestyle factors and medication, which might increase the risk for ICH. The significance of antiplatelet agents as factors affecting outcome after ICH is uncertain. Few studies have assessed the long-term prognosis beyond 2 years and the risk factors for death after ICH.

The aims of the present study were:

1. to identify the role of lifestyle factors, previous diseases, and medication as risk factors for primary ICH (I),
2. to explore platelet activation and primary hemostasis after the onset of acute ICH (II),
3. to explore the role of aspirin medication on hematoma growth in patients with ICH (III),
4. to determine the effect of aspirin on short-term outcome after ICH (III),
5. to determine the long-term survival of patients with ICH compared to community-based control subjects (IV).

4 Subjects and methods

4.1 Subjects

Study I involves 98 consecutive patients (56 men, 42 women; age, 65 ± 11 [mean ± SD] years) who had been admitted into the Department of Neurology, Oulu University Hospital, because of ICH between January 1993 and September 1995. ICH was verified by head CT on admission in all cases. Those with a brain tumor, saccular arterial aneurysm, arteriovenous malformation or head trauma, as well as those not living in the catchment area of the hospital were excluded. Two hundred and six control subjects, matched for age (± 3 years) and sex, were randomly drawn from the population register of the catchment area of Oulu University Hospital.

Study II covers a subsample from the patient population described above, i.e. 43 patients (23 men, 20 women; mean age 66 ± 11 years) for whom serial urine samples obtained in the acute phase for measuring TXA_2 and PGI_2 excretion were available. Urine sampling was only performed between January 1994 and September 1995. In addition to the aforementioned exclusion criteria, those who were on anticoagulant therapy or were treated surgically were excluded. Control data of prostanoid excretion from 23 healthy subjects aged 29–59 (mean 45 ± 8.1) years were available for comparison with the patient data.

For *Study III*, all subjects with incident ICH between January 1993 and September 1995 in the population (356,026 on December 31, 1993) of Northern Ostrobothnia, Finland, were identified (n = 208; mean age, 67 ± 11). In addition to the patients admitted into the Department of Neurology who were already included in Study I, the study included all those patients who were admitted into the other departments of Oulu University Hospital, i.e. the Departments of Neurosurgery and Internal Medicine, because of spontaneous ICH. ICH was verified based on a head CT scan on admission in all cases. Exclusion criteria were the same as in Study I. In addition, the fatal cases of ICH in the community during the study period were identified from the Causes of Death Register provided by Statistics Finland, but cases with the diagnosis of ICH on the death certificate without verification at autopsy or by brain imaging were excluded.

Study IV includes those patients from the population-based cohort of Study III who survived for the first 3 months after ICH (n = 140). The 206 controls of Study I also served as a control group in this study.

4.2 Ethics

The study protocol was approved by the ethics committees of the Medical Faculty, University of Oulu, and Oulu University Hospital. Informed consent was obtained from all subjects (I, II). The data and permission for the study were given by a proxy if the patient was too ill to cooperate. Permissions for the use of the death records and for reviewing the forensic autopsy charts (III, IV) were given by Statistics Finland and Oulu Provincial Government, respectively.

4.3 Clinical assessments

The author interviewed all the patients (I, II) and the control subjects (I, IV). For the ICH patients who were confused, unconscious, or dysphasic or died soon after admission, family members were interviewed. The patients and/or their relatives were personally interviewed, but the control subjects were interviewed over telephone. For Study I, the controls were interviewed on days of the week matched with the bleeding days of the patients. The time of ICH onset was defined to be the acute onset of headache and/or a neurological deficit.

Information was gathered by using a structured questionnaire including items on the use of medicines, the events preceding the onset of stroke, previous diseases, lifestyle factors, exact time of disease onset, and body height and weight. To avoid recall bias, all available hospital records were reviewed for the diagnoses, medications, and blood pressure histories. Previous hospital records were available for all of the ICH patients and 166 (81%) of the control subjects.

The subjects were considered to be hypertensive if their blood pressure readings preceding the index stroke had repeatedly exceeded 160/95 mmHg, or if they were taking antihypertensive medication. Those without antihypertensive medication but with blood pressures repeatedly exceeding 160/95 mmHg and those who had, unsupervised, terminated their medication for blood pressure were classified as subjects having untreated hypertension. Body mass index (BMI) was used as the index of relative weight. The patients were recorded to have diabetes mellitus if they used oral hypoglycemic agents or insulin. Previous hemorrhagic strokes (ICH and subarachnoid hemorrhage) as well as ischemic strokes were recorded. Cardiac disease included myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation. The patients were recorded as having epilepsy if they used antiepileptic medication. The patients were positive for a history of epistaxis if they had had more than one episode of nosebleed during the preceding five years, or if they had visited an outpatient clinic of otorhinolaryngology or had been hospitalized because of epistaxis. For Study II, patients with a history of epistaxis or hematuria were classified as having a bleeding tendency, and the coronary heart disease category also included patients with previous myocardial infarction.

For Studies I and II, recent drinking of alcohol was estimated by asking the patients and controls how many drinks of alcohol (standard drink = 12 g of ethanol) they had consumed during the week preceding the onset of ICH or, in the case of control subjects, during the week preceding the interview. Relatives were also interviewed about the patients' recent consumption of alcohol. The larger amount, reported either by the patient

or the relative, was used in the analysis. To identify problem drinking, the patients were also interviewed with the short GAGE questionnaire (Mayfield *et al.* 1974, Bernadt *et al.* 1982, Bush *et al.* 1987). Recent heavy drinkers were subjects whose alcohol intake had exceeded 300 g of ethanol during the week preceding the index stroke or the interview. Former heavy drinkers included subjects whose recent mean weekly alcohol intake had regularly exceeded 300 g of ethanol, or who gave two or more positive answers to the four questions of the CAGE questionnaire, but reported no alcohol intake during the week preceding the index admission or interview.

Smokers were categorized into current cigarette smokers and nonsmokers. The latter included former regular cigarette smokers who had quit a year or more ago. The use of all kinds of medicines, including nonsteroidal anti-inflammatory drugs (NSAIDs) purchased over the counter, during the week preceding admission for the index stroke or the interview was recorded. Every patient's aspirin medication was discontinued on admission, and none of the patients used aspirin between the acute phase and the follow-up visit 3 months later.

The patients were asked whether they had engaged in exceptionally strenuous physical exertion (for example pushing a car stuck in snow, lifting a heavy weight, heavy household cleaning work, or other physical exertion greatly exceeding their usual level of daily physical activity) within 24 hours before the onset of the index stroke. Likewise, the control subjects were asked about exceptional physical exertion within 24 hours before the interview.

For Studies III and IV, data about previous diseases, blood pressure histories, medications and lifestyle factors were extracted from the hospital records for the subjects not included in Study I. Data were gathered according to the protocol used in interviewing the subjects for Studies I and II. Data were extracted from the forensic autopsy charts of those who had succumbed on the scene and outside the hospital. Medical complications, such as myocardial infarction, heart failure, arrhythmias, infection, deep vein thrombosis, or pulmonary embolus, during hospitalization were recorded, as were also neurosurgical interventions. Subjects with a note about heavy drinking of alcohol in their charts were classified as heavy drinkers. Subjects were categorized into current cigarette smokers and nonsmokers. Other data were recorded according to the same principles as for Studies I and II.

For Study II, the patient's clinical condition was assessed on admission and 1 week after the ICH by using the Glasgow Coma Scale (GCS) score (Teasdale & Jennett 1974) and the prognostic score of the Scandinavian Stroke Scale (SSS-PRG) (Scandinavian Stroke Study Group 1985). If the score on either of these scales was higher after 1 week than on admission, the patient was classified as improved. Outcome was assessed 3 months after the bleeding episode by using the Glasgow Outcome Scale (GOS) (Jennett & Bond 1975) on scheduled follow-up visits or other subsequent hospital visits approximately 3 months after the ICH. Impaired outcome was defined as moderate-to-severe disability, vegetative state, or death.

Table 4. Determination of the ICH Score (Hemphill et al. *2001).*

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

For Study III, the ICH score (Hemphill *et al.* 2001) was calculated as indicated in Table 4. Functional outcome at 3 months was assessed according to GOS as described above. Those who showed good recovery at discharge were assumed to maintain this state after 3 months, if they had not been readmitted.

4.4 Radiological assessments

All the CT scans were analyzed, and the locations and volumes of the hematomas were measured by the same neuroradiologist, who was blind to the patients' clinical conditions, medications and outcomes. The volumes of hematomas were measured in line with the previously described principles (Broderick *et al.* 1993c), and hematomas were divided into categories based on their location in the subcortex, basal ganglia (putamen, nucleus caudatus, and combined, extending into the thalamus and subcortical white matter), thalamus, pons, or cerebellum. The presence of intraventricular bleeding was recorded.

For Studies II and III, the patients underwent repeated head CT scanning to verify possible hematoma enlargement or hydrocephalus. The median time interval between the baseline and the second CT scan was 7 days. For study III, a second CT scan was available for 104/208 patients. A second CT scan was always obtained if clinical deterioration occurred, except for the patients who were already moribund on admission.

4.5 Laboratory procedures (Study II)

Urine was collected for the determination of 11-dehydrothromboxane B_2 (11-dehydro-TXB_2), 2,3-dinor-thromboxane B_2 (2,3-dinor-TXB_2), and 2,3-dinor-6-ketoprostaglandin $F_{1\alpha}$ (2,3-dinor-$PGF_{1\alpha}$) during the night (10 p.m. to 6 a.m.) after admission, during the nights of the first week after admission, and during one night at the follow-up visit. The samples of urine were frozen immediately after collection and stored at -70° C until extraction. 11-dehydro-TXB_2, 2,3-dinor-TXB2, and 2,3-dinor-$PGF_{1\alpha}$ were determined after solid-phase extraction by radioimmunoassay as previously reported (Riutta *et al.* 1992, Riutta *et al.* 1994, Numminen *et al.* 2000). In order to avoid differences due to inter- and intraindividual variations in diuresis, the excretion of prostanoids was correlated with the excretion of creatinine, which was determined from the urine samples spectrophotometrically by the picric acid method using a commercial assay kit (Orion, Espoo, Finland). The urinary excretion rates were expressed as picograms per micromole of creatinine. The investigator of the laboratory parameters was blinded to the patients' clinical condition and use of aspirin.

Bleeding times were assessed on admission, daily during the first week after admission, and at the control visit 3 months after the ICH by the Ivy method (Ivy *et al.* 1941, Mielke *et al.* 1969).

4.6 Mortality data (Studies III and IV)

The patients' survival during the first 3 months after the onset of ICH and the causes of death were checked from hospital and death records (Statistics Finland). For Study IV, the patients and controls were followed up for 7 years. This time point was chosen because it was the longest time for which complete follow-up data of the controls were available.

4.7 Statistical methods

In Study I, the categorical variables were compared using Fisher´s exact two-tailed test or Pearson's χ^2 test. Univariate and multivariate odds ratios (OR) with 95% confidence intervals (CI) were calculated by logistic regression (maximum likelihood method). Stepwise logistic regression ($p < 0.1$ for entry limit and $p > 0.15$ for removal limit) was used to test the significant independent risk factors for ICH. A two-tailed p-value below 0.05 was considered statistically significant.

In Study II, Fisher´s exact 2-tailed test, Pearson's χ^2 test, Mann-Whitney U-test, Student's t-test, analysis of variance (ANOVA) with corrected multiple comparisons in pairs by the Bonferroni method, and Spearman's rank correlation coefficients (r_s) were used as appropriate. Stepwise logistic regression was used to find out significant independent risk factors for impaired outcome after ICH. Adjustments of ORs were made for all the parameters listed in the tables (Study II) by using logistic regression models. In the patients with a complete set of urine samples, the effect of the time elapsed after ICH and the different grouping variables of TXA_2 and PGI_2 metabolites were compared by repeated-measures ANOVA. For ANOVA, the values for prostanoid variables were

analyzed after logarithmic transformation, if necessary, to obtain the equality of variances between the different groups.

In Studies III and IV, categorical variables were compared by Fisher's exact two-tailed test and Pearson's χ^2 test. Continuous variables were compared between the groups by the Mann-Whitney U-test, Student's t-test, and analysis of variance (ANOVA). For life table analysis and the Cox proportional hazards regression model, each patient was followed to death or until 3 months (III) or 7 years (IV) after ICH. 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 Cox proportional-hazards model with a forward stepwise regression procedure served to determine the significance of several variables in predicting relative risks (RR) and 95% CIs for death. The following variables, which were known at the beginning of follow-up, were analyzed: age; sex; history of hypertension, ischemic, and/or hemorrhagic stroke, cardiac disease, diabetes, cancer, and epilepsy; ICH score; warfarin treatment; regular aspirin use; bleeding disorders; current smoking and heavy alcohol drinking; and GOS score at 3 months after ICH (Study IV). The assumption of proportionality was checked. The test for significance was based on changes in log (partial) likelihood.

5 Results

5.1 Risk factors for ICH (Study I)

Treated hypertension was equally common in both the patients with ICH and the control subjects in risk factor analysis (I). However, untreated hypertension was much more common in the patients than in the controls**.** Other significant differences between the groups were observed in the history of epilepsy, hemorrhagic or ischemic stroke, epistaxis, recent heavy drinking of alcohol, recent strenuous physical exertion, and dipyridamole medication. (I; Table 1).

In multivariate analysis, untreated hypertension was the most potent risk factor for ICH (OR 6.95, 95% CI 3.06–15.8, $p < 0.001$), but treated hypertension only tended to associate with the occurrence of ICH (OR 1.76, 95% CI 0.91–3.42). Recent strenuous physical exertion (OR 3.97, 95% CI 1.95–8.10, $p < 0.01$), history of ischemic stroke (OR 3.83, 95% CI 1.70–8.63, $p < 0.01$), epilepsy (OR 13.8, 95% CI 2.49–76.6, $p < 0.01$), and history of epistaxis (OR 2.92, 95% CI 1.28–6.62, $p < 0.05$) were the other significant risk factors for ICH (I; Table 2). When the subjects with anticoagulant treatment were omitted from the model and the subjects using NSAIDs remained, the history of epistaxis was still a significant risk factor for ICH (OR 2.62, 95% CI 1.14–6.01) suggesting that the use of anticoagulants did not influence the epistaxis-associated risk for ICH.

The use of NSAIDs (73% had used aspirin) associated significantly with the history of epistaxis ($p < 0.05$). When a logistic model including aspirin use, history of epistaxis, and their interaction, recent heavy drinking of alcohol, hypertension, ischemic stroke, epilepsy, physical exertion, age, and sex was constructed, history of epistaxis (adjusted OR 2.75, 95% CI 1.11–6.81, $p < 0.05$), aspirin use (OR 14.7, 95% CI 2.03–106, $p < 0.01$), and their interaction (OR 16.9, 95% CI 2.48–114, $p < 0.01$) all turned out to be significant independent risk factors for ICH.

In men, treated and untreated hypertension, previous ischemic stroke, recent strenuous physical exertion, and history of epistaxis were significant risk factors for ICH (I; Table 3). In women, untreated hypertension, epilepsy, and recent strenuous physical exertion were significant risk factors.

5.2 Prostanoid excretion and bleeding time in patients with acute ICH (Study II)

Among the 43 patients included in the analysis of prostanoid excretion and bleeding times, there were 13 regular and 8 occasional aspirin users. The median daily dose of the regular users was 250 mg (range 250 to 600 mg). The maximum dose of aspirin consumed by the occasional users amounted to 1500 mg (median 500 mg) during the week preceding ICH. The aspirin users had more frequently hypertension in their history than the nonusers. History of ischemic stroke, bleeding tendency, coronary heart disease, and hematomas in the basal ganglia were also more common among the aspirin users than the other patients, but these differences were not statistically significant. Hematoma volumes as well as GCS and SSS-PRG scores on admission were similar in the two groups (II; Table 1).

The levels of 11-dehydro-TXB_2, 2,3-dinor-TXB_2, and 2,3-dinor-$PGF_{1\alpha}$ excretion into urine on admission (0–3 days after the onset of ICH) were significantly higher in the patients without prior use of aspirin than the controls ($p < 0.001$, < 0.001, and 0.019, respectively) (II; Table 2). However, the mean urinary excretion rates of 11-dehydro-TXB_2, 2,3-dinor-TXB_2, and 2,3-dinor-$PGF_{1\alpha}$ on admission in the aspirin users did not significantly differ from those of the controls.

Serial measurements of 11-dehydro-TXB_2 excretion into urine showed that the mean 11-dehydro-TXB_2 excretion was significantly ($p = 0.048$) lower in the users than nonusers of aspirin on day 3 after the onset of ICH, but on days 1 and 2 the difference did not reach statistical significance because the number of samples from those days was small (II; Figure 1). When the urinary values of 11-dehydro-TXB_2 on days 1–2 and 5–6 were compared, the values increased significantly ($p = 0.007$) as more time elapsed, and significant interactions between the groups and time were also observed ($p = 0.028$) (i.e. the values changed differently over time, depending on previous aspirin use).

The levels of 2,3-dinor-$PGF_{1\alpha}$ obtained on the first day after the onset of ICH were significantly ($p = 0.001$) lower in the aspirin users than nonusers. The difference disappeared during the following few days. When the urinary values of 2,3-dinor-$PGF_{1\alpha}$ on days 1–2 and 5–6 were compared, there was a significant ($p = 0.015$) effect of the interaction between aspirin use and the time of sampling on the 2,3-dinor-$PGF_{1\alpha}$ excretion levels.

The ratios of 11-dehydro-TXB_2 and 2,3-dinor-TXB_2 to 2,3-dinor-$PGF_{1\alpha}$ did not significantly differ between the groups at any time, and the ratios did not show significant correlations with bleeding time.

Three months after ICH, the excretion levels of 11-dehydro-TXB_2 and 2,3-dinor-TXB_2 (118.2 pg/µmole creatinine; 95% CI, 88.7–147.7 and 71.4 pg/µmole creatinine; 95% CI, 54.9–88.6, respectively) in all patients were at the same high level as in the nonusers of aspirin on admission, but the levels were significantly higher than in the controls ($p < 0.001$ and < 0.001, respectively). On the other hand, the mean level of 2,3-dinor-$PGF_{1\alpha}$ (25.4 pg/µmole creatinine; 95% CI, 17.0–33.9) did not significantly differ from that of the controls any longer ($p = 0.12$). Excretion of 11-dehydro-TXB_2 into urine during the control visit correlated with impaired outcome according to GOS ($r_s = 0.445$, $p = 0.02$).

The aspirin users also had significantly ($p = 0.032$) longer bleeding times on admission than the nonusers. The mean bleeding time on admission was 362 sec (95% CI, 272–451) in the aspirin users and 250 sec (195–306) in the nonusers.

5.3 Short-term outcome after ICH (Studies II and III)

We identified altogether 208 subjects with verified spontaneous ICH during the study period, and the crude annual incidence rate in the population of Northern Ostrobothnia was hence 21/100,000 (III). Two hundred and three patients were admitted into Oulu University Hospital, and the diagnosis was verified based on a head CT scan. Five subjects succumbed elsewhere, and their diagnoses were verified at autopsy. The aspirin users were significantly older than the subjects using neither aspirin nor warfarin ($p = 0.004$). History of cardiac disease ($p < 0.01$) and ischemic stroke ($p < 0.01$) were more common in the group of aspirin/warfarin users than in the nonuser group.

On admission, the aspirin users did not have larger hematomas than the nonusers, but the warfarin users had significantly larger hematomas than the aspirin users ($p = 0.015$) or those who used neither aspirin nor warfarin ($p = 0.012$). The CT scanning after admission was performed on the day when the symptoms of ICH appeared in 76% of the warfarin users and in 73% and 70% of the aspirin users and the nonusers of aspirin/warfarin, respectively. The groups differed significantly by outcome at 3 months ($p < 0.001$), and bleeding into the ventricles was most frequent in the patients who had been on warfarin ($p = 0.001$). Overall mortality within three months was 32.7%. The mortality of the regular aspirin users was 43.2%, whereas the mortality of the nonusers of aspirin/warfarin was only 21.7%. The warfarin users showed the highest mortality (73.1%). The log-rank test revealed significant differences between the survival curves (III; Figure 1) of the aspirin users and the nonusers of aspirin/warfarin ($p = 0.0048$) as well as between the warfarin users and the nonusers of aspirin/warfarin ($p < 0.0001$) and between the aspirin and warfarin users ($p = 0.0026$). The significant predictors of death during the first 3 months after the onset of ICH in multivariate analysis were ICH score > 2 on admission, warfarin use preceding ICH, and regular aspirin use preceding ICH (III; Table 3). Diabetes was also significant in univariate analysis, but the significance was lost in multivariate analysis. Of the 47 patients with ICH score > 2, 55% had GCS scores of 3–4, 40% had GCS scores of 5–12, 74% had hematoma volume ≥ 30 cm^3, 89% had intraventricular and 13% infratentorial hemorrhage, and 28% were aged ≥ 80 years.

The primary bleed was the cause of death in 87% of the subjects who died within 3 months. In the group of aspirin users, 17 (89%) of the 19 fatalities were due to the primary bleed. The two others died of pneumonia and pulmonary embolism. Among the warfarin users, the cause of death was the primary bleed in 18 cases (95%), and one patient died of thrombosis of the abdominal aorta. Thirty nonusers of aspirin/warfarin died within 3 months, the causes of death being the primary bleed in 24 cases (80%) and pneumonia, myocardial infarction, and gastrointestinal bleeding in 3, 2, and 1 cases, respectively.

Regular aspirin use preceding the onset of ICH associated significantly with hematoma growth during the first week in the 104 patients with a second CT scan available ($p = 0.006$). A nearly significant correlation between hematoma enlargement and fatal outcome could be observed ($p = 0.087$). However, 8 aspirin users (18%) died within the first four days after the onset of ICH without a second CT scan. Most warfarin users had

large hematomas on admission already, and 16 (62%) of them died within the first 4 days without a second CT scan. Due to the small number of warfarin users with a second CT scan, the association between warfarin use and hematoma enlargement did not reach statistical significance. In the nonusers of aspirin/warfarin, 4-day-mortality was 11%.

The mean daily dose of aspirin used was 257 ± 88 mg (median, 250 mg; range, 50 to 500). There was no significant difference in the aspirin doses of the patients who died within 3 months after their ICH and those who survived. Nor were there significant differences in the mean platelet count between the study groups or between the survivors and those who died. The mean international normalized ratio (INR) of the warfarin users on admission was 3.8 ± 1.8 (range 1.5 to 7.8), without significant differences between the INRs of those who died within the first 3 months after ICH and the survivors.

The analysis of short-term outcome in this unselected cohort of ICH patients (III) showed conflicting results compared with those obtained previously in a selected group of 43 patients (II). In these patients, repeated head CT scanning revealed hematoma enlargement in 5 (24%) aspirin users and 5 (23%) nonusers. Two (9%) aspirin users and 4 (19%) nonusers failed to improve clinically during the first week after admission. Accordingly, in these patients, the use of aspirin did not associate with clinical deterioration and hematoma enlargement to a greater extent than was the case in the nonusers of aspirin in this subgroup of ICH patients.

5.4 Long-term survival after ICH (Study IV)

One-hundred and forty patients of the original cohort of 208 subjects with ICH survived for 3 months after ICH (IV). Hypertension, especially untreated hypertension, was significantly more common in the patients than in the 208 control subjects.

The total number of observed person-years was 820 for the patients and 1319 for the controls. Annual risk for death during follow-up was 5.6% for the patients and 3.0% for the controls. Seven-year-mortality was significantly higher in the ICH patients than in the controls (32.9 and 19.4%, respectively; $p = 0.0034$) (IV; Figure 1). In the original cohort of 208 subjects with ICH, overall 7-year mortality was 54.8%.

According to GOS, 37.1% of the patients showed good recovery, 19.3% were moderately disabled, and 43.6% were severely disabled at the beginning of the follow-up. The mortality of the patients who were severely disabled was significantly higher than that of the patients who showed good recovery ($p = 0.0056$) (IV; Figure 2). There was no difference in mortality between the patients who showed good recovery and the control subjects ($p = 0.84$).

Significantly more patients (7.9%) than controls (1.0%) died of ICH ($p = 0.002$) (IV; Table 2). The annual risk for fatal recurrent ICH was 1.3% in our cohort. Recurrent ICH and pneumonia were the most common causes of death in ICH patients, killing 8 and 10%, respectively. Mortality due to pneumonia was directly associated with the GOS score at 3 months ($p = 0.026$). Eleven (5.3%) controls died of pneumonia, but the difference in mortality from pneumonia between the patients and controls did not reach statistical significance ($p = 0.064$). Eight patients (5.7%) with ICH and 11 control subjects (5.8%) died of myocardial infarction or other cardiac causes.

Smoking was an independent significant predictor for 7-year mortality in both patients and controls, whereas diabetes reached significance only in patients (IV; Table 3). Age was significantly associated with mortality in the controls but not in the patients.

6 Discussion

6.1 Role of aspirin in ICH

The main finding of the present series of investigations was the diverse role of aspirin in association with ICH. Preceding aspirin use, especially in association with a history of epistaxis, was found to significantly increase the risk for ICH (I). This is a new risk factor combination, which has not been reported before. In addition, regular aspirin use before the onset of primary ICH was found to independently predict death within the first 3 months after the index stroke (III). These adverse effects of aspirin in association with ICH may be explained by the inhibitory effect of aspirin on TXA_2 and PGI_2 biosynthesis (II), which was shown for the first time in acute ICH patients. However, in addition to its blocking effect on cyclooxygenases, high-dose aspirin medication also enhances fibrinolysis and suppresses plasma coagulation (Patrono *et al.* 2001).

6.1.1 Aspirin as a risk factor for ICH (Study I)

Previous studies have shown conflicting results as to whether the intake of aspirin increases the risk for ICH (The Swedish Aspirin Low-dose Trial Collaborative Group 1991, Thrift *et al.* 1999). However, the results of two meta-analyses indicate that aspirin therapy does increase the risk of hemorrhagic stroke (He *et al.* 1998, Antithrombotic Trialists' Collaboration 2002). In the 16 trials included in the meta-analysis by He *et al.* (1998) the mean daily dose of aspirin was 273 mg.

Not only the combination of a history of epistaxis during the five years preceding the index stroke and preceding aspirin use, but also a history of epistaxis independently was established as a significant risk factor for ICH. This is a finding of potential clinical significance. Subjects prone to ICH may show epistaxis as a sign of impaired hemostasis or a coagulation disorder. Epistaxis may also result from nasal abnormalities, and the major risk factors for epistaxis are hypertension, use of aspirin, and alcohol abuse (Jackson & Jackson 1988). Impaired platelet function related to the use of NSAIDs has been observed in patients with idiopathic epistaxis (Livesey *et al.* 1995). Alcohol is also known to impair the hemostatic mechanism (Rubin & Rand 1994, Renaud & Ruf 1996).

Aging may involve an increased risk for epistaxis, as the nasal mucosa becomes atrophic and its physiologic activity less proficient.

A sudden rise of blood pressure in systemic circulation exposes the capillaries to high pressure, which may precipitate both epistaxis and ICH (Caplan 1988). Pre-existing damage either in the capillaries of the nasal mucosa or in the small penetrating cerebral arteries could determine whether the bleeding occurs as epistaxis or ICH. The use of drugs inhibiting the hemostatic mechanism, such as aspirin, could predispose to more profuse bleeding.

6.1.2 Aspirin's effect on outcome after ICH (Study III)

Twofold mortality within 3 months after the onset of spontaneous ICH was found in aspirin users (43.2%) compared to nonusers of aspirin or warfarin (21.7%) (III). With the exception of 2 cases, the deaths of aspirin users during the follow-up were due to ICH. The majority of deaths occurred during the first 2 weeks after ICH. On admission, aspirin-related hemorrhages were of the same size as those seen in nonusers of aspirin, but aspirin use significantly associated with hematoma growth. Fujii *et al.* (1998) have shown hematoma enlargement to be an independent factor increasing mortality after ICH. However, their series did not include patients with antiplatelet medication.

One plausible explanation for the increased mortality of aspirin users would be more frequent hematoma enlargement due to impaired hemostasis during the first few days after the onset of ICH. In Study II, signs of impaired hemostasis were observed in ICH patients who had been using aspirin. On admission, bleeding times were longer, and even after the discontinuation of aspirin, the inhibitory effect of the drug on TXA_2 and PGI_2 biosynthesis persisted for a few days.

However, this hypothesis could not be confirmed, because a second CT scan was available for only 104 patients. CT scanning was usually not repeated in patients who were already moribund on admission. On the other hand, mortality during the first four days after the onset of ICH was higher (18%) among patients with preceding aspirin use than among those who used neither aspirin nor warfarin (11%), despite of the fact that aspirin users did not have larger hematomas on admission than nonusers of aspirin/warfarin. The cause of death in these cases may have been early hematoma growth, but this remained unproven.

All but one of the previous studies (Roquer *et al.* 2005) have failed to detect an association between recent use of antiplatelet agents and an increased risk of hematoma expansion (Flibotte *et al.* 2004) or a higher mortality rate (Nilsson *et al.* 2002, Flibotte *et al.* 2004, Rosand *et al.* 2004). In the two hospital-based studies (Flibotte *et al.* 2004, Rosand *et al.* 2004), however, the most potent antiplatelet drug, aspirin, was not distinguished from the other NSAIDs. In the population-based study by Nilsson *et al.* (2002), a nonsignificant trend for aspirin to predict mortality can be seen after the exclusion of warfarin users. The Swedish Aspirin Low-dose Trial (SALT), where aspirin was used as secondary prophylaxis after cerebrovascular ischemic events, revealed a significant increase in the risk of fatal hemorrhagic strokes among aspirin (75 mg per day) users (The Swedish Aspirin Low-dose Trial Collaborative Group 1991). In another study, patients on nonaspirin NSAIDs were not found to carry an increased risk for ICH (Johnsen *et al.* 2003). While this manuscript was in preparation, Roquer *et al.* (2005)

reported that previous use of antiplatelet drugs (91% of the cases had used aspirin) was an independent predictor of 30-day mortality in patients suffering supratentorial ICH.

Hematoma volume is a potent predictor of mortality and functional outcome after ICH (Broderick *et al.* 1993c, Hemphill *et al.* 2001). The previously known predictors for hematoma enlargement include decreased blood coagulability (Caplan 1992, Takahashi *et al.* 1998, Fang *et al.* 2005), increased blood pressure (Caplan 1992, Kazui *et al.* 1997), liver disease (Kazui *et al.* 1997, Fang *et al.* 2005), thrombocytopenia (Oppenheim-Eden *et al.* 1999, Fang *et al.* 2005), insufficient thrombin generation (Takahashi *et al.* 1998), and elevated INR (Fang *et al.* 2005). This list may also include deficiency of primary hemostasis due to aspirin-induced insufficient platelet function, but the risk of aspirin use should be weighed against each individual's need for medication and the possible risks of alternative medications.

The findings of the present study suggest that prevention of hematoma growth may be needed if aspirin has been used by the ICH patient. Platelet transfusion has been recommended in cases of life-threatening ICH due to autoimmune thrombocytopenia (Olson 1993). However, before recommending platelet transfusion in aspirin-associated ICH, further studies are needed to prove that early hematoma growth actually leads to increased mortality in aspirin users, and that platelet transfusion is efficient and safe as a preventive measure.

6.1.3 Biosynthesis of TXA_2 and PGI_2 in patients with ICH (Study II)

Platelet activation is increased in patients with ischemic stroke and myocardial infarction, and elevated levels of TXA_2 metabolites excreted into urine have been observed in such patients (Henriksson *et al.* 1986, Koudstaal *et al.* 1993, van Kooten *et al.* 1994). However, TXA_2 metabolites as markers of platelet activation have not been investigated specifically in acute ICH. The hypothesis of the present study (II) was that the onset of ICH may modify the biosynthesis of TXA_2 and PGI_2. However, the results of serial measurements of TXA_2 and PGI_2 metabolites excreted in urine conflicted this hypothesis.

ICH patients without aspirin use showed similar levels of TXA_2 and PGI_2 metabolites in urine during the acute phase of ICH and 3 months later, but these levels were significantly higher than those in healthy controls. On the other hand, in ICH patients with previous aspirin use the urinary excretion rates of both TXA_2 and PGI_2 metabolites were only slightly higher or similar compared to controls on admission, but increased after the cessation of aspirin use and reached the levels of nonusers within a few days.

The biosynthesis of TXA_2 seems to be permanently enhanced in patients who have suffered a stroke. TXA_2 biosynthesis has been reported to be increased months after the onset of ischemic stroke (van Kooten *et al.* 1999). Our results and those of van Kooten *et al.* suggest that this also holds for spontaneous ICH. Increased TXA_2 biosynthesis, associated with poor outcome, may reflect the extent of vascular damage due to stroke (van Kooten *et al.* 1999). On the other hand, TXA_2 synthesis in these patients might have been increased even before the onset of stroke, without any temporal relationship with the actual stroke, as also suggested by Liu *et al.* (1994). Moreover, in our study, 11-dehydro-TXB_2 levels did not associate with the severity of stroke on admission. Consequently, the

elevated levels of TXA_2 metabolites could merely be general markers of vascular disease posing the patients to a risk of ICH, ischemic stroke, and myocardial infarction. Cardiovascular diseases are known to enhance platelet aggregation and the excretion of prostanoid metabolites into urine (Catella & FitzGerald 1987).

6.2 Risk factors for ICH other than aspirin (Study I)

In addition to aspirin use and a history of epistaxis, untreated hypertension, previous ischemic stroke, recent acute strenuous physical exertion, and epilepsy were found to be independent risk factors for ICH.

Untreated hypertension was a significant risk factor for primary ICH in both men and women. In men, but not in women, even treated hypertension was a significant risk factor. The latter observation may have been due to the poorer compliance of men with their antihypertensive medication (Klungel *et al.* 1999). Arterial hypertension is the best documented treatable risk factor for ICH (Caplan 1992, Thrift *et al.* 1996), and untreated hypertension may be even more dangerous (Woo *et al.* 2004). Actually, the findings of the present study suggest that adequately treated hypertension may not carry an increased risk for ICH. Numerous studies have reported an association with noncompliance and undertreatment of hypertension and ICH (Hsiang *et al.* 1996, Thrift *et al.* 1998, Klungel *et al.* 1999).

A history of ischemic stroke was a significant and independent risk factor for ICH. An increased risk for ICH following prior cerebral infarction has also been observed in other studies (Okada *et al.* 1976, Brott *et al.* 1986, Woo *et al.* 2004). Ischemic lacunar infarctions and deep ICHs are both complications of small-vessel disease due to hypertension (Cole & Yates 1967, Caplan 1988). The cerebral arteries of patients with a history of ischemic stroke may be more prone to rupture than those of patients with other manifestations of atherosclerotic disease. Kwa *et al.* (1998) found local cerebral hemosiderin deposits, which are signs of old ICHs, more frequently on MRI scans of the patients with ischemic stroke (26%) than in those with myocardial infarction (4%). Cerebral microbleeds appear to be a risk factor for subsequent ICH among patients with ischemic stroke (Nighoghossian *et al.* 2002, Fan *et al.* 2003). The presence of multiple microbleeds suggests that microangiopathy has reached an advanced stage, at which blood vessels are prone to bleeding (Kato *et al.* 2002, Fan *et al.* 2003). These findings might explain the association between previous ischemic stroke and ICH.

Acute strenuous physical exertion significantly associated with the onset of ICH. This was another new finding. Acute exercise may trigger ICH through a sudden increase in blood pressure. It has been shown that exercise-induced blood pressure responses are greater in old than young people (Sugimoto *et al.* 1998). Because elderly people seldom engage in regular physical exercise, acute strenuous physical exertion may markedly increase their systolic blood pressure.

Previous studies have focused on the effects of regular physical activity on the risk for stroke rather than the effects of acute strenuous physical exertion (Menotti & Seccareccia 1985, Lindsted *et al.* 1991, Abbott *et al.* 1994, Fletcher 1994, Lee & Paffenbarger 1998), and the subtypes of stroke have been inaccurately differentiated in these studies. A U-shaped relation between the incidence of stroke and the degree of physical activity has been observed. Moderate physical activity was protective against stroke compared to light

physical activity, but more strenuous physical activity was less protective (Menotti & Seccareccia 1985, Lindsted *et al.* 1991, Lee & Paffenbarger 1998). Nakayama *et al.* (1997) observed that heavy physical activity increased the risk for all strokes in middle-aged and elderly men, whereas avoidance of physical exercise increased the risk for ICH in women.

The alcohol-associated risk for ICH observed in several previous studies (Calandre *et al.* 1986, Monforte *et al.* 1990, Gill *et al.* 1991, Juvela *et al.* 1995, Iso *et al.* 1995, Kiyohara *et al.* 1995) was not significant in this series of middle-aged and elderly people, although recent heavy drinking of alcohol almost reached statistical significance as a risk factor for ICH in men. It is well known that heavy drinking increases untimely deaths, and elderly people are seldom heavy drinkers (Lahelma *et al.* 1994).

Epilepsy appeared to be a risk factor for ICH in women, but not in men. This finding could be a spurious one, because the number of epileptics in the series was small. When the subjects with a history of ischemic stroke were omitted, the remaining three subjects with epilepsy were all women. Cavernous malformation, which is a rare cause of ICH and may also cause epilepsy (Kondziolka *et al.* 1995), could not be excluded as a common etiology for both epilepsy and ICH in these women, because no head MRI or intracranial angiography was done.

6.3 Predictors for short-term outcome after ICH other than aspirin (Study III)

In this study, very high 3-month mortality (73.1%) was recorded for warfarin users. The devastating effect of preceding warfarin use on the outcome after ICH is well-known, and it results from the rapid enlargement of hematomas in the absence of hemostatic therapy (Yasaka *et al.* 2003). Hematoma enlargement in patients who have been using warfarin usually takes place within the first 24 hours after the onset of ICH (Hart *et al.* 1995). The warfarin-related hemorrhages in the present study were larger on admission already than the other hematomas, which is explained by the fact that 24% of the warfarin users had their first CT scanning performed after the day of symptom onset. Many of the patients on warfarin showed high INR values on admission, suggesting unsuccessful control of warfarin dosage. High INR values are known to strongly associate with an increased risk of death from ICH (Rosand *et al.* 2004).

In previous studies, diabetes has been reported to be an independent predictor for death after ICH (Wong 1999, Arboix *et al.* 2000). In the present study, diabetes tended to predict mortality, but the association did not reach statistical significance in multivariate analysis. Diabetics had more often cardiac diseases in their medical history, slightly more frequently complicating infections during the hospital stay, and slightly lower GCS scores on admission than non-diabetics. It is not known which factors impair the prognosis of diabetic stroke patients. Stress hyperglycemia after stroke is a common finding (Melamed 1976). One study showed that high blood glucose on admission predicts death in both diabetic and nondiabetic patients with ICH (Fogelholm *et al.* 2005). Experimental observations suggest that hyperglycemia causes more profound edema and perihematomal cell death (Song *et al.* 2003). The high prevalence of cardiac complaints may partly

explain the association of diabetes with mortality: the basic cardiovascular condition of diabetics might already be compromised before ICH, which worsens their survival.

6.4 Long-term outcome after ICH (Study IV)

The mortality of patients who had survived for 3 months after ICH was significantly higher than that of controls during 7-year follow-up. The increased mortality of ICH patients compared to controls was due to re-bleedings and pneumonia. However, the mortality rates differed significantly according to the GOS score at 3 months after ICH. Mortality was highest among the severely disabled ICH patients, pneumonia being their most common cause of death. On the other hand, the patients with good recovery at 3 months after ICH survived equally to controls. Smoking was a significant preventable risk factor for death in both ICH patients and controls.

The long-term survival of patients with ICH has not before been compared to the survival of a prospectively followed cohort of control subjects from the same population. There is only one previous study suggesting a similar finding in ICH patients. The Oxfordshire Community Stroke Project compared the risk of death for stroke patients with that for people of similar age and sex from the general population (Counsell *et al.* 1995). A higher than expected mortality rate among those who survived beyond the first month was observed in ICH patients, the average annual risk of death being 8% during a follow-up of 5 years. The annual risk for death was slightly lower (5.6%) in the present study. A previous Finnish study also compared the survival of ICH patients to the probability of survival in a general population of similar age and sex (Fogelholm *et al.* 1992). In that study, the long-term prognosis up to five years of the ICH patients who survived the first month did not differ from that of the average Finnish population. In other studies, the patient series have consisted of hospitalized patients, controls have been lacking, or the observation periods have been shorter than 2 years.

In the original cohort of 208 subjects in the present study, the overall 7-year mortality after ICH was 55%, which figure is lower than in the earlier studies reporting mortality beyond 2 years (Fogelholm *et al.* 1992, Counsell *et al.* 1995). The results of the present study support the previous findings showing a decline in mortality from ICH in Finland (Numminen *et al.* 1996, Immonen-Räihä *et al.* 1997, Pajunen *et al.* 2005). Improved acute care of stroke patients, which allows more patients with moderate-to-severe disability to survive beyond the first critical days, may explain the lower mortality in the present study compared with the previous ones (Fogelholm *et al.* 1992, Numminen *et al.* 1996). On the other hand, no improvement in 28- to 365-day case fatality was found during 1991–2001 (Pajunen *et al.* 2005).

The present study indicates that mortality during long-term follow-up is significantly higher in the patients who are severely disabled according to GOS at 3 months after the index stroke compared to those who show good recovery. Pneumonia as a cause of death was most common in the severely disabled patients, probably being a complication of immobility. Those who were moderately disabled also showed somewhat higher mortality than those with good recovery. In previous studies, the severity of stroke based on the GCS score (Teasdale & Jennett 1974) indicating the initial level of consciousness on admission and the handicap caused by the stroke according to the modified Rankin scale (van Swieten *et al.* 1988) in the early phase were shown to predict long-term mortality

after ICH (Franke *et al.* 1992, Juvela *et al.* 1995, Hårdemark *et al.* 1999, Inagawa *et al.* 2000b, Nilsson *et al.* 2002). Stroke severity predicts functional outcome and residual disability similarly in both ischemic and hemorrhagic strokes (Dennis 2003). The findings of the present study suggest that the functional status reached after rehabilitation may be a major factor determining future survival.

Diabetes and current smoking, which may also be risk factors for ICH (Ariesen *et al.* 2003), predicted long-term mortality of ICH patients in the present study. These factors have not been shown to associate with increased long-term mortality after ICH previously, but diabetes has been shown to be an independent risk factor for in-hospital mortality from ICH (Wong *et al.* 1999, Arboix *et al.* 2000). Lifestyle factors have been analyzed in very few studies of survival after ICH. Alcohol consumption within a week before ICH has been shown to predict poor functional outcome, but it did not significantly associate with 1-year mortality (Juvela *et al.* 1995). Nor did heavy drinking of alcohol associate with mortality in the present study. Smoking also predicted death in controls.

Patients' age tended to predict mortality in the cohort of ICH patients who survived the first 3 months after the stroke, but the association was not significant. In a number of previous studies, patient's age has been found to significantly predict long-term survival after ICH (Fogelholm *et al.* 1992, Franke *et al.* 1992, Rosenow *et al.* 1997, Hårdemark *et al.* 1999, Inagawa *et al.* 2000b, Nilsson *et al.* 2002). However, Juvela (1995) did not find patient's age to predict mortality within 1 year after ICH. In the controls, age significantly predicted mortality.

Recurrent ICH accounted for 24% of deaths among patients. A 2.4% annual recurrence rate for ICH has been reported (Hill *et al.* 2000), but due to the study design, only fatal re-bleedings were recorded in the present study. The prognosis after recurrent ICH has been shown to be worse than that after the first ICH, and as high mortality rates as 32 to 70% have been reported (Passero *et al.* 1995, Gonzáles-Duarte *et al.* 1998). Re-bleedings have been observed to associate with poor control of hypertension (Passero *et al.* 1995, Gonzáles-Duarte *et al.* 1998). Therefore, adequate control of hypertension is probably the most important primary and also secondary prophylaxis of ICH.

Although 44% of the patients were severely disabled with limited mobility, there were no cases of fatal pulmonary embolism in the cohort of 140 patients. However, pulmonary embolism may manifest primarily as impaired cardiorespiratory reserve and, frequently, as sudden death (Kelly *et al.* 2001). Thus, some cases of fatal pulmonary emboli may have been misdiagnosed as cardiac deaths.

6.5 Limitations and strengths of the present investigations

In Study I, bias may have resulted from the different techniques used to interview the cases and controls. The cases or their relatives were personally interviewed, while the controls were interviewed over telephone. However, telephone interview has been found to be a reliable procedure for obtaining information on drinking habits (Cohen & Vinson 1995, Greenfield *et al.* 2000), functional capacity (Gloth *et al.* 1999), and quality of life (Fernandez *et al.* 1996).

Recall bias is also possible, because the cases or their relatives may have been better able to remember, e.g., previous bleedings than the controls. To minimize this type of bias, the interviews were conducted according to a structured protocol and all by the same

person, and the previous hospital records of all subjects were carefully reviewed. Previous hospital records were available for 81% of the controls, which enhances the reliability of the results.

Bias due to exclusion of patients admitted into other departments of the hospital is possible. However, this selection was necessary to obtain detailed data by personally interviewing all subjects or their proxies. Attention to careful interviewing of all subjects is a strength of the study, as is also the accurate matching of the control subjects.

In Study II, patient recruitment was limited to conservatively treated patients, to avoid the confounding effects of surgical stress and postoperative medication and complications on the results. Secondly, the healthy controls were younger than the patients. However, the 11-dehydro-TXB_2 and 2,3-dinor-$PGF_{1\alpha}$ levels of the 23 controls did not differ from those of 11 other healthy subjects aged 55–71 years (mean 63.4 ± 8.3) analyzed in the same laboratory as part of other studies (32.0 ± 10.1 and 18.2 ± 8.7 pg/μmole creatinine, respectively). Furthermore, previous investigations have not shown any significant effect of age in healthy subjects (Reilly & FitzGerald 1986, Rångemark *et al.* 1992, McDonnel *et al.* 2001). Consequently, age itself may not affect the 11-dehydro-TXB_2 and 2,3-dinor-$PGF_{1\alpha}$ excretion of healthy subjects. The strengths of the study include the serial measurements of TXA_2 and PGI_2 metabolites after ICH, the careful recording of aspirin use, the careful recording of the clinical parameters during the first week, and the follow-up of recovery until 3 months after the stroke.

In Study III, data was gathered retrospectively for patients admitted into the Department of Neurosurgery or the Department of Internal Medicine. To avoid bias, some detailed data obtained by interviewing the patients admitted into the Department of Neurology could not be used. For example, occasional use of aspirin was omitted from the analyses, because it could not be recorded for all subjects, which is a limitation of the study. Consequently, some patients classified as nonusers of aspirin may have ingested aspirin just before the stroke, which may have worsened their outcome. Such misclassification might underestimate aspirin-associated mortality. The median daily dose of aspirin used by the study population was 250 mg. The currently recommended dose for prophylaxis of cardiovascular diseases and ischemic strokes is somewhat lower (75–100 mg) (Patrono 1994). This may limit the generalizability of the results to some extent. However, very low daily doses of aspirin affect TXA_2 production (Tohgi *et al.* 1992, Patrono 1994) and may carry the same adverse effects on hemostasis as do larger doses.

Nor was it possible to gather detailed data on alcohol consumption by the subjects, and smokers were dichotomized into current smokers and nonsmokers, the latter group also including previous smokers. The lack of systematic second CT scanning of the patients who died soon after the index stroke is another limitation of the study. Those with only a single CT scan had significantly higher mortality than those with several CT scans (79.4% vs. 20.6%). This is likely to result in underestimation of the frequency of hematoma expansion in the cohort. Also, the delay between the symptom onset and the first CT scan was rather crudely estimated.

The strength of the study is that it was based on a defined population. All patients admitted into Oulu University Hospital due to ICH during the study period were included. Because there are no other hospitals in the area admitting acute stroke patients, and such patients are recommended to be immediately referred to the university hospital, selection bias was probably avoided. Of the subjects with ICH who died during the study period without ever reaching the hospital, only those with ICH confirmed at autopsy were

included. This ensures that subjects dying of ischemic strokes were not erroneously included. However, the strict inclusion criteria may result in underestimation of the real incidence rate of spontaneous ICH in the population. Some elderly subjects dying outside Oulu University Hospital may have died of ICH without verification by head CT or autopsy.

For Study IV, patient data, including lifestyle data, were collected during the period of hospitalization due to the index stroke and are thus indicative of the patients' preictal health habits. This is a limitation of the study. Some of the smokers probably gave up smoking after the index stroke. In consequence, not all of the patients classified as smokers continued smoking during the follow-up years. However, if these previous smokers had been classified as nonsmokers, the association between smoking and excess mortality might have been even stronger. Another limitation is the availability of only retrospectively gathered data for a subgroup (36%) of patients. The controls were originally matched to the patients included in Study I. However, the ages, BMI, and sex distribution of the patients in Study IV and the controls matched accurately. The complete follow-up of survival of both patient and control cohorts is a strength of the study. However, there may be some inaccuracy in the causes of death, because they were based solely on register data and not always confirmed by autopsy, neuroimaging, or other reliable methods.

7 Concluding remarks

The significant risk factors for ICH and the predictors of outcome after ICH observed in the present series of investigations are shown in Table 5. Untreated hypertension was found to be the main modifiable risk factor for ICH (I). This finding points out the need for more careful control in the treatment of hypertension. Use of aspirin appeared to be a significant risk factor for ICH in the subjects with a history of epistaxis. Patients with a history of epistaxis should avoid using high doses of aspirin for prophylaxis of atherosclerotic diseases and, for pain, use other kind of analgetics.

Elevated urinary levels of TXA_2 and PGI_2 metabolites were observed in patients with acute ICH without previous aspirin use (II). In aspirin users, this increase in prostanoid synthesis was blocked, but the values increased to the level of the other patients in a few days after the discontinuation of aspirin medication. The levels of TXA_2 metabolites were high 3 months after ICH, suggesting that thromboxane biosynthesis may be chronically enhanced due to generalized vascular disease in patients at risk for hemorrhagic stroke.

Regular use of aspirin preceding ICH was found to double the 3-month mortality rate compared with non-use of either aspirin or warfarin (III). Aspirin use also associated with early hematoma growth. It may be hypothesized that aspirin use may frequently cause enlargement of hematomas shortly after the onset of ICH due to impaired primary hemostasis, and that early platelet transfusions should possibly be attempted to prevent this devastating development. However, this hypothesis and treatment option remains to be tested in future controlled studies with systematic rescanning of hematomas.

Table 5. Risk factors and predictors of outcome after ICH.

Risk factors (I)	Predictors for 3-month-mortality (III)	Predictors for mortality after 3 months to 7 years (IV)
Untreated hypertension	ICH Score > 2 on admission	Diabetes
Previous ischemic stroke	Warfarin use†	Smoking
Epistaxis*	Regular aspirin use†	Severe disability at 3 months‡
Epistaxis + aspirin use		
Epilepsy		
Recent physical exertion		

* > 1 episode during the preceding 5 years, or a previous visit to an outpatient clinic of otorhinolaryngology or hospitalization because of epistaxis. † Preceding ICH. ‡ According to GOS.

Patients with ICH showed increased long-term mortality, even after having survived the first 3 critical months after the stroke, compared to controls (IV). Excess mortality was especially marked among the ICH patients who were severely disabled at 3 months after ICH, and it was mainly due to pneumonia, which is a complication of immobility. Re-bleedings were also quite common but unrelated to the grade of disability. These observations suggest that more attention should be paid to the prevention of infections and the treatment of cardiovascular risk factors, such as hypertension, diabetes, and smoking, in patients surviving their first ICH. Active treatment in the acute phase and rehabilitation may improve not only the short-term outcome but also long-term survival.

Aspirin seems to play some important roles in association with ICH. It increases the risk for ICH at least in subjects with history of epistaxis, which may be a marker of impaired hemostasis. Preceding aspirin use also seems to worsen survival after ICH. These observations may challenge the concept of aspirin as prophylaxis for cardiovascular disease and ischemic stroke. However, the overall benefit of aspirin use on myocardial infarction and ischemic stroke almost certainly overcomes the potential risk of hemorrhagic stroke (He *et al.* 1998). Moreover, according to a meta-analysis, 773 patients with hemorrhagic stroke, who had been inadvertently randomized to take aspirin, showed no evidence of net hazard (Chen *et al.* 2000). However, preceding regular aspirin use may have different adverse effects on patients with ICH compared to low-dose aspirin medication started later, when the bleeding already has stabilized.

Could we identify the subjects at high risk for aspirin-associated major hemorrhagic adverse effects before complications take place? History of epistaxis could be one warning sign of an increased risk for aspirin-associated bleedings. Detection of hemosiderin deposits on head MRI as markers of previous microbleeds in the brain could be another possibility, since microbleeds have been associated with an increased risk for aspirin-associated ICH (Wong *et al.* 2003). Thirdly, the ε2 or ε4 alleles of the apolipoprotein E gene have been shown to increase the risk for recurrent lobar ICH due to cerebral amyloid angiopathy (O'Donnell *et al.* 2000). It is not known whether the presence of these alleles interacts with the use of aspirin and modifies the aspirin-associated risk for ICH. So far, there is no existing evidence that antiplatelet agents other than aspirin would be safer in subjects with increased risk for aspirin-associated ICH. In any case, it is clear that in prophylactic use the lowest effective dose of aspirin should be used. In primary prophylaxis of cardiovascular diseases and ischemic stroke, the use of aspirin should be based on solid evidence that the benefits are greater than the risks.

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