Subarachnoid hemorrhage (SAH) is most often caused by the rupture of a saccular intracranial aneurysm (sIA) at the fork of the intracranial extracerebral artery, affects the working-age population. The mortality rate after acute sIA-SAH is high. Along with various degrees of acute or delayed brain injury, long term survivors of sIA-SAH are often affected by neurological and cognitive disorders. In the current study we analyzed the incidence and risk factors of epilepsy and depression along with the epilepsy-associated causes of death after sIA-SAH in a population based cohort.
Epilepsy and depression and their risk factors after aneurysmal subarachnoid hemorrhage in Eastern Finnish population
JUKKA HUTTUNEN

Epilepsy and depression and their risk factors after aneurysmal subarachnoid hemorrhage in Eastern Finnish population

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**ABSTRACT**
The Kuopio Intracranial Aneurysm Patient and Family Database ([www.kuopioneurosurgery.fi](http://www.kuopioneurosurgery.fi)) includes all patients with subarachnoid hemorrhage from ruptured saccular intracranial aneurysm (sIA-SAH) since 1980 admitted to the Kuopio University Hospital (KUH) from its defined catchment population in Eastern Finland. The use of prescribed medicines, including reimbursable antiepileptic drugs (AEDs) and antidepressants (ATDs), have been entered from the Finnish national registries. And the causes of death (ICD-10) were fused from the Finnish national registries from 1994 to 2014.

The aim was to (I) elucidate the incidence and risk factors of epilepsy after subarachnoid hemorrhage from saccular intracranial aneurysm (sIA-SAH) in a population based cohort. (II) The second aim was to elucidate the predictors of antidepressant (ATD) use after subarachnoid hemorrhage from saccular intracranial aneurysm (sIA-SAH) in a population-based cohort with matched controls. (III) The third aim was to elucidate the epilepsy-associated causes of death and subsequent excess long-term mortality in the 12-month survivors of sIA-SAH.

The cumulative incidence and independent risk factors of epilepsy and death were analysed in 876 sIA-SAH patients admitted from 1995 to 2007. The Competing Risks Analysis was used to correctly estimate the probability of epilepsy, because epilepsy and death after sIA-SAH may share risk factors. The risk factors of the ATD use were analysed in 940 patients alive 12 months after sIA-SAH and their matched population controls between 1994 and 2014, and the classification tree analysis was used to create a predicting model for ATD use after sIA-SAH. ATD use was indicated by two or more purchases of ATDs. The epilepsy-associated causes of death and subsequent excess long-term mortality of 779 12-month survivors of sIA-SAH, admitted from 1995 to 2007 were analysed. Cumulative incidence of epilepsy is 12% at five years. Epilepsy and 12-month mortality after sIA-SAH share poor Hunt and Hess grading as an independent risk factor. Epilepsy in the two-week survivors of sIA-SAH is predicted by signs of primary injury in the brain tissue, most notably ICH. The sIA-SAH survivors use significantly more often ATDs, indicative of depression, than their matched population controls. Even with a seemingly good recovery (mRS 0) at 12 months after sIA-SAH, there is a significant risk for depression requiring ATD medication. Comorbid epilepsy in the 12-month survivors of sIA-SAH is associated with increased risk of death in long term follow up. The survivors of sIA-SAH require long term dedicated follow up, including identification and effective treatment of comorbid epilepsy to prevent avoidable deaths.

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TIIIVISTELMÄ

Tutkimuksen tavoitteena oli selvittää (I) epilepsian yleisyys ja riskitekijät aivovaltimoaneurysmavuodon jälkeen. (II) Toisena tavoitteena oli selvittää masennuslääkekäytön yleisyys ja riskitekijät aivovaltimoaneurysmavuodon jälkeen verrattuna kontrolliväestöön. (III) Kolmantena tavoitteena oli selvittää epilepsiaan liittyvät kuolinsyyt ja selventää epilepsiaan liittyvää kuoleman riskiä potilailla, jotka sairastuvat epilepsiaan aivovaltimoaneurysmavuodon jälkeen ja olivat elossa 12 kuukautta aivovaltimoaneurysmavuodon jälkeen.


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Yleinen Suomalainen asiasanasto: epilepsia; esiintyvyys; ilmaantuvuus; Itä-Suomi; kallonsisäinen aneurysma; kuolleisuus; masennus; riskitekijät
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Kuopio, May 2017

Jukka Huttunen

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Abbreviations

ACA Anterior cerebral artery
ACoA Anterior communicating artery
AED Antiepileptic drug
ATD Antidepressant drug
ADPKD Autosomal dominant polycystic kidney disease
aSAH Aneurysmal subarachnoid hemorrhage
ATC Anatomic therapeutic chemical
BA Basilar artery
CI Confidence interval
CT Computed tomography
CTA Computed tomography angiography
DSA Digital substraction angiography
GCS Glasgow Coma Scale
GOS Glasgow Outcome Scale
HADS Hospital anxiety and depression scale
HR Hazard ratio
ICA Internal carotid artery
ICU Intensive Care Unit
ICH Intracerebral hemorrhage
ISAT International Subarachnoid Aneurysm Trial
ISUIA International Study of Unruptured Intracranial Aneurysms
IVH Intraventricular hemorrhage
KUH Kuopio University Hospital
MCA Middle cerebral artery
MRA Magnetic resonance angiography
MRI Magnetic resonance imaging
NHI National Health insurance
OR Odds ratio
PCoA Posterior communicating artery
sIA Saccular intracranial aneurysm
sIA-SAH Aneurysmal subarachnoid hemorrhage from ruptured sIA
SAH Subarachnoid hemorrhage
SII Social Insurance Institution
SMR Standardised mortality ratio
VA Vertebral artery
1 Introduction

Aneurysmal subarachnoid hemorrhage (aSAH), the third most frequent form of stroke after cerebral infarct and intracerebral hemorrhage, is most often caused by the rupture of a saccular intracranial aneurysm (sIA) at the fork of the intracranial extracerebral artery. Cerebral artery blood bursts into cerebrospinal fluid (CSF) spaces and, occasionally, into brain tissue. Survivors of acute aSAH are at risk for instant and lethal re-bleeding, which indicates the need for acute aneurysm occlusion therapy. The mortality rate after acute aSAH is high, estimated to be 35–50% (van Gijn et al. 2007).

The incidence of aSAH is reported to be 4–7 per 100 000 person-years (Feigin et al. 2009). The risk factors for aSAH include advanced age, smoking, hypertension, excess drinking, and family history of sIA (Feigin et al. 2005) The prevalence of unruptured intracranial aneurysm in studied population is 2.2–3.0% (Feigin et al. 2005). However, most unruptured sIAs are not diagnosed during patients’ lifetime.

Acute aSAH is a condition that requires treatment at a neurointensive care unit. Thorough understanding of the natural course of aSAH and multimodality monitoring for intra- and extracranial complications are required. Treatment aims to prevent further damage from re-bleeding, hydrocephalus, increased intracranial pressure, seizure, electrolyte disturbance, fever, hyperglycemia, cardiac and pulmonary dysfunction, and subacute development of delayed ischemic brain injury (Diringer et al. 2011, Wartenberg et al. 2006b, Bendel et al. 2008).

Epilepsy is defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures (Fisher et al. 2005). This definition is usually practically applied as having two unprovoked seizures more than 24 hours apart. Acute symptomatic seizure is an event occurring within 1 week of the insult to the brain for example stroke, infection or traumatic brain injury. Unprovoked seizures occur after one week of the brain injury and are distinguished from acute seizures (Beghi et al. 2010). Epileptic seizures after aSAH are always focal seizures, which arise in a restricted part of the brain. Focal seizures can be associated with a variety of symptoms, signs and behaviors, a key feature by which the seizure subtypes can be separated is the extent of impairment of awareness. Focal seizures can also evolve to bilateral tonic-clonic seizures.

Previous studies have reported incidences of epilepsy after aSAH that vary from 0.9% to 25% (Byrne et al. 2003, Olafsson et al. 2000b). According to previous studies, the risk factors for symptomatic epilepsy include hypertension, onset of seizures, medial cerebral artery location of aneurysm, initial loss of consciousness (> 1 hour), intracerebral haemorrhage, subdural hemorrhage, ischemia, vasospasm, high cisternal bleeding, young age (< 40 years), and rebleeding (Bidzinski et al. 1992, Buczacki et al. 2004, Butzkueven et al. 2000, Choi et al. 2009, Claassen et al. 2003, Lin et al. 2003, Lin et al. 2008, Ohman 1990, Olafsson et al. 2000a, Keranen et al. 1985b, Ukkola & Heikkinen 1990a). aSAH patients have increased long-term mortality compared to the general population (Huttunen et al. 2011). In addition, epilepsy patients also have increased mortality (Nevalainen et al. 2014, Nevalainen et al. 2013).

Epilepsy is associated with increased risk of depression (Fuller-Thomson & Brennenstuhl 2009, Kanner 2009); depression after aSAH has been reported in 47–51% of survivors (Kreiter et al. 2013, Ronne-Engstrom et al. 2013). Depression is associated with poor quality
of life, and it may slow down rehabilitation and complicate reintegration into living situations and occupations (Rinkel & Algra 2011, Hutter et al. 1999).
2 Review of the Literature

2.1 INTRACRANIAL ANEURYSMS (IAS)

2.1.1 Types of aneurysms of intracranial arteries

There are several types of intracranial artery aneurysms. Aneurysms of major intracranial arteries in the subarachnoid space on the brain surface (“large vessels”) can be (a) saccular, (b) fusiform, (c) traumatic, or (d) mycotic (van Gijn et al. 2007). Penetrating arteries on the brain tissue (“small vessels”) may develop microaneurysms, a major cause of intracerebral hemorrhage (Dye et al. 2014).

2.1.2 Definition of saccular IA (sIA) and fusiform IA (fIA)

Saccular intracranial aneurysm (sIAs) and fusiform IAs (fIAs) develop during lifetime. The sIAs (97%) are saccular pouches at the forks of major intracranial extracerebral arteries near the circle of Willis and its branches, while fIAs (3%) are spindle-shaped fusiform dilatations of major intracranial extracerebral artery trunks.

2.1.3 Prevalence of sIA

A systematic review and meta-analysis estimated the overall prevalence of sIAs to be 3.2% (Vlak et al. 2011). The prevalence of sIA is higher in patients with ADPKD or a family history of subarachnoid hemorrhage and in patients older than 30 years of age. Women have a higher prevalence of sIA than men regardless of age and comorbidities, and this difference increases with age (van Gijn et al. 2007). Somewhat lower rates have also been reported; in a large population-based cohort in Norway, the prevalence of sIA was 1.9% in an unselected population aged 50–65 years (Muller et al. 2013).
2.1.4 Anatomy and pathophysiology of sIA

Blood is supplied to the brain and surrounding structures by the internal carotid arteries, which arise from the common carotid arteries, and by the vertebral arteries, which arise from the subclavian arteries and join to form the basilar artery. The anterior communicating artery and the two posterior communicating arteries complete the anastomosing Circle of Willis in the skull base (Figure 1).

The cerebral artery wall consists of three layers—the tunica intima, tunica media, and tunica adventitia—with an endothelium covering the tunica intima. The tunica media consists of smooth muscles and elastic fiber produced by smooth muscle cells. The main event in the formation of sIA is the breakdown of lamina formed by smooth muscles and elastic tissue (Frosen et al. 2012, Frosen 2014). Nonphysiologic flow dynamics cause stress to the arterial wall, resulting in inflammation in the tunica media and the formation of sIA (Aoki et al. 2009, Moriwaki et al. 2006). Rupture of sIA is most likely related to the destruction of smooth muscle cells in the arterial wall in which the sIA is formed (Frosen et al. 2012, Frosen 2014).

2.1.5 Diagnosis and management unruptured of sIA

Most unruptured sIAs are found incidentally during neuroradiological head imaging. According to the ISUIA study, conditions leading to neuroimaging and incidental diagnosis of unruptured sIA included headache (36%) and cerebrovascular disease (17.6%), cranial nerve deficits (15.4%), sIA mass effect (5.7%), ill-defined spells (4.8%), convulsive disorder (4.2%), subdural or intracerebral hemorrhage (2.7%), brain tumor (1.7%), and nervous system degenerative disease (0.5%) (ISUIA 1998). Some sIAs are found while screening the family members of sIA or sIA-SAH patients (Ronkainen et al. 1998, Ronkainen et al. 1997).

The annual risk of rupture of an sIA is approximately 0.9–2% (Wermer et al. 2007, Korja et al. 2014, Muller et al. 2013). This risk varies depending on the combination of aneurysm- and patient-related risk factors, and treatment should be planned by a dedicated neurovascular team. According to a meta-analysis in 2007, the patient-related risk factors
for sIA rupture are old age and female gender (Wermer et al. 2007). In addition, smoking increases the risk of rupture of sIA, but this increase is not statistically significant. sIA-related risk factors for sIA rupture include location in the posterior cerebral circulation, size of sIA (> 5mm), and sIA-causing symptoms (Wermer et al. 2007). Additionally, increasing the size and irregularity of a sIA increases the risk of rupture (Murayama et al. 2016, Lindgren et al. 2016).

The European Stroke Organisation’s guidelines for the management of unruptured sIA suggest that treatment plans should take into account the possible risks and benefits of the treatment and that the patient’s decision to undergo the treatment should depend on patient-related factors (age, tendency to smoke, and, perhaps, rupture of another aneurysm) as well as aneurysmal factors. In other words, the decision to begin sIA treatment should be based on a number of factors (Steiner et al. 2013b).

2.1.6 Research by Kuopio IA Patient and Family Database

*Kuopio Neurosurgery IA Patient and Family Database (www.kuopioneurosurgery.fi)*

The Department of Neurosurgery of Kuopio University Hospital (KUH) is the sole provider of full-time acute and elective neurosurgical services in the KUH catchment area in Eastern Finland.

KUH’s catchment area contains four central hospitals with their own catchment areas. Patients with acute SAH were acutely admitted to the KUH for angiography and treatment if not moribund or elderly. Cases with unruptured intracranial aneurysms also received a neurosurgical consultation for elective occlusion. In both instances, the exact number of rejections is not available.

KUH Neurosurgery maintains a database on all cases of SAH or unruptured intracranial aneurysms (> 4.500) admitted to the KUH since 1980, retrospectively until 1989, and prospectively since 1990. The database is run by a dedicated full-time Research Coordinator who interviews all new cases of sIA and aSAH, and collects detailed information, including family history for sIA disease. Clinical data from the hospital periods and follow-up visits are also entered. The criteria for an sIA family is at least two affected first-degree relatives. Data of the sIA patients from national registries have been fused in to the Database, including time and causes of deaths, hospital discharge diagnoses, and the use of prescribed medicines before and after the sIA-SAH diagnosis. A matched control cohort, with three citizen controls for each sIA-SAH patient from the KUH catchment area (gender; year of birth; alive at the time of sIA-SAH; place of residence), has been formed for sIA-SAH patients, also including information from the national registries.

*Kuopio Epilepsy Center (www.psshp.fi/neurocenter and www.finnhealth.fi)*

The national Kuopio Epilepsy Center at the Kuopio University Hospital provides diagnostics, improved AED
therapy and epilepsy surgery for the patients with intractable epilepsy in Finland. The multidisciplinary epilepsy team contains over 20 experts from Neurology, Neurophysiology, Neurosurgery, Neuroradiology and Neuropathology. About 120 patients with intractable epilepsy are evaluated yearly, and some 20-30 undergo epilepsy surgery. Kuopio Epilepsy Center aims to increasingly function as center for both basic and applied neuroscience on University of Eastern Finland (UEF) campus, utilizing the unique window to the living brain provided by modern epileptology and epilepsy surgery.

Kuopio Epilepsy Center belongs to the European Reference Network for Rare and Complex Epilepsies established by the European Commission

2.2 SUBARACHNOID HEMORRHAGE FROM RUPTURED SIA (SIA-SAH)

2.2.1 Incidence of sIA-SAH

A recent meta-analysis studied the incidence of SAH with an emphasis on trends in region, age, gender, and time. The overall incidence of sIA-SAH is approximately 9 per 100,000 person-years, but this figure may differ between regions (de Rooij et al. 2007). In populations with a mean age of 35, the incidence of sIA-SAH was 8.6 per 100,000, and with every one-year increase in the mean age, the incidence increased by 1.06 times (de Rooij et al. 2007). The overall incidence of aSAH was higher in women (11.5) than men (9.2) (de Rooij et al. 2007). However, among patients between 25 and 45 years of age, the incidence of sIA-SAH was higher in men than in women (de Rooij et al. 2007).

A recent study determined the nationwide incidence of SAH and sIA-SAH in Finland: 6.2 and 10.0 per 100,000 person-years, respectively (Korja et al. 2016). The incidence of aSAH in Finland seems to be decreasing, which may be due to the decrease in smoking rates (Korja et al. 2016). However, the incidence increased with age and was highest among women aged 70 to 75 (Korja et al. 2016).

2.2.2 Risk factors for sIA-SAH

The strongest independent factors for lifetime risk of sIA-SAH are smoking, family history of sIA or SAH (one first-degree relative who was affected), and hypertension (Vlak et al. 2013). Lifetime risk can be further increased if positive family history is combined with hypertension or smoking (Vlak et al. 2013).

Smoking

Smoking is a significant modifiable risk factor for sIA-SAH. The risk is considerably higher for current smokers compared to former smokers or those who have never smoked, and for former smokers compared to those who have never smoked (Feigin et al. 2005, Anderson et al. 2004). In a recent study, the joint effect of smoking and hypertension on the risk of sIA-SAH was found to be stronger than the independent effects of other risk factors (Lindekleiv et al. 2012).

Hypertension

Hypertension is a modifiable risk factor that increases the risk of sIA-SAH by 2.5 times higher compared to population without hypertension (Feigin et al. 2005). The risk is 3.3
times higher in women than in controls, according to a meta-analysis of risk factors for sIA-SAH (Feigin et al. 2005).

**Excessive alcohol intake**

Excessive alcohol intake is a modifiable risk factor for sIA-SAH; consumption of more than 150g of alcohol per week is associated with increased risk of sIA-SAH (Feigin et al. 2005). The risk is higher in women that consume more than 150g of alcohol per week than in men who consume the same amount (Feigin et al. 2005).

**Female gender**

Female gender was found to be an independent predictor of sIA-SAH in a large population-based study from Finland (Korja et al. 2013a). The risk of sIA-SAH was increased when women were associated with other risk factors, like smoking and high systolic blood pressure (Korja et al. 2013a). A prospective population-based cohort study showed that the risk of sIA-SAH was higher in female smokers than in male smokers and non-smokers (Lindekleiv et al. 2012).

**Positive family history of SAH**

Approximately 10% of sIA-SAH patients have a positive family history of sIA-SAH (Ronkainen et al. 1997, Ronkainen et al. 1999, Huttunen et al. 2010). This factor increases the risk of sIA-SAH four-fold (Vlak et al. 2013).

### 2.2.3 Clinical features of sIA-SAH

The most characteristic symptom of sIA-SAH is rapid onset of headache, and it is the only symptom for approximately one-third of sIA-SAH patients. It is often described as the worst headache they ever had (van Gijn et al. 2007). Seizure occurs at the onset of sIA-SAH in 7.8% of patients (Butzkueven et al. 2000), and two-thirds of patients temporarily suffer from decreased consciousness (van Gijn et al. 2007). Focal neurological symptoms are possible symptoms of sIA-SAH due to intracerebral hematomas, vasoconstriction, or compression of cranial nerves by large sIAs (van Gijn et al. 2007). Intraocular hemorrhages

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**Hunt and Hess scale**

<table>
<thead>
<tr>
<th>grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic, mild headache, slight nuchal rigidity</td>
</tr>
<tr>
<td>II</td>
<td>Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy</td>
</tr>
<tr>
<td>III</td>
<td>Drowsiness, confusion, mild focal neurologic deficit</td>
</tr>
<tr>
<td>IV</td>
<td>Stupor, moderate-severe hemiparesis</td>
</tr>
<tr>
<td>V</td>
<td>Coma, decerebrate posturing</td>
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*Figure 2. Hunt and Hess scale for evaluating the clinical condition on admission of sIA-SAH.*
occur in 11%-13% of sIA-SAH patients (McCarron et al. 2004, Koskela et al. 2014). The most common scale for evaluating patients’ clinical condition upon admission to a hospital for sIA-SAH is the Hunt and Hess scale (Figure 2) (Hunt & Hess 1968).

2.2.4 Diagnosis of sIA-SAH

Non-contrast computed tomography (CT) is the first diagnostic imaging procedure that is performed when sIA-SAH is clinically suspected. Subarachnoid blood is almost always detectable by CT shortly after bleeding (Boesiger & Shiber 2005, Cortnum et al. 2010). CTA with iodinated contrast should follow non-contrast CT as it is highly sensitive and used to detect aneurysms (Lu et al. 2012). In cases of negative CT and unconfirmed diagnosis of sIA-SAH, lumbar puncture should be performed when sIA-SAH is strongly suspected. Cerebral four-vessel angiography is the best procedure for verifying sIA-SAH or excluding other possible etiologies of cerebrovascular bleeding, and when performed by neurointerventionalists, it is associated with a low complication rate (0.30%) (Fifi et al. 2009).

2.2.5 Complications of sIA-SAH

_Elevated intracranial pressure_

Up to 54% of SAH patients present with elevated intracranial pressure (> 20 mm Hg) after onset of SAH (Heuer et al. 2004). High intracranial pressure is a common complication after rupture of an intracranial aneurysm. It may also be due to the amount of blood seen on the initial CT, rebleeding of the aneurysm, acute brain ischemia, severe brain injury, intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), or acute hydrocephalus (Heuer et al. 2004, Zoerle et al. 2015).

_Acute hydrocephalus_

Approximately 20% of SAH patients present with acute hydrocephalus, which is often associated with intraventricular hemorrhage and impaired consciousness. Consciousness can be impaired immediately or gradually one to two days after the onset of hemorrhage (van Gijn et al. 2007, Hasan et al. 1989, Hasan et al. 1991).

_Acute seizures_

Acute symptomatic seizures are distinguished from unprovoked seizures. An acute symptomatic seizure is defined as a clinical seizure occurring within one week of a systemic insult like SAH (Beghi E et al. 2010). Acute seizures correlate with the sum score of blood on the initial CT scan (Butzkueven et al. 2000). More acute seizures are an independent risk factor for late seizures and poor outcomes after SAH (Butzkueven et al. 2000).

Generalized convulsive status epilepticus among patients with SAH is rare, occurring in approximately 0.2% of the patients, as is non-convulsive status epilepticus (Claassen et al. 2007, Little et al. 2007). Status epilepticus is associated with increased patient mortality (Claassen et al. 2007).
Delayed cerebral ischemia

Delayed cerebral ischemia is a relatively frequent complication of SAH, occurring in approximately in 30% of SAH patients, usually four to ten days after subarachnoid hemorrhage (Dorsch 2002, Roos et al. 2000, Vergouwen et al. 2010). It significantly contributes to poor outcomes after subarachnoid hemorrhage (Dorhout Mees et al. 2012, Rabinstein et al. 2004). According to the international subarachnoid aneurysm trial (ISAT), it is more common after surgical clipping of a ruptured aneurysm than after endovascular occlusion of the ruptured aneurysm (Dorhout Mees et al. 2012). A systematic review of predictors of delayed cerebral ischemia found strong evidence supporting the fact that smoking is a risk factor. In addition, moderate evidence was found supporting the fact that history of diabetes mellitus, early systemic inflammatory response syndrome, hyperglycemia upon admission to a hospital, and hydrocephalus are predictors of delayed cerebral ischemia (de Rooij et al. 2013). The symptoms of delayed cerebral ischemia are clinical deterioration, impaired consciousness, and focal neurological signs (Roos et al. 2000, Bacigaluppi et al. 2015). Diagnosis is achieved based on clinical signs, CT angiography, or digital subtraction angiography, which identifies narrowing of cerebral arteries and dynamic changes in cerebral circulation (Bacigaluppi et al. 2015). In addition, perfusion CT can be used as a relative perfusion measurement to diagnose delayed cerebral ischemia (Dankbaar et al. 2009).

Medical complications

Medical complications are common during the acute phase of sIA-SAH. In a large multicenter study, 40% of patients experienced at least one severe medical complication (Solenski et al. 1995). Life-threatening cardiac arrhythmia occurred in 5%, and less severe disturbances in cardiac rhythm occurred in 30% of patients (Solenski et al. 1995). Severe pulmonary edema occurred in 6%, and pulmonary edema occurred in 23% (Solenski et al. 1995).

Another study (Wartenberg & Mayer 2006) that intended to determine the rate of common medical complications after sIA-SAH found that fever occurred in 54% of patients, anemia in 36%, hyperglycemia in 30%, hypertension in 27%, pneumonia in 20%, hypotension in 18%, and hyponatremia in 14% (Wartenberg & Mayer 2006, Wartenberg et al. 2006a).

2.2.6 Management of sIA-SAH

Neurointensive care of sIA-SAH

Acute aSAH is a severe complex systemic condition that requires treatment by a neurointensive care unit with a dedicated team of neurointensivists, neurosurgeons, neuroradiologists and neuronurses. Thorough understanding of the natural course of sIA-SAH and multimodality monitoring for intra- and extracranial complications are required for successful treatment. The treatment aims to prevent further damage due to re-bleeding, hydrocephalus, increased intracranial pressure, seizures, electrolyte disturbances, fever, hyperglycemia, cardiac and pulmonary dysfunction, and subacute development of delayed ischemic brain injury (Diringer et al. 2011, Steiner et al. 2013b, Wartenberg & Mayer 2006, Levine 2009).
Occlusive sIA-SAH therapy

The risk of acute re-bleeding of a ruptured sIA is as high as 15% in the first few hours (‘hyperacute’ re-bleeding) (Ohkuma et al. 2001). Re-bleeding is associated with increased mortality rates (Larsen & Astrup 2013), and thus ruptured sIAs should be occluded from the circulation as soon as possible to avoid re-bleeding. Ruptured sIAs can be occluded by open microsurgical clipping or by endovascular techniques (Steiner et al. 2013a, Pyysalo et al. 2010, Niskanen et al. 2004, Bendel et al. 2006). The method should be chosen by neurosurgeons and neuroradiology interventionists in a dedicated neurovascular group.

Hydrocephalus after sIA-SAH

Hydrocephalus requiring shunt diversion of CSF occurs in approximately 18% of survivors of the acute phase of sIA-SAH (Adams et al. 2016). Hydrocephalus after sIA-SAH is strongly predicted by intraventricular hemorrhage (IVH) and by extraventricular catheter drainage for acute hydrocephalus during the acute phase of sIA-SAH (Adams et al. 2016). Therapies for permanent cerebrospinal fluid diversion include ventriculoatrial shunt, ventriculoperitoneal shunt, and lumboperitoneal shunt (Bederson et al. 2009).

2.3 OUTCOME OF SIA-SAH

2.3.1 Short-term (12-month) outcome of sIA-SAH

A recent population-based study focused on the outcomes of SAH patients one year after onset of the disease using Short Form 36 (Hackett & Anderson 2000). In comparison with age- and sex-adjusted populations, the health-related quality of life (HRQoL) of SAH patients was significantly lower due to role limitations caused by physical problems. Of the interviewed SAH patients, 46% reported incomplete recovery and ongoing problems with memory, mood, speech, and self-care (Hackett & Anderson 2000).

Another prospective study investigated psychosocial outcomes at three and nine months after good neurological recovery from SAH. Patients were matched with healthy controls in terms of age, sex, and occupation (Powell et al. 2002). In comparison to the controls, SAH patients showed increased mood disturbance, subtle cognitive impairment, and abnormally low independence and social functioning (Powell et al. 2002).

A population-based study from Eastern Finland investigated risk factors of 12-month mortality in 1,657 patients after acute aneurysmal subarachnoid hemorrhage (Karamanakos et al. 2012). sIA-SAH caused excess mortality for 12 months after onset, and after that, other causes of death became dominant. The cumulative rates of mortality were 11% at 3 days, 22% at 30 days, and 27% at 12 months after onset of sIA-SAH. Advanced age, Hunt and Hess grades of IV–V, intraventricular hemorrhage, giant ruptured sIA, ruptured saccular IA on the internal carotid artery or basilar artery bifurcation, and severe hydrocephalus predicted mortality more than three days after onset of SAH (Karamanakos et al. 2012).

2.3.2 Long-term outcome of sIA-SAH survivors

A prospective study of 546 consecutive patients from Southern Finland analyzed the clinical data and neuropsychological results of SAH patients approximately one year after onset to predict their work status and HRQoL 9–13 years after onset of SAH (Vilkki et al.
Lower self-ratings of the functional and emotional impairment of patients and their partners predict poor work status and lower HRQoL about 10 years after onset of SAH (Vilkki et al. 2012).

A retrospective population-based study from Eastern Finland with data from the national registries analyzed the long-term excess mortality of patients one year after onset of SAH compared to a matched Eastern Finnish catchment population (Huttunen et al. 2011). The researchers found 12% excess mortality at 15 years after sIA-SAH. Independent risk factors for mortality were male gender, at least 64 years of age, ruptured basilar tip sIA, severe hydrocephalus upon admission to a hospital, a lack of occlusive therapy, and ratings of 2, 3, or 4 on the Glasgow Outcome Scale at 12 months after onset of SAH (Huttunen et al. 2011).

A retrospective population-based study from Southern Finland with data from national registries analyzed the long-term excess mortality of patients who survived one year after onset of SAH with a matched general population (Huhtakangas et al. 2015). After 20 years, SAH patients showed 17% excess mortality in comparison to the general population. The highest excess mortality was found among patients with multiple aneurysms, old age, poor preoperative clinical condition, conservative aneurysm treatment, and unfavorable clinical outcomes at one year after onset of SAH according to the Glasgow Outcome Scale (Huhtakangas et al. 2015).

2.4 EPILEPSY AFTER SIA-SAH

2.4.1 Definition of epilepsy

According to the definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain (Fisher et al. 2005, 2014). The presentation of the seizure depends on the location of onset in the brain. These seizures can affect individuals’ senses, motor and autonomic functions, consciousness, emotional state, memory, cognition, and behavior (Fisher et al. 2005).

Epilepsy is characterized by an enduring predisposition of the brain to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition (Fisher et al. 2014). To be classified as epileptic, an individual must have had at least one epileptic seizure ((Fisher et al. 2014). Currently, epilepsy is considered to be a disease of the brain, and it is defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring less than 24 hours apart, (2) one unprovoked (or reflex) seizure and a probability of further seizures over the next ten years that is similar to the general risk of seizure recurrence (at least 60%) after two unprovoked seizures, and (3) diagnosis of an epilepsy syndrome (Fisher et al. 2014).

Acute symptomatic seizures are defined as seizures that are secondary to substance (including alcohol) abuse or withdrawal or within a week due to an acute illness (Beghi et al. 2010). They do not fulfill the criteria needed for a diagnosis of epilepsy (Beghi et al. 2010).
2.4.2 Incidence of epilepsy after sIA-SAH

There are various difficulties related to reliably determining the incidence of epilepsy in sIA-SAH survivors because prospective studies have limited follow-up times and retrospective studies cannot accurately identify epilepsy patients by only reviewing the patient files.

Between 1958 and 1962, Rose et al. analyzed the cases of 1,009 aSAH patients and found a 10.4% incidence of epilepsy among 508 six-month survivors after retrospective evaluation. They also re-examined a sample series at a follow-up clinic that consisted of 137 survivors of aSAH admitted to a neurosurgical unit between July 1 and December 31 1960. In total, 61 patients attended follow-up examinations, and 14.8% had suffered from epilepsy (Rose & Sarner 1965).

A prospective study from the Kuopio University Hospital catchment area analyzed 177 consecutive patients with acute aSAH between 1977 and 1980. Symptomatic epilepsy was found in 14% of these patients. The mean latency for development of epilepsy was 8.4 months (Keranen et al. 1985a).

Previous studies reported incidences of epilepsy ranging from 0.9% to 25% (Byrne et al. 2003, Claassen et al. 2003, Olafsson et al. 2000a). A study from USA showed similar incidence of epilepsy was found when comparing treatment modalities, clipping and coiling as treatments for aSAH in Nationwide Inpatient Sample Database between 2002 and 2007 (Hoh et al. 2011). To our knowledge, Olafsson et al. were the only researchers to perform a retrospective population-based study to investigate the incidence of epilepsy after aSAH. They identified all SAH cases caused by ruptured intracranial aneurysms diagnosed in Iceland between 1958 and 1968. They included patients who survived six months after aSAH, and 25% of them developed epilepsy. Of them 73% developed epilepsy during the first year after onset of SAH, and 27% developed epilepsy one to four years after onset (Olafsson et al. 2000a). Claassen et al. conducted a prospective study with SAH patients admitted to the hospital between 1996 and 2001. They had 12-month follow-up time. Of the 247 patients included in the study who suffered from aSAH, 7% suffered from epilepsy (Claassen et al. 2003). Another single-institute, single-operator observational study reported an epilepsy incidence of 0.85% among ruptured aneurysm patients treated with endovascular coil embolization (Byrne et al. 2003).

2.4.3 Risk factors for epilepsy after sIA-SAH

Previous studies report independent risk factors for sIA-SAH relating to patient characteristics, such as young age, hypertension, and ruptured aneurysm in the medial cerebral artery, or the impact of rupture of an aneurysm, including initial loss of consciousness, high amount of cisternal blood, intracerebral hemorrhage, subdural hemorrhage, acute seizures, vasospasm, and rebleeding (Bidzinski et al. 1992, Buczacki et al. 2004, Butzkueven et al. 2000, Choi et al. 2009, Claassen et al. 2003, Lin et al. 2003, Lin et al. 2008, Keranen et al. 1985b, Ukkola & Heikkinen 1990a). One prospective study (see above) identified subdural hematoma and ischemia as independent risk factors for epilepsy (Claassen et al. 2003).
2.4.4 Mortality related to epilepsy after sIA-SAH

To date, excess mortality among sIA-SAH patients with epilepsy has not been studied. Our aim was to study and determine whether excess mortality occurs among patients who developed epilepsy after sIA-SAH compared to patients without epilepsy. We were especially interested in determining whether epilepsy could partially explain excess mortality after sIA-SAH.

Previous population-based studies have reported the long-term excess mortality rates of survivors of sIA-SAH (Huttunen et al. 2011, Huhtakangas et al. 2015). Potential risk factors for excess mortality after sIA-SAH include male gender, advanced age, and outcome after treatment of sIA-SAH (Huttunen et al. 2011, Huhtakangas et al. 2015). Vascular diseases may explain the increased mortality after sIA-SAH as well (Nieuwkamp et al. 2014, Nieuwkamp et al. 2011, Korja et al. 2013b).

Excess mortality among epileptic individuals is a well-recognized phenomenon (Nevalainen et al. 2014, Nevalainen et al. 2013, Neligan et al. 2010, Neligan et al. 2011). The etiology of symptomatic epilepsy is associated with increased mortality (Olafsson et al. 1998, Lhatoo et al. 2001). A substantial proportion of sIA-SAH patients develop epilepsy after SAH (Claassen et al. 2003, Olafsson et al. 2000a). The mortality risk of epilepsy patients in the first few years after receiving a diagnosis is increased, possibly due to the etiology of epilepsy (Neligan et al. 2010, Trinka et al. 2013, Forsgren et al. 2005). Late mortality of epilepsy patients may be attributed to epilepsy itself (e.g., accidents, treatment-related deaths, suicide, and sudden unexpected death related to epilepsy), but this is still unproven (Neligan et al. 2010, Forsgren et al. 2005, Jansson & Ahmed 2002, Fazel et al. 2013).

Lindsten et al. linked their prospective cohort to the Swedish Cause of Death Register between 1985 and 1987 to obtain information about epilepsy patients’ date of death and to determine the underlying and contributory causes of death. They examined 107 patients with unprovoked seizures, and the follow-up time was 850 person-years. Patients with symptomatic seizures had elevated risk of death, and cerebrovascular disease contributed significantly to increased mortality (Lindsten et al. 2000).

Lhatoo et al. conducted a prospective, population-based study of mortality of epilepsy patients and reported significantly elevated mortality among those with symptomatic epilepsy (Lhatoo et al. 2001). Recurrent seizures and AED treatment were not found to be significant time-related factors affecting mortality. The cohort included 792 patients from United Kingdom, and the follow-up time was 11,400 person-years (Lhatoo et al. 2001).

A French study determined the mortality rate after individuals’ first seizure, provoked or unprovoked, in a prospective population-based study. Outcomes were assessed one year after seizure. The SMR for symptomatic seizures was 19.8, and the CI was 14.0–27.3. The SMR for remote symptomatic seizures was 6.5 (Loiseau et al. 1999, Loiseau et al. 2005).

Olafsson et al. conducted a population-based study and identified 224 cases of unprovoked seizures in Iceland. They identified all cases of unprovoked seizures between 1960 and 1964. They determined survivorship and date of death for the cases 30 years after diagnosis of unprovoked seizures. Mortality was increased among patients with symptomatic seizures, primarily during the first 15 years after diagnosis of unprovoked seizures (Olafsson et al. 1998).
2.5 DEPRESSION AFTER SIA-SAH

2.5.1 Incidence of depression after sIA-SAH

There are no previous studies that focus on antidepressant use and epilepsy among patients that survived sIA-SAH. Depression makes it difficult for sIA-SAH patients to rehabilitate and recover, and it affects the treatment of epilepsy unfavorably (Hellawell et al. 1999, Hedlund et al. 2011, Springer et al. 2009). According to one study, there is a 23% risk of depression after aSAH (Visser-Meily et al. 2009).

A study focusing on anxiety and depression among SAH survivors reported that anxiety developed in 40% of survivors and depression developed in 20%. The risk factors for depression and anxiety identified by univariate analysis included not returning to work, an inability to engage in social activities, and Grade 4 on the Fisher scale (Morris et al. 2004).

2.5.2 Risk factors for depression after sIA-SAH

A Swedish study prospectively analyzed 83 consecutive patients with acute SAH, admitted between 2002 and 2005 from a total population of 325 to determine those patients' psychiatric outcomes at seven months, especially for patients who were expected to have good prognosis. They used the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) to perform the analysis. The risk of depression was determined to be 25% (21 sIA-SAH patients). Independent risk factors included history of major depression, history of anxiety disorder, history of substance use disorder, history of any psychiatric disorder, and psychiatric comorbidity (Hedlund et al. 2011).

A Swedish retrospective study with ten year follow-up period determined the psychological outcomes of 217 of 468 consecutive SAH patients using the Hospital Anxiety and Depression Scale (HADS). SAH was diagnosed between 1996 and 1999. According to HADS, the risk of depressive symptoms was 23.5% (51 patients) and the only independent risk factor was aneurysm rupture in posterior circulation structures (von Vogelsang et al 2013). Another Swedish study analyzed depressive symptoms among 755 patients from a prospective database using the Euro-Qol-5D. The risk of depressive symptoms was 51% (384 patients) at 12 months after onset of SAH. Independent risk factors were female gender and signs of more severe disease (Ronne-Engstrom et al. 2013).

One prospective study performed in the United States examined depression in 216 of 534 sIA-SAH patients at 12 months after onset of SAH using information obtained from the Center for Epidemiological Studies-Depression (CES-D). SAH was diagnosed between 1996 and 2001. The risk of depressive symptoms was 33%, and the independent risk factors included non-white ethnicity, lack of health insurance, and premorbid social isolation (Kreiter et al. 2013).

2.5.3 Co-occurrence of depression and epilepsy after sIA-SAH

Depression and sIA-SAH

Patients recovering from sIA-SAH often suffer from depressive symptoms (Hellawell et al. 1999, Visser-Meily et al. 2009). Depression after aSAH can have severe consequences for patients as mood disturbances can cause setbacks in the rehabilitation process. To our
knowledge, no previous studies have focused on epilepsy as a risk factor for depression among patients who survived aSAH.

Hutter et al. analyzed the quality of life of 128 of 185 consecutive SAH patients between 1989 and 1992. They reported that higher Hunt & Hess Grade upon admission to a hospital and age were predictors of impairment in individuals’ daily lives after SAH (Hutter et al. 1999, Hutter et al. 2001).

Passier et al. reported a correlation between cognitive complaints and depression and reported that emotional problems, including depression, are strongly correlated to fatigue after aSAH. They also reported that life satisfaction was negatively influenced by depression (Passier et al. 2012, Passier et al. 2010, Passier et al. 2013, Passier et al. 2011).

**Depression and epilepsy**

Epilepsy is a risk factor for depression and anxiety. In addition, high seizure frequency, female gender, and symptomatic epilepsy syndrome were independent risk factors for depression and anxiety among epilepsy patients (Kimiskidis et al. 2007). Attarian et al. reported that there is no difference in the prevalence of depression among intractable epilepsy patients and epilepsy patients with good seizure control (Attarian et al. 2003).

The prevalence of depression among epilepsy patients is relatively high (36.5%) and associated with factors not related to epilepsy. In Ettinger et al.’s study, 22.2% of epilepsy patients were using anti-depression medication. The risk factors for depression among epilepsy patients were identified as sex (female), income (low), and age (young). They also reported that diminished quality of life due to chronic disorders such as epilepsy was closely tied to depression (Ettinger et al. 2004).

Fuller-Thomson et al. investigated a nationally representative sample of patients in Canadian Community Health Survey and found the prevalence of depression among patients with epilepsy to be 13.0%, compared to 7.2% among patients without epilepsy. Their analysis showed that sex (female), food insecurity, and low total household income were independent risk factors for depression after epilepsy (Fuller-Thomson & Brennenstuhl 2009).

Seminario et al. studied all patients seen in the epilepsy clinics, over the 6-month in 2005 in a single center study. They reported that 29.3% of epilepsy patient suffered from depression, more than half of whom were not taking antidepressant medication. Similarly, patients with persistent seizures had higher scores on depression scales. In this study, there was a significant difference between seizure types, symptomatic epilepsy had no preponderance (Seminario et al. 2009).

Grabowska-Grzyb et al. reported a depression prevalence of 49.2% among 203 epilepsy patients from single hospital from Poland. Independent risk factors for depression among patients with epilepsy included complex partial seizures and absence of tonic-clonic seizures, and a preponderance of complex partial seizures was observed (Grabowska-Grzyb et al. 2006).

Mensah et al. conducted a population based study to explore depression prevalence in epilepsy patients. They identified unemployment, poor seizure control, and side effects of AEDs as independent risk factors for depression and reported an 11.2% prevalence of depression among epilepsy patients. The prevalence of depression was higher among
patients with active epilepsy than those whose epilepsy was in remission (Mensah et al. 2006).

Epilepsy patients’ quality of life is affected by comorbid diagnosis of depression. Cramer et al. conducted a survey study of people with epilepsy among community-based neurology practices across the United States. The survey was completed by 201 epilepsy patients. They reported that 38% and 48% of partial epilepsy patients taking two or more antiepileptic drugs suffered from depression and anxiety, respectively, and that quality of life decreased with increasing levels of anxiety and depression (Cramer et al. 2005). Boylan et al. examined the predictors of quality of life among patients with treatment-refractory epilepsy in a prospective study. The data was collected from 2001 to 2002. They found that 54% of patients with refractory epilepsy had depression and 17% used anti-depressant medication. Rather than seizure frequency, depression was found to be a predictor of lower quality of life (Boylan et al. 2004).
3 Aims of the Study

3.1 AIMS OF THE STUDY

There are large amount of survivors of sIA-SAH now living in Finland. There are no longterm follow up data on their neurological morbidity and concomitant diseases (e.g., epilepsy or depression) as compared to matched catchment populations.

The specific aims:

I. To elucidate the incidence and risk factors of epilepsy after subarachnoid hemorrhage from saccular intracranial aneurysm (sIA-SAH) in a defined population based cohort.

II. To elucidate the factors associated with antidepressant (ATD) use after subarachnoid hemorrhage from saccular intracranial aneurysm (sIA-SAH) in a defined population-based cohort with matched controls.

III. To elucidate the epilepsy-associated causes of death and subsequent excess long-term mortality in the 12-month survivors of sIA-SAH in a defined population-based cohort with matched controls.
4 Epilepsy after aneurysmal subarachnoid hemorrhage— a population based long-term follow up study

4.1 INTRODUCTION

Aneurysmal subarachnoid hemorrhage, almost always from a rupture of a saccular intracranial aneurysm (sIA-SAH), affects working age population (Nieuwkamp et al. 2009). The reported incidence is 4 to 7 per 100,000 (Feigin et al. 2009) but is three times higher in Finland (de Rooij et al. 2007). Along with various degrees of acute or delayed brain injury, sIA-SAH may cause systemic manifestations complicating the management (Diringer et al. 2011). Subsequent mortality is high, 22% at one month and 27% at 12 months in our series of 1,657 patients, mainly due to poor condition and signs of brain injury on admission (Karamanakos et al. 2012).

The risk of epilepsy after sIA-SAH has not been studied in large unselected populations. Previous studies report risks from 0.9% to 25% (Byrne et al. 2003, Olafsson et al. 2000b) and independent risk factors such as younger age, hypertension, middle cerebral artery aneurysm, initial loss of consciousness, high amount of cisternal blood, intracerebral hemorrhage, subdural hemorrhage, acute seizures, re-bleeding, and delayed ischemic deficits (Bidzinski et al. 1992, Butzkueven et al. 2000, Choi et al. 2009, Claassen et al. 2003, Lin et al. 2003, Lin et al. 2008, Ohman 1990, Keranen et al. 1985a, Ukkola & Heikkinen 1990b). The problem of two dependent risks, risk factors shared by epilepsy and death, has not been addressed.

The Kuopio sIA Database (www.uef.fi/ns) includes all cases of unruptured and ruptured sIA admitted to the Kuopio University Hospital from its Eastern Finnish catchment population (Huttunen et al. 2010). Data on prescribed medicines, hospital diagnoses, and causes of death are included from the national registries (Huttunen et al. 2011, Huttunen et al. 2010, Lindgren et al. 2014, Lindgren et al. 2013). In the present study, we analysed the cumulative incidence and independent risk factors of epilepsy and death in 876 sIA-SAH patients from 1994 to 2007, alive at two weeks after admission, also applying the competing risks analysis methodology.

4.2 METHODS

4.2.1 Catchment population of KUH

Since 1977, Neurosurgery of Kuopio University Hospital (KUH) has solely provided full-time acute and elective neurosurgical services for the KUH catchment population in Eastern Finland. The KUH area consists of 4 central hospitals with neurological units and catchment areas of their own. During the recruitment period of the present study, 1995 to 2007, the geographic area has remained the same. The population has decreased from 882,671 to 842,931. The median age has increased from 37 to 42 years in men and from 40 to 45 years in women, and the proportion of men has remained unchanged at 49% (Huttunen et al. 2010).
4.2.2 Admission of patients with SAH to KUH
All cases of SAH diagnosed by spinal tap or CT at the KUH catchment area have been acutely admitted to KUH for angiography and treated if not moribund or very aged. The exact number of rejected SAH patients is not available.

4.2.3 Kuopio Neurosurgery Intracranial Aneurysm Database
The database (www.uef.fi/ns) includes all cases of unruptured and ruptured intracranial aneurysm patients admitted to KUH since 1980. The database has been prospective since 1990. The database is run by a dedicated full-time nurse coordinator who interviews all new patients. The criteria for familial saccular intracranial aneurysm (sIA) family are at least 2 affected first-degree relatives (Huttunen et al. 2010). The clinical data from the hospital periods and follow-up visits are coded into an extensive list of variables. The use of prescribed medicines (see below), other hospital diagnoses, and causes of death have been entered from the Finnish national registries (Huttunen et al. 2011, Huttunen et al. 2010, Lindgren et al. 2014, Lindgren et al. 2013). The phenotype, genetics, and outcome of Eastern Finnish sIA disease have been analyzed in several studies (Bilguvar et al. 2008, Gaal et al. 2012, Helgadottir et al. 2008, Karamanakos et al. 2010, Kurki et al. 2014, Kurki et al. 2011, Soppi et al. 2012, van ’t Hof et al. 2014, Yasuno et al. 2010).

4.2.4 Study population of 876 patients with sIA-SAH
The inclusion criteria were:
1. a citizen of Finland and resident of the KUH catchment area at the time of first sIA-SAH between January 1, 1995, and December 31, 2007;
2. verification of sIA(s) by angiography;
3. alive at two weeks after admission.
The exclusion criteria were: rupture of an intracranial aneurysm other than a saccular one (e.g., fusiform, traumatic, mykotic); previous diagnosis of epilepsy (n=14).
Figure 1 presents the flow chart from the basic to the final study cohort of 876 sIA-SAH patients.

4.2.4 Identification of patients with epilepsy after sIA-SAH
The Social Insurance Institution (SII) of Finland is an independent social security institution with its own administration and financing, supervised by the Finnish Parliament. The National Health Insurance (NHI) scheme is part of the Finnish social security system, and it is run by the SII. All permanent residents of Finland are covered under the NHI scheme. The SII maintains a nationwide registry for all patients who have been granted special reimbursement of medicines, including antiepileptic drugs (AEDs). In order to be reimbursed at the pharmacy for epilepsy, patients must submit Medical Certificate to the SII. The medical certificate must be based on examinations and diagnosis of epilepsy made by a neurologist. The entitlement to special reimbursement of AEDs is granted by SII for non-institutionalized patients. The following AEDs are reimbursed: carbamazepine, clobazam, clonazepam, fosphenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, nitrazepam, phenobarbital, phenytoin, pregabalin, rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide.

The case reports of the 876 sIA-SAH patients were reviewed for acute seizures, defined as clinically observed seizures within one week after the onset of sIA-SAH(Beghi et al. 2010). The data on fully reimbursed AEDs between January 1, 1994, and December 31, 2008 was integrated to the Kuopio sIA Database. The recruitment period between January 1, 1995, and December 31, 2007, allowed data on the use of AEDs for at least one year before and after sIA-SAH. We identified 378 AED users among the 876 sIA-SAH patients (Figure 1). Their hospital diagnoses and case reports from all neurology units in the KUH catchment
area during the follow-up were reviewed. None was lost to the follow-up. In the present study, the criteria for the epilepsy diagnosis after sIA-SAH in the AED users, evaluated by neurologist(s), followed the current ILAE definition (Fisher et al. 2014): (a) at least two unprovoked seizures occurring >24 h apart or (b) one unprovoked seizure and high probability of further seizures due to, for example, brain infarct, intracerebral hemorrhage or status epilepticus (Figure 1). Acute seizures within one week after the onset of sIA-SAH were not considered as unprovoked seizures.

4.2.4 Statistical analysis

The clinical variables of the 876 sIA-SAH patients are presented in Table 1. Discrete variables were expressed in proportions and continuous variables in medians, quartiles and ranges. Groups were compared using the χ2 test or the Mann-Whitney U or Kruskal-Wallis tests when appropriate.

The Kaplan-Meier analysis was used to calculate the cumulative mortality rate after sIA-SAH, and the independent risk factors for death were calculated using the Cox proportional hazards model.

The cumulative incidences of epilepsy after sIA-SAH (Figure 2) were calculated with the competing risks analysis method (cprisk R package), because epilepsy and death after sIA-SAH may share risk factors. Likewise, the independent risk factors for epilepsy after sIA-SAH were calculated by the competitive risks cause-specific hazards Cox model(Putter et al. 2007) (Table 2). In these analyses, the patients who died within two weeks from the rupture of sIA (n=169) were excluded. P values <0.05 were considered significant. SPSS 19.0 for Mac (SPSS, Inc, Chicago, IL) and R program were used.

4.2.4 Standard protocol approvals, registrations, and patient consents

The study was approved by the Ethical Committee of the Kuopio University Hospital. Data integration from the national registries was performed with the approval from the Ministry of Social Affairs and Health of Finland.
4.3 RESULTS

4.3.1 Study population
Altogether 876 patients with no previous epilepsy had been alive at two weeks after admission for first sIA-SAH to KUH between January 1, 1995, and December 31, 2007 (Figure 3). Their follow up ended at death (n=200) or December 31, 2008: total follow up 5,616 person years and a median follow up time 76 months. Table 1 presents their characteristics and the variables tested for the competing risks of death or epilepsy after sIA-SAH.

Figure 3. Flowchart of the identification of patients with epilepsy after subarachnoid hemorrhage from saccular intracranial aneurysm (sIA-SAH) among 1,045 patients admitted alive to the Kuopio University Hospital (KUH) from its Eastern Finnish catchment population between 1995 and 2007. The 113 patients with epilepsy were identified according to the use of antiepileptic drugs (AEDs) from the national registry and the diagnoses were verified by neurologists.

4.3.2 Risk factors of mortality after sIA-SAH in 876 two-week survivors
The cumulative mortality rate for the 876 two-week survivors was 6% at one month since their admission, 9% at six months, 11% at one year, 12% at two years, and 34% at five years. The independent risk factors for death were: male gender (HR 2.1); one year increase in age at diagnosis of sIA-SAH (HR 1.07); ruptured sIA on the basilar artery bifurcation (HR 3.2); intraventricular haemorrhage (HR 1.5); severe hydrocephalus (HR 2.0); Hunt and Hess grade 5(Hunt & Hess 1968) (HR 2.9); conservative treatment (HR 3.0).
Table 1. Characteristics of 876 patients alive after two weeks after subarachnoid haemorrhage from saccular intracranial aneurysm (sIA-SAH) between 1995 and 2007 and cumulative incidence of epilepsy until the end of 2008 with the competing risks analysis (epilepsy vs death) from a defined Eastern Finnish catchment population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>876 sIA-SAH patients</th>
<th>Cumulative incidence of epilepsy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>113 epilepsy patients</td>
<td>At 1 year</td>
<td>At 5 years</td>
</tr>
<tr>
<td>Median age years (quartiles)</td>
<td></td>
<td>56 (46 – 66)</td>
<td>56 (45 – 64)</td>
<td>47 (43 – 55)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td>58 (%)</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td>57 (%)</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>Member of sIA family</td>
<td></td>
<td>22 (%)</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>H&amp;H grade I</td>
<td></td>
<td>9 (%)</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>H&amp;H grade II</td>
<td></td>
<td>30 (%)</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>H&amp;H grade III</td>
<td></td>
<td>39 (%)</td>
<td>11%</td>
<td>17%</td>
</tr>
<tr>
<td>H&amp;H grade IV</td>
<td></td>
<td>27 (%)</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td>H&amp;H grade V</td>
<td></td>
<td>8 (%)</td>
<td>21%</td>
<td>24%</td>
</tr>
<tr>
<td>No ICH</td>
<td></td>
<td>55 (%)</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>ICH &lt;15 cm²</td>
<td></td>
<td>14 (%)</td>
<td>9%</td>
<td>17%</td>
</tr>
<tr>
<td>ICH ≥15 cm²</td>
<td></td>
<td>43 (%)</td>
<td>21%</td>
<td>33%</td>
</tr>
<tr>
<td>IVH on admission</td>
<td></td>
<td>29 (%)</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Moderate hydrocephalus</td>
<td></td>
<td>38 (%)</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Severe hydrocephalus</td>
<td></td>
<td>5 (%)</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>No acute seizures</td>
<td></td>
<td>78 (%)</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Acute seizures</td>
<td></td>
<td>35 (%)</td>
<td>14%</td>
<td>25%</td>
</tr>
<tr>
<td>Site of ruptured sIA</td>
<td></td>
<td>24 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AComA</td>
<td></td>
<td>16 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no ICH</td>
<td></td>
<td>16 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with ICH</td>
<td></td>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2-A5</td>
<td></td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td></td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mbif</td>
<td></td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no ICH</td>
<td></td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with ICH</td>
<td></td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PComA</td>
<td></td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA bif</td>
<td></td>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAbif</td>
<td></td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PICA</td>
<td></td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of ruptured sIA (mm)</td>
<td></td>
<td>40 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td></td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-14</td>
<td></td>
<td>49%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15</td>
<td></td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sIAs (≥2)</td>
<td></td>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microsurgical clipping</td>
<td></td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular occlusion</td>
<td></td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative therapy</td>
<td></td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt after sIA-SAH</td>
<td></td>
<td>15%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: sIA-SA H = subarachnoid haemorrhage from saccular intracranial aneurysm; sIA = saccular intracranial aneurysm; H&H = Hunt and Hess scale; ICH = intracerebral hematoma; IVH = intraventricular hematoma; AComA = anterior communicating artery; A2-A5 = A2-A5 segments of anterior cerebral artery; M1 = proximal segment of middle cerebral artery; Mbif = middle cerebral artery bifurcation; PComA = posterior communicating artery; ICA bif = internal carotid artery bifurcation; PICA = posterior inferior cerebellar artery; BAbif = basilar artery bifurcation; N.S. = not significant. *= number of microsurgically vs. endovascularly treated ruptured sIAs by location.
4.3.3 Epilepsy after sIA-SAH
Of the 876 two-week sIA-SAH survivors, 113 developed epilepsy, seizures since one week after sIA-SAH, according to both the AED purchases for epilepsy and the hospital case reports and diagnoses by neurologists (Figure 1). In overall, the median time to the epilepsy diagnosis was eight months (quartiles four and 17 months). The cumulative incidence of epilepsy after sIA-SAH – with death as the competing risk – was 4% at six months after admission, 8% at one year, 10% at two years, and 12% at five years (Figure 4A).

4.3.4 Impact of ICH
The presence and the volume of ICH on acute CT scan, a sign of tearing brain tissue injury, associated significantly with epilepsy after sIA-SAH (Table 1). The most frequent sites of ruptured sIA in the 855 treated patients were the anterior communicating artery (AComA) and the middle cerebral artery bifurcation (Mbif), and ICH of any volume occurred in 40 / 262 (15%) and 109 / 233 (47%) cases, respectively. The cumulative incidences of epilepsy are presented in Table 1.

4.3.5 Acute seizures
Acute seizures, within one week since sIA-SAH, occurred in 134 (15%) of the 876 two-week survivors (Table 1). Significant anatomical risk factors for acute seizures were intraventricular hemorrhage (OR 2.9; CI 95% 1.8-4.6) and intracerebral haemorrhage (OR 2.1; 1.3-3.5) while older age was associated with decreased risk of acute seizures (OR 0.97; 0.96-0.99). (Data not shown)

4.3.6 Independent risk factors for epilepsy after sIA-SAH
In multivariate analysis, Hunt and Hess grades III (HR 2.2) and IV-V (HR 2.6), large intracerebral hemorrhage (≥15cm³) (HR 1.9) and acute seizure (HR 2.3) remained independent risk factors of epilepsy after sIA-aSAH (Table 2). Figures 4B to 4D present the cumulative incidence rates of epilepsy with or without these risk factors.
Table 2. Independent risk factor for epilepsy using competitive risk (epilepsy vs death) regression analysis in 876 patients alive at two weeks after sIA-SAH.

<table>
<thead>
<tr>
<th>Variables</th>
<th>876 patients alive at two weeks after sIA-SAH</th>
<th>113 patients with epilepsy after sIA-SAH</th>
<th>P value</th>
<th>HR</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH &gt; 15cm³ on admission</td>
<td>110</td>
<td>43</td>
<td>0.02</td>
<td>1.9</td>
<td>1.1 - 3.6</td>
</tr>
<tr>
<td>Acute seizure *</td>
<td>134</td>
<td>35</td>
<td>&gt;0.001</td>
<td>2.3</td>
<td>1.5 - 3.8</td>
</tr>
<tr>
<td>Hunt and Hess grade III on admission</td>
<td>224</td>
<td>39</td>
<td>&gt;0.001</td>
<td>2.2</td>
<td>1.2 - 3.7</td>
</tr>
<tr>
<td>Hunt and Hess grades IV-V on admission</td>
<td>161</td>
<td>35</td>
<td>&gt;0.001</td>
<td>2.6</td>
<td>1.4 - 4.8</td>
</tr>
</tbody>
</table>

Abbreviations: sIA-SAH = subarachnoid hemorrhage from saccular intracranial aneurysm; ICH = intracerebral hemorrhage; HR = hazard ratio; CI = confidence interval
* acute seizure = seizure within one week after sIA-SAH.
4.3.7 Microsurgical vs. endovascular occlusive therapy of ruptured sIA
During the recruitment from 1995 to 2007, the choice between the microsurgical vs. endovascular therapy in the KUH Neurovascular Group was influenced by the morphology of the aneurysm, aneurysm neck width, the location of the ruptured sIA and the presence of ICH. Also, between 1995 and 2000, there was a randomized trial on aneurysm treatment with clipping vs. coiling (Koivisto et al. 2000). Endovascular therapy was significantly associated to lower incidence of epilepsy (Table 1) but this disappeared in the multivariate analysis (Table 2). Microsurgical clipping was more often associated with epilepsy because the cases with ICH were more often treated with simultaneous microsurgical clipping and evacuation of ICH.

4.3.7 Patients in good condition on admission
The risk of epilepsy is significant even in the patients with good condition on admission. Of the 876 two-week survivors of sIA-SAH, 266 (30%) had been in good condition (Hunt and Hess grades I and II), and their cumulative epilepsy rates were 6% vs. 8% at five years respectively (Table 1 and Figure 2C).

![Figure 4](image_url)

*Figure 4.* Cumulative incidences of epilepsy among 876 patients alive 2 weeks after subarachnoid hemorrhage from saccular intracranial aneurysm (sIA-SAH), in overall (A) and according to independent risk factors for epilepsy after sIA-SAH, intracerebral hemorrhage (ICH) (B), condition on admission by the Hunt and Hess Scale (C), and the presence or absence of acute seizures within 1 week after sIA-SAH (D).
4.4 DISCUSSION

This is the most comprehensive study of the cumulative incidence and independent risk factors of epilepsy after aneurysmal SAH, so far. This is the largest population-based cohort with saccular intracranial aneurysm (sIA) verified by 4-vessel angiography as the bleeding source and complete follow up for the risk of epilepsy as identified by prescribed AED use from the national registry and by neurologists.

The initial mortality in unselected sIA-SAH cohorts is very high, e.g., 11% at 3 days, 22% at 30 days, and 27% at 12 months in our previous analysis of 1,657 patients admitted to our hospital within 24 hours after sIA-SAH (Karamanakos et al. 2012). In the present study, 169 of the 1,045 sIA-SAH patients admitted between 1995 and 2007 had died within two weeks (Figure 1). The risk of epilepsy for the 876 two-week survivors was analysed, because their probability for extended survival was already high, e.g., 88% at two years. The competing risks analysis was used for the cumulative epilepsy rates (Table 1, Figure 2). The Kaplan-Meier analysis would assume that the censoring of sIA survivors (lost to follow-up) and the probability of epilepsy would be independent of each other. In the present cohort, epilepsy and excess mortality after sIA-SAH share same risk factors known on admission, most notably acute intracerebral hemorrhage and poorer condition on admission. The larger the risk of competing risk the greater the extent of bias (Putter et al. 2007).

The risk of epilepsy is significant even in the patients with good condition and cisternal blood only as the sign of SAH on CT scan on admission. Of the 876 two-week survivors of sIA-SAH, 266 (30%) had been in good condition (Hunt and Hess grades I and II). Their cumulative epilepsy rates were 6% vs. 8% at five years. The presence and the volume of ICH on acute CT scan as a sign of tearing irreversible brain tissue injury was the strongest anatomical predictor of epilepsy after sIA-SAH (Table 1). Of the 113 epilepsy patients, 57 presented with ICH on admission. Rupture of sIA in the middle cerebral artery (MCA) bifurcation was particularly prone (47%) to cause ICH, in the adjacent temporal lobe (Rinne et al. 1996).

Acute seizures, determined as seizures within one week from the rupture of sIA, are also an independent risk factor for epilepsy during follow up. Previous studies indicate that the increasing amount of blood on acute CT scan predispose to acute seizures (Butzkueven et al. 2000, Ibrahim et al. 2013), implying that primary brain damage causes seizures in acute phase. Previous studies suggest that acute seizures predict poor outcome (Taki et al. 2011), but in our study they were not an independent risk factor for poor outcome at one year according to the Glasgow Outcome Scale.

The mode of occlusive therapy of ruptured sIA, whether microsurgical or endovascular, was not an independent risk factor for epilepsy after sIA-SAH. In the univariate analysis endovascular treatment was associated to lower incidence of epilepsy. This was most likely because ruptured sIA in the middle cerebral artery bifurcation often caused intracerebral hemorrhages and in that case were mainly occluded microsurgically.

PubMed search identified only three original studies on epilepsy after aneurysmal SAH since 2000 with a sizable cohort, flow chart, follow up time of at least 12 months, methods of gathering follow up data, proper definition of epilepsy and distinction from acute seizures, and multivariate analyses for independent risk factors for epilepsy (Claassen et al.
Distinction of sIAs from infrequent fusiformic aneurysms was not reported. These three studies did not use the competing risks (death vs. epilepsy) analysis for the cumulative rate of epilepsy. The overall incidences of epilepsy after aneurysmal SAH are not informative because the survivors are heterogeneous in terms of condition on admission, signs of brain injury in neuroimaging and during neurointensive care, and subsequent neurological morbidity.

In the prospective single center study, 305 of the 431 patients were alive one year after aneurysmal SAH, and 247 of them (58 missing) were analysed for epilepsy. Only 17 patients with epilepsy were identified: the epilepsy ratio from 17/305 (5.6%) to 17/247 (6.9%)(Claassen et al. 2003). In the retrospective single center study, 217 of the 274 aneurysmal SAH patients alive at one year, all treated by microsurgical clipping, were analysed for epilepsy during a mean follow up time of 6.6 years. Only 15 epilepsy patients were identified: the epilepsy ratio of 15/217 (6.9%) (Lin et al. 2003). In these two studies, the cumulative epilepsy rates were not reported, and the identification of independent risk factors for epilepsy was flawed by the small numbers of epilepsy patients.

In the prospective International Subarachnoid Aneurysm Trial (ISAT) (Hart et al. 2011), 2143 aneurysmal SAH patients, 1073 randomized to endovascular treatment and 1070 to neurosurgery, were studied for epilepsy. Epilepsy was defined as seizures after randomization. Of the 2143 patients, 88% of patients were WFNS (World Federation of Neurosurgeons) grade 1-2 in both groups. 1084 patients had anterior cerebral artery aneurysm, 698 patients had internal carotid artery aneurysm and only 303 (14%) had middle cerebral artery aneurysm. The authors identified 235 epilepsy patients in a mean follow up time of nine years. The cumulative rates of epilepsy at 5 years were 6.4% after endovascular and 9.6% after surgical occlusive therapy. The independent risk factors for epilepsy were thromboembolic complications (HR 5.1), vasospasm (HR 2.1), additional procedures, craniotomy (1.7), middle cerebral artery location of ruptured aneurysm (HR 2.2), age younger than 50 years (HR 1.5) and neurosurgical occlusion of ruptured aneurysm (HR 1.6). In ISAT study selection was toward patients in good condition with small aneurysm in anterior cerebral artery and internal carotid artery and study was aimed to compare endovascular vs. neurosurgical treatment of SAH in an eligible population. Cumulative incidences of epilepsy at five years in ISAT study after different treatment modalities are comparable to our results in cumulative incidence of epilepsy after sIA-SAH with patients in good condition on admission.

The strengths derive from the Finnish health care system. Finland is divided into mutually exclusive catchment areas between the five university hospitals. This allowed the creation of disease cohorts that are unselected and minimally biased. Very accurate population statistics and a stable population allow long-term follow ups and ensure that few patients are lost to follow up. Our study is retrospective, but we were able to accurately identify the patients diagnosed with epilepsy by neurologists due to the national registry of fully reimbursed medicines and the case reports from the treating hospitals during the follow up.

We did not have valid information about epilepsy in the patients permanently institutionalised after sIA-SAH (7 patients with all GOS 2). Their AEDs are not reimbursed but are included in the institution fees, so the overall incidence may be slightly underestimated.

**4.4 CONCLUSIONS**

Longterm sIA-SAH survivors present significantly with unexpected neurological, cognitive and psychosocial problems (Rinkel & Algra 2011) that may be missed during routine visits
to outpatient clinics. Our data on epilepsy will support the clinical practice of post-SAH outpatient clinics that should be organised in dedicated neurocenters. Epilepsy in the two-week survivors of acute sIA-SAH was predicted by signs of the primary injury in the brain tissue (ICH) on CT scan on admission, the patient’s condition on admission reflecting the extent of the primary impact, and acute seizures within one week after sIA-SAH, reflecting the patient’s individual threshold for seizures. Microsurgical clipping of ruptured sIA was more often associated with epilepsy than endovascular occlusive therapy because the cases with ICH were more often treated with simultaneous microsurgical clipping and evacuation of ICH.
5 Antidepressant use after aneurysmal subarachnoid haemorrhage: A population based case-control study

5.1 INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH), almost always from a rupture of a saccular intracranial aneurysm (sIA), affects the working-age population (Nieuwkamp et al. 2009). The reported incidence is 4 to 7 per 100,000 (Feigin et al. 2009) but is 3 times higher in Finland (de Rooij et al. 2007). Subsequent mortality is high; 22% at 1 month and 27% at 12 months in our series of 1,657 patients, mainly due to poor condition and signs of brain injury on admission (Karamanakos et al. 2012). Along with various degrees of acute or delayed brain injury, long term survivors are often affected by neurological and cognitive disorders (Rinkel & Algra 2011).

Depression after sIA-SAH has been reported in up to 33% of survivors (Kreiter et al. 2013). Depression was associated with a poor quality of life, and it may slow down rehabilitation and complicate reintegration to previous living conditions and occupation (Cleare et al. 2015). Previous studies are mostly cross-sectional, diagnostic criteria of depression vary, and the use of antidepressant (ATD) medication and the impact of comorbid epilepsy have not been comprehensively studied. Recommendations for first-line treatment, especially in moderate and severe depression, include ATDs (Cleare et al. 2015). Depression is the most frequent indication for ATD use in Finland (Sihvo et al. 2008).

The Kuopio Intracranial Aneurysm Database (www.kuopioneurosurgery.fi) includes all cases of ruptured intracranial sIAs admitted to the Kuopio University Hospital (KUH) from its defined Eastern Finnish catchment population (Huttunen et al. 2010, Lindgren et al. 2014). Medical data from the Finnish national registries, including hospital diagnoses and the use of prescribed medicines, have been fused to the database (Lindgren et al. 2014, Lindgren et al. 2013, Huttunen et al. 2015). In this study, we analyzed the use of ATD medication of the 12-month survivors after sIA-SAH and their matched population controls between 1994 and 2014. ATD use was indicated by two or more purchases of ATDs. We conducted a population based case-control study to identify independent risk factors for ATD use after sIA-SAH, and used classification tree analysis to define the best prediction model for ATD use after sIA-SAH.

5.2 METHODS

5.2.1 Kuopio Intracranial Aneurysm Database
Neurosurgery of Kuopio University Hospital (KUH) has solely provided full-time neurosurgical services for the KUH catchment population in Eastern Finland (Huttunen et al. 2010). The KUH area consists of four central hospitals with neurological units and catchment areas of their own. During the recruitment period of the present study, 1995 to 2014, the geographic area has remained the same. The population has decreased from 882.671 to 840.587.
All cases of aSAH diagnosed by spinal tap or CT at the KUH area have been acutely admitted to KUH for angiography and treated if not moribund or very aged. The exact number of rejected aSAH patients is not available.

The database includes all cases of intracranial aneurysm patients admitted to KUH since 1980. The database has been prospective since 1990. The criterion for a familial saccular intracranial aneurysm (sIA) is at least 2 affected first-degree relatives (Huttunen et al. 2011, Huttunen et al. 2010). The clinical data from the hospital periods and follow-up visits are coded into the database. The phenotype, genetics, and outcome of Eastern Finnish sIA disease have been analyzed in several studies (Ronkainen et al. 1998, Bilguvar et al. 2008, Gaal et al. 2012, Helgadottir et al. 2008, Kurki et al. 2014, Kurki et al. 2011, Koivisto et al. 2000, Ronkainen et al. 2001, Yasuno et al. 2011).

5.2.2 Study population
The inclusion criteria were: a citizen of Finland and resident of the KUH area at the time of first sIA-SAHI between January 1, 1995, and December 31, 2007; verification of the ruptured sIA by angiography; alive at 12 months after sIA-SAHI (Figure 5).

The Population Register Centre (PRC) for the Finnish population randomly selected three alive controls for each patient in the study population, matched by age, sex and birthplace. The index date for matching was the date of sIA-SAHI admission, with all controls then alive.
The Social Insurance Institution of Finland (SII) is an independent social security institution. The National Health Insurance (NHI) scheme is part of the Finnish social security system, and it is run by the SII. All permanent residents of Finland are covered under the NHI scheme. The SII of Finland maintains a nationwide registry for all patients who have been granted refundable drugs, including all ATDs.

The ATD use by the 1,187 sIA-SAHC patients (Figure 1) from SII, according to The Anatomical Therapeutic Chemical Classification (ATC) system, was analysed between January 1, 1994, and December 31, 2014. ATD data contained information since the first purchase date and the number of purchases until the last date. The recruitment period, sIA-SAHC between 1995 and 2014, allowed the use of ATD data for at least one year before sIA-SAHC. None was lost to the follow-up. The ATD use was indicated by two or more purchases of ATD. The patients with more than two purchases of ATDs before sIA-SAHC were excluded from the final study cohort (Figure 1). Using this data, we indentified all ATDs purchased by our cohort. There were a total of 24 ATDs: Imipramine, Clomipramine, Opipramol, Trimipramine, Amitriptyline, Nortriptyline, Doxepin, Maprotiline, Fluoxetine, Citalopram, Paroxetine, Sertraline, Fluvoxamine, Escitalopram, Moclobemide, Mianserin, Trazodone, Mirtazapine, Bupropion, Venlafaxine, Milnacipran, Reboxetine, Duloxetine and Agomelatine.
As in our previous study on epilepsy after sIA-SAH in the Kuopio sIA Database (Huttunen et al. 2016), the criterion for the epilepsy diagnosis after sIA-SAH followed the current International League Against Epilepsy definition: (1) at least 2 unprovoked seizures occurring 24 hours apart, or (2) one unprovoked seizure and high probability of further seizures due to, for example, brain infarct, ICH, or status epilepticus (Fisher et al. 2014).

5.2.2 Literature review
PubMed was searched for relevant English articles between 2008 and 2015 with the following search words: depression AND subarachnoid hemorrhage. The cohorts with the definition of depression and multivariate analysis risk analysis for predictors of depression after aSAH were included (Table 3).
Table 3. Previous cohorts published between 2008 and 2015 on depression after aneurysmal subarachnoid haemorrhage with multivariate analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>aSAH study cohort</th>
<th>Follow up time</th>
<th>Diagnosis of depression</th>
<th>Cases of depression (%)</th>
<th>Independent risk factors of depression (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong GKC et al. (2014)</td>
<td></td>
<td>Hong Kong</td>
<td>Cross-sectional</td>
<td>103</td>
<td>12-48 months</td>
<td>NPI</td>
<td>13 (13%)</td>
<td>chronic hydrocephalus requiring a shunt (5.1)</td>
</tr>
<tr>
<td>Kreiter KT et al 2013</td>
<td></td>
<td>United States</td>
<td>prospective</td>
<td>216</td>
<td>complete 12-month follow up</td>
<td>CES-D self-reported</td>
<td>72 (33%)</td>
<td>non-white ethnicity (2.7); lack of health insurance (2.0); premorbid social isolation (3.1)</td>
</tr>
<tr>
<td>Ronne-Engström E et al 2013</td>
<td></td>
<td>Sweden</td>
<td>prospective database</td>
<td>755</td>
<td>median 12 months</td>
<td>EQ-5D self-reported</td>
<td>moderate 39% severe 12%</td>
<td>the best subset of predictive variables: female gender; signs of more severe disease</td>
</tr>
<tr>
<td>Hedlund M et al 2011</td>
<td></td>
<td>Sweden</td>
<td>prospective</td>
<td>83</td>
<td>7 months</td>
<td>DSM-IV</td>
<td>21 (25%)</td>
<td>life time history of major depression(11.9); life time history of anxiety disorder (6.5); life time history of substance use disorder (9.8); any psychiatric disorder history (14.1); psychiatric comorbidity (10.1)</td>
</tr>
<tr>
<td>Visser-Meily AJM et al 2009</td>
<td></td>
<td>Netherlands</td>
<td>cross-sectional</td>
<td>141</td>
<td>24 - 48 months</td>
<td>HADS self-reported</td>
<td>40 (23%)</td>
<td>lower Stroke Specific Quality Of Life scale (SSQOL)</td>
</tr>
</tbody>
</table>

aSAH = aneurysmal subarachnoid hemorrhage; NPI = The neuropsychiatric Inventory Chinese version; CES-D = Center for Epidemiological Studies-Depression; EQ-5D = EuroQol; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; HADS = Hospital, Anxiety and Depression Scale
5.2.2 Statistical analysis
Categorical variables were expressed in proportions and continuous variables in medians, quartiles and ranges. Groups were compared using the Pearson’s chi-squared test or the Mann-Whitney U test or independent samples T-test when appropriate. The differences in frequencies between sIA-SAH patients and controls were statistically examined by the Pearson’s chi-squared test. The odds ratio (OR) and its 95% confidence interval (CI) were estimated by using logistic regression model in which matched variables (gender and age at admission of sIA-SAH) were controlled.

Independent risk factors for ATD use (>2 purchases of ATDs) after sIA-SAH were identified by logistic regression analyse, with variables presented in Table 4. P values <0.05 were considered significant. Independent risk factors were entered into Classification Tree Analysis, using the growing method of Classification and Regression Trees. The splitting criterion was the Gini improvement measure. The minimum number of cases in the parent and child nodes was 100 and 50. SPSS 22 statistical software was used (SPSS, Inc, Chicago, IL).

5.2.2 Ethical aspects
The study was approved by the Ethical Committee of the Kuopio University Hospital. Data fusion from the national registries was performed with the approval from Ministry of Social Affairs and Health of Finland.

5.3 RESULTS

5.3.1 Antidepressant use of patients alive 12 months after sIA-SAH
A total of 1187 patients were followed up for a median of 9.0 years after sIA-SAH, a total follow up of 10.603 patient years (Figure 5). Before sIA-SAH, 167 (14%) of the 1187 patients had ATD use. Of the 1020 patients without previous ATD use, 80 (8%) had purchased ATDs once and 663 (65%) had no ATD use after sIA-SAH. Of the remaining 940 patients without ATD use before sIA-SAH, 277 (29%) had continuous ATD use after sIA-SAH, and the median time from sIA-SAH to their first ATD purchase was 11 months (quartiles of 5 and 48 months). The clinical characteristics of the 940 sIA-SAH patients are presented in Table 4.
Table 4. Characteristics 940 patients alive at 12 months after sIA-SAH between 1995 and 2014 from defined Eastern Finnish population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No ATD use after sIA-SAH (N=663)</th>
<th>≥2 ATD purchases after sIA-SAH (N=277)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age on admission</td>
<td>54</td>
<td>52</td>
<td>0.047</td>
</tr>
<tr>
<td>Female gender</td>
<td>375 (57%)</td>
<td>156 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Familial sIA disease</td>
<td>72 (11%)</td>
<td>33 (12%)</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple sIAs</td>
<td>171 (26%)</td>
<td>86 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>Site of ruptured sIA (left/right)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>AComA</td>
<td>106 (16%) / 124 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2-A5</td>
<td>23 (3%) / 14 (2%)</td>
<td>36 (13%) / 43 (16%)</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>10 (2%) / 10 (2%)</td>
<td>10 (4%) / 7 (3%)</td>
<td></td>
</tr>
<tr>
<td>Mbif</td>
<td>79 (12%) / 92 (14%)</td>
<td>3 (1%) / 9 (3%)</td>
<td></td>
</tr>
<tr>
<td>PComA</td>
<td>3/4</td>
<td>34 (12%) / 46 (17%)</td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>54 (8%) / 61 (9%)</td>
<td>2/1</td>
<td></td>
</tr>
<tr>
<td>ICA bif</td>
<td>10 (2%) / 12 (2%)</td>
<td>25 (9%) / 23 (8%)</td>
<td></td>
</tr>
<tr>
<td>PICA</td>
<td>11 (2%) / 4</td>
<td>5 (2%) / 6 (2%)</td>
<td></td>
</tr>
<tr>
<td>BAbif</td>
<td>27 (4%)</td>
<td>4 (1%) / 3 (%1)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>21 (3%)</td>
<td>10 (4%)</td>
<td></td>
</tr>
<tr>
<td>Hunt and Hess grade</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>grade I</td>
<td>177 (27%)</td>
<td>47 (17%)</td>
<td></td>
</tr>
<tr>
<td>grade II</td>
<td>276 (42%)</td>
<td>35 (13%)</td>
<td></td>
</tr>
<tr>
<td>grade III</td>
<td>128 (19%)</td>
<td>101 (36%)</td>
<td></td>
</tr>
<tr>
<td>grade IV</td>
<td>67 (10%)</td>
<td>55 (20%)</td>
<td></td>
</tr>
<tr>
<td>grade V</td>
<td>15 (2%)</td>
<td>10 (4%)</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>136 (21%)</td>
<td>76 (27%)</td>
<td>0.016</td>
</tr>
<tr>
<td>IVH</td>
<td>136 (21%)</td>
<td>64 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>245 (37%)</td>
<td>114 (41%)</td>
<td>NS</td>
</tr>
<tr>
<td>Therapy of ruptured sIA</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>clipping</td>
<td>378 (57%)</td>
<td>174 (63%)</td>
<td></td>
</tr>
<tr>
<td>endovascular</td>
<td>274 (41%)</td>
<td>102 (37%)</td>
<td></td>
</tr>
<tr>
<td>conservative</td>
<td>11 (2%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Shunt after sIA-SAH</td>
<td>98 (15%)</td>
<td>60 (22%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Epilepsy after sIA-SAH</td>
<td>50 (8%)</td>
<td>64 (23%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modified Rankin scale</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>376 (57%)</td>
<td>82 (30%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>69 (10%)</td>
<td>39 (14%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>37 (6%)</td>
<td>31 (11%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>18 (3%)</td>
<td>30 (11%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>9 (1%)</td>
<td>22 (8%)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

sIA = saccular intracranial aneurysm; sIA-SAH = subarachnoid haemorrhage from sIA; ATD = antidepressant medication; AComA = anterior communicating artery; A2-A5 = A2-A5 segments of anterior cerebral artery; M1 = proximal segment of middle cerebral artery; Mbif = middle cerebral artery bifurcation; PComA = posterior communicating artery; ICA bif = internal carotid artery bifurcation; PICA = posterior inferior cerebellar artery; BAbif = basilar artery bifurcation; ICH = intracerebral hematoma; IVH = intraventricular hematoma
In the sIA-SAH group 167 (14%) patients out of 1187 had used ATDs before sIA-SAH vs. 524 (15%) out of 3561 in the control group until the index date, the difference not statistically significant. In the sIA-SAH group, 277 (29%) out of the 940 patients had ATD use after sIA-SAH vs. 372 (14%) out of the 2304 controls since the index date. The sIA-SAH group included significantly more ATD users (p <0.001, OR 2.6, CI 95% 2.2-3.1) than the control group (Table 3).

| Table 5. The risk of ATD use for patients alive at 12 months after sIA-SAH between 1995 and 2014 from defined Eastern Finnish population compared to matched controls. |
|-------------------------------------------------|-------------------------------------------------|------------------|-----|-----|
| Variables                                      | sIA-SAH patients N=940                          | Controls N=2676  | p-value | OR  | CI 95% |
| No ATD use                                     | 663 (71%)                                       | 2304 (86%)      |      |     |       |
| ATD use after sIA-SAH*                         | 277 (29%)                                       | 372 (14%)       | <0.001 | 2.6 | 2.2 - 3.1 |

sIA-SAH = subarachnoid haemorrhage from sIA; ATD = antidepressant medication
* = At least two purchases of ATD after sIA-SAH

5.3.2 Independent risk factors for antidepressant use after sIA-SAH
In the 940 sIA-SAH patients with no previous ATD use, the independent risk factors in the logistic regression analysis were age on admission for sIA-SAH (OR 0.97 per year), the Hunt and Hess Scale (HHS) grade IV (Hunt & Hess 1968) (OR 2.6), modified Rankin Scale (mRS) grades I (OR 2.7), II (4.3), III (9.9), IV (OR 17.9) and epilepsy after sIA-SAH (OR 2.5) (Table 6).
Table 6. Independent risk factors for drug treated depression for 940 patients alive 12 months after sIA-SAH admitted to Kuopio University Hospital between 1995 and 2014.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with ATD use* per variable</th>
<th>OR</th>
<th>p-value</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age on admission (increase per year)</td>
<td>940</td>
<td>0.97</td>
<td>0.001</td>
<td>0.96 - 0.99</td>
</tr>
<tr>
<td>Hunt and Hess grade IV</td>
<td>55 / 122</td>
<td>2.6</td>
<td>.05</td>
<td>1.0 – 6.9</td>
</tr>
<tr>
<td>mRS I</td>
<td>39 / 108</td>
<td>2.7</td>
<td>&lt;.001</td>
<td>1.8 - 4.9</td>
</tr>
<tr>
<td>mRS II</td>
<td>31 / 68</td>
<td>4.3</td>
<td>&lt;.001</td>
<td>1.7 - 5.3</td>
</tr>
<tr>
<td>mRS III</td>
<td>30 / 48</td>
<td>9.9</td>
<td>&lt;.001</td>
<td>4.6 - 20</td>
</tr>
<tr>
<td>mRS IV</td>
<td>22 / 31</td>
<td>17.9</td>
<td>&lt;.001</td>
<td>6.5 - 47</td>
</tr>
<tr>
<td>Epilepsy diagnosed after sIA-SAH</td>
<td>64 / 114</td>
<td>2.5</td>
<td>.002</td>
<td>1.4 - 4.5</td>
</tr>
</tbody>
</table>

sIA-SAH = subarachnoid hemorrhage from saccular intracranial aneurysm; M1 of MCA = proximal segment of middle cerebral artery; mRS = modified Rankin Scale; ATD = antidepressant medication.

* At least two purchases of ATD after sIA-SAH
5.3.2 Classification tree analysis for drug-treated depression after sIA-SAH
The independent risk factors from the multivariate analysis (Table 4) were entered in the classification tree analysis, and five terminal nodes were produced. The combinations of risk factors for ATD use are presented in Figure 6. Modified Rankin Scale (mRS) emerged as the most potent predictor, with the split between no symptoms (mRS 0) and no significant disability to severe disability (mRS I-V). Epilepsy after sIA-SAH did not improve the final classification tree model.

5.4 DISCUSSION
In our population-based case control study of 940 patients with no ATD use before sIA-SAH and alive at one year after sIA-SAH, we identified 277 (29%) patients with continuous ATD use. They used two times more often ATDs than their matched controls. Furthermore, there was no difference in ATD use before sIA-SAH between the patients and the matched

Figure 6. Classification tree analysis of the risk of ATD use among the 940 patients alive at 12 months after sIA-SAH. The classification tree was constructed according to the independent risk factors identified in the logistic regression analyses. modified Rankin Scale (0-V) after sIA-SAH: 0 = No symptoms; I = No significant disability; II = Slight disability; III = Moderate disability; IV = Moderately severe disability; V = Severe disability.
controls. The patients with continuous ATD use were most likely depressed because ATDs are seldom used continuously in other indications than depression in Finland, 90% of long-term users of ATDs had a history of depression (CIDI diagnosis or self-reported history) (Sihvo et al. 2008). The majority of depression patients in Finland receives treatment consistent with national depression treatment guidelines (Hamalainen et al. 2009).

Classification tree analysis identified the mRS as the most potent predictor of ATD use after sIA-SAH (Figure 2). Condition on admission for sIA-SAH was also an independent risk factor, suggesting that severity of sIA-SAH can predict ATD use by the survivors. In one-year sIA-SAH survivors with mRS I-II, younger age on admission predicted ATD use (Figure 2). With mRS III-IV the rate of ATD use was 63%. The ATD use before sIA-SAH was 14% in the overall cohort of 1187 one-year survivors of sIA-SAH (Figure 1) and 15% in their matched controls.

The one-year sIA-SAH survivors who developed new epilepsy had two times higher risk for ATD use. Several factors may contribute why epilepsy and depression associate in sIA-SAH survivors (Keezer et al. 2016b, Naess et al. 2007). Our data indicates that depression is particularly common in sIA-SAH survivors when they also develop comorbid epilepsy.

We identified five articles in English published between 2008 and 2015 with multivariate analysis of depression after aneurysmal SAH (aSAH), three prospective and two cross-sectional studies (Table 1). The independent risk factors were: chronic hydrocephalus requiring a shunt(Wong et al. 2014); non-white ethnicity(Kreiter et al. 2013); lack of health insurance(Kreiter et al. 2013); premorbid social isolation(Kreiter et al. 2013); history of major depression(Hedlund et al. 2011); anxiety disorders(Hedlund et al. 2011); substance use disorder(Hedlund et al. 2011); any psychiatric disorder or comorbidity(Hedlund et al. 2011) and; female gender(Ronne-Engstrom et al. 2013); signs of more severe aSAH(Ronne-Engstrom et al. 2013).

A Swedish prospective study analysed depressive symptoms a median of 12 months after aSAH in 755 patients with the EuroQol (EQ-5D), a preference-based instrument based on self-reported health status in five dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Comparisons were made with age-matched Swedish reference groups. Female gender and signs of more severe disease were the best subsets predicting worse outcome regarding EQ5 (Anxiety/Depression) (Ronne-Engstrom et al. 2013). A Dutch cross-sectional questionnaire study of 141 patients, living independently after aSAH, reported 23% depression risk after aSAH according to Hospital Anxiety and Depression Scale (HADS) (Visser-Meily et al. 2009). This corresponds to the 20% risk of ATD use in patients with no symptoms after sIA-SAH according to mRS in our study.

Finland is divided into separate catchment areas between the five university hospitals. This allowed the creation of our sIA-SAH cohort that is unselected and minimally biased. Very accurate clinical data from the nationwide registries and a stable population allowed the long-term follow up and ensured that no patient was lost to follow up. We reconstructed the overall medication use of the sIA-SAH patients and their matched controls, avoiding the bias of cross-sectional studies. We avoided the bias of institution-based studies by tracting all prescriptions of ATDs. However, our cohort obviously included patients who were depressive but did not have the diagnosis of depression and ATD medication. Furthermore, ATDs can be used to treat other affective disorders than depression, and some of the patients may have used ATDs for chronic pain. Elderly patients and those with
increased disease burden patients could more likely receive ATD prescriptions for primary or secondary depression, also because of their more frequent use of the health care services.

Development of depression in sIA-SAH survivors may be related to many pathophysiological factors in the acute phase of sIA-SAH, including: increased intracranial pressure; acute or delayed ischemic brain injury; intracerebral hemorrhage; intraventricular hemorrhage; hydrocephalus and shunt dependency; and hypophyseal and hypothalamic disorders (Steiner et al. 2013a, Connolly et al. 2012). Hypophyseal and hypothalamic dysfunctions must be considered when depression after sIA-SAH is diagnosed. We considered 12 months as the minimal period for the survivors to recover adequately from their acute and delayed adversities caused by sIA-SAH (Rinkel & Algra 2011, Karamanakos et al. 2012). Long-term sIA-SAH survivors often experience neurological, cognitive and psychosocial problems (Rinkel & Algra 2011, Huttunen et al. 2015) that may be missed or misinterpreted during their visits to outpatient clinics.

5.5 CONCLUSIONS

Our results help to identify depression in patients surviving sIA-SAH. We present a prediction algorithm for the risk of long term ATD use in sIA-SAH survivors (Figure 2). Importantly, even the patients with a seemingly good recovery at 12 months after sIA-SAH are at a significant risk of depression. Comorbid epilepsy increases the risk of ATD use. The timely identification and subsequent treatment of depression in sIA-SAH survivors could enhance the re-integration to daily life and occupation.
6 Epilepsy-associated long term mortality after aneurysmal subarachnoid hemorrhage

6.1 INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH), almost always from a ruptured saccular intracranial aneurysm (sIA), affects the working-age population (Nieuwkamp et al. 2009). Mortality after sIA-SAH is high, 22% at 1 month and 27% at 12 months in our series of 1,657 sIA-SAH patients, mainly due to poor clinical condition and signs of brain injury on admission (Karamanakos et al. 2012). The effect of sIA-SAH and its sequelae in the central nervous and cardiovascular systems often cause long-term morbidity (Huttunen et al. 2015, Huttunen et al. 2016) and mortality. The 12-month survivors face significant long term excess mortality as compared to the general population (Huttunen et al. 2011, Huhtakangas et al. 2015), 12% at 15 years among 1746 survivors and 17% at 20 years among 3078 survivors in two Finnish IA registries. Data on the long term neuro/psycho/social outcome is scarce (Rinkel & Algra 2011, Huttunen et al. 2015, Huttunen et al. 2016).

The Kuopio Intracranial Aneurysm Patient and Family Database (www.kuopioneurosurgery.fi) includes all cases of ruptured intracranial sIAs admitted to the Kuopio University Hospital (KUH) from its defined Eastern Finnish catchment population. Medical data from the nationwide registries, including the hospital diagnoses, use of prescribed medicines and causes of death have been fused to the database (Huttunen et al. 2011, Karamanakos et al. 2012, Lindgren et al. 2014, Lindgren et al. 2013, Huttunen et al. 2015, Huttunen et al. 2016). The antidepressant use among 940 survivors was significantly higher (OR 2.6) than in their 2676 matched controls. The cumulative incidence of epilepsy was 12% at five years in 876 survivors, with intracerebral hemorrhage (ICH), poor condition on admission, and acute seizures as independent risk factors.

Excess mortality after the diagnosis of symptomatic epilepsy is well recognized (Nevalainen et al. 2014, Neligan et al. 2011, Keezer et al. 2016a), and it is referred, e.g., to epilepsy itself, treatment-related deaths, accidents, suicides, sudden unexpected death in epilepsy, and status epilepticus (Forsgren et al. 2005, Jansson & Ahmed 2002). No comprehensive and population-based studies are available on the long term morbidity and mortality of the patients who survived sIA-SAH but developed epilepsy. In the present study, an extension to our previous study (Huttunen et al. 2015), we compared the circumstances of deaths, including underlying and immediate causes of deaths, in the patients who died with
epilepsy (34/121) or without epilepsy (163/658) in a median follow up of 12 years after sIA-SAH.

6.2 METHODS

6.2.1 Catchment population of Kuopio University Hospital (KUH)
Since 1977, Neurosurgery of Kuopio University Hospital (KUH) has solely provided full-time acute and elective neurosurgical services for the KUH catchment population in Eastern Finland. The KUH area consists of 4 central hospitals with neurological units and catchment areas of their own. During the recruitment period of the present study, 1995 to 2014, the geographic area has remained the same. The population has decreased from 882,671 to 840,587.

6.2.2 Admission of subarachnoid hemorrhage (SAH) patients to KUH
All cases of SAH diagnosed by CT or spinal tap at the KUH catchment area have been acutely admitted to KUH for angiography and treated if not moribund or very aged. The exact number of rejected SAH patients is not available.

6.2.3 Kuopio Neurosurgery Intracranial Aneurysm Patient and Family Database
The database includes all cases of unruptured and ruptured intracranial aneurysm patients admitted to KUH since 1980 (www.kuopioneurosurgery.fi). The database has been prospective since 1990. The database is run by a dedicated full-time research coordinator who interviews all new patients. The criteria for saccular intracranial aneurysm (sIA) family are at least 2 affected first-degree relatives, and sIA disease without family history is considered sporadic (Huttunen et al. 2010). The clinical data from the hospital periods and follow-up visits are coded into an extensive list of variables. The use of prescribed medicines (see below), any hospital diagnoses, and causes of death have been entered from the Finnish nationwide registries (Huttunen et al. 2011, Karamanakos et al. 2012, Lindgren et al. 2014, Lindgren et al. 2013, Huttunen et al. 2015, Huttunen et al. 2016).

6.2.3 Study population of 779 12-month survivors of sIA-SAH
The inclusion criteria were:

1. a citizen of Finland and resident of the KUH catchment area at the time of first sIA-SAH between January 1, 1995, and December 31, 2007;

2. verification of sIA(s) by angiography;

3. alive at 12 months after admission.

The exclusion criteria were: rupture of an intracranial aneurysm other than a saccular one (e.g., fusiform, traumatic, mycotic); previous diagnosis of epilepsy (n=14).

Figure 7. presents the flow chart from the KUH catchment population to the final study cohort of 779 sIA-SAH patients.
Figure 7. Flowchart of the identification of epilepsy and mortality after subarachnoid hemorrhage from saccular intracranial aneurysm (sIA-SAH) among the 779 sIA-SAH patients alive at 12 months after admission to the Kuopio University Hospital (KUH) from its Eastern Finnish catchment population. The 121 patients with newly diagnosed, epilepsy after sIA-SAH were identified according to the reimbursement of physician prescribed antiepileptic drugs (AEDs) in the nationwide registry. Statistics on causes of death and on the development of mortality was produced by the Statistics Finland.
6.2.4 Diagnosis of epilepsy among 779 12-month survivors of sIA-SAH
The National Health Insurance (NHI) scheme is part of the Finnish social security system, and it is run by the The Social Insurance Institution (SII) of Finland. All permanent residents of Finland are covered under the NHI scheme. The SII maintains a nationwide registry for all patients who have been granted special reimbursement of medicines, including antiepileptic drugs (AEDs). In order to be reimbursed at the pharmacy for epilepsy, patients must submit Medical Certificate to the SII. The medical certificate must be based on examinations and diagnosis of epilepsy made by a neurologist. The entitlement to special reimbursement of AEDs is granted by SII for non-institutionalized patients. The following AEDs were reimbursed: carbamazepine; clobazam; clonazepam; gabapentin; lamotrigine, levetiracetam; nitrazepam; oxcarbazepine; phenobarbital; phenytoin; pregabalin; rufinamide; sodium valproate; stiripentol; tiagabine; topiramate; vigabatrin; and zonisamide.

The data on fully reimbursed AEDs between January 1, 1994, and December 31, 2014 was integrated to the Kuopio sIA Database. The recruitment period of patients between January 1, 1995, and December 31, 2007, allowed data on the use of AEDs for at least one year before sIA-SAH and at least seven years after sIA-SAH (Figure 7). Hospital diagnoses and case reports of identified epilepsy patients, from all neurology units in the KUH catchment area during the follow-up, were reviewed. None of the patients was lost to the follow-up. The AED data contained information since the first purchase date, and the number of purchases, until the last date.

In our previous study (Huttunen et al. 2015) and in the present study, the criteria for the epilepsy diagnosis after sIA-SAH in the AED users, evaluated by neurologist(s), followed the current ILAE definition (Fisher et al. 2014): (a) at least two unprovoked seizures occurring >24 h apart or (b) one unprovoked seizure and high probability of further seizures due to, for example, brain infarct, intracerebral hemorrhage or status epilepticus. Acute seizures within one week after the onset of sIA-SAH were not considered as unprovoked seizures (Beghi et al. 2010). Status epilepticus was defined as seizure duration of 30 minutes according to the ILAE guideline in 1993 (Anonymous1993, Trinka & Kalviainen 2016).

6.2.5 Causes of deaths among 779 12-month survivors of sIA-SAH
Statistics Finland produces statistics on all causes of death. The statistics on causes of death cover the persons who have died in Finland or abroad during the calendar year and who at the time of death were domiciled in Finland. This ensures complete identification on causes of death. The statistics are based on data in death certificates and causes of death, the statistics have been compiled according to the 10th revision of the International Classification of Diseases (WHO ICD-10) since 1996. Death certificate is written description of the circumstances of the death produced by a physician. In death certificates conditions contributing to death are reported in two parts, underlying cause of death and immediate cause of death, if determined, and the second part for other factors contributing to death.
The death certificates data and causes of death on all patients who died before end of follow up 31 December 2014 were integrated to the Kuopio sIA Database.

6.2.6 Circumstances and causes of deaths of 34 patients with epilepsy after sIA-SAH
For the 34 patients who died with epilepsy diagnosis after sIA-SAH, the certificates of death and all available clinical records were reviewed to reconstruct the circumstances of the deaths, including underlying causes of death and immediate causes of death, to analyze whether epilepsy was a contributing factor to the death.

6.2.7 Literature review
PubMed was searched for clinically relevant English articles since 1995 with the following search words: aneurysm* AND (subarachnoid haemorrhage) AND epilepsy AND mortality.

6.2.8 Statistical analysis
The clinical variables of the sIA-SAH patients are presented in Table 7. Discrete variables were expressed in proportions and continuous variables in medians, quartiles and ranges. Groups were compared using the $\chi^2$ test or the Mann-Whitney U or Kruskal-Wallis tests when appropriate.

The independent risk factors for death were analysed using the Cox proportional hazards regression. Epilepsy after sIA-SAH was treated as a time-dependent covariate in a Cox regression analysis. Other covariates in Cox regression analysis were age at admission, intracerebral haemorrhage from ruptured sIA, acute seizure within one week after admission, gender and Hunt and Hess grade on admission.
In the mortality analyses, the patients who died within 12 months from the rupture of sIA (n=271) or epilepsy before sIA-SAH (n=9) were excluded. P values <0.05 were considered significant. SPSS 19.0 for Mac (SPSS, Inc, Chicago, IL).

6.2.9 Ethical aspects
The study was approved by the Ethical Committee of the Kuopio University Hospital. Data integration from the national registries was performed with the approval from the Ministry of Social Affairs and Health of Finland.
Table 7. Characteristics of 779 patients alive at 12 months after sIA-SAH from a defined Eastern Finnish population between 1995 and 2014.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with no epilepsy after sIA-SAH (n = 658)</th>
<th>Patients with epilepsy after sIA-SAH (n = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All 163 deaths</td>
<td>All 34 deaths</td>
</tr>
<tr>
<td>Median age (years) on admission for sIA-SAH</td>
<td>50 63</td>
<td>47 57</td>
</tr>
<tr>
<td>Males</td>
<td>273 81 (30%)</td>
<td>58 18 (31%)</td>
</tr>
<tr>
<td>Females</td>
<td>385 82 (21%)</td>
<td>63 16 (25%)</td>
</tr>
<tr>
<td>Familial sIA disease</td>
<td>95 13 (14%)</td>
<td>23 3 (13%)</td>
</tr>
<tr>
<td>Sporadic sIA disease</td>
<td>563 150 (27%)</td>
<td>98 31 (32%)</td>
</tr>
<tr>
<td>Location of ruptured sIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AComA</td>
<td>221 56 (25%)</td>
<td>27 7 (26%)</td>
</tr>
<tr>
<td>A2-A5</td>
<td>39 11 (28%)</td>
<td>6 2 (33%)</td>
</tr>
<tr>
<td>M1</td>
<td>16 4 (25%)</td>
<td>11 5 (45%)</td>
</tr>
<tr>
<td>Mbif</td>
<td>166 32 (19%)</td>
<td>54 14 (26%)</td>
</tr>
<tr>
<td>PComA</td>
<td>86 36 (42%)</td>
<td>14 2 (14%)</td>
</tr>
<tr>
<td>PICA</td>
<td>23 2 (9%)</td>
<td></td>
</tr>
<tr>
<td>ICA bif</td>
<td>17 5 (29%)</td>
<td>1 1 (100%)</td>
</tr>
<tr>
<td>BA bif</td>
<td>24 4 (17%)</td>
<td>3 2 (67%)</td>
</tr>
<tr>
<td>Others</td>
<td>66 13 (20%)</td>
<td>5 1 (20%)</td>
</tr>
<tr>
<td>Two or more sIAs</td>
<td>183 51 (28%)</td>
<td>45 13 (29%)</td>
</tr>
<tr>
<td>Hunt and Hess Scale on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade I</td>
<td>101 18 (18%)</td>
<td>11 3 (27%)</td>
</tr>
<tr>
<td>grade II</td>
<td>322 86 (27%)</td>
<td>31 11 (35%)</td>
</tr>
<tr>
<td>grade III</td>
<td>147 39 (27%)</td>
<td>42 14 (33%)</td>
</tr>
<tr>
<td>grade IV</td>
<td>76 18 (24%)</td>
<td>29 6 (21%)</td>
</tr>
<tr>
<td>grade V</td>
<td>12 2 (17%)</td>
<td>8 8</td>
</tr>
<tr>
<td>Intracerebral hematomata from ruptured sIA</td>
<td>114 33 (29%)</td>
<td>60 20 (33%)</td>
</tr>
<tr>
<td>Intraventricular hematomata from ruptured sIA</td>
<td>121 34 (28%)</td>
<td>30 7 (23%)</td>
</tr>
<tr>
<td>Acute hydrocephalus after sIA-SAH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>236 70 (30%)</td>
<td>39 14 (36%)</td>
</tr>
<tr>
<td>severe</td>
<td>25 9 (36%)</td>
<td>6 3 (50%)</td>
</tr>
<tr>
<td>Occlusive therapy of ruptured sIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>microsurgery</td>
<td>409 94 (23%)</td>
<td>96 28 (29%)</td>
</tr>
<tr>
<td>endovascular therapy</td>
<td>541 63 (12%)</td>
<td>21 5 (24%)</td>
</tr>
<tr>
<td>conservative treatment</td>
<td>8 6 (75%)</td>
<td>4 1 (25%)</td>
</tr>
<tr>
<td>Acute seizure</td>
<td>577 66 (11%)</td>
<td>84 9 (11%)</td>
</tr>
<tr>
<td>Shunt for hydrocephalus after sIA-SAH</td>
<td>86 35 (41%)</td>
<td>25 10 (40%)</td>
</tr>
<tr>
<td>Antidepressant use after sIA-SAH</td>
<td>185 55 (30%)</td>
<td>50 17 (34%)</td>
</tr>
<tr>
<td>GOS at 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>good recovery</td>
<td>501 104 (21%)</td>
<td>60 17 (28%)</td>
</tr>
<tr>
<td>moderate disability</td>
<td>114 37 (32%)</td>
<td>42 12 (29%)</td>
</tr>
<tr>
<td>severe disability</td>
<td>37 16 (43%)</td>
<td>18 5 (28%)</td>
</tr>
<tr>
<td>vegetative state</td>
<td>6 6 (100%)</td>
<td>1 1</td>
</tr>
</tbody>
</table>

sIA = saccular intracranial aneurysm; SAH = subarachnoidal hemorrhage; AComA = anterior communicating artery; A2-A5 = A2-A5 segments of anterior cerebral artery; M1 = proximal segment of middle cerebral artery; Mbif = middle cerebral artery bifurcation; PComA = posterior communicating artery; ICA bif = internal carotid artery bifurcation; PICA = posterior inferior cerebellar artery; BA bif = basilar artery bifurcation; GOS = Glasgow Outcome Scale.
6.3 RESULTS

6.3.1 Mortality of 779 patients alive 12 months after sIA-SAH with or without epilepsy
The final study cohort, 779 12-month survivors of sIA-SAH (Figure 7, Table 7), had been followed up for a median of 12 years after the time of sIA-SAH, a total follow up of 9,394 patient years. Epilepsy after sIA-SAH had been diagnosed in 121 patients, in a median time of 8 months after sIA-SAH (Figure 7, Table 7). Of the 121 epilepsy patients, 34 had died from 12 months until 31 December 2014 (Figure 7) at median age of 66 years, a cumulative mortality of 7% at five years and 21% at ten years. Of the 658 non-epilepsy patients, 164 had died at median age of 74 years, a cumulative mortality of 6% at five years and 16% at ten years, and 28% at 15 years.

6.3.2 Underlying and immediate causes of death of 34 epilepsy patients vs. 163 non-epilepsy patients
Among the underlying causes of deaths (Table 8), only the category `external causes, injury or poisoning` was more frequent in the 121 patients who developed epilepsy after sIA-SAH: 5/34 deaths (15%) vs. 9/163 deaths (6%) (p 0.07). Epilepsy was the immediate cause of death in 7/34 (21%) patients; four of the deaths were associated to status epilepticus, one AED intoxication and two seizure-related pneumonias. In retrospect, epilepsy seemed to associate with 12 (35%) of the 34 deaths.
Table 8. Underlying and immediate causes of death among 779 patients alive 12 months after sIA-SAH and without or with epilepsy during a median follow up of 12 years after sIA-SAH.

<table>
<thead>
<tr>
<th>Underlying causes of death</th>
<th>No epilepsy n=658</th>
<th>Epilepsy n=121</th>
<th>Immediate causes of death</th>
<th>No epilepsy n=658</th>
<th>Epilepsy n=121</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at sIA-SAH</td>
<td>63</td>
<td>57</td>
<td>Median age at sIA-SAH</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>Median age at death</td>
<td>74</td>
<td>66</td>
<td>Median age at death</td>
<td>74</td>
<td>66</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>42 (26%)</td>
<td>10 (29%)</td>
<td>Epilepsy after sIA-SAH</td>
<td>-</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>28 (17%)</td>
<td>8 (23%)</td>
<td>Pneumonia</td>
<td>30 (18%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>17 (10%)</td>
<td>3 (9%)</td>
<td>Sepsis</td>
<td>0</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (2%)</td>
<td>2 (6%)</td>
<td>Cerebrovascular</td>
<td>3 (2%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>4 (2%)</td>
<td>2 (6%)</td>
<td>Ischemic heart disease</td>
<td>7 (4%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Digestive system</td>
<td>3 (2%)</td>
<td>2 (6%)</td>
<td>Other heart diseases</td>
<td>3 (2%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Endocrine / metabolic</td>
<td>2 (1%)</td>
<td>1 (3%)</td>
<td>Mental disorders</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (2%)</td>
<td>1 (3%)</td>
<td>Cancer</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>51 (31%)</td>
<td>0</td>
<td>Other</td>
<td>18 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>External causes, injury or poisoning (Fisher’s exact test p 0.07)</td>
<td>9 (6%)</td>
<td>5 (15%)</td>
<td>Immediate = underlying cause of death</td>
<td>102 (63%)</td>
<td>14 (41%)</td>
</tr>
</tbody>
</table>

Abbreviations: sIA-SAH = subarachnoid hemorrhage from saccular intracranial aneurysm
6.3.1 AED use of epilepsy patients
The 121 epilepsy patients had used AEDs from the date of epilepsy diagnosis until death or 31 December 2014 for a median time of 127 months; among them the 34 deceased for a median of 83 months until death. Among the 34 deceased, the median time from the last AED purchase to the death was 4 months; importantly, 12/34 (35%) had not purchased AEDs within 12 months prior to the death.

6.3.2 Independent risk factor for mortality after sIA-SAH
We studied whether epilepsy after sIA-SAH would be an independent risk factor of death by comparing the mortality in the two groups (34/121 vs. 163/658; Table 2). In Cox proportional hazards regression analysis, we also tested the three factors that independently predicted epilepsy in our previous study (Huttunen et al. 2015). The independent risk factor associated with the death from any cause in the 779 12-month survivors of sIA-SAH were: male gender (HR 2.0); advanced age (HR 1.1 per year); and epilepsy (HR 1.8) (Table 9).
<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>p-value</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>2.0</td>
<td>&lt;0.001</td>
<td>1.5 – 3.0</td>
</tr>
<tr>
<td>Age on admission for sIA-SAH (one year increase)</td>
<td>1.1</td>
<td>&lt;0.001</td>
<td>1.06 – 1.09</td>
</tr>
<tr>
<td>Hunt and Hess Scale on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade I</td>
<td>1.5</td>
<td>ns</td>
<td>1.0 – 2.5</td>
</tr>
<tr>
<td>grade II</td>
<td>1.1</td>
<td>ns</td>
<td>0.8 – 1.9</td>
</tr>
<tr>
<td>grade III</td>
<td>1.1</td>
<td>ns</td>
<td>0.6 – 2.1</td>
</tr>
<tr>
<td>grade IV</td>
<td>0.6</td>
<td>ns</td>
<td>0.1 – 2.7</td>
</tr>
<tr>
<td>grade V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracerebral hematoma from ruptured sIA</td>
<td>1.3</td>
<td>ns</td>
<td>1.0 – 1.9</td>
</tr>
<tr>
<td>Acute seizures within one week after admission</td>
<td>1.1</td>
<td>ns</td>
<td>0.7 – 1.7</td>
</tr>
<tr>
<td>Epilepsy after sIA-SAH</td>
<td>1.8</td>
<td>0.015</td>
<td>1.1 – 3.0</td>
</tr>
</tbody>
</table>

Abbreviations: sIA-SAH = subarachnoid hemorrhage from saccular intracranial aneurysm; ns = not significant.
6.4 DISCUSSION

We studied the epilepsy-related mortality among the survivors of sIA-SAH, with complete data for the underlying and immediate causes of death in a population-based cohort. In our previous analysis of 1,657 sIA-SAH patients, the mortality after acute sIA-SAH was 27% at 12 months, mainly due to poor clinical condition and signs of brain injury on admission; after 12 months other causes of death than acute brain injury became more prevalent (Karamanakos et al. 2012). In the present study, 121 of the 779 12-month sIA-SAH survivors had developed epilepsy, and they had used AEDs for a median of 127 months. Among these 121 patients, epilepsy was the immediate cause of seven (21%) of the 34 deaths, four of them related to status epilepticus. In our retrospective analysis, epilepsy was associated to a total of 12 (35%) of the 34 deaths.

The mechanisms with which epilepsy in AED-treated adult patients still causes excess mortality have not been fully elucidated (Dalic & Cook 2016). In our series, external causes of death (e.g., accident, intoxication, suicide) were more common in the 34 deceased epilepsy patients than in the 163 deceased non-epilepsy patients after sIA-SAH (Table 2). In a recent study from Sweden with population and unaffected sibling controls, 16% of deaths in epilepsy patients were from external causes, with high odds for non-vehicle accidents and suicide. Of those who died from external causes, 75% had comorbid psychiatric disorders, with strong associations with co-occurring depression and substance abuse (Fazel et al. 2013). In Finland, prescriptions are valid for one year, while pharmacies give out medications for three months at one purchase. In the present cohort, the compliance of the 121 epilepsy patients for AED use was good in general. However, 12 (35%) of the 34 deceased epilepsy patients had not purchased AEDs one year prior to death. Poor compliance or sustainability of long-term AED treatment in epilepsy may be an avoidable risk factor for death in dedicated follow-up services for sIA-SAH survivors.

Finland offers its residents publicly funded healthcare which decreases the socioeconomic differences in the access to the healthcare. Finland is divided into mutually exclusive catchment areas of tertiary care between the five university hospitals. Finnish healthcare system allows the creation of disease cohorts that are unselected and minimally biased. Very accurate population statistics and a stable population allow long-term follow-up and ensure that few patients are lost to follow up. Our study is retrospective, but we were able to confirm diagnoses of the patients with epilepsy by neurologists due to the national registry of fully reimbursed medicines and the causes of death produced by Statistics Finland (Huttunen et al. 2015). We did not have valid information about epilepsy in the patients permanently institutionalized after sIA-SAH. Their AEDs are not reimbursed but are included in the institution fees, so the overall incidence may be slightly underestimated.

The survivors of sIA-SAH – whether sporadic or members of sIA families – would benefit from dedicated eHealth services designed to improve the awareness of the disease and its risks and outcomes. Our present and previous data on epilepsy (Huttunen et al. 2015) in sIA-SAH survivors, as well as their long-term risks for depression (Huttunen et al. 2016), shunt-dependent hydrocephalus (sAdams et al. 2016), and excess mortality (Huttunen et al. 2011, Karamanakos et al. 2012) would support the development of accurate medical risk and outcome calculators for clinicians, patients and their relatives, and general public. Such calculators are already found in the Internet for many diseases, but at best they should
be supported by data from population-based neurodisease cohorts, with clinical lifelines constructed from follow-up and national registry data.

6.5 CONCLUSIONS

Comorbid epilepsy in the 12-month survivors of sIA-SAH is associated with increased risk of death in long term follow up. Our present and previous data (Huttunen et al. 2015) on epilepsy in sIA-SAH survivors, as well as the risk of depression (Huttunen et al. 2016), suggests that dedicated evaluation and follow up practices should be organized for sIA-SAH survivors (Rinkel & Algra 2011).
7 General Discussion

7.1 EPILEPSY IN TWO-WEEK SURVIVORS OF SIA-SAH

In the present population-based and unselected cohort, the cumulative incidence of and independent risk factors for epilepsy were determined in 1,045 sIA-aSAH patients first admitted to KUH between 1994 and 2008 from its defined Eastern Finnish catchment. The cumulative incidence of epilepsy after aSAH was 8% at one year and 12% at five years. Half of the epilepsy diagnoses were made within eight months after sIA-SAHA and the majority were made within 17 months. However, epilepsy could develop even years after sIA-SAH.

Hunt and Hess grades III and IV-V upon admission are independently associated with a higher risk of epilepsy in the present cohort. This indicates that patients with more severe sIA-SAHA are more likely to develop epilepsy compared to patients who are in good condition, according to Hunt and Hess grading. The cumulative 12-month mortality in this cohort was 25%, and a Hunt and Hess grade V upon admission was the strongest risk factor for mortality. Hunt and Hess grading was an independent risk factor for both epilepsy after sIA-SAHA and 12-month mortality. Acute seizures were also independent risk factors for epilepsy after sIA-SAHA. It is possible that such seizures are the first manifestation of epilepsy after sIA-SAHA and can also be an indicator of more severe initial sIA-SAHA. A large intracranial hemorrhage was an independent risk factor for epilepsy, and the cumulative incidence of epilepsy increased with the increasing volume of intracerebral hemorrhage. This was the only independent risk factor that is a single manifestation of sIA-SAHA and that causes direct brain damage. The cumulative incidence of epilepsy was 36% at 10 years in patients with a large intracerebral hemorrhage.

The 12-month mortality and permanent morbidity after sIA-SAHA was largely determined by the condition upon admission and during the acute phase of neurointensive care. The cumulative 12-month mortality in this cohort was 25%, and a Hunt and Hess grade V (extension reaction to pain) upon admission was the strongest risk factor. Hunt and Hess grading was an independent risk factor for both epilepsy after sIA-SAHA and 12-month mortality. Based on competitive risk (death) analysis, the cumulative epilepsy rate was 19% at five years for grade IV (flexion reaction) but only 6% and 8% at five years for grade I (mild headache, slight nuchal rigidity) and grade II (moderate to severe headache, nuchal rigidity, no neurological deficits other than cranial nerve palsies), respectively. The sign of local brain damage in acute neuroimaging that independently predicted epilepsy was a large intracerebral hemorrhage, usually from a ruptured sIA on the middle cerebral artery bifurcation or the anterior communicating artery.

Due to the unselected nature of sIA-SAHA patients and the large sample size, the present study provides new information on the incidence of and risk factors for epilepsy after sIA-SAHA. Calculations regarding the incidence of and risk factors for epilepsy after sIA-SAHA were accomplished using the competitive risks method to make analyses more accurate in the presence of the competing event of early death. Patients who survived the initial bleeding were included in the analysis of independent risk factors to minimize the impact of the high early mortality of sIA-SAHA patients in the first two weeks. The registry of full reimbursements for AEDs of the Social Insurance Institution of Finland was reliable in identifying the patients with epilepsy, even a long time after sIA-SAHA. Only a few patients were lost from follow up.
The use of prophylactic AEDs varies in different studies. This study was not designed to address the question of whether to use anticonvulsant prophylactic medication, but a number of the patients received prophylactic phenytoin after discharge because it was the current treatment protocol in the past. Rosengart et al. reported that prophylactic AED treatment is associated with in-hospital complications and worse outcomes at three months’ follow-up (Rosengart et al. 2007). Rhoney et al. investigated the effect of anticonvulsant prophylaxis after aSAH; they found that 14% of patients had late seizures and that half of them were using AEDs. All the patients except one had received in-hospital AEDs. The median time to outpatient seizures was 326.5 days (Rhoney et al. 2000).

The present study reports more detailed information on the predictors of epilepsy after sIA-SAH for legislators and health care employees. aSAH patients would benefit from studies that specify and advance the treatment of epilepsy and comorbidities relating to epilepsy after sIA-SAH. Unfortunately, epilepsy is most likely the result of many different components, and confounding is present in research. Therefore, determining influencing risk factors for epilepsy after sIA-SAH is difficult.

We do not have information about those patients with epilepsy after sIA-SAH who were permanently institutionalized, and therefore our figures might slightly underestimate the incidence of epilepsy. Patients who are permanently institutionalized are not fully reimbursed for AEDs because their medication is included in their institution fee. A few patients may be missed, as some refuse to apply for full reimbursement in order to protect their privacy. We did not have information concerning the use of prophylactic AEDs during the acute phase of sIA-SAH and for late prophylaxis of seizures, but this limitation does not change the overall incidence of epilepsy.

Epilepsy is common after sIA-SAH. The cumulative risk of epilepsy is 8% at one year and 13% at 10 years. The majority of epilepsy diagnoses are made within 17 months, but a diagnosis can be made years after the rupture of an sIA. Patients with intracerebral hemorrhage in particular are at great risk of developing epilepsy. Independent risk factors included intracerebral hemorrhage, early epileptic seizures during the acute phase of sIA-SAH, and worse initial clinical presentation (Hunt and Hess grades III and IV–V). One should interpret that epilepsy is caused by the first impact of sIA-SAH to the brain and not the consequent treatment with caution.

A recent study determined that the nationwide incidence of SAH seems to be decreasing in Finland to the level found in other Nordic countries. Finnish studies on sIA-SAH can provide generalizable data on the epidemiology of SAH (Korja et al. 2016). Current studies provide generalizable information due to targeting the surviving, unselected portion of sIA-SAH patients with a long follow-up. aSAH patients would benefit from studies aimed at preventing epilepsy and studies that specify and advance the treatment of epilepsy and comorbidities relating to epilepsy after sIA-SAH.
7.2 DRUG-TREATED DEPRESSION IN 12-MONTH SURVIVORS OF SIA-SAH

Recovering aSAH patients are often burdened with depressive symptoms. Depression after sIA-SAH can have severe consequences for individuals, as mood disturbances can cause setbacks in the rehabilitation process. In addition, patients report fatigue (Kutlubaev et al. 2012) and posttraumatic stress disorder (Hedlund et al. 2011), and only 35% return to full-time work after a seemingly good recovery (Passier et al. 2011).

This is the first population-based study with case controls and complete follow-up for continuous ATD use verified using a national registry. We describe independent risk factors for continuous depression medication use after sIA-SAH, verified using four-vessel angiography. At least two purchases of ATD was chosen as an indicator of continuous use of ATDs, as pharmacies give out a maximum of three months’ medication at one purchase. At least two purchases would mean at least six months’ use of ATDs and repeated purchases.

In our population-based case control study of 940 patients with no ATD use before sIA-SAH and who were alive one year after sIA-SAH, we identified 277 (29%) patients with continuous ATD use compared to 14% of the control population. The 940 12-month survivors of sIA-SAH had significantly more ATD use (OR 2.6) than their 2,676 matched controls. Outcome at one year after the acute phase of sIA-SAH was the strongest predictor of drug-treated depression, based on multivariate analysis and classification tree analysis.

The modified Rankin Scale (mRS; 12 months) was used as the most potent predictor of ATD use after sIA-SAH; 22% of the patients with no symptoms (mRS 0) used ATDs vs. 47% of the patients with no significant disabilities to severe disabilities who required constant nursing care and attention (mRS I-V). Furthermore, in the sub group of patients with no symptoms (mRS 0), the condition upon admission for sIA-SAH according to Hunt and Hess grades II–IV compared to Hunt and Hess grade I predicted ATD use; 25% of the patients had Hunt and Hess grades II–IV and 12% had Hunt and Hess grade I. The condition upon admission for sIA-SAH was also an independent risk factor for ATD use, suggesting that the severity of aSAH based on the patient’s clinical condition can be used as a predictor of their ATD use. In one-year survivors after sIA-SAH with no significant disability or who were able to look after their own affairs without assistance but were unable to carry out all previous activities, age at admission predicted ATD use, suggesting that younger age at admission increases the risk of ATD use when recovery from sIA-SAH is incomplete. Patients younger than 55 had an ATD use rate of 48% compared to patients older than 55, who had an ATD use rate of 29%. The patients alive one year after sIA-SAH in a condition that required some help but who were able to walk unassisted (mRS III), those who were unable to attend to their own bodily needs without assistance, and those who were unable to walk unassisted (mRS IV) had a high rate of ATD use at 63%.

Epilepsy as a comorbidity in the late phase of sIA-SAH is associated with an increased risk of ATD use. Epilepsy in the two-week survivors of acute sIA-SAH was predicted by signs of the primary impact on the brain tissue (ICH) on a CT scan upon admission, the patient’s condition upon admission, and acute seizures within one week after sIA-SAH. Depression is also reported as an independent risk factor for unprovoked seizures (Hesdorffer et al. 2006). Low socioeconomic status of adults is also associated with epilepsy (Hesdorffer et al. 2005).

Age was significantly associated with ATD use. The odds of ATD use decrease with increasing age at admission. This was also reported in a 2011 Swedish prospective study of
710 aSAH patients. The authors suggested that this could be related to anxiety caused by greater expectations of returning to work (Ronne-Engstrom et al. 2013). This could also be related to the increased mortality of elderly patients with more severe sIA-SAHS.

Long-term sIA-SAHS survivors experience neurological, cognitive, and psychosocial problems that may be missed during routine visits to outpatient clinics. The patients with a seemingly good recovery at 12 months after sIA-SAHS and no epilepsy are at a significant—and possibly underestimated—risk of drug-treated depression. Epilepsy more than doubles their risk. Almost half of the patients with worse outcomes at 12 months used ATDs; this is also possibly underestimated.

In our study, we did not have Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria, but depression is characterized by a unique set of symptoms and DSM-IV helps in its diagnosis. The diagnosis of depression is based mainly on a clinical interview and the duration of symptoms. Patients with depression often use ATDs, which have been shown to improve depression for people who are physically ill (Rayner et al. 2010). Our follow-up method with information from national registries about continuous ATD use allowed us to reconstitute reliable analysis concerning drug-treated depression in sIA-SAHS patients without bias originating from cross-sectional data acquisition. Depression evaluated with medication use also allows us to take into account moderate depression managed apart from psychiatric clinics. We did not have valid information about depression medication use in the patients permanently institutionalized after sIA-SAHS.

Future studies should focus on the relationship between depression and epilepsy after sIA-SAHS to investigate the role of seizure balance, treatment, medication, and the stigma of epilepsy as a confounding factor in diagnosing and treating depression in sIA-SAHS patients, recognizing the fact that sIA-SAHS patients already suffer from a devastating disease with or without any comorbid disease. When sIA-SAHS patients are burdened with depression and epilepsy, recovering and returning to daily activities or to salaried work is most likely even harder. Possible interventions should focus on finding a means to prevent depression in sIA-SAHS patients. Depression should be actively screened for among sIA-SAHS patients, especially those with epilepsy after sIA-SAHS.

### 7.3 Epilepsy and Mortality in 12-Months Survivors of SIA-SAHS

Predictors for mortality in one-year survivors after sIA-SAHS were being older, being male, and having epilepsy after sIA-SAHS. According to Hunt and Hess grading, the severity of the initial sIA-SAHS, reflecting a combined effect of brain tissue damage and the condition upon admission, was not a predictor for mortality. Previous studies have also found older age and male gender to be predictors of mortality after sIA-SAHS (Huttunen et al. 2011, Huhtakangas et al. 2015). However, post sIA-SAHS epilepsy has not been previously reported as a predictor of mortality after sIA-SAHS.

This study gives the opportunity to analyze the circumstances of death provided by Statistics Finland from two standpoints, sIA-SAHS and epilepsy. Cerebrovascular diseases and malignant neoplasms were the most frequent underlying causes of death in one-year survivors after sIA-SAHS with or without post sIA-SAHS epilepsy. Previous studies have reported similar causes of death for epilepsy patients (Trinka et al. 2013, Keezer et al. 2016a, Aurlien et al. 2012) and for sIA-SAHS patients (Huhtakangas et al. 2015, Korja et al. 2013b, Zaroff et al. 2012). External causes and injury as immediate causes of death were more common in post sIA-SAHS epilepsy patients compared to patients without epilepsy, and this
risk needs to be taken into account when clinicians are counselling post sIA-SAH epilepsy patients. Pneumonia was the most frequent immediate cause of death after sIA-SAH in one-year survivors with or without epilepsy, which was also suggested in a previous study (Keezer et al. 2016a).

Our results suggest that the comorbid disease of post sIA-SAH epilepsy has a significant role in mortality. Pneumonia and external causes of death are possible post sIA-SAH seizure related causes of death, even if death certificates fail to acknowledge epilepsy as a contributing factor. Among the post sIA-SAH epilepsy patients in this study, the immediate cause of death was epilepsy in 15%, and epilepsy was a contributing factor in the deaths of 21% of the patients. A previous study from the United Kingdom reported that 23% of deaths were directly related to epilepsy etiology (Keezer et al. 2016a).

In this population-based cohort, the compliance with AED use was good. However, of the post sIA-SAH epilepsy patients who died during follow-up, 35% had not purchased AEDs one year prior to death. In Finland, a physician’s prescription is valid for one year during the study period, and pharmacies give out medication for out-patients only for a maximum of three months at one purchase. Hence, 35% of the patients were not using AEDs prior to death, unless they were institutionalized. Some of the post sIA-SAH epilepsy patients might have been permanently institutionalized before death and therefore had no need for out-patient AED prescriptions, but our results indicate that not all post sIA-SAH patients were on adequate AED medication before death. Post sIA-SAH epilepsy is an important predictor of mortality after sIA-SAH, and post sIA-SAH epilepsy itself causes excess mortality in addition to comorbid disease, explained by the related causes of death.

Male gender was an independent risk factor for death in one-year survivors of sIA-SAH. This could be explained by the possible differences in lifestyles between males and females. In addition, the life expectancy of males is shorter than that of females in Finland.

Conservative treatment modalities were chosen for patients who were mortally ill after sIA-SAH. Being in a vegetative state at one year and the conservative treatment of mortally ill sIA-SAH patients are obvious predictors for death and are significantly associated with mortality in univariate analyses.

The Finnish healthcare system is publicly funded, which may decrease socioeconomic differences in access to healthcare. Finland is divided into mutually exclusive catchment areas between the five university hospitals. This allowed the creation of disease cohorts that are unselected and minimally biased. Very accurate population statistics and a stable population allow long-term follow-up and ensure that few patients are lost to follow up. Our study is retrospective, but we were able to confirm neurologists’ diagnoses of the patients with epilepsy due to the national registry of full reimbursement for medicines and the causes of death produced by Statistics Finland.

We did not have valid information about epilepsy in the patients permanently institutionalized after sIA-SAH. The cost of their AEDs is not reimbursed but is included in the institution fees, so the overall incidence may be slightly underestimated. We did not have information about each AED prescription, and the exact use of AEDs cannot be estimated from the SII nationwide registry.

Epilepsy had been diagnosed in 15% of patients after sIA-SAH. Post sIA-SAH epilepsy is associated with excess mortality in addition to comorbid disease. The prognosis associated with post sIA-SAH epilepsy differs from that for recovering sIA-SAH patients without epilepsy, and patients at risk of death should be identified to possibly prevent any
unnecessary deaths of post sIA-SAH epilepsy patients. This study can potentially facilitate decisionmaking when considering how to inform post sIA-SAH epilepsy patients about the increased risk of death. The public health burden of sIA-SAH and epilepsy is substantial and deserves attention from clinicians, as both sIA-SAH and epilepsy result in years of potential life lost. The treatment and counselling of post sIA-SAH epilepsy patients could enhance the prognosis for life. The sustainability of epilepsy treatment is an important objective for post sIA-SAH epilepsy patients to decrease mortality. Our data on epilepsy will support the clinical practice of post-SAH outpatient clinics that should be organized in dedicated neurocenters.
8 Conclusions

I. Cumulative incidence of epilepsy is 12% at five years. Epilepsy and 12-month mortality after sIA-SAH share poor Hunt and Hess grading as an independent risk factor. Epilepsy in the two-week survivors of sIA-SAH is predicted by signs of primary injury in the brain tissue, most notably ICH.

II. The sIA-SAH survivors use significantly more often ATDs, indicative of depression, than their matched population controls. Even with a seemingly good recovery (mRS 0) at 12 months after sIA-SAH, there is a significant risk for depression requiring ATD medication. The independent risk factors for ATD use were age on admission for sIA-SAH, the Hunt and Hess Scale grade IV, modified Rankin Scale (mRS) grades I, II, III, IV and epilepsy after sIA-SAH.

III. Comorbid epilepsy in the 12-month survivors of sIA-SAH is associated with increased risk of death in long term follow up. Among the underlying causes of deaths, only the category ‘external causes, injury or poisoning’ was more frequent in the 121 patients who developed epilepsy after sIA-SAH. Epilepsy was the immediate cause of death in 21%) patients. The survivors of sIA-SAH require long term dedicated follow up, including identification and effective treatment of comorbid epilepsy to prevent avoidable deaths.
9 References


Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 1993;34:592-596.


Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK & Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet neurology 2009;8:635-642.


Trinka E & Kälviäinen R. 25 Years of Advances in Definition, Classification and Treatment of Status Epilepticus. Seizure 2016;.


van de Beek D, Rinkel GJ & Ruigrok YM. Genetic risk load according to the site of intracranial aneurysms. Neurology 2014;83:34-39.


Subarachnoid hemorrhage (SAH) is most often caused by the rupture of a saccular intracranial aneurysm (sIA) at the fork of the intracranial extracerebral artery, affects the working-age population. The mortality rate after acute sIA-SAH is high. Along with various degrees of acute or delayed brain injury, long term survivors of sIA-SAH are often affected by neurological and cognitive disorders. In the current study we analyzed the incidence and risk factors of epilepsy and depression along with the epilepsy-associated causes of death after sIA-SAH in a population based cohort.