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ACADEMIC DISSERTATION
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Abstract

Intracranial aneurysms are treated by either microsurgical clipping or endovascular coiling (i.e. embolization), the latter being a much newer treatment method. Thus, long-term outcome studies after endovascular coiling are still sparse. In addition, imaging modalities are more and more frequently used to study patients for many different reasons, and unruptured intracranial aneurysms are detected incidentally. Treatment of those incidentally found unruptured aneurysms is debated a lot because complication rate after both clipping and coiling is high, risk of bleeding is low and we still do not know which aneurysms will eventually rupture. In spite of highly developed imaging methods, there are still patients with subarachnoid bleeding without any etiological factor. This bleeding of unknown etiology has been studied much less than aneurysmal disease in recent years. The aim of this thesis was to determine the long-term outcome of patients treated with embolization and patients with subarachnoid hemorrhage (SAH) of unknown etiology.

This study is based on 1294 patients treated in Tampere University Hospital during 1989-1999. Surviving patients treated with endovascular coiling (n=185) and patients with SAH of unknown etiology (n=97) were studied with magnetic resonance imaging (MRI) 9-18 years (median 9 yrs, mean 11yrs) after hospitalization and the clinical outcome of all treated patients was assessed.

Patients with previous SAH of unknown etiology have a good clinical outcome with no vascular changes in MR-images and they have no excess mortality compared to matched general population. Patients with unruptured aneurysms, however, have excess long-term mortality, especially if the aneurysm is left untreated. Both ruptured and unruptured intracranial aneurysms are stable in long-term MRI studies but complete occlusion should be the goal of the treatment to prevent rebleedings. Brain infarctions without clinical consequences are common after embolization.

Tiivistelmä

Aivovaltimon pullistumia (aneurysma) hoidetaan sekä kallonavausleikkauksella että suonensisäisesti embolisoimalla. Embolisaatio on menetelmänä selvästi uudempi ja sen vuoksi hoitomuodon pitkäaikaistuloksia ei juuri ole julkaistu. Myös kuvantamistekniikat ovat kehittyneet viime vuosina ja sen vuoksi sattumalta löydettyjen aneurysmien määrä on lisääntynyt. Näiden sattumalöydösaneurysmien hoidosta kiistellään, sillä hoitoon liittyvät riskit ovat joissain tutkimuksissa suurempia kuin aneurysman puhkeamisriski. Vaikka aivoverisuonten kuvantamismenetelmät ovat kehittyneet, on edelleen potilaita, joiden lukinkalvonalaiselle verenvuodolle (subaraknoidaalivuoto, SAV) ei löydy syytä. Tämän väitöstutkimuksen tavoite oli selvittää aneurysma- ja SAV-potilaiden pitkäaikaisennustetta ja kuvantamislöydöksiä lähes 10 vuoden seuranta-aikana.

Tutkimusaineisto koostui 1294 SAV- ja aneurysmapotilaasta, jotka olivat hoidossa Tampereen yliopistollisessa sairaalassa vuosina 1989-1999. Potilaat, joita oli hoidettu suonensisäisesti embolisoimalla (n=185) tai jotka olivat olleet hoidossa etiologialtaan epäselväksi jääneen subaraknoidaalivuodon vuoksi (n=97), kutsuttiin uuteen pään magneettitutkimukseen. Magneettikuvaus tehtiin keskimäärin 11 vuotta (9-18 vuotta) primaarihoidon jälkeen ja lisäksi kaikkien potilaiden toipuminen arvioitiin.

Potilaat, joiden SAV:n syy ei selvinnyt, toipuivat hyvin ja pitkäaikaiskuolleisuus oli normaaliväestön tasolla. Magneettikuvissa ei löytynyt poikkeavia suonirakenteita, jotka olisivat selittäneet aiempaa vuotoa. Vuotamattoman aneurysman omaavilla potilailla on lisääntynyttä pitkäaikaiskuolleisuutta erityisesti, jos aneurysma on jätetty hoitamatta. Potilailla on suurempi riski sydän-ja verisuonitautikuolemiin kuin normaaliväestöllä. Vuotaneet aneurysmat säilyttävät hoitotuloksen pitkäaikaisseurannassa mutta embolisaatiossa pitäisi pyrkiä aneurysman kokonaistäyttöön uusintavuotojen estämiseksi. Aivoinfarkti on yleinen embolisaation komplikaatio kuvantamistutkimuksissa, mutta vain harvoin aiheuttaa kliinisiä oireita.

Abstrakt

Hjärnaneurysm kan behandlas kirurgiskt genom kraniotomi eller med endovaskulär ocklusion. Eftersom endovaskulär ocklusion är en nyare behandlingsform finns få studier om metodens långtidseffekter. I och med snabb utveckling av radiologiska undersökningsmetoder har det skett en ökning av antalet aneurysm som upptäcks slumpmässigt. Åsikterna om hur dessa slumpmässigt upptäckta aneurysm bör behandlas varierar stort. Vissa undersökningsresultat tyder på att behandling av dessa aneurysm medför en större komplikation risk än risken för ruptur av aneurysmet. Även om de radiologiska undersökningsmetoderna av hjärnans blodkärl är avancerade finns det fortfarande patienter där orsaken till subaraknoidalblödningen (SAB) inte kan påvisas. Målet med denna avhandling var att undersöka långtidsprognosen av aneurysm- och SAB-patienter samt deras radiologiska fynd under en nästan tio års uppföljningstid.

Materialet för undersökningen bestod av 1294 patienter som behandlats på Tammerfors universitetssjukhus under åren 1989-1999 på grund av SAB och aneurysm. De patienter som behandlats genom endovaskulär ocklusion (n=185) eller som behandlats för SAB av oklar etiologi (n=97) kallades för ny magnetundersökning av hjärnan. Magnetundersökningen gjordes i genomsnitt 11 år (9-18 år) efter det initiala vårdtillfället. Dessutom bedömdes alla patienters återhämtning efter given behandling.

De patienter som behandlats för SAB av oklar etiologi visade sig i studien ha återhämtat sig bra och långtidsmortaliteten motsvarade normalbefolkningens. I magnetkameraundersökningen konstaterades inga blodkärlsförändringar som hade kunnat förklara den tidigare blödningen. Däremot uppvisade patienter med konstaterat obrustet aneurysm en högre långtidsmortalitet, vilket i synnerhet gällde om aneurysmet lämnats obehandlat. Dessa patienter löper en större risk att avlida i hjärt- och kärlsjukdom än normalbefolkningen. Aneurysm som brustit och som behandlats med endovaskulär ocklusion uppvisade goda resultat i långtidsuppföljningen. För att undvika nya blödningar bör man eftersträva fullständig ocklusion av aneurysmet. Radiologiskt konstaterad hjärninfarkt är en vanlig komplikation efter endovaskulär ocklusion av aneurysm, men leder sällan till kliniska symptom.

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ABBREVIATIONS

ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
ACoP	Posterior communicating artery
ACT	Activated clotting time
BA	Basilar artery
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CE-MRA	Contrast-enhanced magnetic resonance angiography
CMI	Cella media index
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
CTP	Computed tomography perfusion
DSA	Digital subtraction angiography
FLAIR	Fluid-attenuation inversion recovery
GCS	Glasgow coma scale
GDC	Guglielmi detachable coils
GOS	Glasgow outcome scale
GRE	Gradient echo sequence
H&H	Hunt and Hess scale
ICA	Internal carotid artery
ICG	Indocyanine green
ICH	Intracerebral hematoma
IVH	Intraventricular hemorrhage
MCA	Middle cerebral artery
MIP	Maximum intensity projection
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MTT	Mean transit time
PCA	Posterior cerebral artery
RSR	Relative survival ratio

SAH	Subarachnoid hemorrhage
TOF-MRA	Time-of-flight magnetic resonance angiography
TTP	Time to peak
VBA	Vertebrobasilar artery
WFNS	World Federation of Neurosurgical surgeons

List of original publications

This thesis is based on the following publications, referred to in the text by their Roman numerals:

I Pyysalo, L.M., Keski-Nisula, L.H., Niskakangas, T.T., Kähärä, V.J. & Öhman, J.E. 2010, "Long-term follow-up study of endovascularly treated intracranial aneurysms.", Interventional Neuroradiology, vol. 16, no. 3, pp. 231-239.

II Pyysalo, L.M., Keski-Nisula, L.H., Niskakangas, T.T., Kähärä, V.J. & Öhman, J.E. 2011, "Long-term MRI findings of patients with embolized cerebral aneurysms.", Acta radiologica, vol. 52, no. 2, pp. 204-210.

III Pyysalo L, Luostarinen T, Keski-Nisula L, Öhman J: Long-term excess mortality of patients treated for unruptured intracranial aneurysms. Submitted.

IV Pyysalo LM. Niskakangas TT. Keski-Nisula LH. Kähärä VJ. Öhman JE. 2011, “Long term outcome after subarachnoid haemorrhage of unknown aetiology. Journal of Neurology, Neurosurgery & Psychiatry. 82(11):1264-6, 2011 Nov.

1. Introduction

Aneurysmal subarachnoid hemorrhage (SAH) has high mortality due to bleeding itself, vasospasm and possible rebleeding before occlusion. Approximately 50% of SAH patients still die in spite of modern diagnostic and treatment methods (Ingall et al., 1989; Sarti et al., 1991; Broderick et al., 1994; Hop et al., 1997; Inagawa, 1997; Inagawa, 2001; Pobereskin, 2001; Stegmayr et al., 2004; Inagawa, 2005; Pajunen et al., 2005). Early treatment is preferable to prevent rebleeding and also to give the opportunity to implement intensive and safe vasospasm treatment (Ohman and Heiskanen, 1989). Endovascular coiling started two decades ago and is widely used nowadays. Coiling has been found to be safe and sufficient to prevent rebleeding after aneurysmal SAH, although the rebleeding rate is higher after coiling than clipping (Raymond and Roy, 1997; Vinuela et al., 1997; Byrne et al., 1999; Molyneux et al., 2009). However, patients with coiled aneurysms do have better clinical recovery than patients treated with microsurgical clipping (Molyneux et al., 2005; Molyneux et al., 2009). Long-term outcome studies after endovascular coiling have been limited because this is a relatively new treatment method.

Treatment of unruptured aneurysms has recently been discussed a lot because treatment morbidity is still relatively high and speculated to be higher than the risk of rupture of small incidental aneurysms (Juvela et al., 1993; Juvela et al., 2000; Wiebers et al., 2003). Further, although aneurysm rupture risk correlates to the aneurysm size, most ruptured aneurysms are small, less than 7mm. Thus, mechanisms of rupture and long-term outcome following different treatment methods have to be studied further.

SAH is usually caused by a rupture of intracranial, saccular aneurysm. In 5-15% of cases no cause of bleeding can be found despite repeated angiographic studies. Such SAH of unknown etiology is less studied than aneurysmal bleeding and the benign nature of this entity is based more on clinical experience than evidence-based medicine.

2. Review of the literature

2.1 Aneurysmal subarachnoid hemorrhage (SAH)

Intracranial saccular aneurysms account for approximately 85% of cases of nontraumatic SAH (Kassell et al., 1990b; van Gijn and Rinkel, 2001; van Gijn et al., 2007). The other, rare, causes are listed in Table 1. Despite repeated angiographies, no source of bleeding is identified in up to 15% of SAH cases (Ruigrok et al., 2000). This entity "SAH of unknown etiology" is discussed separately at the end of this literature review.

2.1.1 Aneurysm characteristics

2.1.1.1 Classification

An aneurysm is a localized and persistent out-poutching of the vessel. Aneurysms can be divided into saccular and non-saccular types and saccular aneurysm account for more than 85% of all intracranial aneurysms (Kassell et al., 1990b; van Gijn and Rinkel, 2001; van Gijn et al., 2007). Saccular aneurysms involve part of the circumference of the artery arising from vascular bifurcations, or from the side of a vessel, and they have a single neck. Saccular aneurysms can arise as solitary (70-75%) or multiple (25-30%) lesions. Cerebral aneurysms are rare in children: 2% of SAH patients are under 19 and only 0.1% are under 5 years old (Heiskanen, 1989; Koroknay-Pál et al., 2012). Nonsaccular aneurysms involve the entire arterial wall and do not have a neck. Non-saccular aneurysms can be divided into several types: fusiform, dissecting, mycotic, flow-related and traumatic aneurysms.

Table 1. Rare causes of subarachnoid hemorrhage. Adapted from van Gijn et al. (2007).

Non-inflammatory lesions of intracerebral vessels
Arterial dissection
Arteriovenous malformation
Dural fistulae
Intracerebral cavernous angiomas
Cerebral venous thrombosis
Cerebral amyloid angiopathy
Moyamoya disease
Inflammatory lesions of cerebral arteries
Behçet's disease
Primary angiitis
Polyarteritis nodosa
Churg-Strauss syndrome
Wegener's granulomatosis
Infectious (mycotic) aneurysms
Bacterial aneurysms (Streptococcus, Stafylococcus, Enterococcus)
Fungal aneurysms (Aspergillus, Candida)
Vascular lesions in the spinal cord
Saccular aneurysm of spinal artery
Spinal arteriovenous fistula or malformation
Cavernous angioma at spinal level
Sickle cell disease, coagulopathies
Tumours
Pituitary apoplexy
Cerebral metastases of cardiac myxoma
Malignant glioma
Angiolipoma
Schwannoma of cranial nerve
Cervical meningiomas
Cervical spinal cord hemangioblastoma
Spinal meningeal carcinomatosis
Radiation-induced aneurysms
Drugs
Cocaine abuse
Anticoagulant drugs
Trauma
Direct injury to the arterial wall
Acceleration-induced shear

2.1.1.2 Location

The majority of aneurysms arise at the bifurcation of arteries near the circle of Willis and most, about 85% arise in the anterior circulation. The most common sites of ruptured aneurysms are the takeoff of the posterior communicating artery (ACoP) from the internal carotid artery (ICA, 24-41%), anterior communicating artery (ACoA)/ anterior cerebral artery (ACA, 30-39%), and middle cerebral artery (MCA, 20-33%) (Wiebers et al., 2003; Clarke et al., 2005). However, in the Finnish population, MCA aneurysms have predominance compared to other locations; up to 35% of ruptured aneurysms and 57% of unruptured aneurysms are located in MCA (Rinne et al., 1994; Huttunen et al., 2010). Approximately 15% of aneurysms occur in the posterior, vertebro-basilar, circulation (Clarke et al., 2005). Table 2 shows aneurysm location distribution in a Finnish study (Huttunen et al., 2010).

Table 2. Location of intracranial aneurysms adapted from Huttunen et al. (2010).

	Ruptured		**Unruptured**	
	n	**%**	**n**	**%**
ICA bifurcation	41	4	50	4
ACoP	153	13	93	8
ACoA	369	32	152	13
ACA	76	7	87	8
MCA	404	35	651	57
VBA	119	10	113	10
Total	1162		1146	

ACA=Anterior cerebral artery; ACoA=Anterior communicating artery; ACoP=Posterior communicating artery; ICA=Internal carotid artery; MCA=Middle cerebral artery; VBA= Vertebrobasilar artery

2.1.1.3 Size

Aneurysms are usually defined as small (<10 mm), large (10–25 mm), or giant (>25 mm) on the basis of their maximum fundus dimension. Giant aneurysms account for 4-8% of intracranial aneurysms (Vinuela et al., 1997). Giant aneurysms rupture more often than smaller aneurysms and they are also more often symptomatic because of mass effect or thromboembolic events caused by aneurysm thrombosis (Wiebers et al., 1981; Investigators, 1998; Rinkel et al., 1998; Forget et al., 2001; Juvela et al., 2001; Wiebers et al., 2003). Although risk of aneurysm rupture correlates to the aneurysm size, up to 86% of ruptured aneurysms are small, less than 10mm (Rinkel et al., 1998; Forget et al., 2001). Table 3 presents size relations from a study of Forget et al. (2001).

Table 3. Sizes of ruptured aneurysms (Forget et al., 2001).

Fundus size	n	%
<5mm	86	35
6–10mm	124	51
11–15mm	17	7
16–20mm	6	2
21-25mm	3	1
>25mm	9	4

2.1.2 Epidemiology of intracranial aneurysms

2.1.2.1 Incidence

The overall incidence of aneurysmal SAH is approximately 9 (6-12) per 100 000 persons-years in western countries (Sarti et al., 1991; Broderick et al., 1994; Ostbye et al., 1997; Cesarini et al., 1999; Anderson et al., 2000; Ingall et al., 2000; Inagawa, 2001; Pobereskin, 2001; van Gijn and Rinkel, 2001; de Rooij et al., 2007; van Gijn et al., 2007; Koffijberg et al., 2008). However, rates are much higher in Finland and Japan which range from 17 up to 37/100000 (Sarti et al., 1991; Broderick et al., 1994; Ostbye et al., 1997; Cesarini et al., 1999; Ingall et al., 2000; Inagawa, 2001;

Pobereskin, 2001; de Rooij et al., 2007; Koffijberg et al., 2008). The decline in incidence of SAH over the past decades is moderate compared with that for strokes in general (de Rooij et al., 2007).

2.1.2.2 Prevalence

In autopsy and radiological studies, the prevalence of intracranial aneurysms in the general population is around 2% (0.2-9%) (Rinkel et al., 1998; Ronkainen et al., 1998). Most aneurysms never rupture and the prevalence is much higher than the incidence of SAH. Prevalence increases with age and is higher in females than in males, and in those with a family history of SAH (Ronkainen et al., 1993; Ronkainen et al., 1998; van Gijn et al., 2007).

2.1.2.3 Risk factors for SAH

The incidence of SAH increases with age to a peak in the fifth and sixth decades of life (Ingall et al., 2000). Thereafter, the incidence remains stable or even decreases slightly with further aging (Ingall et al., 2000). For unknown reasons the incidence of aneurysmal SAH in women is 1.2-1.6 times higher than in men (Ingall et al., 1989; Ostbye et al., 1997; de Rooij et al., 2007; Koffijberg et al., 2008). This gender difference starts at age 55 years and increases thereafter (de Rooij et al., 2007; Koffijberg et al., 2008). Aneurysms in posterior circulation and anterior communicating artery have a higher rupture rate than aneurysms in other locations (Kaminogo et al., 2003; Clarke et al., 2005; Huttunen et al., 2010). ACoA aneurysms are responsible for approximately 40% of SAH in the Finnish population (Huttunen et al., 2010). Large and symptomatic aneurysms have higher rupture risk than smaller and asymptomatic lesions (Juvela et al., 1993; Juvela et al., 2000; Wiebers et al., 2003). Persons having close relatives with SAH and patients with autosomal dominant polycystic kidney disease have a higher risk for aneurysm formation than the general population (Ronkainen et al., 1997; Rinkel et al., 1998; Gieteling and Rinkel, 2003).

Independent, acquired, risk factors for SAH include hypertension (relative risk 2.5 to 2.6), cigarette smoking (relative risk, 2.2 to 3.1) and heavy alcohol

consumption (relative risk 1.5 to 2.1) (Rinkel et al., 1998; Juvela et al., 2000; Feigin et al., 2005; Sandvei et al., 2009).

2.1.2.4 Familial factors

In Finland, about 10% of SAH cases are familial, with at least two affected first degree family members harbouring aneurysms (Ronkainen et al., 1993; Ronkainen et al., 1997). Individuals with one affected first-degree relative have 3-4 times higher risk of harbouring an aneurysm than the general population (Schievink et al., 1995a). Patients with two affected relatives have 7-10% lifetime risk for SAH (Ronkainen et al., 1997; Teasdale et al., 2005; van Gijn et al., 2007). Persons with familial intracranial aneurysms have an increased risk of aneurysm formation and rupture, and familial SAH patients are younger at the time of bleeding than patients with sporadic SAH (Wermer et al., 2006; van Gijn et al., 2007). Patients with familial intracranial aneurysms also have more multiple aneurysms and larger aneurysms than those with sporadic aneurysms (Wermer et al., 2006; van Gijn et al., 2007). However, only a minority of familial SAH cases seem to be due to the clustering of susceptibility genes, but clustering of confounding risk factors might play a larger role in familial aneurysms (Korja M et al., 2010). A multistage genome-wide association study (GWAS) of Finnish, Japanese and Dutch cohorts identified five common SNPs associated with intracranial aneurysms on chromosomes 2q, 8q and 9p (Bilguvar et al., 2008). An aneurysm is detected in 16% of people with familial aneurysms, so screening of these patients is reasonable (Ronkainen et al., 1993; Wermer et al., 2006). In Finland, screening of first degree relatives of saccular aneurysm patients is performed in families with two first-degree relatives with aneurysmal disease (Ronkainen et al., 1998; Jaaskelainen, 2007).

2.1.2.5 Multiple aneurysms

Multiple aneurysms are detected in 8-34% of SAH patients (Broderick et al., 1994; Rinne et al., 1994; Raymond and Roy, 1997; Qureshi et al., 1998; Byrne et al., 1999; Juvela, 2000; Kaminogo et al., 2003; Holmin et al., 2008; Diringer, 2009;

Huttunen et al., 2010). Smoking, female gender and hypertension increase the risk of multiple aneurysms (Rinne et al., 1994; Qureshi et al., 1998; Juvela, 2000; Kaminogo et al., 2003). A Finnish study comprising 114 patients showed that patients with multiple aneurysms had more carotid and pericallosal aneurysms compared to patients with one aneurysm (Rinne et al., 1994). In patients with multiple aneurysms, it may be difficult to identify which aneurysm has bled. The localization of blood on the computed tomograghy (CT) scan can help to identify the aneurysm responsible for the SAH (Karttunen et al., 2003). Ruptured aneurysms are also usually the largest and the most irregular shaped and ACoA aneurysm in patients with multiple aneurysms is more prone to bleed than aneurysms at other locations (Kaminogo et al., 2003).

2.1.3 Pathogenesis of intracranial aneurysms

Most aneurysms are idiopathic with no specific etiology. A minority of aneurysms have a specific etiological factor, like dissecting aneurysms, infectious aneurysms or flow-related aneurysms, as stated in Table 1. Changes in cerebral vessel hemodynamics is considered predisposing aneurysm formation in acquired factors like cigarette smoking as well as in congenital deformities like polycystic kidneys (Juvela et al., 2001; Gieteling and Rinkel, 2003).

The layers of intracranial arteries are adventitia (outer loose connective tissue), media (muscular layer) and intima (inner layer with smooth muscle cells and endothelial layer). The wall of the cerebral arteries is thinner than in peripheral arteries and thus has a higher rate of aneurysm development. The wall of the ruptured aneurysm is thinner than in unruptured aneurysms and the structure is disorganized with no clearly defined layers (Kataoka et al., 1999). There are also excess inflammatory cells compared to unruptured aneurysms. Before the aneurysm rupture, the wall undergoes morphological changes like apoptosis, de-endothelialization, luminal thrombosis, smooth muscle cell proliferation, T-cell and macrophage infiltration and complement activation (Kataoka et al., 1999; Frosen et al., 2004; Tulamo et al., 2006).

2.1.4 Clinical presentation

The classic presentation of acute aneurysm rupture is sudden headache, nausea, vomiting, nuchal rigidity and syncope, followed typically by a gradual improvement in level of consciousness (van Gijn et al., 2007). Focal neurological signs may be seen due to mass effect from a giant aneurysm, parenchymal hemorrhage or seldom due to a subdural hematoma (van Gijn et al., 2007). Third and sixth cranial nerve palsies may be present because of aneurysmal compression of the nerve or increased intracranial pressure, respectively (Diringer, 2009). Seizures may occur in up to 20% of patients after SAH (Claassen et al., 2003; Bederson et al., 2009).

Aneurysms located around the cavernous sinus may cause cranial nerve III-VI palsies or visual deficits, and ACoP aneurysms can cause third nerve palsy. Pericallosal aneurysms are rare, being only 6% of all aneurysms, and those are frequently associated with ICH, IVH and blood along the corpus callosum or anterior interhemispheric fissure (Lehecka et al., 2010).

Hunt and Hess scale (H&H, Table 4) and the World Federation of Neurologic Surgeons (WFNS, Table 5) grading scales are the most frequently used to assess the clinical condition of SAH patients (Hunt and Hess, 1968; Report of World Federation of Neurological Surgeons Committee, 1988).

Table 4. Hunt&Hess grading scale following subarachnoid hemorrhage (Hunt and Hess, 1968).

Grade	
I	Asymptomatic or mild headache
II	Moderate to severe headache, nuchal rigidity, with or without cranial nerve deficits
III	Confusion, lethargy, or mild focal symptoms
IV	Stupor and/or hemiparesis
V	Comatose and/or extensor posturing

Table 5. WFNS grading scale (Report of World Federation of Neurological Surgeons Committee, 1988).

WFNS grade	Glasgow Coma Scale	Motor deficit
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

Increased cerebrospinal fluid pressure causes obstruction of the central retinal vein as it traverses the optic nerve sheath. This may cause intraocular hemorrhage and vision impairment. Preretinal hemorrhage extending into the vitreous body (Terson's syndrome) is seen in 13% of SAH patients (McCarron et al., 2004). It is detected more in poor-grade patients than in patients with good H&H grades (McCarron et al., 2004).

Unruptured aneurysms are either detected after SAH from another aneurysm, or because of symptoms caused by the mass effect of the aneurysm, or are discovered during the screening for an incidental aneurysm or most often incidentally during neuroradiological imaging because of an unrelated medical condition such as cerebrovascular ischemia, headache, dizziness, head trauma etc. Unruptured aneurysms are most often asymptomatic, but those can cause neurological symptoms like pain, cranial nerve palsies, visual disturbances, seizure, vertigo or ischemic events due to thromboembolism. In a series of 269 patients with unruptured aneurysms, 3.3% of patients had ischemic strokes due to embolization from the aneurysmal sac (Qureshi et al., 2000).

2.1.5 Diagnosis and imaging

CT scanning is the first investigation if subarachnoid hemorrhage is suspected. A CT scan has 98-100% sensitivity for SAH in the first 12 hours after bleeding. Sensitivity decreases after several hours so that after one week it is only 50% (van Gijn and van Dongen, 1982; Edlow, 2005). Lumbar puncture and analysis of the

cerebrospinal fluid for xanthochromia is performed if the initial CT scan is negative (Zacharia et al., 2010).

CT is not always performed immediately after the insult and there can be patient or hospital related delays. Misdiagnosis of SAH occured in 12% of patients in a single-center study with 482 consecutive patients and misdiagnosis was associated with higher mortality and morbidity due to the increased risk of rebleeding, hydrocephalus and vasospasm (Kowalski et al., 2004).

After the SAH diagnosis, the cause of bleeding should quickly be defined. DSA has been the golden standard but newer, non-invasive and fast imaging modalities (CTA and MRA) are used more and more to detect the bleeding site immediately.

2.1.5.1 Catheter angiography with digital subtraction angiography technique

Digital subtraction angiography (DSA) is a traditional imaging modality with a very high sensitivity and specificity to detect intracranial aneurysms. A complete four-vessel angiography is performed to detect multiple aneurysms and 3D rotational angiography helps to detect small aneurysms and define the aneurysm configuration (van Rooij et al., 2008). If no aneurysm is found in four-vessel angiography, selective catheterization of both external carotid arteries is performed to exclude a dural arteriovenous fistula and/or DSA is repeated after a week to exclude a thrombosed aneurysm.

DSA is an invasive diagnostic modality with an overall complication rate between 0.4 and 3%. Symptomatic complications occur in 0.4-0.5% of procedures (Willinsky et al., 2003; Ringer et al., 2008; Agid et al., 2010). Also, allergic reactions to contrast medium, renal failure and bleeding at the puncture site are possible complications.

The advantage of DSA is that aneurysms detected in DSA can be directly treated using an endovascular coiling procedure during the same session and thus minimizing the risk of rebleeding in the hospital. DSA can also be used as a follow-up modality after aneurysm treatment in both clipped and coiled aneurysms. It has the highest sensitivity to detect postoperative occlusion grades compared to other angiographic methods. However, because of its invasive nature, postoperative angiograms are nowadays often done with MRA in coiled aneurysms and

intraoperative with indocyanine green (ICG) fluorescence angiography, or on first postoperative day with CTA in clipped aneurysms (Raabe et al., 2005).

2.1.5.2 Computed tomography (CT), CT angiography (CTA) and CT perfusion (CTP)

CT is performed as soon as possible after SAH. Typically, the subarachnoid blood appears hyperdense on an unenhanced CT. The sensitivity of CT in SAH is 98-100% in the first 12 hours after SAH, declining to 93% at 24 hours and to 57-85% after 6 days (van Gijn and van Dongen, 1982; Kassell et al., 1990b; Edlow, 2005). Blood in initial CT is graded with the Fisher grading system (Table 6**)** (Fisher et al., 1980). The pattern of SAH in the first CT scan may suggest the location of the ruptured aneurysm (Karttunen et al., 2003). Intracerebral hematoma (ICH) occurs in 20-30% of patients with aneurysmal rupture, but subdural hematomas are rare (about 2%) (van Gijn and van Dongen, 1982; Kassell and Torner, 1984; Kivisaari et al., 2001; van Gijn et al., 2007). Blood in ventricles is detected in 20-50% of initial CTs (Kassell and Torner, 1984; Le Roux and Winn, 1998).

Table 6. Fisher grading system for initial CTs (Fisher et al., 1980).

1	No subarachnoid blood
2	A diffuse deposition or thin layers (<1mm) of blood
3	Clots or thick layers (>1mm) of blood
4	Subarachnoid hemorrhage of any thickness with intra-ventricular or intraparenchymal hemorrhage.

CT is usually followed by CTA to detect aneurysms instantly. The sensitivity for detecting ruptured aneurysms is currently approximately 95% (92-98%) (Lenhart et al., 1997; White et al., 2000; Young et al., 2001; Kangasniemi et al., 2004; van Gijn et al., 2007; Zacharia et al., 2010). The sensitivity and specificity of CTA for aneurysm detection depends on aneurysm location and size, quality of images and experience of the radiologist (White et al., 2000; Kangasniemi et al., 2004). In the study of Dammert et al. (2004) comprising of 50 patients, the sensitivity was 100% for aneurysms larger than 12mm, 91% for aneurysms 5 to 12mm in size and 83%

for aneurysms smaller than 5mm. Disadvantages of CTA also include the need of iodinated contrast medium and artefacts from bone. CTA is better than DSA to define aneurysmal wall calcification and orientation of aneurysm with respect to intraparenchymal hemorrhage and bony structures and thus helping the neurosurgical planning (Bederson et al., 2009).

CTA can be used to detect vasospasm after SAH with sensitivity rates as high as 98% (Yoon et al., 2006; Binaghi et al., 2007). CTA can also be used to evaluate occlusion rates after surgical clipping with titanium clips, but it can not be used after endovascular treatment because of coil artefacts (Kahara, 2006).

Computed tomography perfusion (CTP) is used in combination with CT and CTA to detect ischemic brain lesions caused by vasospasm after SAH (Harrigan et al., 2005). Perfusion images can be early predictors of secondary cerebral infarction in patients with vasospasm because these perfusion changes may occur up to three days before infarction can be detected on CT (Marshall et al., 2010). Perfusion images consist of different maps: mean transit time (MTT), time to peak (TTP), cerebral blood volume (CBV) and cerebral blood flow (CBF). Elevated MTT/TTP with normal CBF and normal or increased CBV indicates perfusion abnormality that is adequately compensated by autoregulation. Elevated MTT/TTP with reduced CBF and normal or increased CBV indicates perfusion abnormality with reversible cerebral ischemia (penumbra). Elevated MTT/TTP with reduced CBF and reduced CBV indicates perfusion abnormality with irreversible cerebral ischemia (Marshall et al., 2010).

2.1.5.3 Lumbar puncture

If CT is negative, lumbar puncture and amount of red blood cells in CSF is performed. Xantochromia is present 6 to 12 hours after SAH and thus lumbar puncture should be done more than 6 hours and preferably 12 hours after the headache onset to differentiate true SAH from a traumatic lumbar puncture (van Gijn et al., 2007). Bilirubin remains detectable until 2 to 3 weeks after bleeding (van Gijn et al., 2007; Zacharia et al., 2010).

2.1.5.4 Magnetic resonance imaging (MRI) and MR angiography (MRA)

MRI is not usually used in emergency settings because the study time is long, it is sensitive to motion artefacts and not as widely available as CT (van Gijn and Rinkel, 2001; Bederson et al., 2009). Furthermore, conventional MRI sequences are less sensitive to SAH than CT scanning (Mitchell et al., 2001; van Gijn and Rinkel, 2001; Wiesmann et al., 2002). Blood in the subarachnoid space detected in MRI depends on sequences used as shown in Figure 1 (Noguchi et al., 1995; Mitchell et al., 2001; Rumboldt et al., 2003; Yuan et al., 2005). Fluid-attenuation inversion recovery (FLAIR) and T2* sequences are as sensitive as CT in the acute period (<4 days from SAH) with a sensitivity rate 81-100% in FLAIR and 91-94% in T2* sequences, respectively (Mitchell et al., 2001; van Gijn and Rinkel, 2001; Wiesmann et al., 2002). The sensitivity of T2- weighted GRE images obtained in subacute period (4–30 days from hemorrhage) is 100% (Mitchell et al., 2001; Yuan et al., 2005). However, FLAIR sensitivity reduces in the subacute period, changing from 33% to 87% between studies (Mitchell et al., 2001; Yuan et al., 2005). MRI can be used if CT shows no blood, in subacute cases, or to detect other causes of SAH in patients with negative catheter angiograms (Yuan et al., 2005).

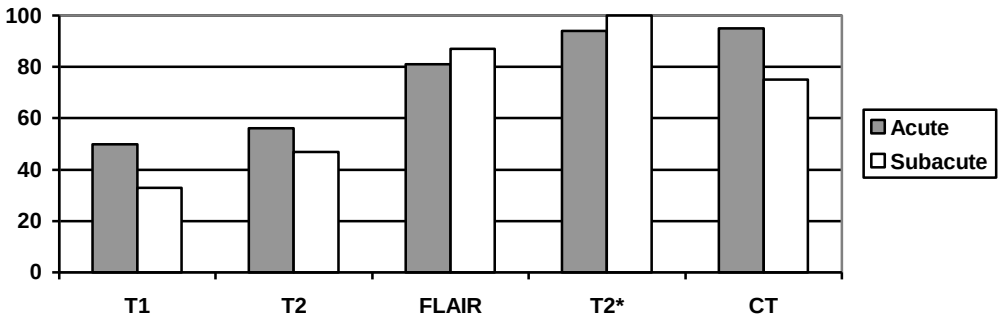

Figure 1. Histogram showing the sensitivities of the four MRI sequences and of CT in the acute and subacute periods adapted from Mitchell et al. (2001).

MRI is much more sensitive than CT detecting parenchymal lesions after SAH in the late phase (Awad et al., 1986; Kivisaari et al., 2001). Parenchymal lesions detected on late MRIs can be caused by a bleed itself (superficial hemosiderin, residual sign of hematoma), by vasospasm or by a treatment complication. The etiology of lesions can be determined on the basis of vascular anatomy when

comparing primary CTs with late MRIs and knowing the clinical data of each patient (Hadjivassiliou et al., 2001; Kivisaari et al., 2001). Thus, ischemic lesions in parental artery territory (vascular territory of the ruptured aneurysm) and other vascular territories (caused by vasospasm) can thus be differentiated. Parental artery infarctions can be related to the primary bleeding or complications of treatment, such as vessel rupture, dissection or thromboembolism (Rabinstein et al., 2005). Surgical treatment when inadvertently using brain retractors may cause injuries to frontotemporal lobes and those do not follow the vascular anatomy of the brain (Kivisaari et al., 2001). Therefore, avoiding usage of retractors is important whenever possible.

Magnetic resonance angiography (MRA) is used to detect unruptured intracranial aneurysms. It does not require iodinated contrast or ionizing radiation and is thus safer for screening than CTA or DSA (Bederson et al., 2009). Sensitivity of three-dimensional time-of-flight (TOF) MRA for cerebral aneurysms is between 55% and 93% (White et al., 2000; Bederson et al., 2009). Sensitivity depends on the size of the aneurysm: aneurysms more than 3mm have a sensitivity of around 94%, whereas sensitivity for aneurysms less than 3mm is as low as 38% (White et al., 2000; Zacharia et al., 2010).

MRA can also be used to follow-up previously coiled aneurysms; the sensitivity to detect a residual aneurysm is approximately 90% (Kahara et al., 1999; Kwee and Kwee, 2007; Urbach et al., 2008). Both TOF-MRA and contrast-enhanced MRA (CE-MRA) are good follow-up sequences after coiling (Kahara et al., 1999; Gauvrit et al., 2006; Anzalone et al., 2008) and majority of aneurysms can be followed up solely with TOF-MRA (Kahara, 2006). Sensitivity and specificity of CE-MRA in detection of residual flow are 87-93% and 92-96%, respectively (Gauvrit et al., 2006; Kwee and Kwee, 2007; Lubicz et al., 2008). Follow-up of clipped aneurysms is not possible due to artefacts.

2.1.6 Complications of SAH

High mortality and morbidity of SAH is not only connected to the initial bleeding but also to many complications, the most common are listed in Table 7. Aneurysmal rupture may lead to a prolonged period of global cerebral ischemia at the time of

bleeding, probably as a result of increased intracranial pressure to a level of arteries. Outcome is generally fatal due to progressive dysfunction of the brainstem. Because of high mortality of recurrent SAH, early treatment is nowadays preferred in most centres (Ohman and Heiskanen, 1989; Bederson et al., 2009). Tranexamic acid is used in many centers to prevent ultra-early rebleedings (Hillman et al., 2002). Vasospasm and hydrocephalus are discussed below, and rebleeding in Chapter 2.1.10.

Table 7. Common complications of aneurysmal subarachnoid hemorrhage (Wartenberg and Mayer, 2010).

Immediate cerebral ischemia
Rebleeding
Vasospasm
Delayed cerebral ischemia
Hydrocephalus
Seizures
Cardiopulmonary dysfunction: hypo/hypertension, pneumonia, pulmonary edema
Electronic disturbances: hypo/hypernatremia, hypomagnesemia
Fever
Anemia
Hyperglycemia

2.1.6.1 Vasospasm

Cerebral vasospasm is the delayed narrowing of cerebral arteries after SAH, which is often associated with diminished perfusion in the distal territory of the affected artery. A typical onset for vasospasm is three to five days after the hemorrhage, maximal narrowing at five to 14 days, and a gradual resolution over two to four weeks (Fisher et al., 1977; Bederson et al., 2009). Vasospasm affects 60 to 70% of patients after SAH, resulting in symptomatic delayed ischemia in approximately 20-35% of SAH patients (Raymond and Roy, 1997; Debrun et al., 1998; Koebbe et al., 2006). Half of these patients have disability or death resulting from clinical vasospasm (Raymond and Roy, 1997; Debrun et al., 1998). With early surgery and optimal medical management the morbidity and mortality rate from vasospasm has

decreased to approximately 4 to 12% (Ohman and Heiskanen, 1988; Ohman and Heiskanen, 1989; Ohman et al., 1991a; Raymond and Roy, 1997).

For patients over 60 years, higher Fisher grade on initial CT scan and higher H&H on admission are important predictors for the development of vasospasm (Schievink et al., 2000; Feigin et al., 2005; Harrod et al., 2005; van Gijn et al., 2007). Hypertension is also a risk factor for developing clinical vasospasm (Ohman et al., 1991b). There does not seem to be a difference between surgical clipping and endovascular coiling regarding the risk of vasospasm (de Oliveira et al., 2007a).

Vasospasm can be treated by controlling intracranial pressure, decreasing brain oxygen use, and improving CBF. Triple-H therapy is a traditional treatment method for vasospasm with hypervolemia, hypertension and hemodilution, but there is no good evidence for a positive effect (Bederson et al., 2009). Hypertension is more effective in increasing cerebral blood flow than hemodilution or hypervolemia (Dankbaar et al., 2010). Altogether, strict avoidance of hypovolemia, hypotension, hyponatremia, hyperglycemia and hyperthermia are important in preventing delayed cerebral ischemia in SAH patients (Diringer, 2009).

Calcium channel blocker nimodipine reduces the risk of secondary ischemia and poor outcome (Ohman and Heiskanen, 1988; Ohman et al., 1991a; Zacharia et al., 2010). Hypomagnesemia appears to be common after SAH and has been associated with both poor outcome and vasospasm. Intravenous magnesium infusion seems to reduce delayed cerebral ischemia but did not improve the clinical outcome in a recent large, randomized placebo-controlled trial (van den Bergh et al., 2005; Dorhout Mees et al., 2012).

Endovascular transluminal angioplasty or intra-arterial infusion of vasodilators can be used to treat vasospasm. Transluminal balloon angioplasty can be used in large, proximal vessels and it is effective. However, major complications like vessel rupture, occlusion, dissection, hemorrhagic infarction and hemorrhage from untreated aneurysms occur in approximately 5% of procedures (Diringer, 2009).

2.1.6.2 Hydrocephalus

Hydrocephalus is detected in up to 30% of SAH patients (Mehta et al., 1996; Findlay and Deagle, 1998; Sheehan et al., 1999; Franz et al., 2001). Acute

hydrocephalus develops between 24 hours and three days after the hemorrhage, subacute hydrocephalus four to 13 days after SAH, and chronic hydrocephalus develops more than two weeks after the bleeding (Vale et al., 1997; Jartti et al., 2004; Jartti et al., 2008). The incidence of acute hydrocephalus after SAH is between 15 and 30% (Mehta et al., 1996; Findlay and Deagle, 1998; Sheehan et al., 1999; Franz et al., 2001). Slow pupillary responses to light, deviation of the eyes and loss of consciousness are characteristic for acute hydrocephalus. Poor-grade patients and patients with high Fisher grade on initial CT, intraventicular hemorrhage and posterior circulation aneurysms have a high risk developing hydrocephalus (Graff-Radford et al., 1989; Vermeij et al., 1994; Mehta et al., 1996; Sheehan et al., 1999). Less than half of the patients with acute hydrocephalus will require external ventricular drainage (Mehta et al. 1996, Sethi et al. 2000). Ventriculostomy is an effective procedure for management of acute hydrocephalus, but it has been connected to an increased rebleeding rate (Pare et al., 1992). However, more recent data suggests that ventriculostomy followed by early treatment of the ruptured aneurysm does not increase the risk of rebleeding (Mehta et al., 1996; McIver et al., 2002). Drainage of CSF can also be achieved by opening the basal cisterns, fenestration of the lamina terminalis or third ventriculostomy through the fenestrated lamina terminalis during the aneurysm surgery (Lehto H et al., 2009).

Subacute hydrocephalus is detected in only 2-3% of SAH patients (Mehta et al., 1996; Sethi et al., 2000). Chronic hydrocephalus with gait disturbance, impaired intellectual function or progressive lethargy is observed in about 20% of patients after SAH (Tapaninaho et al., 1993; Sheehan et al., 1999; Sethi et al., 2000; Widenka et al., 2000; Kim et al., 2006; Varelas et al., 2006; de Oliveira et al., 2007b; Jartti et al., 2008). Development of chronic hydrocephalus correlates with clinical grade on admission, Fisher grade, acute hydrocephalus and intraventricular hemorrhage (Tapaninaho et al., 1993; Vermeij et al., 1994; Vale et al., 1997; Sheehan et al., 1999; Widenka et al., 2000; Yoshioka et al., 2000). Patients with ruptured vertebrobasilar area aneurysms have more (28%) chronic hydrocephalus than patients with aneurysms in ACoA (14%) or MCA (4%) (Tapaninaho et al., 1993; Yoshioka et al., 2000).

2.1.6.3 Other complications

Electrocardiographic changes, elevated cardiac enzymes and arrhythmias are common in the first two days after SAH. However, those are typically benign (Diringer, 2009). Hyponatremia after SAH ranges from 10 to 30%, being more common in poor-grade patients, patients with ACoA aneurysms and hydrocephalus (Bederson et al., 2009; Diringer, 2009). Hyponatremia may be an independent risk factor for poor outcomes (Bederson et al., 2009; Diringer, 2009). Seizures are common after SAH with up to 14% of SAH patients suffering from secondary epilepsy (Kassell et al., 1990b).

2.1.7 Management

The goal of aneurysm treatment is to prevent rebleeding, which is associated with high mortality (Hijdra et al., 1987). Rebleeding is prevented by eliminating the aneurysm from the circulation while preserving blood flow in the parental artery and perforating arteries. The aneurysm can be treated either with microsurgical or endovascular techniques. Parent artery occlusion is an option for aneurysms not suitable for clipping or coiling, and for peripheral aneurysms if collaterals allow. Some aneurysms are best treated with multimodality approaches using both techniques (hybrid treatment) (Pearl et al., 2010). Early treatment is widely used to prevent in-hospital rebleeding (Ohman and Heiskanen, 1989; Kassell et al., 1990a).

Treatment of unruptured aneurysms is debated a lot because a large international study of unruptured intracranial aneurysms, ISUIA, showed that rupture risk in small aneurysms (<7mm) is very low, especially in patients with no previous SAH (Wiebers et al., 2003; Mitchell et al., 2004). In 2000, an expert panel of the American Heart Association recommended that aneurysms in patients with long life expectancy, previous SAH, a family history of aneurysm rupture, large aneurysms (≥10mm), symptomatic aneurysms or observed aneurysm growth, should be treated (Bederson et al., 2000). However, risk of aneurysm rupture is higher in Finnish and Japanese populations compared to other industrialized countries, and most ruptured aneurysms are less than 10mm so treatment is recommended to be more aggressive in Finland (Sarti et al., 1991; Broderick et al., 1994; Ostbye et al., 1997; Rinkel et

al., 1998; Cesarini et al., 1999; Ingall et al., 2000; Forget et al., 2001; Inagawa, 2001; Juvela 2001; Pobereskin, 2001; de Rooij et al., 2007; Koffijberg et al., 2008).

2.1.7.1 Microsurgical clipping

Aneurysms can be isolated from the circulation with microsurgical clipping. In rare cases aneurysms are treated by trapping, wrapping or proximal vessel occlusion with or without extracranial-intracranial bypass (Andaluz and Zuccarello, 2011). The operation is performed under a high magnification microscope, preferably with intraoperative ICG angiography and advanced neuroanesthesiolgy (Hernesniemi et al., 2005b; Raabe et al., 2005; Randell et al., 2006). CSF drainage can be achieved during surgery by opening the basal cisterns, fenestration of the lamina terminalis or catheterization of the third ventricle through fenestrated lamina terminalis to reduce intracranial pressure (Lehto et al., 2009). Anterior circulation aneurysms can be clipped by using the pterional approach, the lateral supraorbital approach, the orbitozygomatic approach or the interhemispheric approach (Hernesniemi et al., 2005a). Posterior circulation aneurysms are clipped by pterional, subtemporal, lateral suboccipital or anterior petrosectomy approaches.

Postoperative complete occlusion grade has been found in 74-88% and incomplete occlusion has been found in 3-6% of aneurysms, respectively (Vanninen et al., 1999; Thornton et al., 2000; Kivisaari et al., 2004; Molyneux et al., 2005). Nowadays, intraoperative ICG videoangiography is widely used to documentate clip positioning and aneurysm occlusion and to detect the patency of adjacent arteries (Raabe et al., 2005). Posterior circulation aneurysms and large aneurysms often have more incomplete occlusions of the aneurysms and higher morbidity and mortality after surgery than anterior circulation aneurysms (Schievink et al., 1995c; Kivisaari et al., 2004). Overall, the complication rate has been as high as 30% with permanent morbidity 4-10% and mortality of 2-4% (Raaymakers et al., 1998; Vanninen et al., 1999; Johnston et al., 2000). Major vessel occlusion was detected in 6% of clipped, ruptured aneurysms in a Finnish study with 493 consecutive patients (Kivisaari et al., 2004).

The randomized International Subarachnoid Aneurysm Trial (ISAT) comprising of 2143 SAH patients found rebleeding risk after surgery to be 1.2% in a four year

mean follow-up time (Molyneux et al., 2005). Cumulative risk of recurrent aneurysmal bleeding has been as high as 3.2% at 10 years and 9.0% at 20 years after the surgical treatment, counting both de novo bleedings and bleedings from a residual aneurysm (Tsutsumi et al., 1998; Wermer et al., 2005). Risk of recurrence of a completely clipped aneurysm is 0.3-0.9% per patient-year (Tsutsumi et al., 2001; Fulkerson et al., 2009).

Surgery-related death in patients with unruptured intracranial aneurysms is 1-3% and morbidity 10-30% with permanent disability approximately 3% (Raaymakers et al., 1998; Johnston et al., 2000; Pierot et al., 2008a).

2.1.7.2 Endovascular treatment

Guglielmi detachable coils (GDC) were introduced in 1991 by Guglielmi et al. (1991). Platinum coils are placed into the aneurysm through a microcatheter and detached from a stainless steel microguidewire by electric current. The aneurysm is packed with several coils. The coils induce thrombosis, thereby excluding the aneurysm from the circulation. Traditionally, coiling is considered feasible if the neck of the aneurysm is not wide (a dome-neck ratio is more than 1.5) and perforating branches do not arise from the aneurysm. Coils have been developed further (2D-coils, 3D-coils, soft coils, ultrasoft coils, biologically active coils, hydrogel coils etc.) to enable better aneurysm filling and to decrease the recanalization rate (Pearl et al., 2010). Matrix-type coils are modified GDCs with polyglycolic-polylactic acid polymer coating and HydroCoils are platinum coils coated with an expanding polymer that reacts to blood (Niimi et al., 2006; Ishii et al., 2008; Pierot et al., 2008b; Marjamaa et al., 2009). However, the benefit compared to GDCs is not proved (Niimi et al., 2006; Ishii et al., 2008; Pierot et al., 2008b). Balloon remodelling techniques and stent-assisted coiling also made coiling of wide neck aneurysms possible. The balloon is temporary inflated across the aneurysm neck during embolization to avoid coil migration into the parent artery. Stent-assisted coiling can be used to treat large, fusiform or wide-necked aneurysms (Tahtinen et al., 2009). New generation flow-diverter stents may induce thrombosis in the aneurysm sac by reducing flow even without subsequent coiling of the aneurysm (Nelson et al., 2011; Tahtinen et al., 2012). The disadvantage of stents is

the need for antiaggregative medication because of the risk of stent thrombosis (Pearl et al., 2010).

Complications related to endovascular coiling are aneurysm rupture, tromboembolic events and arterial dissection. Complication rate is approximately 10% (8-21%) but symptomatic complications occur in 5% (1-9%) of patients, and 3% are permanent (Table 8) (Casasco et al., 1993; Raymond and Roy, 1997; Vinuela et al., 1997; Kuether et al., 1998; Brilstra et al., 1999; Vanninen et al., 1999; Roy et al., 2001; Ng et al., 2002; Friedman et al., 2003; Murayama et al., 2003; Willinsky et al., 2003; Niimi et al., 2006; Pouratian et al., 2006; Ishii et al., 2008; Peluso et al., 2008; Pierot et al., 2008b; van Rooij et al., 2009). Mortality related to endovascular treatment is around 1% (0.5-2%) (Johnston et al., 1998; Lanterna et al., 2004; Niimi et al., 2006; Pierot et al., 2008a; van Rooij et al., 2009).

Perforation of the aneurysm sac occurs in 2-3% of patients during aneurysm coiling and the rate is higher in small and ruptured aneurysms (Vinuela et al., 1997; Debrun et al., 1998; Sluzewski et al., 2001; Murayama et al., 2003; Wiebers et al., 2003; van Rooij et al., 2009). Thromboembolic complications are the most common type of complication in the endovascular treatment of intracranial aneurysms and are affected by aneurysm size (van Rooij et al., 2009). The deficits were noticed during or immediately after the procedure in 59% of cases, while 41% occurred 12-48 hours after treatment (Pelz et al., 1998). Heparinization is used to minimize thromboembolic complications. Activated clotting time (ACT) should be 250-300 seconds during the intervention. Aspirin is used routinely in some centres after endovascular coiling.

Morbidity and mortality rates among patients with unruptured aneurysms are comparable to that of the endovascular treatment of ruptured aneurysms (Standhardt et al., 2008). The case-fatality rate in unruptured aneurysm embolization is 0.6% and the permanent morbidity rate is between 4-7% (Brilstra et al., 1999; Roy et al., 2001; Lanterna et al., 2004). Morbidity has decreased from the years when endovascular coiling began (Debrun et al., 1998; Johnston et al., 1998; Roy et al., 2001; Ng et al., 2002; Lanterna et al., 2004; Pouratian et al., 2006; Pierot et al., 2008a).

Table 8. Overview of mortality and permanent morbidity rates in coiled aneurysms.

Series	No of patients	No of aneurysms	Ruptured/ Unruptured	Procedure-related mortality (%)	Permanent morbidity rate (%)
Johnston et al., 2000		62	U	1.6	8
Murayama et al., 1999	115	120	U	0	4.3
Brilstra et al., 1999		1256	R+U		3.7
Roy et al., 2001	116	125	U	0	5.2
Goddard et al., 2002	62	73	U	0	0
Ng et al., 2002	81	81	R	2.5	2.5
Ng et al., 2002	63	79	U	0	0
Vinuela et al., 1997	403	403	R	1.7	
Niimi et al., 2006	70	74	R+U	1.4	1.4
van Rooij et al., 2009	187	196	R+U	1.1	2.1
Lanterna et al., 2004	1379		U	0.6	7
Willinsky et al., 2009	377	391	R	1.6	1.3
Pierot et al., 2008b	127		R	1.4	3.6
Pierot et al., 2008b	98		U	0	1.0
Pierot et al., 2008a		739	U	1.7	1.4

R=Ruptured aneurysm; U=Unruptured aneurysm

2.1.7.3 Retreatment

Retreatment is needed more often after endovascular coiling than after surgical clipping (Campi et al., 2007; van Rooij et al., 2009). Risk factors for retreatment are aneurysm size >10mm, neck width >4mm and initial incomplete aneurysm occlusion (Ries et al., 2007; van Rooij et al., 2009). Retreatment rate is about 10% (range 5-21%) (Kuether et al., 1998; Ng et al., 2002; Niimi et al., 2006; Ries et al., 2007; van Rooij et al., 2009; Willinsky et al., 2009). Complication rate after retreatment differs between studies with no mortality or permanent morbidity in some studies (Slob et al., 2004; Ries et al., 2007). However, in other studies severe morbidity and mortality have been between 3 and 11% (Park et al., 2005; Carat Investigators, 2006; Henkes et al., 2006). Additional microsurgical treatment after incomplete coiling is challenging and has a high morbidity rate (Romani et al., 2011).

2.1.8 Outcome

2.1.8.1 Clinical outcome

Glasgow Outcome Scale (GOS, Table 9) and modified Rankin scale (mRS, Table 10) are commonly used for outcome assessment following SAH.

Table 9. Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975).

1	Death
2	Persistent vegetative state
3	Severe disability: conscious, but totally dependent on others
4	Moderate disability: neurological deficit or intellectual impairment, but independent life
5	Good recovery: full and independent life, no or minimal neurological deficit

Table 10. Modified Rankin Scale (mRS) (Farrell et al., 1991).

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

Rupture of intracranial aneurysm is associated with 24-77% mortality and 15-30% morbidity (Ingall et al., 1989; Sarti et al., 1991; Broderick et al., 1994; Hop et al., 1997; Inagawa, 1997; Inagawa, 2001; Pobereskin, 2001; Stegmayr et al., 2004; Inagawa, 2005; Pajunen et al., 2005). About 12% (3-17%) of all SAH patients die without reaching medical attention (Broderick et al., 1994; Fogelholm et al., 1995; Schievink et al., 1995a; Schievink et al., 1995b; Truelsen et al., 1998) and 25-37% die within 24 hours after bleeding (Hop et al., 1997; Stegmayr et al., 2004). Overall case fatality rate is 27- 43% in the first week, 33-61% at one month, and 33-77% at one year (Ingall et al., 1989; Sarti et al., 1991; Broderick et al., 1994; Hop et al., 1997; Inagawa, 1997; Inagawa, 2001; Pobereskin, 2001; Stegmayr et al., 2004; Inagawa, 2005; Pajunen et al., 2005). Mortality has slightly decreased over the decades with previous death rates around 50% when compared to the less than 24% in more recent studies (Ingall et al., 1989; Sarti et al., 1991; Broderick et al., 1994; Ostbye et al., 1997; Truelsen et al., 1998; Cesarini et al., 1999; Inagawa, 2001; Stegmayr et al., 2004; Qureshi et al., 2005; Koffijberg et al., 2008; Molyneux et al., 2009). The direct causes of death and major morbidity according to Kassell et al. (1990a) are: cerebral infarction due to vasospasm (34%), direct effect of hemorrhage (26%), rebleeding before treatment (17%), treatment complications (11%), intracerebral hematoma (5%), and hydrocephalus (3%). Patients with sudden death

have more posterior circulation aneurysms, IVH and acute pulmonary edema than patients who reach hospital (Schievink et al., 1995b). Patient age, poor clinical grade on admission and high Fisher grade on initial CT scan are directly associated with 30-day mortality (Kassell et al., 1990b; Saveland et al., 1993; Inagawa, 2001; Claassen et al., 2002; Mocco et al., 2006; Koffijberg et al., 2008). Also, aneurysm size >13mm, aneurysm rebleeding, clipping as treatment modality and delayed cerebral ischemia from vasospasm are predisposing factors to poor outcomes in some studies (Kassell et al., 1990b; Broderick et al., 1994; Shimoda et al., 2001; Claassen et al., 2002; Yamada et al., 2003; Mocco et al., 2006; Wartenberg et al., 2006).

Favorable outcomes are detected in approximately 62% (40-87%) of SAH patients (Table 11). However, even the 59-80% of patients with good outcomes have a reduced quality of life after SAH (Hutter and Gilsbach, 1993; Ogden et al., 1993; Hop et al., 1997). Cognitive impairment occurs in approximately one third of patients with favourable outcomes (Scott et al., 2010). Verbal and visual memory are frequently (14-61%) impaired in these patients (Hackett and Anderson, 2000; Al-Khindi et al., 2010; Scott et al., 2010). However, cognitive deficits improve slowly within a few years after SAH (Hutter and Gilsbach, 1993; Ogden et al., 1993; Hop et al., 1997). Even 40-94% of patients with good outcomes are unable to return to their previous occupation (Ogden et al., 1993; Hackett and Anderson, 2000; Al-Khindi et al., 2010). Some patients return to work with less responsibility or as part-time workers because of depression, fatigue and cognitive problems (Al-Khindi et al., 2010).

Patients with anterior circulation aneurysms and surgically treated aneurysms have slightly more cognitive deficits than patients with posterior circulation aneurysms or coiled aneurysms (Hadjivassiliou et al., 2001; Bendel et al., 2008; Scott et al., 2010). SAH patients with good outcomes at one year after the bleeding have higher long-term mortality rates than the general population, mainly due to cerebrovascular and cardiovascular deaths and cancer (Ronkainen et al., 2001; Lehecka et al., 2007; Molyneux et al., 2009; Huttunen et al., 2011).

The outcome after treatment of unruptured aneurysms is not as widely studied as the outcome after SAH. The short-term outcome is good in spite of remarkable morbidity and mortality related to aneurysm treatment. In recent studies, 94-100% of patients were asymptomatic at the time of discharge (Ng et al., 2002; Pierot et al., 2008a). Most long-term outcome studies of patients with unruptured aneurysms include patients with previous SAH and thus the outcome can be related to SAH, not truly to unruptured aneurysms (Juvela et al., 1993; Juvela et al., 2000). Long-term survival among patients with unruptured aneurysms has been studied in only one study (Britz et al., 2004). It showed that survival among SAH patients was significantly lower than among patients with unruptured aneurysms, but after the first-year post clipping, differences in the survival rate diminished (Britz et al., 2004). They compared ruptured with unruptured aneurysms and untreated with clipped aneurysms. The study showed that patients with untreated unruptured aneurysms were 30% more likely to die than patients in the clipped group, and untreated patients were more likely to die from neurologically related causes (5.6%) than patients with clipped aneurysms (2.3%) (Britz et al., 2004).

Table 11. Summary of largest long-term clinical outcome studies. The H&H and GOS figures represent percentages of patients.

Series	Number of patients	Ruptured/ Unruptured	Treatment method	Mean age	Good-grade (H&H 1-2)	Poor-grade (H&H 4-5)	Follow-up months	Dead (GOS 1)	Disability (GOS 2-3)	Favourable outcome (GOS 4-5)
Kremer et al., 2002	79	R	coiling	51	67	33	41	29	11	60
Molyneux et al., 2005	1063	R	coiling		88	5	12	8	16	76
Molyneux et al., 2009	857	R	clipping	52	88	10	60	17	15	68
Molyneux et al., 2009	867	R	coiling	52	85	11	60	13	15	72
Mocco et al., 2006	98	R	coiling+clipping	55	0	100	12	43	18	39
Ng et al., 2002	73	R	coiling	52	65	13	2	26	5	70
Pierot et al., 2008b	127	R	coiling	49	79	21	12	11	2	87
Pierot et al., 2008b	98	U	coiling	49	100	0	12	0	1	99
Willinsky et al., 2009	377	R	coiling	55	62	15	22	9	18	74
Wartenberg et al.,2006	576	R	coiling+clipping	53	42	27	3	21	17	62
Koivisto et al., 2000	57	R	clipping	50	63	12	12	16	9	75
Koivisto et al., 2000	52	R	coiling	49	60	17	12	13	8	79

GOS= Glasgow outcome scale; H&H=Hunt and Hess scale; R=Ruptured aneurysm; U=Unruptured aneurysm

2.1.8.2 Angiographic occlusion grade after aneurysm treatment

Occlusion grade is subjectively estimated and thus reported occlusion grades vary a lot. Two most often used methods to assess occlusion grade are: Raymond classification scale (Raymond et al., 1997) and a quantitative classification system, Figure 2 (Raymond et al., 2003). Occlusion grade is complete (100%) if there is no contrast filling in the aneurysm. Aneurysm has a neck remnant (90-100%) if there is small contrast filling in the neck of the aneurysm. Residual aneurysm (<90%) shows contrast filling in the body of the aneurysm. The results in angiographic follow-up examinations can be classified as stable (no increase in contrast filling in the aneurysm), further thrombosis (i.e. progression, decrease in contrast filling), and recanalization (any increase in contrast filling, with or without coil compaction).

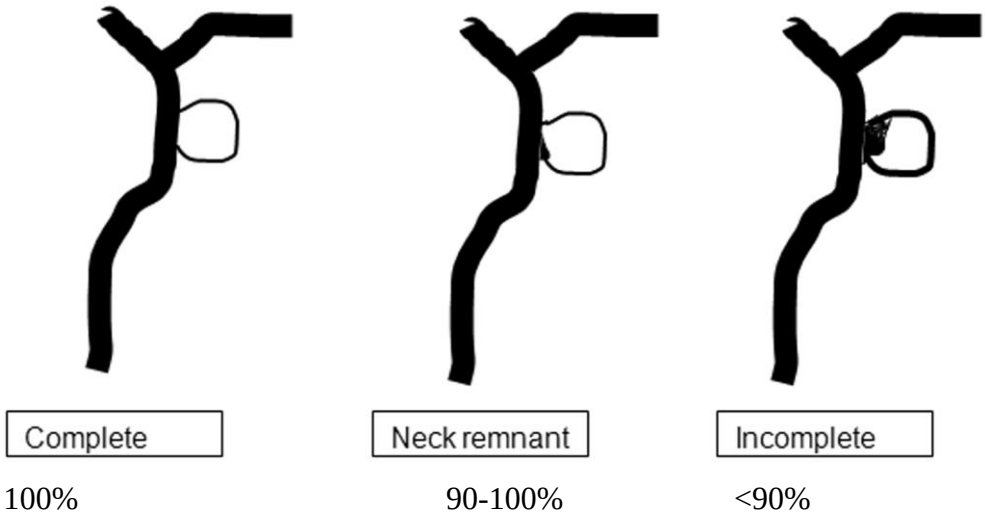

Figure 2. Modified Raymond classification with three different categories. In original scale neck remnant is divided into dog ear and neck remnant (Raymond et al., 1997).

Initial complete obliteration has previously been reported in approximately 54% (26-88%) of ruptured aneurysms, neck remnant in 34% (18-50%) and incomplete occlusion in 12% (2-26%) of ruptured aneurysms (Raymond and Roy, 1997; Kuether et al., 1998; Byrne et al., 1999; Cognard et al., 1999; Murayama et al., 1999; Solander et al., 1999; Vanninen et al., 1999; Koivisto et al., 2000; Molyneux et al., 2005; Rabinstein et al., 2005; Ferns et al., 2009). Complete occlusion has been directly associated with small aneurysm size and dome-neck ratio more than 1.5 (Casasco et al., 1993; Debrun et al., 1998; Ng et al., 2002).

Clipped aneurysms have a better primary occlusion grade than endovascularly treated aneurysms. In a review by Thornton et al. (2000), incomplete aneurysm occlusion was seen in approximately 5% of clipped aneurysms. In a Finnish study (Kivisaari et al., 2004), surgically treated aneurysms had a complete obliteration rate in 88% of aneurysms (86% in ruptured, 91% in unruptured), 9% had neck remnant and 3% were incompletely clipped. Surgically treated aneurysms are thought to be stable after treatment and no long-term follow-up is routinely used. However, 3% of clipped aneurysms had recanalization in angiogram performed approximately nine years after the operation (Tsutsumi et al., 2001) and the annual regrowth rate is 0.3-0.5% for completely clipped aneurysms (Juvela et al., 1993; David et al., 1999; Tsutsumi et al., 2001).

Endovascularly treated aneurysms, however, need long-term angiographic follow-up because recanalization occurs more often (Hayakawa et al., 2000; Koivisto et al., 2000; Thornton et al., 2002; Raymond et al., 2003). Recanalization rate is approximately 25% (15-57%) (Byrne et al., 1999; Ng et al., 2002; Murayama et al., 2003; Niimi et al., 2006; Piotin et al., 2007; Ishii et al., 2008; Willinsky et al., 2009) and at least three years follow-up is required (Ng et al., 2002).

Mid-term follow-up studies have demonstrated that aneurysm growth appears in up to 49% of coiled aneurysms when complete occlusion is not achieved primarily or angiographic stability is not achieved during the 12 -month follow-up (Hayakawa et al., 2000). However, a stable morphological result, with or without a remnant, during a 12-month interval predict a low (4.8%) recanalization risk (Holmin et al., 2008; Sprengers et al., 2008). Other risk factors for reopening are large aneurysm size (>10mm), packing ratio less than 50% and initial presence of intraluminal thrombus (Casasco et al., 1993; Kuether et al., 1998; Solander et al., 1999;

Hayakawa et al., 2000; Raymond et al., 2003; Kai et al., 2005; Sprengers et al., 2008; Standhardt et al., 2008; Willinsky et al., 2009). Ruptured aneurysms have a higher recanalization rate than unruptured aneurysms (Cognard et al., 1999; Piotin et al., 2007).

Long-term (>5 years) follow-up studies with most patients included are still limited (Table 12). In a study by Holmin et al. (2008) long-term follow-up results in ruptured aneurysms were as follows: 62% (197/320) were completely occluded, 30% (97/320) had a neck remnant, and 8% (26/320) were incompletely occluded. Aneurysms that were stable during a 12-month interval had a low risk of morphological deterioration. In conclusion, adequately coiled aneurysms are thought to be stable and the rebleeding rate low (Holmin et al., 2008; Sprengers et al., 2008; Schaafsma et al., 2009).

Table 12. Recanalization rates in studies with follow-up time of one year or more.

Series	Number of patients (aneurysms)	Ruptured/ Unruptured	Initial occlusion grade			Follow-up months (range)	Follow-up occlusion grade			Progression	Stable occlusion	Recanalization
			Complete	Neck remnant	Incomplete		Complete	Neck remnant	Incomplete			
Molyneux et al., 2005	881	R	-	-	-	12	66	26	8	-	-	-
Pierot et al., 2008b	165 (171)	R+U	44	26	29	12	-	-	-	31	43	26
Pierot et al., 2008a	(739)	U	59	22	19	-	-	-	-	-	-	-
Raymond et al., 2003	466 (501)	R+U	36	46	14	12	38	46	15	-	-	34
Niimi et al., 2006	70 (74)	R+U	18	41	42	12 (0-34)	-	-	-	17	55	28
Piotin et al., 2007	223 (255)	R+U	65	19	16	12 (3-43)	-	-	-	-	-	29
Koivisto et al., 2000	52	R	55	38	6	12	77	19	4	-	-	-
Gauvrit et al., 2006	106 (107)	R+U	83	15	2	13 (5-27)	61	20	20	-	-	31
Urbach et al., 2008	50 (58)	R	90	4	4	14	78	2	18	-	-	-

Hayakawa et al., 2000	71 (73)	R+U	0	100	0	17	-	-	-	25	26	49
Thornton et al., 2002	130 (141)	R+U	39	46	15	17 (6-62)	61	22	17	46 *)	26 *)	28*)
Kole et al., 2005	160 (163)	R+U	16	57	27	18 (1-76)	19	-	-	9	-	-
Willinsky et al., 2009	377 (391)	R	43	36	20	22	-	-	-	22	59	19
Ng et al., 2002	144 (160)	R+U	46	16	38	24	-	-	-	-	-	33
Mejdoubi et al., 2006	222 (234)	R	81	11	8	26 (0-69)	73	21	5	7	75	18
Ries et al., 2007	323 (342)	R+U	70	20	11	29 (6-132)	-	-	-	-	-	21
Roy et al., 2001	116 (125)	U	50	45	5	32 (1-81)	49	38	14	-	-	-
Standhardt et al., 2008	173 (202)	U	58	34	9	35	48	24	28	-	-	-
Sprengers et al., 2008	104 (111)	R+U	100	-	-	72 (60-120)	96	3	1	0	96	4

R=Ruptured aneurysm; U=Unruptured aneurysm

*)of incomplete aneurysms

2.1.8.3 Long-term MRI findings

Patients with surgically treated aneurysms have a higher infarction rate than patients with coiled aneurysms (Koivisto et al., 2000; Hadjivassiliou et al., 2001; Kivisaari et al., 2001; Bendel et al., 2008). Infarction rate after aneurysmal SAH is as high as 79-89% in clipped patients compared to 57% in endovascularly treated patients (Koivisto et al., 2000; Hadjivassiliou et al., 2001; Kivisaari et al., 2001; Bendel et al., 2008). Infarction in the vascular territory of the ruptured aneurysm was detected in 21% of endovascular and 46% of the surgical patients (Koivisto et al., 2000; Bendel et al., 2008). Although lesions consistent with infarction seen in CT or MRI sometimes appear extensive, patients may in fact be asymptomatic and patients with deep infarctions are more often asymptomatic than those with cortical lesions (Rabinstein et al., 2005). Ischemic lesions seen in MRIs correlate with neuropsychological deficits (Bendel et al., 2008; Al-Khindi et al., 2010).

2.1.9 Follow-up strategy

2.1.9.1 De novo aneurysm formation

De novo aneurysms are new aneurysms that have not been verified in previous angiographies. The annual rate of new aneurysm formation in patients with previous SAH is 0.8-2% per year (Juvela et al., 1993; David et al., 1999; Tsutsumi et al., 2001; Bederson et al., 2009; Sprengers et al., 2009). Patients with multiple intracranial aneurysms, hypertension, young age at the time of SAH, and smokers have a higher risk for de novo aneurysm formation (Bederson et al., 2009).

2.1.9.2 Angiographic follow-up

Angiographic follow-up is not routinely done for clipped aneurysms. However, coiled aneurysms need follow-up, but the recommendable length of follow-up has not been established. Age of the patient, comorbidities, size and shape of the aneurysm, location, rupture state and initial occlusion grade are taken into account

when deciding the follow-up duration. Sprengers et al. (2008) suggested that adequately occluded aneurysms at six months after coiling do not need imaging follow-up, except aneurysms that are partially thrombosed or larger than 15mm. Other aneurysms need long-term follow-up (Sprengers et al., 2008). However, some researchers argue that at least three years follow-up is mandatory for all coiled aneurysms (Raymond et al., 2003).

2.1.10 Rebleeding

2.1.10.1 Risk of rupture in previously unruptured aneurysms

Unruptured aneurysms have an annual risk of rupture of 0-10%, depending on the aneurysm size, location and patient history of previous SAH (Table 13) (Juvela et al., 1993; Investigators, 1998; Juvela et al., 2000; Wiebers et al., 2003). The cumulative bleeding rate in a Finnish study was 10.5% at 10 years, 23% at 20 years and 30% at 30 years after the diagnosis of unruptured aneurysm (Juvela et al., 1993). The median time between discovery of an unruptured aneurysm and SAH was 9.6 years (Juvela et al., 1993). Rupture risk is higher among posterior circulation aneurysms than anterior circulation aneurysms and among larger aneurysms (Wiebers et al., 2003; Clarke et al., 2005). Risk of hemorrhage is also higher in patients with previous SAH than in patients with no SAH (Investigators, 1998; Juvela et al., 2000; Wiebers et al., 2003). In an ISUIA study, 1692 patients with unruptured aneurysms were followed up without treatment and 3% of them had SAH during the mean follow-up of 4.3 years (Wiebers et al., 2003). Table 14 shows rupture risks for anterior and posterior circulation aneurysms according to ISUIA. Overall annual bleeding rate was 0.8% (Wiebers et al., 2003).

Table 13. Annual risk of hemorrhage from unruptured aneurysms according to Mitchell et al., (2004).

	Incidental aneurysm	Additional aneurysm
<7mm	0.1	0.4
7-12mm	1.5	0.8
13-24mm	2.7	1.2
>24mm	5.3	-

Table 14. Annual risk of hemorrhage from unruptured aneurysms according to size and location in ISUIA study (Wiebers et al., 2003).

Size/location	<7mm		7-12mm	13-24mm	>25mm
	no SAH	previous SAH			
Anterior	0	0.3	0.52	2.9	8
Posterior/ACoP	0.5	0.68	2.9	3.68	10

ACoP=Posterior communicating artery; SAH= Subarachnoid hemorrhage

2.1.10.2 Rebleeding after SAH conservative treatment

The risk of rebleeding is highest within the first day after initial bleeding with a rebleeding rate approximately 15%, Figure 3 (Winn et al., 1977; Hijdra et al., 1987; Fujii et al., 1996). Another rebleeding peak is seven days after SAH and rebleeding rate within two weeks is 20% and within one month 30-40% (Hijdra et al., 1987; Fujii et al., 1996). Notably, within six months, 40-50% of conservative treated SAH patients have a rebleeding episode. After the first month the risk decreases gradually from 1–2%/day to 3%/year (Winn et al., 1977; Fujii et al., 1996; Juvela et al., 2000).

The mortality after rebleeding is high and thus early management is preferable (Ohman and Heiskanen, 1989; Kassell et al., 1990a). The rate of early rebleeding is higher in cases with ventricular drainage, poor clinical grade and large aneurysm size (Pare et al., 1992). Conservative prevention methods of rebleeding are pain management, sedation, and control of hypertension (Feigin and Findlay, 2006). Antifibrinolytic therapy with tranexamic acid reduces rebleedings by about 60% but has been linked to increased risk for delayed cerebral ischemia in some studies and

results are not ambiguous (Torner et al., 1981; Hillman et al., 2002; Roos et al., 2003).

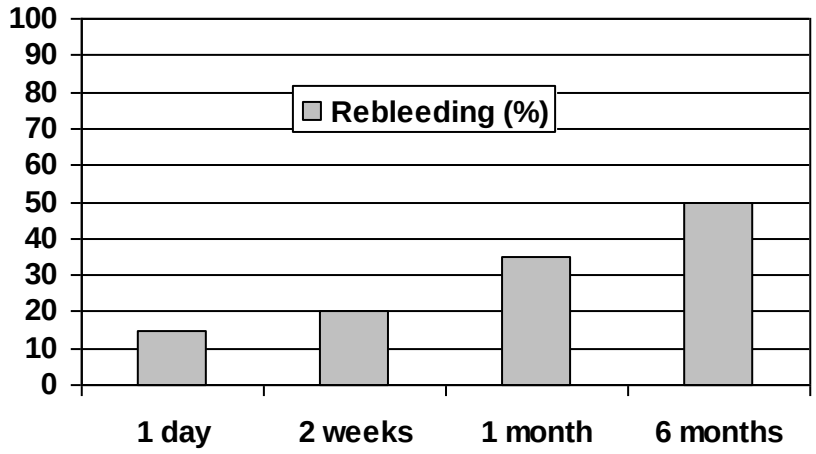

Figure 3. Rebleeding rate in different time periods in SAH patients treated conservatively.

2.1.10.3 Rebleeding after aneurysm clipping

The risk of rebleeding is lower after surgical clipping than endovascular coiling (Molyneux et al., 2005). Rebleeding rate after successful surgical clipping is 1-3% in 10 years and the annual risk is 0.3-0.9% (Tsutsumi et al., 1998; David et al., 1999; Tsutsumi et al. 2001; Molyneux et al., 2005; Wermer et al., 2005; van Gijn et al., 2007; Fulkerson et al., 2009). That is more than 20 times the risk of SAH in the general population (Wermer et al., 2005). Rebleeding risk is higher in incompletely than in completely treated aneurysms (David et al., 1999). Other risk factors for rebleeding are smoking, female gender, young age and multiple aneurysms at the time of the initial SAH (David et al., 1999; Juvela et al., 2001; Wermer et al., 2005).

2.1.10.4 Rebleeding after aneurysm coiling

Overall rebleeding rate after coiling is 3% (Molyneux et al., 2005). Rebleeding is highest within the first weeks following treatment and such early rebleeding within 30 days after treatment is detected in approximately 1% of SAH patients (Vanninen et al., 1999; Molyneux et al., 2005; Sluzewski and van Rooij, 2005; Willinsky et al., 2009). Late rebleeding rate is between 0.5% to 2.6% (Kuether et al., 1998; Byrne et al., 1999; Kremer et al., 2002; Ng et al., 2002; Raymond et al., 2003; Kole et al., 2005; Sluzewski et al., 2005; Ries et al., 2007; Willinsky et al., 2009). Incomplete occlusion and aneurysm size are risk factors for rebleeding (Kuether et al., 1998; Raymond et al., 2003). The largest studies reporting rebleeding rates after endovascular coiling are gathered in Table 15.

2.1.10.5 Bleeding after treated unruptured aneurysms

The bleeding rate in treated, unruptured aneurysms is not widely studied and most studies report no bleedings after coiling (Roy et al., 2001; Goddard et al., 2002). In a study of Standhardt et al. (2008), three (1.5%) out of 202 unruptured aneurysms ruptured after embolization during a 12-year follow-up. All three aneurysms were partially thrombosed giant posterior circulation aneurysms (Standhardt et al., 2008). In a review by Lanterna et al. (2004), 13 postprocedural bleedings occurred in 703 patients (1.8%) and overall annual bleeding rate was 0.9% (95% CI, 0.41-1.4%). Only incompletely coiled aneurysms more than 10mm in size bled after coiling (Lanterna et al., 2004).

Table 15. Rebleeding rates after coiling.

Series	Ruptured/ Unruptured	Patient- years	No. of postembolization bleedings	Bleeding rate	Annual bleeding rate	Notes
Lanterna et al., 2004	U				0.9	review
Gruber et al., 1999	R+U	79.2	2	6.7	2.5	giant
Eskridge and Song, 1998	R		2	3.3		
Eskridge and Song, 1998	U		2	4.1		
Murayama et al., 1999	U	1255	1	1.3	0.08	
Kuether et al., 1998	R+U		1	1.4	0.7	*)
Ng et al., 2002	R+U		2		1.5	
Willinsky et al., 2009	R	691	8	2.1	1.2	
Byrne et al., 1999	R	590	4	1.3		no after 3 yrs
Raymond et al., 2003	R+U	-	3	0.8		
Thornton et al., 2002	R+U		1	0.8		
Ries et al., 2007	R+U	-	7	2.2		
Sluzewski et al., 2005	R	1559	5	1.3	0.3	
Holmin et al., 2008	R+U	1810	1	0.2	0.06	
Kremer et al., 2002	R	270	2	2,5	0.7	
Kole et al., 2005	R+U	448	2	1.5	0.5	
Koivisto et al., 2000	R	52	1	1.9	1.9	
Friedman et al., 2003	R	131	0	0	0	
Molyneux et al., 2005	R	3258	52	3.3	1.1	
van Rooij et al., 2009	R+U	94	2	1.1	2.1	<4mm
Schaafsma et al., 2009	R	1778	3	1.1	0.2	adequately coiled

R=Ruptured aneurysm; U=Unruptured aneurysm

*) 0% in completely coiled, 2.6% (1.4%/yr) in incompletely coiled

2.2 Subarachnoid hemorrhage of unknown etiology

Etiology of subarachnoid bleeding may remain unclear despite repeated four-vessel angiography. Vascular abnormalities are identified in 2 to 24% of patients on repeat DSA, but in most of these patients the etiology of SAH remains unknown (Iwanaga et al., 1990; Farrés et al., 1992; Ronkainen and Hernesniemi, 1992; Kaim et al., 1996; Schwartz and Solomon, 1996; du Mesnil de Rochemont et al., 1997; Urbach et al., 1998; Rogg et al., 1999; Topcuoglu et al., 2003; Jung et al., 2006; Little et al., 2007; Andaluz and Zuccarello, 2008; Agid et al., 2010). Patients with this type of SAH have a more favourable prognosis than patients with aneurysmal SAH (Rinkel et al., 1991b; Schievink and Wijdicks, 1997).

Patients can be classified according to the pattern of hemorrhage on initial CT. In two thirds of these patients the CT scan shows a perimesencephalic pattern of hemorrhage (i.e. blood around the midbrain). Patients with perimesencephalic type of bleeding have a good prognosis, and a repeated angiography is thought to be unnecessary (Rinkel et al., 1991b; du Mesnil de Rochemont et al., 1997). Some researchers have recommended changing the name "perimesencephalic SAH" to "pretruncal" SAH because blood is mainly located in the prepontine cistern. Patients with diffuse or anteriorly located blood on CT (i.e. nonperimesencephalic hemorrhage, aneurysmal pattern of bleeding) are thought to be at risk of rebleeding and repeated angiography is necessary (van Gijn et al., 1985; Rinkel et al., 1991b; Rinkel et al., 1993). Blood does not extend into the parenchyma in perimesencephalic pattern of hemorrhage and also seldom in aneurysmal pattern of hemorrhage (Rinkel et al., 1991b; Ruigrok et al., 2002). Rinkel et al. (1991a) found sedimented blood in lateral ventricles in 21% of patients. However, depending of the timing of the initial CT, classifying bleedings as perimesenchephalic or nonperimesencephalic is not reliable (Schwartz and Solomon, 1996).

2.2.1 Anatomy

In perimesencephalic hemorrhage, the blood is centered in the perimesencephalic cisterns, mostly in the prepontine and interpeduncular cisterns (Figure 4) (Hijdra et al., 1990; Ruigrok et al., 2002). The Liliequist membrane (Figure 5**)** forms the anterosuperior border of the interpeduncular cistern and a border between

interpeduncular cistern and the carotid cisterns laterally and the chiasmatic cisterns medially (Fushimi et al., 2003). Mesencephalic part of the Liliequist membrane forms the border between the interpeduncular and prepontine cisterns. The diencephalic membrane is thicker and is not perforated in minor bleedings. However, the interpeduncular cistern communicates with the carotid cisterns via crural cistern and blood in the carotid cistern is common in SAH of unknown etiology (Rinkel et al., 1991a). Mesencephalic part of the membrane of Liliequist is incomplete, allowing passage of the basilar artery and therefore perimesenchephalic bleeding is often seen in both interpeduncular and prepontine cisterns (Matsuno et al., 1988). Blood in the chiasmatic cistern is due to a high pressure bleeding and raises suspicion of aneurysmal etiology (Schwartz and Solomon, 1996). In conclusion, according to Rinkel et al. (1991a) perimesencephalic hemorrhage can extend into the crural, ambient and quadrigeminal cisterns, sometimes into the suprasellar cistern and proximal part of the interhemispheric fissure and Sylvian fissure, but not into the distal parts of the latter fissures.

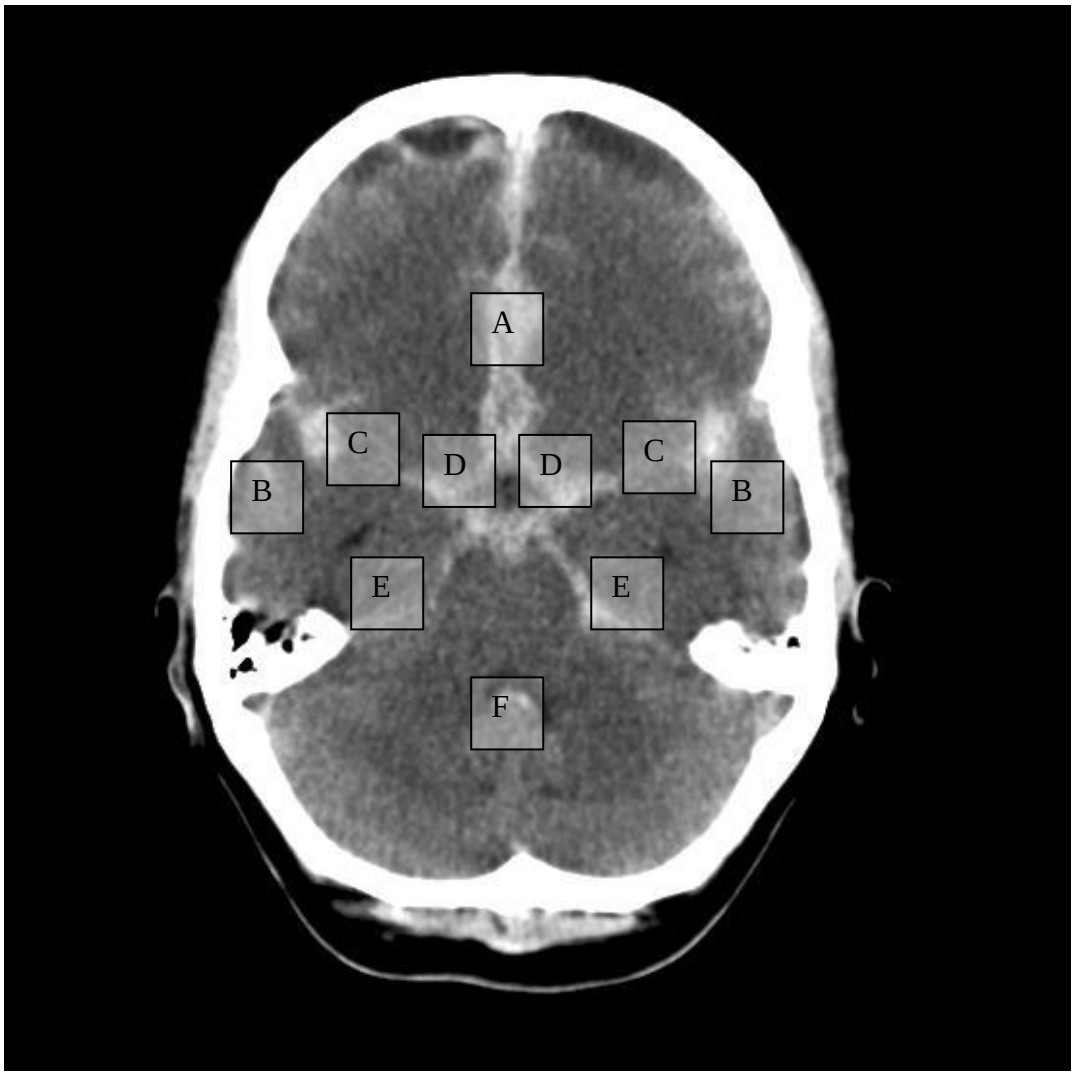

Figure 4. Schematic illustration of basal cisterns.

A=interhemispheric fissure

B=lateral sylvian fissure

C=basal sylvian fissure

D=interpeduncular fissure and suprasellar cistern

E=ambient cistern

F=quadriceminal cistern

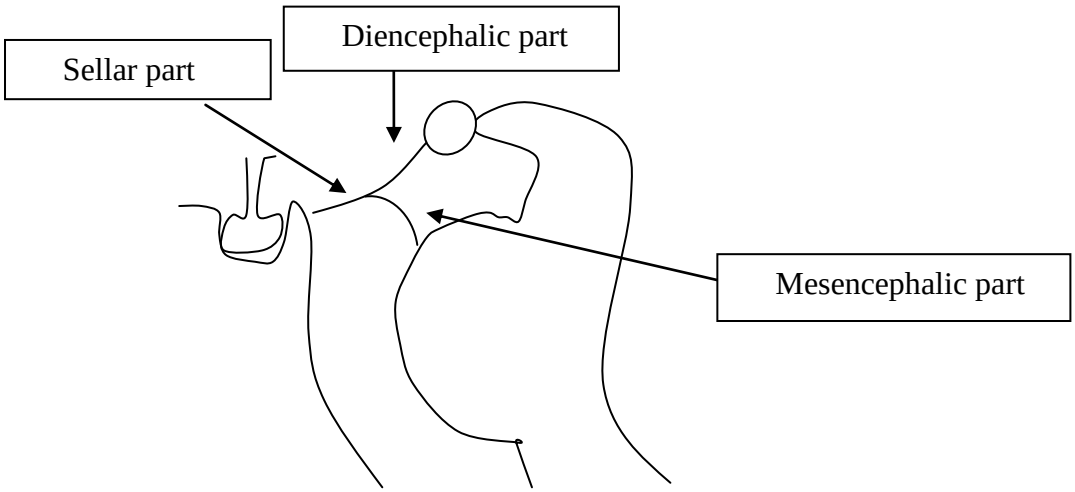

Figure 5. Membrane of Liliequist has diencephalic, mesencephalic and sellar part in the sagittal segment.

2.2.2 Incidence

Subarachnoid hemorrhage with normal cerebral angiography is seen in about 15% (9–30%) of spontaneous SAH cases (Gomez et al., 1989; Kawamura and Yasui, 1990; Broderick et al., 1994; Schaller et al., 1996; McMahon and Dorsch, 1999; Pobereskin, 2001; Claassen et al., 2002; Andaluz and Zuccarello, 2008). Perimesencephalic hemorrhage constitutes 21-68% of all angiogram-negative SAH (van Gijn et al., 1985; Rinkel et al., 1990; Van Calenbergh et al., 1993; Tatter et al., 1995, Agid et al., 2010). The overall annual incidence rate for perimesencephalic SAH is 0.5/100000 in the North American population and it is a rare condition compared to aneurysmal SAH (Flaherty et al., 2005). Incidence in aneurysmal bleeding in the Finnish population is higher than in other European countries (Sarti et al., 1991; Broderick et al., 1994; Ostbye et al., 1997; Cesarini et al., 1999; Ingall et al., 2000; Inagawa, 2001; Pobereskin, 2001; de Rooij et al., 2007; Koffijberg et al., 2008) but incidence of nonaneurysmal SAH is not well studied. Etiology for SAH was not found in 8.6-10% of SAH in two early Finnish studies (Juvela, 1992; Ronkainen and Hernesniemi, 1992).

2.2.3 Pathogenesis

The cause of angiogram-negative SAH has not been established and various pathogenetic mechanisms, such as venous or capillary bleeding (Wijdicks and Schievink, 1997; Watanabe et al., 2002; Mathews et al., 2008), a ruptured perforating artery (Kuker et al., 1999), a low-flow vascular malformation, or a short-segment arterial dissection (Kuker et al., 1999; van der Schaaf et al., 2004; Mathews et al., 2008) have all been postulated. The only anatomically unique vascular structure in the prepontine and interpeduncular cisterns is the basilar artery, not veins or perforating arteries, which are found throughout the major intracranial subarachnoid cisterns (Schievink and Wijdicks, 2000). However, there are no variations in the configurations of the BA which could explain the origin of a hemorrhage (Lang et al., 2003). Some researchers think this entity does not exist at all, but reasons for not detecting aneurysms include spontaneous thrombosis, vasospasm, destruction of the aneurysm by hemorrhage, narrowing of the aneurysmal neck, alterations in blood flow, inadequate angiographic techniques or observer error (McMahon and Dorsch, 1999; Little et al., 2007; van Rooij et al., 2008; Park et al., 2009). Microaneurysms were detected as a source of the hemorrhage in exploration or 3D-angiography in 10 out of 53 patients (19%) in cases of CTA and conventional angiograms were negative (Tatter et al., 1995; Park et al., 2009). However, although imaging methods have been developed a lot, there are still subarachnoid bleedings with unknown etiology.

2.2.4 Clinical presentation

Symptoms in patients with SAH of unknown etiology are similar to aneurysmal SAH: sudden onset of headache, meningismus, photophobia and nausea. However, symptoms are milder and consciousness is usually not lost (van Gijn et al., 1985; Rinkel et al., 1991b; Agid et al., 2010). Patients with both perimesencephalic and non-perimesencephalic hemorrhages have Hunt and Hess grade I or II in 74-94% of cases (Schwartz and Solomon, 1996; Brilstra et al., 1997). “Warning leaks” are detected in 13% of patients compared to 37% in aneurysmal bleedings (Juvela, 1992).

Studies report a mean age of 50 years and there is no female predominence (van Gijn et al., 1985; Schievink et al., 1994; Schwartz and Solomon, 1996; Agid et al., 2010). Patients with nonaneurysmal SAH have less hypertension and smoke less than aneurysmal SAH patients (Canhao et al., 1999; Lang et al., 2003; Flaherty et al., 2005; Agid et al., 2010). However, multivariate analysis confirmed that hypertension is an independent vascular risk factor also associated with perimesencephal SAH (Canhao et al., 1999).

2.2.5 Diagnosis

2.2.5.1 CT

CT is usually immediately performed on admission and blood can be detected with a perimesencephalic pattern of SAH, with a nonperimesencephalic pattern of SAH or CT may be normal. Fisher grade is often lower than in patients with aneurysmal SAH (Schwartz and Solomon, 1996). The chance of finding an aneurysm is less than 5% in patients with a perimesencephalic pattern of hemorrhage (Rinkel et al., 1991a; Pinto et al., 1993; Velthuis et al., 1999; Kershenovich et al., 2006; Brinjikji et al., 2010). Nonperimesencephalic SAH can further be classified as diffuse aneurysmal pattern and peripheral sulcal pattern. Peripheral sulcal nontraumatic SAH without blood in the basal cisterns raises a suspicion of vasculitis or coagulation disorders which are found in a third of cases (Little et al., 2007; Agid et al., 2010). Aneurysmal type bleeding means that blood is diffusely distributed throughout the basal cisterns and extends distally into the Sylvian fissures, into the ventricles and seldom into the parenchyma.

Initial CT shows no blood in 9-65% of cases, depending on the timing of the initial CT (Gomez et al., 1989; Iwanaga et al., 1990; Van Calenbergh et al., 1993; Schwartz and Solomon, 1996; Urbach et al., 1998; Rogg et al., 1999; Lang et al., 2003; Topcuoglu et al., 2003; Little et al., 2007). Complete washout of blood is seen in 92% of cases one week after ictus, and scans obtained >3 days after bleeding cannot reliably identify different patterns of hemorrhage (Schwartz and Solomon, 1996).

Diagnosis is confirmed by cerebrospinal fluid analysis if initial CT is normal. However, lumbar puncture should be done more than six hours and preferably 12 hours after the headache onset to differentiate true SAH from a traumatic lumbar puncture (van Gijn et al., 2007).

MR imaging is not widely used at the acute stage after SAH (Wijdicks et al., 1998b Topcuoglu et al., 2003; Little et al., 2007). However, in some studies MRA demonstrated the cause of SAH even when repeated DSA studies were negative (Rogg et al., 1999; White et al., 2000; Morita et al., 2001).

2.2.5.2 Angiography

CTA is performed at the acute stage and if the initial angiogram is negative, DSA is usually performed for detection of initially unrecognised aneurysms. 3D rotational angiography may help to detect small aneurysms (van Rooij et al., 2008). Angiography is usually repeated one week after the first angiogram and an aneurysm can be detected in approximately 10% (0-24%) of those cases (Kaim et al., 1996; du Mesnil de Rochemont et al., 1997; Urbach et al., 1998; Rogg et al., 1999; Topcuoglu et al., 2003; Jung et al., 2006; Little et al., 2007). An aneurysm could be found in a second angiogram in 0% of patients with normal CT on admission, 0-7% in patients with perimesencephalic SAH and 4-46% in patients with non-perimesencephalic SAH (Kaim et al., 1996; Urbach et al., 1998; Rogg et al., 1999; Topcuoglu et al., 2003; Jung et al., 2006; Little et al., 2007). Many researchers thus recommend that in cases with a clear perimesencephalic hemorrhage pattern, a negative CTA is enough to rule out intracranial aneurysms and DSA is done only if CTA results are unsure (Velthuis et al., 1999; Ruigrok et al., 2000; Kershenovich et al., 2006; Agid et al., 2010). However, patients who have nonperimesencephalic SAH need repeated angiography (McMahon and Dorsch, 1999; Hashimoto et al., 2000; van Dijk et al., 2001; Topcuoglu et al., 2003; Jung et al., 2006; Agid et al., 2010). A second angiogram is also needed when the initial CT scan is performed many days after the ictus and washout of blood may have occurred. Some centres also do a third angiography at six to eight weeks to exclude a thrombosed aneurysm (McMahon and Dorsch, 1999; Topcuoglu et al., 2003; Little et al., 2007).

2.2.6 Complications

2.2.6.1 Vasospasm

Radiographic vasospasm is seen in up to 20% of patients with angiogram-negative SAH, but symptomatic vasospasm is a rare complication (Gomez et al., 1989; Schaller et al., 1996; Wijdicks et al., 1998a; Madureira et al., 2000; Schievink et al., 2000; Franz et al., 2001; Lang et al., 2003; Topcuoglu et al., 2003; Andaluz and Zuccarello, 2008). Cerebral vasospasm is related to the amount of blood noted on the primary CT scan (Wijdicks et al., 1998a).

2.2.6.2 Hydrocephalus

There is a positive correlation between acute hydrocephalus and the amount of subarachnoid blood in the initial CT (Jartti et al., 2004). Thus, ventricular enlargement is a more common complication after aneurysmal bleeding than after perimesencephalic bleeding. Incidences of hydrocephalus are 4-18% in perimesencephalic bleeding and 7-26% in nonperimesencephalic bleeding. However, a permanent CSF drainage system is rarely needed. (Wijdicks et al., 1998a; Madureira et al., 2000; Franz et al., 2001; Lang et al., 2003; Andaluz and Zuccarello, 2008; Beseoglu et al., 2010)

2.2.6.3 Rebleeding

Rebleeding rate is considerably lower than in aneurysmal SAH. Rebleeding rate in patients with non-perimesencephalic bleeding is between 2 and 5%. Patients with perimesencephalic bleeding have lower rebleeding rates, with non-existing rates in recent studies (Greebe and Rinkel, 2007; Little et al., 2007).

2.2.7 Management

There is no specific treatment for patients with nonaneurysmal SAH. Symptomatic care, cardiac and serum chemistry monitoring and symptoms of hydrocephalus are

followed (Schwartz and Solomon, 1996; Wijdicks et al., 1998a). There is no proof about efficacy of bed rest, blood pressure control, and hypertensive or hypervolemic therapy, or about calcium channel blockers in achieving a better prognosis (Schwartz and Solomon, 1996; Wijdicks et al., 1998a). Surgical exploration is not indicated if adequate angiography has been performed (Schievink et al., 1994; Tatter et al., 1995; Schaller et al., 1996).

2.2.8 Outcome

Outcome in patients with nonaneurysmal SAH is significantly better than in patients with aneurysmal bleeding (Jain et al., 1987; Gomez et al., 1989; Kawamura and Yasui, 1990; Rinkel et al., 1991b; Juvela, 1992; Ronkainen and Hernesniemi, 1992; Schaller et al., 1996; Madureira et al., 2000; Franz et al., 2001; Lang et al., 2003; Greebe and Rinkel, 2007; Andaluz and Zuccarello, 2008; Beseoglu et al., 2010). Good outcomes are reported in 64-100% of patients and mortality is 0-15% (Jain et al., 1987; Gomez et al., 1989; Kawamura and Yasui, 1990; Rinkel et al., 1991b; Juvela, 1992; Ronkainen and Hernesniemi, 1992; Schaller et al., 1996; Madureira et al., 2000; Franz et al., 2001; Lang et al., 2003; Greebe and Rinkel, 2007; Andaluz and Zuccarello, 2008; Beseoglu et al., 2010). In patients with perimesencephalic SAH, the outcome is better than in nonperimesencephalic patients with 89-100% of good outcomes and less than 2% mortality (Van Calenbergh et al., 1993; Franz et al., 2001; Andaluz and Zuccarello, 2008; Beseoglu et al., 2010; Alfieri A et al., 2011). The outcomes do not differ in patients with SAH on initial CT or in CT negative cases (Van Calenbergh et al., 1993). Although outcome is good, when assessed with Glasgow outcome scale, up to 72% of patients with nonaneurysmal SAH have neuropsychological deficits, depressive symptoms and symptoms including headaches, dizziness, fatigue, forgetfulness or irritability, even years after bleeding (Madureira et al., 2000; Greebe and Rinkel, 2007). Brilsta et al. (1997) reported that quality of life and capacity to work is not reduced in patients with perimesencephalic hemorrhage. Patients with an aneurysmal pattern of hemorrhage have a high cerebrovascular morbidity and poorer long-term outcome than patients with perimesencephalic SAH (Hawkins et al., 1989; Ruigrok et al., 2002; Alfieri A et al., 2011). Long-term mortality in patients with perimesencephalic SAH does not

differ from that observed in the general population (Gomez et al., 1989; Greebe and Rinkel, 2007).

3. Aims of the study

The purpose of the present study were

I To evaluate the long-term occlusion grade in aneurysms treated with endovascular coiling.

II To evaluate the permanent focal changes of the brain tissue after endovascular treatment for both ruptured and nonruptured aneurysms.

III To assess the long-term mortality compared with the general population among patients with unruptured aneurysms with no previous SAH, and to compare mortality after coiling, clipping and without treatment.

IV To assess the incidence, clinical findinds, long-term outcome and long-term MRI and MRA findings in patients with SAH of unknown origin.

4. Materials and methods

4.1 Patient population

All hospital records of patients with a diagnosis of "SAH" or "unruptured aneurysm" in Tampere University Hospital between 1989 and 1999 were reviewed. A total of 1571 patients were scrutinized, and 313 patients were excluded because of a false diagnosis, SAH caused by trauma, AVM, mycotic or dissecting aneurysm, and patients under 18 years old. All the included patients were treated either because of SAH (1,154) or unruptured aneurysms (307), at the neurosurgical department at Tampere University Hospital. Of those, 617 patients with 513 ruptured and 189 unruptured intracranial aneurysms were treated, and 185 patients with 200 aneurysms were treated with endovascular coiling. Figure 6 summarizes the included and excluded patients.

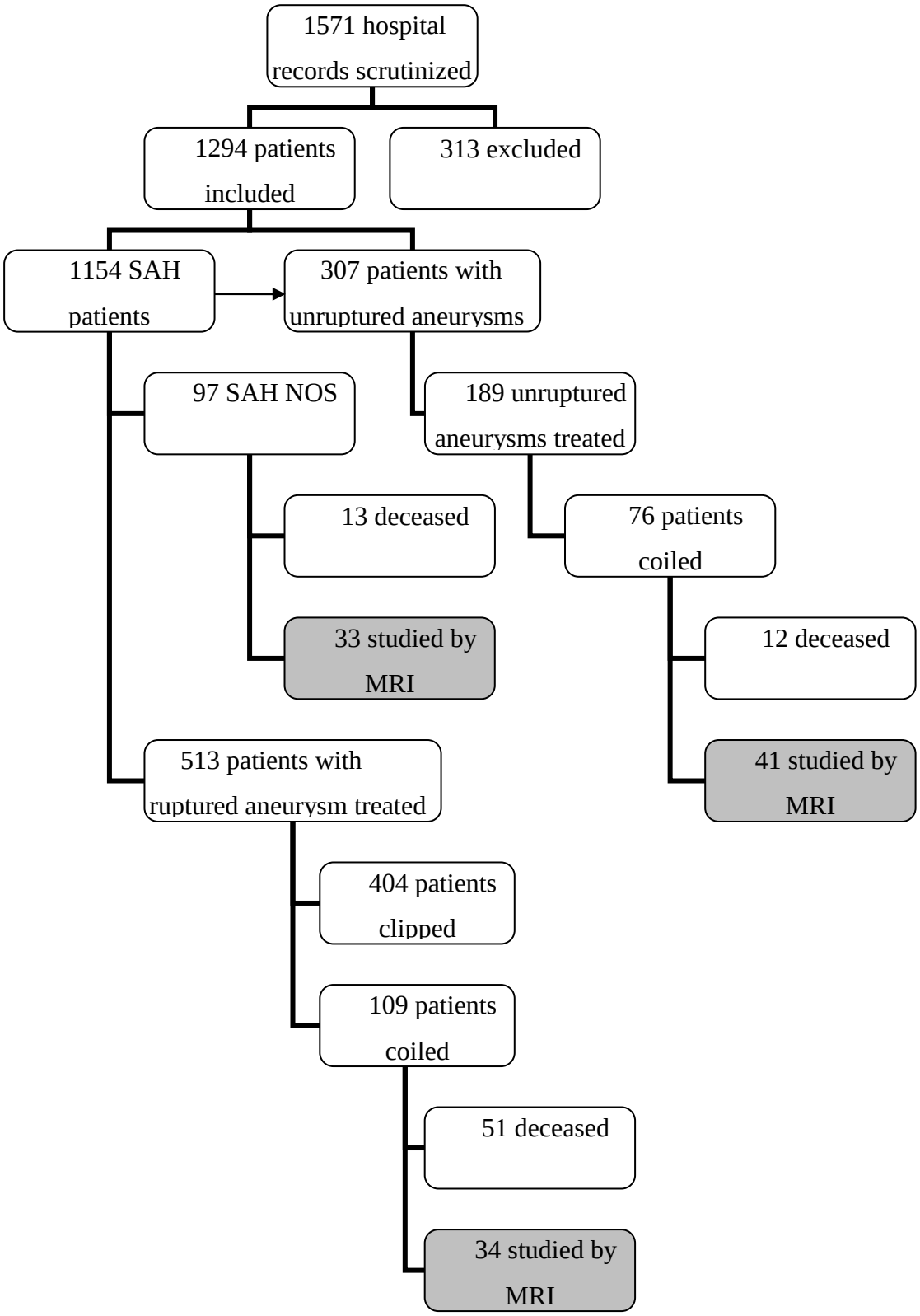

Figure 6. Flowchart summarizing the included and excluded patients.

MRI= Magnetic resonance imaging; SAH=Subarachnoid hemorrhage; SAH NOS= Subarachnoid hemorrhage not otherwise specified

4.1.1 Patients with embolized aneurysms

The study population consisted of 185 patients treated with endovascular coiling between 1992 and 1999. Coiling was performed in 109 patients with ruptured aneurysms and 76 patients with unruptured aneurysms (Figure 6). A total of 63 patients had died at the time of follow-up. The clinical outcome could be evaluated in 116 (95%) out of the 122 surviving patients. The surviving patients (except for 26 excluded patients) were contacted by letter proposing an MRI investigation. Patients were excluded if they lived outside our hospital catchment area or had contraindications to MRI. In study II, patients who also had one or more aneurysms clipped, were excluded. Seventy-seven patients were examined with MRI and MRA approximately 11 years after initial coiling (range 9-16 years). Follow-up time was 792 patient-years in the unruptured group and 688 patient-years in the ruptured group. The demographic data of patients studied with long-term follow-up MRI is shown in Table 16.

Table 16. Baseline characteristics of the patients with long-term follow-up of embolized aneurysms (% in parenthesis).

	Patients with ruptured aneurysms	Patients with unruptured aneurysms
	n=34	n=43
Male/Female	15/19	15/28
Mean age, years (range)	54 (34-73)	50 (21-79)
Number of aneurysms		
1	26	29
2	6	10
3	2	4
Number of aneurysms coiled	34	50
Indication for angiography		
SAH	34 (100)	7 (16)
familial history of SAH	-	4 (9)
cranial nerve dysfunction	-	4 (9)
incidental	-	28 (65)
H&H at the time of diagnosis		
I	12 (35)	-
II	12 (35)	-
III	6 (18)	-
IV	4 (12)	-
V	0	-
Fisher grade		
1	3 (9)	-
2	1 (3)	-
3	9 (26)	-
4	9 (26)	-
Missing	12 (35)	-
GOS at discharge		
1	0	0

2	1 (3)	0
3	7 (21)	2 (5)
4	16 (47)	10 (23)
5	10 (29)	31 (72)
GOS at follow-up		
1	0	0
2	0	0
3	3 (9)	6 (14)
4	8 (24)	13 (30)
5	23 (68)	24 (56)
Aneurysm location		
ICA	2 (6)	20 (40)
MCA	3 (9)	14 (28)
ACoA	13 (38)	5 (10)
ACoP	3 (9)	1 (2)
ACA/pericallosa	2 (6)	5 (10)
Vertebrobasilar circulation	11 (32)	5 (10)
Aneurysm size		
<7mm	27 (79)	29 (58)
7-12mm	5 (15)	16 (32)
13-24mm	2 (6)	3 (6)
≥25mm	0	2 (4)
Initial angiographic result		
complete	14 (41)	24 (48)
neck remnant	9 (26)	10 (20)
incomplete	11 (32)	16 (32)

ACA=Anterior cerebral artery; ACoA=Anterior communicating artery; ACoP=Posterior communicating artery; GOS=Glasgow outcome scale; H&H=Hunt&Hess scale; ICA=Internal carotid artery; MCA=Middle cerebral artery; SAH=Subarachnoidal hemorrhage

4.1.2 Unruptured aneurysms in patients with no previous SAH

Between 1989 and 1999, 140 patients with 178 intracranial unruptured aneurysms without previous SAH were admitted to Tampere University Hospital. Patients (75 women and 65 men) were aged 18-86 years (mean 54 yrs) at the time of diagnosis of the unruptured intracranial aneurysm. A total of 66 out of 178 aneurysms were left untreated, 64 were treated with endovascular coiling and 48 were treated surgically (Figure 7). All patients were followed up until death or the end of April 2011 and no patients were lost from follow-up. Fifty out of 140 patients (36%) had died during the 1702 patient-year follow-up period.

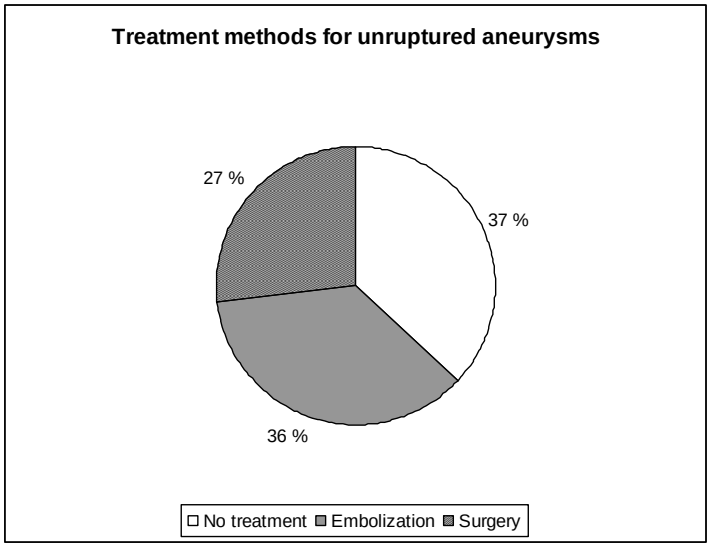

Figure 7. Distribution of treatment methods for unruptured aneurysms in patients without previous SAH.

4.1.3 SAH of unknown etiology

The study IV population consisted of 97 patients with SAH of unknown etiology. Patients older than 18 were included if SAH was diagnosed by CT or by positive lumbar puncture and no vascular pathologies were detected in repeated four-vessel cerebral angiography or in postmortem examinations. SAH was diagnosed by computed tomography (CT) in 80 (82%) cases and xanthochromia of the CSF in 17 (18%) cases. The diagnosis was based on DSA in 96 patients and postmortem examinations on one patient. The demographic data is shown in Table 17.

Table 17. Demographics of patients with SAH of unknown etiology.

	Surviving group	Deceased group
	N=84	N=13
Mean age (years)	52	53
Male/Female	31/53	4/9
Diagnosis		
CT	67	13
Lumbar puncture	17	0
Fisher grade		
1	16	0
2	17	4
3	20	5
4	23	4
Missing	8	-
Hydrocephalus	30	4
Hunt&Hess grade		
I	40	2
II	32	2
III	10	5
IV	1	3
V	1	1
GOS at discharge		
I	0	2
II	0	1
III	10	1
IV	41	7
V	33	2
GOS at follow-up		
I	0	13
II	0	0
III	4	0
IV	18	0
V	62	0

GOS=Glasgow outcome scale

4.2 Data collection

All hospital records, CT scans, MR-images and DS-angiograms were studied retrospectively. The surviving patients in study groups I, II and IV living in the hospital catchment area were contacted by letter proposing an MRI investigation, and were then interviewed to assess clinical outcome and possible rebleeding episodes. A total of 110 were interviewed and studied with MRI and MRA between 2007 and 2008. Surviving patients not studied with MRI either lived outside the hospital catchment area (n=22), did not answer the invitation letter (n=13), were unwilling to participate in the study (n=6) or had contraindications to MRI (n=4). The latest outcome of patients was evaluated by telephone interview, or from the latest notes in the hospital records. A total of 504 out of 1294 patients were deceased, and death certificates were obtained from Statistics Finland to ascertain the date and cause of death.

4.3 Embolization procedures

Endovascular procedures were performed in cases where the aneurysm seemed to be treatable in a consensus meeting of an interventional radiologist and a neurosurgeon. Procedures were performed between 1992 and 1999. Aneurysms were embolized with platinum Guglielmi detachable coils (GDC, Target Therapeutics, Fremont Calif., USA). Intravenous nimodipine was used routinely and 5000 IU unfractionated heparin was given intravenously before coiling in unruptured cases and after two coils in ruptured cases.

4.4 Follow-up

The clinical outcome was evaluated using the Glasgow Outcome Score (GOS, Table 9**)** (Jennett and Bond, 1975). Mean follow-up time of patients studied with MRI was 11 years (median 9 yrs, range 9-18yrs). Patients studied with MRI were interviewed

and the clinical outcome was assessed using both GOS and GOSE (Wilson et al., 1998). The latest outcome was evaluated from the latest notes in the hospital records or by telephone interview in patients not studied with MRI. Possible rebleeding episodes were elicited. In studies I, II and IV, patients were followed up until death, until the last MRI or phone contact or latest hospital records between 2007 and 2008. In study III the patients were followed up until death or the end of April 2011.

4.5 Imaging protocol

The follow-up MR imaging was performed with 1.5 T unit (GE Signa HD, Milwaukee, Wisc., USA) with 1-channel head-coil. The MRA was supplemented with cross-sectional imaging including FLAIR and T2* weighted sequences mainly to detect ischemic parenchyma, the size of the CSF spaces and signs of persistent blood degradation deposits. The imaging parameters for the non-contrast 3D time-of-flight angiography were: TR 30, TE 2.5, FOV 22 x 16.5 cm, slice thickness 1.0 mm/interpolated to 0.5 mm, matrix 320 x 224. Magnetization transfer contrast and flow compensation were included. The imaging parameters for the FLAIR were: TR 9001 ms, TE 125 ms, TI 2250 ms, FOV 22 cm, slice thickness 5/1mm, matrix 224 x 256, NEX 1 and for T2* weighted images: TR 460 ms, TE 20 ms, flipangle 20°, FOV 22 cm, slice thickness 5/1mm, matrix 160 x 256 (interpolated to 512), NEX 2. Areas of increased signal intensity of vascular territories in T2* weighted images were considered as infarctions. Small high signal foci on T2* weighted images were considered as leukoaraiosis.

All radiological images were reviewed independently by a neuroradiologist, an interventional radiologist and a neurosurgeon and thereafter a consensus statement for each study was made. Primary CT images were re-evaluated to assess Fisher grades, existence and grade of ventricular enlargement and possible parenchymal lesions. Previous MRI and MRA studies were compared with the present images. Aneurysm neck and fundus sizes were measured and dome-neck ratios were calculated. The degree of aneurysm occlusion was classified according to the modified Raymond's classification (Figure 2) (Raymond et al., 1997) and also as loose or dense, the former meaning that there was opacification between coils and

the latter meaning no contrast media was detected between coils. Parenchymal lesions were considered aneurysm-related if they appeared during acute hospitalization; aneurysmal ICH was seen in primary CT or detected in parental artery territory after the treatment period. Infarctions in MRI were divided into parental and non-parental artery territory infarctions.

4.6 Statistical analysis

Statistical analysis was performed using NCSS (NCSS, Kaysville, Utah, USA) statistical software. Categorical variables were compared using Fisher exact two-tailed test. Continuous variables between groups were compared using the Mann-Whitney U-test or Student T-test. The level of significance was set at $p<0.05$. Correlation between variables was analyzed with Spearman's rank correlation test. Excess mortality of the patients was measured by one minus relative survival ratio (RSR). The RSR is the ratio of the actuarial observed survival proportion divided by the expected survival proportion of a comparable group of the Finnish general population matched for sex, age and calendar time. The expected survival proportions were estimated by Ederer II method (Ederer, Heise 1959). Relative survival measures the survival experience of the patients corrected for competing risks of death. Relative survival ratios were estimated by survival package SURV3 version 3.01 (Finnish Cancer Registry, Helsinki, Finland). Differences in relative survival between patient groups were tested applying likelihood ratio tests (Hakulinen et al. 1987).

4.7 Ethical issues

The present study was approved by the Ethics Committee of Tampere University Hospital and Statistics Finland. Informed consent was obtained from all patients studied with MRI.

5. Results

5.1 Long-term occlusion grade after endovascular coiling

Long-term follow-up MRAs showed complete occlusion in 18 ruptured aneurysms (53%), 11 (32%) had neck remnants and 5 (15%) were graded as incomplete (Figure 8). Unruptured aneurysms (Figure 9) were graded as complete in 20 (40%) aneurysms, neck remnant in 11 (22%) and incomplete in 18 (38%). Unruptured aneurysms were incompletely occluded more often than ruptured ones, and this difference reached statistical significance (p=0.03). Although incomplete occlusion was seen in 23 aneurysms (27%), only three had poorer occlusion grades than in previous follow-up images. Table 18 shows the stability of aneurysms in both groups. A change to a better occlusion grade (i.e. progression) was detected in 17% of aneurysms. Stable occlusion was detected in 60% of aneurysms, 14% had remnant growth and 8% had recurrence at long-term follow-up MRI. Incompletely occluded aneurysms were monitored for many (up to ten) years after the initial treatment and when the occlusion grade was assessed to be stable, follow-up images were discontinued. Four of these incompletely coiled aneurysms are still being followed up. Incompletely occluded aneurysms had wider necks and fundi than aneurysms with a higher occlusion grade. No de-novo aneurysms were detected.

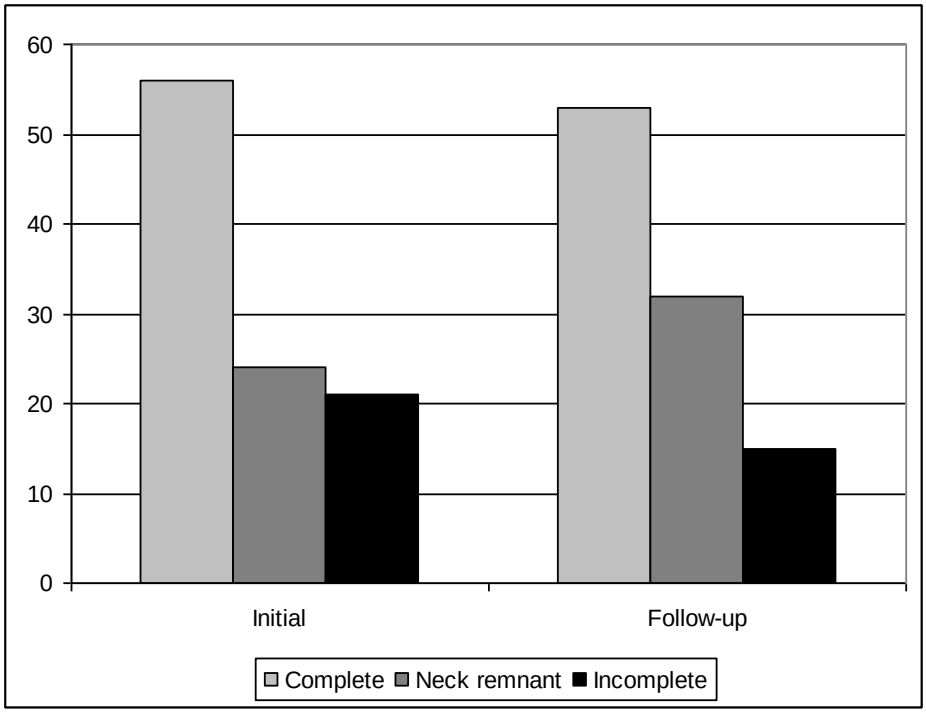

Figure 8. Distribution (%) of occlusion grades after treatment and at long-term follow-up MRI in ruptured aneurysms.

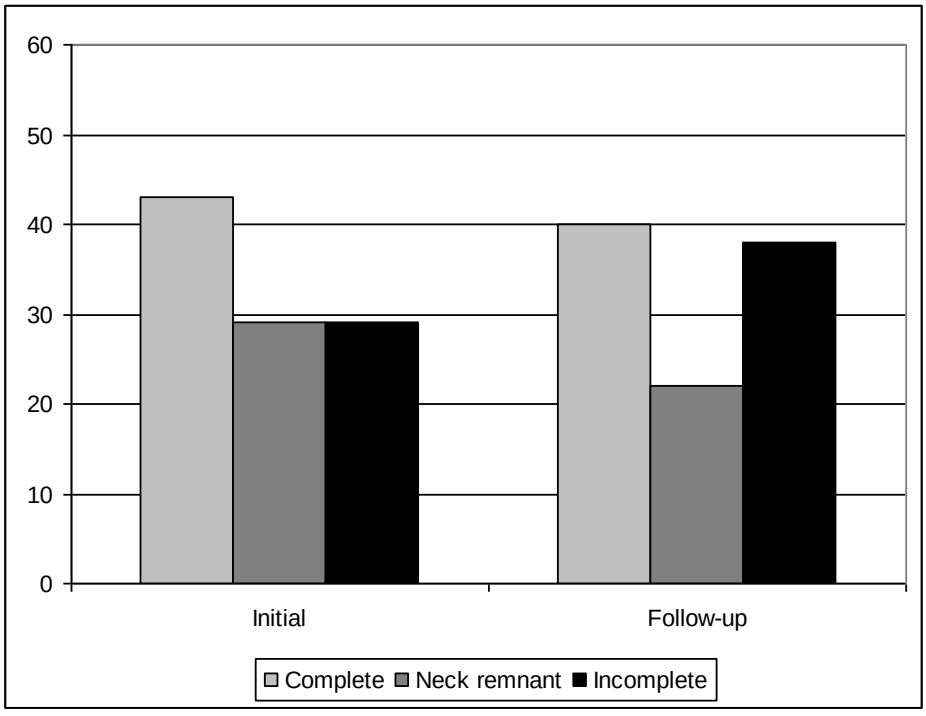

Figure 9. Distribution (%) of occlusion grades after treatment and at long-term follow-up MRI in unruptured aneurysms.

Table 18. Changes in aneurysm occlusion grade after initial treatment and long-term follow-up images in ruptured and unruptured group.

	Ruptured aneurysms	**Unruptured aneurysms**
	n=34	n=49
Progression	7 (21%)	7 (14%)
Stable	20 (59%)	30 (61%)
Recanalization	7 (21%)	12 (24%)

5.2 Long-term MRI findings after endovascular coiling

5.2.1 Ruptured aneurysms

Parenchymal lesions of various causes (infarctions or previous ICH) were detected in 14 (44%) SAH patients and 18 (56%) had normal brain parenchyma on T2-weighted MR images (Figure 10). High signal intensity lesions on T2-weighted images indicating infarction in the vascular territory of the aneurysm were seen in six (19%) SAH patients. Four patients (13%) had infarctions in vascular territories other than that of ruptured aneurysms (non-parental artery territories) and three (9%) of them were considered to be caused by vasospasm. All aneurysm-related lesions were detected during the initial treatment period, and no aneurysm-related delayed infarctions were seen. Figures 11 and 12 show typical examples of aneurysm-related lesions detected.

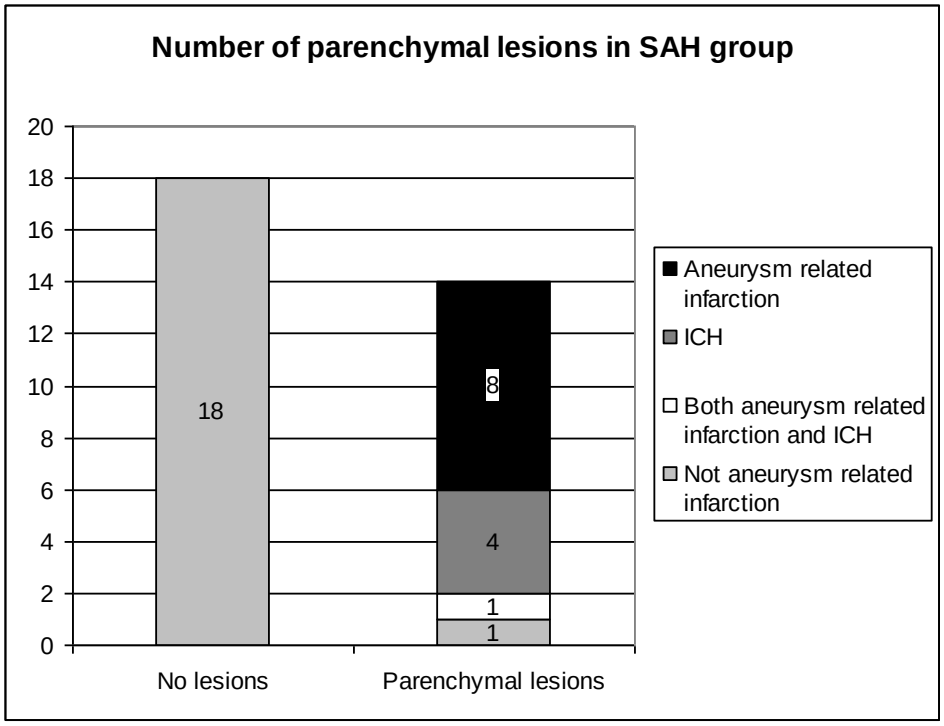

Figure 10. Number of parenchymal lesions in SAH group.

ICH=Intracerebral hemorrhage; SAH=Subarachnoid hemorrhage

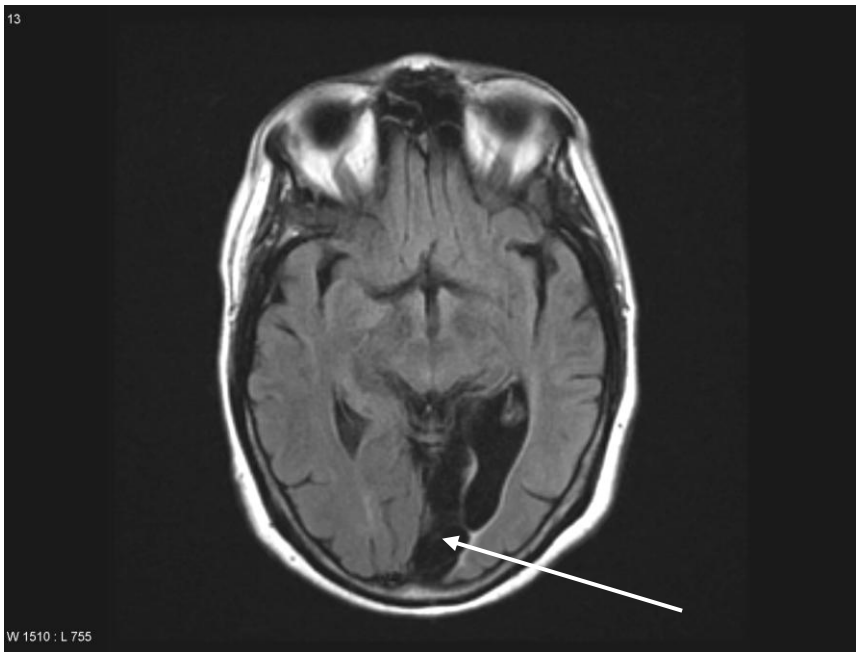

Figure 11. Large left side occipital infarction (white arrow) nine years after thromboembolic complication during endovascular coiling of a ruptured BA aneurysm. Infarction was detected during initial hospitalization.

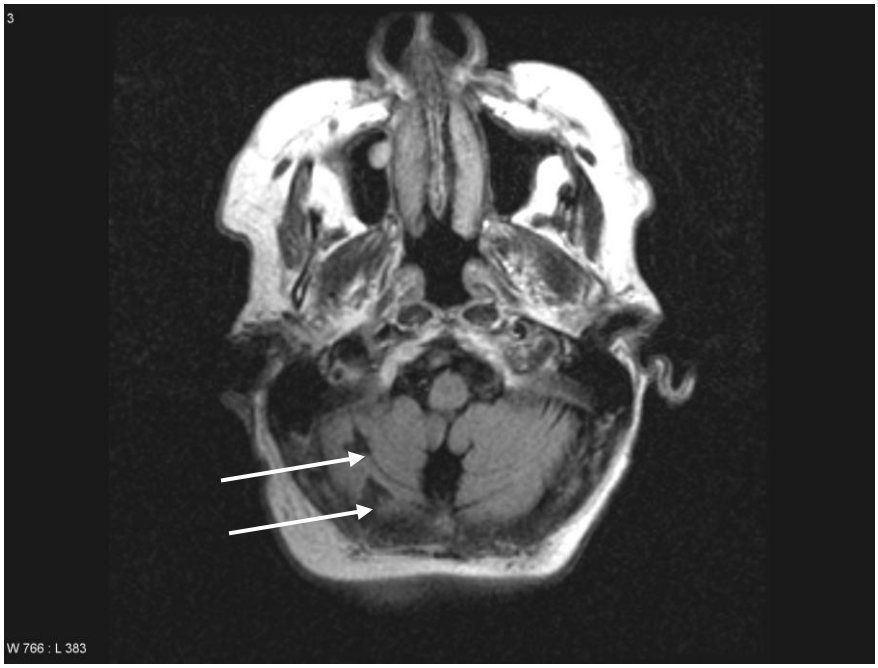

Figure 12. Small cerebellar infarctions (white arrows) detected after coiling of a ruptured right vertebral artery aneurysm without any clinical complications during acute hospitalization 13 years earlier.

5.2.2 Unruptured aneurysms

Normal brain parenchyma was detected in 21 (66%) patients with unruptured aneurysms in long-term follow-up MRIs (Figure 13**).** Parenchymal high signal intensity lesions on T2-weighted MR images were detected in 11 (34%) patients with unruptured aneurysms. Infarction in the vascular territory of the aneurysm was seen in six (19%) patients and two of them were not detected during the treatment period. One of them was caused by coil migration without any clinical symptoms, and the other was probably caused by delayed embolic complications after a treated giant ICA aneurysm.

Non-parental artery infarctions occurred in six (19%) patients, and these lesions were not aneurysm-related: four infarctions were detected before aneurysm treatment and two were detected years after the coiling.

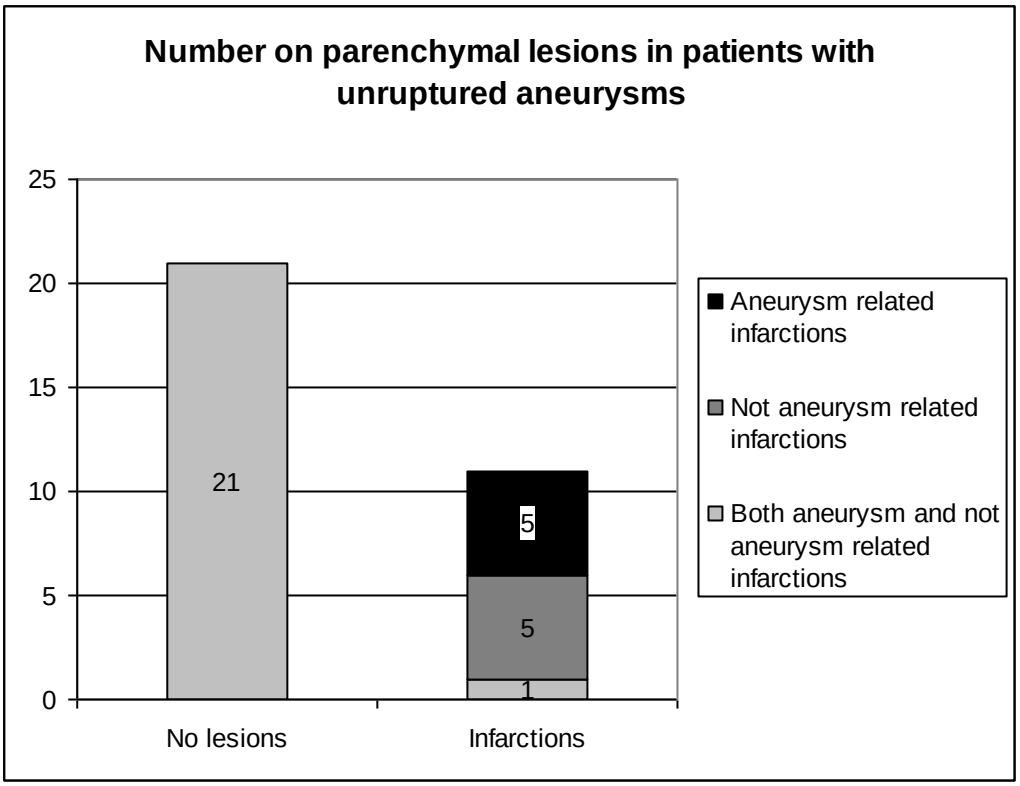

Figure 13. Number of parenchymal lesions in patients with embolized unruptured aneurysms.

5.3 Long-term excess mortality of patients treated for unruptured intracranial aneurysms

5.3.1 Untreated aneurysms

Patients with untreated unruptured aneurysms had excess long-term mortality compared to the general population (Figure 14). The five year cumulative RSR was 0.78 among males and 0.56 among females with untreated unruptured aneurysms, implying 22% and 44% excess mortality, respectively. The 10 year cumulative RSR was 0.80 in males and 0.49 in females with untreated aneurysms. The 15 year cumulative RSR was 0.50 among both males and females with untreated unruptured aneurysms, implying 50% excess mortality.

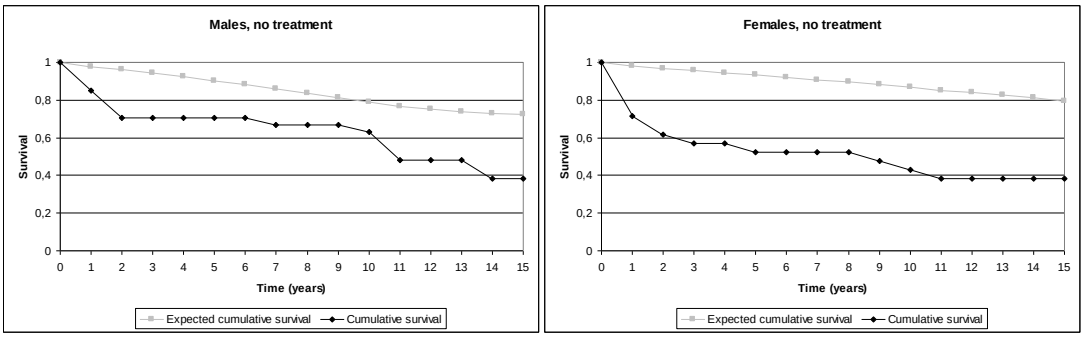

Figure 14. Cumulative observed and expected survival proportions in males and females with no treatment of unruptured aneurysms. Adapted from Pyysalo et al. (2012).

5.3.2 Clipped aneurysms

Mortality among surgical group did not differ from the general population at a five year follow-up, neither did it in males after 10 years (Figure 15). However, women had 8% excess mortality after a 10 year follow-up, and 28% excess mortality after 15 years (RSR: 0.72) compared with the matched Finnish population. Males had 8% excess mortality at 15 years (RSR: 0.88) in the surgical group.

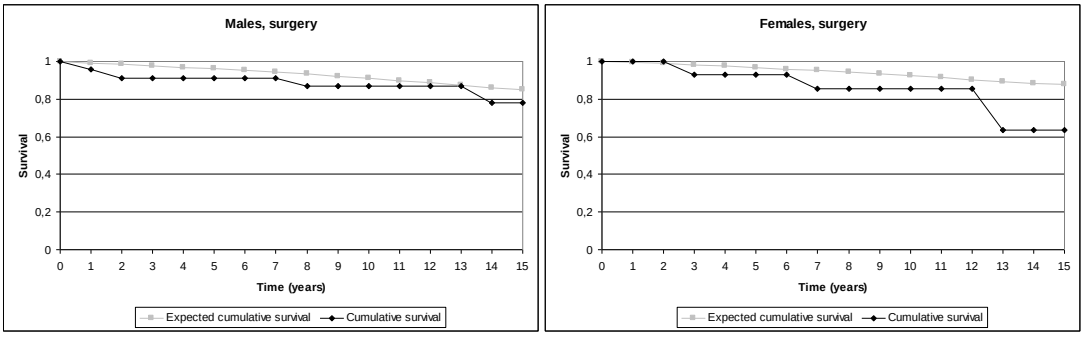

Figure 15. Cumulative observed and expected survival proportions in males and females after surgery. Adapted from Pyysalo et al. (2012).

5.3.3 Coiled aneurysms

Men with embolized aneurysms had no excess mortality when compared to the matched Finnish male population (Figure 16). However, women had 19% excess mortality at a five year follow-up, and 23% excess mortality at 15 year follow-up, respectively. Mortality among women over 50 years of age was higher than in coeval men. Both genders under 50 years of age had a 15 year cumulative RSR of around 0.90, but the 15 year cumulative RSR in patients over 50 years differed significantly between men (0.91) and women (0.49, p=0.018).

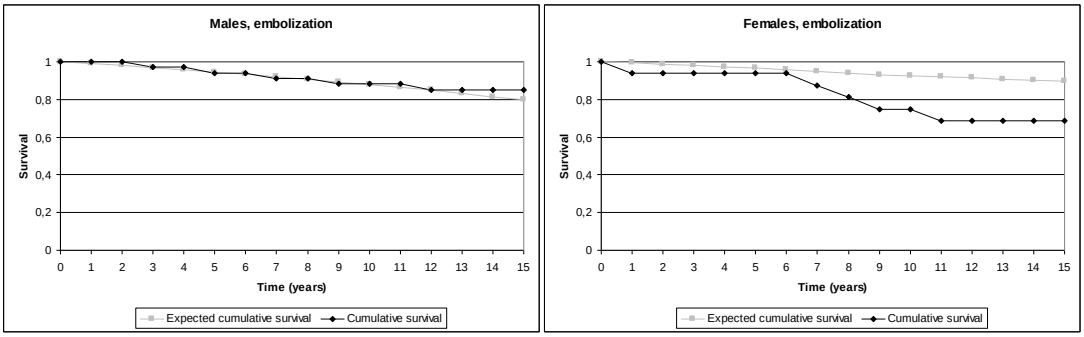

Figure 16. Cumulative observed and expected survival proportions in males and females after embolization. Adapted from Pyysalo et al. (2012).

5.3.4 Causes of death in patients with unruptured aneurysms

Fifty out of the 140 patients (36%) had died during the 1702 patient-years follow-up period. Half of the deaths (48%) were cerebrovascular events and 58% of them occurred within five years after diagnosis (Figure 17). Eleven patients died of cardiovascular diseases (22% of deaths), six of malignancies (12% of deaths) and eight due to other causes (16% of deaths). The cause of death in one patient was stroke with unverified etiology. Patients with treated aneurysms were less likely to die from neurologically related causes than patients with untreated aneurysms; 32% and 61%, respectively. Figure 18 shows causes of death in study III compared to other studies and the Finnish general population.

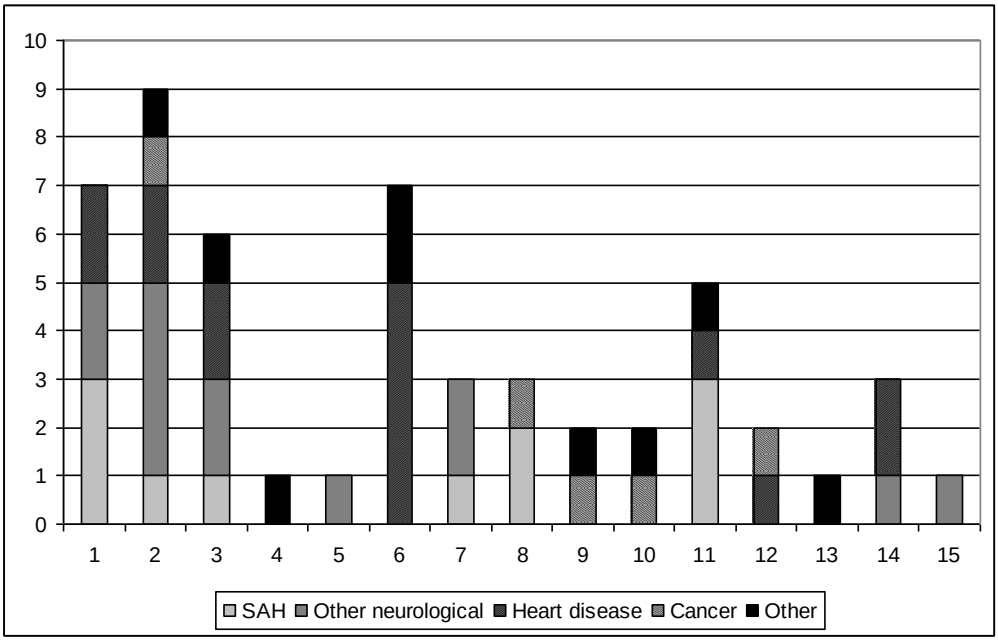

Figure 17. Number of deaths and distribution of causes of deaths in every follow-up year.

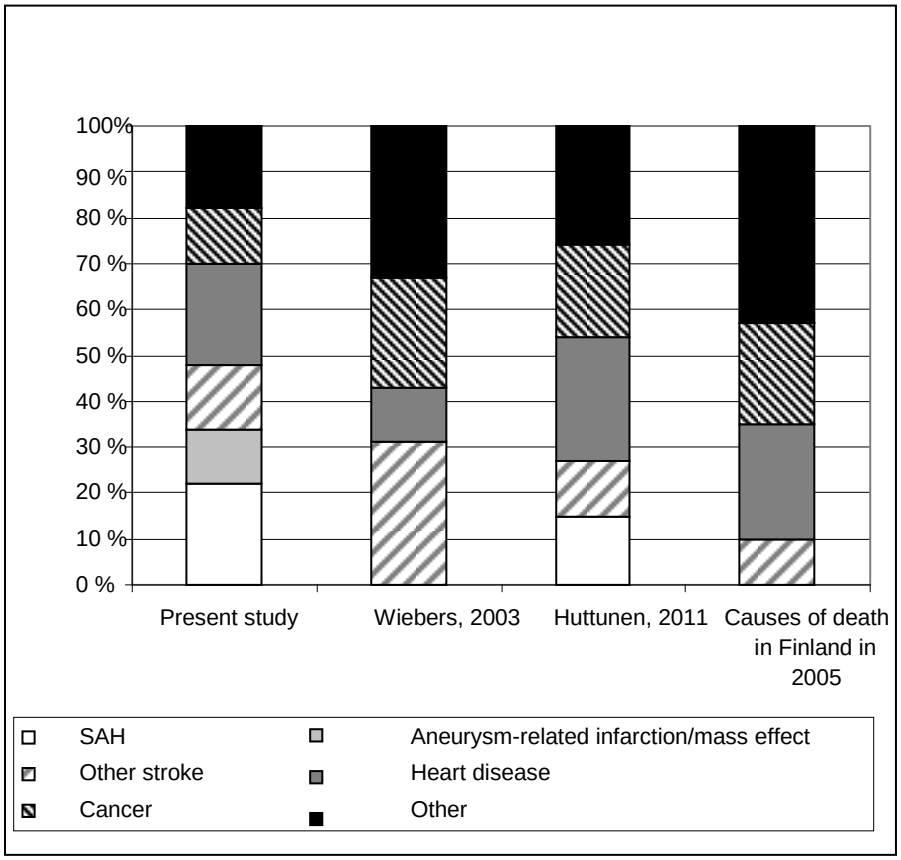

Figure 18. Causes of death in study III compared to other studies. Type of strokes were not differentiated in a study by Wiebers et al. (2003) neither in statistics of death causes in Finnish population.

5.4 Nonaneurysmal SAH

5.4.1 Clinical condition of patients with nonaneurysmal SAH

Most patients were in good clinical condition on admission (80% H&H 1-2) and 94% of surviving patients had a good recovery (GOS 4-5) after a mean follow-up time of 12 years (range 9-18yrs, Figure 19). There were no rebleedings.

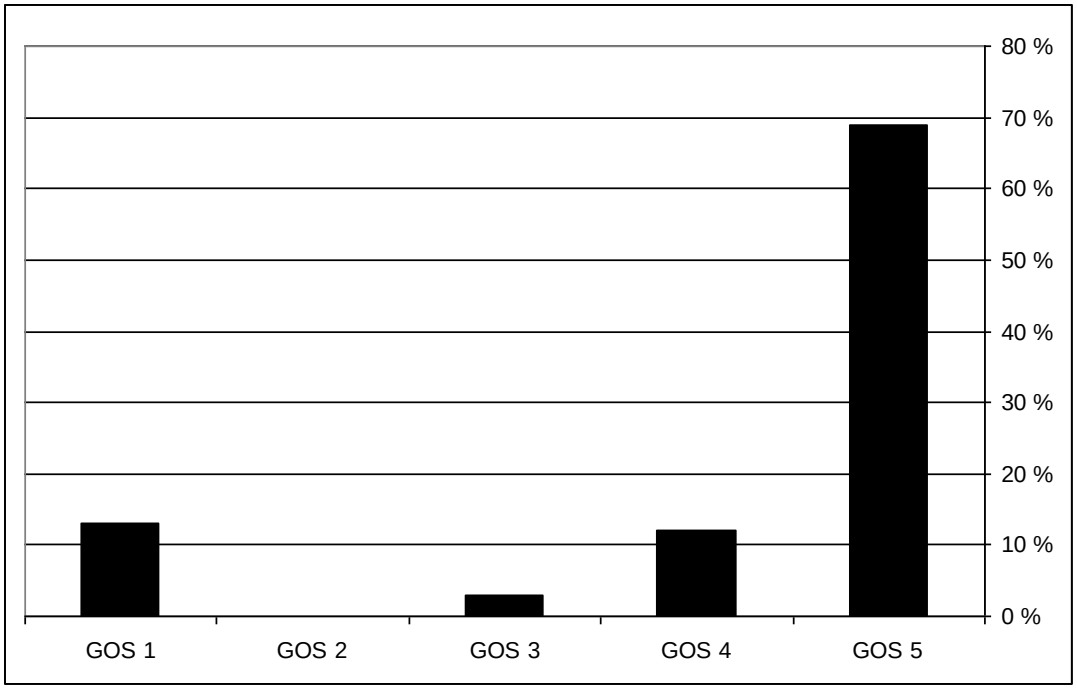

Figure 19. Present GOS of patients with SAH of unknown etiology.
GOS=Glasgow outcome scale

5.4.2 Mortality of patients with nonaneurysmal SAH

Thirteen out of the 97 patients (13%) had died during the follow-up period (mean 12 years, range 9-18 years, 868 patient-years). Four of them (4%) had died from the initial bleeding of nonaneurysmal SAH: two immediately and another two in one month after poor clinical state. All four patients had severe bleeding on the initial CT (Fisher 3 or 4, nonperimesencephalic type of bleeding). Clinical condition on admission and Fisher grade on primary CT were predisposing factors for poor outcomes. Three patients died of cardiovascular diseases, three of malignancies, and

three due to traumatic causes. Mortality in the first year after the bleeding was 4% in excess of that expected in a comparable group from the general population. Thereafter, mortality of the patients was close to the level of the general population.

5.4.3 Long-term MRI and MRA findings in patients with nonaneurysmal SAH

Thirty-three patients were studied with MRI and MRA. Neither new aneurysms nor other vasculopathies which could explain the previous SAH were detected in MRA images. Six patients (18%) had infarctions in MRI. Two of them were already seen during the treatment period after clinically and radiologically proven vasospasm. Four infarctions were not detected in earlier images, and only two of those four patients had been treated for clinical stroke. Leukoaraiosis was seen in 11 (34%) patients. Signs of superficial hemosiderin were still present in two patients (6%).

6. Discussion

Tampere University Hospital started endovascular coiling procedures for cerebral aneurysms in 1992, and it has become a routine treatment method; 50% of all treated aneurysms are coiled nowadays. The present study has a very long follow-up period with most of the treated patients included (792 patient-years in the unruptured group and 688 patient-years in the ruptured group).

6.1 Long-term occlusion grade after embolization

We found unfavourable occlusion grades in embolized aneurysms; 27% of aneurysms were incompletely occluded. Most of those angiographic results would not be accepted in the clinical practice today because endovascular techniques have developed markedly since the early 90's. Regardless of these unfavorable angiographic occlusion grades, most aneurysms have remained stable during follow-up and only three aneurysms were retreated following this study. Unruptured aneurysms were less well occluded than ruptured aneurysms in the follow-up angiogram and this is probably because of lower packing density at the initial treatment. No recurrences occurred in completely occluded ruptured aneurysms and complete occlusion should be the aim of the treatment to prevent recurrences and the need for subsequent follow-up images. This concurs with earlier studies (Raymond and Roy, 1997; Kuether et al., 1998; Holmin et al., 2008; Sprengers et al., 2008; Schaafsma et al., 2009).

6.1.1 Does coiling prevent rebleedings?

Earlier studies have reported rebleeding rates of coiled, ruptured aneurysms to be between 0% and 6.5% (Cognard et al., 1999; Gruber et al., 1999; Ng et al., 2002; Willinsky et al., 2003). The annual rebleeding rate in earlier reports is between 0% and 3.5% (Cognard et al., 1999; Gruber et al., 1999; Willinsky et al., 2003). In present study annual rebleeding rate was 1.3% and concurs thus with earlier studies. Risk of recurrence of a completely clipped aneurysm is 0.3-0.9% per patient-year (Tsutsumi et al., 2001; Fulkerson et al., 2009) and both treatment methods prevent rebleedings, especially after proper occlusion.

6.2 Parenchymal lesions after endovascular coiling

6.2.1 Ruptured aneurysms

Aneurysm-related parenchymal lesions are frequent, 40% in study II and as high as 57% infarction rates found in earlier studies (Hadjivassiliou et al., 2001; Bendel et al., 2008). However, infarction rates after surgical clipping are even higher, up to 89% (Hadjivassiliou et al., 2001; Kivisaari et al., 2001; Koivisto et al., 2000; Bendel et al., 2008). Lesions develop during the acute hospitalization so prevention of rebleeding by clipping or coiling is not enough, but effort should further be made to prevent cerebral infarctions caused by vasospasm or treatment related thromboembolic complications. Although 5 out of 14 patients (36%) with radiological infarction were asymptomatic, patients with infarction have poorer clinical outcome than patients with no ischemic lesions in MRI. Lesion volume is detected to correlate with the neuropsychological test performance in previous study by Bendel et al. (2008).

6.2.2 Unruptured aneurysms

In study II, 19% of patients had aneurysm-related parenchymal lesions in MRI, which compares favourably with earlier studies (Debrum et al., 1998; Roy et al., 2001). Many infarctions detected in MRI were not aneurysm-related and were instead reason to detect the incidental unruptured aneurysms. Four out of 32 (13%) patients had clinical aneurysm-related ischemic events during the treatment period, but treatment of unruptured aneurysms did not cause permanent deterioration in outcomes. Two out of 32 (6%) patients had aneurysm-related infarction after the treatment period. These late parental artery territory infarctions were uncommon although occlusion grade was incomplete in 36% of cases and thus incomplete occlusion does not seems to add risk for late embolic complications.

6.3 The excess long-term mortality among patients with unruptured aneurysms

The long-term survival among patients with unruptured aneurysms has been studied in only one large, administrative database study (Britz et al., 2004). It was stated in that study that survival among SAH patients was lower than among patients with unruptured aneurysms, but after the first year post clipping, differences in the survival rate diminished (Britz et al., 2004). However, there are no studies about long-term survival among patients with endovascularly treated unruptured aneurysms.

The majority of deaths in patients with unruptured aneurysms were attributable to cerebrovascular and cardiovascular diseases, supporting the hypothesis that aneurysmal disease is part of a more generalized vascular disease and excess long-term mortality is related to aneurysm formation, not SAH as previously found (Ronkainen et al., 2001; Huttunen et al., 2011). Patients with untreated unruptured aneurysms had a higher mortality rate than patients with treated aneurysms and this difference has been noticed in a previous study supporting treatment of unruptured aneurysms (Britz et al., 2004).

We found that women had lower relative survival than men. Male patients treated with endovascular coiling or surgical clipping had no significant difference in mortality compared to the general matched population. However, women had 20% excess mortality in endovascular and 28% excess mortality in the surgical group at the 15 year follow-up. The reason for this is unclear and further studies with larger patient groups are needed.

6.3.1 Should unruptured aneurysms be treated?

The ISUIA study reported annual rupture rate of 0.1% in patients with unruptured aneurysms of less than 7mm in diameter and without previous SAH (Wiebers et al., 2003). Rupture risk is so low that the overall treatment risks have been thought to outweigh the treatment benefits. In the present study, 56% of unruptured aneurysms were less than 7mm, raising the question as to if the treatment of these was pointless or even harmful to patients. It is suggested that patients should have a life expectance more than 13-20 years before the treatment would be beneficial (Mitchell et al., 2004). Patients with unruptured aneurysms are not, however, comparable to the general population, because they have excess mortality compared to age, sex and calendar time matched population. In addition, aneurysm rupture incidence is much higher in Finland than in other western countries and thus treatment strategy for unruptured aneurysms should possibly differ in Finland.

The mortality of the patients with treated unruptured aneurysms did not differ significantly between endovascular and surgical groups, supporting the opinion that unruptured aneurysms can either be coiled or clipped. However, patients with untreated, unruptured aneurysms had a significantly higher mortality than patients with treated aneurysms. The same was found by Britz et al. (2004). In both studies, higher mortality among untreated and treated may be attributable to bias. Conservatively treated patients may be older, may have more comorbidities, may smoke more etc. The difference between treated and untreated aneurysm patients was found also after adjusting age and comorbidities supporting the treatment of unruptured aneurysms (Britz et al., 2004).

Despite infarctions in 34% of unruptured patients, treatment of unruptured aneurysms did not cause permanent deterioration in outcome. Taken that into

account, treatment of patients with unruptured aneurysms without previous SAH may be indicated if life expectancy is more than one decade and patient have risk factors to bleeding (smoking, hypertonia, heavy alcohol consumption etc.).

6.4 SAH of unknown etiology

Study IV is the only study in the modern imaging era to assess the long-term outcome of patients with SAH of unknown etiology. Perimesencephalic bleeding is just a subgroup of SAH of unknown etiology (SAH NOS, SAH NAS, kryptogenic SAH etc.) and even term perimesencephalic SAH is not exact. Therefore Schievink and Wijdicks (1997) have suggested the term pretruncal SAH to be more correct. However, such terminological snobbism is not relevant in clinical practise because blood distribution is related to time between bleeding and imaging, and some patients are diagnosed late after bleeding. Some researchers do not believe this diagnosis at all, but think there is a tiny aneurysm which is not found. However, patients with nonaneurysmal SAH have more benign disease than patients with aneurysmal SAH, supporting different etiology of bleeding. Most patients (81%) in Study IV recovered well (GOS 4 or 5) and poor outcome was related to SAH in only six (6%) patients. Infarctions were detected in six (18%) patients, which is significantly less than in patients with aneurysmal SAH (Kivisaari et al., 2001; Bendel et al., 2008). We found no rebleedings, no vasculopathies explaining previous SAH and no excess mortality compared to age-and gender matched general population. The risk of death from nonaneurysmal bleeding was 4% in present study and compares favourable with earlier studies reporting risk of death 0-15% (Jain et al., 1987; Gomez et al., 1989; Hawkins et al., 1989; Kawamura and Yasui, 1990; Rinkel et al., 1990; McMahon and Dorsch, 1999; Lang et al., 2003; Greebe and Rinkel, 2007; Andaluz and Zuccarello, 2008). Overall mortality was 13% compared with 47% mortality in aneurysmal SAH patients at the same time.

7. Conclusions

1) Coiled unruptured aneurysms showed incomplete occlusion grades in 37% of cases. However, the annual bleeding rate was as low as 0.1%. Endovascular treatment of ruptured aneurysms showed incomplete angiographic outcomes in 15% of cases and annual rebleeding rate was 1.3%. Occlusion grades were stable in most cases, but long-term imaging follow-up is needed after endovascular coiling.

2) Parenchymal lesions in brain tissue seen on postoperative MRI are common. Aneurysm-related parenchymal lesions were seen in 41% SAH patients and in 19% of patients with unruptured aneurysms. Most lesions were detected during the acute treatment period and aneurysm-related infarctions after the treatment period are uncommon.

3) Patients with untreated, unruptured aneurysms have excess long-term mortality compared to the general population. The majority of deaths, 48%, were caused by cerebrovascular diseases. Treatment of unruptured aneurysms is associated with a decreased risk of death, and survival does not differ between patients with coiled and clipped aneurysms. Men with coiled unruptured aneurysms have a survival rate comparable to that of the general matched population and only 8% excess mortality in the surgical group. Women have excess mortality after both surgical and endovascular treatment of unruptured aneurysms.

4) Patients with SAH of unknown etiology have a better long-term outcome than patients with aneurysmal SAH. There is a 4% excess mortality during the first year after SAH and thereafter mortality is on the same level as the

comparable general population. There is no risk of rebleeding and long-term follow-up MRI is not needed.

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Original publications

Long-term Follow-up Study of Endovascularly Treated Intracranial Aneurysms

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Summary

Long-term follow-up studies after endovascular treatment for intracranial aneurysm are still rare and inconclusive. The aim of this study was to assess long-term clinical and angiographic outcome of patients with endovascularly treated aneurysms.

The Clinical outcome of all 185 patients with endovascularly treated aneurysms were analyzed and 77 out of 122 surviving patients were examined with MRI and MRA nine to 16 years (mean 11 years) after the initial endovascular treatment.

Sixty-three patients were deceased at the time of follow-up. The cause of death was aneurysm-related in 34 (54%) patients. The annual rebleeding rate from the treated aneurysms was 1.3% in the ruptured group and 0.1% in the unruptured group. In long-term follow-up MRA 18 aneurysms (53%) were graded as complete, 11 aneurysms (32%) had neck remnants and five aneurysms (15%) were incompletely occluded in the ruptured group. Occlusion grade was lower in the unruptured group with 20 aneurysms (41%) graded as complete, 11 (22%) had neck remnants and 18 (37%) were incomplete. However, only three aneurysms were unstable during the follow-up period and needed retreatment.

Endovascular treatment of unruptured aneurysms showed incomplete angiographic outcome in 37% of cases. However, annual bleeding rate was as low as 0.1%. Endovascular treatment of ruptured aneurysms showed incomplete angiographic outcome in 15% of cases and the annual rebleeding rate was 1.3%.

Introduction

Endovascular coiling has been increasingly used for intracranial aneurysm occlusion since its introduction in 1991. Our hospital started endovascular treatment in 1989 and the first coiling with Guglielmi detachable coils (GDCs) was done in 1992. Nowadays in our institution 70% of aneurysms are coiled. While short and mid-term results are encouraging for endovascular procedures, there are still only few long-term follow-up studies [1-4]. In approximately 20% of patients, the coiled aneurysm reopens in follow-up [2,5-8]. Thus, delayed bleeding rate after endovascular coiling is slightly higher than after surgical clipping [1,2,9,10]. The aim of this study was to assess the long-term angiographic results after endovascular coiling and to ascertain rebleeding rate for embolized aneurysms.

Materials and Methods

Patient population: A total of 617 patients with 513 ruptured and 189 unruptured intracranial aneurysms were treated between 1992 and 1999. Of these, 185 patients with 200 aneurysms were treated with endovascular coiling. Coiling was done for 109 patients with ruptured aneurysms and 76 patients with unruptured aneurysms (Figure 1). Endovascular procedures

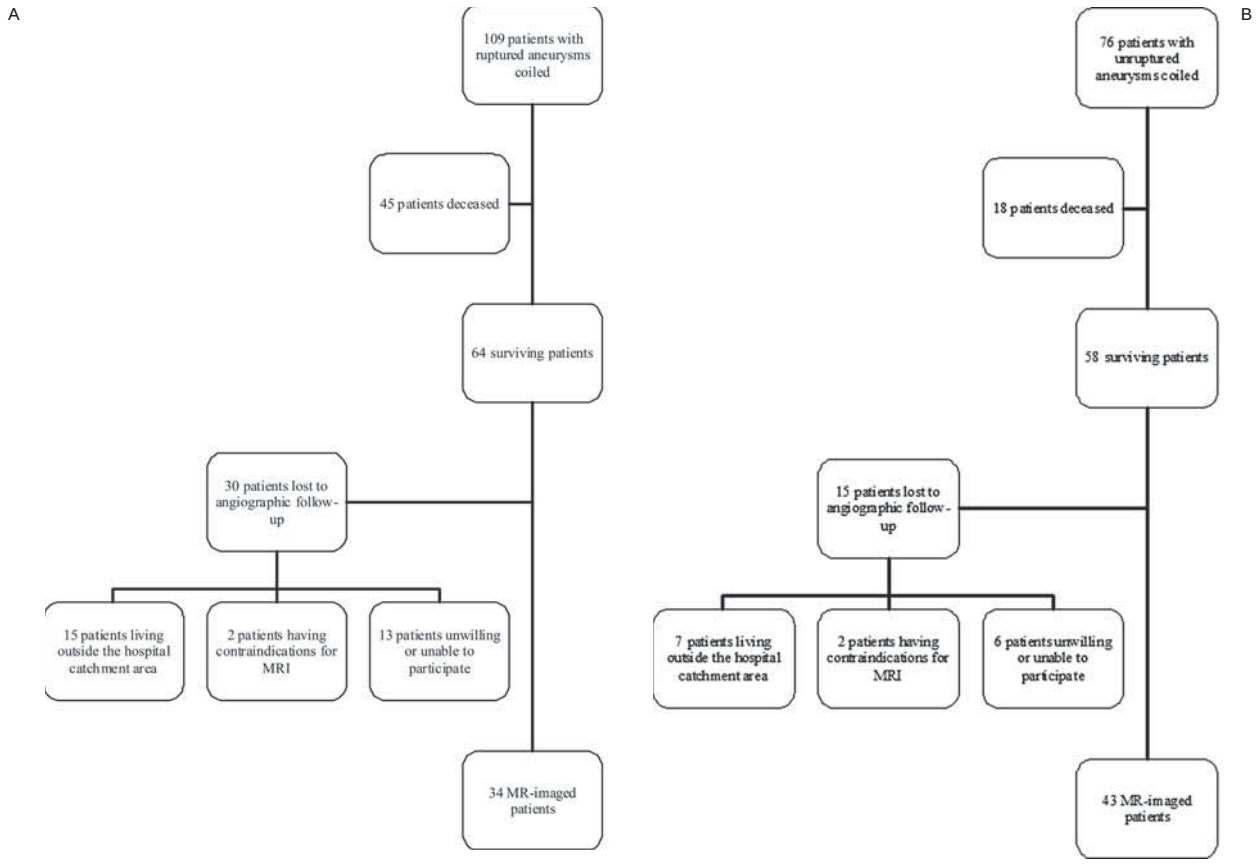

Figure 1 A,B) Flow chart summarizing the included and excluded patients in ruptured (A) group and unruptured (B) group.

were carried out in cases where the aneurysm seemed to be treatable in the estimation of the endovascular radiologist and neurosurgeon. Aneurysms were embolized with platinum Guglielmi detachable coils (GDC, Target Therapeutics, Fremont California, USA) and periprocedural medication was 5000 IU unfractionated heparin intravenously before coiling in unruptured cases and 5000 IU unfractionated heparin intravenously after two coils in ruptured cases. Intravenous nimodipine was used routinely. A total of 63 patients were deceased at the time of follow-up. Clinical outcome could be evaluated from 116 (95%) out of 122 surviving patients. Surviving patients, except 26 patients excluded were contacted by letter proposing an MRI investigation. Patients were excluded if they lived outside our hospital catchment area or had contraindications to MRI. Seventy-seven patients were examined with MRI and MRA approximately 11 years after initial coiling (range 9-16 years). Follow-up time was 792 patient-years in the unruptured group and 688 patient-years in the ruptured group.

Data collection: All hospital records, cerebral images and angiograms were evaluated retrospectively. Death certificates were examined to ascertain the date and cause of death. Surviving patients were contacted by letter proposing an MRI investigation. A total of 77 patients were examined neurologically and studied with MRI and MRA (magnetic resonance angiography) between the years 2007 and 2008. The clinical outcome evaluation was done with the Glasgow Outcome Score (GOS). Surviving patients not imaged by MRI were interviewed by phone and GOS was assessed and possible rebleeding episodes were elicited. The study was approved by the Hospital Ethics Committee and all patients gave their informed consent to the study.

Imaging protocol: The follow-up MR imaging was performed with a 1.5 T unit (GE Signa HD, Milwaukee, USA) with a one channel head coil. The MRA was supplemented with cross-

sectional imaging including FLAIR, T1 and T2* sequences mainly to detect ischemic parenchyma, size of the CSF spaces and superficial siderosis. The imaging parameters for the non-contrast 3D time-of-flight angiography were: TR 30, TE 2.5, FOV 22×16.5 cm, slice thickness 1.0 mm/interpolated to 0.5 mm, matrix 320×224. Magnetization transfer contrast and flow compensation were included.

Imaging assessment: The diagnostic, procedural and follow-up angiograms were reviewed independently by a neuroradiologist, an interventional radiologist and a neurosurgeon. Thereafter the results were reviewed and a consensus statement for each study was made. Aneurysm neck and fundus sizes were measured and dome-neck ratio was calculated. The degree of aneurysm occlusion was classified according to modified Raymond's classification [2] as follows: complete occlusion, neck remnant and incomplete occlusion. Treatment result was also classified as loose or dense, the former meaning that there was opacification between coils and the latter meaning no contrast media was detected between coils.

Statistical analysis: The patient population was divided into two different groups: ruptured and unruptured aneurysms. Statistical analysis was performed using NCSS (NCSS, Kaysville, Utah, USA) statistical software. Categorical variables were compared using Fisher's exact two-tailed test. Continuous variables between groups were compared using the Mann-Whitney U-test or Student T-test. The level of significance was set at $p<0.05$. Correlation between variables was analyzed with Spearman's rank correlation test.

Results

Part I

Outcome of all endovascularly treated patients

Population characteristics: A total of 109 patients with ruptured aneurysms and 76 patients with unruptured aneurysms were treated with endovascular coiling. Unruptured aneurysms were detected because of previous SAH (subarachnoid hemorrhage) in 14 patients (18%). Nine (12%) were studied because of a family history of SAH. Forty-two (55%) were detected incidentally and 11 (14%) presented with cranial nerve dysfunction. The anterior communicating artery was the most frequent location in the ruptured group and internal carotid artery in the unruptured group. The ruptured group had more posterior circulation aneurysms than the unruptured group and this difference was statistically significant ($p=0.02$). Aneurysm mean size was 4.7 mm in the ruptured group and 6.3 mm in the unruptured group. Size varied more in the unruptured group and aneurysms tended to be bigger and have higher fundus-neck ratio than ruptured aneurysms but the difference was not statistically significant ($p=0.16$). Primary occlusion grade did not differ between ruptured and unruptured aneurysms ($p=0.7$). However, packing density differed significantly between the groups ($p=0.04$) being denser in the ruptured group. Angiographic occlusion grade and packing density were not related to the locations of aneurysms ($p>0.7$). There was a weak negative correlation between aneurysm size and occlusion grade (rho -0.3, $p<0.03$). Aneurysms, with fundi less than 5 mm, were totally occluded in 46% of cases whereas aneurysms over 10 mm wide were completely occluded in only 29% of cases.

Retreatment: Retreatment was provided for 27 patients with ruptured aneurysms (25%) and for 16 (21%) patients with unruptured aneurysms. Retreatment within 6 months after initial coiling was done for 15 (56%) patients with ruptured aneurysms and for eight (50%) patients with unruptured aneurysms. Nineteen (70%) patients with ruptured aneurysms were retreated once, three (11%) were retreated twice, three (11%) patients were retreated three times and one (4%) patient five times and one (4%) patient six times. Ten (63%) patients with unruptured aneurysms were retreated once, five (30%) patients were retreated twice and one (6%) patient was retreated six times. Retreated aneurysms were larger than others: mean fundus diameter was 7.8 mm compared to 4.8 mm in aneurysms treated only once. The aneurysm neck was also wider in retreated aneurysms than in once treated aneurysms (mean 3.6 mm compared to 2.8 mm).

Rebleedings: There were ten postprocedural bleedings in all 185 endovascularly treated patients. Nine out of 109 SAH patients and one out of 75 patients with unruptured aneurysms bled after coiling procedure (Odds ratio 6.7, 95% CI 0.9 to 295.8, $p=.05$). One (1.3%) large unruptured aneurysm bled seven years after incomplete coiling. The annual bleeding rate was 0.1% in the unruptured group. Two patients were lost to follow-up and the bleeding rate, as-

Table 1 **Cause of death of the 63 deceased patients**

	Patients with SAH	Patients with unruptured aneurysms
Aneurysmal disease	32	2
Other cerebral diseases	4	2
Other cardiovascular diseases	9	3
Cancer	4	2
Respiratory	1	0
Trauma	1	0
Other	0	3
Total	51	12

suming these had rebleedings, was 3.9% (0.4% annual bleeding rate).

Nine ruptured aneurysms rebled (8.3%). Four rebleedings (3.7%) occurred within five weeks after coiling and five aneurysms (4.6%) rebled more than four years after initial treatment. One aneurysm was completely occluded, three had neck remnant and five were incompletely occluded in the post-procedural angiogram. Only three aneurysms were monitored after treatment. The reason for this was advanced patient age or poor clinical outcome after initial treatment. All but one patient died from rebleeding. The annual rebleeding rate was 1.3%. Four patients were lost to follow-up and bleeding rate, assuming all those had rebleedings, was 11.9% (annual bleeding rate 1.9%).

Mortality: Thirty-four (54%) out of 63 deceased patients died due to aneurysmal disease (Table 1). Eighteen patients with ruptured aneurysms died from acute SAH, one patient died from treatment complications, one patient from brain infarcts caused by vasospasm and two patients survived many months in poor clinical outcome and the cause of death was primary SAH. Three (5%) patients died from bleeding of aneurysms that were left untreated before. Nine (14%) patients died from rebleeding. Twenty-nine (46%) out of 63 deceased patients died from diseases not related to aneurysm.

Clinical outcome of all patients: Most surviving SAH patients were in good clinical condition after follow-up: 34 (57%) patients had a GOS score of 5, and 12 (20%) patients had a GOS score of 4. Thirteen patients (22%) were dependent (GOS score of 3) and one (2%) patient was vegetative. Four patients were lost to clinical outcome. A total of 31 (55%) patients with unruptured aneurysms had a GOS score of 5 and 16 (29%) patients had a GOS score of 4. Nine patients (16%) were dependent after 11 years of follow-up. Two patients with unruptured aneurysms were lost to clinical follow-up. The poor outcome in patients with unruptured aneurysms was related to aneurysm in three patients only.

Part II

A subgroup analysis of 77 patients studied with MRI

Follow-up angiographic results: MR imaging was done for 34 patients with ruptured aneurysms and 43 patients with unruptured aneurysms (Table 2) more than nine years after the coiling procedure. MRA showed complete occlusion in 18 aneurysms (53%) in the ruptured group and 20 aneurysms in the unruptured group (40%). Angiographic results could not be evaluated from one patient because of artifacts in MRI. Eleven ruptured aneurysms (32%) and 11 (22%) unruptured aneurysms had neck remnants in MRA. Five aneurysms (15%) in the ruptured group and 18 (38%) in the unruptured group were graded as incomplete.

A change to a better occlusion grade (i.e. progression) was detected in seven (21%) ruptured aneurysms, 20 (59%) were stable, six (18%) had remnant growth and one (3%) had recurrence in the follow-up MR images (Figure 2). In the unruptured group, seven (14%) aneurysms progressed, 30 (61%) were stable, six

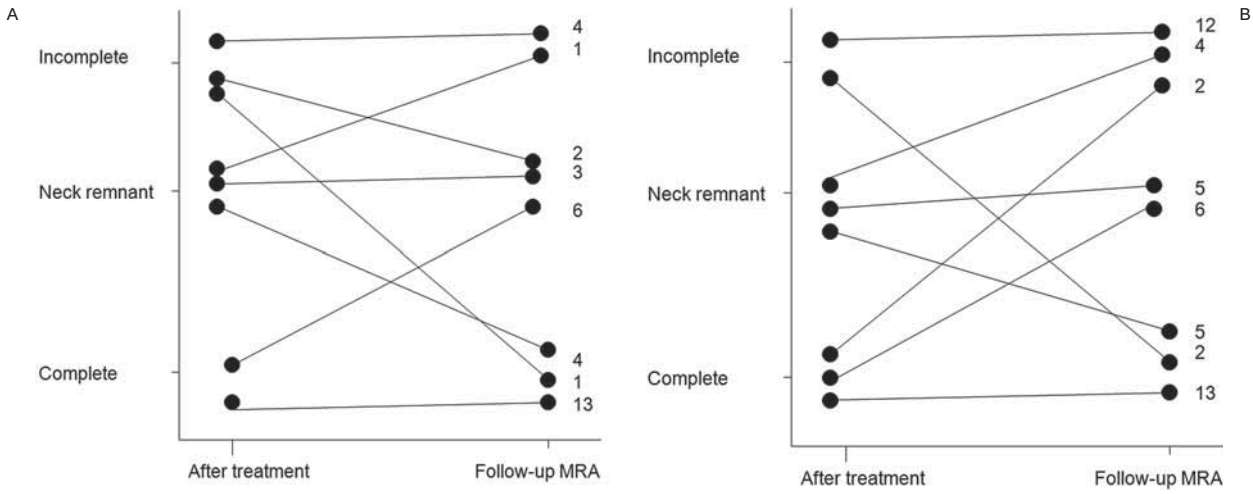

Figure 2 A,B) Changes in occlusion grades per aneurysm in the ruptured group (A) and in the unruptured group (B). Number on the right indicates number of cases.

(12%) had remnant growth and six (12%) had recurrence. Although incomplete occlusion was seen in 23 aneurysms (27%), only three had poorer occlusion grade than in previous control images. Twenty incompletely occluded aneurysms were monitored for many years after the initial treatment. If the occlusion grade was stable, follow-up images were discontinued. Four of these incompletely coiled aneurysms are still being followed-up.

Unruptured aneurysms were more incompletely occluded than ruptured ones and this difference reached statistical significance (p=0.03). Incompletely occluded aneurysms had wider necks and fundi than better occluded aneurysms. No de-novo aneurysms were detected in this series.

Only nine (36%) retreated aneurysms were graded as complete in MRA compared to 82 (51%) of once-treated aneurysms. Neck remnant was detected in eight (32%) and occlusion grade was incomplete in eight (32%) of retreated aneurysms.

Discussion

Our institution started coil embolization in 1992. In the early years of endovascular treatment, coiling was mainly used for patients with high surgical risk [11]. However, in our institution endovascular treatment was approved for standard treatment at an early stage. Our aim was to examine all surviving patients with follow-up MRI, but because of the voluntary nature of the study, we could reach only 79% of included patients. Those patients we could not reach may be in poorer clinical condition and unable or unwilling to participate. However, this selection bias is unlikely to influence the angiographic occlusion grades. To the best of our knowledge, this series has the longest follow-up period published with most of the treated patients included (792 patient-years in the unruptured group and 688 patient-years in the ruptured group).

We conducted this long-term follow-up study with MRI because it is noninvasive and cost-effective compared to DSA (digital subtraction angiography) [12,13]. The sensitivity of MRI has been demonstrated [14-16]. We studied patients with 1.5T rather than with 3.0T because they had previously been studied with 1.5T MRI as well in a study that ascertained the feasibility of MRA in our material [14]. The follow-up images were thus comparable with each other.

Endovascular treatment is less frequently complete than surgical clipping of aneurysms. Furthermore, recurrences are more frequent. It has been shown that complete or near complete occlusion of the aneurysm sac is sufficient to prevent rebleeding in 98% of cases treated in the acute phase of SAH [17]. Conversely, the presence of a residual aneurysm is associated with subsequent bleeding [17,18]. Neck remnant obliteration may be sufficient to protect against rebleeding after SAH, but the recurrence risk is higher, and longer follow-up is needed.

Table 2 **Baseline characteristics of the 77 included patients**

	Patients with ruptured aneurysms n=34	**Patients with unruptured aneurysms n=43**
Gender		
Male	15	15
Female	19	28
Mean age (range)	54 years (34-73)	50 years (21-79)
Number of aneurysms		
1	26	29
2	6	10
3	2	4
Number of aneurysms coiled	34	50
Reason for initial angiography		
SAH	34 (100%)	7 (16%)
family history of SAH		4 (9%)
cranial nerve dysfunction		4 (9%)
incidental		28 (65%)
Hunt & Hess at the time of diagnosis		
I	12	
II	12	
III	6	
IV	4	
V	0	
Fisher	10 primary CT scans were missing	
1	3	
2	1	
3	9	
4	9	
Intraventricular hemorrhage	2	
Intracerebral hemorrhage	9	
Hydrocephalus in primary CT	10	
Aneurysm location		
Anterior circulation		
ICA	2 (6%)	20 (40%)
MCA	3 (9%)	14 (28%)
ACoA	13 (38%)	5 (10%)
ACoP	3 (9%)	1 (2%)
ACA/pericallosa	2 (6%)	5 (10%)
Vertebrobasilar circulation	11 (32%)	5 (10%)
Aneurysm size		
≤5mm	23 (68%)	29 (58%)
6-10mm	9 (26%)	16 (32%)
>10mm	2 (6%)	5 (10%)
Initial angiographic result		p=0.7
complete	14 (41%)	24 (48%)
neck remnant	9 (26%)	10 (20%)
incomplete	11 (32%)	16 (32%)
Packing density		
densely occluded	22 (65%)	19 (38%)
Retreatment	13 (38%)	12 (28%)
GOS at follow-up		
1	0	0
2	0	0
3	3	6
4	8	13
5	23	24

Earlier reports have discussed a wide variety in occlusion grades in earlier reports because anatomic results are subjective and difficult to standardize. Complete obliteration has previously been reported in 26%-88% of ruptured aneurysms, neck remnant in 18% to 50% and incomplete occlusion in 2% to 26% [5,8,9,17-20]. In our study 27% of aneurysms were incompletely occluded and many of our angiographic results reported here would not be accepted today in our clinical practice. The aneurysms in our series were treated before the advent of newer techniques such as balloon-assisted remodeling, three-dimensional GDC or stents. These new techniques may decrease recurrence rates.

Gallas et al. [21] found total or subtotal occlusion in 97% of ruptured and unruptured aneurysms. This is the best angiographic outcome published and better than in our series or in earlier published series [2,3]. Complete occlusion or neck remnant was found in 63% of unruptured aneurysms in our series and this is less than previously reported [3,19]. Regardless of unfavorable angiographic occlusion grades, most of these were stable in follow-up. Only three aneurysms out of 23 incompletely occluded cases were unstable in follow-up and were retreated after this study. No recurrences occurred in completely occluded ruptured aneurysms in our series. These results are comparable to those of earlier reports [2-4,21].

Although the initial angiographic occlusion grade was similar in the ruptured and unruptured groups, unruptured aneurysms had lower packing density. In the early years it was thought that change in flow would prevent bleeding. This is probably the reason why unruptured aneurysms were less well occluded in the follow-up angiogram than ruptured aneurysms. Retreatment was performed for 43 aneurysms (23%) which is higher than previously reported [5,8,9,17,18,20,21].

Earlier studies have reported rebleeding rates after coiled, ruptured aneurysms to be between 0% and 6.5% [5,11,21,22]. The annual rebleeding rate in earlier reports is between 0% and 3.5% [5,13,21,22]. In our series annual rebleeding rate was 1.3% and concurs with earlier studies.

Only a few studies have reported delayed bleeding rates for coiled unruptured aneurysms [11,23-25]. Rates have varied from 0% to 2.4% [19,23,25,26]. The annual rupture rate in our series was 0.1%. The ISUIA study [27] reported annual rupture rate of 0.1% in patients with unruptured aneurysms of less than 7 mm in diameter who had not had a previous SAH. The rupture risk is so low that the overall treatment risks outweigh the treatment benefits. In our series 56% of unruptured aneurysms were less than 7 mm raising a question if the treatment of these was pointless or even harmful to patients. However, it is difficult to believe that coiling increases the risk for delayed bleeding in unruptured aneurysms. In our series 81% of ruptured aneurysms were less than 7 mm and thus beside aneurysm size, inflammation of the aneurysm wall also seems to play important role in aneurysm degeneration and rupture [28,29].

Conclusions

Endovascular treatment of unruptured aneurysms had incomplete angiographic outcome in 37% of cases. However, the annual bleeding rate was as low as 0.1%. Endovascular treatment of ruptured aneurysms had incomplete angiographic outcome in 15% of cases and the annual rebleeding rate was 1.3%.

Acknowledgement

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Original article

Long-term MRI findings of patients with embolized cerebral aneurysms

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Abstract

Background: Long-term follow-up studies after endovascular treatment for intracranial aneurysm are still rare and inconclusive. Parenchymal infarctions related to aneurysms have mostly been studied in patients with subarachnoidal hemorrhage (SAH) but infarction rates in patients with endovascularly treated unruptured aneurysms have been little studied.

Purpose: To determine the frequency of permanent parenchymal lesions as detected in magnetic resonance imaging (MRI) in patients treated with endovascular coiling and to assess aneurysm-related infarctions after the initial treatment period.

Material and Methods: A total of 64 patients (32 with primarily ruptured aneurysms) with 69 embolized aneurysms were examined neurologically and by MRI and magnetic resonance angiography (MRA) more than 9 years after the initial endovascular treatment.

Results: A total of 14 out of 32 (44%) SAH patients and 11 (34%) patients with unruptured aneurysms had parenchymal lesions in MRI. Infarctions were detected in 10 (31%) SAH patients and the majority (9/10, 90%) of them were aneurysm-related. All aneurysm-related infarctions were detected at the acute hospitalization stage. A total of six (55%) out of 11 infarctions in patients with unruptured aneurysms were aneurysm-related and two of them appeared after the treatment period. Patients with infarction had poorer clinical outcome than patients with no ischemic lesions in MRI.

Conclusion: Nineteen percent of patients with unruptured and 41% with ruptured aneurysms had aneurysm-related parenchymal lesions in MRI. Most of these were detected during acute treatment period. Aneurysm-related infarctions after treatment period are uncommon.

Keywords: CNS, interventional, MR imaging, embolization, aneurysms

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Morbidity after subarachnoid hemorrhage (SAH) is still high despite developed treatment methods, anesthesiological modalities, and intensive rehabilitation (1–7). Bleeding itself, vasospasm or treatment-related causes can cause cerebral lesions visible in computed tomography (CT) or magnetic resonance imaging (MRI). MRI is more sensitive for detecting parenchymal lesions than CT (8, 9). Infarction rate after aneurysmal SAH is as high as 79–89% in clipped patients (8, 10–12). Aneurysm treatment with endovascular coiling seems to be safer than clipping (10, 13) and fewer infarctions are seen in coiled patients (10, 12). Although lesions consistent with infarction seen in CT or MRI sometimes appear extensive, patients may in fact be asymptomatic (14, 15). The treatment of small unruptured aneurysms is much debated because the International Study of Unruptured Intracranial Aneurysms (ISUIA) showed that surgical morbidity and mortality from unruptured aneurysms was higher than risk of rupture for aneurysms less than 10 mm over a 7.5-year period (16). Morbidity related to endovascular coiling in unruptured aneurysms is between 1.7 and 8.6% (16–20) and lower than in patients receiving surgical treatment (16, 17, 21). The incidence of parental artery infarction after unruptured aneurysm coiling is not known. The aim of this study was to ascertain the frequency of permanent parenchymal lesions as detected in MRI in patients treated with endovascular

coiling and to assess aneurysm-related infarctions after the initial treatment period.

Material and Methods

Patient population

A total of 185 patients with 200 aneurysms were treated between 1992 and 1999 with endovascular coiling in our hospital (Fig. 1). Twenty patients had one or more aneurysms clipped and were excluded from this study. A further 22 patients living outside our hospital catchment area were excluded because follow-up and possible re-treatment was not done in our hospital. Endovascular procedures were done in cases where the aneurysm seemed to be treatable in the estimation of the endovascular radiologist and neurosurgeon. Aneurysms were embolized with platinum Guglielmi detachable coils (GDC, Target Therapeutics, Fremont, CA, USA) and peri-interventional medication was 5000 IU unfractionated heparin intravenously before coiling in unruptured cases and 5000 IU unfractionated heparin intravenously after two coils in ruptured cases. Intravenous nimodipine was used routinely. The clinical status of patients with aneurysmal SAH was assessed at the time of onset and treatment according to the Hunt & Hess scale (H&H) (22). Glasgow Outcome Score (GOS) (23) was used to evaluate clinical status at the time of discharge and at follow-up visits.

A total of 63 patients were deceased at the time of follow-up and 34 (54%) of them died due to aneurysmal disease (Table 1). Sixteen patients were lost from MRI follow-up either due to refusal to participate in follow-up studies or to having contraindications to magnetic field studies. Sixty-four patients harbouring 72 aneurysms were studied for more than 9 years after the initial coiling procedure (Table 2). Mean follow-up time was 11 years (range 9–16 years, median 10). Sixty-nine aneurysms were coiled and three were left untreated due to small size. Thromboembolic events occurred in seven coiling procedures (10%) and coil migration in one (1%) case. Neurological deterioration was detected in 15 procedures (22%) and infarction verified by CT was seen in 11 cases (16%). Three patients suffered re-bleeding in hospital before treatment and aneurysmal rupture occurred in two cases during coiling (3%). One patient (1%) re-bled 13 days after incompletely coiled aneurysm procedure. Re-treatment was provided for 23 aneurysms (33%) from one month to six years after the initial treatment (mean 15 months).

Table 1. Cause of death of the 63 deceased patients

	Patients with SAH	Patients with unruptured aneurysms
Aneurysmal disease: acute SAH	20	0
Aneurysmal disease: primary SAH after long vegetative state	2	0
Aneurysmal disease: SAH from untreated aneurysm	2	1
Aneurysmal disease: re-bleeding	8	1
Other cerebral diseases	4	2
Other cardiovascular diseases	9	3
Cancer	4	2
Respiratory	1	0
Trauma	1	0
Other	0	3
Total	51	12

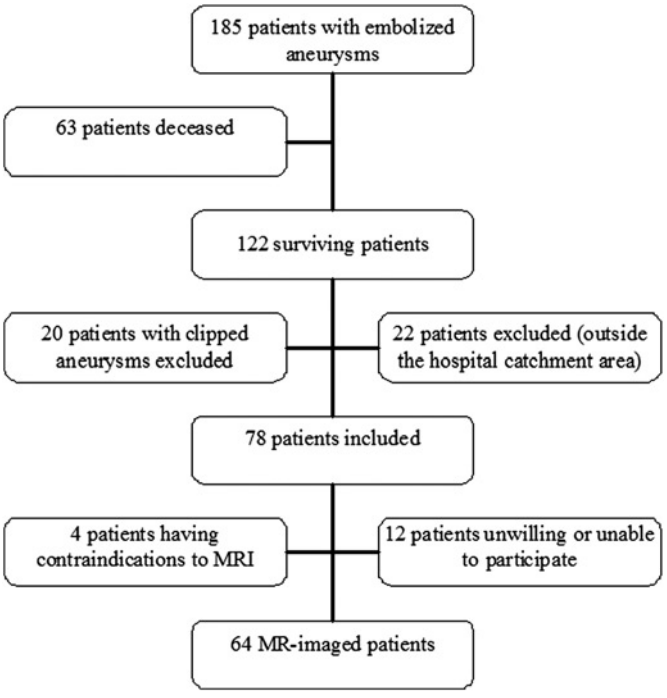

Fig. 1 Flowchart summarizing the included and excluded patients

Data collection

All hospital records were studied retrospectively and all CT scans, MR images and angiograms performed from 1992 to 2008 were analyzed. Preoperative CTs were done for 32 SAH patients and 15 patients with unruptured aneurysms. Preoperative MRIs were done for two SAH patients and 21 patients with unruptured aneurysms. Postoperative CTs during the acute stage of the disease were done for 17 SAH patients and seven patients with unruptured aneurysms. Postoperative MRIs were done for four SAH patients during the initial treatment period. Surviving patients included were contacted by letter offering an MRI examination. A total of 64 patients were studied with MRI between the years 2007 and 2008 and patients were interviewed and examined neurologically by the author. The study was approved by the Hospital Ethics Committee and all patients gave their informed consent to the study.

Imaging protocol

The follow-up MR imaging was performed with 1.5 T unit (GE Signa HD, Milwaukee, WI, USA) with 1-channel headcoil. The MRA was supplemented with cross-sectional imaging including fluid attenuated inversion recovery (FLAIR) and T2* weighted sequences mainly to detect ischemic parenchyma, the size of the CSF spaces and

Table 2. Population characteristics

	MRI patients with ruptured aneurysms (n = 32)	MRI patients with unruptured aneurysms (n = 32)
Gender		
Men	14	12
Women	18	20
Mean age at diagnosis (years)	53	49
Mean age at follow-up MRI (years)	64	60
Preoperative diseases		
Hypertension	10	10
Smoking history	17	13
Diabetes	0	1
Alcohol heavy user	4	5
Anticoagulant therapy	3	5
SAH in family	5	7
Reason for initial angiography		
SAH	32	
Familial history of SAH		7
Cranial nerve dysfunction		4
Incidental		21
Hunt & Hess		
0	–	32
1	10	–
2	12	–
3	6	–
4	4	–
Fisher grade	9 primary CT images were missing	
1	3	–
2	1	–
3	9	–
4	10	–
Hydrocephalus	10	
External ventricular drainage	6	
Aneurysm location		
Anterior circulation	23	35
ICA	2	15
MCA	3	11
ACoA	13	5
ACoP	3	1
ACA/pericallosa	2	3
Vertebrobasilar circulation	9	2
Aneurysm size (mm)		
<7	26	22
7–12	4	11
13–24	2	2
≥ 25	0	2
Initial angiographic result		
Complete	13	14
Neck remnant	9	8
Incomplete	10	15
Present co-morbidities		
No other illnesses	5	7
Depression	3	7
Epilepsy	2	3
Hypertension	19	10
COPD/asthma	2	3
Diabetes	2	1
Present GOS		
3	2	3
4	7	11
5	23	18

ICA = internal carotid artery; MCA = middle cerebral artery; ACoA = anterior communicating artery; ACoP = posterior communicating artery; ACA = anterior cerebral artery; COPD = chronic obstructive pulmonary disease; SAH = subarachnoidal hemorrhage; GOS = Glasgow Outcome Scale

signs of persistent blood degradation deposits. The imaging parameters for the non-contrast 3D time-of-flight angiography were: TR 30, TE 2.5, FOV 22 × 16.5 cm, slice thickness 1.0 mm/interpolated to 0.5 mm, matrix 320 × 224. Magnetization transfer contrast and flow compensation were included. The imaging parameters for the FLAIR were: TR 9001 ms, TE 125 ms, TI 2250 ms, FOV 22 cm, slice thickness 5/1 mm, matrix 224 × 256, NEX 1 and for T2* weighted images: TR 460 ms, TE 20 ms, flipangle 20°, FOV 22 cm, slice thickness 5/1 mm, matrix 160 × 256 (interpolated to 512), NEX 2. Areas of increased signal intensity of vascular territories in T2* weighted images were considered as infarctions. Small high signal foci on T2* weighted images were considered as leukoaraiosis.

Imaging assessment

The diagnostic, procedural and follow-up images were reviewed independently by a neuroradiologist, a neurointerventionalist and a neurosurgeon. Thereafter, the results were reviewed and a consensus statement for each study was issued. MRI and MRA studies done prior to this study were analyzed and compared with the present study results. Primary CT images were re-evaluated to assess Fisher grades, existence and grade of ventricular enlargement and possible parenchymal lesions. Parenchymal lesions were considered aneurysm-related if they appeared during acute hospitalization, aneurysmal ICH was seen in primary CT or detected in parental artery territory after treatment period. Infarctions in MRI were divided into parental and non-parental artery territory infarctions.

Statistical analysis

Statistical analysis was performed using NCSS statistical software (NCSS, Kaysville, UT, USA). Categorical variables were compared using Fisher's exact two-tailed test. Continuous variables between groups were compared using the Mann-Whitney U-test. The level of significance was set at $p < 0.05$.

Results

MRI findings at long-term follow-up

Parenchymal lesions

Ten years after embolization, 18 (56%) SAH patients and 21 (66%) patients with unruptured aneurysms showed normal brain MRI. Parenchymal lesions on FLAIR images of different cause (infarctions or previous ICH) were seen in 14 (44%) SAH patients (Fig. 2) and 11 (34%) patients with unruptured aneurysms (Fig. 3).

Infarctions in the parental artery territory

Lesions on FLAIR images indicating infarction in the vascular territory of the aneurysm were seen in six (19%) SAH patients and six (19%) patients with unruptured aneurysms (Fig. 4). All but two of these lesions were detected during

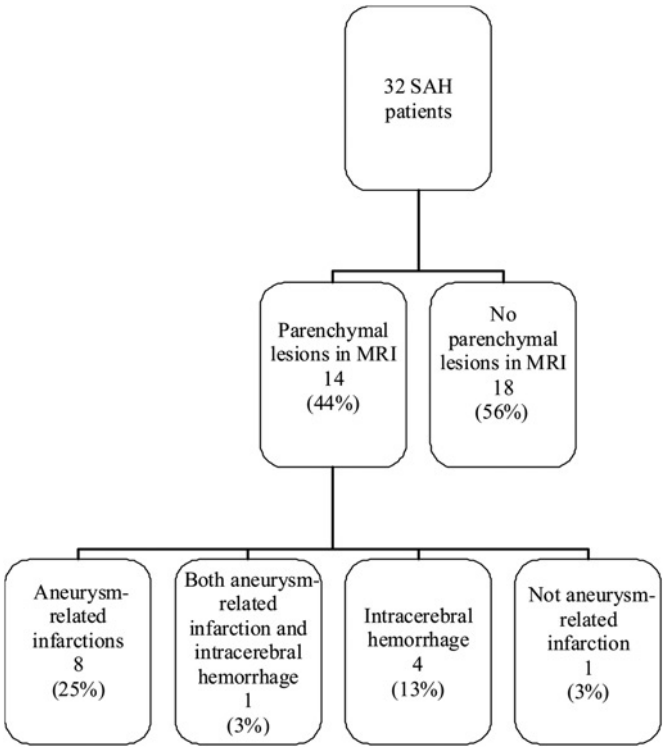

Fig. 2 Flowchart summarizing parenchymal lesions in SAH group

the treatment period (Fig. 5). Infarctions were detected in patients who had either thromboembolic complications or clinical or angiographic vasospasm and infarctions in CT images. Two patients had infarctions in parental artery

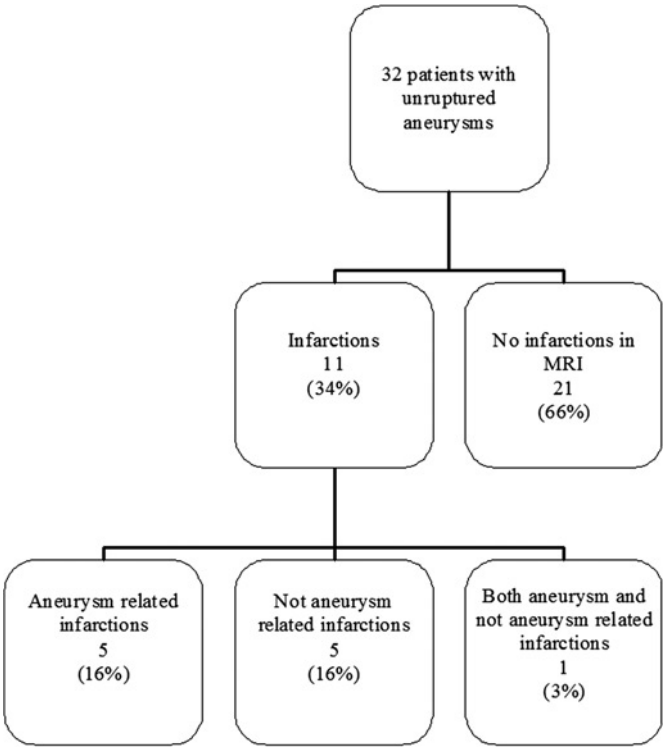

Fig. 3 Flowchart summarizing parenchymal lesions in patients with unruptured aneurysms

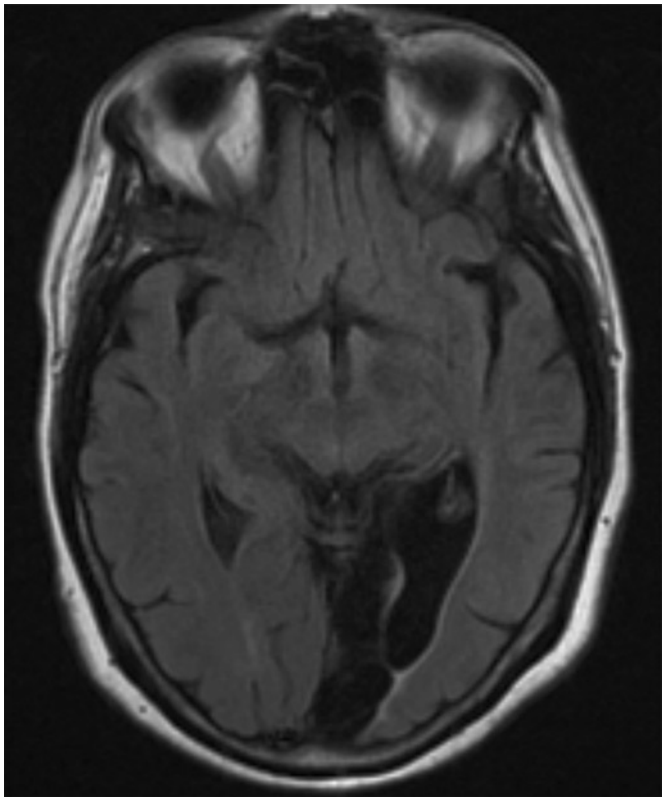

Fig. 4 Fluid-attenuated inversion recovery image shows large infarction in the left posterior cerebral artery territory caused by thromboembolic complication in coiling procedure

territory that were not detected during acute hospitalization. One of these patients had a small infarction in middle cerebral artery aneurysm territory without any clinical defects after coil migration in primary treatment procedure. The other patient had two infarctions at separate locations which occurred 10 years after primary stenting and coiling and 3 years after re-embolization of a giant ICA aneurysm.

Infarctions in other vascular territories

Brain infarctions in vascular territories other than that of the ruptured aneurysm were seen in four (13%) SAH patients and three (9%) of them were considered to be caused by vasospasm. Six (19%) patients with unruptured aneurysms

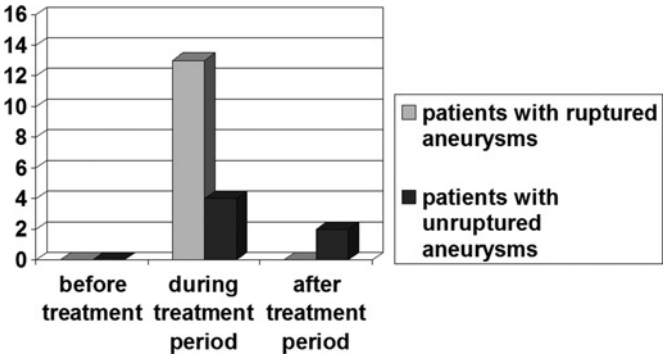

Fig. 5 Aneurysm-related infarction rates

had infarctions in non-parental artery territory. In four (13%) of these the infarctions were detected by CT before aneurysm treatment and in two patients years after the coiling. None of them were considered to be aneurysm-related.

Residual signs of hematoma and superficial siderosis

Signal intensity changes seen on FLAIR images due to previous ICH were detected in five (16%) SAH patients (Fig. 6). Signs of superficial siderosis were present in six (19%) SAH patients.

Ventricular enlargement and leukoaraiosis

Five patients (8%) had ventricular enlargement. Leukoaraiosis was seen in 25 (39%) patients: in 16 (50%) patients with ruptured aneurysms and in nine (28%) patients with unruptured aneurysms.

Clinical outcome

Most patients were in good clinical condition after follow-up: 41 (64%) patients had a GOS score of 5 and 18 (28%) patients had a GOS score of 4. Only five patients (8%) were dependent (GOS score of 3). GOS tended to be lower in patients with unruptured aneurysms than in patients with ruptured aneurysms but the difference was not statistically significant ($p > 0.08$). Poor outcome in patients with unruptured aneurysms was related to aneurysm in one patient only who had brainstem compression caused by a large basilar aneurysm. In others the reason for poor outcome was not related to aneurysms. Patients with unruptured aneurysms had more depression but less hypertension than patients with previous SAH (Table 2). Other diseases and medication were comparable between patients with ruptured and unruptured aneurysms.

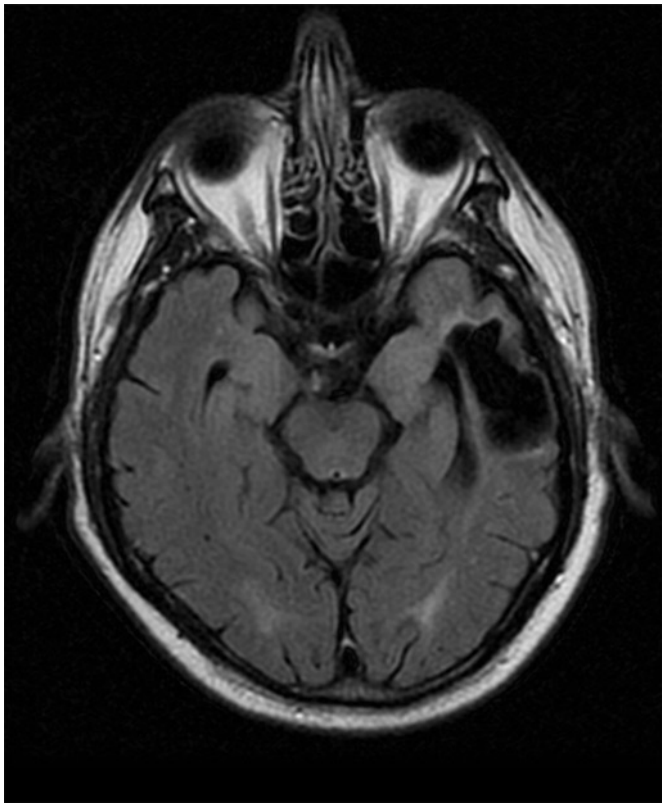

Fig. 6 Fluid-attenuated inversion recovery image shows retractive lesion in the left temporal lobe caused by intraparenchymal haemorrhage from a ruptured medial cerebral artery aneurysm

Table 3. Correlation between infarction prevalence and clinical outcome

	GOS 3	GOS 4	GOS 5
Infarction	4	5	16
No infarction	1	14	24

GOS = Glasgow Outcome Scale

Patients with infarction had poorer clinical outcome than patients with no ischemic lesions in MRI ($p < 0.05$, Table 3). Five out of 14 (36%) SAH patients with radiological infarction were asymptomatic. Four patients (29%) had global deficits and five patients (36%) had focal deficits. Patients with unruptured aneurysms and parenchymal lesions in follow-up MRI were mostly (70%) asymptomatic. Only three out of 11 patients (30%) had focal deficits.

Discussion

Our aim was to determine the frequency of permanent parenchymal lesions in patients treated with endovascular coiling and to assess aneurysm-related infarctions after the initial treatment period. Thirty-four percent of patients with unruptured aneurysms had infarctions in MRI and 19% were aneurysm-related. Patients with unruptured aneurysms had high incidence of parenchymal lesions not related to aneurysm because most aneurysms were found incidentally during cerebral imaging for some neurological symptoms other than SAH. Forty-four percent of SAH patients had parenchymal lesions in follow-up MRI and most of these were aneurysm-related. Aneurysm-related infarctions were detected in 25% of SAH patients and all were detected during acute treatment period. Only two patients with unruptured aneurysms had aneurysm-related infarctions after the treatment period.

Because of the voluntary nature of the imaging study, we were only able to study 82% of included patients with follow-up MRI. Those we could not reach may be in poorer clinical condition and unable or unwilling to participate. It is thus likely that there is selection bias in our study and SAH patients may have a higher prevalence of parenchymal lesions than our 44%. Earlier reports have documented infarction rates of 57% (10, 11).

In follow-up images it is difficult to assess the cause of infarction and for this reason we classified lesions as parental artery territory or non-parental artery related. Taking into account only infarctions in parental artery territory, our figure of 19% compares favourably with earlier studies reporting parental artery territory infarction rates of 20% to 22% (10, 12). A total of 16% of patients had lesions caused by ICH, which is slightly lower than in the series of Koivisto and co-workers (12), who reported a rate of 25%. Lesions caused by ICH were detected in 22% in the series of Bendel (10). Unfortunately, in some studies

patients with ICH were excluded. Incidence of infarctions not related to aneurysm territory in SAH patients was similar to that reported in earlier studies (10, 12).

To the best of our knowledge, there are no studies on infarctions long after embolized unruptured aneurysms. Patients with unruptured aneurysms had parental artery territory infarctions during the treatment period in 12% of cases, which compares favorably with earlier studies (20, 24). Late parental artery territory infarctions were uncommon although occlusion grade was incomplete in 36% of cases.

Small, high signal foci in the white matter are common incidental findings in T2-weighted images. As many as 79% of neurologically healthy people over 55 years have leukoaraiosis in MRI (25). In earlier reports, the frequency of leukoaraiosis in SAH patients was between 32–60% (8, 10, 11). In our study leukoaraiosis was present in 50% of SAH patients and 28% of patients with unruptured aneurysms. The clinical relevance of these small incidental findings remains unclear.

Clinical symptoms of ischemia were detected during the treatment period in all SAH patients who developed a parental artery territory infarction. Two out of six patients with unruptured aneurysms did not have any symptoms of ischemic episode during the treatment period and infarcts after the treatment period were related to coil migration, stenting procedure or giant aneurysm. Despite infarctions in unruptured patients, treatment of unruptured aneurysms did not cause permanent deterioration in outcome.

Bryan *et al.* reported that fewer than half of patients with cerebral lesion caused by SAH or its treatment have symptoms of stroke (26). We found higher symptom rates for SAH patients, of whom five out of 14 (36%) were asymptomatic. Four patients (29%) had global deficits and five patients (36%) had focal deficits. Patients with unruptured aneurysms were more often asymptomatic than SAH patients. Global deficits were not associated with unruptured aneurysms. Seventy per cent of patients with unruptured aneurysms were asymptomatic and 30% had focal deficits. Although SAH patients had more symptoms of cerebral infarctions, GOS was not lower than in the group with unruptured aneurysms. Actually, patients with unruptured aneurysms had poorer outcome but the difference was not statistically significant. The reason for this poorer outcome may be that depression was more common in the group with unruptured aneurysms. It is important to note that sample sizes in both groups were small and cannot be generalized in a straightforward manner to all aneurysm patients. Our outcome measure, GOS, may be too crude to measure outcome as reported in earlier studies (11, 27). In addition to primary analyses with GOS, we did some secondary analyses with the Extended Glasgow Outcome Scale (GOSE) (28). However the results were similar and patients with unruptured aneurysms had lower GOSE than SAH patients. In addition to small sample sizes there are other limitations in our study. Patient population is selected and infarction rates might thus be too low. MRIs in the acute hospitalization period were not done for every patient. Patients with ruptured and unruptured aneurysms had differences in population characteristics and cannot be compared in a straightforward manner.

This was a retrospective series and embolization technique has subsequently developed a lot. The aneurysms in our series were treated before the advent of newer techniques such as balloon-assisted remodeling or 3-dimensional GDC. These new techniques improve occlusion grades and probably also decreases complication rates.

In conclusion, 19% of patients with unruptured and 41% with ruptured aneurysms had aneurysm-related parenchymal lesions in MRI. Most of these were detected during acute treatment period. Aneurysm-related infarctions after treatment period are uncommon.

ACKNOWLEDGEMENT

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Conflict of interest: None.

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Long-term excess mortality of patients treated for unruptured intracranial aneurysms

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ABSTRACT

Background and Purpose SAH patients have an excess mortality proportion in long-term outcome studies because of the high rate of cerebrovascular and cardiovascular deaths. The aim of the present study was to assess the excess long-term mortality among patients with unruptured aneurysms with no previous SAH and to compare mortality after coiling, clipping and without treatment.

Methods 291 patients with 379 unruptured aneurysms were admitted to our hospital between 1989 and 1999. Patients with previous SAH were excluded (151) leaving 140 patients with 178 unruptured aneurysms as the study population. The patients were followed up until death or the end of April 2011. Causes of death were determined. Relative survival ratios (RSR) were calculated and compared with the matched general population.

Results Mean follow-up time was 13 years (range 1-19). During the follow-up period, 50 patients (36%) died. Death was caused by cerebrovascular event in almost half of cases (24 out of 50, 48%). There was 12% excess mortality at 15 years (cumulative relative survival ratio (RSR): 0.88, in males and 35% excess mortality in females (RSR: 0.65). Mortality among females over 50 years was significantly higher than among males (p=0.018).

Conclusions Patients with untreated unruptured aneurysms have excess long-term mortality compared to general population. Males with treated unruptured aneurysms have a survival proportion comparable to general matched population. Females, instead, have excess mortality after both surgical and endovascular treatment of unruptured aneurysms.

Keywords: Unruptured intracranial aneurysm, mortality, outcome, risk of death, relative survival ratio

Mortality after aneurysmal subarachnoid haemorrhage (SAH) remains high in spite of the treatment methods developed. Overall case fatality rates have been shown to be between 33% and 77% at 1 year after bleeding with only slightly decreased in-hospital mortality from 1986 to 2001.[1-12] Even patients with successfully treated ruptured aneurysms and good outcome 1 year after bleeding have an excess mortality rate in long-term outcome studies.[13-15] General cerebrovascular and cardiovascular causes of death are higher among SAH patients than in general population.[12-13,15] However, long-term mortality in patients with unruptured aneurysms is not well studied inspite of

increasing number of incidentally discovered and aggressively treated aneurysms. The management of unruptured aneurysms is controversial because the risk of treatment is thought to be greater than the risk of rupture.[16] Thus our aim was to assess excess long-term mortality among patients with unruptured aneurysms.

METHODS

Patients

Our hospital serves as a primary and secondary care centre for patients with intracranial aneurysms, with a catchment area of ca. 1.2 million inhabitants. Between 1989 and 1999, a total of 1,294 patients with intracranial aneurysms were admitted to our hospital. Of these, 1,154 had previous SAH and were excluded leaving 140 patients with 178 intracranial unruptured aneurysms as the study population. All patients were followed up until death or the end of April 2011 and no patients were lost from follow-up. Fifty of the 140 patients (36%) died, and death certificates were obtained from Statistics Finland. The study was approved by the Hospital Ethics Committee and Statistics Finland.

Statistical analysis

Excess mortality of the patients was measured by one minus relative survival ratio (RSR). The RSR is the ratio of the observed survival proportion divided by the expected survival proportion of a comparable group of Finnish general population matched for sex, age and calendar time. The expected survival proportions were estimated by Ederer II method.[17] Relative survival measured the survival experience of the patients corrected for competing risks of death. Relative survival ratios and 95% CI were estimated by survival package SURV3 V.3.01 (Finnish Cancer Registry, Helsinki, Finland). Differences in relative survival between patient groups were tested applying likelihood ratio tests.[18]

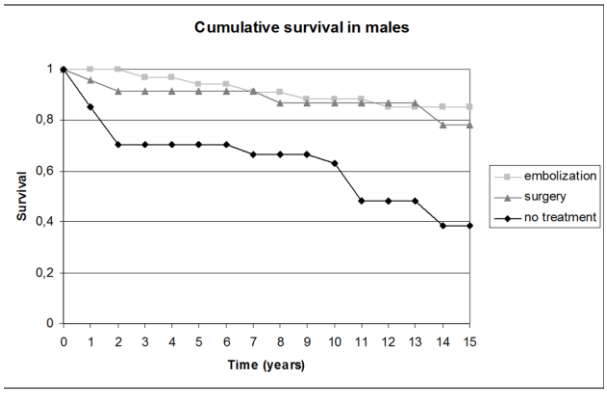
RESULTS

Patients (65 men and 75 women) were aged 18-86 years (mean 54) at the time of diagnosis of the unruptured intracranial aneurysm (Table 1.).

Table 1. Patient demographics (% in parenthesis)

	Males				Females				
	No treatment	Embolization	Surgery	Males total	No treatment	Embolization	Surgery	Females total	P
Mean age at diagnosis	57.4	49.0	49.6	52.1	64.1	52.5	50.0	54.6	0.1
Hypertension	13 (57)	7 (30)	8 (42)	28	11 (58)	10 (30)	11 (48)	32	1.0
Diabetes	1 (4)	1 (4)	1 (5)	3	1 (5)	2 (6)	1 (4)	4	1.0
Hypercholesterolemia	2 (9)	1 (4)	2 (11)	5	1 (5)	1 (3)	2 (9)	4	0.7
Previous stroke	8 (35)	4 (17)	4 (21)	16	8 (42)	7 (21)	4 (17)	19	1.0
Anticoagulant therapy	4 (17)	2 (9)	1 (5)	7	5 (26)	4 (12)	3 (13)	12	0.5
Aneurysm with neurological (mass) symptom	6 (26)	3 (13)	3 (16)	12	7 (37)	8 (24)	5 (22)	20	0.3
Location									0.5
Anterior circulation	19 (83)	23 (100)	19 (100)	61	13 (68)	32 (97)	23 (100)	68	
Vertebrobasilar	4 (17)	0 (0)	0 (0)	4	6 (32)	1 (3)	0 (0)	7	
Mean fundus size	15.5	8.2	10.3	11.4	13.2	10.7	12.5	11.9	1.0
Multiple aneurysms	4 (17)	5 (22)	3 (16)	12	6 (32)	7 (21)	7 (30)	20	0.3

A total of 66 out of 178 aneurysms were left untreated. Sixty-four aneurysms were treated with endovascular coiling and 48 aneurysms were treated surgically. Fifty out of 140 patients (36%) died during the 1702 patient-year follow-up period. Eleven patients (8%) died from aneurysmal bleeding and 13 died due to cerebrovascular disease other than SAH. Cause of death in one patient was unverified stroke. Nine out of 11 patients who died due to SAH had large aneurysms (>15mm, mean 24mm) and 6 aneurysms were symptomatic. Eleven patients died of cardiovascular diseases (22% of deaths), 6 of malignancies (12% of deaths) and 8 for other causes (16% of deaths). Patients with treated aneurysms were less likely to die from neurologically related causes than patients with untreated aneurysms (32% versus 61% of deaths). Cumulative observed survival proportions are shown in Figure 1.



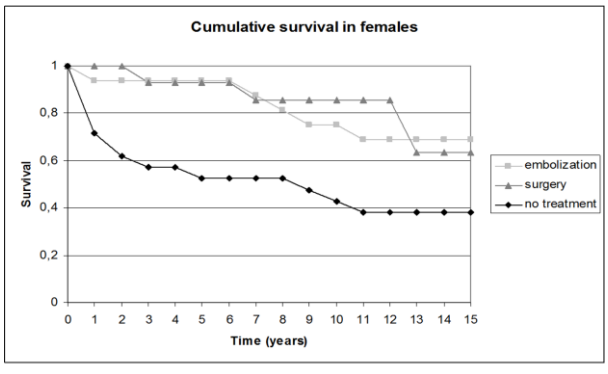
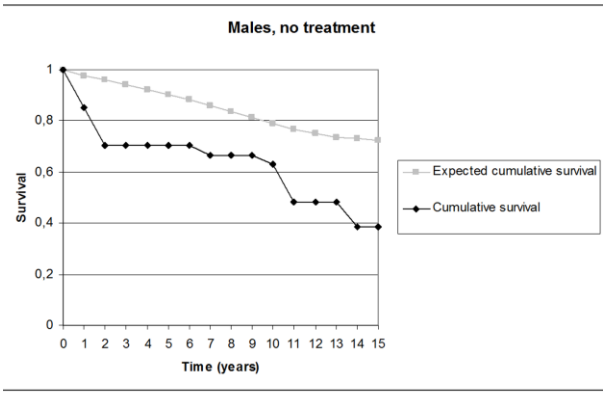


Figure 1. Cumulative observed survival proportions in males and females.

The 5-year cumulative RSR was 0.78 among male and 0.56 among females with untreated unruptured aneurysms, implying 22% and 44% excess mortality, respectively (Table 2). Mortality among treated groups did not differ from general population at 5-year follow-up period. The 10-year cumulative RSR was 0.80 in males and 0.49 in females in untreated aneurysms. Females had 19% excess mortality in embolization group and 8% excess mortality in surgical group at 10-years follow-up. Such difference was not found in males.

There was 12% excess mortality at 15 years in males and 35% excess mortality in females compared with the matched Finnish population. The 15-year cumulative RSR was 0.50 among both women and men with untreated unruptured aneurysms, implying 50% excess mortality (Figure 2).



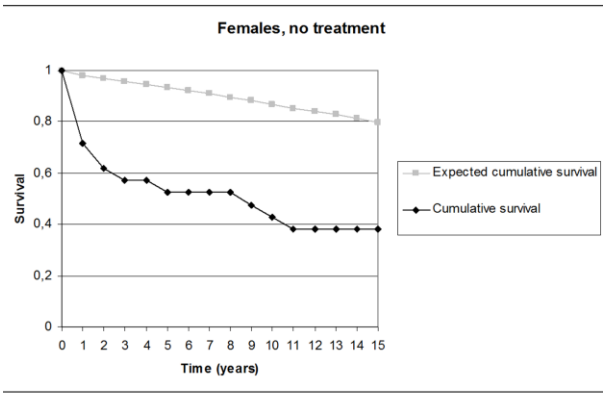


Figure 2. Cumulative observed and expected survival proportions in males and females with no treatment.

Table 2. Cumulative RSR in different treatment groups.

		at 1 year	at 5 years	at 10 years	at 15 years
NO TREATMENT					
Males (31)	Alive	27	19	18	4
	Cumulative RSR	0.87072	0.77865	0.79619	0.53259
	95%CI	0.690-0.962	0.570-0.931	0.559-0.992	0.276-0.846
Females (27)	Alive	21	12	10	3
	Cumulative RSR	0.72735	0.56173	0.49419	0.47843
	95%CI	0.510-0.878	0.347-0.768	0.282-0.732	0.261-0.743
EMBOLIZATION					
Males (34)	Alive	34	33	30	15
	Cumulative RSR	1.00988	0.99549	1.00257	1.06370
	95%CI	0.000-0.000	0.856-1.040	0.834-1.083	0.870-1.168
Females (17)	Alive	16	15	12	10
	Cumulative RSR	0.94297	0.97004	0.81039	0.76765
	95%CI	0.721-0.995	0.742-1.023	0.546-0.971	0.496-0.958
SURGERY					
Males (24)	Alive	23	21	20	8
	Cumulative RSR	0.96374	0.94982	0.95419	0.92089
	95%CI	0.796-1.000	0.762-1.015	0.745-1.048	0.631-1.080
Females (14)	Alive	14	13	12	8
	Cumulative RSR	1.00547	0.95945	0.92754	0.72207
	95%CI	0.000-0.000	0.708-1.020	0.650-1.039	0.428-0.949

Males with embolized aneurysms had no excess mortality compared with the matched Finnish male population (Figure 3) and males with clipped aneurysms had approximately 8% excess mortality (Figure 4). However, females had excess mortality in all subgroups (Figure 1). The 15-year cumulative RSR was 0.77 in the embolization group and 0.72 in the surgical group, implying 23% and 28% excess mortality respectively (Figure 3 and 4). Excess mortality was related to age and mortality among females over 50 years was higher than among males. Both genders under 50 years had 15-year cumulative RSR around 0.90 but the 15-year cumulative RSR in patients over 50 years was 0.91 in males and 0.49 in females (p=0.018).

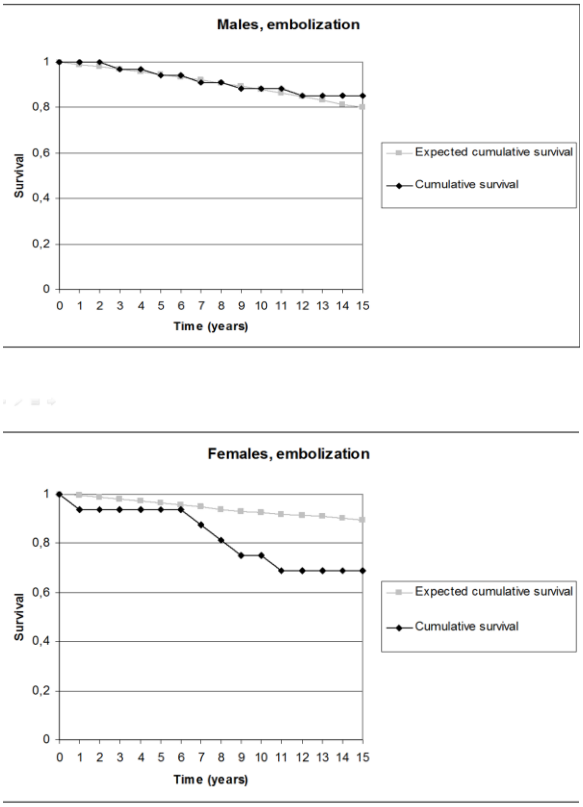


Figure 3. Cumulative observed and expected survival proportions in males and females after embolization.

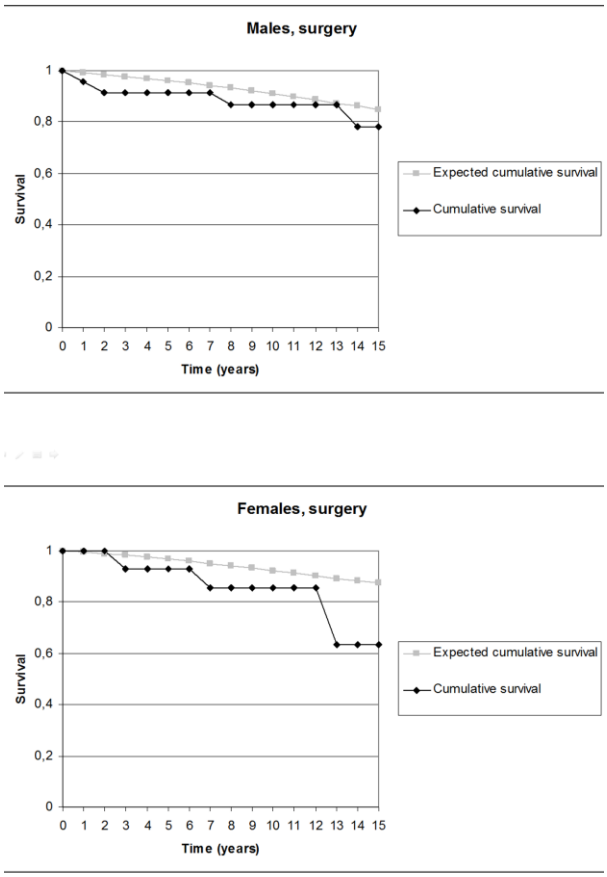


Figure 4. Cumulative observed and expected survival proportions in males and females after surgery.

DISCUSSION

SAH patients have an excess mortality proportion in long-term outcome studies because of the high rate of cerebrovascular and cardiovascular deaths.[12-15] To the best of our knowledge there are no studies comparing outcomes of patients with clipped, coiled and untreated unruptured aneurysms. In previous outcome studies of patients with unruptured aneurysms, patients have had a previous SAH and thus outcome can be related to previous SAH, not truly to unruptured aneurysms.[19-20] Long-term survival among patients with unruptured aneurysms has been studied in only one large, administrative database study.[21] In that study it was stated that survival among SAH patients was significantly lower than among patients with unruptured aneurysms, but after the first-year post clipping, differences in the survival rate diminished.[21]

Britz et al. found that patients with untreated unruptured aneurysms were 30% more likely to die than patients in the clipped group.[21] Our study corroborates this and we found that patients with untreated unruptured aneurysms had excess long-term mortality compared to age, sex and calendar time matched population. However, in both studies demographic features differed between groups: patients with untreated aneurysms were older, more likely to be male and had more comorbidities. Thus, higher mortality among untreated and treated may be attributable to bias. However, Britz et al.[21] found that survival differed between the surgically treated group and the untreated group also after controlling for age and comorbidities using proportional hazards modelling. The question of confounding by indication is difficult to assess in our retrospective study. Indication for treatment or no treatment was not clear and about 150 out of 380 unruptured aneurysms were left untreated in our hospital between 1989 and 1999. Patients over 60 years were usually not treated, likewise patients with numerous comorbidities and non-independent status. Posterior circulation aneurysms were not as often treated as anterior circulation aneurysms. Decisions were made individually and are difficult to assess retrospectively.

Our study is the first study to scrutinize all death certificates of patients with unruptured aneurysms. We found that a majority of deaths, 48%, were caused by cerebrovascular diseases and one third of deaths were aneurysm related, either due to SAH or giant aneurysm mass effect. Most deaths (70%) were attributable to cerebrovascular and cardiovascular diseases supporting the hypothesis that aneurysmal disease is part of a more generalized vascular disease. Britz et al. found that patients with unruptured aneurysm who underwent clipping were less likely to die from neurologically related causes (2.3%) than untreated patients (5.6%).[21] These

rates are much lower than in our series with 3 out of 10 (30% of deaths, 7% of clipped patients) and 17 out of 28 deaths (60% of deaths, 40% of untreated patients). Mortality did not differ significantly between endovascular and surgical groups supporting the opinion that unruptured aneurysms can be coiled or clipped.

We found, unexpectedly, that females had lower RSR than males. Male patients treated with endovascular coiling or surgical clipping had no statistically significant excess mortality compared to general matched population. However, females had 20% excess mortality in endovascular and 28% excess mortality in the surgical group at 15 years follow-up. It is known that the incidence of SAH is higher among females than males and females have more often multiple aneurysms.[19,22-25] However, outcome after SAH has not differed between the genders[22] and thus the difference in long-term mortality rate is somewhat surprising. The reason for this is unclear. The study population was small and may lack precision. However, in recent studies vascular physiology has been found to differ between genders and cardiovascular risk increases with age more sharply in women than in men.[26-27] Our finding confirms that there may be differences between female and male aneurysm patients and further studies with larger population are needed.

CONCLUSION

Patients with untreated unruptured aneurysms have excess long-term mortality compared to general population. Males with treated unruptured aneurysms have a survival proportion comparable to general matched population. Females, instead, have excess mortality after both surgical and endovascular treatment of unruptured aneurysms.

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Competing interests: None

Contributorship statement:LP designed the study, collected the data, analysed the data and drafted the manuscript ; TL designed the study, analysed the data and edited the manuscript; LK-N designed the study, analysed the data and edited the manuscript; JÖ designed the study and edited the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data.

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Long term outcome after subarachnoid haemorrhage of unknown aetiology

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ABSTRACT

Background and purpose The aim of this study was to assess the long term outcome after non-aneurysmal subarachnoid haemorrhage (SAH).

Methods 1154 patients with SAH were treated in our hospital between 1989 and 1999. From this patient population, 97 patients had a non-aneurysmal SAH. All hospital records and death certificates were studied and 33 patients were examined by MRI and MR angiography more than 9 years (mean 12 years) after the initial bleeding.

Results The cohort consisted of 97 patients. Mean follow-up time was 9 years (range 0–19). During the follow-up period, 13 patients (13%) died. Four (4%) died from the initial bleeding less than 5 weeks after the initial haemorrhage. There was no delayed mortality due to SAH or subsequent bleedings. MR angiography revealed no new findings in 33 surviving patients.

Conclusions Excess mortality during the first year after SAH was higher than 4%, and remained thereafter comparable with the general population. There were no rebleedings and MR imaging did not reveal any vascular pathology that could explain the earlier SAH.

INTRODUCTION

On average, in 15% (5–30%) of patients with spontaneous subarachnoid haemorrhage (SAH), no obvious source of bleeding can be demonstrated, even with high quality four vessel cerebral digital subtraction angiography (DSA).[1–8] The cause of angiogram negative SAH has not been established but a venous or capillary source, ruptured perforating artery, low flow vascular malformation and short segment arterial dissection have all been postulated.[9–11] Some researchers do not accept this and speculate that spontaneous thrombosis, vasospasm, destruction of the aneurysm by haemorrhage, narrowing of the aneurysmal neck, alterations in blood flow, inadequate angiographic technique or observer error may be responsible.[2] Outcome of angiogram negative SAH is good in 90% of cases.[4 7 8 12 13] However, many groups report non-specific symptoms such as headache, neuropsychological deficits or depressive symptoms in up to 62% of patients.[14–16] The rebleeding rate is approximately 5% (0–10%)[7 8 15–18] and the risk of death in non-aneurysmal bleeding has been estimated to be 0–15%[2 4 7 8 12 13 15 17 18] Greebe and Rinkel[15] concluded that patients with an angiographic negative perimesencephalic pattern of SAH have a normal life expectancy but Hawkins *et al*[17] found the cumulative proportional survival after 22 years to be 69% compared with an expected survival of 89% in patients with SAH of unknown aetiology.

To the best of our knowledge there are no studies analysing intracranial arterial status very long after initial bleeding or that have reported the incidence of de novo aneurysms in patients having SAH of unknown aetiology. The aim of this study was to assess long term outcome after non-aneurysmal SAH.

METHODS

Patients

Our hospital serves as a primary and secondary care centre for patients with SAH, with a catchment area of more than 1 million. Between 1989 and 1999, a total of 1154 patients with symptoms and signs of spontaneous, non-traumatic SAH were admitted to our hospital. Of these, 97 (8.4%) patients were included in the study because the aetiology of the SAH could not be verified by repeated four vessel cerebral angiography or post-mortem examination. SAH was diagnosed by CT in 80 (82%) cases and by a blood positive lumbar puncture in 17 (18%) cases. The diagnosis 'SAH NOS' was based on DSA in 96 patients and post-mortem examination in one patient. All hospital records were studied and the latest outcome of patients was evaluated from the most recent notes in the hospital records or by telephone interview. Clinical status at the time of the bleeding was assessed according to the Hunt and Hess scale.[19] Glasgow Outcome Scale (GOS)[20] was used to evaluate clinical status at the time of discharge and at follow-up visits. Primary CT images were re-evaluated to assess Fisher grades and the presence of hydrocephalus. All angiograms were reviewed independently by a neuroradiologist, neurointerventionalist and neurosurgeon. Thereafter, the results were reviewed and a consensus statement for each study was produced. Surviving patients resident in our hospital catchment area were contacted, offered an MRI examination and interviewed to assess clinical outcome and possible rebleeding episodes. A total of 33 were studied with MRI and MR angiography (MRA), and interviewed at our outpatient clinic. Follow-up MRI and MRA were compared with the findings of earlier studies. Surviving patients not studied with MRI lived outside our hospital catchment area, did not answer our letter, were unwilling to participate in the study or had contraindications to MRI. Two surviving patients were lost to clinical follow-up. Thirteen of 97 patients died, and death certificates were obtained from Statistics Finland. The study was approved by the Hospital Ethics Committee and Statistics Finland.

MRI protocol

The follow-up MR imaging was performed with the 1.5 T unit (GE Signa HD, Milwaukee, USA) with one channel head coil. MRA was supplemented with cross sectional imaging, including fluid attenuation inversion recovery, and T1 and T2* sequences, mainly to identify ischaemic parenchyma, ascertain the size of the CSF spaces and persisting blood degradation deposits. The imaging parameters for the non-contrast three-dimensional time of flight angiography were: TR 30, TE 2.5, FOV 22×16.5 cm, slice thickness 1.0 mm/interpolated to 0.5 mm, matrix 320×224. Magnetisation transfer contrast and flow compensation were included.

Statistical analysis

Statistical analysis was performed using NCSS (NCSS, Kaysville, Utah, USA) statistical software. Categorical variables were compared using the Fisher exact two tailed test. The level of significance was set at $p<0.05$. Excess mortality of the patients was measured by one relative survival ratio. The relative survival ratio is the ratio of the actuarial observed survival rate divided by expected survival rate of a comparable group of patients from the Finnish general population matched by sex, age and calendar time. Relative survival measures the survival experience of the patients corrected for competing risks of death. Relative survival ratios were estimated by survival package SURV3 V.3.01 (Finnish Cancer Registry, Helsinki, Finland).

RESULTS

Patients were aged 21—76 years (mean 52) at the time of bleeding. There were 35 men and 62 women. Most patients had a good clinical status on admission (table 1). In the deceased group, patients had a poorer clinical status and higher Fisher grades on primary CT compared with the surviving group. There was no other statistically significant difference between the surviving and deceased groups.

Thirteen of 97 patients (13%) died during the 868 patient-year follow-up period. Four (4%) died from the initial bleeding of the non-aneurysmal SAH: two immediately and two patients in 1 month after a poor clinical state. All four patients had severe bleeding on the initial CT (Fisher 3 or 4, non-perimesencephalic type of bleeding). Three patients died of cardiovascular diseases, three of malignancies and three due to traumatic causes. Mortality in the first year after bleeding was more than 4% in excess of that expected in a comparable group from the general population, both among women and men. Thereafter, mortality of the patients was close to the level in the general population. There were no rebleedings. Ninety-four per cent of the surviving group (79/84) had recovered well (GOS 4 or 5) and the reason for the lower GOS was related to SAH in only two (2%) patients (figure 1). There was no difference in outcome between patients studied with and without MRI.

Thirty-three patients were studied with MRI. Mean follow-up time was 12 years (range 9—18). No new aneurysms were detected in MRA images or any other vascular pathology that could explain the previous bleeding. Six patients (18%) had infarctions in MRI. Two were already seen during the treatment period after clinically and radiologically proven vasospasm. Four infarctions were not detected in earlier images and only two of those four patients had been treated for clinical stroke. Leukoaraiosis was seen in 11 (34%) patients. Signs of superficial haemosiderin were present in two patients (6%).

Table 1 Population characteristics

	Surviving group (n=84)	Deceased group (n=13)
Mean age (years)	52	53
Sex		
Male	31	4
Female	53	9
Diagnosis		
CT	67	13
Lumbar puncture	17	0
Fisher		
1	16	0
2	17	4
3	20	5
4	23	4
Hydrocephalus	30	4
Hunt and Hess		
I	40	2
II	32	2
III	10	5
IV	1	3
V	1	1
GOS at discharge		
I	0	2
II	0	1
III	10	1
IV	41	7
V	33	2

GOS, Glasgow Outcome Score.

DISCUSSION

After SAH, initial angiographic findings are negative for a bleeding source in approximately 15% of patients.[1–8] A traditional concept states that angiogram negative SAH carries a more benign prognosis than aneurysmal SAH. However, some patients experience morbidity and mortality because of recurrent haemorrhage or vasospasm.[14 21–23] Repeat DSA within 2 weeks after the bleeding is commonly performed. Although repeat DSA provides identification of the source of bleeding in up to 20% of cases, the source remains undetected in the majority of patients.[22–24] The incidence of angiogram negative SAH was 8.4% in our series and this concurs with recent series.[1–8]

We found no new arterial vasculopathies or other aetiologies for previous SAH in those 33 patients studied. It is a weakness of our study that we performed MRI in only 34% of patients. However, those surviving patients we could not reach had a poorer clinical status and we believe that this selection bias is unlikely to influence the MRI findings. Infarctions were detected in six (18%) patients, which is significantly less than in patients with aneurysmal SAH.[25–27] Two infarctions were caused by vasospasm and

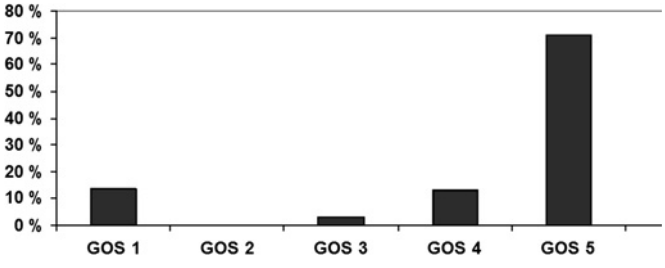

Figure 1 Present Glasgow Outcome Score (GOS) of patients with subarachnoid haemorrhage of unknown aetiology.

two were incidental findings. Leukoaraiosis was seen in 11 (34%) patients and this was less than in aneurysmal SAH patients and not more than the prevalence in a neurologically health age cohort.[25–28] Earlier studies of angiogram negative SAH have reported a subsequent bleeding rate of up to 10%.[7 8 17 18 29] However, the latest reports have detected no rebleedings and neither did we.[15 16]

The outcome is much better in SAH patients with unknown aetiology than in aneurysmal SAH patients.[2 4 7 8 12 13 15 17 18] Eighty-one per cent of patients had recovered well (GOS 4 or 5) and poor outcome was related to SAH in only six (6%) patients in our series. The risk of death from non-aneurysmal bleeding has been estimated to be 0–15%.[2 4 7 8 12 13 15 17 18] In our series, 4% of patients died of angiogram negative SAH. Overall mortality in our series was 13% compared with 47% mortality in aneurysmal SAH patients in our hospital at the same time.[30] In the long term outcome study, patients with SAH of unknown cause had reduced life expectancy compared with expected numbers.[17] However, in that study, as many as 22% of all SAH patients had no cause on angiogram, which was not repeated, raising the suspicion that aneurysms were missed. Greebe and Rinkel,[15] however, found no difference in mortality between the general population and patients with a perimesencephalic pattern of non-aneurysmal SAH. This study was, however, involved only a subgroup of all patients with SAH of unknown aetiology and to the best of our knowledge our study is the only one in the modern imaging modality era to assess the long term outcome of patients with SAH of unknown aetiology.

CONCLUSION

Excess mortality during the first year after SAH was higher than 4%, and remained thereafter comparable with the general population. There were no rebleedings and MR imaging did not reveal any vascular pathology that could explain the previous SAH. Based on our results, long term follow-up is not needed, and after appropriate angiographic studies, patients should be informed about the benign nature of this rare type of SAH.

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Competing interests None.

Ethics approval The study was conducted with the approval of the Tampere University Hospital Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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