Intracerebral Hemorrhage In Southern Norway

A study of incidence and outcome

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Abstract

Aims

We aimed to assess the incidence and baseline characteristics of first ever intracerebral hemorrhage (ICH) in Southern Norway leading to hospitalization, mortality rates after ICH and factors associated with 30-day mortality and long term mortality. We further aimed to assess clinical functioning including cognition in long term survivors and associations between baseline factors and 1) functional dependency and 2) cognitive impairment. We also aimed to assess the rate of recurrent ICH and late seizures.

Materials and methods

All consecutive patients hospitalized with a first-ever ICH in the period 2005-2009 in a well-defined area were identified. Risk factors, clinical-, and radiological data were recorded in a stroke register from September 2007 and retrieved from patient files in cases prior to that. In Paper I we calculated the crude incidence and the incidence adjusted to the standard European population. In paper II death registered up to December 31.2011 in the National Population Register was recorded and causes of death were obtained from Statistics Norway and patient files. The prognostic value of various baseline clinical and radiologic factors for 30-day and long term mortality was assessed. Information on recurrent ICH was obtained by review of patient files. In Paper III we did an extensive in person follow up of all long term survivors between August and November 2011. This included the National Institute of Health Stroke Scale (NIHSS), the modified Rankin Scale (mRS), the Barthel Index (BI) and the Montreal Cognitive Assessment (MoCA). Information on late seizures was obtained through the in person follow up and by review of patient files.

Results

Incidence (Paper I)

We identified 134 patients, 74 (55%) men and 60 (45%) women with first ever ICH. The crude annual incidence rate per 100.000 per year was 19.6 for men, 15.7 for women and 17.6 for both sexes. Adjusted to the standard European population it was 16.9 for men, 8.8 for women ($p<0.001$) and 12.5 for both sexes. The overall age adjusted rate ratio men/women was 1.78 ($p=0.001$). Hematoma location was lobar in 36.6%, deep cerebral in 45.5%, cerebellar in 9.7%, and brain stem in 8.2%. Intraventricular hemorrhage occurred in 37%. The proportion with oral anticoagulant treatment associated ICH (OAT-ICH) was 26.9%.

Mortality (Paper I and II)

Overall mortality at 2 days was 23%, at 7 days 30%, at 30 days 36.6%, at 1 year 46 % and at 2 years 53%. Factors independently associated with 30-day mortality were warfarin, Glasgow Coma Scale (GCS) score, intraventricular hemorrhage, and leukoaraiosis (LA) score. Factors independently associated with long term mortality in 30-day survivors were coronary heart disease (CHD), GCS score, and LA score. Median follow up time was 4.7 years.

Recurrent ICH (Paper II)

Recurrent ICH was seen in 4 of 36 patients (11.1%) discharged alive after a lobar index ICH versus 0 of 52 (0%) after index ICH in other locations ($p=0.025$).

Clinical functioning in long term survivors (Paper III)

Of 51 patients alive 50 (24 men and 26 women) had an in person follow up after a median of 3.8 years. Men were younger than women (70.4 versus 78.7 years, $p=0.019$). Forty one (82%) lived in their private homes and 9 (18%) in nursing homes, 34 (68%) were independent (mRS 0-2) and 16 (32%) were dependent (mRS

3-5). Factors independently associated with dependency were female sex and LA score.
The proportion with cognitive impairment (MoCA≤23) was 61.4%. Factors independently associated with cognitive impairment were age and lobar ICH location.

Late seizures (not published)

Late seizures occurred in 5 of 50 (10%) long term survivors; 5 of 19 (26%) with lobar ICH versus 0 of 31 (0%) with ICH in other locations (p=0.005). Patients with late seizures had larger median ICH volumes than patients without seizures, 39 ml (IQR 23.5- 58.5) versus 7 ml (IQR 2.5-16.5), p=0.004.

Conclusions

The incidence of first ever ICH in Southern Norway is in the mid range in Europe and lower than in the only prior Norwegian incidence study. Men are at higher risk than women.
The proportion with OAT-ICH is higher than in most reports reflecting a well implemented use of warfarin in atrial fibrillation in the elderly (Paper I).
LA is independently associated with both 30-day mortality and long term mortality in 30-day survivors. Warfarin is independently associated with 30-day mortality and coronary heart disease with long term mortality in 30-day survivors. Recurrent ICH is more frequent after lobar ICH than after ICH in other locations (Paper II).
The majority of long term survivors live in their private homes. Two thirds are functionally independent. Dependency is associated with LA and female sex. Cognitive impairment is common and associated with lobar location of ICH (Paper III).
Late seizures were associated with lobar index ICH and larger ICH volumes (not published).

List of publications

The thesis is based on the following papers:

Paper I

Tveiten A, Ljostad U, Mygland A, Thomassen L, Pripp AH, Naess H. Intracerebral Hemorrhage in Southern Norway - A Hospital-Based Incidence Study. European Neurology. 2012 Mar 15;67(4):240-5.

Paper II

Tveiten A, Ljostad U, Mygland A, Naess H. Leukoaraiosis is Associated with Short- and Long-term Mortality in Patients with Intracerebral Hemorrhage. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association. 2013 Feb 21.

Paper III

Tveiten A, Ljostad U, Mygland A, Naess H. Functioning of long term survivors of first-ever Intracerebral Hemorrhage (accepted for publication in Acta Neurologica Scandinavica).

Abbreviations

ADL	activities of daily living
AHA	American Heart Association
ASA	American Stroke Association
BI	Barthel Index
CAA	cerebral amyloid angiopathy
CHD	coronary heart disease
CT	computer tomography
ESO	European Stroke Organisation
EUSI	European Stroke Initiative
HR	hazard ratio
ICH	intracerebral hemorrhage
ICU	intensive care unit
INR	International Normalized Ratio
LA	leukoaraiosis
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NINDS	National Institute of Neurological Disorders and Stroke
OAT	oral anticoagulant treatment
OAT-ICH	oral anticoagulant treatment associated intracerebral hemorrhage
OR	odds ratio
SAH	subarachnoid hemorrhage
fFVIIa	Recombinant factor VIIa
rtPA	tissue plasminogen activator

Contents

1. Background

Intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality throughout the world [1]. It is the most serious type of stroke and accounts for 10-15% of all strokes in Western countries [2-5]. Mortality is higher than in ischemic stroke with 35–52% of patients dead within 1 month.

1.1 Intracerebral Hemorrhage - definition

ICH is defined as the abrupt onset of severe headache, altered level of consciousness, or focal neurological deficit associated with a focal collection of blood within the brain parenchyma on neuroimaging or at autopsy which is not due to trauma or hemorrhagic conversion of a cerebral infarction [6]. The international classification of disease (ICD) uses the diagnosis “nontraumatic ICH” in both ICD 9 (code 431) and ICD 10 (codes I 61.0-9) [7] . The updated American Heart Association (AHA)/American Stroke association (ASA) definition of stroke (2013) uses the term “Intracerebral Hemorrhage” with the criterion non traumatic incorporated in this term [8].

In the literature the terms “spontaneous ICH” and ”primary ICH” are often used. Neither is clearly defined or consistently used. Neither is used in ICD 10 or the updated AHA/ASA definition [7, 8]. Exclusion criteria vary between publications. Most consistently excluded are, hemorrhages related to intracerebral malignant tumors, surgery and aneurysms. Patients with oral anticoagulant treatment (OAT) are often included and patients with vascular malformation are to a various degree excluded. The inconsistent use of the term “Primary ICH” is illustrated in a review of population based studies of ICH in which a web appendix reveals interchangeable use of terms, highly varying definitions and frequently “no definition” [9].

1.2 Incidence of Intracerebral Hemorrhage

In a recent European multi-population study the annual incidence of ICH per 100,000 adjusted to the standard European population was 16.9 in men and 12.4 in women in 2004–2006, but there was considerable variation between different European regions [10]. In Italy in 1994–1998 a crude annual incidence rate for a first-ever ICH was 36.9 per 100,000. When standardized to the 2006 European population it was 32.9 per 100,000 [11].

Stroke incidence has decreased by 42% in the past four decades in high-income countries. This is driven by a reduction in incidence of ischemic stroke [12]. Whether incidence of ICH has also fallen is unclear. In a recent review of population based studies there was no substantial decrease in incidence over time when only studies with excellent case-finding and no age limit were included [9].

Incidence – need for new data

Norwegian data on the incidence of ICH prior to the current study are limited to one study of stroke epidemiology in mid-Norway in 1994–1996 with only 45 cases of ICH. The crude annual incidence was 32 per 100,000. Sex distribution and adjustment to the standard European population were not reported, nor imaging findings such as ICH location and volume [13].
Therefore there was a need for new Norwegian incidence data with age and sex distribution, adjustment to the standard European population, and details on ICH locations and volume, rate of intraventricular hemorrhage and rate of oral anticoagulant treatment (OAT).

1.3 ICH Locations

Bleeding often occurs in the cerebral lobes, basal ganglia, thalamus, brain stem (predominantly the pons) and cerebellum [14, 15]. In studies of epidemiology and prognosis, ICH is frequently divided into subtypes by location. The origin of the bleeding is sought on computed tomography (CT), magnetic resonance imaging

(MRI) or autopsy. A classification with four categories is often used; lobar (cortical or subcortical white matter), deep cerebral (periventricular white matter, basal ganglia, internal capsule, thalamus), brain stem (midbrain, pons, medulla) and cerebellar ICH [16]. This classification is used in the present study.

Extension into the ventricles is common. It has been reported in 36-42 % of cases [17-19], and is found particularly in large deep hemorrhages [20] .

1.4 Causes of ICH

ICH is bleeding into the brain parenchyma. Most cases are caused by spontaneous-rupture of small vessels affected by hypertension-related degenerative changes or cerebral amyloid angiopathy. Other more rare causes include vascular malformations and impaired coagulation [14]. In patients younger than 40 years vascular malformations are the most common single cause of ICH [21].

1.5 Evolution of hematoma

Hematoma growth

ICH is a dynamic process. Ongoing hematoma growth at the time of admission to hospital is common. This was first reported in the 1990`s [22, 23]. The most common definitions are a proportional increase of ICH volume on CT (>33%) or an absolute increase (typically 3, 6 or 12 ml) or a combination of both [24, 25]. Since hematoma growth is most common in the first hours, the delay from symptom onset to first imaging influences the observed proportion with hematoma growth. In a study of 218 patients who had a CT within 3 hours of symptom onset and a 24 hour control CT, some degree of hematoma expansion was seen in 73% and significant (>33%) expansion in approximately one third of the patients [26]. Hematoma growth is directly associated with clinical deterioration and poor outcome [22, 23, 26, 27]. Risk factors for hematoma growth include the initial ICH volume: larger hematomas are more likely to expand [28, 29] and OAT [30, 31] . The possession of an APOE ε2

allele is also associated with increased risk of hematoma growth in lobar ICH [32]. A recent study of 79 patients in the US showed an association between LA and greater ICH volumes and a trend towards more hematoma growth [33].

The avalanche model

Hematoma expansion is often explained as continuous bleeding from a single vessel that bursts. In the early 1970`s Dr. Miller Fisher proposed an alternative "avalanche model" in which the ICH spreads in a domino fashion in the cerebral parenchyma. He observed multiple recently ruptured vessels at the periphery of hematomas and suggested that expansion of the initial hematoma caused secondary mechanical shearing of neighboring vessels [34]. In a recent review the authors state that several recent observations support the "avalanche model" including the common finding of multiple spot signs (see next paragraph) within a single hematoma indicating multiple bleeding sites [35, 36].

Extravasation of contrast – the Spot Sign

The spot sign was first reported in 2007 and has since that been extensively studied. It is the appearance of contrast extravasation into the hematoma on CT. It is a strong predictor of hematoma expansion, poor functional outcome and death [36-39]. Multiple spot signs are often found and it has been shown that the number of spot signs is predictive for hematoma expansion [36, 40].

The presence of contrast extravasation on MRI was also shown to be closely correlated with hematoma enlargement on follow-up CT scans in 1998, but has since been far less studied than the CTA spot sign [41].

1.6 Risk factors for Intracerebral Hemorrhage

1.6.1 Sex and Age

The risk of ICH is associated with increasing age and male sex. In a systematic review of case control and cohort studies the relative risk for ICH increased nearly 2-fold per decade. The crude relative risk for men compared with women was 3.3-4.3 [42] .

1.6.2 Hypertension

Hypertension is the most important risk factor for ICH [14]. In a systematic review of 11 case control studies all studies showed a positive association between hypertension and the risk of ICH. The overall odds ratio was 3.7 [42]. Hypertension is more common in deep cerebral than in lobar ICH [43, 44]. In hypertension related ICH it has been demonstrated, in histopathology studies, that the site of rupture typically is at or near a vessel bifurcation. The vessels show severe degeneration with breakage of the lamina elastica, atrophy and fragmentation of smooth muscle and dissections [45] .

1.6.3 Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is a common small vessel disease of the brain, characterized by the progressive deposition of amyloid b protein in the walls of small to medium sized arteries. It favors cortical regions. CAA is associated with increased risk of ICH, particularly lobar [46]. There is evidence of CAA as an important underlying cause of OAT-ICH. In patients with CAA transient focal neurological episodes interpreted as TIA`s often prove to be small hemorrhages which may carry a high risk of future symptomatic hemorrhages [47]. CAA is associated with cognitive impairment. Population based autopsy studies indicate a prevalence of 20-40% in non demented, 50-60% in demented elderly and more than 90% in persons with Alzheimer's disease [46].

The gold standard for diagnosing CAA is a neuropathological examination. In the absence of direct neuropathological examination the Boston Criteria, based on age, clinical and radiological criteria are commonly used for research. They were validated more than a decade ago and showed high specificity, but moderate sensitivity [48]. In a Dutch study the sensitivity of the Boston Criteria improved with the use of T2* weighted MRI and inclusion of microbleeds [49]. Since then susceptibility weighted imaging (SWI) MRI has gained importance in the detection of microbleeds [50].

1.6.4 Leukoaraiosis

Leukoaraiosis (LA) is a common finding in CT and MRI of stroke patients. It is the radiological appearance of tissue changes in the white matter of the brain. It is a feature of cerebral small vessel pathologies including hypertensive arteriopathy, amyloid angiopathy and CADASIL. Pathogenesis of LA is probably multifactorial. A proportion of LA is caused by small infarcts in the periventricular white matter in patients with small vessel disease [51]. The severity of LA on CT or MRI is usually graded with a visual rating scale [52, 53].

LA has been shown to be associated with an increased risk of total stroke (ischemic stroke or ICH). Recently it was shown in the Framingham Heart Study that severe LA at baseline more than doubled the odds of future stroke and all cause mortality, and quadrupled the odds of dementia [54] . Stroke subtypes however were not assessed. No studies have assessed the association between LA and the risk of ICH in an unselected population. However a decade ago LA was shown to be a dose dependent risk factor for OAT-ICH in patients who receive OAT after an ischemic stroke. The association was seen for both lobar and deep cerebral OAT-ICH [55]. LA has also been shown to be an independent risk factor for ICH after thrombolytic treatment for acute ischemic stroke [56]

1.6.5 Oral anticoagulant treatment

Oral anticoagulant treatment (OAT) increases the risk for ICH. The rate is 7-10 fold that of the non treated population [57]. In the United States a fourfold increase in the rate of OAT related ICH (OAT-ICH) was shown between 1988 and 1999 and linked to the increasing use of warfarin in atrial fibrillation in the elderly [58]. Most cases of OAT-ICH occur with an International Normalized Ratio (INR) within the therapeutic range, but it has been shown that increasing intensity of anticoagulation is associated with increased risk of getting an OAT-ICH and increased mortality in those who suffer it [57, 59].

It has been suggested that OAT merely unmasks hemorrhages that otherwise would have remained asymptomatic; that risk factors for OAT-ICH are the same as for ICH in persons without OAT and that the risk of getting an OAT-ICH is the risk of ICH in a person without OAT multiplied with a factor which represents the intensity of anticoagulation [57, 60].

Hence the risk of both lobar and deep cerebral ICH increases with OAT. This might explain that the relative distribution of ICH locations is not different between patients with and without OAT [57, 59, 61].

European data on occurrence of OAT-ICH are scarce regarding both the incidence and the relative proportion of OAT-ICH in total ICH. In a review from 2006 an annual incidence of 2-9 per 100.000 per year was estimated [57]. This was based on a proportion of 12% OAT-ICH in Southern Sweden in 1996 and available incidence data for total ICH [57, 61].

Prior to the present study no Norwegian data on occurrence and outcome of OAT-ICH existed

1.6.6 Race

Racial variations have been shown with increased rates of ICH in Hispanic, Asian and African-American populations [42, 62-64]. Racial differences are most prominent for deep cerebral hemorrhages and in young and middle aged [64, 65]. Two studies from the United States have shown an age dependent race difference with a 5-6 fold increased rate in African-Americans at age 45 compared to whites, but no increased rates in the highest age groups [63, 66] .

1.6.7 Genetic factors

Apolipoprotein E4 and E2 are associated with lobar ICH. Recently it has been shown that Apolipoprotein E4 may also be associated with deep cerebral ICH [67]. Having a first degree relative who has had an ICH is an independent risk factor for both lobar and non lobar ICH [68].

1.6.8 Lifestyle

In a recent large case control study performed in 22 countries 3000 stroke patients of whom 663 (22%) had ICH were compared with 3000 stroke free controls matched for age and sex. Hypertension, smoking, waist-to-hip ratio, diet and alcohol intake were significant risk factors for ICH. Regular physical activity was associated with a reduced risk of stroke which was significant for all stroke and ischemic stroke. For ICH alone the association was not statistically significant, but the direction was the same [69].

1.6.9 Low cholesterol and statin therapy

A finding in several studies that is poorly understood is that higher total cholesterol and lower HDL cholesterol have been associated with reduced risk of ICH [69, 70]. In one study which included ICH location this association was found for non lobar ICH, but not for lobar ICH [71].

There has been concern that the use of statins may increase the risk for ICH. A post hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) showed an increased risk of ICH in patients randomized to 80 mg atorvastatin compared to controls [72]. A pooled analysis of four randomized studies including 8832 patients showed a significant 1.7 (1.19-2.50) fold increased risk of ICH in patients on statin therapy compared to controls [73]. However a more recent and larger meta-analysis of 31 randomized studies including 91 588 patients on statin therapy and 91 215 controls showed no increased risk of ICH in patients on statins. Statin therapy was associated with a significant reduction in total stroke and all cause mortality [74].

1.7 Outcome after Intracerebral Hemorrhage

1.7.1 Short term mortality

The 30-day mortality in ICH is high, between 40 and 50% in most studies [75]. In a recent review of population based studies the median 30-day mortality was 40.4% (range 13.1-61.0%) and the median 1-year mortality was 54.7% (range 46.0-63.6%) [9]. Short term mortality is higher than in ischemic stroke in a time dependent manner. In a study from Denmark there was an initial 4-fold excess mortality risk in ICH compared to ischemic stroke. After 1 week it was 2.5-fold. After 3 weeks it was 1.5-fold. After 3 months there was no difference in mortality [76].

Factors consistently found to be associated with 30-day mortality include age, GCS score, ICH volume, ICH location, presence of intraventricular hemorrhage and OAT [11, 19, 61, 77-81]. The single most important prognostic factor for 30-day mortality is the initial ICH volume. [81]. The association between 30-day mortality and ICH volume also relates to ICH location. If lobar and deep cerebral hemorrhages are equally sized, the lobar are more often survived [81].

Numerous prognostic tools have been created based on the most consistently found prognostic factors [82].

1.7.2 Long term mortality

The median 1-year mortality was 54.7% (range 46.0-63.6%) in review of population based studies [9]. For longer term mortality rates, data are fewer. Mortality was 49% at 3 years in a study from Sweden [19] and 75% at 5 years in a study from Finland [83].

Factors found to be associated with long term mortality include age, male sex, diabetes mellitus, anticoagulation, heart disease, ICH location and volume [19, 78, 83, 84].

Of the studies providing these data only one, performed in Finland more than 20 years ago, specifically assessed mortality in those who had survived the first month [83]. Prior to the present study, data on factors associated specifically with long term mortality after the early phase were therefore very limited.

Mortality – association with Leukoaraiosis

There is increasing evidence of an association between severe LA and outcome in ischemic stroke [51, 85, 86]. For intracerebral hemorrhage we have found only two studies reporting an association between LA and outcome, both from South Korea. A single center study showed an increased 90 day poor outcome (dependency or death, mortality not specified) and a nationwide multicenter study of 1321 patients showed that LA was associated with increased early and long term mortality. Both studies had a low mean age of 60 years [87, 88].
Prior to the present study no European studies and no studies based on unselected patients regarding age and severity have included LA in prediction of mortality in ICH.

Mortality – need for new data

Based on the points made above there was a need for more data on LA as an independent prognostic factor for short and long term mortality. There was also a need for more data on long term mortality assessed specifically in those who survive the early phase.

1.7.3 Functional dependency

Overall there are very limited data on functional outcome in ICH, particularly long term data. In a recent review the authors concluded that more data on functional outcome after ICH are needed [9]. The scarcity of data can be illustrated by a frequently quoted estimate that only 20% will be functionally independent at six months. This is for instance quoted in the American guidelines for management of ICH [5]. It is based on the Oxfordshire Stroke Study. It is nearly thirty years old and the number of cases was low. In total 66 patients with verified or probable ICH were included, 35 were imaging confirmed, 22 with autopsy and 9 non-confirmed. At 6 months 14 patients (21%) were functionally independent [89]. In another publication from the same cohort patients alive after 1 year (n=25) were followed up at their places of residence by study nurses. After 1 year 17 of 25 survivors (68%) were functionally independent [90]. This latter report is of particular interest for the current study since, to the best of our knowledge; it is the only prior study that has used a direct in person follow up of long term survivors of ICH. The survivors included both verified and probable cases of ICH. The overall imaging rate in the study was 80%, but in the highest age group stroke of "unknown type" was most common.

The largest study that we have found, and the largest cited in a recent review [9], that reported long term functional outcome was performed in Finland twenty years ago [91]. It was based on 158 consecutive unselected patients with ICH. Functional status was assessed by use of a telephone interview of patients or care givers. After a median follow up of 2.7 years there were 55 survivors of whom 28 (51%) were

independent in activities of daily living. Age >70 years was the only identified factor independently associated with a poor functional outcome [91].

In a study from Estonia 14 of 26 (54%) one-year survivors of ICH were functionally independent [92]. A questionnaire sent by mail was used to score the BI from which independence defined as mRS<3 was derived.

1.7.4 Cognitive impairment

Very few data on cognitive impairment in survivors of ICH exist; a paradox considering that ICH is a common and serious disease of the brain.

In a study in the United States restricted to lobar ICH severe white matter changes were independently associated with cognitive impairment that existed prior to the ICH, but not with development of incident cognitive impairment during follow up (mean 32 months). The authors suggested an underlying vasculopathy, possibly CAA causing cognitive impairment. Pre-ICH cognitive impairment was assessed with a questionnaire after the ICH and incident cognitive impairment was assessed by telephone interview [93].

In a recent study from France, 48 of totally 80 survivors of ICH underwent assessment for cognitive impairment with a neuropsychological examination. Cognitive impairment was found in 77%. The 48 who were examined were younger, had less disability and more rarely lived in nursing homes than the survivors who were not examined and were therefore a selection. No analysis of prognostic factors for cognitive impairment was reported.

Overall data on cognitive impairment based on survivors with the full range of clinical severity and data based on a face to face follow up are very scarce. To the best of our knowledge no prior data exist on associations between cognitive impairment and ICH location.

1.7.5 Recurrent ICH

In a systematic review of 10 studies the overall rate of recurrent ICH was 2.3% per patient-year. It was higher after lobar than deep cerebral index ICH (4.4% versus 2.1% per patient year, p 0.002) [94]. In a study from the United States the results were similar with an overall recurrence rate of 2.4 % per year and an increased the risk with lobar location with an OR of 3.8 [95].

Overall the rate of recurrent ICH is similar across studies, but findings are conflicting regarding an increased risk associated with lobar index ICH. In Izumo City, Japan, the annual recurrence risk was also 2.3%. Lobar location was not associated with increased risk [96]. It has been speculated that this could express an epidemiological difference between an Asian and a Caucasian population [75]. However there are also studies from Sweden [19] and Finland [97] in which there was no higher risk of recurrent ICH after lobar compared to deep cerebral index ICH.

In an MRI based follow up study of survivors of lobar index ICH an increasing number of macro and micro hemorrhages on the baseline gradient echo MRI was associated with an increased risk of recurrent ICH [98].

1.7.6 Late seizures

Early seizures after an ICH have been reported in 4-16%, with varying definitions of early from 7 to 30 days [99-102], and are associated with lobar ICH location [100].

Data on late seizures, occurring after the acute phase of an ICH, however are fewer. In a multicenter study of 2021 stroke patients 7 of 265 patients with ICH (2.6%) developed late seizures defined as after 2 weeks. Mean follow up time was 9 months [102].

1.8 Acute treatment

General stroke treatment and monitoring

Both European and American guidelines recommend that patients with acute ICH should be monitored and treated in specialized units [1, 4, 103].
In a controlled trial in Norway, patients with ICH were allocated to either a general medical ward (n=65) or a stroke unit (n=56). The study showed a significant reduction in 1-year mortality in the stroke unit group driven by a difference in the first 30 days [104] .

In the United States the mortality has been shown to be lower in patients treated in intensive-care neurology units compared with general intensive care units (ICU) [105] and associated with the frequency of use of do-not-resuscitate orders [106]. Admissions for ICH to urban teaching hospitals increased from 30% to 49% over a decade from 1990-1991 to 2000-2001. Mortality decreased substantially in urban teaching hospitals, but not urban non-teaching hospitals and rural hospitals [107]. In a recent review the authors suggest that these studies provide indirect evidence that aggressive medical management and specialist care can improve the overall outcome in patients with ICH and that the changing trends in admissions might be beneficial [65]. Recently 26 quality indicators for the systematic evaluation of ICH patient care were proposed. Validation and further refinement of the indicators are planned [108].

Acute blood pressure lowering

The results from Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) 2 were released at the European Stroke Conference on May 29th 2013 and published simultaneously online in the New England Journal of Medicine [109]. In this large phase 3 trial 2839 patients with ICH within the last six hours were randomized to either intensive blood pressure treatment (target systolic level of <140 mm HG within 1 hour) or guideline-recommended treatment (target systolic level of <180 mm HG). The choice of agent was left to the treating physician. The primary endpoint of death or major disability (mRS 3-6) after 90 days showed a trend towards

significance (p=0.06) with this endpoint being reached in 52.0% in the intensive group and 55.6% in the guidelines group, OR 0.87 (0.75-1.01). As discussed in the paper and the accompanying editorial [110] there was a significant treatment benefit when using an ordinal analysis of the mRS or (p=0.04) or the common dichotomy of mRS 2-6 (p=0.03). Health related quality of life after 90 days was significantly better in the intensive treatment group. There was no increase in adverse effects by intensive treatment. The editorial concludes that "given the trend toward significance for the primary endpoint, the significant improvement in secondary endpoints and the reassuring safety, acute blood pressure lowering to a target systolic blood pressure of 140 mm Hg appears to be a "reasonable option". "Reasonable" is a preferred wording in recommendations based on level B evidence in American guidelines. The thresholds for blood pressure lowering in the current guidelines are based on expert opinions (level C) [1]. The new INTERACT 2 data are now the best data available and it is likely that guidelines will be changed although probably still not with the highest level of evidence.

INTERACT 2 can be the start of a breakthrough in ICH management. We may see a new perception of ICH as a no time to lose emergency equal to ischemic stroke. Potentially it can influence the choice and design of environments for the hyperacute care of patients with ICH. Many traditional Scandinavian model stroke units may not be adequately staffed and equipped for semi intensive care for patients with ICH. An upgrading of stroke units or a shift towards initial allocation of patients with ICH to an ICU are possible consequences.

Hemostatic therapy

The effect of recombinant factor VIIa (rFVIIa) given within four hours after symptom onset in ICH has been studied in two large randomized, blinded, placebo-controlled trials. The first study showed a marked reduction in haematoma growth, and improved clinical outcome [111]. The second study reproduced the finding of reduced hematoma growth, but disappointingly did not show significantly improved clinical outcome [112]. It has been suggested that a clinical treatment effect may have escaped significance in the second study due to the study design. A post hoc analysis

showed that a subset with age ≤70 years, ICH volume <60 ml, intraventricular hemorrhage volume <5 ml, and time from onset-to-treatment <2.5 hours may benefit from treatment [113]. The currently recruiting study Spot Sign for Predicting and Treating ICH Growth (STOP-IT) compares rFVIIa with placebo in patients with spot sign positive baseline CTA and hence an increased risk of hematoma expansion and poor outcome [114].

Another attractive candidate for haemostatic therapy is tranexamic acid. Several ongoing and planned studies compare tranexamic acid with placebo with [115] or without [116] including the spot sign in the selection of patients.

Early surgery

Early surgery for acute ICH is still controversial. A Cochrane review of 10 trials with a total of 2059 patients showed a statistically significant benefit of surgery with reduced odds for death or dependency, but the authors conclude that the result is not very robust and that further randomized trials are indicated to identify which patients benefit from surgery and to evaluate less invasive methods [117]. The International Surgical Trial in Intracerebral Haemorrhage (STICH) trial (n=1033) published in 2005 showed no benefit from early surgery (at a median time of 30 hours from symptom onset) compared to conservative treatment [118]. The results from STICH 2 were released at the European Stroke Conference on May 29th 2013 and published simultaneously online in the Lancet [119]. This trial tested if a subgroup of conscious patients with superficial lobar hemorrhages (<1cm from the brain surface) and no intraventricular hemorrhage would benefit from early surgery (<12 hours) compared to initial conservative treatment. The primary endpoint was a prognosis based dichotomized favorable or unfavorable outcome that adjusted for age GCS and ICH volume. An unfavorable outcome was seen in 59% in the early surgery group and 62% in the initial conservative group. This was not statistically significant (p=0.367). There was a significant benefit of early surgery in a subset with poor prognosis. However the authors underline that this was not a prespecified endpoint and therefore needs cautious interpretation. There was a large crossover with 21% in the conservative group having delayed surgery. The authors conclude that early surgery

does not increase the rate of death or disability and that there might be a small but clinically important benefit of early surgery [119]. Both the original paper and the accompanying comment [120] emphasize the persisting uncertainty as to which patients might benefit from early surgery and call for more data, in particular within the field of minimally invasive surgery.

Minimally invasive surgery combined with catheter delivered tissue plasminogen activator (rtPA) has shown promise. The Minimally Invasive Surgery plus rtPA for ICH Evacuation (MISTIE) trial was a proof of concept trial. Patients with an acute supratentorial ICH with volume >20 ml were randomized to either a control group (n=39) or to active treatment (n=54) with a CT guided minimally invasive surgery (MIS) procedure with application of a catheter into the clot and a three times daily injection of 1 mg rtPA for 1-3 days and drainage of superfluous liquid through the catheter. One year follow up results were presented at the International Stroke Conference in February 2013. The active treatment group had better outcomes than the control group on several measures including mRS, length of hospital stay, need of nursing home and costs [121]. A larger phase 3 trial is planned aiming to confirm these encouraging findings.

In patients with intraventricular hemorrhage (IVH) a common complication is obstructive hydrocephalus. Recent studies have shown that application of rtPA through a catheter directly into the intraventricular blood clot safely enhances clot resolution [122, 123]. A larger phase 3 study is currently recruiting [124].

For cerebellar hemorrhages there are no randomized data to guide treatment decisions. However the ASA guidelines (2010) state that the differences in outcome in the earlier non randomized studies are such that clinical equipoise does not exist for a trial. Therefore it is recommended that ”patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible” [1].

Acute treatment – summary

In summary as of July2013 it seems likely that guidelines and clinical practice will change as the result of INTERACT II with rapid blood pressure lowering as a standard treatment that is safe and probably beneficial. The answer to the question of which patients may benefit from early surgery is unfortunately still not clear. The results from the studies of minimally invasive surgery are eagerly awaited.

2. Aims of the thesis

The overall aim of this project was to assess the incidence, characteristics and outcome of ICH in Southern Norway.

Aims:

1. To assess the incidence and baseline characteristics of first ever ICH in Southern Norway leading to hospitalization (Paper I).
2. To assess short- and long term mortality after first ever ICH (Paper I and II).
   - Mortality rates at standardized time points; 2 days, 7 days, 30 days, 1 year, and two years (Paper I and II).
   - Baseline factors associated with 30-day mortality and with long term mortality in those who survive the first 30 days (Paper II).
3. To assess the rate of recurrence after first ever ICH (Paper II).
4. To assess the clinical functioning in long term survivors (Paper III).
   a. Functional dependency – rate and association with baseline factors
   b. Cognitive impairment – rate and association with baseline factors
5. To assess the rate of late seizures occurring after the index hospital stay (not published).

3. Materials and methods

3.1 Study population and area

Sørlandet Hospital Kristiansand in Vest-Agder County in Southern Norway serves a well-defined core catchment area from which all patients with acute stroke are admitted to the department of neurology 24/7/365. The population on January 1st of the midyear 2007 was 152276. Approximately 80.000 live in the city of Kristiansand, and the rest in smaller towns and rural areas.

Cases were found by computer search in the hospital register for all in- and outpatients with International Classification of Disease 10 (ICD 10) codes I61, I62 and I64.

For Paper I and II all consecutive patients hospitalized with a first ever ICH in the five year period 2005-2009 were included. Cases with traumatic ICH, ICH related to intracranial malignant tumor, ruptured aneurysm, or thrombolytic treatment and cases with isolated intraventricular hemorrhage without visible affection of cerebral parenchyma were excluded. Patients from the study area who were hospitalized elsewhere with ICH and subsequently transferred to SSK were included.

For the long term follow up study (Paper III) all patients in the initial cohort who were not registered as dead were contacted and invited to participate. Patients or care givers were first contacted by telephone. The reasons for this approach were two fold. Firstly, since we did not know the functional status of each individual or the ability to comprehend written information about the research project, we expected a direct contact by telephone to carry a lower risk of causing insecurity and anxiety than a letter. Secondly we assumed that the response rate would be higher with the use of telephone. If no contact was obtained by telephone a written invitation was sent. The means of obtaining contact were approved by the regional committee of medical research ethics.

3.2 Baseline assessment

Risk factors

Risk factors were recorded in a stroke registry from September 2007 and retrieved from patient files in cases prior to that. Hypertension and diabetes mellitus (diabetes mellitus, insulin-dependent or -independent) were defined as present if a history was known. Atrial fibrillation was defined as present if documented prior to or during hospital stay. Coronary heart disease (CHD) was defined as having had an acute myocardial infarct, coronary bypass surgery or percutaneous coronary intervention.

Clinical severity

Glasgow Coma Scale score (GCS) score was categorized into three groups 3-4, 5-12 and 14-15. These are the cut offs used in the ICH score published by Hemphill et al [77].

Imaging

All patients had a non contrast CT scan at baseline. One of the authors (AT) assessed all CT images. Hematoma location was classified as lobar (predominantly cortical or subcortical white matter), deep cerebral, brainstem or cerebellum. Thalamic hemorrhages were allocated to the category deep cerebral. The category brain stem included pontine and mesencephalic hemorrhages. Hematoma volume was calculated with the A x B x C /2 formula. The CT slice with the largest area of hemorrhage is identified. A is the greatest diameter of the hemorrhage, B is the diameter 90° to A, and C is the approximate number of CT slices with hemorrhage multiplied by the slice thickness [125]. The presence of intraventricular blood was registered. The severity of LA was graded as described by Van Swieten. The anterior and posterior regions were examined separately. LA was distinguished from infarction by its ill-defined borders. The severity of hypodensity, if present, was expressed in one of two degrees for each of the two regions. In grade 1 the abnormality was restricted to the region adjoining the ventricles. In grade 2 the increased hypodensity involved the

entire region from lateral ventricle to the cortex. The scores of the two regions were added giving an overall score from 0 to4 [126].

3.3 Outcomes assessment

Mortality

Death was automatically updated monthly through a linkage to the National Population Register [127]. The follow up was closed on 31.12.11. Patients not registered as dead by this date were considered alive. Causes of death, updated to 31.12.11, were obtained from the cause of death registry/Statistics Norway [128]. In addition, patient files were reviewed for clinical and radiological information on cause of death.

Recurrent ICH

In all patients who were discharged alive we checked for recurrence of ICH by combining information from the cause of death registry and from review of patient files and interview with the patients and care givers at follow up for information on readmission, neuroimaging or outpatient contact.

Functional dependency

The Barthel Index (BI) measures dependency in activities of daily living (ADL), by scoring three degrees of dependency for ten common ADL activities giving a total score from 0 (complete dependency) to 100 (complete independency). Eight of the ten items represent activities related to personal care; the remaining 2 are related to mobility. It is one of the most used measures of functional disability [129]. The scale was introduced in 1965 [130]. It has later been refined [131, 132].
The modified Rankin Scale (mRS), shown in Table 1, is a widely used global outcomes rating scale for stroke patients. It measures the ability to perform activities

the patient carried out previously. It was first developed in 1957 and was modified to its current form in 1988 [133, 134]. It ranges from 0 (no symptoms at all) to 6 (dead) [129]. In the present study mRS 3-5 was defined as dependency.

Table 1 Modified Rankin Scale (mRS)

Grade	Description
0	No symptoms at all
1	No significant disability, despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Cognitive impairment

The Montreal Cognitive Assessment (MoCA) is a brief screening tool designed to detect mild forms of cognitive impairment not captured by other cognitive screening instruments. It contains the following six domains: memory, visuospatial ability, executive functioning, attention and concentration, language, and orientation The maximum total score is 30 [129]. In the original publication a cut off at 26 points was recommended with scores ≤ 25 indicating the presence of cognitive impairment

[135]. More recent studies however have found improved balance between sensitivity and specificity with a lower cut-off [136, 137]. In the current study we used the cut off ≤ 23 recommended as the optimal by Luis et al., providing both excellent sensitivity and specificity for detecting mild cognitive impairment [136]. We used the approved Norwegian version of the MoCA [138].

Late seizures

Patient files of the long term survivors were reviewed for clinical and radiological information on readmission, neuroimaging or outpatient contact between the Index ICH and the follow up. At the long term follow up we asked the patient and accompanying relatives, friends or care givers about seizures occurring after discharge for the index ICH.

3.4 Statistics

For the calculation of incidence (Paper I) we used the population on January 1st of the midyear 2007. Pearson's Chi Square, Fisher's exact test, a t test, one-way ANOVA, Mann-Whitney, Pearson Correlation, the Spearman Rank Order Correlation, the Mantel-Haenszel test, logistic regression and Cox proportional hazard regression were used as appropriate. Statistical analysis was performed with SPSS version 18.

3.5 Ethics approval

The study was approved by the regional committee of medical research ethics (S-07227a).

4. Summary of results

In total 134 patients were hospitalized with first ever ICH in the period 2005-2009. Ethnicity was Caucasian in 97.8%. Age ranged from 33 to 100 years. Fifty five percent were men and 45% were women. Men were significantly younger than women (72.9 versus 78.2 years, p=0.010).

4.1 Incidence (Paper I)

The crude annual incidence rate per 100.000 was 19.6 for men, 15.7 for women and 17.6 for both sexes. Adjusted to the standard European population it was 16.9 for men, 8.8 for women (p<0.001) and 12.5 for both sexes. The incidence rates rose continuously with increasing age through all age groups in both sexes. The overall age adjusted rate ratio men/women analyzed with the Mantel-Haenzel test was 1.78 (p=0.001)

4.2 Hematoma location (Paper I)

The hematoma location was lobar in 36.6%, deep cerebral in 45.5%, cerebellar in 9.7%, and brain stem in 8.2%. Intraventricular hemorrhage occurred in 37% and was more frequent in patients with deep cerebral than lobar hematomas (50.8% versus. 24.5%, p=0.005).

4.3 Oral anticoagulant treatment associated ICH (Paper I)

The proportion with OAT-ICH was 26.9%. The annual incidence of OAT-ICH was 4.7 (95% CI 3.4-6.5) per 100.000. The median international ratio (INR) was 2.6 (interquartile range 2.2-2.9). Only 2 patients (5.6%) had an INR of more than 4. The cause for taking warfarin was atrial fibrillation in 30 of 36 patients (83.3%). Warfarin users were older than non users (78.6 versus 74.0 years, p=0.054) and more often had hypertension (70.6% versus 49.0%, p=0.029), atrial fibrillation (83.3% versus 5.1%, p<0.001) and a previous TIA or ischemic stroke (33.3% versus 16.3%, p=0.032). The

median ICH volume was non-significantly greater in warfarin users versus non users (25 ml (IQR 13-68) versus 17 ml (IQR 5-39), p=0.065).

4.4 Early hospital admission (Paper I)

The proportion of patients admitted within 3 hours of symptom duration was 49% for men, 32% for women (p=0.047) and 41% for both sexes.

4.5 Mortality (Paper I and II)

4.5.1 Mortality rates (Paper I and II)

Overall mortality at 2 days was 23.1%, at 7 days 29.9%, at 30 days 36.6%, at 1 year 46.3%, and at 2 years 53.0%.

After a median of 4.7 years (inter quartile range 2.5-6.6) follow up 84/134 patients (63%) were dead. There were 85 30-day survivors of whom 35 died.

4.5.2 Factors associated with 30-day mortality (Paper I and II)

In multivariate analysis the significant factors independently associated with 30-day mortality were warfarin (OR 4.4, p=0.022); GCS score 5-12 (OR 9.6, p<001); GCS score 3-4 (OR 102.6, p<001); intraventricular hemorrhage (OR 5.7, p=0.008) and LA (OR 1.6, p=0.026).

The two independent variables that showed the highest correlation were ICH volume and GCS score (Pearson Correlation 0.569, p<0.001). When both were included in the multivariate regression model GCS was a significant factor for 30-day mortality whereas ICH volume was not. As discussed in paper II we view ICH volume as the more causative of the two. When GCS score was removed from the model ICH volume and brain stem location were significant factors in addition to the otherwise unaltered warfarin, intraventricular hemorrhage, and LA score.

30-day mortality was 61.1% in the 36 patients on warfarin therapy versus 27.6% in the 99 not using warfarin (p< 0.001).

4.5.3 Factors associated with long term mortality (Paper II)

In multivariate analysis the significant factors independently associated with long term mortality in 30-day survivors were CHD (HR 2.7, p<0.001); GCS score 3-12 (HR 3.5, p=0.008), and LA score (HR 1.6, p=0.001).

4.6 Recurrent ICH (Paper II)

Four of the 88 patients (4.5%) who were discharged alive after the index ICH had an imaging confirmed recurrent ICH during follow up. One was fatal. Recurrent ICH was more frequent after lobar index ICH (4/36 (11.1%)) than after index ICH in other locations (0/52 (0%)), (p=0.025). Median time to recurrent ICH was 42 months.

4.7 Functional dependency (Paper III)

Of the 51 patients alive 50 (24 men (48%) and 26 (52%) women) agreed to participate in the follow up study. The median time from the ICH to the final follow up was 3.8 years (IQR 2.7-5.6). Amongst the 50 long term survivors 34 (68%) were independent (mRS 0-2). Sixteen (32%) were dependent (mRS 3-5).

There were some sex differences amongst the long term survivors. Men were younger than women both at baseline (66.4 versus 74.9 years, p=0.019) and at follow up (70.4 versus 78.7 years, p=0.019). Men had more education, were more often smokers, and had larger hematomas at baseline than women (14 ml (IQR 5.3-23.5) versus 4.5 ml (IQR2.0-15.5), p=0.027).

Forty one patients (82%) lived in their private homes and 9 patients (18%) lived in nursing homes.

In multivariate analysis the significant factors independently associated with mRS 3-5 were female sex (OR 5.1 (1.1-23.6), p=0.038) and LA score (OR 2.3 (1.3-4.0), p=0.003).

4.8 Cognitive impairment (Paper III)

The MoCA could be assessed in 44 patients (88%). The proportion with MoCA≤23 was 27 of 44 patients (61.4%).

In multivariate analysis the significant factors independently associated with MoCA≤23 were age (OR 1.1 per year/2.4 per 10 years p=0.010) and lobar ICH location (OR 14.1, p=0.016).

4.9 Late seizures (not published)

Five long term survivors (10%) had documented late seizures after discharge from the index hospital stay. All were generalized tonic clonic. The mean time from ICH to first seizure was 2.4 (SD 2.2) years, with the first occurring after 1.1 years. None of these patients had known epilepsy prior to the ICH, and none had early seizures during the index hospital stay.

Seizures occurred in 5 of 19 patients (26%) with lobar ICH versus 0 of 31 patients (0%) with ICH in other locations (p=0.005). Patients with seizures had larger median ICH volumes than patients without seizures, 39 ml (IQR 23.5- 58.5) versus 7 ml (7 ml (IQR 2.5-16.5), p=0.004. Seizures were not related to age or sex.

5. Discussion

5.1 Methodological considerations

Case finding

Case finding was done retrospectively. This may potentially have led to the loss of cases. The magnitude of this risk depends on the quality of the ICD 10 coding entered into the hospital database. The daily clinical activity in the stroke unit of the Department of Neurology, Sørlandet Hospital Kristiansand was lead by the same senior neurologist (AT) throughout the whole study period. From 2006-2009 one single senior neurologist reviewed all patient files before final ICD 10 coding in the hospital database.

Case finding was hospital based. As discussed in Paper I this gave a community based assessment of cases that lead to hospitalization. An important question is to which extent the number of cases with verified ICH identified by this approach differs from a population based stroke incidence study. Since the ICH diagnosis requires either brain imaging or autopsy, ICH is basically a hospital diagnosis. The Malmgren criteria for the "ideal stroke incidence study" were published twenty five years ago and have been updated later [139-143]. These include multiple overlapping sources of case finding. In the updated list these are in addition to hospitals: outpatient clinics including regular checking of general practitioners` databases and death certificates [143]. However none of these publications have reported data on which proportion of patients with verified ICH could be identified amongst out-of-hospital cases. The only Norwegian stroke incidence study (Innherred) prior to the present study did not report cases of verified ICH that were identified amongst out-of-hospital cases [13, 61]. Overall such data are extremely scarce. An autopsy based estimate of 5% of ICH cases being fatal out-of-hospital cases appears in a report from Finland twenty five years ago [91].

The estimated hospitalization rate was 95% of all strokes in a population based study from Sweden including ages 50-79 years in the period 1993-1998 [144]. This is

identical to the findings in the multipopulation EROS study (94.6%) in which all ages were included [10]. Sørlandet Hospital Kristiansand has a long history of encouraging rapid hospitalization of all cases of suspected stroke regardless of age sand stroke severity. As discussed in Paper I the finding that the incidence increased with age including the highest age group indicates that few cases were lost. We did perform a search in the hospital autopsy register for the study period. No additional cases were found. This information was not included in Paper I since the chosen design was limited to cases leading to hospitalization. It is unlikely that many fatal out-of hospital cases would have been verified as ICH by additional case finding methods such as a weekly query to general practitioners. As discussed in Paper II the quality of data in the cause of death registry is poor [145, 146]. Adding this source to the methods could have identified some cases with possible or probable strokes, but these would have been of undetermined subtype and it is very unlikely that additional cases with verified ICH would have been identified. An additional point is that the CT and MRI facilities lie in immediate proximity of the neurological department and any outpatient case revealing an unexpected ICH will trigger immediate alert of the neurology staff. No such cases occurred.

The difference between a hospital based and multiple overlapping source based catchment approach is therefore probably not large when it comes to the specific subset of verified ICH.

Incidence

In the estimation of incidence attention must be given to both the numerator and the denominator. An issue rarely discussed is that in studies that include both ischemic and hemorrhagic strokes and at the same time include only first ever strokes, all patients with a first ever ICH and a known history of a previous ischemic stroke will be excluded. This will reduce the calculated incidence and influence the composition of risk factors. If the aim is to assess the incidence of first ever ICH it seems illogical to exclude patients because of a prior history of another disease. The current study and the Southern Sweden study both included patients with a prior ischemic cerebral

event and the proportions with prior ischemic events were very similar, 21% and 19% respectively [61].

Concerning the denominator, the population used to calculate the incidence will influence the crude incidence. For instance the population < 15 years is a considerable proportion of the total population, but have an extremely low incidence rate of ICH and therefore the exclusion of the population < 15 (or any other low age limit) will give a higher total crude incidence. The Innherred study included ages > 15 years [13]. In the current study the total population was used and pediatric strokes sought. No pediatric strokes occurred. The Southern Sweden study also reported inclusion of all ages and the search for pediatric strokes [61].

Number of cases and events

Overall the numbers in the present study are relatively small, especially in some subgroups. The results must therefore be interpreted with caution. In particular the findings on recurrent ICH and late seizures are based on very low numbers of events. Both were associated with lobar ICH. This is discussed in more detail below. However the low numbers and the possibility that findings may be caused by the play of chance must be kept in mind.

Leukoaraiosis assessment

LA was assessed on the baseline CT. It has been shown that MRI is superior to CT in the detection of smaller white matter changes, but that the two modalities are equal in the detection of larger changes [85]. In the present study priority was given to completeness in scoring and therefore the baseline CT was chosen. Since MRI was not performed in all patients and probably in a selection of the less severely injured, we decided when designing the study not to include MRI in the assessment to avoid selection bias.

Long term follow up

A major strength in this study is that in contrast to most studies all survivors had a direct in person follow up with a thorough examination and a comprehensive questionnaire. It is also a strength that none were lost to follow up and all but one of the survivors agreed to participate.
The mRS at follow up was scored based on changes in abilities compared to the situation prior to the ICH. The patients, accompanying person, and care givers were asked whether each limitation in abilities that was identified was present prior to the ICH. However some blurring of the borders between preexisting and acquired limitations due to recall bias cannot be ruled out.

Data on pre-ICH cognition were not available. A firm knowledge of pre-ICH cognition would be desirable, but from a practical standpoint a direct compare of an in person examination like the MoCA before and after the ICH is probably unachievable. Therefore importantly the present study assessed the rate of cognitive impartment irrespective of which proportion was caused by the ICH.

5.2 Discussion of results

5.2.1 Incidence (Paper I)

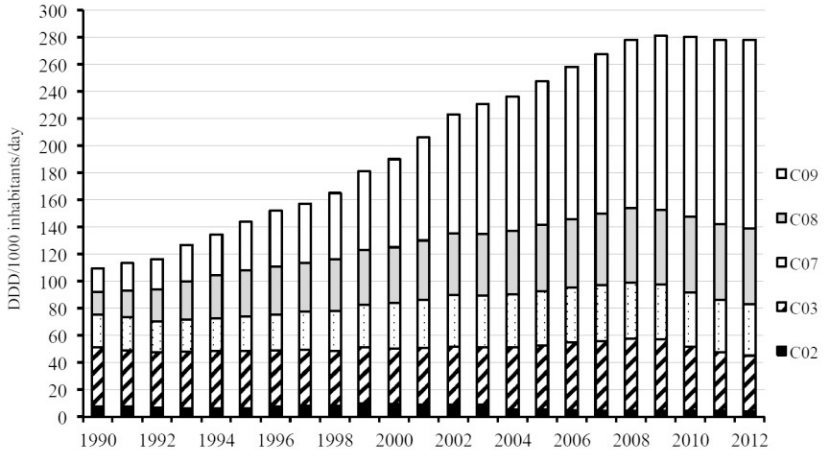
An overall interpretation is that the current age-adjusted incidence of first ever ICH of 12.5 per 100000 per year in Southern Norway is in the mid range of recent population based findings in Europe [10]. The present study does not support that an incidence in the higher range in Europe as found in the only prior Norwegian study reflects the current situation in Southern Norway [13, 61]. Additional support for this interpretation is provided by a population based study from Iceland, published online in may 2013, reporting a crude annual incidence of 13 per 100.000 in 2007/2008 [147]. The incidence in the present study is probably representative and unlikely to be substantially underestimated.
A possible contributor to a lower incidence than seen in prior Scandinavian studies is improved blood pressure control. In several countries including Sweden, Denmark and Finland a decreasing prevalence of hypertension has been found and blood pressure control has improved [148-151]. There are no Norwegian studies on trends in the quality of blood pressure control. However the sales statistics clearly show a markedly increased sale of blood pressure lowering medication over the last two decades (Figure 1).

The present study contains the first Norwegian data on the sex distribution of ICH. The incidence was higher for men than women. Our findings thereby support that men are at higher risk than women for ICH in Southern Norway in line with the dominating finding in the EROS study where five out of six centers had a male predominance. Men also had increased risk in Southern Sweden in 1996 [61]. Summing up these elements of evidence, the present study contributes to a now solid indication of an increased risk in Scandinavian men versus women that is reproducible over time and in different regions.

The incidence in our study increased with age through all age groups in both sexes. Some studies including two Scandinavian studies have shown a decreasing incidence in the highest age group [13, 61]. As discussed in Paper I it has been suggested that

incomplete case finding and stroke subtype classification can be contributing factors to this otherwise surprising finding [9]. The current study supports the more intuitive continuous association between age and risk. Our finding is supported by a recent report from Dijon, France. In the 24 year period from 1985 to 2008 a time trend was evident with an increase of the incidence (nearly doubled) in the highest age group, and a decrease in the lowest age group. Importantly, a lower cut off (>75 years) was used to define the highest age group, but the finding is still of interest. Through the whole time period the highest incidence was found in the highest age group. The authors link the increase in the incidence in the highest age group to trends in the use of antithrombotic treatments. The total crude incidence was stable [152].

Figure 1 Sales of antihypertensives (C02), diuretics (C03), beta blocking agents (C07) calcium channel blockers (C08) and ACE inhibitors/angiotensin II antagonists (C09) 1990-2012 in DDD/1000 inhabitants/day



Source: Sakshaug S. Drug Consumption in Norway 2008-2012 (Legemiddelforbruket i Norge 2008-2012), Norwegian Institute of Public Health, Oslo, legemiddelstatistikk 2013:1. 2013. [153]

5.2.2 Hematoma location (Paper I)

There were more deep cerebral than lobar hemorrhages. This is in agreement with several previous studies and the proportional distribution of locations is almost identical to findings in Jyvaskyla region, Finland and Greater Cincinnati, USA. This is illustrated in Table 2 (not published). In Southern Sweden the opposite relation was found with more lobar than deep cerebral ICH [61]. No previous Norwegian data exist. The present study supports that there is a moderate predominance of deep cerebral ICH in Southern Norway in general agreement with studies cited in both American and European guidelines [4, 5]. Deep cerebral location was associated with hypertension and smoking.

The proportion of patients with intraventricular hemorrhage (37%) was in agreement with findings by others ranging from 36% to 42% [17-19].

Table 2 Proportional distribution of ICH location in Kristiansand and other studies (not published)

	Total	Lobar	Deep cerebral	Brain stem	Cerebellum
	n	%	%	%	%
Kristiansand, present study	134	37	46	8	10
Greater Cincinnati, USA	1038	35	49	6	10
Izumo City, Japan	350	15	69	9	25
Southern Sweden	341	52	36	4	9
Jyvaskyla region, Finland	158†	34	49	7	11
Dijon, France	87	18	67	6	9
Perth, Australia	60*	40	52	7	10

*13 'massive cortical' hemorrhages included in the deep group. †9 intraventricular hemorrhages included in the deep group.
Source: [16]

5.2.3 OAT-ICH (Paper I and II)

The present study provides data on the burden of OAT-ICH from a setting in which anticoagulant therapy for atrial fibrillation in the elderly was reasonably well implemented and still entirely warfarin based. It may serve as a reference for future studies.

The study provides supportive evidence of a rise in the proportion of OAT-ICH amongst total ICH and confirms a very poor prognosis of OAT-ICH. Consistent with several other reports most cases occurred with therapeutic levels of the INR [58, 154, 155]. Therefore the high proportion of OAT-ICH amongst total ICH can be viewed as the calculated risk of the active treatment policy. The finding is not an argument for withholding anticoagulant treatment in elderly patients with atrial fibrillation given the high level of evidence of its beneficial effect in the prevention of ischemic stroke [156]. However it does address the need for a careful individual approach particularly in the oldest patients. The burden of OAT-ICH is also highly relevant for current ongoing shift towards new oral anticoagulants. As of July 2013 recent changes in reimbursement have boosted this shift in Norway. What the burden of OAT-ICH is after an anticipated greater shift towards the new agents needs to be seen. The new agents may carry a lower risk of OAT-ICH. A more liberal prescription policy could however possibly to some extent counterbalance this, a scenario hopefully avoided through adherence to evidence based implementation.

5.2.4 Early hospital admission (Paper I)

The proportion admitted within three hours of symptom duration was 41% (Paper I). It was higher in men than women and higher than the corresponding proportion for ischemic stroke (23%) in our center [157]. This proportion is rarely reported but highly relevant for the eligibility to acute treatments. It is also important for the planning of studies of acute treatments. Based on the present study the inclusion criteria hospital admittance < 3 hours and ICH volume < 60 ml would retain 31% of the patients and give approximately 5.5 eligible patients per 100.000 inhabitants per year. If age < 80 years is added to the criteria, the number drops to 3.5. Additional

exclusion criteria such as warfarin use or a GCS score cut-off will further reduce the number. This readily illustrates the likely need for multinational studies for testing treatment effects on clinical endpoints if for instance a sample size of 500-1000 is required.

5.2.5 Mortality rates (Paper I and II)

The overall mortality rates of 23.1 %, 29.9 %, 36.6 %, 46.3 % and 53.0 %, at 2 days, 7 days, 30 days 1 year and 2 years respectively are in general agreement with previous reports [10, 19, 78, 83, 84, 158, 159].

5.2.6 Factors associated with 30-day mortality (Paper I and II)

We identified warfarin, GCS score, intraventricular hemorrhage, and LA score as independent prognostic factors for 30-day mortality.

The prognostic impact of LA is discussed separately below.

Warfarin was as expected a significant independent prognostic factor for 30-day mortality as seen in several studies [58, 155, 160]. Importantly, the present study confirmed this in an unselected cohort with many old patients. The very high 30-day mortality of 61.1% in warfarin users is similar to several prior studies [161-163]. Others have found somewhat lower rates, 52% in the united States [59] and 54% in Finland [155]. A 30-day mortality in OAT-ICH in the higher end in the present study might be explained by the high age and comorbidity in the warfarin users (Paper I).

The interplay between ICH volume and GCS score is important for the interpretation of data concerning their impact on short term outcome. Both are well established prognostic factors for early mortality [81, 164-166]. In the present study ICH volume was not independently associated with 30-day mortality in multivariate analysis when GCS score was in the model, but highly significant when GCS was removed from the model (Paper II). ICH volume is the more causative of the two. Increasing ICH volume correlated significantly with a lower GCS score.

5.2.7 Factors associated with long term mortality (Paper II)

For long term mortality in 30-day survivors we identified CHD, GCS score, and LA score as independent prognostic factors.
The prognostic impact of LA is discussed separately below.

The finding that CHD was associated with long term mortality in 30-day survivors contributes to an overall interpretation that mortality after survival of the acute phase greatly relates to the burden of vascular disease.

Warfarin had no independent impact on long term mortality in 30-day survivors. This is in agreement with a report from Finland [155]. In a large study from the United States warfarin was associated with increased long term mortality. A likely explanation (suggested in Paper II) is that this may have been driven by an excess early mortality in warfarin users since all patients were assessed, not only 30-day survivors [78]. This seems more plausible than an independent long term effect after the acute phase.

5.2.8 Leukoaraiosis - prognostic impact on mortality (Paper II)

An important finding in this unselected Caucasian cohort is that LA is independently associated with both 30-day mortality and long term mortality in those who survive the first 30 days. Only two prior studies, both from South Korea and both in younger and more selected patients had reported on this association [87, 88].
Almost simultaneously with the publication of Paper II a study of 95 patients with ICH in the United States which supports our findings was published. It showed an association between increasing LA score on MRI and being dependent or dead at 14 days and 3 months in univariate analysis and 3 months in multivariate analysis [167]. The patients were more selected than ours. Since the study was MRI based and imaging was performed 1.8 days after symptom onset, only 95 of 196 consecutive patients were included. Patients were younger than ours (mean age 63.9±13.5 years versus 75.3 ±12). Only 6% used warfarin compared to 26.9% in our study. 38% of the patients were white compared to 97.8% in our study. The study did not report

long term results. Neither the American nor our study showed an association between LA and ICH volume.

As of April 2013 the present study is still the only European study on the association between LA and ICH outcome, the only study on Caucasians, the only study on an unselected cohort and one of only two studies with long term data. With contribution from the present study the amount of data supporting the prognostic impact of LA has increased.

5.2.9 Sex – not associated with mortality

Sex was not associated with mortality, neither 30-day nor long term mortality. For 30-day mortality this is in general agreement with the literature, illustrated for instance by its absence in the various published prognostic tools [82]. For long term mortality data are more conflicting with some studies showing a higher risk in men [19, 83], one study a higher risk in women [84] and several showing no associations [11, 78, 80].

5.2.10 Recurrent ICH (Paper II)

Our rate of recurrent ICH was in the low range compared with the literature. Importantly the number of recurrent ICH in our study was very low, only four cases. The findings must therefore be interpreted with great caution. When looking at only lobar index ICH in our study, recurrent ICH was seen in 4 of 36 cases (11.1%) over 4.7 years. In a systematic review the overall rate of recurrent ICH was 2.3% per year and 4.4% for the subset with a lobar index ICH [94]. Notably 5 European studies were included, 4 of which were smaller than ours.

Recurrent ICH was associated with lobar index ICH. This is in line with a common opinion and the AHA/ASA guidelines [1] which refer to a review and a cohort study in the United States [94, 168]. In Japan no association was found between ICH location and the risk of recurrent ICH [96]. It has been suggested that these differences may be related to epidemiological differences between Asian and Caucasian populations [75]. However there are also recent studies from Sweden and Finland,

both larger than ours, that did not show a higher risk of recurrent ICH after lobar than deep cerebral index ICH [19, 97].

A speculation is that differences in secondary prevention may contribute to the inconsistent results. The aggressiveness in blood pressure control and the threshold for antithrombotic treatment after ICH may vary. The impact of these treatment strategies on recurrence could in theory be different in patients with deep cerebral and lobar index ICH. Rigorous blood pressure control could for instance prevent recurrence more effectively after a hypertension related deep cerebral ICH than after a CAA associated lobar ICH.

5.2.11 Functional dependency (Paper III)

At long term follow up after a median of 3.8 years 82% of the survivors lived in their private homes with or without assistance from the public home nursing service. No data for comparison exist. Two thirds were functionally independent with mRS 0-2. The only data for comparison are from Finland in the 1980`s showing a corresponding proportion of 51% [91]. We found that mean age was lower in men than women amongst long term survivors as it was in the full cohort at baseline. Functional dependency expressed as mRS 3-5 was associated with LA. This is a novel finding in survivors of ICH. In ischemic stroke prior studies have shown a link between LA and a higher mRS [85, 169]. This association has been shown to be independent of the infarct volume [85]. In agreement with this the present study showed that LA was, but ICH volume was not associated with dependency. Hence new findings in the current study regarding ICH fits with prior knowledge from ischemic stroke supporting an association between LA and outcome caused by dysfunction in areas other than the acute injury. In a recent review the author concludes that in ischemic stroke LA affects outcome after multivariable adjustment for other patient characteristics and infarct volume. The author also concludes that further studies are needed on the mechanisms and to determine whether neurorehabilitation strategies need to take LA into account [51].

Functional dependency was associated with female sex. The reason for this is not clear. It is a novel finding and needs confirming from other studies before conclusions can be drawn. One can speculate that older women have a lower physical capacity and or less assistance in their immediate surroundings causing a more frequent shift towards dependency after an ICH. But first of all the finding should draw attention to the possibility of an excess dependency in female long term survivors and encourage further studies on this topic.

5.2.12 Cognitive impairment (Paper III)

Cognitive impairment on the MoCA was a very frequent finding in the long term survivors. Lobar ICH location was independently associated with cognitive impairment. This has not been shown before. The cutoff for cognitive impairment of MoCA ≤23 was chosen to give priority to specificity. As expected the proportion with cognitive impairment was higher when the original cut off of MoCA≤25 was used. However the factors independently associated with the odds for having cognitive impairment did not change.

The study does not discriminate cognitive impairment caused by the ICH from pre-ICH impairment or evolving impairment after the ICH that relates to other pathologies. However the observations that the median ICH volume was relatively small (8.5 ml) and that ICH volume was not associated with cognitive impairment suggest that the cognitive impairment to some degree is independent of the acute ICH. It has been shown that vascular risk factors are associated with the progression from mild cognitive impairment to dementia [170-172] and that treatment of vascular risk factors is associated with reduced or delayed conversion to dementia [172, 173]. Recognition of mild cognitive impairment is therefore very important. The present study contributes to increased awareness of this important issue. A practical implication is that a rigorous blood pressure control may be at least as important after lobar as after deep cerebral ICH and not just for the prevention of recurrent stroke, but for the prevention of progressive loss of function including cognitive function.

5.2.13 Late seizures (not published)

Late seizures in long term survivors were associated with lobar ICH location and also with greater ICH volume. The association with lobar location is well known for early seizures [99, 100], but prior to ours we found no studies showing this for late seizures. However findings in a study from France published online in may 2013 showed several similarities with ours. From 325 patients with ICH 10% developed late seizures. The only independent prognostic factor was cortical involvement of the hemorrhage. Seizures were associated with a larger ICH volume in univariate analysis (Table 1 in their report); a point not commented on by the authors. Late seizures were not related to the occurrence of early seizures. Lobar microbleeds on MRI were associated with late seizures after adjustment for age, sex and cortical involvement of ICH. The authors suggested CAA as an underlying cause [174]. Since late seizures in our study were associated with greater ICH volumes an intuitive mechanism is that a larger tissue injury predisposes for later seizures. An alternative speculation is that an underlying pathology such as CAA could increase the vulnerability both to the evolution of larger hematomas and to the evolution of epileptic foci which might not necessarily be restricted to the site of injury from the ICH. Other recent studies support that CAA can be an underlying cause of seizures; In Alzheimer's disease a subset of patients experience unprovoked seizures [175] and in transgenic mice accumulation of β-amyloid in the brain can causes epilepsy [176].

Patients who suffer a lobar ICH have a substantial risk of experiencing seizures and the risk persists even if no seizure has occurred at one year follow up.

5.2.14 Lobar ICH – the burden hidden beneath

Lobar ICH location was associated with increased risk of recurrent ICH (Paper II), cognitive impairment (Paper III) and late seizures (not published). Based on findings in this thesis it seems justified to speculate that lobar ICH may appear as a marker of an underlying cerebral pathology with an increased risk of several serious clinical manifestations. A lobar ICH may be a "tip of the iceberg". In clinical routine the patient with an acute lobar ICH may be a patient with a progressive cerebral

condition with an increased risk of several important clinical manifestations. As discussed the underlying pathology could be CAA.

5.2.15 Implications for secondary prevention

This thesis suggests that a thorough diagnostic work up of patients with ICH including detailed imaging studies for evidence of vasculopathy yields a potential for improved assessment and handling of the individual risk profile. A thorough work up of patients with an ICH should include a screening for cognitive impairment with a recommended tool such as the MoCA.
Patients who suffer an ICH, in particular a lobar ICH have a high risk of having or developing cognitive impairment. This knowledge further strengthens the reasons for optimizing primary and secondary prevention focusing on both live style interventions and medication.

Findings in this thesis suggest that rigorous blood pressure control may be at least as important after a lobar as after a deep cerebral ICH. The target for blood pressure control has traditionally been the prevention of subsequent strokes and death. This thesis suggests that attention also should be given to the high rate of cognitive impairment and that more knowledge is needed about the possibility that optimized blood pressure control after an ICH could contribute to delaying or preventing overt dementia. Although no prospective studies of stroke survivors have explored the long term benefit of blood pressure control with dementia as the primary end point [177] evidence from studies of hypertension strongly suggests a treatment benefit. In a review of randomized trials of treatment of hypertension in which dementia was an included outcome measure the author concludes that “treatment of hypertension is an effective way to prevent dementia” [178].

Evidence also exists for preventive effects of non pharmaceutical measures on cognition. In a recent review of studies evaluating the preventive effect of physical activity on vascular dementia the authors conclude that there is evidence supporting the beneficial effect and that physical activity should be highlighted as part of secondary prevention in people at risk for cerebrovascular disease [179].

Whether to (re-)start oral anticoagulation or platelet inhibitors in patients who have had an ICH demands cautious individual consideration. There is limited evidence to guide decisions. For platelet inhibitors it has been suggested that it may be relatively safe and justified in patients with risk factors for thromboembolic events [168]. The recommendations in the AHA/ASA guidelines are; “After a lobar ICH avoidance of anticoagulation is probably recommended, anticoagulation after nonlobar ICH and antiplatelet therapy after all ICH might be considered, particularly when there are definite indications for these agents” [1].

This study supports that after lobar ICH the risk of recurrent ICH is increased and special caution needed when considering the balance between potential benefit and risk for the individual patient. Improved MRI detection of CAA in clinical routine may possibly also contribute improved individual risk stratification.

6. Conclusions

The incidence of first ever ICH in Southern Norway is in the mid range in Europe, and lower than in the only prior Norwegian incidence study in the mid nineteen nineties. Men are at higher risk than women. Deep cerebral ICH is somewhat more common than lobar ICH.

The proportion with OAT-ICH in Southern Norway is higher than in most reports reflecting a well implemented use of warfarin in atrial fibrillation in the elderly. Most cases of OAT-ICH occur with an INR in the therapeutic level. The mortality of OAT-ICH is very high.

The proportion of patients admitted to hospital within three hours of symptom duration was higher than the corresponding proportion in ischemic stroke.

LA is independently associated with both short and long term mortality in unselected Caucasians with a first ever ICH. Long term mortality is also associated with CHD.

The majority of long term survivors live in their private homes with or without assistance from the public home nursing system. Two thirds are functionally independent. Dependency is associated with LA and female sex.

Cognitive impairment is very common in long term survivors of ICH and associated with lobar ICH location.

Recurrent ICH and late seizures were more frequent after lobar than non lobar ICH. Late seizures were associated with larger ICH volumes.

7. Clinical implications and future perspectives

The mortality of ICH is high. Improvements in the prevention and treatment of ICH are strongly needed.

OAT-ICH accounts for a large proportion of ICH and carries a particularly high mortality. Efforts to reduce the occurrence of OAT-ICH and improve the prognosis are needed.

The well known crucial impact of the hematoma volume on outcome was seen clearly in this study. Hematoma volume will probably be the main target for future acute treatments. Efforts to combat the initial hematoma growth as early as possible are needed, preferably starting in the pre-hospital phase.

This study suggests that a large proportion of patients with ICH arrive at hospital within three hours of symptom duration. This means that a large proportion may be eligible for and potentially benefit from new acute treatments of ICH.

A thorough clinical and radiological work-up after an ICH is important for the individual risk factor assessment and handling. This thesis has shown that LA, readily assessable on non contrast baseline CT scans, is independently associated with short and long term mortality and with functional dependency in long term survivors. In the future the radiological work-up should preferably include studies of underlying vasculopathies, specifically CAA. Findings in this thesis support the speculation that an underlying vasculopathy, probably CAA may be interrelated with Lobar ICH, cognitive impairment, recurrent ICH, and possibly also late seizures after ICH.

Clinical work up after an ICH should preferably include a screening for cognitive impairment with a recommended tool such as the MoCA or an equivalent. Cognitive impairment should have increased attention in both clinical practice and research and gain recognition in our striving to reduce the burden of cerebrovascular disease.

8. References

1. Morgenstern, L.B., et al., *Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association*. Stroke, 2010. **41**(9): p. 2108-29.

2. Thrift, A.G., G.A. Donnan, and J.J. McNeil, *Epidemiology of intracerebral hemorrhage*. Epidemiologic Reviews, 1995. **17**(2): p. 361-81.

3. Sudlow, C.L. and C.P. Warlow, *Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration*. Stroke, 1997. **28**(3): p. 491-9.

4. European Stroke Initiative Writing, C., et al., *Recommendations for the management of intracranial haemorrhage - part I: spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee*. Cerebrovasc Dis, 2006. **22**(4): p. 294-316.

5. Broderick, J., et al., *Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group*. Stroke, 2007. **38**(6): p. 2001-23.

6. *Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III*. Stroke, 1990. **21**(4): p. 637-76.

7. WHO, *World Health Organisation International Classification of Diseases (ICD)*. http://www.who.int/classifications/icd/en/.

8. Sacco, R.L., et al., *An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association*. Stroke, 2013.

9. van Asch, C.J., et al., *Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis*. Lancet Neurol, 2010. **9**(2): p. 167-76.

10. Heuschmann, P.U., et al., *Incidence of stroke in Europe at the beginning of the 21st century*. Stroke, 2009. **40**(5): p. 1557-63.

11. Sacco, S., et al., *Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry*. Stroke, 2009. **40**(2): p. 394-9.

12. Feigin, V.L., et al., *Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review*. Lancet Neurol, 2009. **8**(4): p. 355-69.

13. Ellekjaer, H., et al., *Epidemiology of stroke in Innherred, Norway, 1994 to 1996. Incidence and 30-day case-fatality rate*. Stroke, 1997. **28**(11): p. 2180-4.

14. Qureshi, A.I., et al., *Spontaneous Intracerebral Hemorrhage*. New England Journal of Medicine, 2001. **344**(19): p. 1450-1460.

15. Mutlu, N., R.G. Berry, and B.J. Alpers, *MASSIVE CEREBRAL HEMORRHAGE. CLINICAL AND PATHOLOGICAL CORRELATIONS*. Arch Neurol, 1963. **8**: p. 644-61.

16. Flaherty, M.L., et al., *Racial variations in location and risk of intracerebral hemorrhage*. Stroke, 2005. **36**(5): p. 934-7.

17. Tuhrim, S., et al., *Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage*. Crit Care Med, 1999. **27**(3): p. 617-21.

18. Steiner, T., et al., *Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII*. Neurosurgery, 2006. **59**(4): p. 767-73; discussion 773-4.

19. Zia, E., et al., *Three-year survival and stroke recurrence rates in patients with primary intracerebral hemorrhage*. Stroke, 2009. **40**(11): p. 3567-73.

20. Morris, J., *The nervous system: In: Cotran RS, Kumar V, Robbin SL, eds. Pathologic basis of disease. 3rd ed. Philadelphia: W.B. Saunders, 1999:1385-450*.

21. Warlow, C., et al., *What Caused This Intracerebral Haemorrhage?*, in *Stroke*2008, Blackwell Publishing Ltd. p. 411-456.

22. Kazui, S., et al., *Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course*. Stroke, 1996. **27**(10): p. 1783-7.

23. Brott, T., et al., *Early hemorrhage growth in patients with intracerebral hemorrhage*. Stroke, 1997. **28**(1): p. 1-5.

24. Delcourt, C., et al., *The second (main) phase of an open, randomised, multicentre study to investigate the effectiveness of an intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT2)*. Int J Stroke, 2010. **5**(2): p. 110-6.

25. Qureshi, A.I. and Y.Y. Palesch, *Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: design, methods, and rationale*. Neurocrit Care, 2011. **15**(3): p. 559-76.

26. Davis, S.M., et al., *Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage*. Neurology, 2006. **66**(8): p. 1175-81.

27. Dowlatshahi, D., et al., *Defining hematoma expansion in intracerebral hemorrhage: Relationship with patient outcomes*. Neurology, 2011.

28. Broderick, J.P., et al., *Determinants of intracerebral hemorrhage growth: an exploratory analysis*. Stroke, 2007. **38**(3): p. 1072-5.

29. Dowlatshahi, D., et al., *Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes*. Neurology, 2011. **76**(14): p. 1238-44.

30. Flibotte, J.J., et al., *Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage*. Neurology, 2004. **63**(6): p. 1059-64.

31. Cucchiara, B., et al., *Hematoma growth in oral anticoagulant related intracerebral hemorrhage*. Stroke, 2008. **39**(11): p. 2993-6.

32. Brouwers, H.B., et al., *Apolipoprotein E genotype predicts hematoma expansion in lobar intracerebral hemorrhage*. Stroke, 2012. **43**(6): p. 1490-5.

33. Lou, M., et al., *Relationship between white-matter hyperintensities and hematoma volume and growth in patients with intracerebral hemorrhage*. Stroke, 2010. **41**(1): p. 34-40.

34. Fisher, C.M., *Pathological observations in hypertensive cerebral hemorrhage*. J Neuropathol Exp Neurol, 1971. **30**(3): p. 536-50.

35. Brouwers, H.B. and S.M. Greenberg, *Hematoma Expansion following Acute Intracerebral Hemorrhage*. Cerebrovasc Dis, 2013. **35**(3): p. 195-201.

36. Delgado Almandoz, J.E., et al., *Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the spot sign score*. Stroke, 2009. **40**(9): p. 2994-3000.

37. Wada, R., et al., *CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage*. Stroke, 2007. **38**(4): p. 1257-62.

38. Goldstein, J.N., et al., *Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage*. Neurology, 2007. **68**(12): p. 889-94.

39. Demchuk, A.M., et al., *Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study*. Lancet Neurol, 2012.

40. Huynh, T.J., et al., *Spot Sign Number Is the Most Important Spot Sign Characteristic for Predicting Hematoma Expansion Using First-Pass Computed Tomography Angiography: Analysis From the PREDICT Study*. Stroke, 2013.

41. Murai, Y., et al., *Magnetic resonance imaging-documented extravasation as an indicator of acute hypertensive intracerebral hemorrhage*. J Neurosurg, 1998. **88**(4): p. 650-5.

42. Ariesen, M.J., et al., *Risk factors for intracerebral hemorrhage in the general population: a systematic review*. Stroke, 2003. **34**(8): p. 2060-5.

43. Jackson, C.A. and C.L. Sudlow, *Is hypertension a more frequent risk factor for deep than for lobar supratentorial intracerebral haemorrhage?* J Neurol Neurosurg Psychiatry, 2006. **77**(11): p. 1244-52.

44. Anderson, C., *Differential effects of hypertension in the aetiology of major intracerebral haemorrhage subtypes*. J Neurol Neurosurg Psychiatry, 2006. **77**(11): p. 1206.

45. Takebayashi, S. and M. Kaneko, *Electron microscopic studies of ruptured arteries in hypertensive intracerebral hemorrhage*. Stroke, 1983. **14**(1): p. 28-36.

46. Charidimou, A., Q. Gang, and D.J. Werring, *Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum*. J Neurol Neurosurg Psychiatry, 2012. **83**(2): p. 124-37.

47. Charidimou, A., J.C. Baron, and D.J. Werring, *Transient focal neurological episodes, cerebral amyloid angiopathy, and intracerebral hemorrhage risk: looking beyond TIAs*. Int J Stroke, 2013. **8**(2): p. 105-8.

48. Knudsen, K.A., et al., *Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria*. Neurology, 2001. **56**(4): p. 537-9.

49. van Rooden, S., et al., *Descriptive analysis of the Boston criteria applied to a Dutch-type cerebral amyloid angiopathy population*. Stroke, 2009. **40**(9): p. 3022-7.

50. Ayaz, M., et al., *Imaging cerebral microbleeds using susceptibility weighted imaging: one step toward detecting vascular dementia*. J Magn Reson Imaging, 2010. **31**(1): p. 142-8.

51. Smith, E.E., *Leukoaraiosis and stroke*. Stroke, 2010. **41**(10 Suppl): p. S139-43.

52. Scheltens, P., et al., *White matter changes on CT and MRI: an overview of visual rating scales. European Task Force on Age-Related White Matter Changes*. European Neurology, 1998. **39**(2): p. 80-9.

53. Pantoni, L., et al., *Visual rating scales for age-related white matter changes (leukoaraiosis): can the heterogeneity be reduced?* Stroke, 2002. **33**(12): p. 2827-33.

54. Debette, S., et al., *Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study*. Stroke, 2010. **41**(4): p. 600-6.

55. Smith, E.E., et al., *Leukoaraiosis is associated with warfarin-related hemorrhage following ischemic stroke*. Neurology, 2002. **59**(2): p. 193-7.

56. Neumann-Haefelin, T., et al., *Leukoaraiosis is a risk factor for symptomatic intracerebral hemorrhage after thrombolysis for acute stroke*. Stroke, 2006. **37**(10): p. 2463-6.

57. Steiner, T., J. Rosand, and M. Diringer, *Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions*. Stroke, 2006. **37**(1): p. 256-62.

58. Flaherty, M.L., et al., *The increasing incidence of anticoagulant-associated intracerebral hemorrhage*. Neurology, 2007. **68**(2): p. 116-21.

59. Rosand, J., et al., *The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage*. Archives of Internal Medicine, 2004. **164**(8): p. 880-4.

60. Hart, R.G., *What causes intracerebral hemorrhage during warfarin therapy?* Neurology, 2000. **55**(7): p. 907-8.

61. Nilsson, O.G., et al., *Incidence of intracerebral and subarachnoid haemorrhage in southern Sweden*. Journal of Neurology, Neurosurgery and Psychiatry, 2000. **69**(5): p. 601-7.

62. Feldmann, E., et al., *Major risk factors for intracerebral hemorrhage in the young are modifiable*. Stroke, 2005. **36**(9): p. 1881-5.

63. Sturgeon, J.D., et al., *Risk factors for intracerebral hemorrhage in a pooled prospective study*. Stroke, 2007. **38**(10): p. 2718-25.

64. Morgenstern, L.B. and W.D. Spears, *A triethnic comparison of intracerebral hemorrhage mortality in Texas*. Ann Neurol, 1997. **42**(6): p. 919-23.

65. Qureshi, A.I., A.D. Mendelow, and D.F. Hanley, *Intracerebral haemorrhage*. Lancet, 2009. **373**(9675): p. 1632-44.

66. Howard, G., et al., *Risk Factors for Intracerebral Hemorrhage: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study*. Stroke, 2013.

67. Biffi, A., et al., *Variants at APOE influence risk of deep and lobar intracerebral hemorrhage*. Ann Neurol, 2010. **68**(6): p. 934-43.

68. Woo, D., et al., *Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study*. Stroke, 2002. **33**(5): p. 1190-5.

69. O'Donnell, M.J., et al., *Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study*. Lancet, 2010. **376**(9735): p. 112-23.

70. Prospective Studies, C., et al., *Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths*. Lancet, 2007. **370**(9602): p. 1829-39.

71. Martini, S.R., et al., *Risk factors for intracerebral hemorrhage differ according to hemorrhage location*. Neurology, 2012. **79**(23): p. 2275-82.

72. Goldstein, L.B., et al., *Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study*. Neurology, 2008. **70**(24 Pt 2): p. 2364-70.

73. Vergouwen, M.D., et al., *Statin treatment and the occurrence of hemorrhagic stroke in patients with a history of cerebrovascular disease*. Stroke, 2008. **39**(2): p. 497-502.

74. McKinney, J.S. and W.J. Kostis, *Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials*. Stroke, 2012. **43**(8): p. 2149-56.

75. Mathew L. Flahery, D.W., and Joseph P. Broderick, *The epidemiology of intracerebral hemorrhage*, in *Intracerebral Hemorrhage*, J.H.H. J. Ricardo Carhuapoma, Baltimore, C.U. Stephan A. Mayer, New York, and J.H.H. Daniel F. Hanley, Baltimore, Editors. 2009, Cambridge University Press. p. 1-16.

76. Andersen, K.K., et al., *Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors*. Stroke, 2009. **40**(6): p. 2068-72.

77. Hemphill, J.C., 3rd, et al., *The ICH score: a simple, reliable grading scale for intracerebral hemorrhage*. Stroke, 2001. **32**(4): p. 891-7.

78. Flaherty, M.L., et al., *Long-term mortality after intracerebral hemorrhage*. Neurology, 2006. **66**(8): p. 1182-6.

79. Inagawa, T., et al., *Primary intracerebral hemorrhage in Izumo City, Japan: incidence rates and outcome in relation to the site of hemorrhage*. Neurosurgery, 2003. **53**(6): p. 1283-97; discussion 1297-8.

80. Hosomi, N., et al., *Predictors of intracerebral hemorrhage severity and its outcome in Japanese stroke patients*. Cerebrovascular Diseases, 2009. **27**(1): p. 67-74.

81. Broderick, J.P., et al., *Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality*. Stroke, 1993. **24**(7): p. 987-93.

82. Hwang, B.Y., et al., *Clinical grading scales in intracerebral hemorrhage*. Neurocrit Care, 2010. **13**(1): p. 141-51.

83. Fogelholm, R., et al., *Long term survival after primary intracerebral haemorrhage: a retrospective population based study*. Journal of Neurology, Neurosurgery and Psychiatry, 2005. **76**(11): p. 1534-8.

84. Nilsson, O.G., et al., *Prediction of death in patients with primary intracerebral hemorrhage: a prospective study of a defined population*. Journal of Neurosurgery, 2002. **97**(3): p. 531-6.

85. Arsava, E.M., et al., *Severity of leukoaraiosis correlates with clinical outcome after ischemic stroke*. Neurology, 2009. **72**(16): p. 1403-10.

86. Oksala, N.K., et al., *Age related white matter changes predict stroke death in long term follow-up*. J Neurol Neurosurg Psychiatry, 2009. **80**(7): p. 762-6.

87. Won, Y.S., et al., *Leukoaraiosis predicts poor outcome after spontaneous supratentorial intracerebral hemorrhage*. Eur Neurol, 2010. **64**(5): p. 253-7.

88. Lee, S.H., et al., *White matter lesions and poor outcome after intracerebral hemorrhage: a nationwide cohort study*. Neurology, 2010. **74**(19): p. 1502-10.

89. Counsell, C., et al., *Primary intracerebral haemorrhage in the Oxfordshire community stroke project*. Cerebrovascular Diseases, 1995. **5**(1): p. 26-34.

90. Bamford, J., et al., *A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage*. Journal of Neurology, Neurosurgery and Psychiatry, 1990. **53**(1): p. 16-22.

91. Fogelholm, R., M. Nuutila, and A.L. Vuorela, *Primary intracerebral haemorrhage in the Jyvaskyla region, central Finland, 1985-89: incidence, case fatality rate, and functional outcome*. Journal of Neurology, Neurosurgery and Psychiatry, 1992. **55**(7): p. 546-52.

92. Vibo, R., J. Korv, and M. Roose, *One-year outcome after first-ever stroke according to stroke subtype, severity, risk factors and pre-stroke treatment. A population-based study from Tartu, Estonia*. Eur J Neurol, 2007. **14**(4): p. 435-9.

93. Smith, E.E., et al., *White matter lesions, cognition, and recurrent hemorrhage in lobar intracerebral hemorrhage*. Neurology, 2004. **63**(9): p. 1606-12.

94. Bailey, R.D., et al., *Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage*. Neurology, 2001. **56**(6): p. 773-7.

95. Hill, M.D., et al., *Rate of stroke recurrence in patients with primary intracerebral hemorrhage*. Stroke, 2000. **31**(1): p. 123-7.

96. Inagawa, T., *Recurrent primary intracerebral hemorrhage in Izumo City, Japan*. Surgical Neurology, 2005. **64**(1): p. 28-35; discussion 35-6.

97. Huhtakangas, J., et al., *Predictors for Recurrent Primary Intracerebral Hemorrhage: A Retrospective Population-Based Study*. Stroke, 2013.

98. Greenberg, S.M., et al., *Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage*. Stroke, 2004. **35**(6): p. 1415-20.

99. De Herdt, V., et al., *Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome*. Neurology, 2011. **77**(20): p. 1794-800.

100. Passero, S., et al., *Seizures after spontaneous supratentorial intracerebral hemorrhage*. Epilepsia, 2002. **43**(10): p. 1175-80.

101. Alberti, A., et al., *Early seizures in patients with acute stroke: frequency, predictive factors, and effect on clinical outcome*. Vasc Health Risk Manag, 2008. **4**(3): p. 715-20.

102. Bladin, C.F., et al., *Seizures after stroke: a prospective multicenter study*. Archives of Neurology, 2000. **57**(11): p. 1617-22.

103. Juttler, E. and T. Steiner, *Treatment and prevention of spontaneous intracerebral hemorrhage: comparison of EUSI and AHA/ASA recommendations*. Expert Rev Neurother, 2007. **7**(10): p. 1401-16.

104. Ronning, O.M., B. Guldvog, and K. Stavem, *The benefit of an acute stroke unit in patients with intracranial haemorrhage: a controlled trial*. J Neurol Neurosurg Psychiatry, 2001. **70**(5): p. 631-4.

105. Diringer, M.N. and D.F. Edwards, *Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage*. Crit Care Med, 2001. **29**(3): p. 635-40.

106. Hemphill, J.C., 3rd, et al., *Hospital usage of early do-not-resuscitate orders and outcome after intracerebral hemorrhage*. Stroke, 2004. **35**(5): p. 1130-4.

107. Qureshi, A.I., et al., *Changes in cost and outcome among US patients with stroke hospitalized in 1990 to 1991 and those hospitalized in 2000 to 2001*. Stroke, 2007. **38**(7): p. 2180-4.

108. Qureshi, A.I., *Intracerebral hemorrhage specific intensity of care quality metrics*. Neurocrit Care, 2011. **14**(2): p. 291-317.

109. Anderson, C.S., et al., *Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage*. N Engl J Med, 2013.

110. Frontera, J.A., *Blood Pressure in Intracerebral Hemorrhage - How Low Should We Go?* N Engl J Med, 2013.

111. Mayer, S.A., et al., *Recombinant activated factor VII for acute intracerebral hemorrhage*. New England Journal of Medicine, 2005. **352**(8): p. 777-85.

112. Mayer, S.A., et al., *Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage*. New England Journal of Medicine, 2008. **358**(20): p. 2127-37.

113. Mayer, S.A., et al., *Can a subset of intracerebral hemorrhage patients benefit from hemostatic therapy with recombinant activated factor VII?* Stroke, 2009. **40**(3): p. 833-40.

114. *Spot Sign for Predicting and Treating ICH Growth (STOP-IT) study*. http://clinicaltrials.gov/ct2/show/NCT00810888?term=stop-it&rank=1.

115. *STOP-AUST: The Spot Sign and Tranexamic Acid On Preventing ICH Growth - AUStralasia Trial* http://clinicaltrials.gov/ct2/show/NCT01702636?term=tranexamic+acid+intracerebral&rank=1.

116. *Tranexamic acid for IntraCerebral Haemorrhage TICH-2: a pragmatic phase III prospective double blind randomised placebo controlled trial*. http://apps.who.int/trialsearch/Trial.aspx?TrialID=ISRCTN93732214.

117. Prasad, K., A.D. Mendelow, and B. Gregson, *Surgery for primary supratentorial intracerebral haemorrhage*. Cochrane Database Syst Rev, 2008(4): p. CD000200.

118. Mendelow, A.D., et al., *Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial*. Lancet, 2005. **365**(9457): p. 387-97.

119. Mendelow, A.D., et al., *Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial*. Lancet, 2013.

120. Gautschi, O.P. and K. Schaller, *Surgery or conservative therapy for cerebral haemorrhage?* Lancet, 2013.

121. Hanley, D.F., *Mistie Trial: 365-day Results Demonstrate Improved Outcomes and Cost Benefit*. Abstract International Stroke Conference February 2013, 2013. http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_448655.pdf.

122. Morgan, T., et al., *Preliminary report of the clot lysis evaluating accelerated resolution of intraventricular hemorrhage (CLEAR-IVH) clinical trial*. Acta Neurochir Suppl, 2008. **105**: p. 217-20.

123. Naff, N., et al., *Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial*. Stroke, 2011. **42**(11): p. 3009-16.

124. *Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR III)*. http://clinicaltrials.gov/ct2/show/NCT00784134?term=clear+IVH&rank=2.

125. Kothari, R.U., et al., *The ABCs of measuring intracerebral hemorrhage volumes*. Stroke, 1996. **27**(8): p. 1304-5.

126. van Swieten, J.C., et al., *Grading white matter lesions on CT and MRI: a simple scale*. Journal of Neurology, Neurosurgery and Psychiatry, 1990. **53**(12): p. 1080-3.

127. *National Population Register*. p. http://www.norway.no/temaside/tema.asp?stikkord=94303.

128. *Statistics Norway*. p. http://www.ssb.no/en/.

129. Salter, K., *Outcome Measures in Stroke Rehabilitation*. The Evidence-Based Review of Stroke Rehabilitation (EBRSR) reviews current practices in stroke rehabilitation 2011. http://www.ebrsr.com/uploads/Module-21_outcomes.pdf.

130. Mahoney, F.I. and D.W. Barthel, *FUNCTIONAL EVALUATION: THE BARTHEL INDEX*. Md State Med J, 1965. **14**: p. 61-5.

131. Granger, C.V., et al., *Stroke rehabilitation: analysis of repeated Barthel index measures*. Arch Phys Med Rehabil, 1979. **60**(1): p. 14-7.

132. Sulter, G., C. Steen, and J. De Keyser, *Use of the Barthel index and modified Rankin scale in acute stroke trials*. Stroke, 1999. **30**(8): p. 1538-41.

133. Rankin, J., *Cerebral vascular accidents in patients over the age of 60. II. Prognosis*. Scott Med J, 1957. **2**(5): p. 200-15.

134. van Swieten, J.C., et al., *Interobserver agreement for the assessment of handicap in stroke patients*. Stroke, 1988. **19**(5): p. 604-7.

135. Nasreddine, Z.S., et al., *The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment*. J Am Geriatr Soc, 2005. **53**(4): p. 695-9.

136. Luis, C.A., A.P. Keegan, and M. Mullan, *Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US*. Int J Geriatr Psychiatry, 2009. **24**(2): p. 197-201.

137. Dong, Y., et al., *The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke*. J Neurol Sci, 2010. **299**(1-2): p. 15-8.

138. *MoCA Norwegian version*. http://www.mocatest.org/pdf_files/test/MoCA-Test-Norwegian.pdf.

139. Malmgren, R., et al., *Geographical and secular trends in stroke incidence*. Lancet, 1987. **2**(8569): p. 1196-200.

140. Bonita, R., et al., *Approaches to the problems of measuring the incidence of stroke: the Auckland Stroke Study, 1991-1992*. International Journal of Epidemiology, 1995. **24**(3): p. 535-42.

141. Sudlow, C.L. and C.P. Warlow, *Comparing stroke incidence worldwide: what makes studies comparable?* Stroke, 1996. **27**(3): p. 550-8.

142. Feigin, V.L., et al., *Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century*. Lancet Neurol, 2003. **2**(1): p. 43-53.

143. Feigin, V. and S.V. Hoorn, *How to study stroke incidence*. Lancet, 2004. **363**(9425): p. 1920.

144. Pessah-Rasmussen, H., et al., *Increasing stroke incidence and decreasing case fatality, 1989-1998: a study from the stroke register in Malmo, Sweden*. Stroke, 2003. **34**(4): p. 913-8.

145. Reseland, S., *[Bad quality of the Cause of Death Registry]*. Tidsskr Nor Laegeforen, 2009. **129**(9): p. 894.

146. Gjersoe, P., et al., *[Reliability of death certificates. The reproducibility of the recorded causes of death in patients admitted to departments of internal medicine]*. Ugeskr Laeger, 1998. **160**(35): p. 5030-4.

147. Hilmarsson, A., O. Kjartansson, and E. Olafsson, *Incidence of First Stroke: A Population Study in Iceland*. Stroke, 2013.

148. Ng, N., et al., *Trends of blood pressure levels and management in Vasterbotten County, Sweden, during 1990-2010*. Glob Health Action, 2012. **5**.

149. Wilhelmsen, L., et al., *Secular changes in cardiovascular risk factors and attack rate of myocardial infarction among men aged 50 in Gothenburg, Sweden. Accurate prediction using risk models*. J Intern Med, 2008. **263**(6): p. 636-43.

150. Andersen, U.O. and G.B. Jensen, *Trends and determinant factors for population blood pressure with 25 years of follow-up: results from the Copenhagen City Heart Study*. Eur J Cardiovasc Prev Rehabil, 2010. **17**(6): p. 655-9.

151. Vartiainen, E., et al., *Thirty-five-year trends in cardiovascular risk factors in Finland*. Int J Epidemiol, 2010. **39**(2): p. 504-18.

152. Bejot, Y., et al., *Intracerebral haemorrhage profiles are changing: results from the Dijon population-based study*. Brain, 2013. **136**(Pt 2): p. 658-64.

153. Sakshaug, S., *Drug Consumption in Norway 2008-2012 (Legemiddelforbruket i Norge 2008-2012), Norwegian Institute of Public Health, Oslo, legemiddelstatistikk 2013:1*. 2013.

154. Sjalander, A., et al., *Risk of haemorrhagic stroke in patients with oral anticoagulation compared with the general population*. Journal of Internal Medicine, 2003. **254**(5): p. 434-8.

155. Huhtakangas, J., et al., *Effect of increased warfarin use on warfarin-related cerebral hemorrhage: a longitudinal population-based study*. Stroke, 2011. **42**(9): p. 2431-5.

156. You, J.J., et al., *Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*. Chest, 2012. **141**(2 Suppl): p. e531S-75S.

157. Tveiten, A., et al., *Intravenous thrombolysis for ischaemic stroke: short delays and high community-based treatment rates after organisational changes in a previously inexperienced centre*. Emerg Med J, 2009. **26**(5): p. 324-6.

158. Dennis, M.S., et al., *Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project*. Stroke, 1993. **24**(6): p. 796-800.

159. Hardemark, H.G., N. Wesslen, and L. Persson, *Influence of clinical factors, CT findings and early management on outcome in supratentorial intracerebral hemorrhage*. Cerebrovascular Diseases, 1999. **9**(1): p. 10-21.

160. Tveiten, A., et al., *Intracerebral Hemorrhage in Southern Norway - A Hospital-Based Incidence Study*. European Neurology, 2012. **67**(4): p. 240-245.

161. Hart, R.G., B.S. Boop, and D.C. Anderson, *Oral anticoagulants and intracranial hemorrhage. Facts and hypotheses*. Stroke, 1995. **26**(8): p. 1471-7.

162. Flaherty, M.L., et al., *Location and outcome of anticoagulant-associated intracerebral hemorrhage*. Neurocrit Care, 2006. **5**(3): p. 197-201.

163. Franke, C.L., et al., *Intracerebral hematomas during anticoagulant treatment*. Stroke, 1990. **21**(5): p. 726-30.

164. Qureshi, A.I., et al., *Predictors of early deterioration and mortality in black Americans with spontaneous intracerebral hemorrhage*. Stroke, 1995. **26**(10): p. 1764-7.

165. Lisk, D.R., et al., *Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation*. Neurology, 1994. **44**(1): p. 133-9.

166. Tuhrim, S., et al., *Validation and comparison of models predicting survival following intracerebral hemorrhage*. Crit Care Med, 1995. **23**(5): p. 950-4.

167. Caprio, F.Z., et al., *Leukoaraiosis on Magnetic Resonance Imaging Correlates With Worse Outcomes After Spontaneous Intracerebral Hemorrhage*. Stroke, 2013.

168. Viswanathan, A., et al., *Antiplatelet use after intracerebral hemorrhage*. Neurology, 2006. **66**(2): p. 206-9.

169. Kissela, B., et al., *Clinical prediction of functional outcome after ischemic stroke: the surprising importance of periventricular white matter disease and race*. Stroke, 2009. **40**(2): p. 530-6.

170. Solfrizzi, V., et al., *Vascular risk factors, incidence of MCI, and rates of progression to dementia*. Neurology, 2004. **63**(10): p. 1882-91.

171. Di Carlo, A., et al., *CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia*. Neurology, 2007. **68**(22): p. 1909-16.

172. Li, J., et al., *Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease*. Neurology, 2011. **76**(17): p. 1485-91.

173. Deschaintre, Y., et al., *Treatment of vascular risk factors is associated with slower decline in Alzheimer disease*. Neurology, 2009. **73**(9): p. 674-80.

174. Rossi, C., et al., *Incidence and Predictors of Late Seizures in Intracerebral Hemorrhages*. Stroke, 2013.

175. Palop, J.J. and L. Mucke, *Epilepsy and cognitive impairments in Alzheimer disease*. Arch Neurol, 2009. **66**(4): p. 435-40.

176. Minkeviciene, R., et al., *Amyloid beta-induced neuronal hyperexcitability triggers progressive epilepsy*. J Neurosci, 2009. **29**(11): p. 3453-62.

177. Hachinski, V., *Vascular behavioral and cognitive disorders*. Stroke, 2003. **34**(12): p. 2775.

178. Staessen, J.A., T. Richart, and W.H. Birkenhager, *Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain*. Hypertension, 2007. **49**(3): p. 389-400.

179. Aarsland, D., et al., *Is physical activity a potential preventive factor for vascular dementia? A systematic review*. Aging Ment Health, 2010. **14**(4): p. 386-95.

9. List of errors

The following errors have been found in the thesis:

Paper I

Paper contains two incorrect citations discovered after publication. Neither affects findings or conclusions.

1. “In Norway published incidence data are limited to one study of stroke epidemiology in mid-Norway in 1994–1996 with only 55 cases of ICH”. The correct number in the reference is 45 not 55 cases [13].
2. “In the Swedish study neither bleeding in tumor nor recurrent incidents were excluded”. This is incorrect. Such cases were included in the study but excluded from calculation of the incidence [61].

Paper II

Paper III

Arnstein Tveiten August 2013