Intracerebral Hemorrhage. Influence of Clinical Characteristics on Prognosis and Treatment Options

Hansen, Björn

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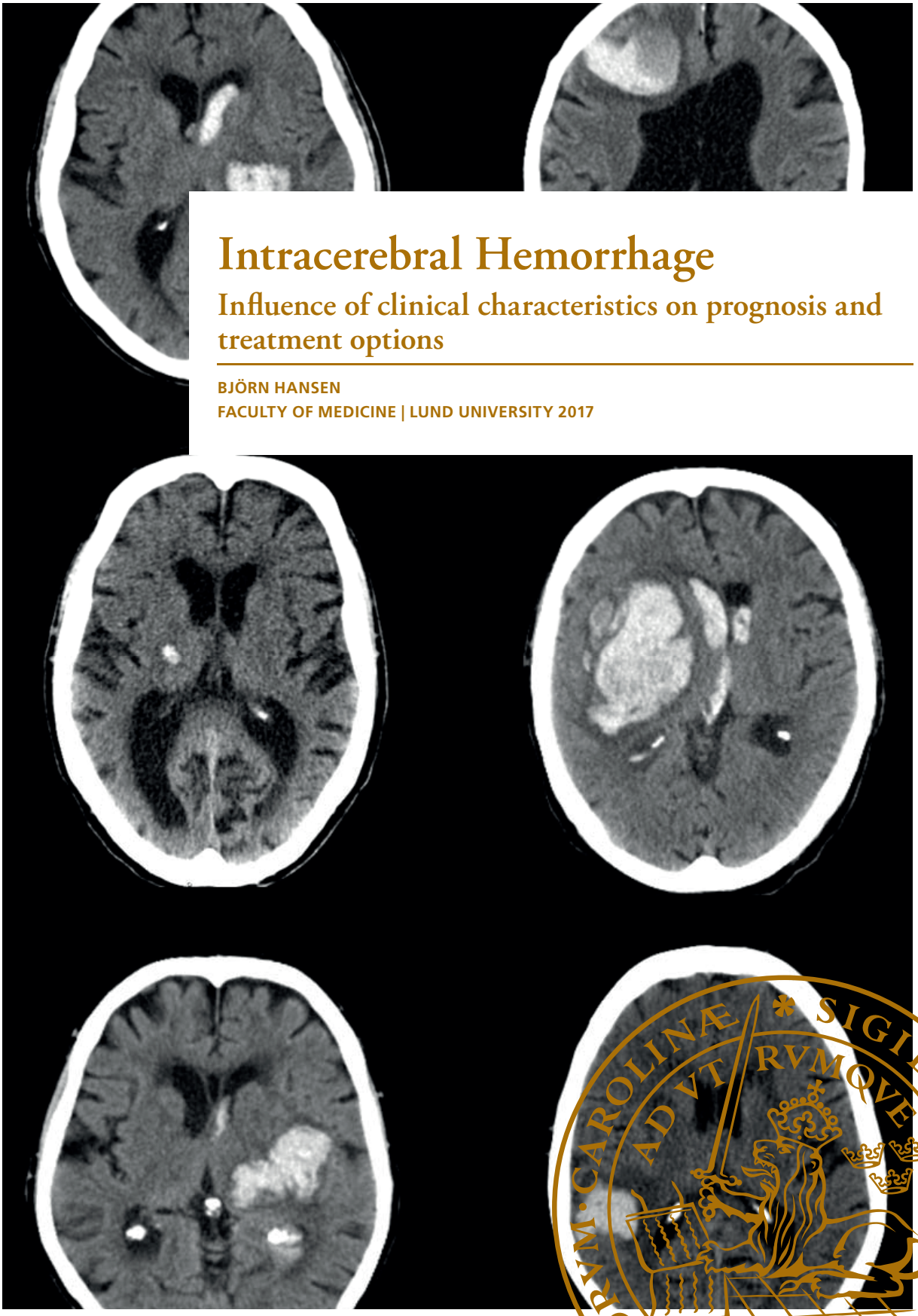

Intracerebral Hemorrhage

Influence of clinical characteristics on prognosis and treatment options

BJÖRN HANSEN
FACULTY OF MEDICINE | LUND UNIVERSITY 2017

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Björn Hansen

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Professor Rustam Al-Shahi Salman PhD FRCP (Edin)

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Title and subtitle: Intracerebral Hemorrhage. Influence of clinical characteristics on prognosis and treatment options

Abstract

Background: Stroke is a leading causes of death and disability globally and 10-15% of all strokes are caused by intracerebral hemorrhage (ICH). An increased knowledge of factors affecting prognosis after ICH is needed to guide the development of possible interventions to improve outcome.

Aim: To investigate how clinical andimaging factors affect survival and functional outcome after ICH and how these factors influence therapeutic options after ICH.

Methods:

Paper I: A 13-year prospective follow-up of 323 ICH patients from a population based cohort was performed to assess factors influencing long-term survival, excess mortality and causes of death.

Paper II: The semi quantitative scale modified Graeb Scale (mGraeb), for estimation of intraventricular hemorrhage (IVH) severity, was evaluated for outcome prognostication after ICH in a cohort of 198 supratentorial ICH patients from Lund Stroke Register (LSR).

Paper III: 635 ICH patients were included from the clinical ICH treatment trials MISTIE-II and CLEAR-III. White matter lesions (WML) at baseline CT was evaluated as a prognostic marker for hematoma expansion and 180-day functional outcome after ICH.

Paper IV: Eligibility criteria from 11 large interventional trials on ICH were applied to 253 consecutive first-ever ICH patients from LSR to assess eligibility rates in an unselected ICH cohort. Prognostic differences between eligible and non-eligible patients were evaluated.

Results:

Paper I: One-year survivors after ICH had persisting and continuing excess mortality compared to the general population (27% 13 years after ictus). Major causes of death were stroke and ischemic heart disease. Diabetes mellitus, age, and oral anticoagulant therapy at ICH-onset negatively affected long-term mortality.

Paper II: The mGraeb predicted 30-day mortality (OR 1.16; CI 95% 1.06-1.27; p=0.002) and poor functional outcome (OR 1.11; CI 95% 1.02-1.20; p=0.011) after ICH. The mGraeb improved outcome prediction beyond previously established factors.

Paper III: The 349 (55%) patients with WML did not have increased odds for hematoma expansion in median 39 hours after ictus (IQR, 22.5-54.5). However, increasing WML severity was associated with worse 180-day functional outcome in univariate and multivariate analyses.

Paper IV: Estimated eligibility proportions ranged between 2-36% for 11 identified clinical trials. Patients not eligible for any trial (n=96) had more severe baseline ICH characteristics, higher 30-day case fatality and worse functional outcome compared to trial eligible patients (n=157).

Conclusions: ICH patients have a high short-term and long-term mortality. IVH and WML are important risk factors for poor outcome. However, the patient group is diverse and good prognostic estimations are therefore essential to develop optimal treatment for ICH patients in general clinical practice and in clinical trials

Key words: stroke, cerebral hemorrhage, intracerebral hemorrhage, prognosis, survival, functional outcome, clinical trials, intraventricular hemorrhage, white matter lesions, cause of death

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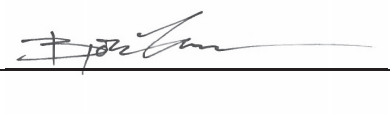
Signature  Date 2016-12-16

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Björn Hansen

LUND
UNIVERSITY

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Faculty of Medicine
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To my family

Content

List of Publications

This thesis is based the following papers referred to in the text by their roman numerals. The papers are appended in the end of the thesis with permission from the publishers.

I. Hansen BM, Nilsson OG, Anderson H, Norrving B, Säveland H, Lindgren A. Long term (13 years) prognosis after primary intracerebral haemorrhage: a prospective population based study of long term mortality, prognostic factors and causes of death. Journal of Neurology, Neurosurgery, and Psychiatry. 2013;84:1150-1155

II. Hansen BM, Morgan TC, Betz JF, Sundgren PC, Norrving B, Hanley DF, Lindgren A. Intraventricular extension of supratentorial intracerebral hemorrhage: the modified Graeb scale improves outcome prediction in Lund Stroke Register. Neuroepidemiology. 2016;46:43-50

III. Hansen BM, Ullman N, Norrving B, Dlugash R, Awad I, Zuccarello M, Ziai WC, Hanley DF, Thomson RE*, Lindgren A*; for the MISTIE and CLEAR Investigators.*) contributed equally. White matter lesions influence on intracerebral hemorrhage expansion and functional outcome: a secondary analysis of MISTIE-II and CLEAR-III. Manuscript

IV. Hansen BM, Ullman N, Norrving B, Hanley DF, Lindgren A. Applicability of clinical trials in an unselected cohort of patients with intracerebral hemorrhage. Stroke. 2016;47:2634-2637

Abbreviations

CAA	Cerebral amyloid angiopathy
CT	Computed tomography
CLEAR-III	Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage phase III trial
CI	Confidence interval
GCS	Glasgow coma scale
HR	Hazard ratio
HS	Hemorrhagic stroke (ICH and SAH)
ICC	Intraclass correlation coefficient
ICD-10	International statistical classification of diseases and related health problems, 10th Revision
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
IVH	Intraventricular hemorrhage
IS	Ischemic stroke
LOC	Level of consciousness
LSR	Lund Stroke Register
mGraeb	Modified Graeb scale
MISTIE-II	Minimally Invasive Surgery Plus Recombinant Tissue-Type Plasminogen Activator for Intracerebral Hemorrhage Evacuation-II trial
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
OR	Odds ratio
RCT	Randomized clinical trial
ROC	Receiver operating characteristic
RR	Relative risk
RSR	Relative survival ratio
rt-PA	Recombinant tissue plasminogen activator
SVD	Small vessel disease
SAH	Subarachnoid hemorrhage
WML	White matter lesions

Definitions

Case fatality rate: The proportion of deaths during a specified time-period after disease onset.

Incidence rate (IR): The number of outcomes (e.g. disease occurrence) per time at risk (e.g. person years).

Incidence rate ratio (IRR): The ratio between incidence rates which indicate how much incidence rates differ.

Hazard: The probability that an event (e.g. death) occurs around specific time-point in a person under observation. The hazard rate is the hazard over a defined time period, and can be derived as a function of survival.

Hazard ratio (HR): A measurement of differences between hazard rates and the result of Cox regression analyses. In prospective studies HR is further from unity compared to RR, but closer to unity compared to OR; these differences increases with longer follow-up times, higher event-rates, and larger risks[1].

Mortality: The number of persons that die from a disease. In epidemiology, the term is often used to describe death in a population and presented as a rate (deaths per person-years at risk).

Odds: The ratio between the probability that the outcome will occur and the probability that it will not occur i.e. how much more likely it is that something will happen compared than it will not happen.

Odds ratio (OR): The ratio between two odds indicates how much odds differ. When the outcome is rare the OR corresponds well with RR but with higher prevalence of outcome the agreement decreases. Used in case-control studies and logistic regression.

Prospective study: A study where patients are followed over time. Factors of interest are collected/recorded prior to the event that is studied.

Relative risk (RR): A comparison of two risk estimates. Can be used in cohort studies and randomized clinical trials.

Retrospective study: A study where the event or exposure has occurred prior to the study start. Subject to recall bias.

Survival: The probability that death will not occur between disease onset and a future time-point.

Unity: The state when two ratios are equal (= 1). Statistical testing of HR/OR/RR aims to determine if they are separated from unity (either lower or higher) or not.

Introduction

Stroke

Stroke is caused either by cerebral ischemia (ischemic stroke, IS) or hemorrhage (hemorrhagic stroke, HS) and has been defined by the World Health Organization as:

> "Rapidly developed clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin"[2]

The WHO stroke criteria are used until today even though it has been suggested that these criteria should be updated to focus less on symptom duration and more on radiological and pathological findings[3].

Stroke is one of the leading causes of death[4] and disability globally with 10.3 million new strokes per year the global burden of stroke is increasing[5]. Globally, HS contributes to a third of all new strokes and half of the 6.5 million stroke related deaths in the world.[5] Approximately two thirds of HS are caused by hemorrhage into the brain parenchyma, also known as intracerebral hemorrhage (ICH), while the remaining third is caused by subarachnoid hemorrhage (SAH)[6, 7].

Intracerebral Hemorrhage

Definitions and Terminology

The American Heart Association/American Stroke Association has defined the term intracerebral hemorrhage as "A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma"[3] which corresponds with the term *spontaneous ICH*. Due to specific etiology and prognosis, ICH is separated from other intracranial hemorrhages such as subarachnoid hemorrhage (commonly caused by cerebral arterial aneurysms), and

epidural and subdural hematomas (commonly caused by trauma and not considered to be stroke)[8]. However, several types of intracranial hemorrhage can be present simultaneously as illustrated in Figure 1.

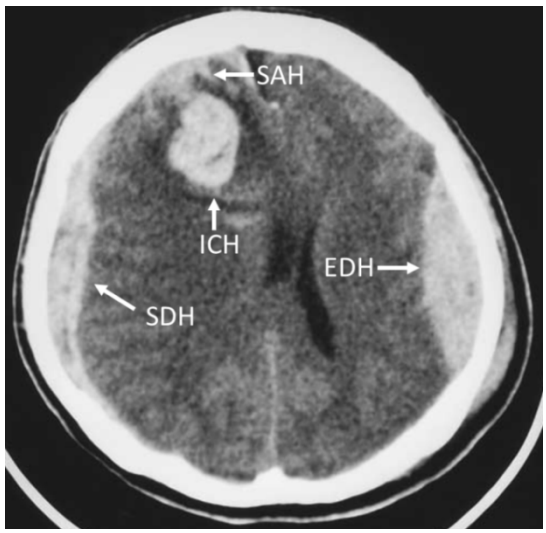

Figure 1. Four different intracranial hematomas after head trauma, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), and epidural hemorrhage (EDH). Reproduced with permission from Mattiello JA, Munz M. Four Types of Acute Post-Traumatic Intracranial Hemorrhage. N Engl J Med. 2001;344:580, Copyright Massachusetts Medical Society.

The term spontaneous ICH was preceded by the terms, *secondary* and *primary* ICH, which were used to denote whether the etiology of the hemorrhage could be detected or not. Traditionally, primary ICHs are attributed to vascular changes due to hypertension, atherosclerosis, and cerebral amyloid angiopathy[9]. Secondary ICHs are hematomas caused by: cerebral arteriovenous malformations, cavernous malformations, and arterial aneurysms, intracranial venous thrombosis or hemorrhagic transformation of cerebral infarction, cerebral tumors, and illicit drug use. Additionally, hemorrhages caused by coagulation deficiencies secondary to anticoagulant/thrombolytic therapy are sometimes regarded as secondary ICH[9].

The primary/secondary terminology is complicated to use because many causative factors may be present at the same time and because the prevalence of primary and secondary ICH is heavily dependent on what kind of diagnostic investigations that are done.

Henceforth, in this thesis, the abbreviation ICH denotes intracerebral hemorrhage not caused by trauma, vascular malformations, venous thrombosis, hemorrhagic transformation of cerebral infarction, or cerebral tumor, unless otherwise specified.

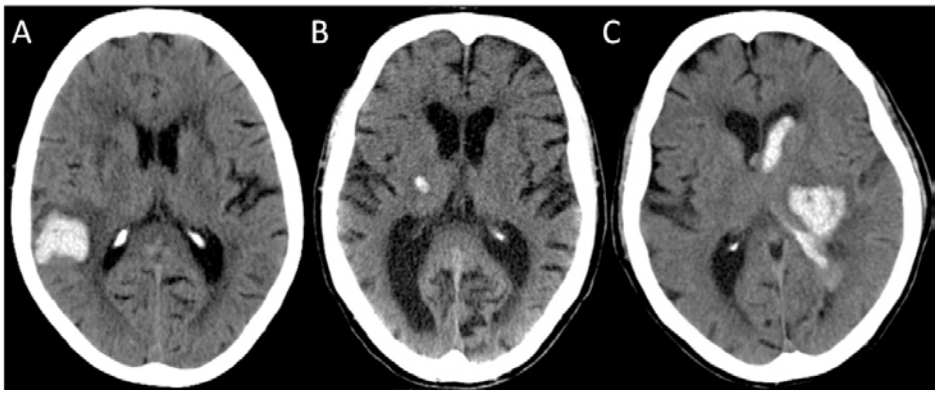

Figure 2. Three types of intracerebral hemorrhage (ICH). A) lobar ICH, B) small deep ICH, and C) deep ICH with intraventricular hemorrhage

Clinical Presentation and Diagnosis

Intracerebral hemorrhage cannot accurately be separated from ischemic stroke based on clinical examination alone[10] and imaging or autopsy is required for a definite diagnosis. The neurological ICH symptoms ranges from isolated and transient deficits[11] too deep coma and death, depending on ICH location and volume. In addition to specific neurological symptoms patients with ICH often have headache (36% versus 16% in IS)[12], vomiting (29% versus 1-8% in IS)[13], and decreased level of consciousness at admission (39% versus 13% in IS)[14].

ICH is often divided into anatomic locations, lobar (cortex and immediately underlying white matter, Figure 2A), deep (or non-lobar, Figure 2B and 2C), and infratentorial (cerebellar or brainstem). How locations are defined and categorized often vary between studies[15] and proportions of lobar, deep (supratentorial, not lobar), infratentorial ICH, range between 15-52%, 35-69%, and 9-16%, respectively[16-26].

Before computerized tomography (CT) became standard for stroke diagnostics, many severe IS were likely misdiagnosed as ICH and less severe ICH were misdiagnosed as IS, causing wrongful estimations in ICH incidence.[27] Since the end of the 1990's the absolute majority of Swedish stroke patients have been diagnosed with CT at hospital[14, 28, 29]. The accurate differentiation between IS and ICH is time dependent since the blood resolves over time[30]. Both CT and MRI (with gradiant echo and T2 sequences) can be used to identify acute ICH (<7 days of onset) while MRI has a greater accuracy in later stages[30, 31]. CT angiography (CTA) and MR angiography (MRA) are useful for detecting vascular malformations as cause for ICH[32]. However, a recent study showed that the

accuracy of for detection of macrovacular causes of ICH with CTA/MRA is modest and that digital subtraction angiography might have added value if CTA/MRA is negative and there is suspicion of a macrovacular cause[33].

Incidence

Worldwide

Globally, the proportion of strokes caused by ICH varies from 9% (Dijon, France) to 27% (Tiblisi, Georgia)[34], and might be as high as 33% in Chinese populations (pooled proportion of five community-based studies).[35] The age-adjusted HS incidence has remained unchanged in the world between 1990 and 2013[5]. The last two decades, the HS incidence has decreased in high income countries with 19% while it has increased by 22% in low and middle-income countries[36]. The over-all crude annual ICH incidence has been estimated to 24.4 per 100,000 persons (95% CI 19.7-30.7) in pooled estimate from a meta-analysis, and has remained unchanged between 1980 and 2008[34, 37]. Three western European studies report a decline in ICH incidence among younger persons (<75 years) but stable or increasing incidence among those older than 75 years[16, 38, 39]. A recent Italian population-based study showed a decline in incidence in all age groups between 1994-1998 and 2011-2012[40]. The decreased incidence in younger persons has been attributed to a decrease in hypertension related ICH while the incidence in older patients has been connected to an increased amount of lobar ICH and, possibly, to an increased use of antithrombotic medications[16, 39].

The HS incidence varies notably across the world (Figure 3)[36], and so do the ICH incidence. The highest annual ICH incidence rates are found in east and south-east Asian ethnic groups (51.8 per 100,000 persons), where the incidence is twice that of white ethnic groups (IRR 2.1)[37]. In a meta-analysis of 17 studies, the age-adjusted ICH incidence (adjusted to the WHO world population) was higher for men (IRR 1.60; 95% CI, 1.47-1.74)[41]. However, the majority of European and Australasian studies have not shown a connection between sex and age-adjusted ICH incidence, while, in North American and east Asian populations, men are generally at higher risk for ICH[42].

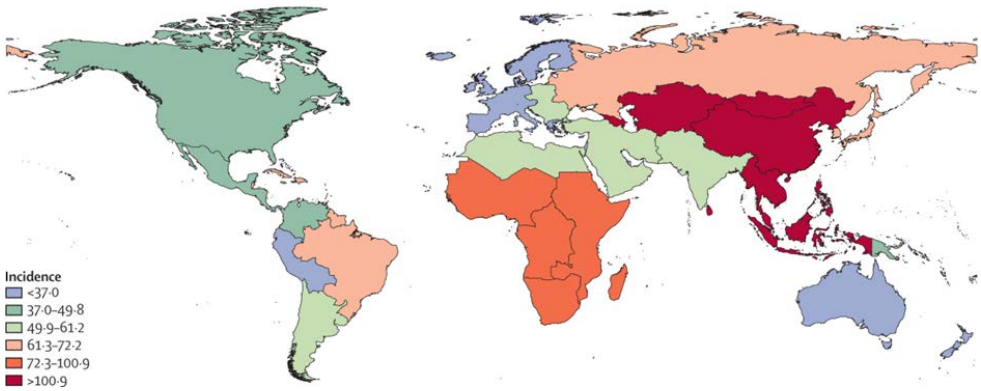

Figure 3. Age-standardized incidence of hemorrhagic stroke per 100 000 person-years for 2010, from Krishnamurthi et al. 2013 [36] © 2013 Krishnamurthi et al. Open Access article distributed under the terms of CC BY-NC-ND l (http://www.thelancet.com/journals/langlo/article/PIIS2214-109X(13)70089-5/fulltext#)

Sweden

Between 1998 and 2014 the age-standardized over-all stroke incidence has declined in Sweden according to the National Board of Health and Welfare (Figure 4). In concordance with the decrease in over-all stroke incidence, the absolute number of patients annually diagnosed with ICH (ICD-10 code I.60) has also decreased during the same time period (Figure 5) from 53 to 41 per 100,000 persons[43].

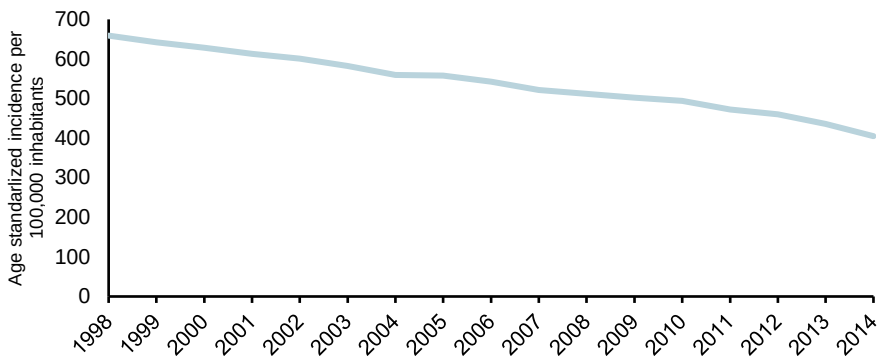

Figure 4. Stroke incidence in Sweden 1998 to 2014, age-standarlized to the Swedish population in 2015. Data from the National Board of Health and Welfare, Sweden[44]

In Swedish population-based estimates the annual ICH incidences have ranged from 23 and 36 per 100,000 person years, when age-standardized to Swedish populations (1996, 1999 and 2001), and from 14.4 and 29 when age-standardized

to a European population[6, 45, 46]. The incidence of ICH increases with age (Figure 6) and men tend to get ICH at an earlier age compared to women[6]. In 2015, 13% of patients included in the Riksstroke – The Swedish Stroke Register, had stroke due to ICH while 86% had IS and 1% had unspecified stroke[14].

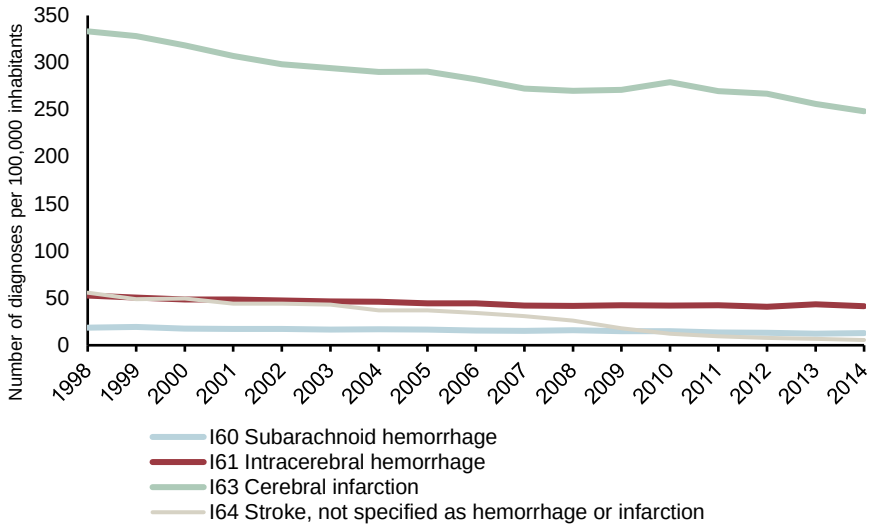

Figure 5. Temporal changes in stroke diagnoses (ICD-10 codes I60, I61, I63, and I64) per 100,000 inhabitants. Please note that these data are not age-standarlized. Data from the National Board of Health and Welfare, Sweden[43].

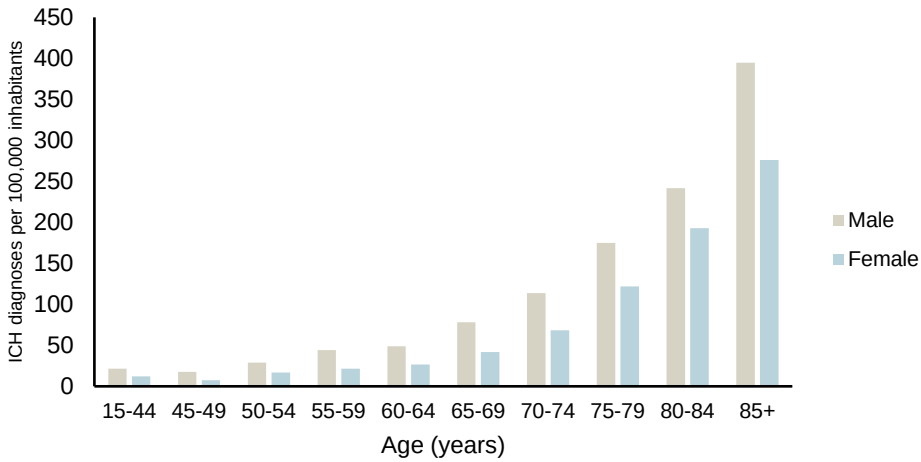

Figure 6. Age distribution among patients diagnosed with ICH (ICD-10 code I-61) in in-patient care during 2014 in Sweden. Data from the National Board of Health and Welfare, Sweden[43].

Causes

It is often not possible to determine what caused the vessel rupture leading to an ICH, since several short and long-term endogenous and exogenous factors are likely to add up to the final rupture[47]. Nevertheless, hypertension related degenerative changes and cerebral amyloid angiopathy (CAA) have become two dominant explanatory models for spontaneous ICH[47]. The effects of both hypertension and CAA accumulates over time and ICH thereby becomes more common with increasing age[6].

The etiologic classification system SMASH-U, implements a hierarchical order to determine the most likely mechanistic cause of ICH[48]. SMASH-U was developed in a Finish ICH patient cohort (N=1013)[48] and validated in a Taiwanese study (N=4578)[49]. In both the development cohort and the validation cohort, ICH due to trauma, tumor, hemorrhagic transformation of IS, and "primary SAH" were cause for exclusion. The distribution of etiological causes of ICH in the Finish and Taiwanese cohort, respectively, were: 5% and 8% structural lesions (cavernomas and AVMs), 5% and 12% systemic disease (liver cirrhosis, thrombocytopenia, illicit drug use, and a range of other conditions), 14% and 3% anticoagulant therapy (warfarin, direct acting oral anticoagulants, heparin, and thrombolysis not due to IS), 20% and 12% CAA (using the Boston criteria[50]), 35% and 55% hypertensive (pre-ICH blood pressure ≥160/100 mmHg, or history of hypertension and left ventricular hypertrophy, or on antihypertensive medications), and 21% and 10% undetermined[48, 49]. A German population-based study (N=152) applied a modified version of the SMASH-U, without systemic disease as a category, and found the following distribution of etiologies, 3% structural lesions, 11% anticoagulant therapy, 31% CAA, 51% hypertension, and 4% unknown[23].

Histopathology

Spontaneous ICH secondary to hypertension usually originates from the small arteries and arterioles (differentiated by the presence of a continuous elastic lamina in the former[51]) ranging from 50 to 700μm in diameter[52, 53]. The non-terminal arterioles (30-100 μm in diameter) have 2-3 smooth muscle cell layers, while larger cerebral arteries (>100 μm in diameter) have between 4-20 layers[54].

The connection between hypertension and ICH originates from the observations of cerebral microaneurysms by Charcôt and Bouchard in 1868[55]. The existence of Charcôt-Bouchard aneurysms and their association with ICH have been debated since then but fusiform segmental widenings found on arterioles are considered to play a minor role in the cause of ICH[53, 56]. Other forms of pathology in small cerebral vessels that have been attributed to hypertension includes: lipohyalinosis

(characterized by destructive lesions in 40-300 μm vessels) including the acute form fibrinoid necrosis; and hyaline arteriolosclerosis (hyaline wall thickening and loss of smooth muscle cells in 40-150 μm vessels) which in turn might affect autoregulation and expose distal vessels to tare [57, 58]. Fisher introduced a model for hematoma growth which suggests that the clot puts strain on vessel in its periphery which causes additional vessel ruptures and more bleeding[59].

Hypertension associated ICH are primarily located deep within the brain tissue[21] (locations B-E in Figure 7), close to the proximal, deeply located, small direct branches of the main cerebral arteries (anterior, medial and posterior cerebral arteries, and the basal artery)[9]. This might be explained by a somewhat abrupt increased pulse pressure and thereby increased vessel stress, in the relatively small arterioles branching directly from the proximal parts of the larger major cerebral arteries compared to arterioles originating from branches that are more distal[56].

While hypertension traditionally has been regarded to affect blood vessels located deeply within the cerebrum, CAA is associated with ICH in the cortex and subcortical white matter also known as lobar ICH[60]. CAA is caused by accumulation of β-amyloid depositions in the vessel walls of small leptomeningeal and cortical arteries and arterioles, which causes the vessels to become fragile, and prone to rupture[56]. The diameter of cortical and meningeal arteries range from 30 to 700 μm[61], and it has been suggested that CAA occurs from capillaries (<10 μm) up-to small arteries (<2 mm)[58]. The β-amyloid deposition in cerebral vessels is connected to the ε2 and ε4 alleles of the apolipoprotein E coding gene (APOE) which have also been associated with an increased risk for lobar ICH[62]. Additionally, the APOE ε2 allele has been associated with larger ICH volumes among patients with lobar ICH[63].

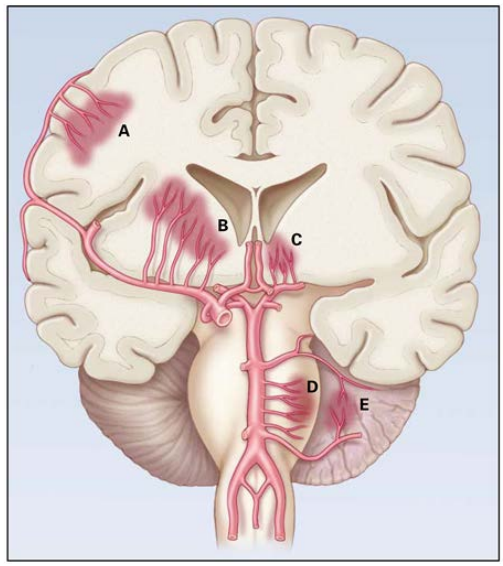

Figure 7. Common ICH locations. A) Lobar ICH, hemorrhage from cortical and leptomeningeal arteries, B) basal ganglia ICH, originating from lenticulostriate arteries, C) thalamic ICH, from thalmogeniculate arteries, D) pontine ICH, from braches from the basal artery, and E) cerebellar ICH, from branches of cerebellar arteries. Reproduced with permission from Qureshi et al.[9], Copyright Massachusetts Medical Society

Hemostasis

When a cerebral blood vessel ruptures, it induces local vasoconstriction followed by a cascade of different mechanisms to repair the damage.[64] The first step is aggregation of thrombocytes into a primary hemostatic plug that is reinforced by fibrin threads. Tissue factor released from the damaged endothelium and phospholipid complexes, exposed by activated thrombocytes, trigger a series of enzymatic conversion that ends with the activation of thrombin that converts fibrinogen into fibrin forming a clot[64]. Antiplatelet therapy and anticoagulant therapy inhibits the hemostasis and may increase the risk for ICH occurrence[21, 65] and expansion[66, 67]. Hart hypothesized that the anticoagulative effects of warfarin might exacerbate hemorrhages that would otherwise have been sub-clinical[68]. However, another possibility is that vitamin-K dependent coagulation factors are needed to counteract the normal tear on blood vessels, and by counteracting this, warfarin therapy leads to an increased ICH risk [69].

Risk Factors

Hypertension

Worldwide, hypertension is the leading risk factor for stroke in general[70] and for ICH in particular, since hypertension is a stronger risk factor for ICH than for IS

(population attributable risk 56% versus 46%)[71]. In a population-based study hypertension (≥160/110 mmHg) was associated with a five-fold increased risk for ICH (RR 5.55; 95% CI: 3.07-10.03)[72], and odds ratios from studies with varying hypertension definitions, range from 1.97 to 9.46[21, 24, 71, 73]. Hypertension is twice as common among patients with deep ICH compared to patients with lobar ICH but results are hetrogenous[74]. This is reflected by three recent studies where hypertension have ranged from not being a risk factor for either lobar or non-lobar ICH[15], to a risk factor for non-lobar ICH only[21]; and, most recently hypertension was associated with increased risk for both lobar and deep ICH[24].

Diabetes Mellitus

Patients with diabetes mellitus have an increased risk for cerebral small vessel disease[75], possibly due to hyaline arteriolosclerosis or impaired vascular reactivity which is associated with diabetes[57]. Additionally, hyperglycemia has been indicated to increase risk for ICH expansion[76] even though results have been mixed[77]. The connection to ICH occurrence is modest in a meta-analysis of 19 case-controlled studies (OR 1.23; 95% CI 1.04–1.45) and no connection was observed in the 3 included cohort studies (RR 1.27; 95% CI 0.68-2.36)[78]. In a recent case-control study (not included in the meta-analysis), patients with diabetes mellitus on antidiabetic treatment had a reduced likelihood to develop ICH (OR 1.18 versus 2.47) compared with untreated patients who had two-fold increased odds for both lobar and deep ICH (OR 2.30 and 2.58, respectively)[24].

Hypercholesterolemia

Several studies have observed an inverse connection between hypercholesterolemia (both total cholesterol and LDL) and ICH[21, 24, 72, 79, 80]. Additionally, there might be a genetic link between ICH risk and high-density lipoprotein (HDL) cholesterol levels, as explained below. One study showed that the protective effect of high total serum cholesterol levels is larger among patients with deep ICH than among patients with lobar ICH[21] while no differences were observed in another study[24]. Two large meta-analyses have concluded that HMG-CoA reductase inhibitors (statins) do not seem to increase the risk for ICH[81, 82] while a recent large Italian study indicated the opposite[24].

Alcohol

A high alcohol intake (cut-offs ranging from >36 to >100 g of alcohol/day) increases the odds for ICH three-fold (OR 3.36; 95% CI: 2.21-5.12) with a clear dose-response effect in a metanalysis[73]. A reduced platelet count and decreased production of pro-coagulative factors produced in the liver among patients with high alcohol consumption might contribute to the increased risk[83].

Smoking

While current smoking is an established risk factor for IS[71], a meta-analysis of 10 case-control studies did not show any increased risk for ICH among current smokers compared to non-smokers[73]. A possible explanation for this is that smoking affects large-artery atherosclerosis rather than small-artery occlusions[84] which, as a manifestation of small-vessel disease, is likely to be more closely linked to ICH[51]. However, current smoking was more common among patients with IS due to small-artery occlusions when compared to patients with deep ICH in a recent study[85]. Even though current smoking in the INTERSTROKE study did not increased the odds for ICH, patients smoking more than >11 cigarettes per day did have increased odds for ICH, albeit with approximately half the effect sizes in comparison with IS[71]. There have been indications that smoking might increase the risk for lobar ICH[86] but later studies have not been able to reproduce this[21, 24].

Ethnicity

As mentioned above, there are large geographical differences in ICH incidence. Ethnic origin explained 42% of the variance in incidence in one large meta-analysis[37]. Differences in environmental and lifestyle risk-factor distribution[70, 71] is a likely cause for geographical differences as immigrant populations have been shown to differ from their region of origin[37]. Nevertheless, one study has shown that immigrants to Sweden, born in east and southeast Asia, retain an excess risk for ICH occurrence[87]. One of the most pronounced differences in ICH risk are between black and white Americans, where black persons have an up-to four-fold increased risk (RR 1.6-3.8) and this difference seems to be the greatest for deep ICH (RR 1.7-4.8) possibly due to differences in hypertension prevalence and controll[17, 19].

Genetics

Genetic differences also explain differences in ICH incidence between different populations. Heritability has been estimated to explain 44% of the risk for ICH with a larger impact of genetics on lobar ICH compared to deep ICH (73% versus 34%)[88]. APOE is primarily associated with lobar ICH (discussed above) and only accounts for a third of the total heritability estimate for ICH risk[88]. Gene variants which impacts the risk for deep ICH have been connected to small vessel disease (COL4A2[89], oxidative phosphorylation genes[90], and the chromosomal region 1q22[91]) and hypertension[92]. Another interesting and rather contra intuitive observation is the connection between ICH risk and cholesteryl ester transfer protein gene (CETP) variants, which in turn have been connected to increased HDL cholesterol levels[93].

Pathophysiology

Acute Phase (0-4 hours)

Immediately in connection with the vessel rupture, the leakage of blood into the brain parenchyma triggers a sequence of mechanical disruption of neurons and glia followed by ischemia and physical deformation of the brain tissue and subsequent necrosis and cytotoxic edema[94]. Larger clots volumes increase intracranial pressure due to the limited intracranial volume and may thereby cause both distant mechanical damage (e.g. via herniation) and decreased cerebral perfusion pressure with subsequent global ischemia[95]. Perihematomal hypoperfusion might occur but is difficult to assess since mitochondrial dysfunction can affect metabolism and edema can affect blood flow in the tissue surrounding the ICH[94, 95]. It is therefore still debated if perihematomal hypoperfusion inflicts ischemia in the clot perifery[94, 95].

Subacute Phase (4 h to 7 days)

Several different biochemical factors are released from the clot into the surrounding tissue. One of these is thrombin, which affects endothelial cells and increase blood brain barrier disruption[95]. Thrombin also asserts a toxic effect in neurons and astrocytes, and triggers microglia activation[94, 95]. The breakdown of erythrocytes triggers a release of ferrous iron (from hemoglobin) and other breakdown products, which induces additional brain injury[94, 95]. The hematoma triggers an inflammatory response, first with activation of microglia (within the first hours) which in turn triggers a cascade of reactions ending in neural and glial apoptosis, and breakdown of connective tissues[94, 95]. Secondly, an influx of neutrophils cause formation of vasogenic edema (by disruption of the blood brain barrier), releases reactive oxygen species and proinflammatory proteases, and facilitates monocyte entry over the blood-brain barier[95].

Chronic Phase (days-months)

Microglia and macrophages gradually phagocyte the components of the blood clot and thereby reduce the hemorrhage until only a fluid filled cyst or collapsed brain defect remains.[30, 95] The perihematomal edema also usually resolves 2-4 weeks after ICH onset.[96] Recovery of function could be mediated by normalization of function in perihematomal tissue when the clot and edema decreases, and neuronal plasticity and neurogenesis[95]. Nevertheless, it is common that a decreased neurological function persists, as discussed blow.

Complications and Therapeutic Options

Therapeutic interventions in ICH focus on managing acute/sub-acute phase complications such as mass effect by hemorrhage and edema, increased intracranial pressure (ICP), and hematoma expansion, as well as on longer-term consequences of ICH such as deep vein thrombosis, infection, or ICH reoccurrence. Additionally, early multidisciplinary rehabilitation can improve functional outcomes after ICH[31].

A wide range of therapeutic options have been tested for ICH but few of these have shown a substantial benefit and stroke unit care is the only intervention which is strongly recommended by the European treatment guidelines on the basis of high quality evidence[97]. Even though many large well organized RCTs on ICH have been neutral, many new therapies are under investigation. To properly interpret and implement the results from RCTs it is important to understand how the trials' inclusion criteria impact on case-mix and how the case-mix affect prognosis[98]. By estimating how many ICH patients are possible to include in different RCTs, Fonville et al. and others have shown that the applicability of previous and ongoing ICH treatment trials might be limited[98-100].

Hematoma Expansion

A significant ICH expansion occurs in the acute phase among a third of all patients and the risk is largest within 24 hours of ICH onset[101]. Ongoing bleeding, or later re-bleeding from the original ruptured vessel or the vessels in the periphery of the ICH, are potential causes for expansion[101]. An increase in hematoma volume leads to more tissue damage and increases the risk for neurological deterioration and hematoma expansion is one of the most important predictors for poor functional outcome and short-term case fatality[102]. ICH expansion has been defined in many different ways using absolute, (volume) relative (percentage), and combined absolute and relative[103]. The time intervals between ictus (for which exact time is often unknown), baseline CT, and follow-up CT have also differed between trials which further complicates the interpretation of results.

Much effort has gone into trying to establish what factors drive expansion and how it can be prevented. Four different prognostic scores have been developed for ICH expansion, all including ictus to baseline CT and anticoagulation as prognostic factors[104-106].

Acute Blood Pressure Reduction to Reduce Hematoma Expansion

Two large randomized phase-III trials (the Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial, INTERACT-2[107]; and the Antihypertensive Treatment of Acute Cerebral Hemorrhage, ATACH-II trial[108])

tested if blood pressure (BP) lowering in the acute-phase (<6 hours) reduced hematoma expansion and improved outcomes after ICH. In summary, the two trials indicate that a moderate blood pressure reduction (systolic BP [SBP] <140 mmHg versus <180 mmHg) might be beneficial (intensive therapy arm in INTERACT-2; mRS 0-2 vs 3-6; OR 0.87; 95% CI 0.75-1.01) but that a more aggressive reduction (SBP<130 mmHg) might be harmful, possibly due to an increased frequency of renal failure (ATACH-II intensive therapy arm). There was no benefit of a more aggressive blood pressure reduction in ATACH-II (mRS 0-3 vs 4-6; RR 1.04; 95% CI 0.85-1.27). No ICH volume reduction could be observed in ATACH-II or INTERACT-2 but a meta-analysis (not including ATACH-II) showed a small reduction in ICH volume (1.54 mL) among patients who received more intensive BP reduction[109].

Hemostatic Therapies to Reduce Hematoma Expansion

Hemostatic therapy has been the second main strategy for preventing hematoma expansion and can be divided in therapies focusing on enhancement of hemostasis or reversion of anticoagulation/antithrombotic therapies.

Recombinant factor-VIIa reduced hematoma growth but did not increase functional outcome or survival after ICH[110]. Currently, the effects of tranexamic acid are tested in the randomized controlled trial -Tranexamic acid for intracerebral haemorrhage 2 trial (TICH-2)[111]. Several other ongoing trials are randomizing patients to hemostatic therapies if they have spot-sign, a radiological sign on CT angiography, which is a strong predictor of hematoma expansion[101, 112].

Ongoing antiplatelet therapy at ICH onset increased the odds for death after ICH (OR 1.27; 95% CI 1.10-1.47), but not for poor functional outcome (OR 1.10; 95% CI 0.93-1.29), in a meta-analysis of 25 cohorts[113]. Desmopressin and platelet transfusion have been suggested as possible treatments for patients with ICH during antiplatelet therapy. Nonetheless, desmopressin in ICH is poorly studied[114] and platelet transfusion was connected to an increased risk for death or dependence in a recent RCT (adjusted OR 2·05; 95% CI 1.18-3.56)[115].

Oral anticoagulant therapy increases the risk for ICH occurrence[21] and hematoma expansion[106]. Warfarin therapy reversal to < INR 1.3 within 4 hours of hospital admission reduced expansion rates and in-hospital mortality in one study[116] and it has been suggested that prothrombin complex concentrate may be superior to fresh frozen plasma in restoring INR and preventing ICH expansion[117].

Perihematomal Edema

The ICH induces an edema in surrounding tissue, which further increases the risk for increased intracerebral pressure and neuronal damage[96]. The perihematomal edema (PHE) expands rapidly the first 48 hours after ICH onset and reaches a

maximum 2 weeks after onset[118]. There has been mixed results on how PHE size and growth affect early neurological deterioration, functional outcome and case fatality after ICH, and therapeutic options are currently tied to control of ICP[96].

Intraventricular Hemorrhage

Approximately 40% of patients with ICH also have a ventricular extension of the ICH (intraventricular hemorrhage, IVH)[119]. IVH can cause mechanical obstruction of cerebrospinal fluid flow and thereby hydrocephalus, and induces inflammation that may cause harm to periventricular tissue[119]. Consequently, IVH may lead to a markedly increased risk for death and disability after ICH[96]. ICHs situated closely to the ventricles are more likely extend into the ventricles[120]. As with ICH, the ventricular hemorrhage is dynamic and in a study where the first CT was done within 3 hours of ictus, IVH expansion (>2 mL) occurred within 24 hours of ictus in 26% of patients with IVH at baseline[121]. Additionally, in ICH patients without IVH, late ventricular extension can occur up to 72 hours post-ictus[122, 123].

IVH volume is a strong predictor of post-ICH outcomes[124] but the degree of IVH extension and severity is often not quantified. Two possible reasons for this is that ventricular extension is a strong prognostic factor by it self[125] and exact volumetric assessments of IVH are laborious. Hence, well validated semi-quantitative methods for assessing IVH severity are needed to improve the understanding of which IVH patients make better treatment decisions and assess eligibility for novel treatments.

A novel therapy that has recently been tested is if intraventricular administrated rt-PA reduces the impact of IVH by facilitating clot resolution. However, in the RCT - Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR III), no difference in the primary outcome (mRS 0-3 versus 4-5 and death) was observed between patients receiving rt-PA versus saline (47% versus 45%) even though the rt-PA treated patients had improved survival up to 365 days post ictus, adding up to a 10% absolute reduction of mortality[126].

Hydrocephalus and Mass Effect

The mechanical neuronal disruption caused by larger ICHs may cause a rapid neurological deterioration and death. Additionally, increased ICP reduces the cerebral perfusion pressure which might result in hypo-perfusion and also subsequent death. Evacuation of supratentorial ICH might be lifesaving in these instances as might decompressive craniectomy albeit evidence is scarce[31, 97].

For most patients with supratentorial ICH there is still uncertainty regarding indications and timing for surgical evacuation[31, 97] despite two large randomized controlled trials have increased the knowledge about surgical treatment of ICH considerably[127, 128]. Currently, minimally invasive surgical methods for removal of

supratentorial ICH are tested in the - Minimally invasive surgery plus alteplase in intracerebral hemorrhage evacuation (MISTIE) phase-III trial (ClinicalTrials.gov identifier NCT01827046), and intraoperative stereotactic computed tomography-guided endoscopic surgery (ICES) has showed promise[129].

Surgical evacuation of larger cerebellar ICH is less controversial[31], even though evidence is scarce[97], as patients with these hematomas are at increased risk for deleterious mass effect and hydrocephalus due to the confined space in the posterior fossa and close proximity to the IV-ventricle and brainstem. External ventricular drainage (EVD) can be used to reduce the effects of hydrocephalus second to ICH[97].

Other Complications

The neural damage caused by stroke in general can have a broad range of consequences including e.g. seizures, immobilization, and dysphagia, which in turn can lead to further neurological damage, venous thromboembolism, and infection, respectively. Stroke unit care enables close monitoring and treatment of possible complications and is recommended for patients with ICH since it reduces both death and disability[97]. A full summary of ICH complications is beyond the scope of this introduction, but some frequently discussed complications are separately addressed below.

Between 14% and 16% of patients with ICH develop seizures in the acute phase (<7 days of stroke)[130, 131] and seizures are more common among ICH patients compared with IS patients (16% versus 4.2%)[130]. Cortical ICH involvement is a strong risk factor for post-ICH seizures[130, 131]. Symptomatic seizures should be treated[31] even though early seizures do not seem to affect 7-day or 6-month case fatality, or 180-day functional outcome[131].

ICH patients who are immobilized due to motoric deficits or reduced level of consciousness are at increased risk for venous thromboembolic disease[31, 97]. One study estimated that 1% and 2% of all patients with ICH had symptomatic deep vein thrombosis and pulmonary embolism, respectively, during hospital stay[132]. Another study reported that up-to 16% of patients with ICH had asymptomatic DVT at 10 days post-stroke[133] and early intermittent pneumatic compression is recommended to prevent DVT occurrence[31, 97].

In a longer perspective, 19% of patients develop dementia with-in 6-months of ICH onset[134], and among 6-month ICH survivors without pre-existing dementia 14% and 28% had developed dementia 1 and 4 years post-ICH, respectively[135]. Patients with lobar ICH are at increased risk for post-ICH dementia compared with patients with non-lobar ICH and CAA might be a common contributing factor[134, 135].

White Matter Lesions

Cerebral small vessel disease (SVD) is associated with ICH, lacunar ischemic stroke (small vessel occlusion), cerebral microbleeds, and degenerative changes[51]. Wardlaw et al. concluded that vessel diameter limit could not be used to define the "small" perforating arteries and arterioles affected by SVD[136]. SVD is commonly caused by degenerative changes second to hypertension and CAA[51, 137].

White matter lesions of presumed vascular origin (WML), are also known as leukarosis, white matter hypodensities/hypoatenuations (on CT), and white matter hyperintensities (WMH) (on MRI), and have been described as a radiological manifestation of SVD[136]. These lesions predict a three-fold risk increase for stroke, and a two-fold risk increase for dementia and death, respectively[138]. WML increase the risk for ICH[139] and IVH occurrence[140], and have been connected to worse ICH outcomes, as described below.

One possible explanation for the negative effect WML have on post-ICH outcome is that the histological changes connected to WML also alter the tissues ability to mechanically withhold the clot and thereby increase the risk for ICH expansion[141].

The histopathologic correlates of WML are heterogeneous, and include reduced tissue density due to loss of myelin, axons, and oligodendroglial cells, as well as gliosis[137] Gouw et al. suggest that the histopathological changes are "suggestive of incomplete infarctions" but also concludes that blood-brain barrier dysfunction, and microglia activation may play a role[137]. Additionally, different radiological WML findings might correspond to different pathologies, since irregular periventricular WML and confluent deeply located WML have more severe tissue changes, compared to smooth periventricular and punctate WML[137].

MRI is superior to CT in identifying and quantifying WMH/WML[136] and a plethora of different rating scales had been developed for both modalities[136, 142] with the Fazekas score being commonly used for MRI assessments[143]. However, only a few scales are adapted for both CT and MRI[144]. Scheltens et al. recommended the use of the visual semi-quantitative scale developed by van Swieten et al. (vSS)[145] for its simplicity and good reliability for use in both MRI and CT (weighted kappa 0.78 and 0.63, respectively)[142, 145]. Since then, the more complicated age-related white matter changes (ARWMC) scale has been introduced which can be used for both MRI and CT with good and fair interrater agreement, respectively (kappa 0.67 and 0.48)[146].

The vSS for CT scans, classifies WML severity in two regions, (a) the anterior periventricular area, and (b) the posterior periventricular area and centrum semiovale[145]. The WML grade for each region is classified as either: no WML

(score 0), WML that do not expand to the cortex (score 1), and WML that extend from the ventricles to the cortex (score 2). Scores from the two regions are then combined (range 0-4). If severity differs between sides or within regions, the highest score is used. Previous studies on ICH and WML on CT have primarily used the vSS[20, 147, 148]. The ARWMC scale rates WML from 0-3 (no lesion to involvement of entire region) separately for each hemispheres frontal, parietooccipital, and temporal lobes, and brainstem/cerebellum[146]. Additionally, lesions in the left and right basal ganglia are rated from 0 to 3 (no lesion to confluent lesions)[146].

Outcome

Case Fatality

Worldwide

The median 30-day and 1-year case fatality after ICH have been estimated to 40.4% (range 13.1%-61.0%) and 54.7% (range 46.0%–63.6%), respectively[37]. In another meta-analysis based on 9 population-based studies, the 1-year case fatality was almost identical (54%)[149]. The short-term (21/30-day) case fatality is lower in high-income countries (25%-35%) compared to low-income countries (30%-48%)[34], and the lowest rates are found in Japan (13.1%)[37]. The 30-day and 1-year case fatality has remained stable[37] but in a study from the Netherlands a decline was reported among younger patients (<75 years) while the case fatality remained unchanged among older patients (≥75)[38].

The high short-term case fatality after ICH makes long-term follow-ups more difficult due to small number of short-term survivors. The 5-year survival, based on 3 population-based studies[150-152], was 29.2% (95% CI 26%-33%) in a meta-analysis[149]. Several aspects of long-term survival after ICH has been studied in prospective and retrospective, hospital-based[49, 153-155] and population-based cohorts[25, 150-152, 156-158] but few studies have covered very long-term survival (>10 years)[25, 49, 151, 156-158]. Even fewer studies have given a fuller picture what prognostic factors and causes of death affect the long-term prognosis[151] which is needed to improve the long-term prognosis of ICH survivors.

Sweden

Riksstroke – a Swedish national quality register for stroke care, has reported that the 3-month case fatality for patients with ICH in Sweden has remained stable between 2012 and 2014 at 32.5% to 34%[159-161]. These 3-month case fatality rates

are similar to the 20%-36% 28/30-day case fatality rates that were reported in Swedish cohorts from 1993 to 2000[22, 26, 45].

In contrast, in data from the Swedish National Board of Health (NBHSD)[43, 162] there has been a decrease the number of patients with ICH (ICD-10 code I61) as underlying cause of death between 1998 and 2014 (N=1618 and 1044). At the same period, the number of patients diagnosed with ICH (ICD-10 code I61) in in-patient care has also decreased from 3795 to 3323. However, in the NBHSD data, the proportion of ICH deaths by incident ICH cases has also decreases (Figure 8) which might indicate a trend towards better survival. Nonetheless, trends in this kind of register data should be interpreted with great caution as the accuracy of diagnoses might vary[163].

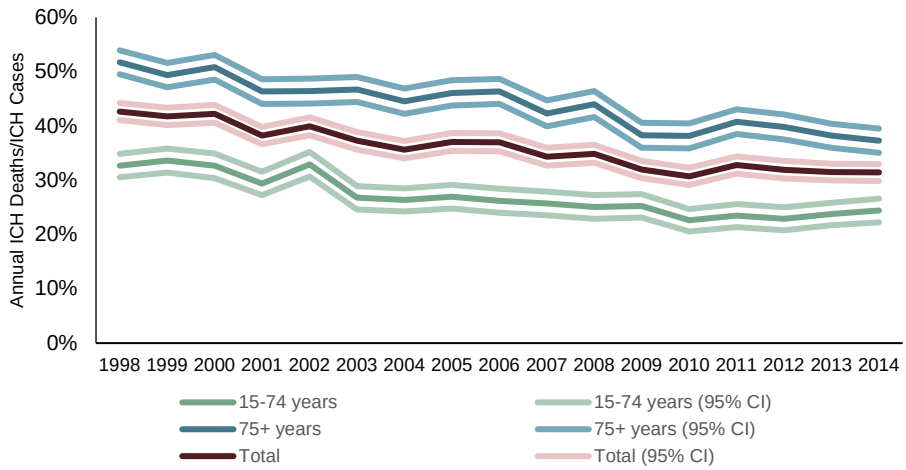

Figure 8. Unadjusted proportions of deaths caused by ICH (ICD-10 code I61) and number of incident ICH cases (ICD-10 code I61). Based on 20 855 cases with ICH as underlying cause of death divided by 57 786 in-patient care ICH diagnoses (counted once per patient per calendar year). Data from National Board of Health and Welfare, Sweden[43, 162].

Functional Outcome

Disability is more common after ICH than after IS and 3-month functional status is an important predictor of long-term survival after all-cause stroke and ICH[164, 165]. Among patients who were independent in activities of daily life (ADL) prior to the stroke 28% were dependent on others for help with ADL 3 months post ictus compared to 18% among patients with IS[159]. The questions used by Riksstroke for 3-month follow-up of ADL can be converted to the most commonly used functional outcome measurement in stroke research, the modified Rankin Scale (mRS)[166, 167].

The mRS rates post-stroke disability on a six grade scale (seven grade if death is included), from no symptoms at all (0) to severe disability (5; bedridden, incontinent, and requiring constant nursing care and attention) and death (6). What constitutes as a good or poor functional outcome depends on the expected severity of the studied disease and a mix of binary mRS endpoints has previously been used in stroke studies. Some frequently used cut-offs for moderately severe stroke are 0-1 versus 2-6, and 0-2 versus 3-6; whiles studies on severe stroke have used mRS 0-3 versus 4-6, and even 0-4 versus 5-6[168]. The 0-2 versus 3-6 cut-off can be used to differentiate non-dependent from dependent patients; while the 0-3 versus 4-6 separate patients requiring some help but are able to walk by them self from patients who are unable to walk and attend to own bodily needs without assistance[167]. Different forms of statistical analyses have also been used to fully utilize the ordinal scale properties of the mRS[168].

There are also several other grading scales such as the Barthel ADL index[169] and Functional independence measure (FIM)[170]. Furthermore, the Glasgow Outcome Scale (GOS)[171], originally developed for traumatic brain injury, and its extended variant (eGOS; range 1-8 from death to vegetative state, and upper and lower: severe disability, moderate disability, and good recovery)[172] have been used in ICH studies[127, 128].

In 4 population-based studies, 32.8% to 42.4% of the ICH patients were independent (mRS 0-2) 6 months after ictus while only 17 to 24% were independent one year after ictus[149]. However, in the same study the corresponding proportions of functional independence (mRS 0-2) among 6-month and 1-year ICH survivors were 54-84% and 54-57%, respectively[149] which highlights how much survival impacts functional outcome estimates. In another summary, the proportions of patients living independently ranged from 12% (Estonia) to 39% (Italy) but follow-up times and outcomes assessments differed considerably between the 6 included studies[37].

Recurrent Stroke

The annual risk for recurrent ICH ranged from 1.3-7.4% in 9 different studies and the recurrence risk was increased among patients with lobar ICH in 2 of the 3 studies reporting on ICH location[149]. In a Swedish study, 12% of the 28-day ICH survivors had recurrent stroke during a 3-year follow-up period (5.1 per 100 patient years) and about half of these where due to recurring ICH (2.3 per 100 patient years)[26]. The link between CAA and ICH recurrence[49] is supported by that ε2 and ε4 APOE alleles, lobar ICH are risk factors of recurrent ICH[173].

Factors Influencing Outcome

The risk for death and poor functional outcome after ICH increases with age and the total burden of co-morbidities[22, 125, 174, 175]. The impact of sex on case fatality after ICH is unclear as results have been mixed[42] and in south Swedish studies, men have had both higher[26] and lower[22] 28/30-day case fatality. No clear differences in age-adjusted neurological outcome have been consistently observed between sexes[42] and no differences were observed between men and women in 3-month or 1-year functional outcome in two recent hospital-based studies[176, 177].

Short-term Survival and Functional Outcome (<1 year after ICH)

ICH volume is one of the most important factors for 30-day and, and 90-day functional outcome[125, 175]. The ABC/2 method is frequently used for ICH volume assessments[178] because it is easy to use and have a good agreement with exact volume[179]. However, the ABC/2 method tends to overestimate clot volumes slightly and the methods accuracy decreases with larger, irregular, and lobar hemorrhages[179]. The ABC/2 method uses three measurements to estimate the ICH volume where: A) is the greatest clot diameter, B) is the largest diameter perpendicular to A, and C) is the number of slices with blood multiplied by the slice thickness[178]. Common cut-offs for ICH volumes are <30 mL (smaller), 30-60 mL (mid-range), and >60 mL (large)[180].

The location on the hemorrhage is also important and patients with lobar ICH seem to have lower age-adjusted 30-day and 1-year case fatality[15, 26]. Patients with infratentorial ICH have a worse short-term survival (30-day and 1-year) compared to patients with supratentorial ICH[15, 125] and patients with brainstem ICH have a worse prognosis compared with cerebellar ICH patients[26]. Among patients with non-lobar supratentorial ICH, those with thalamic ICH have similar case fatality and functional outcome as patients with putaminal ICH, despite smaller ICH volumes[18].

Larger IVH volumes also increase the risk for 30-day case fatality and poor 180-day functional outcome[124, 181]. However, IVH in the IIIrd and IVth ventricle confers an increased risk of hydrocephalus[182] due to obstruction of CSF flow, and smaller IVH volumes in the IIIrd and IVth ventricle may be of prognostic importance[183]. Different scales for IVH severity have incorporated different aspects of IVH volume and location[182-185] and the three older scales (original Graeb scale, IVH score, and LeRoux score)[182, 183, 185] have been shown to perform similarly in functional outcome prediction (mRS $\geq$3)[186]. The modified Graeb scale (mGraeb) has been shown to correlate well with absolute IVH volume and to prognosticate poor functional outcome (mRS$\geq$4) with a higher accuracy than the

original Graeb scale[181], but has mainly been used in clinical trials cohorts[181] and convenience samples[187].

Decreased level of consciousness (LOC) is another well-established short-term risk factor for poor outcomes after ICH[125]. Another indicator for stroke severity that is connected to short-term mortality and morbidity after ICH is the degree of neurological deficit as assessed by the National Institutes of Health Stroke Scale (NIHSS)[188].

Other factors that have been associated with poor short-term outcome after ICH are: hematoma expansion (discussed above), white matter lesions[20, 147, 189], elevated white-blood cell count[190, 191], elevated serum C-reactive protein[192, 193], elevated blood glucose[194, 195] and diabetes mellitus[196], antiplatelet[113] and anticoagulant therapy at ICH onset[66].

Long-term Survival (>1 year after ICH)

The factors that influence short term death and disability after ICH are well described while studies on factors influencing long-term (>1 year) are less common. Higher age, male sex, baseline ICH volume have been associated with three-year case fatality after ICH in two studies[20, 26]. Baseline age, diabetes mellitus, brainstem ICH, and anticoagulation therapy increased odds for long-term mortality (up- to 16-years post ictus) in a study from USA, while cerebellar ICH and surgery for ICH was associated with decreased odds[157]. In a Finish study among 3-month survivors after ICH, baseline diabetes mellitus and smoking were prognostic factors for 7-year case fatality. [165] Old age, history of heart failure, and male sex, were prognostic factors for long-term survival (up-to 16 years) in another Finish ICH cohort with 30-day ICH survivors[151]. In a Taiwanese cohort, ICH due to systemic disease and medication were negative prognostic factors for long-term survival[49].

Survival Analysis and Prognostic Models

Survival Analysis

When studying survival over longer time periods the normal (expected) mortality in a comparable population without the disease studied needs to be accounted for, otherwise the disease specific mortality might be overestimated. One way to address this is by only including the deaths caused by the studied disease, i.e. cause-specific deaths. A major limitation to cause-specific survival is that the cause of death is often difficult to determine[197]. An alternative way to address

competing risks for mortality is by using relative survival ratio (RSR), derived from the observed (all-cause) survival rate among cases with the disease and the expected survival rate in the general population (often weighted for demographic factors to match the cases)[198].

Survival studies are characterized by two factors that limit the usefulness of traditional statistical methods like logistic regression (assuming binary outcomes e.g. survival/death) and linear regression (assuming a continuous outcome such as time to death). First, study participants can be lost to follow-up before an event (e.g. death) has occurred and the full follow-up period is completed. This introduces a possible error when classifying patients into a binary outcome since they may have a substantial event-free follow-up period. Secondly, not all patients experience an event (such as death) during a reasonable follow-up period, which is required for tests using a continuous outcome such as time to death[199].

To address these two issues, specific statistic methods have been developed to study survival. Kaplan-Meier survival estimates (KM) describes the probability of survival over a time interval assuming a non-parametric distribution of survival times. As long as cases are event-free, they contribute to the survival time in KM, and cases are removed (censored) from the model if they have not had an event but can no longer be followed[199]. KM survival curves are commonly used to illustrate survival and can also be used to estimate median survival time[199]. Stratification on groups is possible with KM but not adjustment for several covariates. The logrank test is a non-parametric method to compare if survival curves differ between groups in KM. However, the logrank tests do not allow for inclusion of several covariates into the same model and does not estimate effect sizes (such as HR)[199].

Prognostic Factors

To estimate HRs of several different covariates, accounting for time to death, the semiparametric Cox regression (or Cox proportional hazards model) can be used[199]. Like KM, Cox regression allows for censoring of cases and do not assume that survival time is normally distributed. However, Cox regression requires that the hazards studied are proportional over time. Additionally, both KM and Cox requires that censored cases have the same probability of experience an event as cases kept in the model, i.e. censoring should be non-informative[200]. Results from studies with different follow-up times can be compared if Cox regression has been used since the model incorporate time to death. This is in contrast to logistic regression[201]. Nevertheless, with short follow-up times Cox regression models generate “essentially the same results” for risk factor coefficients as logistic regression models[201].

Prognostic Models in General

Prognostication models for disease outcome can identify potentially modifiable factors, optimizing patient care, and improve patients and healthcare personnel's understanding of how the disease might progress.

The development of prognostic models can be divided into three stages from (a) initial development including internal validation (i.e. estimate of how well the model work in the development cohort) to (b) external validation (i.e. how well the model perform in a different cohort) and then to (c) assessment of clinical usefulness. While the amount of studies reporting on new prognostic models is large (and sometimes include internal validation), studies on external validation and clinical usefulness are scarce[202]. To obtain clinically useful prognostic models the Prognosis Research Strategy (PROGRESS) studies has suggested that the models should be 1) "developed using a large, high quality dataset" 2) "based on a study protocol with a sound statistical analysis plan", and 3) "validated in independent datasets obtained from different locations"[202].

Statistical models for survival analysis can be used to identify factors for prognostic models of disease outcome. The accuracy of the prognostic model depends on the agreement between predicted probabilities and actual observed risk (calibration), and how well the model can separate high and low risk patients, respectively (discrimination)[200, 203]. Receiver operating characteristics (ROC) curves and corresponding c-statistics, can be used to determine the probability that a person who experienced an event also has a high risk estimate, i.e. discrimination. A higher discriminative ability comes at the cost of lower calibration[203] and several methods for evaluation of calibration and clinical usefulness have been suggested[203, 204]. Other testable aspects of prognostic models are the abovementioned internal and external validity[204].

Prognostic Models in ICH

There is a large amount of different prognostic scales and models for short-term outcomes after ICH[205-207] with different combinations and weights of the abovementioned short-term risk factors (Table 1). One of the most used and well-validated scales for 30-day and 1-year case fatality is the Hemphill ICH-score[60, 125]. However, the prognostic accuracy of GCS alone for 30-day case fatality might actually be fairly well comparable with the more elaborate scales[208]. For functional outcome the FUNC-score[175] is an often cited scale even though clinical assessments might have a better correlation to functional outcome[209], possibly because experienced clinicians can apply a broader range of parameters in addition to the factors used in any prognostic scale[210].

One of the most discussed limitations of prognostics scales in ICH is that early decisions of withdrawal of care and do-not-resuscitate/do-not-intubate (DNR/DNI) increases case fatality after ICH despite adjustment for baseline ICH severity[211]. Current guidelines urge to a cautious approach in applying prognostic scales on an individual level as de-escalation of care intensity might have influenced patients' prognosis in the cohorts from which the scales are derived, causing "self-fulfilling prophesies"[31, 212]. Nevertheless, there is a great variability between clinicians in assessments of 30-day case fatality, which prognostic scales might reduce[213].

Table 1. Summary of prognostic scores for ICH. Risk factor weights (points) are within parantheses.

	ICH score[125]	ICH score modified by Cheung et al.[188]	ICH score modified by Godoy et al (A and B, respectively)[214]		Essen ICH score[215]	ICH grading scale[216]	FUNC score[175]
Score range	0-6	0-6	0-11	0-9	0-10	6-16	0-11
Age (years)	<80 (0) ≥80 (1)	<80 (0) ≥80 (1)	<50 (0) 50-64 (1) ≥65 (2)	<65 (0) ≥65(1)	<60 (0) 60-69 (1) 70-79 (2) ≥80 (3)	<45 (1) 45-64 (2) ≥65 (3)	<70 (2) 70-79 (1) ≥80 (0)
ICH volume (mL)	<30 (0) ≥30 (1)	<30 (0) ≥30 (1)	<30 (0) 30-50 (1) >50 (2)	<30 (0) 30-50 (1) >50 (2)	-	Supratentorial: <40 (1); 40-70 (2); >70 (3) Infratentorial: <10 (1); 10-20 (2); >20 (3)	<30 (4) 30-60 (2) >60 (0)
IVH	No (0) Yes (1)	No (0) Yes (1)	Graeb score 0 (0) 1-4 (1) 5-8 (2) ≥9 (3)	Graeb score 0 (0) ≤3 (1) >3 (2)	-	No (1) Yes (2)	-
ICH location	Supratentorial (0) Infratentorial (1)	Supratentorial (0) Infratentorial (1)	-	-	-	Supratentorial (1) Infratentorial (2)	Lobar (2) Deep (1) Infratentorial (0)
Level of consious-ness (LOC)	GCS 3-4 (2) 5-12 (1) 13-15 (0)	-	GCS 3-5 (3) 6-8 (2) 9-13 (1) 14-15 (0)	GCS 3-4 (3) 5-8 (2) 9-13 (1) 14-15 (0)	NIHSS LOC Coma (3) Stupor (2) Drowsy (1) Alert (0)	GCS 3-8 (3) 9-12 (2) 13-15 (1)	GCS <9 (0) ≥9 (2)
NIHSS	-	0-10 (0) 11-20 (1) 21-40 (2)	-	-	0-5 (0) 6-10 (1) 11-15 (2) 16-20 (3) >20 (4)	-	-
Additional factors	-	-	Age 50-64 + Comorbidity (1)	Age ≥65 + Comorbidity (1)	-	-	Pre-ICH cognitive impairment Yes (0); No (1)
Outcomes	30-day case fatality	30-day case fatality, and 30-day mRS 0-2	30-day case fatality, and 6-month GOS 4-5	30-day case fatality, and 6-month GOS 4-5	100-day Barthel index ≥95 vs <95, and in-hospital death or at 120-days	30-day case fatality and 30-day GOS 4-5	90-day GOS≥4

Aims

The overall aim of this study was to investigate how clinical factors and imaging factors affect the survival and functional outcome after ICH and how these factors may influence therapeutic options after ICH.

Specific aims were:

I. To identify risk factors that affect short-term and long-term survival and functional outcome after ICH (Paper I, II, and IV)

II. To investigate long-term causes of death among 1-year survivors after ICH and if these patients have an excess mortality compared with the population (Paper I)

III. To assess if IVH severity quantification using the modified Graeb scale improves outcome prediction after ICH (Paper II)

IV. To explore the effects if the presence of white matter lesions influences the important short-term risk factor, hematoma expansion (Paper III)

V. To study how clinical and imaging factors influence patient selection in large clinical trials on ICH regarding overall applicability of trial results and eligible patients prognosis (Paper IV)

Methods

Study Populations

Patients in Studies I, II, and IV are all from Southern Sweden and patients in Paper III are from an international multicenter study as described in the overview of the included studies in Table 2.

Table 2. Overview of methodological aspects of the four papers in the thesis.

	Paper I	Paper II and IV		Paper III
Inclusion time	1996	2001-2007		2006-2015
Catchment area	South Sweden	Eight municipalities covered by Lund University Hospital		North America, Europe, and Israel
Inhabitants	1 140 000	240 000		NA
Patients	323 (173 one-year survivors)	Paper II: 196 (supratent-orial ICH)	Paper IV: 253 (any ICH location)	635
Study focus	Long-term prognosis	IVH severity	RCT eligibility	White matter lesions
End-points	Long-term survival (13-year) and causes of death	30-day mortality and 90-day functional outcome		Hematoma expansion and 180-day functional outcome
Study design	Prospective observational cohort study	Prospective observational cohort study, first ever stroke		Not prespecified post-hoc study from treatment trials
Case ascertainment	Patients admitted to Hospital in- or out-patient services; Autopsy	Patients admitted to Hospital in- or out-patient services		Screening for the clinical trials MISTIE-II and CLEAR-III
Information sources for baseline variables	Questionaire completed in the acute-phase by treating physician. Radiology reports. Baseline CT.	Form completed by research nurse using information from patient, relatives, and medical files. Baseline CT and radiology reports. Medical files.		Form completed by enrolling physician using information from patient, relatives, and medical files. Baseline CT.
Outcome assesment	Survival: the Swedish Population Registry (National Census). Causes of Death: National Cause of Death Registry	Survival: the Swedish Population Registry (National Census). Functional status: Riksstroke telephone follow-up or medical files		Clot expansion: basline and pre-randomization CT. Functional status: clinical examination

Paper I - Southern Sweden 1996

Patients with ICH in a defined uptake area in South Sweden (1.14 million inhabitants) were prospectively registered during a one year period (1996)[6]. Patients were identified via CT or autopsy at one of the 12 hospitals (including 4 forensic/pathology departments) serving the catchment area. The clinician at the department of neurology, internal medicine, pathology, or neurosurgery, identifying the patient filled out a form during the acute-phase. The form was then sent to the study administration. Patients with ICH who were only treated as outpatients were not identified.

To reduce possible influence of short-term risk factors we only included patients who survived the first year after ICH onset for further follow-up. The first studies on this cohort[6, 22] included both first-ever and recurrent ICH while the long-term follow up of one-year survivors only included patients with first-ever ICH at baseline. Other causes for exclusion were ICH due to: AVM, arterial aneurysm, trauma, tumor, or cerebral infarct.

Paper II and IV - Lund Stroke Register

The Lund Stroke Register (LSR) was used to identify patients (>15 years) with ICH for Paper II and IV. First-ever stroke patients (according to the WHO criteria above) who were admitted to hospital with from 8 municipalities in the up-take area of Skåne University Hospital, Lund, have been prospectively and consecutively registered in LSR since 2001[28, 217].

To identify possible patients, study nurses monitor emergency department visits, hospital admission lists, neurology consultations, neurology out-patient visits, and in-patient lists at the departments of neurology, neurosurgery, neurointensive care, and internal medicine. In the first year of LSR (March 2001 to February 2002) patients were also identified via contact with general practitioners, department of pathology, and forensic medicine. However, since these screening methods differed from later years and patients identified by these methods lacked baseline characteristics and CT, hence patients identified at autopsy or via primary care were not included in Paper II or IV.

Patients with ICH due to vascular malformations, arterial aneurysm, trauma, tumor, sinus thrombosis, or cerebral infarct, were excluded in further analyses even though they were registered in LSR. Only patients with supratentorial ICH were included in Paper II while no selection on ICH location was made in Paper IV.

All patients or their relatives have given consent for participation in LSR. At study inclusion baseline characteristics are completed using standardized questionnaires and medical files. Original radiological images and reports were accessed via an electronic database.

Paper III- MISTIE-II and CLEAR-III

Patients from the international (North America, Europe, and Israel) randomized clinical trials MISTIE-II[129, 218] and CLEAR-III[219] were included in Paper III.

We included both pilot and randomized patients from the MISTIE-II trial[218], including patients from the sub-study ICES (on endoscopic clot evacuation)[129]. The ICES patients had identical inclusion criteria as patients in the main MISTIE-II study. MISTIE-II patients had larger supratentorial ICH (>20 mL), small/no IVH (not requiring EVD), and baseline CT within 12 hours of ICH. The last CT performed prior to randomization to surgery/medical therapy was used for hematoma expansion assessment and was performed between 6 and 48 hours after the baseline CT.

Patients from the phase-III study CLEAR-III all required EVD, had IVH obstructing IIIrd and/or IVth ventricles, and had small ICH (<30 mL). CLEAR-III patients were randomized to intraventricular infusions with rtPA or saline[219]. Baseline CT was performed within 24 hours of ictus. The last CT before randomization to saline or rtPA was used to rate hematoma expansion. That CT was performed more than 6 hours after EVD placement and within 72 hours of the baseline CT.

In both MISTIE-II and CLEAR-III hematoma stability was required prior to randomization since the experimental treatment in both trials might cause further bleeding. Specifications on the clot-stability criteria are found in Paper III, and the full list of eligibility criteria for MISTIE-II and CLEAR-III can be found in the original publications[218, 219].

Paper IV - Clinical Trial Selection and Eligibility Assessment

In Paper IV, eleven large (>300 patients) finished, ongoing, and planned phase II–IV interventional trials on ICH therapy were assessed. The included clinical trials were identified by searching the clinical trials registers ClinicalTrials.gov (http://www. ClinicalTrials.gov), ISRCTN registry (http://www.isrctn.com), and the Stroke Trials Registry (http://www.strokecenter.org).

The eligibility criteria for the clinical trials were gathered from the original publications or from the clinical trials registers. Trial eligibility was determined in two steps. First, radiological and clinical data that had already been collected for Paper II (including infratentorial ICH patients) was used to identify patients that were potentially eligible for the 11 trials. Secondly, additional data was collected from medical files and CT scans to determine if the potentially eligible patients detected in the first step also meet the remaining eligibility criteria not covered by the data collected for Paper II. Since we did not collect further information in step 2 on patients who were deemed ineligible in step 1, all patients in Paper IV did not have information on every eligibility criteria for each of the 11 included trials.

To minimize the risk of under estimating potential trial eligibility, patients missing data on eligibility criteria, other than time from ictus to CT, were considered eligible. Additionally, all eligible patients were assumed to consent to inclusion.

Risk Factor Assessments

Clinical Factors

Paper I

The treating physician completed baseline clinical characteristics including: previous cerebrovascular or ischemic heart disease, hypertension, diabetes mellitus and ongoing antiplatelet or anticoagulant therapy, in the acute phase in 1996, using a questionnaire. Level of consciousness at admission was assessed according to the Reaction Level Scale-85 (RLS-85) which was then categorized into corresponding GCS groups[220, 221].

Paper II and IV

Clinical baseline characteristics and risk factors were prospectively recorded in LSR and additional data were available from medical files. Admission level of consciousness according to the GCS was estimated from medical records. If GCS could not be assessed by medical files due to missing information on verbal or eye response, a translation from baseline RLS-85 was used to estimate the corresponding GCS[221]. The definition of the cardiovascular risk factors used in Paper II have been previously described by Starby et al[217]. The large number of clinical characteristics used in Paper IV was mainly collected from medical files as further described in the Supplemental material of Paper IV.

Paper III

The local physicians responsible for trial enrollment of each individual patients gathered information on patient history of hypertension, hyperlipidemia, and diabetes mellitus, using information from history from patient and family, as well as medical files. Additionally, NIHSS and GCS were completed at randomization. Ongoing warfarin therapy and INR >1.5 at baseline were combined into a dichotomous variable.

Neuroimaging

In Paper I, neuroimaging were determined by a neurosurgeon or a radiologist using the baseline CT scan. In the LSR cohort (Paper II and IV) neuroimaging assessments were done by two independent readers using the baseline CT scan; a neuroradiologist adjudicated the assessments if needed. In Paper III, the neuroimaging, except WML severity, were assessed at the MISTIE-II and CLEAR-III study reading center using baseline (diagnostic) CT scan and subsequent pre-randomization CTs. In Paper IV, a large number of additional imaging characteristics were collected in addition to the one described below using the baseline CT scan.

ICH Location

Anatomic classification of ICH is important and can be performed with high inter-rater and intra-rater reliability[222]. In Paper I, ICH location was categorized into lobar (cortical or subcortical), central (caudate, putamen, globus pallidus, thalamus, internal capsule, deep periventricular white matter, or intraventricular), cerebellar, and brainstem. The same classification was used in Paper II-IV, with the addition of a “mixed” category, when the supratentorial ICH was so large that it could not be determined if the epicenter of the ICH was lobar or deep (i.e. central). In Paper III, 46% of the included patients had thalamic ICH, and only 7% had lobar ICH, and we therefore dichotomized hematoma location into thalamic/non-thalamic ICH.

ICH Volume

The ABC/2 method[178]was used for estimations of ICH volumes in Studies I, II, and IV. Planimetric methods were used in Paper III and give more exact approximations of ICH volumes but are more laborious to perform. In these methods the borders of the clot are outlined automatically or semi-automatically; the areas covered by blood on each slice are multiplied with the thickness of each slice to create volumes which are then summarized into a total clot volume.

Intraventricular Hemorrhage

In Paper I, a significant ventricular extension of the ICH was defined as IVH present in two or more ventricles. In the MISTIE-II and CLEAR-III cohorts (Paper III), IVH volumes were quantitatively estimated using a planimetric method.

In LSR patients (Paper II and IV), IVH was classified according to the modified Graeb scale (mGraeb)[181, 184], (range 0-32, Table 3) which has been shown to improve functional outcome prognostication compared to the original Graeb score (oGraeb, range 0-12) and to correspond well with planimetric IVH volume measurements[181, 182, 184].

In Paper II and IV mGraeb was assessed by two independent readers. A consensus decision was made if: 1) the total mGraeb score differed more than 5 points between readers, 2) the score for one single ventricle differed two or more points between readers, and 3) one reader regarded the ventricle as empty of blood while the other scored for presence of IVH.

Table 3. Summary of the original Graeb scale[182] and the modified Graeb scale[181, 184] evaluated in Paper II and used for eligibility estimation in Paper IV.

Ventricle:	Lateral (sides scored separately)			IIIrd	IVth
Ventricle filled with blood %	**Temporal tip**	**Main body**	**Occipital horn**		
Original Graeb Scale[182]					
Trace of blood or mild bleeding	1			1	1
<50%	2				
>50%	3				
100% and expanded	4			2	2
Modified Graeb Scale[181, 184]					
No IVH	0	0	0	0	0
≤ 25%	1	1	1	2	2
> 25 to ≤ 50%		2			
> 50 to ≤75%	2	3	2	4	4
>75%		4			
100% and expanded	3	5	3	5	5

Hematoma Expansion

In Paper III we primarily defined hematoma expansion as an ICH increase of more than 33% *or* 6 mL, a combination of two frequently used cut-offs[103]. We also used absolute change in ICH volume (continuous) and the recently suggested 10.4 mL cut-off for total clot expansion (IVH+ICH)[223]. In Paper III, patients were screened for pre-randomization stability up to 48/72 hours (MISTIE-II/CLEAR-II) after baseline (diagnostic) CT and the last CT prior to randomization was used to assess hematoma expansion.

White Matter Lesions

There are several rating scales for WML as described in the introduction. In Paper III we choose to use the van Sweiten scale (vSS)[145] since it is easy to use and has had a fair interrater agreement in previous CT based studies. Additionally, the vSS has often been used in previous studies on WML and ICH which facilitates comparison with prior results.

Two independent readers assessed all baseline CTs according to the vSS. We rated a test set of 50 LSR patients with ICH, prior to scoring the MISTIE-II and CLEAR-III patients, to calibrate vSS assessments and increase the inter-rater agreement, as suggested by Wardlaw et al[136]. The 50 LSR patients were not included in Paper III. Based on the experiences from scoring the test set we decided that for a vSS score of more than 0, the periventricular hypoatenuation had to distend ≥5 mm from the ventricle into the white matter. Additionally, to reduce the risk of scoring perihematomal edema as WML, we also decided that only the contralateral side would be rated if the area of interest was affected by hemorrhage.

All vSS assessments were done using non-contrast, baseline CT scans with the window set at 100-HU width and 50-HU level. Both readers completed the vSS assessments separately and we pre-specified that scores that differed by more than 1 point between readers were to be discussed. We also formed a consensus decision in the cases where one reader had scored for WML while the other had scored 0 point. A third adjudicator assessed cases where consensus could not be reached or if specific question arose.

Follow-up

Survival and Causes of Death

Personal identity numbers are assigned to all persons who are residing in Sweden since 1947 and this ID number is kept for life.[224, 225] In Paper I, II, and IV, personal identity numbers were used to obtain the date of death or emigration via the Population register (National census), which is kept by the Swedish Tax Agency.[224] When a person is declared dead, a certificate is without undue delay submitted to the Swedish Tax Agency and the census data is therefore continuously up-dated.[224] Of all deaths, 93% and 100% are estimated to have been reported within 10 and 30 days, respectively[225]. An additional form is completed with the causes of death and then submitted to the national Cause of Death Registry, kept by the National Board of Health and Welfare[226]. Between 1996 and

2009 less than 1% of the patients who died lacked a causes of death certificate[226]. In Paper I, personal identity numbers were linked to causes of death (coded according to ICD-10) by the National Board of Health and Welfare.

Functional Outcome

In Papers II-IV we used functional outcome assessments according to the mRS and in Paper III the eGOS was also used as a secondary outcome measurement. Due to the case-mix in all three papers a large proportion of patients were expected to have a more severe prognosis compared a general patient population with stroke. We therefore choose to dichotomize mRS at 0-3 versus 4-6 (including death), in all three papers. In Paper III, mRS was also analyzed as an ordinal scale.

In LSR (Paper II and IV), there is no standardized follow-up of functional status so we relied on data from the Riksstroke 3-month telephone ADL follow-up that was converted into the mRS categories: 0-2, 3, 4, and 5 [166]. If a follow-up had not been completed via Riksstroke, an additional retrospective review of medical records was done using information closest to 90-days post-ICH.

In Paper III, functional outcome was assessed by a certified trained expert according to mRS and eGOS at a clinical visit 180 days post ICH.

Statistical Methods

Paper I

Univariate and multivariate Cox regression analyses were used to evaluate possible risk-factors for long-term all-cause mortality. Multivariate analyses included age, sex, and risk factors with $P<0.05$ in univariate analyses. The expected survival was calculated for age, sex, and current calendar year specific Swedish mortality rates[198]. The observed survival among one-year ICH survivors was compared with the expected survival in the corresponding general population using relative survival ratio (RSR). The observed causes of deaths among the one-year ICH survivors were compared to the expected number of deaths in four categories (cerebrovascular disease, ischemic heart disease, cancer, and other). The expected numbers of deaths were calculated using the observed follow-up time divided into sex and 10-year age groups which then were multiplied with the average mortality rates (by calendar year) for each cause of death category. Statistics was done using STATA Statistical Software Release 11.0 (StataCorp College Station, TX) with the addition of a routine developed by Dickman et al[227].

Paper II

We used Fishers exact test and Pearson's χ^2 test to compare frequency distributions of baseline characteristics between patients with and without IVH, in 2 x 2 and 2 x *k* tables, respectively. Correspondingly, Mann-Whitney U-test was used to compare distribution of continuous variables between groups. We used the intraclass correlation coefficient (ICC) to compare pre-adjudication mGraeb scores. Univariate and multivariate logistic was used to compare risk factors for 30-day case fatality and 90-day functional outcome (mRS 0-3 versus 4-6). Covariates with $P<0.1$ in univariate analyses were included in the multivariate analyzes. IVH as a dichotomous covariate and mGraeb were included into separate, otherwise identical, multivariate models. Multiple imputations were used to reduce impact of missing data in logistic regression models. Kaplan-Meier survival curves with logrank test were used to compare patients with and without IVH, and IVH patients grouped on mGraeb quartiles. We used ROC curves, the DeLong test, and Vuong´s test to assess if the addition of mGraeb improved the prognostic accuracy of a logistic regression model, including ICH volume and age, for patients with IVH. Statistical analyses were performed with IBM SPSS version 20.0, and R version 3.1.0 with mitools package and pROC package.

Paper III

Univariate and multivariate logistic regression were used to assess which covariates that were associated with hematoma expansion and functional outcome. All covariates in the multivariate analyses were pre-specified, i.e. no P-value thresholds were used. Additionally, univariate and multivariate linear regression analyses and ordinal logistic regression analyses (assuming proportional odds) were used to assess the impact of WML severity on absolute ICH volume expansion and mRS as a continuous ordinal scale. Pearson's χ^2 test and the two-sample *t*-test were used for descriptive statistics and the ICC was used to test interrater agreement of pre-adjudication vSS scores. STATA Statistical Software Release version 13.0 (StataCorp College Station, TX) was used for statistical analyses.

Paper IV

Differences in baseline characteristics and functional outcome were assessed with Mann–Whitney U test and Pearson χ^2 test. Since eligibility proportions were close to zero in many trials, Wilson's method was used to calculate CIs. Kaplan–Meier plots with log-rank test were used for 30-day and 365-day survival analysis. IBM SPSS version 22.0 was used for statistics.

Ethical Approval

Ethical approval or patient consent was not required in 1996 when patients included in Paper I were registered. For the long-term follow-up via official registers in Paper I we did obtained approval from the Ethical Review Board, Lund (2009/653 and 2011/183). Written or oral consent was obtained from the patient or their relatives at LSR inclusion (Paper II and IV) and the studies were approved by the Ethical Review Board, Lund (2004/711, 2008/543, 2009/610). Several ICH patients had died before consent in LSR was possible to obtain, in these cases we got a separate permission from the Ethical Review Board, Lund (2010/603) to include them in Paper II and IV. All patients in the CLEAR-III and MISTIE-II trials gave written approval for participation in the respective trial and we obtained approval from the Institutional Review Board at Johns Hopkins Medical institutions, Baltimore, MD, USA (IRB00096276), for including these patients in a secondary analysis for Paper III.

Results

Demographics and baseline characteristics for the 1211 patients included in the four studies are summarized in Table 4. The studies used somewhat different risk factor definitions and data collection methods which should be taken into account when comparing the studies.

Table 4. Demographics and baseline characteristics of Papers I to IV.

	Paper I		Paper II	Paper IV	Paper III
Study cohort	South Sweden 1996		Lund Stroke Register		CLEAR-III & MISTIE-II
Selection	All patients	One-year Survivors	Supra-tentorial	All patients	Baseline CT <24h of ICH
Total number	323	172	198	253	635
Age, years (IQR)	73 (62-80)	71 (59-77)	74 (64-81)	74 (63-81)	59 (51-67)
Female	145 (45%)	68 (39%)	87 (44%)	116 (46%)	266 (42%)
IVH	77 (24%)*	21 (12%)*	86 (43%)	115 (45%)	545 (86%)
ICH volume, mL (IQR)	15 (4-40)	10 (4-24)	16 (5-58)	15 (5-43)	10 (4-20)
GCS (IQR)	13 (10-15)	15 (13-15)	14 (10-15)	14 (10-15)	10 (7-13)
ICH location					
Lobar	170 (53%)	86 (50%)	66 (33%)	68 (27%)	47 (7%)
Deep	113 (35%)	66 (38%)	127 (64%)	131 (52%)	489 (77%)
Infratentorial	40 (12%)	20 (12%)	0 (0%)	49 (19%)	0 (0%)
Other	N/A	N/A	5 (2%)	5 (2%)	65 (10%)
Hypertension	118 (37%)	71 (41%)	128 (65%)	158 (62%)	579 (91%)
Diabetes mellitus	33 (10%)	18 (10%)	53 (27%)	68 (27%)	90 (14%)
Surgical treatment	31 (10%)	17 (10%)	16 (8%)	25 (10%)	593 (93%)
Anticoagulant therapy	42 (13%)	17 (10%)	23 (12%)	29 (11%)	60 (9%)**

Data presented as numbers (%) unless median (IQR) is indicated. *Defined as hemorrhage in two or more ventricles **Anticoagulant therapy or INR>1.5 at baseline. Abbreviations: CT = computerized tomography; IVH = intraventricular hemorrhage; ICH = intracerebral hemorrhage; GCS = Glasgow Coma Scale

Paper I

We identified 329 unique patients who had ICH during 1996. Six of these lacked complete personal identification numbers. Of the 323 remaining patients, 172 (52%) survived one year after ICH. All the one-year survivors were then followed

at least 13 years (December 2009). Of the one-year ICH survivors, 115 (67%) died during the follow-up period.

Long-term Mortality

Of 172 one-year ICH survivors, 74% (95% CI 67-80%) and 43% (95% CI 36-50%) survived 5 and 10 years after the index ICH, respectively. The corresponding expected survival rates were 85% and 68%, respectively. The one-year ICH survivors had a 27% difference between observed and expected cumulative survival 13 year after the index ICH, as illustrated in Figure 9A. The annual RSR (Figure 9B) was below one for each follow-up year indicating an excess mortality among the ICH patients during the complete follow-up period.

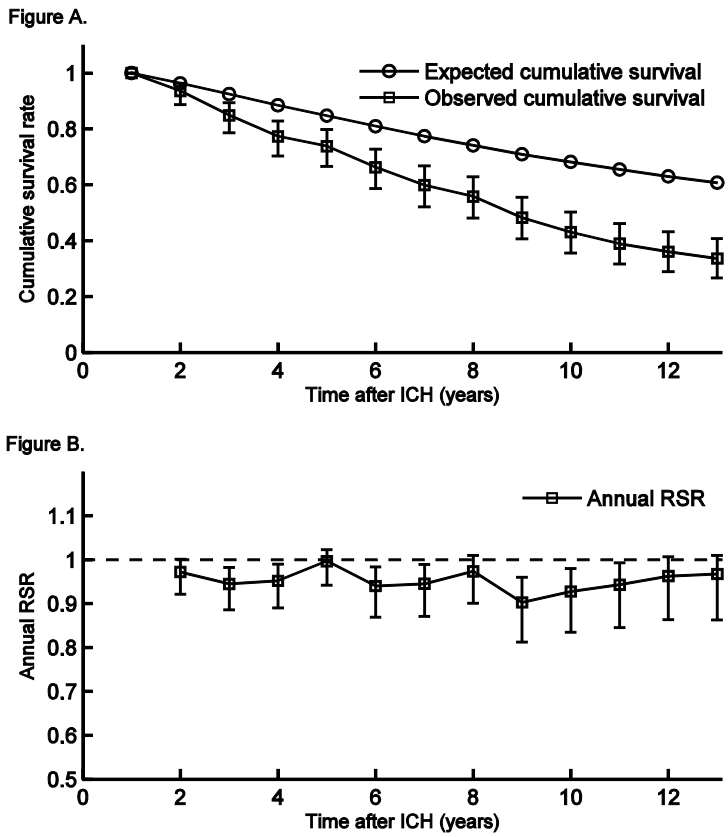

Figure 9. (A) Differences in expected and observed cumulative survival and,(B) annual Relative Survival Ratio (RSR), for 172 one-year survivors after intracrebral hemorrhage (ICH) 1-13 years after the index ICH.

Risk Factors for Long-term Mortality

In univariate analyses baseline age, diabetes mellitus, and anticoagulant therapy increased the risk for death during 1-13 year after ICH, while established short-term risk factors such as GCS, ICH volume, and IVH, did not increase the risk for death during this time interval. Both diabetes mellitus and baseline anticoagulant therapy were associated with a two-fold risk increase for long-term mortality (HR 2.10 and 2.31; 95% CI 1.18-3.74 and 1.33-4.03, respectively) in the multivariate analysis in addition to the risk increase conveyed by age (HR 1.08 per year; 95% CI 1.06-1.10).

Causes of Death

Of the 115 observed deaths among one-year ICH survivors (1304 patient years at risk), 42 (36%) were due to cerebrovascular disease, 22 (19%) were due to ischemic heart disease, 13 (11%) were due to cancer, and 38 (33%) were due to other causes. The corresponding numbers of expected causes of death were: 6.8 due to cerebrovascular disease, 13.8 due to ischemic heart disease, 14.1 due to cancer and 18.9 due to other causes. Among the one-year ICH survivors, cerebrovascular disease and ischemic heart disease were the dominating causes of death 1-9 years after the index ICH (Figure 10).

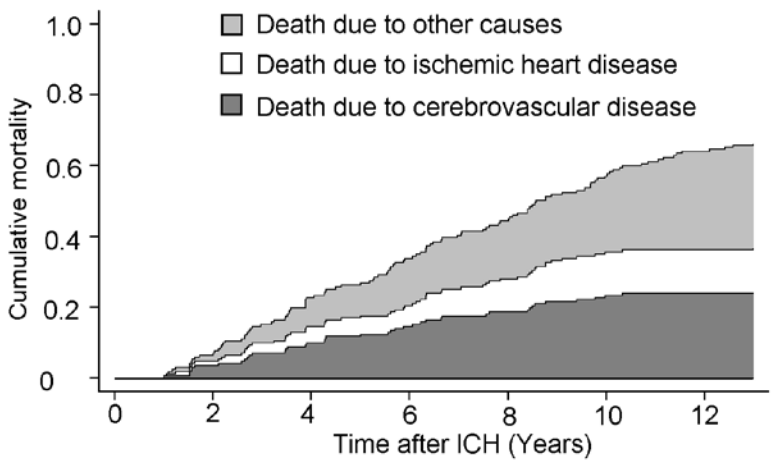

Figure 10. The cumulative mortality in cerebrovascular disease, ischemic heart disease, and other causes among one-year intracerebral hemorrhage (ICH) survivors

Paper II

Of 291 patients first-ever stroke classified as ICH, 30 were excluded due the following causes: misclassification (N=3), trauma (N=4), aneurysms (N=5), AVM (N=7), cavernoma (N=3), hemorrhagic transformation of infarct (N=5), cerebral sinustrombosis (N=2), and tumor (N=1). Additionally, 15 patients were excluded due to first CT scan performed ≥7 days after ictus or initial hospitalization elsewhere. Forty-eight of the remaining 246 patients had infratentorial ICH and were not included in the outcome analyses.

Of the remaining 198 patients with supratentorial ICH, 86 (80%) had IVH (median mGraeb 12; range 1–28). The inter-rater reliability of pre-consensus mGraeb scores was good (ICC 0.95) and 93% of the 71 individual mGraeb assessments were within ±3 points. ICH patients with IVH had lower admission GCS, larger ICH volumes, more often deep ICH, elevated CRP and WBC count, and higher prevalence of diabetes mellitus ($P \leq 0.005$) (see Paper II Supplementary Table e-2).

Table 5. Univariate associations with 30-day mortality and poor functional outcome (mRS≥4, including death) 90 days after supratentorial ICH

Endpoint:	30-day survival		Poor functional outcome (mRS≥4)	
	OR (CI 95%)	***P***	**OR (CI 95%)**	***P***
Sex (Female)	1.07 (0.59-1.97)	0.815	1.16 (0.65-2.08)	0.613
Age (per year)	1.05 (1.02-1.08)	0.001	1.06 (1.03-1.09)	<0.001
IVH (yes/no)	10.09 (4.92-20.69)	<0.001	7.19 (3.56-14.5)	<0.001
mGraeb (per point)	1.22 (1.15-1.28)	<0.001	1.18 (1.10-1.25)	<0.001
ICH volume (per mL)	1.04 (1.02-1.05)	<0.001	1.04 (1.02-1.05)	<0.001
GCS (per point)	0.57 (0.49-0.67)	<0.001	0.59 (0.48-0.74)	<0.001
Deep ICH	1.60 (0.81-3.17)	0.137	1.53 (0.82-2.85)	0.183
Hypertension	0.94 (0.48-1.85)	0.858	0.86 (0.46-1.62)	0.647
Diabetes mellitus	2.08 (1.05-4.11)	0.035	2.72 (1.35-5.51)	0.005
Ischemic heart disease	1.35 (0.60-3.03)	0.468	1.20 (0.56-2.58)	0.642
Atrial fibrillation	3.22 (1.34-7.71)	0.009	2.16 (0.85-5.55)	0.108
Hypercholesterolemia	0.81 (0.41-1.59)	0.536	0.78 (0.40-1.51)	0.456
Previous TIA	2.66 (1.06-6.67)	0.038	2.20 (0.83-5.83)	0.113
Smoking	0.92 (0.39-2.21)	0.858	1.04 (0.47-2.30)	0.918
CRP >5 mg/L	2.27 (1.22- 4.25)	0.010	1.74 (0.96-3.15)	0.066
WBC >11.0 x10^9/L	4.16 (2.15-8.03)	<0.001	4.64 (2.18-9.86)	<0.001
Anticoagulant therapy	1.47 (0.60-3.60)	0.398	1.63 (0.66-4.06)	0.293
Antiplatelet therapy	2.33 (1.20-4.55)	0.013	2.03 (1.03-4.02)	0.042

OR = Odds Ratio; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin scale; mGraeb = modified Graeb scale; GCS = Glasgow Coma Scale; CRP = C-reactive protein; TIA = transient ischemic attack; WBC = White blood cell count

Short-term (30-day) Case Fatality

The 30-day case fatality among patients with IVH was 57% (95% CI 46–67%) compared to 12% (95% CI 6–17%) among ICH patients without IVH ($p < 0.001$) as illustrated in Figure 11A. When IVH patients were stratified into mGraeb quartiles (Figure 11B), the survival of patients in the first quartile (mGraeb1-5.5) was similar to the survival among patients without IVH, while patients in the third and fourth quartiles (mGraeb13.0-16.0 and 16.5-28.0, respectively) had a higher case fatality compared to IVH patients in general.

In univariate analyses (Table 5), the presence of any IVH increased the odds for 30-day mortality 10-fold (OR 10.09; 95% CI 4.92-20.69) and each mGraeb point increased the odds by 22% (OR 1.22; 95% CI 1.15-1.28). The corresponding ORs were 4.87 for any IVH (95% CI 1.35-17.48), and 1.16 for each mGraeb point (95% CI 1.06-1.27), after adjustment for age, ICH volume, GCS, diabetes mellitus, WBC count, CRP, antiplatelet therapy, atrial fibrillation, and previous TIA, in multivariate analyses (Table 6).

Table 6. Multivariate models for 30-day case fatality based on a multiple imputation analysis of all covariates with univariate associations significant at the 0.1 level. The variables mGraeb and IVH (dichotomous) were included into the separate models A and B, respectively.

Endpoint: 30-day case fatality	Model A (Including mGraeb)		Model B (Including IVH yes/no)	
	OR (CI 95%)	***P***	**OR (CI 95%)**	***P***
mGraeb (per point)	1.16 (1.06-1.27)	0.002	-	-
IVH	-	-	4.87 (1.35-17.48)	0.015
Age (per year)	1.05 (1.00-1.10)	0.058	1.05 (1.00-1.10)	0.056
ICH volume (per mL)	1.04 (1.02-1.06)	<0.001	1.03 (1.01-1.05)	0.001
GCS (per point)	0.77 (0.60-0.98)	0.031	0.71 (0.57-0.87)	0.001
Diabetes mellitus	0.87 (0.22-3.48)	0.838	0.84 (0.21-3.34)	0.801
WBC count >11.0 10^9/L	1.48 (0.42-5.20)	0.539	1.42 (0.42-4.83)	0.572
CRP >5.0 mg/L	1.49 (0.43-5.20)	0.530	1.16 (0.35-3.89)	0.812
Antiplatelet therapy	1.05 (0.26-4.17)	0.949	0.72 (0.19-2.79)	0.635
Atrial fibrillation	6.39 (1.32-30.89)	0.021	6.31 (1.37-29.04)	0.018
Previous TIA	1.72 (0.29-10.19)	0.550	1.44 (0.25-8.33)	0.682

OR = Odds Ratio; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mGraeb = modified Graeb scale; GCS = Glasgow Coma Scale; CRP = C-reactive protein; TIA = transient ischemic attack; WBC = White blood cell count

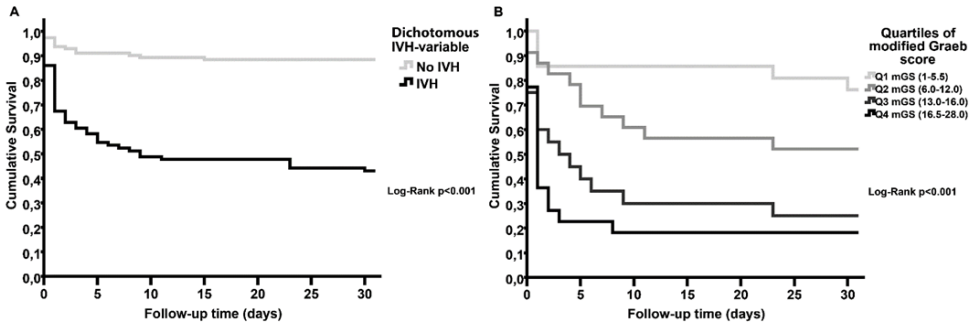

Figure 11. 30-day survival after intracerebral hemorrhage (ICH) stratified by the presence of (A) intraventricular hemorrhage (IVH) in 198 patients with supratentorial ICH, and (B) mGraeb quartiles for 86 patients with IVH**.**

Functional Outcome 90-days After ICH

Patients with IVH had a 7-fold increase in odds for poor functional outcome 90 days after ICH (OR 7.19; 95% CI 3.56–14.50) in univariate analyses (Table 5) which persisted after adjustment for age, ICH volume, GCS, diabetes mellitus, WBC count, CRP, and antiplatelet therapy, in multivariate analyses. When IVH severity was subdivided by mGraeb each point increased the odds for poor functional outcome by 18% (OR 1.18; 95% CI 1.10-1.25) and mGraeb also remained an important risk factor after adjusting for the abovementioned factors in multivariate analyses (Table 7).

Table 7. Multivariate models for 90-day poor functional outcome (mRS ≥4) based on a multiple imputation analysis of all covariates with univariate associations significant at the 0.1 level. The variables mGraeb and IVH (dichotomous) were included into the separate models A and B, respectively.

Endpoint: mRS 0-3 vs. 4-6	Model A (Including mGraeb)		Model B (Including IVH yes/no)	
	OR (CI 95%)	***P***	**OR (CI 95%)**	***P***
mGraeb(per point)	1.11 (1.02-1.20)	0.011	-	-
IVH	-	-	4.17 (1.48-11.75)	0.007
Age (per year)	1.08 (1.04-1.12)	<0.001	1.10 (1.05-1.15)	<0.001
ICH volume (per mL)	1.03 (1.01-1.05)	0.002	1.03 (1.01-1.04)	0.005
GCS (per point)	0.84 (0.68-1.04)	0.115	0.74 (0.59-0.94)	0.014
Diabetes mellitus	2.17 (0.83-5.68)	0.114	2.54 (0.85-7.59)	0.096
WBC count >11.0 10^9/L	2.69 (1.01-7.18)	0.048	2.36 (0.79-7.01)	0.122
CRP >5.0 mg/L	1.03 (0.44-2.43)	0.944	0.87 (0.35-2.15)	0.768
Antiplatelet therapy	1.24 (0.49-3.15)	0.657	1.19 (0.42-3.34)	0.741

OR= Odds Ratio; ICH= intracerebral hemorrhage; mRS= modified Rankin scale; mGraeb= modified Graeb scale; GCS= Glasgow Coma Scale; WBC= White blood cell; CRP= C-reactive protein

Modified Graeb Scale versus Dichotomized IVH

In ROC analyses of all patients with IVH, the prognostic model for 30-day survival with mGraeb instead of IVH (yes/no), in addition to age and ICH volume, had a trend toward higher AUC (0.886 vs. no mGraeb 0.812; P = 0.053) and better model fit (χ^2=12.59; P<0.001). At an 80% specificity cut-off, the addition of mGraeb increased sensitivity from 67 to 88%. However, with poor functional outcome as endpoint, the mGraeb did not increased the prognostic models AUC (0.83 vs. no mGraeb 0.82; P = 0.563) nor did it reduce model deviance (χ^2=1.56; P=0.211)

Paper III

Of 641 patients included in MISTIE-II and CLEAR-III, 635 had diagnostic (baseline) CT scan performed within 24 hours of ICH onset. Of these, 6 had missing hemorrhage expansion outcomes, 16 had missing mRS assessments, and 55 had missing eGOS assessments. In total 629 patients were included in the hematoma expansion analyses, and 619 and 580 were included functional outcome analyses with mRS and eGOS, respectively. The inter-reader reliability for vSS assessments was good (ICC 0.76), and 145 cases were adjudicated due to interrater differences exceeding the prespecified limits mentioned above. The median time from ictus to baseline CT was 2.19 hours (IQR 1.30-4.69) and HE was assessed at a median of 39 hours (IQR, 22.50-54.51) after symptom onset. Hematoma expansion (ICH volume increase >33% or >6 mL) occurred among 13% of the 629 patients and was more frequent among MISTIE-II patients compared to CLEAR-III patients (34% versus 8%; P<0.001). Hematoma expansion was associated with larger baseline ICH volumes (mean 20.5 versus 14.9 mL) but smaller baseline IVH volumes (mean 11.0 versus 25.7 mL).

WML and Hemorrhage Expansion

The amount of WML according to vSS grades did not affect the odds for hematoma expansion according to the primary definition (p>0.05) while age, baseline IVH volume, and time between ictus and dCT, did (Table 8). Likewise, no consistent connection between vSS and hematoma expansion according to secondary definitions was observed (Paper III Supplemental Tables S1 and S2).

Table 8. Univariate and multivariate analyses of hematoma expansion defined as a ICH volume increase >33% or >6 mL.

Endpoint: Hematoma expansion		Univariate Analyses		Multivariate Analysis	
		OR (95% CI)	P	OR (95% CI)	P
vSS	**0**	Reference	-	Reference	-
	1	0.63 (0.29-1.34)	0.230	0.55 (0.25-1.23)	0.148
	2	0.47 (0.21-1.10)	0.081	0.46 (0.19-1.14)	0.095
	3	0.82 (0.38-1.78)	0.618	0.72 (0.33-1.54)	0.396
	4	0.61 (0.32-1.18)	0.140	0.52 (0.25-1.07)	0.077
Baseline ICH volume, (per mL)		1.02 (1.01-1.03)	0.003	0.99 (0.98-1.01)	0.548
Baseline IVH volume, (per mL)		0.95 (0.93-0.97)	<0.001	0.95 (0.93-0.98)	<0.001
Thalamic ICH location		0.66 (0.41-1.06)	0.086	0.73 (0.42-1.28)	0.275
Diabetes mellitus		1.47 (0.81-2.67)	0.206	1.26 (0.65-2.44)	0.494
Warfarin treatment or INR>1.5		1.57 (0.80-3.11)	0.192	1.64 (0.74-3.63)	0.219
Age (per year)		1.03 (1.01-1.05)	0.004	1.03 (1.01-1.05)	0.008
Time ICH to dCT (per hour)		0.85 (0.76-0.94)	0.003	0.85 (0.76-0.95)	0.003

ICH = Intracerbral hemorrhage; IVH = Intraventricular hemorrhage; dCT = diagnostic computed tomography scan; vSS = van Swieten Scale

WML and Functional Outcome

Patients with vSS grades 2, 3, and 4 had increased odds for poor 180-day functional outcome (mRS ≥4 including death) in univariate analyses (Table 9). However, only vSS grade 4 was connected to poor functional outcome after adjustment for other potential risk factors in multivariate analyses.

In univariate ordinal logistic regression models vSS grades 2, 3, and 4 were associated with higher mRS values (indicating worse outcomes) as illustrated in Figure 12. In the multivariate ordinal logistic regression model, only vSS 2 and 4 were associated with increased mRS scores (see Paper III, Supplemental Table S3). Correspondingly, vSS 2, 3, and 4 were associated with poor outcome according to eGOS (Lower severe disability to death) in univariate analyses, while the association only remained for vSS 2 and 4 in the multivariate analysis (see Paper III, Supplemental Table S4 for effect sizes).

Table 9. Univariate and multivariate analyses of poor functional outcome (mRS≥4 or death).

Endpoint: mRS 0-3 vs. 4-6	Univariate Analyses		Multivariate Analysis	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
vSS **0**	Reference	-	Reference	-
1	1.11 (0.67-1.82)	0.689	0.98 (0.50-1.96)	0.967
2	2.24 (1.33-3.78)	0.002	1.48 (0.76-2.90)	0.246
3	1.81 (1.04-3.16)	0.035	1.41 (0.70-2.87)	0.348
4	4.16 (2.54-6.83)	<0.001	2.92 (1.45-5.86)	0.003
Baseline ICH volume, (per mL)	1.04 (1.02-1.05)	<0.001	1.06 (1.04-1.09)	<0.001
Baseline IVH volume, (per mL)	1.01 (1.00-1.02)	0.001	1.03 (1.02-1.05)	<0.001
Thalamic ICH location	1.70 (1.23-2.35)	0.001	3.78 (2.36-6.06)	<0.001
Diabetes mellitus	2.00 (1.23-3.27)	0.005	3.09 (1.58-6.03)	0.001
Warfarin treatment or INR>1.5	1.48 (0.85-2.59)	0.168	0.84 (0.38-1.83)	0.654
Age (per year)	1.06 (1.04-1.07)	<0.001	1.06 (1.04-1.08)	<0.001
Sex (female)	0.92 (0.67-1.27)	0.623	1.48 (0.96-2.30)	0.078
Experimental therapy (vs. standard)	0.90 (0.65-1.24)	0.525	1.20 (0.79-1.83)	0.396
GCS (per point)	0.78 (0.73-0.83)	<0.001	0.80 (0.74-0.86)	<0.001
Hematoma expansion*	2.73 (1.59-4.70)	<0.001	5.00 (2.43-10.27)	<0.001

*ICH volume increase >33% or >6 mL. ICH = Intracerbral hemorrhage; IVH = Intraventricular hemorrhage; dCT = diagnostic computed tomography scan; GCS = Glasgow Coma Scale; mRS = modified Rankin scale; vSS = van Swieten Scale

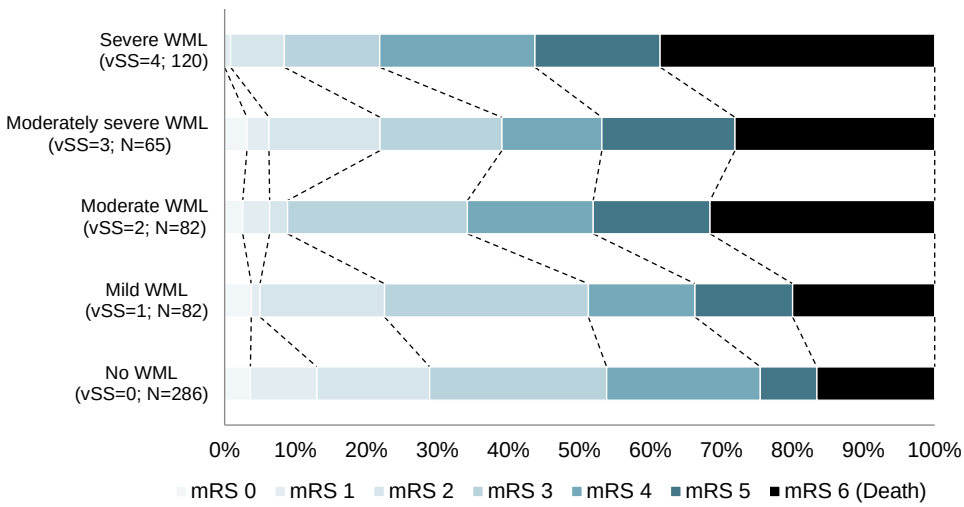

Figure 12. Unadjusted distribution of modified Rankin (mRS) outcomes for ICH patients with different grades of white matter lesion (WML) severity according to the van Swieten scale (vSS)

Paper IV - Clinical Trial Eligibility and Effects on Prognosis

We identified 59 unique clinical trials on ICH of which 6 were phase 0/I trials, 5 were phase II trials succeeded by a phase III trial, 13 were inactive/suspended, 23 had <300 patients with ICH, and 1 had unclear inclusion criteria. The remaining 11 trials were included for further analysis.

In contrary to Paper II, patients with infratentorial ICH (N=48) or first CT performed ≥7 days of ictus (N=7) were included. In 10 of the included trials, the secondary causes listed above for Paper II (Results, Paper II, first paragraph) were cause for exclusion; hence, 253 patients were included for eligibility estimations for the 10 trials. Since the RESTART trial allows for inclusion of patients with "traditionally" secondary causes for ICH, the 27 patients with secondary ICH (not including the 3 misclassified patients) were added to eligibility estimations for RESTART.

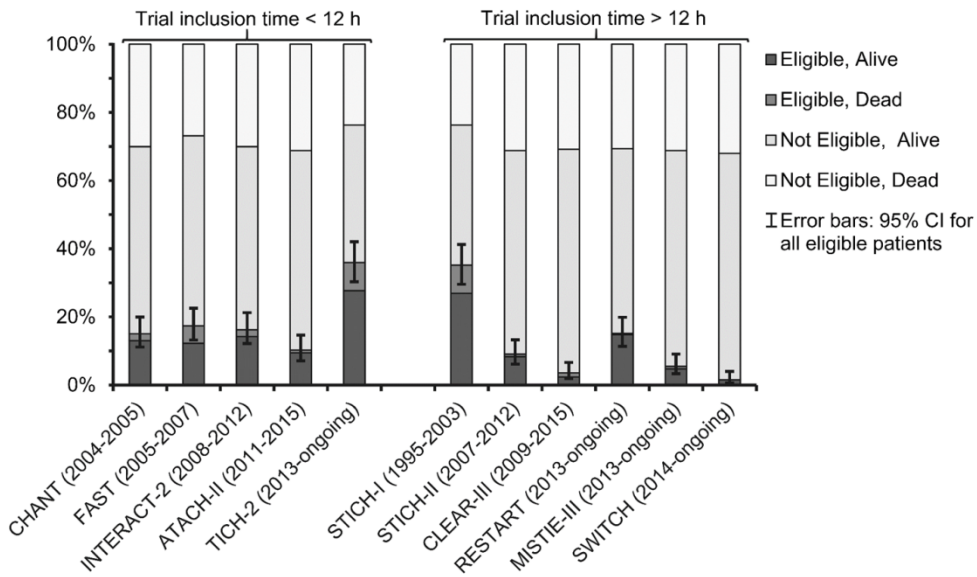

Figure 13. Estimated eligibility and 30-day case fatality rates for 11 clinical treatment trials for patients with intracrebral hemorrhage.

The estimated proportion of LSR patients that would have been possible to include in the 11 trials ranged from 2% to 36% (Figure 13). More than a third of the LSR patients (N=96; 38%) were not eligible for any trial. The patients that were not eligible for any trial had lower admission level of consciousness (median GCS 8 versus 15; IQR 4-15 versus 13.5-15) and more severe IVH (mGraeb 0 versus 4.5; IQR 0-6.5 versus 0-13), compared with patients eligible for one or more trials

(Paper IV Supplemental Table I). Additionally, non-eligible patients more often had cerebellar ICH (19% versus 8%), and less often lobar ICH (15% versus 34%), while age, sex, and ICH volume did not differ between groups.

Non-eligible patients also had a notably higher 30-day and 1-year case fatality (54% and 59%; 95% CI, 44%–64% and 49%–69%) compared to patients eligible for one or more trials (18% and 28%; 95% CI 13%–25% and 22%–36%). Likewise, poor 90-day functional outcome was more prevalent among the non-eligible patients (75% versus 48% for the eligible patients; 95% CI 65%–83% versus 40%–56%).

Discussion

Methodological Considerations

Case Ascertainment and Representativeness of Included Patients

None of the included Papers in this thesis fulfilled the all criteria for an optimal stroke population-based *incidence* study proposed by Feigin and Carter in 2004[228]. These criteria focus on the need for multiple overlapping sources of information, prospective study design, and large well defined populations. To get accurate population estimates, incidence studies need to find all stroke patients, including those who die before a healthcare contact is established, are so ill prior to the stroke that no diagnostics are performed, or are so "mildly" affected that they do not seek health care. However, these three groups of patients might be of less importance in studies on prognostic factors where the over-all aim is to identify factors that can help alter the clinical course of the disease.

Two Swedish studies have assessed how well prospective hospital based screening for stroke patients compare to population-based screening (using the Feigin and Carter 2004 criteria) during the time of Paper I and Paper II and IV. In these two studies 95%[229] and 92%[28] of patients were examined at hospital, respectively.

The first, by Appelros et al. (1999-2000), described a 92% (93% for ICH only) overlap between hospital-based and population-based screening with 4% of the patients diagnosed in primary care or at autopsy, and 3% diagnosed at emergency and consulting rooms[229]. In that study, 15% and 13% had stroke of undetermined type (i.e. not established whether ischemic or hemorrhagic stroke) in the population based and hospital based screening, respectively.

The second, by Hallström et al. (2001-2002), showed that by adding retrospective screening methods to LSR, case ascertainment increased from 412 cases to 456 i.e. the regular LSR screening detected 90.2% of all patients[28] (subtracting 0.2% found via prospective contact with GPs, since this was not done later in LSR). In that study, 4% were solely cared for within the primary care system (none of these patients examined with CT), 1% were diagnosed at autopsy (N=5, of which 3 had had ICH), and 3% had no healthcare contact within 14 days of stroke onset[28]. Furthermore, 6% of all patients had undetermined type of stroke and 62% of these

were patients solely cared for within the primary care system, i.e. 2% of patients examined at hospital were not diagnosed according to stroke subtype.

Paper I

Prospective hospital-based case ascertainment was combined with autopsy findings and no retrospective methods were used. In this paper, patients treated solely within the primary care system will not have been identified, i.e. between 4% and 5% of all ICH patients, assuming that the proportion of stroke in general corresponds to ICH in the studies above. Moreover, a smaller proportion (6%-13%) with unknown stroke type might have been due to ICH. Diagnoses in Paper I were validated at the study center where baseline imaging and radiology reports were assessed. Nevertheless, registration was based on reporting from several different physicians and since thoroughness in case ascertainment might have varied it would have been good if complementary information sources had been used.

In summary, Paper I patients are likely representative of most one-year survivors after ICH, especially those who were hospitalized due to ICH.

Paper II and IV

LSR is estimated to identify between 90.2% and 95% (Appelros' hospital based estimate and patients diagnosed at emergency and consulting rooms) of all first-ever stroke patients. Since inclusion in LSR does not require imaging validation of diagnosis, patients with undetermined stroke type might have in fact had ICH. It should also be acknowledged that patients who actively declined participation in LSR are not included, and 1.4% of the screened patients declined participation (mean for years 2001-2006). A large number of ICH patients were identified in LSR screening but had died before consent could be obtained. In order to make results more representative we obtained approval from the Ethical Review Board, Lund, to include these patients. Another important aspect is that patients diagnosed with structural vascular lesions (e.g cavernoma and AVM) were excluded in the main analyses of both papers. On the other side, since no standardized radiological follow-up was required as part of LSR inclusion we might also have some included patients with structural vascular causes if the treating physician decided that further investigation was not indicated.

In summary, Paper II and IV patients are representative of ICH patients diagnosed and cared for at hospital, while the representativeness is limited for the small proportion of patients that are exclusively cared for in primary care and at nursing homes.

Paper III

In this paper patients were included if they fulfilled the strict trial eligibility criteria which reduce generalizability of results. However, our study population became more representative for the general ICH patients because MISTIE-II and CLEAR-III included different kinds of patients (larger ICH and less severe IVH versus smaller ICH and severe IVH). In Paper IV we estimate that 10% of the LSR patients could have been included in either trial (using the MISTIE-III estimate for MISTIE-II which had similar eligibility criteria). When directly compared to the other papers (Table 4), patients in Paper III could be characterized to more often have deeply located smaller ICH with ventricular extension, decreased admission LOC, and a history of hypertension. Nevertheless, 55% of the patients in Paper III had poor functional outcome (mRS≥4) at 180-days, which was comparable to outcomes in patients with supratentorial ICH in Paper II (52%, mRS≥4 at 90-days). Another important issue is that both MISTIE-II and CLEAR-III required clot stability prior to randomization. In the trials' screening logs only 3% of patients were deemed ineligible due to instable clots. Yet, patients with a large early expansion might not have entered for screening at all by the requiting physician.

In summary, Paper III patients represent a special sub-set of ICH patients which needs to be taken into account when interpreting the study results.

Clinical and Radiological Characteristics

Paper I

Baseline characteristics clinical prospectively evaluated by the registering physician and we cannot assess the accuracy of these registrations. No clinical follow-up was performed of the one year ICH survivors so we had to rely on the registered baseline characteristics as potential risk factors for long-term mortality. This does not affect results for demographic factors or ICH characteristics but needs to be taken into account when interpreting results regarding long-term effects of baseline medications since they might have been suspended after the ICH. It is also possible that some patients later developed risk factors that had not been present at baseline

Paper II and IV

A large number of clinical characteristics are prospectively gathered in LSR. For Paper II and particularly Paper IV, we also depended on retrospective reviews of medical files. The baseline CT was available for assessment of radiological characteristics in the majority of cases. It would have been valuable to have exact hemorrhage volumes when evaluating the mGraeb. However it is very labor intensive to obtain exact volumes and they are seldom used in clinical practice. In

retrospect, it would also have been good to include other semi-quantitative scales for IVH severity (e.g. the IVH score or original Graeb scale)[182, 183], for a direct comparison between mGraeb and the other scales.

Paper III

The WML assessments according to the vSS was performed independently by two readers with extensive experience in assessing CT scans of ICH patients after assessment calibration had been performed in a separate cohort. However, neither of the reviewers is a licensed neuroradiologist, which could be of importance since the lack of attenuation cut-offs makes vSS assessments subjective. It should also be noted that perihematomal and periventricular edema could have impacted assessments even though measures were taken to prevent this. Additional MRI estimations would have been possible to perform for approximately 10% of the patients in Paper III and that could potentially have increased the interrater agreement and minimized the impact of disturbing factors such as edema. The volumetric hematoma measurements were made with high accuracy techniques by trained readers at the study center which increases the accuracy of assessments. Baseline clinical characteristics were systematically and prospectively reported as part of the trial protocols.

Outcome Assessments

Paper I

The survival follow-up was obtained from the Population register, an official, high quality source, which is continuously up-dated. We could also obtain expected survival estimates stratified for age, sex and calendar year from official sources and use this to calculate expected survival rates for the one-year survivors. The observed causes of death were based on registry data which is not always reported correctly to the official registers[163]. Validation of diagnoses via alternative sources might have given an even more accurate estimate. We did not have information on the risk factor distribution in the general population and since the one-year ICH survivors may have a greater burden of co-morbidities this could have led to an over-estimation of the excess mortality.

Paper II and IV

In both papers we used the same, high quality source, for obtaining survival status as discussed above for Paper I. The functional outcome estimates were based on telephone interviews and retrospective reviews of medical files which reduces quality compared to standardized face-to-face clinical follow-up.

In Paper IV we actively decided that patients with missing data (except ictus to CT time) would be regarded as potentially eligible. This likely caused overestimations

of eligibility proportions, which was further influenced by our assumption that all patients who fulfilled the trial inclusion criteria would also have consented to inclusion.

Paper III

The high quality functional outcome assessment and standardized radiological follow-up in Paper III would have been difficult to achieve in an observational study, which motivates the use of clinical trial data.

Since the study was a secondary analysis of already included patients we had no possibility to affect the final sample size by using statistical power estimations. Nevertheless, in the analysis plan we estimated that at least 80 events of hematoma expansion were needed to accommodate the 8 covariates included in expansion analyses. Considering that previous studies (with the same expansion cut-off) had expansion frequencies of 16% to 33%[104, 112] it seemed reasonable that we would observe at least 80 events since that corresponded to 12% of our planned cohort of about 640 patients.

The risk for hematoma expansion decreases with time from ictus. Our patients had baseline (diagnostic) CT performed within 12 and 24 hours of ictus, respectively, and despite a short median time between ictus and CT (2.19 hours) a few clot expansion events occurring prior to first CT were not identified in ours study. We used a composite expansion measurement (ICH increase of >33% or 6mL) to detect a wider range of expansions. Since many of the CLEAR-III patients had smaller ICH the absolute volume increases might have been below what could be regarded as clinically relevant even though the relative volume increase was >33%. The proportions of hematoma expansions differed between trials which is likely due to differences in baseline characteristics. Particularly the differences in ICH volume between trials might have affected expansion proportions because a large initial ICH is in itself a risk factor for hematoma expansion[104, 106]. Since the different inclusion criteria of the trials might have influenced the results for other factors in the expansion outcome analyses it is important to note that the observed vSS scores did not differ between trials.

There were 351 events of poor outcome which adequate to accommodate the 11 covariates in the multivariate analyses on functional outcome. The functional outcome assessments are regarded to be of high quality since they were performed at clinical visits by certified examiners.

General Discussion

A wide range of known prognostic factors for ICH have been identified, including demographical and genetic factors (such as age, APOE alleles), biomarkers (e.g. CRP and WBC count), clinical markers (e.g. GCS, ongoing medications and co-morbidities), radiological factors (e.g. ICH and IVH volume, ICH location) but the question is how the knowledge about these and other factors improve clinical patient care.

The Prognosis Research Strategy (PROGRESS) collaboration has addressed this by dividing prognostic research into four categories:

I. The first is "Prognostic fundamentals" i.e. survival estimates, which increases the broader understanding of a disease and can be used to compare diseases and determine resource allocation[230]. Aspects of Paper I and II can be included in this category.

II. The second category is "Prognostic factor research", how individual factors affect prognosis [231], which can be used to find treatment targets and aid clinical decision making.

III. Prognostic factors can also be incorporated into the third category of research "prognostic models". By assigning risk factors different weights, prognostic models can be used for more individualized prognostic assessments and thereby improve treatment decisions and patient information[202]. All papers in the thesis cover different aspects of two later categories.

IV. The fourth research category, how patient stratification can be used to further individualize treatment and thereby optimizing therapeutic benefits[232] was not directly addressed by any of the papers. Nevertheless, results from Paper III increases the understanding of what factors that affect outcomes in the clinical trials CLEAR-III and MISTIE-II besides experimental therapy.

RCT design can also benefit from prognostic research by implementing adaptive randomization, based on prognostic factors, which has been used in ICH RCTs such as CLEAR-III and MISTIE-III. Adaptive randomization ensures that major prognostic factors are evenly distributed between trial arms by letting randomization of new patients be controlled by the risk factor distribution of already randomized patients. If adaptive randomization is not used, there is a risk that an uneven risk factor distribution (by chance) impacts outcomes between trial arms, and thereby influences how well the therapy under investigation performs. Prognostic models have also been used in ICH trials (such as STICH-II)[128] to determine if treatment effects differ between patients with good and poor expected

outcomes. This is important for risk-benefit analyses especially when more invasive procedures are tested.

However, not all clinical situations can be reduced one core issue that can be easily being tested in RCTs. Hence, in clinical situations, where high grade evidence of how to act (i.e. RCT results) is scarce, knowledge of prognostic factors increases the possibilities to make informed decisions.

Short-term Prognosis

We could confirm that the overall short-term prognosis after ICH is often serious (Paper II) especially so in patients with IVH. However, the individual prognosis is also highly variable, as illustrated by Figure 11A and B.

In Paper II, we could validate that IVH severity according to the mGraeb is a prognostic factor for case fatality and functional outcome after supratentorial ICH[181, 187] in a cohort that is representative for a broad range of ICH patients. In an era where novel therapies are used to target IVH, easy and validated methods for stratifying patients on IVH severity is needed to better understand which patients are likely to benefit the most from new therapies.

In Paper III, we could confirm the strong impact of WML severity on functional outcomes after ICH[148, 233]. Additionally, our results in Paper III indicate that the negative effect of WML severity on post-ICH function is likely not mediated via an increased risk for ICH expansion which was suggested in a previous study[141]. When clinically evaluating patients' possibilities to recover from ICH, WML severity should be taken into account since it is may represent an important surrogate of the brains ability to recover from damage. This also needs to be accounted for in RCTs where functional outcome is a common end-point.

In both Paper II and III we could confirm that age, IVH (including mGraeb), ICH volume, and LOC are important prognostic factors for 30-day case fatality and 90/180 day functional outcome[125, 175, 188, 214-216]. This, despite the fact that the patients in Paper III represent a sub-set of ICH patients (shown in Paper IV) specifically selected on, e.g. age, ICH and IVH volume, and GCS.

LOC is an important factor that has consistently been connected to case fatality and functional outcomes (see Table 1). Parry-Jones et al. showed that the GCS level, by itself, is a strong prognostic model for survival after ICH[208] which we could confirm in Paper II, where 93% of patients who were comatose at admission died within 30 days. LOC is a surrogate marker for many for different factors, such as ICH and IVH volume, clot location, hydrocephalus, withdrawal of care etc., and it might be argued that it should be regarded as an early outcome. This should be kept in mind when investigating new prognostic factors since

adjustment for LOC might reduce chances to show additional benefit. In Paper II we could observe that only 13% patients with supratentorial ICH without ventricular extension (median volume 10.3 mL; IQR 4.1-25.5 mL) died within 30-day (compared to 31% for all supratentorial ICH patients). Taken together, these results indicate that it is fairly easy to differentiate between patients in the two ends of the outcome spectrum range but the usefulness of prognostic models (scales) might be overrated when considering patients in the midrange of the outcome spectrum. It was therefore interesting that we in Paper II observed that the addition of mGraeb might add prognostic accuracy for the, large and diverse, sub-group of ICH patients with concomitant IVH.

Our results further high-light the limitations of current prognostic scales and instead of developing new scales it might be better if future studies focused more on identifying potentially modifiable factors and defining patients sub-groups where novel therapy forms are likely to be most beneficial.

Long-term Prognosis and Causes of Death

In Paper I we cover several aspects of the long-term survival after ICH such as prognostic factors and causes of death. The five-year survival for all ICH patients in Paper I was 39% which is higher than the pooled estimate of 29% (95% CI 26-33%) for three population based studies presented by Poon et al[149]. Our 10-year case fatality estimate of 23% was in range with other studies where results have ranged from 18%-24%[25, 151, 156-158].

Diabetes mellitus and anticoagulant therapy at index ICH onset were risk factors for long-term survival in Paper I and have previously been shown to affect long-term survival after ICH[157, 165]. Both factors are directly or indirectly (anticoagulant therapy as a surrogate for atrial fibrillation) connected to vascular disease and established risk factors for stroke reocurrence[152]. Since the dominating causes of death among the one-year ICH survivors were cerebrovascular and ischemic heart disease, better prevention of vascular disease might be a way to reduce ICH survivors' excess mortality.

When the baseline data were gathered for Paper I, anatomical classifications of ICH subtypes were dominant. It would also have been interesting to determine if the long-term survival differed between etiological subgroups (e.g. CAA and anticoagulant related ICH), which has been indicated in a previous study[49].

The survival plots after ICH are consistently showing a steep initial decline during the first months after ictus followed by a gentler decline up to a year after ICH onset. [17, 22, 26] This corresponds to the two phases (before and after approximately one month), where factors related to baseline ICH severity might be most

important in the early phase and factors influencing rehabilitation and stroke reoccurrence are more dominant in the late phase. It can therefore be argued that studies on prognostic factors for long-term survival should be restricted to include patients that have survived the acute/subacute phase of the disease like we do in Paper I and this has been done previously[151]. By using this design we could observe how the impact of traditional short term-risk factors (described above) diminished in importance in favor of factors connected to vascular disease in general.

Applicability of Clinical Trial Results

To implement results from clinical trials into practice, an understanding is needed of how applicable these results are for a general patient population. In Paper IV we identified a large patient stratum (38%) for which clinical trial results, and thereby clinical treatment guidelines, might be less applicable. Still, strict patients selection in RCTs might be necessary to ensure patient safety and possibility to detects therapeutic benefits, especially so in ICH where prognosis is highly variable. It is also important to recognize that a proportion of the patients we found to be in-eligible for all the trials, are likely to have had nonsurvivable hemorrhages or ICH that require life-saving surgery. These patients will likely not be candidates in future trials either since it would be unethical to randomize them to experimental therapy

Previous studies on ICH trial eligibility have also found that RCTs in ICH has limited applicability in a larger clinical context [98-100] and together with our results highlight the need for real-world effectiveness trials to confirm results from RCTs. Fonville et al. suggested that case ascertainment rates and applicability of results in RCT could be improved by applying possible eligibility criteria to epidemiological data during trial design[98] which is in line with the PROGRESS criteria discussed above.

Conclusions

ICH patients have a high short-term and long-term mortality. IVH and WML are important risk factors for poor outcome. However, the patient group is diverse and good prognostic estimations are therefore essential to optimize treatment for patients with ICH both in general clinical practice as well as in clinical trials.

In response to the specific aims introduced above it can be concluded that:

- Baseline age, ICH volume, GCS, and IVH severity have consistently been shown to impact the prognosis after ICH. However, only ICH and IVH volume are potential targets for direct treatment.
- One-year survivors after ICH have a substantial and persisting excess mortality 1 to 13 years after the stroke onset. Cerebrovascular and ischemic heart disease are the dominating causes of death while baseline age, diabetes mellitus, and anticoagulation therapy, are risk factors for long-term survival. This suggests that the excess mortality among ICH survivors might be improved by optimizing preventive therapies for cerebrovascular and cardiovascular disease.
- Patients with ventricular extension of supratentorial ICH have varied short-term outcomes and the modified Graeb scale can be used to determine IVH severity for both research and bedside situations. This is of special importance because interventions targeting IVH have shown promise but are likely to be better for some sub-groups of IVH patients than others.
- WML severity is an important prognostic factor for post-ICH functional outcome but this effect is probably not mediated by an increased risk for early hematoma expansion. The baseline WML severity should be taken into account when developing therapies to improve post-ICH functional outcome.
- Even though specific inclusion criteria are probably often needed for detecting therapeutic effect in clinical trials on ICH, they also reduce the applicability of trial results. Since trial results form the basis for clinical treatment guidelines it should be noted that many trial results might not be applicable for the third of all ICH patients with the most severe prognosis.

Future Aspects

Hemorrhagic stroke will likely continue to be an important cause of death and disability in the future because its incidence increases in developing countries although it decreases in developed countries[5, 36]. Disease prevention is preferable to treating the consequences of disease and several modifiable factors such as hypertension, psychosocial factors, obesity, and physical inactivity can be targeted to prevent ICH[71]. Yet, there is also a need to improve the care for those who have ICH to reduce the short-term and long-term consequence of the disease.

In 2011 the European Research Network on Intracerebral Haemorrhage summarized priorities for future ICH research[234]. Several of these topics have since been addressed, but many remain. One of the topics that have been addressed is the need for an etiological classification system for ICH to improve the understanding of how the underlying etiology affects incidence patterns and prognosis[48]. This can possibly be used to improve post-ICH care and reduce the large long-term excess mortality among ICH survivors.

Several prognostic models have been developed for ICH but few are actually generally used in clinical practice and it is uncertain if they improve clinical decision making[209, 213]. A future study showing that the use of a prognostic model improves outcome after ICH would be valuable. Prognostic research has also identified several targets for intervention, such as hematoma expansion and IVH[102, 124], but while many promising therapies have been tested, the majority of trials have been neutral. This may be the result of a heterogeneous prognosis which makes it difficult to assess which patients will benefit from a novel therapy. Hence, to optimize the chances of finding therapeutic benefits of new therapies patient stratification, based on knowledge on disease prognosis and etiology, may be needed.

When the efficacy of a new therapy has been shown in a RCT the therapy also needs to be shown to be effective outside the trial. If the therapy is effective, indication might carefully be broadened to include other similar patient groups. One way to study new therapies' real world effectiveness is via quality registers where patients are prospectively enrolled. Follow-up on survival and therapy compliance can be obtained via official registers. Swedish registry data could for example be used to identify which patients develop ICH during oral anticoagulant therapy (OAC), what characterizes OAC associated ICH, and for a risk-benefit analysis of whether OAC should be restarted. With large, nation-wide, registers with rapid prospective reporting there is a possibility of cost-effective register-based RCTs. However, high quality evidence for how ICH patients should be cared for is scarce despite much research[31, 97] and high quality observational research will also be needed in the future.

Sammanfattning (Summary in Swedish)

Varje år får över 10 miljoner människor stroke i världen och många lever med kvarstående funktionsnedsättning efter stroke[5]. Stroke kan orsakas av en blodpropp (85%) eller blödning (15%) som skadar hjärnvävnaden. Trots att hjärnblödningarna är färre orsakar de hälften av alla dödsfall efter stroke och orsakar i högre utsträckning funktionsnedsättning.

Två av tre hjärnblödningar orsakas av att mindre kärl i hjärnan brister, denna typ av hjärnblödningar kallas då intracerebral blödning (ICH, intracerebralt hematom). Flera faktorer kan påverka att ett kärl i hjärnan brister och orsakar ICH, däribland högt blodtryck, nedsatt levringsförmåga samt åldersrelaterade kärlväggs försvagningar. Av de cirka 3000 personer som får ICH varje år i Sverige, överlever ungefär två tredjedelar den första månaden efter insjuknandet. Av dem som överlever behöver sedan cirka en tredjedel hjälp med att klara sin vardag.

I avhandlingens fyra delarbeten har vi studerat vilka faktorer som påverkar överlevnad och funktionsgrad efter ICH för att förbättra behandlingsbeslut samt för att kunna ge patienter och anhöriga bättre information om det förväntade sjukdomsförloppet.

I den första studien kunde vi se att patienter som haft ICH och överlevt det första året efter insjuknandet hade en fortsatt lätt ökad risk för död 1-13 år efter det ursprungliga insjuknandet, jämfört med normalbefolkningen. Diabetes och blodförtunnande läkemedel vid insjuknandet hade en negativ inverkan på överlevnaden. Stroke och hjärtinfarkt var de dominerande dödsorsakerna.

I den andra studien fann vi att ett nytt sätt att bedöma mängden av blod i hjärnans vätskefyllda hålrum, ventriklarna, förbättrade möjligheterna att identifiera vilka patienter som hade bra respektive dålig prognos, vilket är av vikt för beslut kring vilken behandling patienter med ICH skall rekommenderas.

I den tredje studien kunde vi bekräfta att patienter som har förändringar i hjärnans djupa vita substans hade en försämrad återhämtning av funktionsgrad efter ICH. Vi kunde inte bekräfta att vitsubstansförändringar ökar risken för att blödningen tilltar i storlek vilket är kopplat till en sämre prognos, något det tidigare funnits indikationer på.

I den fjärde studien undersökte vi hur urvalskriterier i behandlingsstudier för ICH påverkar vilka patienter som deltar i studierna vilket i sin tur i hög grad påverkar hur studieresultaten kan tolkas. Mindre än två tredjedelar av alla våra patienter med ICH skulle kunna ha inkluderas i någon enda av de 11 olika studierna. De patienter som inte kunde inkluderas i någon av studierna var de patienter som

också hade sämst prognos och där det alltså hade varit extra intressant att kunna erbjuda behandling

Sammantaget visar avhandlingen att prognosen efter ICH generellt är dålig på kort och lång sikt och att blod i hjärnans ventriklar och vitsubstansförändringar är kopplade till sämre prognos. Dock varierar prognosen påtagligt mellan olika patienter och prognosskattningar behövs för att optimera behandling i den kliniska vardagen och för att utveckla, testa och införa nya behandlingsformer.

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