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Juha-Matti Isokangas

ENDOVASCULAR TREATMENT OF 467 CONSECUTIVE INTRACRANIAL ANEURYSMS IN OULU UNIVERSITY HOSPITAL

ANGIOGRAPHIC AND CLINICAL RESULTS

FACULTY OF MEDICINE,
DEPARTMENT OF DIAGNOSTIC RADIOLOGY,
UNIVERSITY OF OULU
OULU UNIVERSITY HOSPITAL

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Supervised by
Docent Topi Siniluoto
Docent Tapani Tikkakoski

Reviewed by
Docent Leo Keski-Nisula
Docent Jaakko Rinne

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Faculty of Medicine, Department of Diagnostic Radiology, University of Oulu, P.O.Box 5000, FI-90014 University of Oulu, Finland; Oulu University Hospital, P.O. Box 10, FI-90029 OYS, Finland
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Abstract

The purpose of the study was to analyze the angiographic and clinical results of endovascularly treated intracranial aneurysms in Oulu University Hospital, Finland.

The study population consisted of 416 consecutive patients (467 aneurysms, 332 ruptured), who were referred for endovascular treatment of intracranial aneurysm(s) between December 1993 and July 2004. Technical failures were analyzed for an assesment of technical feasibility. Angiographic results were assessed using modified Raymond Classification. Clinical results were analyzed from patient files using the Glasgow Outcome Scale (GOS). Patient, aneurysm, and procedure related variables were tested with an intention to find the predictors of the angiographic and clinical outcome. The clinical effects on presenting symptoms were analyzed for a subgroup of patients with a symptomatic unruptured aneurysm (n = 30). The mean results on technical feasibility, complications, and angiographic results were separately assessed for three time periods (1993–1997, 1998–2000 and 2001–2004) to demonstrate potential significant changes in outcome.

Endovascular treatment of saccular aneurysms was technically feasible in 91.4% of the treatments. Initially, 25.7% of the aneurysms were completely occluded, 57.9% had a neck remnant, and 16.3% remained incompletely occluded. In follow-up, the rates for complete occlusions, neck remnants and incomplete occlusions were 37.6%, 49.7% and 12.7%, respectively. Small aneurysm size predicted complete aneurysm occlusion, while a wide aneurysm neck and location in the posterior circulation predicted incomplete occlusion. In follow-up (mean 38.2 months), 78.1% of the patients with a ruptured aneurysm and 92.3% of the patients with an unruptured aneurysm had resumed independent life (GOS 4-5). The predictors of good outcome were young age, good preprocedural clinical condition, small amount of blood in CT scan, and uncomplicated procedure. Ten of the treated aneurysms involved intracranial bleeding in follow-up, and the annual risk for bleeding after endovascular treatment was 0.95% among the patients with ruptured aneurysms and 0.33% among those with unruptured aneurysms. The risk of bleeding was associated with larger aneurysm size and lower occlusion grade. In the subgroup of symptomatic unruptured aneurysms, 53.4% of the patients showed either resolution or improvement of the symptoms after treatment. The rates of procedural complications, morbidity, and mortality were 16.5%, 6.7%, and 1.7%, respectively. The risk for procedural complications was higher when the balloon remodeling technique was used and lower in retreatments. Technical feasibility (85.6%, 90.6%, and 95.7%, respectively) and the percentage of complete occlusions (initially 16.5%, 23.0%, and 32.9%, respectively) were significantly improved by increased experience, while no statistical difference was detected in the total procedural complication rates (15.4%, 15.7%, and 18.3%, respectively) or the combined procedural morbidity and mortality rates (8.0%, 8.3%, and 9.1%, respectively). All six dissecting aneurysms treated with parent artery occlusion or the stent remodeling technique resulted in complete occlusions.

The present results confirmed endovascular treatment of intracranial aneurysms as a feasible, safe, and effective method in preventing further bleeding of aneurysms. Increased experience in a single center improved the feasibility of the treatment as well as the angiographic results.

Keywords: dissecting aneurysm, intracranial aneurysm, subarachnoid hemorrhage, therapeutic embolization, treatment outcome

To Leena

”Experience is what other people call mistakes”
Oscar Wilde

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Jääli, October 2006 Matti Isokangas

Abbreviations

ACA	anterior cerebral artery
AchorA	anterior choroidal artery
AcomA	anterior communicating artery
ACT	activated clotting time
AICA	anterior inferior cerebellar artery
ADPKD	autosomal dominant polycystic kidney disease
AVF	arteriovenous fistula
AVM	arteriovenous malformation
A1	1st segment of anterior cerebral artery
A2	2nd segment of anterior cerebral artery
BA	basilar artery
BI	Barthel Index
Ci	Curie, radioactivity unit (1Ci=3,7x10^{10} Becquerel)
CT	computerized tomography
CTA	computerized tomography angiography
dnr	dome-to-neck ratio
DSA	digital subtraction angiography
DWI	diffusion-weighted imaging
FIA	familial intracranial aneurysm
GDC	Guglielmi detachable coil
GOS	Glasgow Outcome Scale
HES	Hydrocoil embolic system
H&H	Hunt & Hess grading scale
ICA	internal carotid artery
ICH	intracerebral hemorrhage
ISAT	International Subarachnoid Aneurysm Trial
ISUIA	International Study of Unruptured Intracranial Aneurysms
IVH	intraventricular hemorrhage
IU	international unit
KS	Karnofsky Scale
MCA	middle cerebral artery

MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
M1	1st segment of middle cerebral artery
M2	2nd segment of middle cerebral artery
NA	not applicable
OphtA	ophthalmic segment of internal carotid artery
PA	parent artery
PAO	parent artery occlusion
PCA	posterior cerebral artery
PcomA	posterior communicating artery
PICA	posterior inferior cerebellar artery
PPT	Physical Performance Test
P1	1st segment of posterior cerebral artery
P2	2nd segment of posterior cerebral artery
SAH	subarachnoid hemorrhage
SCA	superior cerebellar artery
SD	standard deviation
SEM	electron microscopic scanning
ShypA	superior hypophyseal artery
SPECT	single photon emission computed tomography
TIA	transient ischemic attack
UCLA	University of California, Los Angeles
VA	vertebral artery
VBA	vertebrobasilar arteries
2D	two-dimensional
3D	three-dimensional
3DRA	three-dimensional rotational angiography

Contents

1 Introduction

The prevalence of intracranial aneurysms in the general population has been estimated to be 1.4-1.6% (Bannerman *et al.* 1970, Jellinger 1979). The most important clinical manifestation of intracranial aneurysm is subarachnoid hemorrhage (SAH), which occurs when an intracranial aneurysm ruptures. Aneurysmal SAH is a medical emergency with about 50% case mortality (van Gijn & Rinkel 2001). Of the patients who survive the hemorrhage, approximately one third remain dependent (Hop *et al.* 1997). Without treatment, it has been estimated that at least 50% of ruptured aneurysms will rebleed in four weeks, 15% of them within the first 24 hours already (Hijdra *et al.* 1987, van Gijn & Rinkel 2001). Obliteration of the ruptured aneurysm from circulation is essential in preventing rebleedings among SAH patients.

Unruptured intracranial aneurysms may be discovered coincidental to SAH in patients with multiple aneurysms or in patients undergoing imaging for other intracranial diseases. Some of the unruptured aneurysms may cause clinical symptoms, depending on their size and location. Treatment of an unruptured aneurysm aims either to prevent its rupture in the future or to alleviate the symptoms. Contrary to ruptured aneurysms, the natural course of unruptured aneurysms is much more favorable: the annual bleeding risk is estimated to be 1.3% on an average (Juvela *et al.* 2000) and even substantially lower among small aneurysms (Wiebers *et al.* 1998). The cumulative risk of rupture is higher in younger patients, in smokers, and for aneurysms that are large or located in the posterior circulation (Juvela *et al.* 2000, Wiebers *et al.* 2003).

Surgical obliteration of the intracranial aneurysm has been the mainstay of treatment for decades. Endovascular treatment for intracranial aneurysms was first described by Serbinenko, who used detachable balloons to occlude the carotid artery in unclippable cases (Serbinenko 1974). Later on, balloons and pushable coils were used for occluding aneurysm sacs. However, endovascular treatment became a respectable option for surgery only after the introduction of the Guglielmi Detachable Coil (GDC) in the early 1990's (Guglielmi *et al.* 1991a). This novel technique revolutionized the endovascular treatment of intracranial aneurysms and rapidly spread around the world. Nowadays, endovascular treatment is widely accepted and has proved to have many advantages over surgery (Molyneux *et al.* 2005). It has therefore superseded surgery as the first-line treatment in many centers. Because aneurysm treatment involves complications, mortality, and

morbidity, the decision to treat should be made by the patient after being adequately informed about the natural course of such lesions and the risks related to the treatment. Every center treating intracranial aneurysms should analyze their procedural complication, mortality, and morbidity rates for adequate patient information. Treatment may be indicated if the risks of procedural complications do not exceed the risk of the natural course of the disease.

In Oulu University Hospital, the first endovascular treatment of an intracranial aneurysm was performed in December 1993. By July 2004, a total of 467 aneurysms had been treated successfully or unsuccessfully in 416 patients. In this single-center study, the angiographic and clinical results of this consecutive series of patients were analyzed. The predictors of angiographic and clinical outcomes were also determined as well as the evolution of these outcomes during the study period. In the present literature, only limited data exist concerning the long-term evolution of outcomes.

2 Review of the literature

2.1 Classification and pathogenesis of intracranial aneurysms

2.1.1 General classification

The term ‘aneurysm’ is derived from the Greek word *aneurysma*, *ana* meaning ‘across’ and *eurys* ‘broad’. An aneurysm is defined as a localized and persistent dilatation of the blood vessel wall, and it is formed by dilatation of the constituents of the vessel wall, which exhibit profound structural alterations (Stehbens 1963). Intracranial aneurysms have traditionally been classified based on morphologic or etiologic criteria. Morphologically, aneurysms can be divided into saccular and nonsaccular (or fusiform) types. Saccular aneurysms involve part of the circumference of the artery from which they arise and have a single opening or neck. Nonsaccular aneurysms involve the entire arterial wall and do not have a neck. Etiologically, most aneurysms are idiopathic and thought to be the result of a combination of structural and hemodynamic factors. Specific etiology can rarely be identified, but some aneurysms can be etiologically classified as dissecting, infectious (or mycotic), traumatic, or flow-related aneurysms.

2.1.2 Saccular aneurysms

Saccular aneurysms are the most common type, and they account for up to 98% of all intracranial aneurysms (Yasargil 1984). They are characteristically located on the circle of Willis or its major branches and develop at bifurcations or the origins of branching arteries. They are pouch-like dilatations of the vessel and consist of a neck, body, and fundus. Blood flow enters the aneurysm at the neck. The body and the fundus are typically in line with the blood flow in the parent artery. Aneurysms may have two or more lobules, and recently ruptured aneurysms usually have a small lobule called “secondary pouch” at the point of rupture (Suzuki & Ohara 1978).

The walls of intradural arteries have three layers: adventitia, media, and intima. The intima comprises an inner endothelial layer, a thin collagen layer, and a prominent

internal elastic lamina. The muscular media is thin (compared to peripheral arteries) or absent at bifurcations, and there is no external elastic lamina (Sahs 1966). The adventitia is thinner than in extradural arteries, and there are no vasa vasorum beyond the most proximal part of the intradural arteries (Zervas *et al.* 1982). Because the walls of intradural arteries are thinner than those of more peripheral arteries, they are more prone to develop aneurysms.

Most saccular aneurysms occur at the apical angle of arterial bifurcations, where the inner vascular layers herniate through a localized defect in the internal elastic lamina. Therefore, the walls of saccular aneurysms do not have media or internal elastic lamina. The integrity of the endothelial layer varies and is complete only in small aneurysms. The wall principally consists merely of acellular fibroid tissue continuous with the adventitia of the parent artery, but the walls of large aneurysms may contain some cellular elements. Foam cells, lipophages, and cholesterol clefts may be found around the neck if there are atherosclerotic changes in the parent artery. The inner surface of the aneurysm is smooth if the endothelium is complete, but adherent blood clots can be seen in areas where the endothelium is incomplete (Sahs 1966, Suzuki & Ohara 1978). Thinning of the wall is common at the fundus, where the aneurysm usually ruptures. Rupture is presumably secondary to mechanical pressure due to blood flow dynamics (Crompton 1966).

The pathogenesis of saccular aneurysms is still unclear, and most of them are thought to be due to a combination of structural and hemodynamic factors. The main factor contributing to the strength of cerebral arteries is an intact internal elastic lamina of the intima, which is the only elastic layer in cerebral arteries (Stehbens 1963). It has therefore been suggested that degenerative disruption of the internal elastic lamina due to hemodynamic stress is necessary for an aneurysm to develop (Glynn 1940, Crawford 1959). Most saccular aneurysms develop at the apex of a bifurcation, where hemodynamic stress is maximal and degeneration of the internal elastic lamina occurs. The blood flow inside the aneurysm is turbulent, causing it to enlarge and possibly to rupture (Ferguson 1972). Before the rupture, the wall of a saccular aneurysm undergoes morphological changes, such as apoptosis, de-endothelization, luminal thrombosis, smooth muscle cell proliferation, and macrophage infiltration, associated with remodeling of the aneurysm wall (Frösen *et al.* 2004). The receptors found to be regulating the remodeling process are vascular endothelial growth factor, transforming growth factor beta, and basic fibroblast growth factor receptors (Frösen *et al.* 2006). These receptors are potential targets for bioactive endovascular devices or drug therapy aiming to reinforce the aneurysm wall and to prevent its rupture (Frösen *et al.* 2006).

2.1.3 Nonsaccular aneurysms

Nonsaccular aneurysms vary in shape, and the parent artery may have undergone complicated distortions. They are usually related to arterial enlargement caused by atherosclerosis but may also result from focal arterial injury. Loss of the normal mural elasticity of the arterial wall leads to ectatic dilatation, which most commonly takes place in the vertebral, basilar, or internal carotid arteries (Anson *et al.* 1996). The progression from ectatic dilatation to nonsaccular aneurysm is presumably initiated by degeneration

of the wall and exacerbated by pulsatile blood flow. The slower blood flow inside the aneurysm may lead to intra-aneurysmal thrombosis, and intimal hemorrhage may also occur. Intraluminal thrombosis may send thromboembolies into peripheral arteries. According to their radiographic appearance, nonsaccular intracranial aneurysms can be classified as fusiform, dolichoectatic, and transitional (Flemming *et al.* 2004). The risk of hemorrhage is highest among transitional type of nonsaccular aneurysms, which carry a significant risk of death (Flemming *et al.* 2004). Giant fusiform aneurysms present with symptoms of mass effect in 50% of cases and hemorrhage in 20% (Drake 1979a). Surgical clipping or reconstructive endovascular treatment is often impossible, because normal vessel branches (perforators) may originate from the aneurysm. Among fusiform middle cerebral artery aneurysms, hemorrhage is the most common presentation in small lesions, while giant or serpentine aneurysms are most often associated with clinical presentation prompted by a mass effect or thromboembolic stroke (Day *et al.* 2003). Based on the spectrum of clinical, pathological, neuroimaging, and intraoperative findings, dissection is proposed as the underlying cause of fusiform MCA aneurysms (Day *et al.* 2003).

2.1.4 Traumatic and iatrogenic aneurysms

Traumatic aneurysms account for 0.2% – 1.0% of all intracranial aneurysms. They are usually false aneurysms (all the wall layers are breached), where a local blood clot has organized to form a fibrous sac. According to the review by Fox, 75% of these cases occurred after closed head injury, 14% after penetrating trauma, and 11% after craniotomy and transphenoidal or other types of paranasal sinus surgery (Fox 1983).

2.1.5 Dissecting aneurysms

Intracranial dissection is characterized by disruption of the intima and the internal elastic lamina and accumulation of blood between the internal elastic lamina and the media. Intradural dissections are rare, and their etiology usually remains unknown, though possible associations with trauma, young age, male gender, and vascular disorders have been reported (Halbach *et al.* 1993, Pozatti *et al.* 1994). Dissecting aneurysms develop when the dissection proceeds through the media into the subadventitial layer and causes dilatation of the outer wall of the vessel (Hart & Easton 1983, O'Connell *et al.* 1985). SAH may result if the intradural dissection ruptures through the adventitia (Adams *et al.* 1982). In a recent retrospective analysis by Ramgren *et al.* (2005), a dissecting aneurysm was found in 69% of the cases with SAH caused by dissection in the vertebrobasilar territory. In a study by Pelkonen *et al.* (1998), DSA revealed an aneurysm in 30% of the intracranial dissections, all of them located in either VA or PICA.

2.1.6 Infectious aneurysms

Infectious (formerly called “mycotic”) aneurysms typically occur in patients with a history of drug abuse or with infective endocarditis. Infectious aneurysms tend to be located in peripheral branches distal to the circle of Willis and develop due to septic emboli, which cause a local inflammation, vessel wall disruption, and aneurysm formation (Roach & Drake 1965, Khayata *et al.* 1993). Spreading of an extravascular infection, such as meningitis, osteomyelitis, or sinusitis, may occasionally cause the formation of infectious aneurysms (Molinari *et al.* 1973). The organisms causing the infection may be bacterial (Streptococcus, Stafylococcus, Enterococcus) or fungal (Aspergillus, Candida) (Khayata *et al.* 1993).

2.1.7 Flow-related aneurysms

Flow-related aneurysms can be demonstrated in some patients with abnormally high flow in the cerebral arteries due to a pre-existing arteriovenous malformation (AVM), anatomical variant, or occlusion of ICA (George *et al.* 1971, Salar & Mingrino 1981, Bucciero *et al.* 1994, Lasjaunias *et al.* 1994, Redekop *et al.* 1998, Senn *et al.* 2000). They may regress spontaneously after the treatment of the underlying pathology and the consequent cessation of the high-flow state and the normalization of hemodynamic stress against the arterial walls (Redekop *et al.* 1998, Senn *et al.* 2000). Flow-related aneurysms may rupture and cause hemorrhage (Marks *et al.* 1990, Redekop *et al.* 1998). The presence of flow-related aneurysms further supports the theory of hemodynamic stress as a factor promoting aneurysm formation and growth (Miyasaka *et al.* 1982, Bederson 1995).

2.1.8 Giant aneurysms

Giant aneurysms, defined as larger than 25mm in diameter, account for 5% - 8% of intracranial aneurysms. Presenting symptoms, in addition to SAH, are commonly due to a mass effect, intracerebral hemorrhage, or thromboembolism. Giant aneurysms are frequently (in at least 60% of cases) associated with either partial or, less commonly, complete thrombosis (Wanke *et al.* 2004). A completely thrombosed giant aneurysm may spontaneously recanalize (Lee *et al.* 1999).

While the etiology of saccular aneurysms remains unclear, an interesting hypothesis concerning the pathogenesis of partially thrombosed giant aneurysms has been proposed (Krings *et al.* 2005). The formation of such lesions might be explained by an extraluminal inflammation process promoted by an enzyme called 5-lipo-oxygenase, which generates different forms of leukotriens. Leukotriens in turn are potent mediators of inflammation. Adventitial inflammation leads to weakening of the media, thereby degrading the extracellular matrix, the internal elastic lamina, and finally, the integrity of the vessel lumen. This in turn results in dilatation of the vessel and aneurysm formation. In addition

to this biological cascade, neoangiogenesis of vasa vasorum, promoted by 5-lipo-oxygenase activated macrophages, results in repeated subadventitial hemorrhages, creating new layers of intramural haematoma within the vessel wall. The increasing number of such hemorrhagic layers causes progressive growth of aneurysm size. A giant intracranial aneurysm can therefore be regarded as a proliferative disease of the vessel wall induced by extravascular activity. (Krings *et al.* 2005).

2.1.9 Pediatric aneurysms

Intracranial aneurysms in children are rare. In an analysis of 3000 ruptured aneurysms by Patel & Richardson (1971), 2% of the patients were aged under 19 and only 0.1% under 5 years. In a large cooperative study of intracranial aneurysms and subarachnoid hemorrhage, including 2627 aneurysms, only 1.5% of the patients experienced rupture of the aneurysm by age 19 (Locksley *et al.* 1966).

There are several specific features of pediatric intracranial aneurysms that differ from those seen in the adult population. Compared with adults, posterior circulation aneurysms and infectious aneurysms are more common in the pediatric population (Allison *et al.* 1998), and aneurysms tend to be more frequently large or giant in size (Ferrante *et al.* 1988). Location of the aneurysm in the distal part of ACA, MCA, or PCA is much more common among children compared to adults (Allison *et al.* 1998). In children, a male predominance is seen, contrary to the female predominance in adults (Locksley 1966, Allison *et al.* 1998). In the study by Allison *et al.* (1998), 16% of the aneurysms in infants and children were associated with intracranial vascular variations or anomalies. In a consecutive series of 59 children with intracranial aneurysms, Lasjaunias *et al.* (2005) found dissecting aneurysms in 33 (56%), post-traumatic aneurysms in 2 (3%), infectious aneurysms in 8 (14%), and saccular aneurysms in 16 (27%) patients. Most of the dissecting lesions were located in the posterior circulation, while the saccular lesions mostly occurred in the anterior circulation (Lasjaunias *et al.* 2005).

2.1.10 De novo *aneurysms*

De novo aneurysms are new aneurysms that have not been verified in previous angiographies. *De novo* aneurysms are located at sites remote from the sites of previously treated aneurysms (i.e. regrowths of previously treated aneurysms are not *de novo* aneurysms). They are occasionally detected in patients undergoing angiographic follow-up of previously treated aneurysms. *De novo* aneurysms have been demonstrated to be histologically similar to usual saccular aneurysms (Sakaki *et al.* 1993).

CTA screening of patients with a history of aneurysmal SAH revealed new aneurysms in 16% of the patients during a mean follow-up of 8.9 years, and approximately 26% of these new aneurysms could be categorized as *de novo* aneurysms (Wermer *et al.* 2005a). Wermer *et al.* (2005a) found the risk factors for aneurysm formation to be multiple aneurysms at time of SAH, current smoking, and hypertension. A review study by Tonn *et al.* (1999) disclosed that patients with *de novo* aneurysms were younger and had more

frequently a history of smoking and hypertension than the patients in the control cohort. Altogether 44% of the *de novo* aneurysms became symptomatic after the first SAH, and this interval was significantly shorter in the hypertensive patients. The incidence of *de novo* aneurysm formation and rupture has been found to be 63 per 100 000 per year among patients known to have had a subarachnoid hemorrhage (although treated successfully), which is about threefold compared to the general population (Rinne & Hernesniemi 1993). The patients with *de novo* aneurysms were 10 years younger at the time of their first SAH compared to the whole series of patients with intracranial aneurysms (Rinne & Hernesniemi 1993). These data suggest that young patients who have their first SAH at or under the age of 40 benefit from long-term angiographic follow-up after a 5-year interval in addition to strict control of blood pressure (Rinne & Hernesniemi 1993, Tonn *et al.* 1999). The findings on *de novo* aneurysms suggest that intracranial aneurysms are acquired lesions that should not be considered as single events in a lifetime but rather as a continuous process (Wermer *et al.* 2005a).

2.1.11 Familial intracranial aneurysms

Approximately 10% of the patients harboring intracranial aneurysms in the Finnish population have a family history with at least two persons affected (Ronkainen *et al.* 1993, Ronkainen *et al.* 1997). Studies in other populations have reported the prevalence of familial intracranial aneurysms (FIA) to be either 6.7% or 23.4% among all intracranial aneurysms detected (Norrgård *et al.* 1987, Kissela *et al.* 2002). The risk of intracranial aneurysm rupture has been found to be 4-fold in the first-degree relatives of patients with aneurysmal SAH and 6-fold in their siblings compared to the the general population (Schievink *et al.* 1995, Ronkainen *et al.* 1997).

The familial occurrence of intracranial aneurysms suggests a genetic factor in the development of these aneurysms (Roos *et al.* 2004). In a study of 346 Finnish families with at least two members with a verified diagnosis of FIA (families with a diagnosis of other heritable disorders associated with intracranial aneurysms were excluded), inheritance patterns with multiple modes were found; autosomal recessiveness was present in 57.2%, autosomal dominance in 36.4%, and autosomal dominance with incomplete penetrance in 5.5% of the families (Wills *et al.* 2003). Both autosomal dominant and recessive patterns of inheritance indicate genetic heterogeneity (Roos *et al.* 2004). In genetic studies with different populations (Dutch, Finnish, and Japanese), suggestive gene linkage was found at distinct locations, underlining genetic heterogeneity (Onda *et al.* 2001, Olson *et al.* 2002, Roos *et al.* 2004, van der Voet *et al.* 2004).

Positive family history, defined as two or more first-degree relatives with subarachnoid hemorrhages, is a powerful risk factor for intracranial aneurysm (relative risk 6.6)(Rinkel 2005). The advent of non-invasive methods of imaging intracranial vessels has facilitated screening for FIAs in members of risk families (Ronkainen *et al.* 1995, Rinkel 2005). Due to the relatively late age at onset, there is a high risk of new aneurysm formation in 5 years, even when the initial screening shows no abnormality. Repeated screening might be indicated, although the optimal interval between screening assessments and the duration of repeated screening is so far unclear (Rinkel 2005).

Because of the limited ability of non-invasive imaging methods to detect small or very small aneurysms, even small-probability findings should be confirmed or excluded by DSA (Vanninen *et al.* 1996).

2.1.12 Intracranial aneurysms and heritable diseases

A small fraction of intracranial aneurysms are associated with heritable connective-tissue diseases such as autosomal dominant polycystic kidney disease (ADPKD), Ehler-Danlos syndrome type IV, neurofibromatosis Type 1, and Marfan syndrome (Schievink 1997, Schievink *et al.* 2005). ADPKD has been found to be a powerful risk factor for intracranial aneurysm formation (relative risk 4.4), indicating a need for aneurysm screening (Rinkel 2005).

2.2 Natural history and clinical presentation of intracranial aneurysms

2.2.1 Epidemiology

The prevalence of intracranial aneurysms among the general population has been difficult to assess, because there used to be no non-invasive method available to diagnose intracranial aneurysms. According to autopsy studies, the prevalence of unruptured intracerebral aneurysms varies from 0.8% to 8.1% (Byrne & Guglielmi 1998).

The largest series included data from 87 772 autopsies, and the prevalence of intracerebral aneurysm was reported to be 1.6% (Jellinger 1979). Bannerman *et al.* reviewed 51 360 autopsies and reported a 1.43% prevalence of intracranial aneurysms, of which 0.34% were ruptured and 1.09% unruptured (Bannerman *et al.* 1970).

In large forensic clinical and autopsy studies, the following locations of cerebral aneurysms have been reported: internal carotid artery (ICA) 24-41%, anterior cerebral artery (ACA) 30-39%, middle cerebral artery (MCA) 20-33%, and vertebrobasilar arteries (VBA) 4-12% (Weir & MacDonald 1996). In Finland, the predominance of MCA aneurysms has been reported in several series (Pakarinen 1967, Fogelholm 1981, Rinne *et al.* 1994). In epidemiologic studies of the population in Eastern Finland, up to 43% of the aneurysms were located in MCA, and one third were multiple (Rinne *et al.* 1994, Rinne *et al.* 1996).

2.2.2 Subarachnoid hemorrhage

The typical clinical presentation of SAH includes sudden and severe headache, which may be associated with loss of consciousness, nausea, vomiting, neck stiffness, or focal neurological deficits (Mayberg *et al.* 1994). Historically, SAH was diagnosed by lumbar

puncture, but CT scanning has become the primary diagnostic tool since its introduction in the 1970´s. SAH is a medical emergency associated with a high rate of mortality.

According to the literature, the global incidence of SAH is 10.5 per 100 000 person years (van Gijn & Rinkel 2001). The incidence has been reported to be higher in Finland and in Japan than elsewhere in the world (Linn *et al.* 1996, van Gijn & Rinkel 2001). According to the combined data of three Finnish studies, the incidence of SAH is 21.4 (95% CI, 19.5 to 23.4) per 100 000 person years (Aho & Fogelholm 1974, Sivenius *et al.* 1985, Sarti *et al.* 1991). Among adults aged >30 years, the annual incidence rates of SAH have been estimated to range from 30 to 60 per 100 000 (Juvela 2001, Juvela 2004). In a historical series by Pakarinen (1967), the incidence of SAH was highest during the 6th decade (38.6 per 100 000 person years), but in a more recent study by Fogelholm (1981), the incidence of aneurysmal SAH increased almost linearly with increasing age. Female gender predisposes towards SAH in the age group of over 40 years, most probably due to hormonal factors (Kongable *et al.* 1996). In Finnish series, however, males have been more often affected than females (Sarti *et al.* 1991, Hernesniemi *et al.* 1993, Rinne *et al.* 1995). The male dominance may result from a high incidence of atherosclerosis, which is also assumed to be one etiological factor for aneurysm formation (Rinne *et al.* 1993). In addition to advanced age and female gender, cigarette smoking, hypertension, and alcohol abuse have also been recognized as risk factors for SAH (Juvela *et al.* 1993, Teunissen *et al.* 1996, Juvela *et al.* 2000).

The etiology of SAH includes a ruptured intracranial aneurysm in more than 80% of cases (van Gijn & Rinkel 2001). Intracranial dissections, cerebral AVMs and other cerebral vascular malformations, dural AVFs, trauma, bleeding disorders, substance abuse, spinal origin of the hemorrhage, and other rare conditions explain less than 5% of primary SAH (van Gijn & Rinkel 2001). Perimesencephalic nonaneurysmal SAH accounts for up to 15% of cases (Ronkainen & Hernesniemi 1992). In cases of perimesencephalic SAH, CT and MRI findings differ from those in aneurysmal SAH in that the maximum amount of blood is located anterior to the pons, possibly extending to the ambient cisterns or the basal parts of Sylvian cisterns (Rinkel *et al.* 1991). However, 16.6 % of ruptured VBA aneurysms have the typical perimesencephalic SAH pattern in CT scans (Alen *et al.* 2003), indicating the need for angiography for all cases of SAH. The etiology of perimesencephalic SAH is still unknown, but it may result from the rupture of a small perforating artery or micro-AVM or be of venous origin, reflecting their benign natural history (Ronkainen & Hernesniemi 1992, van der Schaaf *et al.* 2004).

2.2.3 Symptomatic unruptured aneurysms

Depending on their size and location, unruptured aneurysms may cause symptoms such as pain, cranial nerve dysfunction, sensory-motoric disturbance, seizure, or cerebral ischemia.

Aneurysms may exert a mass effect on the adjacent neuronal and vascular structures and thereby produce progressive neurological deficits (Barrow & Cowley 1995). Raps *et al.* (1993) found that more than 80% of the aneurysms in symptomatic patients were at least 11 mm in diameter, but only 32% of the aneurysms in asymptomatic patients

reached this size. Approximately half of the symptoms due to discovered unruptured aneurysms are attributable to cranial nerve compression (Wiebers *et al.* 1987). When such symptomatic aneurysms were embolized, Halbach *et al.* (1994) noticed that the size of the aneurysm markedly decreased in some patients but remained unchanged in others. However, alleviation of symptoms occurred both in the patients whose aneurysm was reduced in size and in those with no size reduction. Rodriquez-Catarino *et al.* (2003) noticed alleviation of symptoms (cranial nerve dysfunction and/or headache) in the patients whose aneurysms actually increased in size after the embolization. These findings suggest that the resolution or improvement of the symptoms may be related to the reduction of the pulsatile effect of the aneurysmal sac rather than the size of the aneurysm (Rodriquez-Catarino *et al.* 2003).

Intracavernous ICA aneurysms may cause ophthalmoplegias associated with compression of the oculomotor, trochlear, and/or abducens nerves (Linskey *et al.* 1990, Wallace *et al.* 1990) or may trigger trigeminal dysaesthesia and pain (Rodman & Awad 1993). Such an aneurysm may also compromise orbital venous drainage and result in exophthalmus (Rhoton & Day 1990). Ophthalmic artery aneurysms may cause central scotoma or nasal hemianopia by compression of the optic nerve (Day 1990). PcomA aneurysms may compress the oculomotor nerve with a clinical presentation of ipsilateral ptosis, mydriasis, and paralysis of the dependent extraocular muscles (Kissel *et al.* 1983, Wallace *et al.* 1990). Large MCA aneurysms may cause contralateral hemiparesis, contralateral sensory loss, or seizures (Stewart *et al.* 1980). Large AcomA aneurysms may present with hypothalamic-pituitary dysfunction (Rodman & Awad 1993), visual field defects (Aoki 1988), or paresis (Maiuri *et al.* 1986). BA tip or BA trunk aneurysms can cause symptoms associated with brainstem compression such as lower cranial nerve palsies or tetraparesis, or they may obstruct the aqueduct of Sylvius and lead to hydrocephalus (Barnett 1968, Bull 1969, Ekbom & Greitz 1971). Aneurysms at the VA-BA junction or the PICA origin may cause lower cranial nerve palsies or a partial lateral medullary (Wallenberg's) syndrome (Salcman *et al.* 1990).

Presentation with symptoms of cerebral ischemia or TIA is not directly related to the aneurysm site (Khanna *et al.* 1996). Intra-aneurysmal thrombus formation is typically associated with large and giant aneurysms, but may occasionally also be present in small aneurysms (Wiebers *et al.* 1987). An unstable intraluminal thrombus can migrate and thus cause thromboembolic symptoms in the vascular territory adjacent to the aneurysm, which increases the risk of complications in the treatment of such aneurysms (Wirth *et al.* 1983, Wiebers *et al.* 1987).

2.2.4 Asymptomatic unruptured aneurysms

Asymptomatic aneurysms are most commonly discovered coincidental to SAH in patients with multiple intracranial aneurysms (Byrne & Guglielmi 1998). Up to one third of the patients have multiple aneurysms (Rinne *et al.* 1994, Wiebers *et al.* 2003). During the past two decades, the new and improved diagnostic tools (DSA, CTA, MRI, MRA) have increased the number of asymptomatic unruptured aneurysms detected (Juvela *et al.* 2000, Wiebers *et al.* 2003). The current active treatment of even old patients with poor

grade SAH also reveals more unruptured aneurysms compared to the more conservative treatment policy applied to this group of patients in the past (Fogelholm *et al.* 1993, Juvela *et al.* 2000).

As previously reviewed, the relatively high prevalence of intracranial aneurysms in the general population (Bannerman 1970, Jellinger 1979, Byrne & Guglielmi 1998) compared with the low incidence of SAH (Linn *et al.* 1996, van Gijn & Rinkel 2001) indicates that the majority of the population with intracranial aneurysm(s) do not suffer aneurysm rupture. Because the treatment of asymptomatic unruptured aneurysms is focused on preventing future bleeding, the risks related to treatment must be evaluated in the light of the present knowledge of the natural course of such aneurysms.

The natural course of unruptured aneurysms has been poorly understood because of the paucity of studies with sufficiently large patient series and sufficiently long follow-up. The studies have also been biased due to surgical selection (only old and poor grade patients remained untreated and constituted the patient series of the studies) (Juvela *et al.* 2000). In the study by Juvela *et al.* (2000), 181 unruptured aneurysms were followed for a mean of 19.7 years, and the annual average incidence of rupture was 1.3%. The cumulative rate of bleeding was 10.5% at 10 years, 23.0% at 20 years, and 30.3% at 30 years after the diagnosis. Cigarette smoking, aneurysm size, and age (inversely) were found to be important factors determining the risk for subsequent aneurysm rupture. The recent large multi-center study (ISUIA) included 1077 patients with no history of SAH (Wiebers *et al.* 2003). In this cohort of patients, the 5-year cumulative rupture rates for anterior circulation aneurysms were 0%, 2.6%, 14.5%, and 40% for aneurysms less than 7mm, 7-12mm, 13-24mm, and 25mm or more in size, respectively, compared with the rates of 2.5%, 14.5%, 18.4%, and 50%, respectively, for the same size categories of posterior circulation aneurysms (PcomA aneurysms were categorized as posterior circulation aneurysms). Overall, three percent of the patients in the untreated cohort experienced aneurysm rupture during the mean follow-up of 4.3 years (Wiebers *et al.* 2003).

2.3 Imaging of intracranial aneurysms

2.3.1 Digital subtraction angiography and 3D rotational angiography

Digital subtraction angiography (DSA) is the gold standard for aneurysm detection (van Gijn & Rinkel 2001). DSA is an invasive technique with a reported complication rate of 1.8-2.1% (Haley *et al.* 1992, Cloft *et al.* 1999). During the past decade, safer contrast agents have become available, and important technical advances have been made, including digital imaging systems, smaller catheters, and hydrophilic guidewires. Dion *et al.* (1987) prospectively analyzed 1002 cerebral angiographies and found the postprocedural ischemic complication rate to be 1.7% during 24 hours, but only one (0.1%) of them was permanent. In addition, 1.8% of the patients suffered ischemia (0.3% permanent) between 24 and 72 hours after angiography. In a more recent prospective

series of 2899 angiographic procedures, the neurologic complication rate was 1.3% (0.7% transient, 0.2% reversible, and 0.5% permanent) (Willinsky *et al.* 2003). The risk of neurologic complications was higher in patients aged 55 years or older, in patients with cardiovascular disease, and when the fluoroscopic time was ten minutes or more. In their prospective study, Bendszus *et al.* (1999) detected new bright lesions by diffusion-weighted MRI in 26% of 66 consecutive patients after diagnostic cerebral angiography. No new neurological deficits were found in any of the patients, indicating that embolic events after diagnostic cerebral angiography are much more frequent than apparent neurological complications. The appearance of lesions correlated significantly with difficulties in catheterization, the amount of contrast media needed, and the fluoroscopy time (Bendszus *et al.* 1999).

Three-dimensional rotational angiography (3DRA) involves a novel software application that reconstructs standard rotational angiographic data into a computer rendering that can be manipulated by the operator at any angle or viewpoint (Albuquerque *et al.* 2002). A good correlation of 3DRA images with surgical anatomy has been demonstrated by Tanoue *et al.* (2000). The utility of this technique in planning either surgical or endovascular treatment of cerebral aneurysms has also been demonstrated (Tanoue *et al.* 2000, Anxionnat *et al.* 2001, Albuquerque *et al.* 2002).

2.3.2 Computerized tomography angiography

Computerized tomographic angiography (CTA) is based on volumetric scanning of the brain after intravenous administration of contrast medium. The quality of CTA images has been improved by the multislice technology and the development of postprocessing hardware and software. Single-row helical CT scanners have been reported to yield 91% sensitivity and 95% specificity (Pedersen *et al.* 2001), when compared to DSA, whereas the reported rates of multislice CT scanners are 96% and 97%, respectively (Kangasniemi *et al.* 2004). CTA is less invasive than DSA and has the potential advantage that it can be performed at the time when SAH is detected by CT. However, small (<2mm) and partially thrombosed aneurysms may be missed by CTA even in experienced centers (Kangasniemi *et al.* 2004). In the study by Kangasniemi *et al.* (2004), the patients were studied with a 4-row CT scanner. By now, 64-row scanners enabling ≤0.4 mm isotropic voxel are available, but no comparative studies with DSA have yet been published. The value of CTA is limited to postoperative imaging due to the artefacts caused by clip or coil mesh, which make the evaluation of the aneurysm base very difficult. In a series by Kivisaari (2005), a remarkably low rate, i.e. 2%, of incomplete closures after microsurgical clipping of intracranial aneurysms was detected by CTA, while in their previous series (Kivisaari *et al.* 2004) DSA revealed an unexpected aneurysm residual in 7.3% of the clipped aneurysms. The low figures for residual necks raise a question of the reliability of CTA in the postoperative evaluation of treated aneurysms.

2.3.3 Magnetic resonance angiography

Magnetic resonance angiography (MRA) is a non-invasive method for the detection of intracranial aneurysms. MRA source images are usually acquired through the circle of Willis, using a three-dimensional single slab time of flight technique (3D TOF) (Kähärä *et al.* 1999a, Adams *et al.* 2000). The source images are postprocessed equally to CTA. The advantages of MRA include non-invasiveness, lack of radiation, and good visualization of the intra-aneurysmal thrombus and the adjacent brain parenchyma. Its usefulness is, however, limited in the case of small aneurysms and aneurysms located close to the skull base. In the series of Okahara *et al.* (2002), the sensitivity of 3D TOF in detecting intracranial aneurysms varied from 60% to 79%, depending on the experience of the reader, and its specificity was 77-86%, respectively, when compared to 3DRA. Contrast-enhanced MRA with ultrafast imaging sequences and image subtraction has been established as superior to 3D TOF in accurately depicting experimental lateral aneurysms in canines (Masaryk *et al.* 2000) and also in the assessment of recently ruptured intracranial aneurysms in a clinical trial (Unlu *et al.* 2005). Phase-contrast MRA has also been used in detecting intracranial aneurysms. However, this technique has pitfalls arising from the complex flow within aneurysms, and some aneurysms may be missed due to signal loss (Araki *et al.* 1994). MRA has also been used in follow-up studies of previously coiled aneurysms. The sensitivity of 3D TOF MRA compared with DSA for the detection of residual aneurysm has ranged between 71% and 97% and the specificity in ruling out residual filling in aneurysms from 89% to 100%, respectively (Nome *et al.* 2002, Okahara *et al.* 2004, Yamada *et al.* 2004, Westerlaan *et al.* 2005).

2.4 Surgical treatment of intracranial aneurysms

The goal of the treatment of an intracranial aneurysm is to prevent rupture or rerupture by excluding the aneurysm from the circulation. In the case of symptomatic unruptured aneurysms, the indication for treatment may also be a need for resolution or improvement of the symptoms.

2.4.1 History

A ruptured intracranial aneurysm was operated for the first time in 1931, when the surgeon Dott packed an aneurysm sac with muscle (Dott 1933). In 1938, Walter Dandy was the first surgeon to clip the aneurysm neck (Dandy 1938). However, the results of surgical treatment remained poor until the 1960's, when the advanced neurosurgical techniques and neuroanesthesia enabled better patient outcomes (Drake 1981).

Microsurgical aneurysm clipping was introduced by Yasargil in the 1970's, after which it has been the gold standard technique in aneurysm surgery (Yasargil & Fox 1975). Alternative surgical techniques for treating unclippable aneurysms include proximal

vessel occlusion with or without extracranial-intracranial bypass, trapping, wrapping, or excision of the aneurysm (Yasargil 1984, Drake *et al.* 1996, Roski & Spetzler 1996).

2.4.2 Angiographic results

When an aneurysm is clipped, the base of the aneurysm is closed, and the walls of the parent artery are apposed for continuous endothelial lining. When the clip is optimally positioned, the aneurysm is totally occluded, leaving the parent artery intact. Complete closure of the aneurysm is crucial to prevent its rupture (Drake *et al.* 1984, Hernesniemi *et al.* 1993). Despite the importance of optimal clip positioning, postoperative angiograms are seldom performed after aneurysm clipping in many centers. In a recent study by Kivisaari *et al.* (2004), a consecutive series of 808 patients with surgically clipped aneurysms (493 ruptured and 315 unruptured) underwent postoperative angiography, and 88% of the aneurysms were completely occluded, 9% had a neck remnant, and 3% were found to have a fundus remnant. In 61% of the cases, the incomplete closure was unexpected. The results of posterior circulation aneurysms or large to giant aneurysms were inferior to those of anterior circulation aneurysms or small aneurysms. In this series, major vessel occlusion occurred in 5% of the procedures. In another consecutive series of 305 clipped aneurysms by Sindou *et al.* (1998), 5.9% of the aneurysms were incompletely occluded in control angiography performed two weeks after the operation. A literature review of six series of surgically treated aneurysms during 1979-1999 (1569 clipped aneurysms) reported a summarized overall incidence of 5.2% of incompletely occluded aneurysms (Thornton *et al.* 2000). In a prospective randomized study by Vanninen *et al.* (57 patients), 74% of the surgically treated aneurysms were considered to be totally occluded (though only 50 of these patients underwent control angiography). In an international subarachnoid aneurysm trial (ISAT), 47% of the surgically treated patients (965 alive at one year) underwent control angiography 6 months after the treatment. Complete occlusion was detected in 82% of the aneurysms, while 12% had a neck remnant or subtotal occlusion, and 6% were incompletely occluded (Molyneux *et al.* 2005).

2.4.3 Clinical results

2.4.3.1 Procedural complications, morbidity and mortality

In a prospective multi-center study from Sweden including 355 operations for acutely ruptured aneurysms, a 30 % procedural complication rate was reported, resulting in 6.2% procedural morbidity and 1.7% procedural mortality (Fridriksson *et al.* 2002). Intraoperative aneurysm rupture occurred in 18% of the procedures, brain edema in 8.5%, and arterial occlusion in 3.4%. Seiler *et al.* (1988) reported procedural morbidity and mortality rates of 2.6% and 3.5% in their series of 115 ruptured aneurysms. In the retrospective analysis of 1150 patients by Hernesniemi *et al.* (1993), the procedural

morbidity and mortality rates were 6.9% and 3.9%, respectively. Vanninen *et al.* (1999) reported procedural morbidity and mortality rates of 4% and 4%, respectively, in a surgically treated series of patients with acutely ruptured intracranial aneurysms.

2.4.3.2 Rebleedings

The purpose of aneurysm treatment is to prevent ruptured aneurysms from rebleeding and unruptured aneurysms from rupturing. Rebleeding after surgical clipping is rare. However, incomplete treatment of an aneurysm may result in recurrent hemorrhage (Lin *et al.* 1989). Aneurysm regrowth is possible even after a successful operation with perfect clip positioning on immediate control (based on angiography or the surgeon's judgment). The clip may slip from the aneurysm neck, or growth may apparently occur from a tiny neck remnant that has remained unobserved after the clipping (Drake *et al.* 1984, Lin *et al.* 1989).

In the ISAT study, 13 of the 1070 surgically treated patients (1.2%) experienced rebleeding after clipping within a mean follow-up of four years (Molyneux *et al.* 2005). Most of the rebleedings (11) occurred during the first year, and 7/13 (54%) of them were fatal. In a national study in Sweden, 5 rebleedings with poor outcome were reported among 355 clipped aneurysms (1.4%) during six months of follow-up (Fridriksson *et al.* 2002). Tsutsumi *et al.* (1998) reported six rebleedings among 220 patients with angiographically proven, completely clipped aneurysms (2.7%) during a mean follow-up of 9.9 years (range 3-17 years). Two of the rebleedings were judged to be from *de novo* aneurysms, while four were considered recurrences of previously clipped aneurysms. By the Kaplan-Meier method, the cumulative risk for recurrent SAH was calculated to be as high as 2.2% at ten years and 9.0% at twenty years after the initial treatment (Tsutsumi *et al.* 1998).

In a recent long-term clinical follow-up analysis by Wermer *et al.* (2005b), a cohort of 752 patients (mean follow-up 8.0 years) who had undergone successful aneurysm clipping due to ruptured intracranial aneurysms were interviewed about new episodes of SAH after discharge. A recurrent SAH was detected in 18 patients (2.4%), and ten of them died due to recurrent bleeding. In addition, there were two patients who suffered a sudden death with a history suggestive of SAH. The annual incidence of recurrent SAH in this cohort was calculated to be 286 per 100 000, which is 22 times higher than the population-based incidence (13 per 100 000). The cumulative incidence of recurrent SAH in the first ten years after the index SAH was 3.5%, if the two patients with sudden death due to possible SAH were included. In an analysis of CTA or DSA images, 19 aneurysms were found in 18 patients with recurrent bleeding. Four of the aneurysms were classified as possible regrowth of the clipped aneurysm, four as additional aneurysms, four as *de novo* aneurysms and the remaining seven as possible *de novo* aneurysms (Wermer *et al.* 2005b).

2.4.3.3 Clinical outcome

The clinical outcome after aneurysm surgery is strongly dependent on the severity of the subarachnoid hemorrhage. In a prospective International Cooperative Study on the Timing of Aneurysm Surgery in a total of 3521 SAH patients (2922 of the patients underwent surgery) with ruptured aneurysm, the prognostic factors for poor clinical outcome were a high H&H grade (Table 1) at admittance, a high Fisher grade (Table 2) in CT scan, a large size of the aneurysm, advanced age, and high blood pressure (Kassell *et al.* 1990a, Kassell *et al.* 1990b). The clinical outcomes (graded by Glasgow Outcome Scale, Table 3) in a recent large selected surgical series are summarized in Table 4. All the patients in Table 4 had SAH due to a ruptured intracranial aneurysm.

Table 1. Hunt & Hess grading scale for evaluating the clinical condition of patients with a history of subarachnoid hemorrhage (Hunt & Hess 1968).

Grade	Description
0	No bleeding
1	Asymptomatic, or minimal headache and slight nuchal rigidity
2	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
3	Drowsiness, confusion, or mild local deficit
4	Stupor, moderate to severe hemiplegia, possibly early decerebrate rigidity, and vegetative disturbances
5	Deep coma, decerebrate rigidity, moribund appearance

Table 2. Fisher grading scale for evaluating the amount of blood in CT scan (Fisher et al. *1980).*

Grade	Description
0	No CT scan
1	No SAH
2	Diffuse SAH, less than 1 mm thick
3	Localized clots of layers of hemorrhage 1mm or thicker
4	IVH or ICH with or without SAH
5	SAH, unknown grade

Table 3. Glasgow Outcome Scale for assessing clinical outcome after treatment (Jennet & Bond 1975).

Grade	Brief description	Full description
5	Good recovery	Full and independent life, no or minimal neurological deficit
4	Moderately disabled	Moderately disabled, neurological deficit, or intellectual impairment, but independent life)
3	Severely disabled	Conscious, but totally dependent on others
2	Vegetative stage	Vegetative survival
1	Dead	Dead

Table 4. Clinical outcomes in a surgical series. The numbers in H&H and GOS grades represent percentages of patients in the current study. The results of the study by Molyneux et al. *(2005) are modified according to H&H and GOS.*

Study	No. of patients	Mean f-u months	H&H 1-2	H&H 3	H&H 4-5	GOS 4-5	GOS 2-3	GOS 1
Seiler *et al.* 1988	115	6	66	17	17	85	7	8
Kassell *et al.* 1990b	2922	6	64	25	11	78	8	14
Hernesniemi *et al.* 1993	947	12	59	31	10	78	9	13
Osawa *et al.* 2001	2055	at discharge	51	31	21	69	19	12
Molyneux *et al.* 2005	1055	12	88 (WFNS)	6 (WFNS)	4 (WFNS)	69 (mRS0-2)	21 (mRS3-5)	10 (mRS6)

No. = number, H&H = Hunt & Hess grade, GOS = Glasgow outcome scale, WFNS = World Federation of Neurological Surgeons grading scale (Johnson *et al.* 2001), mRS = modified Rankin scale (Rankin 1957)

2.5 Endovascular treatment

2.5.1 Development of endovascular techniques

2.5.1.1 History

Endovascular techniques were first developed for aneurysms that were considered inoperable due to their location, size, intraluminal thrombosis, atherosclerosis in the neck or dome, or calcifications in the wall. Several endovascular techniques have been introduced during the past decades. Serbinenko (1974) published the first results of endovascular balloon occlusion of the carotid artery for treatment of unclippable aneurysms. Endovascular parent artery occlusion by detachable balloons had several advantages over surgical ligation. It enabled clinical and angiographic test occlusion prior to permanent occlusion and subsequent analysis of collateral flow and evaluation of the need for preliminary bypass surgery (Higashida *et al.* 1989, Halbach *et al.* 1990, Higashida *et al.* 1991). Unlike proximal surgical ligation, the detachable balloon could be positioned more cranially in ICA, i.e. in the C3-C4 segment, to prevent collateral flow from the external carotid artery. Satisfactory results were published on the treatment of inoperable ICA and VBA aneurysms (Berenstein *et al.* 1984, Fox *et al.* 1987,Higashida *et al.* 1990, Aymard *et al.* 1991, Larson *et al.* 1995). Despite the different test occlusion protocols and bypass operations, watershed infarctions occurred in about 10% of the cases in the ipsilateral hemisphere after permanent occlusion (Linskey *et al.* 1994).

Later on, detachable silicone balloons were also used to fill the lumen of the aneurysm instead of sacrificing the parent artery in an attempt to prevent future bleeding (Romodanov & Shcheglov 1982, Higashida *et al.* 1991, Moret 1991). The initial results

obtained with this technique were good, but due to technical problems, including high morbidity and mortality rates, and poor long-term results, it has since been abandoned. In the late 1980's, coils were introduced to fill the lumen of an inoperable aneurysm (Hilal & Solomon 1992, Casasco *et al.* 1993). The coils were made of steel or platinum, and they were pushed through a microcatheter with a separate steel wire, called coilpusher. These free coils were impossible to control during deposition, and coil migrations into the parent vessel complicated the procedures. The rigidity of these free coils did not allow the aneurysm to be completely filled in many cases.

2.5.1.2 Introduction of GDC

Guido Guglielmi introduced his Guglielmi Detachable Coils (GDC) in 1991, which revolutionized the endovascular treatment of cerebral aneurysms (Guglielmi *et al.* 1991a, Guglielmi *et al.* 1991b). The GDC is made of platinum and attached to a stainless steel wire. These coils are longer and softer than free coils and thus easier to deploy. GDCs are pushed into the aneurysm sac through a microcatheter, and they can be repositioned, retrieved, or replaced by a coil of different size, until the situation is considered satisfactory. GDCs are detached from the deploying wire by electrolysis. The electric current for detachment is created by an external power supply, which is connected to the pushing wire at its proximal part and to the patient (needle inserted through the skin into soft tissue, usually groin). On January 29, 1991, the first patient was treated in the clinical trial at UCLA. This novel technique spread rapidly throughout the world, and by September 1996, more than 16000 patients had already been treated with the GDC technique (Malisch *et al.* 1997).

2.5.1.3 Further development in coil technology

In the late 1990's, softer GDC Soft coils were introduced as well as 2D and 3D shaped coils. Later, even softer GDC Ultrasoft coils have become available. The development of softer coils enabled better filling of the aneurysms and safer deployment in small aneurysms compared to the original GDC. Three-dimensional coil (3D-GDC) was developed for wide-necked aneurysms, to prevent coil protrusion when additional coils are inserted into the aneurysm (Cloft *et al.* 2000). Later on, different platinum coils with different detachment technologies have become commercially available. Some of them are mechanically (IDC, Target Therapeutics, Fremont, CA and DCS, William Cook Europe A/S, Bjeverskov, Denmark) and some hydraulically (TruFill DCS, Cordis, Miami, Fl and Microplex, Microvention, Aliso Viejo, CA) detached (Cekirge *et al.* 1996, Reidy & Qureshi 1996, Sugiu *et al.* 2004, Lubicz *et al.* 2005a). Competitive platinum coils (Dendron /Sapphire, Micro Therapeutics, Bochum, Germany and Micrus Microcoil System, Micrus Corporation, Mountain View, CA) with an electrolytic detachment system were developed (Lubicz *et al.* 2004). Despite the variety of detachment systems used, the basic procedure is similar to GDC, enabling repositioning, retrieval, and replacement of the coil before detachment. Cordis developed complex-shaped TruFill

coils, which enable concentric packing of the aneurysm with 3D-shaped coils used alone. New TruFill Orbit (Cordis, Miami, Fl) coils have recently been introduced and are the first 3D coils available in all sizes from 2mm to 20 mm. In an experimental study, Piotin *et al.* (2003a) showed that optimal packing of a small silicone aneurysm model was achieved with 3D-shaped coils used only in a concentric fashion. Lubicz *et al.* (2005b) reported, in their preliminary study with TruFill Orbit coils, that complex coils have a propensity to form a 3D cage after deployment, and their conformability is superior to that of helical coils, with subsequently less compartmentalization and more homogenous aneurysm filling. In a recent study by Slob *et al.* (2005), complex TruFill coils with a wire diameter of 0.012 inches enabled significantly better packing compared with helical GDC with a wire diameter of 0.010 inches, and the retreatment rate was lower for Trufill coils than GDC.

Although GDC and other detachable platinum coils have proved to be reliable and effective in the short term (to be reviewed later in detail), aneurysm recanalization due to coil compaction has emerged as a major long-term drawback of this technique. To avoid recanalization, several new types of coils have been under investigation. So far, clinical experience is available of biologically active coils (Murayama *et al.* 2003a), radioactive coils (Raymond *et al.* 2002), and hydrogel-coated coils (Cloft & Kallmes 2004). The aims of these new therapeutic tools are to promote intra-aneurysmal clot organization and fibrosis (Raymond *et al.* 2002, Murayama *et al.* 2003a) or to increase packing attenuation (Cloft & Kallmes 2004), which is associated with a higher long-term occlusion rate (Tamatani *et al.* 2002, Sluzewski *et al.* 2004).

Matrix (Boston Scientific, Target Therapeutics, Fremont, CA) consists of a thin platinum coil covered with bioabsorbable, polymeric material (polyglygolic acid/lactide) (Murayama *et al.* 2003a). Murayama *et al.* (2003a) compared Matrix and GDC in experimental aneurysms in swine. They found that aneurysms treated with Matrix coils exhibited a more extensive area of organized thrombus than those treated with GDC at 14 days after embolization. At 3 months, both Matrix and GDC-treated aneurysms demonstrated complete clot organization. Neck tissue thickness was greater in the Matrix-treated aneurysms at 14 days and 3 months, but not at 6 months. No untoward parent artery stenosis during follow-up was observed in the aneurysms treated with Matrix. The angiographic cross-sectional area at 3 months was smaller in the Matrix-treated aneurysms than in those treated with GDC. A prospective, multicenter study (called ACTIVE study) evaluated the potential benefits of Matrix coils in the treatment of cerebral aneurysms (*Matrix newsletter* 2004). During 12 months' follow-up, 16% of the aneurysms were retreated and 7% of the aneurysms had bled. On the basis of the ACTIVE study, the benefits of Matrix over standard platinum coils remained questionable (Sluzewski & van Rooij 2005a). In a recent sigle-center analysis, Niimi *et al.* (2006) reported their experience of Matrix coils in the treatment of 74 aneurysms. The use of Matrix coils resulted in a 17.6% complete occlusion rate and a 57.4% overall recanalization rate, which figures are worse than those reported for GDC bare platinum coils. The main cause for the poor initial occlusion grades was considered to be the high friction of Matrix coils, which might result in compartmentalization of the coils within the aneurysm and prevent dense packing. The absorbable nature of the bioactive coating may also explain the high recanalization rate. However, a new generation of Matrix coils

(Matrix 2, Boston Scientific, Fremont, CA) have already been available since 2005. They cause less friction and have a complex shape meant to overcome these problems.

Beta radiation has proved to be effective in preventing recanalization of coiled aneurysms in experimental models (Raymond *et al.* 2002a). To assess the feasibility of radioactive coils in clinical use, Raymond *et al.* (2003a) treated 40 aneurysms with platinum coils, which were ion-implanted with 0.13 to 0.26 microCi/cm of phosphorus (isotope 32) prior to deployment. The calculated target volumetric activity of 0.018 microCi/mm3 could be reached in 88% of the aneurysms. Angiographic recurrences occurred in 31% of the patients during 6 months' follow-up, which the authors think is within the expected range for standard coils. On the basis of this initial clinical experience, the target activities in intracranial aneurysms can be reached by inserting radioactive coils into the aneurysm sac, but the clinical benefits of radioactive coils over standard platinum coils in preventing recanalization could not be proved (Raymond *et al.* 2003a).

The Hydrocoil Embolic System (HES; Micro Vention, Aliso Viejo, CA) consists of a hybrid hydrogel-platinum coil with an initial diameter of 0.009 inch and an expanded diameter of 0.027 inch. In blood, the Hydrocoil swells to its maximum diameter in about 20 minutes (Kallmes & Fujiwara 2002). Cloft & Kallmes (2004) reported their initial experience with the HES in 11 cerebral aneurysms. The authors compared their findings to size-matched cases they had previously treated with platinum coils. They used standard platinum coils at the beginning of the coiling procedure to create a basket, which they then filled with Hydrocoils, and they finished the procedure with soft platinum coils. The HES provided improved packing of the aneurysm lumen relative to standard platinum coils (volumetric filling of the aneurysm 72% vs. 32%, p=0.001). Although these initial results of the HES were promising, showing improvement of aneurysm packing, further larger series with follow-up will be necessary to investigate whether the findings ultimately correlate with a decreased rate of aneurysm recurrence and better clinical outcomes.

2.5.1.4 Liquid embolic material

Ethylene vinyl alcohol copolymer dissolved in the organic solvent dimethyl sulfoxide (Onyx, Micro Therapeutics, Irvine, CA) is a liquid embolic material meant for endovascular use. In contact with an aqueous solution, Onyx precipitates and forms a soft spongy polymer cast, initially with a more solid outer layer and a semi-liquid center. As further material is injected into the cast, it fills the space into which it is injected before breaking out through the outer layer of the existing cast. In the treatment of intracranial aneurysms, the material is constrained by the placement of a balloon over the neck of the aneurysm. It takes about ten minutes for Onyx to completely solidify. (Molyneux *et al.* 2004)

Despite the good overall initial and follow-up results of embolization with detachable coils, the results in cases of large and giant aneurysms are significantly inferior to those of small aneurysms due to coil compaction and recanalization (Gruber *et al.* 1999, Murayama *et al.* 2003b, Sluzewski *et al.* 2003). Surgical clipping of large and especially

giant aneurysms carries high risks for morbidity and mortality, and surgery is not a good option to treat such aneurysms, either (Brennan & Schwartz 2000, Thorell *et al.* 2004). In the reported clinical series, the use of Onyx for intracranial aneurysm embolization, has been mainly targeted to treat these challenging lesions (Mawad *et al.* 2002, Molyneux *et al.* 2004, Lubicz *et al.* 2005b, Weber *et al.* 2005, Cekirge *et al.* 2006).

In the Cerebral Aneurysm Multicenter European Onyx (CAMEO) trial, complete occlusion was achieved in 79% of the 71 aneurysms for which the results of 12-month follow-up angiography were available (Molyneux *et al.* 2004). The procedure or device related permanent morbidity and mortality rates were 8.2% and 2.1%, respectively. Delayed parent artery occlusion was detected in 9% of the cases. Weber *et al.* (2005) reported their experience of 22 unruptured, wide-necked large or giant aneurysms treated with Onyx. In follow-up, they had total occlusion in 90% of the cases without permanent morbidity or mortality. Parent artery occlusion or stenosis was detected in 19% of the cases. In the study of Lubicz *et al.* (2005b), 11 small and 30 large or giant aneurysms were treated with Onyx. All aneurysms were judged to be unsuitable for regular treatment. In the case of small aneurysms, total occlusion was initially achieved in all of the aneurysms, and procedure related morbidity and mortality rates were 10% and 0%, respectively. In the case of large or giant aneurysms, total occlusion was achieved in 63% of the aneurysms, with procedural morbidity and mortality rates of 7% and 3%, respectively. The combined procedural complication rate for both groups was 21%. Liquid migration was observed in 10% of the treatments and parent artery stenosis in 5%. In a recent single-center analysis by Cekirge *et al.* (2006), the angiographic and clinical results of 100 consecutive intracranial aneurysms (all except two were located in ICA) treated by Onyx with or without an adjunctive stent were reported. Complete occlusion was achieved in 90% of the aneurysms, and the recanalization rate in follow-up angiography was 12.5%. Permanent neurological morbidity was assessed to be 8.3% and mortality 3.2%. The authors concluded that this treatment provides more stable results than any other treatment option in internal carotid artery aneurysms (Cekirge *et al.* 2006).

2.5.1.5 Remodeling techniques

The standard coil embolization technique is limited by its inability to occlude wide-necked aneurysms (Fernandez *et al.* 1994, Debrun *et al.* 1998). To overcome this problem, the balloon-assisted remodeling technique was first introduced by Moret *et al.* (1994). This technique consists of temporary inflation of a balloon across the aneurysm neck during embolization to avoid inadvertent coil protrusion into the parent artery. Traditionally, two types of balloon have been available to perform balloon-assisted coil placement in cerebral aneurysms: oval, guide-dependent balloons for sidewall aneurysms and round, flow-directed balloons for bifurcation aneurysms. A novel, more compliant, guide-dependent oval balloon (Hyperform, Micro Therapeutics, Irvine, CA) has been developed for the difficult anatomical situations where regular balloons are not feasible (Baldi *et al.* 2003). The compliance of this balloon is a mechanical property defined by the propensity of the balloon to change its cylindrical shape to fit the anatomy of the vessel in which it is inflated. It is more effective than round, flow-directed balloons in the

treatment of bifurcation aneurysms, because it is easier to position adequately (Baldi *et al.* 2003).

Moret *et al.* (1997) reported the first large series of aneurysms treated with a balloon-assisted technique. They were able to perform successfully 93% of the procedures with morbidity and mortality rates of 1% and 0%, respectively. According to follow-up data, 77% of the treated aneurysms were completely occluded, 17% of them were subtotally occluded, and only 6% of the aneurysms had incomplete occlusion. In two retrospective studies on the use of the balloon-assisted technique in the endovascular treatment of wide-necked aneurysms, the technique appeared to be feasible in 88%-92% of the cases (Aletich *et al.* 2000, Cottier *et al.* 2001). The technical failures were due to the tortuosity of the access vessel or to balloon inadequacies. In a multicenter analysis by Cottier *et al.* (2001), total occlusion of the aneurysms was achieved in 67% of the cases and subtotal occlusion in 24% of the cases, with a complication rate of 4.1% (all of them thromboembolic). Aletich *et al.* (2000) reported total or subtotal occlusion in 78% of the aneurysms, with procedural morbidity and mortality rates of 5.1% and 3.8%, respectively.

A specific neck bridge device was developed to overcome the problems, such as coil protrusion and coil migration, associated with the coil treatment of wide-necked intracranial aneurysms. The Trispan (Boston Scientific/ Target therapeutics, Fremont, CA) device can be placed at the neck of the aneurysm prior to the coil embolization procedure. The device has been designed to allow safe and controlled placement of coils inserted through a second microcatheter (Turk *et al.* 2001). The initial clinical experience with 23 aneurysms reported by Raymond *et al.* (2001) showed that Trispan can be helpful in some situations, but the angiographic results were not very encouraging (total occlusion was achieved in 3 cases, 13%). In one case, the device failed to protect the parent artery, resulting in coil protrusion and parent artery occlusion. The results of this study are not comparable with the other endovascular or surgical series, because only difficult cases were included in this study. However, better anatomic results have been achieved in these difficult aneurysms by the stent-assisted technique, as reviewed later. In accordance with this initial experience by Raymond *et al.* (2001), no other clinical series have been reported. In some extremely difficult cases, however, this technique has been shown to be of great value (Henkes *et al.* 2004a, Mounayer *et al.* 2005).

Endovascular stents can be useful in the treatment of intracranial aneurysms in cases that otherwise could not be treated even with the balloon remodeling technique and when the parent artery cannot be sacrificed. Such aneurysms are either very wide-necked, fusiform, or dissecting (Higashida *et al.* 1997, Lylyk *et al.* 1998, Mericle *et al.* 1998, Sekhon *et al.* 1998, Wilms *et al.* 2000). The stent placed across the aneurysm neck alters the blood flow and redirects the shear stress in such a way that it may lead to partial thrombosis (Barath *et al.* 2005, Canton *et al.* 2005a, Canton *et al.* 2005b, Ohta *et al.* 2005), and in some cases stent(s) alone can be sufficient to occlude the aneurysm (Vanninen *et al.* 2003a, Jamous *et al.* 2005). However, both experimental and clinical results have led to the conclusion that an additional embolic device, for instance, coils or Onyx, is usually needed to occlude the aneurysm sac (Szikora *et al.* 1994, Turjman *et al.* 1994, Lylyk *et al.* 2002, Mawad *et al.* 2002, Kessler *et al.* 2005). The first intracranial stent placements were performed with balloon-expandable stainless-steel stents developed for cardiac use, and the navigation of the device into the tortuous intracranial vasculature was challenging and frequently impossible. Kessler *et al.* (2005) published

the results of 59 patients who underwent combined intracranial stenting with balloon-expandable stent and aneurysm occlusion with either coils or Onyx. They reported a 32% technical complication rate, including seven artery wall perforations (12% of the cases) and nine cases of thrombotic complications (15%). Additionally, they had eight technical complications, including migration or rupture of the stent (14%). The procedural morbidity and mortality rates were 12% and 7%, respectively. The initial angiographic results revealed total occlusion in 75% of the cases. In the series of Lylyk *et al.* (2002) the procedural morbidity and mortality rates were 11% and 6%, respectively. In 93% of the 67 aneurysms, complete or nearly complete occlusion was achieved (Lylyk *et al.* 2002).

Recently, technological developments have enabled the production of more flexible stents with better properties, allowing them to be advanced into the tortuous intracranial vasculature and also allowing treatment of complex wide-necked aneurysms in which endovascular reconstruction of the parent vessel is necessary (Fiorella *et al.* 2005, Higashida *et al.* 2005, Lylyk *et al.* 2005, Pumar *et al.* 2005). These new very-low profile self-expandable stents are made of nitinol, and they are specifically designed for intracranial use. The preliminary clinical results of these stents have been very favorable, but only limited follow-up data are available so far (Fiorella *et al.* 2005). Using the Neuroform stent (Boston Scientific/ Target Therapeutics, Inc., Natick, MA), Lylyk *et al.* (2005) reported procedural morbidity and mortality rates of 8.6% and 2.1%, respectively, among the 48 aneurysms treated. The properties of these novel stents also enable Y-shaped reconstructions of parent vessels in cases of complex very wide-necked bifurcation aneurysms as well as retrograde access to the lesion, as first described by Moret *et al.* (Moret *et al.* 2000, Perez-Arjona & Fessler 2004, Cross *et al.* 2005, Sani & Lopes 2005).

There are limited data in the literature concerning the use of covered stents, called stent-grafts, in the treatment of intracranial aneurysms. When deployed across the aneurysm neck, the stent-graft simply hampers the entry of blood flow into the aneurysm sac and occludes the aneurysm with no need to place any embolic material inside the aneurysm. The use of intracranial stent-grafts is, however, limited to vessel segments where the arterial branches do not originate from the landing area of the device. The currently available devices are relatively stiff and have a poor profile for intracranial navigation, which restricts their use intracranially. Saatci *et al.* (2004) reported 24 patients with ICA aneurysms treated with stent-grafts. Only four of these aneurysms were located intradurally (OphtA), and the rest were located in either petrous or cavernous segments of ICA. Most of the aneurysms were posttraumatic, secondary to motor vehicle accidents or surgical injury. Their outcomes were very promising, as only two endoleaks were noticed, and both of them disappeared during follow-up. Thus, the complete occlusion rate was 100% in follow-up. No procedural complications, morbidity or mortality occurred in this series, and all the symptoms in the patients who had initially presented with mass effects resolved after treatment. Anecdotal case reports of successful stent-graft treatment of lesions in the intracaranial vertebral artery and at the vertebro-basilar junction have also been published (Chiaradio *et al.* 2002, Burbelko *et al.* 2004). The feasibility of this technique was also demonstrated in the emergency treatment of a ruptured iatrogenic intrasellar carotid pseudoaneurysm (Vanninen *et al.* 2003b).

2.5.1.6 Histological findings in coiled aneurysms

The goal of aneurysm treatment by coil embolization is to isolate the lumen of the aneurysm from circulation by neointimal proliferation of the aneurysm orifice. In experimental aneurysms in swines described by Hino *et al.* (2004), electron microscopic scanning (SEM) immediately after the procedure showed platelets and fibrin adherent to the coil surface. A fibrin network had already been formed, but no migration of endothelial cells had occurred. At one week after the procedure, SEM revealed the development of a thick fibrin network, which extensively covered the coil surface, but there were also portions where the coil remained uncovered. Some endothelial cells had entered from the periphery toward the aneurysm orifice. At 3 weeks, the aneurysm orifice was macroscopically covered with a transparent neointima, and in 40% of the aneurysms SEM showed the aneurysm orifice to be covered sufficiently by the vascular endothelial cells, while in 60% of the cases endothelization was not complete. (Hino *et al.* 2004).

The histopathological findings of coil-embolized human aneurysms are based on autopsy reports. Castro *et al.* (1999) reported histopathological findings in two aneurysms of a patient who died 33 months after embolization by GDC. In gross examination, the coils were so firmly attached in the aneurysmal lumen that they could not be removed. In microscopic study, the fundi of both aneurysms were filled with vascular fibrous connective tissue scars that were more dense on the periphery of the sac, where proliferation of inflammatory cells was evident. There was no evidence of residual thrombus. Sections through the neck of one of these aneurysms (OphtA, neck remnant in follow-up angiography) revealed that the ostium was covered by a neointima organized in two layers. The superficial endothelial layer was continuous with the endothelium extending from the lumen of the parent artery. The deeper layer consisted of dense, vascular, and collagenous fibrous tissue aligned parallel to the long axis of the parent vessel (Castro *et al.* 1999). Similar histologic findings were reported by Mawad *et al.* (1995) in experimental work on canines, but in accordance with the findings by Castro *et al.* (1999), they also found smooth muscle cells in the neointima covering the aneurysm neck.

Bavinzki *et al.* (1999) studied 18 aneurysms (17 were harvested at autopsy and one was removed at subsequent surgery) 3 days to 54 months after embolization with GDC. Within one week from the treatment, naked coils embedded in an unorganized thrombus were found. Incomplete replacement of the intraluminal clot by fibrous tissue and partial membranous covering at the aneurysm orifice were observed in the aneurysms that had been treated 2 to 3 weeks prior to the examination. At 6 weeks, an endothelium-lined layer of connective tissue was found at the orifice. The authors concluded that endothelization of the aneurysm orifice after coiling can occur, but tiny open spaces between the coils and incomplete membranous covering of the aneurysm neck were frequently seen, especially in large aneurysms, due to delayed and incomplete clot organization. In 50% of the angiographically completely occluded aneurysms, gross examination revealed tiny open spaces between the coils at the neck. (Bavinzki *et al.* 1999).

Endothelial lining of the aneurysmal wall has been shown to be necessary for the persistence of residual necks as well as for the development of recurrences in

experimental aneurysms (Raymond *et al.* 2002b). Early endothelial invasion of the clot leads to recanalization and recurrence after embolization of aneurysms (Raymond *et al.* 2002b). In addition, endothelial denudation by a neck bridge device before coil deposition has been able to prevent recanalization in canine arteries and to significantly improve angiographic results 3 months after endovascular treatment of experimental bifurcation aneurysms (Raymond *et al.* 2004a). No clinical series using this principle of endothelial denudation prior to coil embolization have been reported.

2.5.2 Angiographic results of endovascular treatment

The initial angiographic results of ten clinical series published after March 1997 are shown summarized in Table 5. Brilstra *et al.* (1999) systematically reviewed all publications from January 1990 to March 1997 and found a total of 48 studies including 1383 patients. A subgroup of this meta-analysis involving seven high-quality studies is also represented in Table 5. Five of these series included only ruptured aneurysms, while the others included both ruptured and unruptured aneurysms. Follow-up results of the series by Vanninen *et al.* (1999) have been published separately by Koivisto *et al.* (2000). These studies cover the same group of patients.

The success of endovascular therapy is usually reported in terms of occlusion rates. Regardless of the ability of endovascular therapy to completely occlude the aneurysm initially, there is also concern regarding the long-term follow-up results for aneurysms that have been completely or incompletely coiled. It has been demonstrated that aneurysm recurrence, coil compaction, and enlargement of residual neck may occur after endovascular treatment. It is thus generally agreed that long-term angiographic follow-up is necessary (Hayakawa *et al.* 2000, Tatamani *et al.* 2002, Thornton *et al.* 2002, Raymond *et al.* 2003b, Sluzewski *et al.* 2004). So far, no studies reporting really long-term angiographic follow-up data (at least 3 years) were found by literature search. The impact of long-term angiographic follow-up for individual patients still needs to be evaluated, as well as the costs for the health care system.

Table 5. Summary of initial and follow-up angiographic results of endovascular series. The percentage in parenthesis indicates the percentage of unruptured aneurysms.

Study	Number of aneurysms	Initial			Follow-up months	Follow-up		
		Complete Occlusion %	Neck remnant %	Incomplete occlusion %		Complete occlusion %	Neck remnant %	Incomplete occlusion %
Brilstra *et al.* 1999	201 (24%)	61	26	13	NA	NA	NA	NA
Raymond& Roy 1997	75 (0%)	40	37	23	6	46	42	12
Kuether *et al.* 1998	74 (60%)	40	52	8	26	41	46	13
Byrne *et al.* 1999	317 (0%)	NA	NA	NA	22	64	34	2
Vanninen *et al.* 1999	52 (0%)	50	35	15	3	67	28	5
Koivisto *et al.* 2000	52 (0%)	50	35	15	12	77	19	4
Ng *et al.* 2002	136 (44%)	46	16	38	NA	NA	NA	NA
Friedman *et al.* 2003	83 (0%)	33	63	5	19	35	61	3
Murayama *et al.* 2003	818 (42%)	55	35	10	NA	NA	NA	NA
Sluzewski *et al.* 2003	160 (0%)	71	22	8	6	59	25	16
Henkes *et al.* 2004	1811 (45%)	66	21	13	NA	NA	NA	NA
Cronqvist *et al.* 2005	46 (65%)	37	50	13	NA	NA	NA	NA
Molyneux *et al.* 2005	881 (0%)	NA	NA	NA	NA	66	26	8
Norbäck *et al.* 2005	239 (0%)	53	21	26	NA	NA	NA	NA

NA = data not applicable

2.5.3 Procedural complications of endovascular treatment

2.5.3.1 Incidence

According to the recent literature, the reported procedural complication rates in clinical series range between 8.4% and 23% (Brilstra *et al.* 1999, Vanninen *et al.* 1999, Ng *et al.* 2002, Friedman *et al.* 2003, Murayama *et al.* 2003b, Henkes *et al.* 2004b, Cronqvist *et al.*

2005, Norbäck *et al.* 2005). In the large series of Henkes *et al.* (2004b), complications occurred in 16% of the procedures in the treatment of ruptured aneurysms and in 19% of the procedures when the treated aneurysm was unruptured. In the meta-analysis of Brilstra *et al.* (1999), the complication rate was 9.6% for ruptured aneurysms and 20% for unruptured aneurysms. Most of the procedural complications are transient or reversible, and only a minority of them cause permanent morbidity and mortality. The reported procedural morbidity and mortality rates range between 3.7% and 9.1%, and between 1.5% and 7.8%, respectively (Raymond & Roy 1997, Kuether *et al.* 1998, Brilstra *et al.* 1999, Vanninen *et al.* 1999, Ng *et al.* 2002, Murayama *et al.* 2003b, Henkes *et al.* 2004b). Friedman *et al.* (2003) reported a procedural complication rate of 13.2%, but their procedural morbidity and mortality rates were as low as 0.8% and 0.8%, respectively.

2.5.3.2 Thromboembolic complications

The endovascular treatment of intracranial aneurysms may be complicated by a transient ischemic attack (TIA) or ischemic stroke (Guglielmi *et al.* 1992, Malich *et al.* 1997, Kuether *et al.* 1998, Murayama *et al.* 1999, Qureshi *et al.* 2000, Derdeyn *et al.* 2002, Henkes *et al.* 2004b). The reported rates for procedural ischemic complications following endovascular treatment of cerebral aneurysms range from 2.7% to 17% (Malich *et al.* 1997, Kuether *et al.* 1998, Pelz *et al.* 1998, Brilstra *et al.* 1999, Murayama *et al.* 1999, Henkes *et al.* 2004b), which means that thromboembolic complications are the most common type of complication in the endovascular treatment of intracranial aneurysms. In the study of Pelz *et al.* (1998), 17 out of 59 patients experienced thromboembolic events (29%), including ten strokes and seven TIAs. In ten patients, the deficits occurred during or immediately after the procedure (17% of the patients), while in seven patients the complications were delayed (12% of the patients). Most of these events can be attributed to thrombosis of the parent or branch arteries from which the aneurysm arises or to distal embolization of a thrombus from the treated aneurysm (Guglielmi *et al.* 1991, Klotzsch *et al.* 1998). The occurrence of ischemic attacks during the embolization procedure can also be caused by a thrombus from the catheter tip or by air embolism (Markus *et al.* 1993). Large aneurysm diameter and coil protrusion have been found to be independent risk factors for postprocedural thromboembolic events (Derdeyn *et al.* 2002). Concerning patients with a ruptured aneurysm and acute SAH, on the basis of their personal experience, Lylyk & Gioino (1996) concluded that thromboembolic complications may be explained by the patient's hypercoagulable stage. Delayed ischemic events occurring hours or days after the procedure may be due to extension of a thrombus into the parent artery from the aneurysm in which coils have been placed or from fragments that break free from within the coil mesh of a treated aneurysm with residual flow in the coil interstices (Derdeyn *et al.* 2002). Occasionally, a delayed ischemic complication may occur as long as nine weeks after the embolization procedure (Studley *et al.* 2002).

Although there is no definitively proved benefit of heparin administration in neuroangiography or in neurointerventional procedures, the anticoagulant effect of heparin should be useful in preventing ischemic periprocedural complications. On the

other hand, excessive concentrations of heparin may induce spontaneous bleeding (Fernandez *et al.* 1986). It is therefore important to use both an adequate and a safe dose of heparin. Continuous administration of heparin in a dose of 20-60 IU/kg/hour has been recommended to maintain an adequate heparin concentration during neurointerventional procedures (Nagai *et al.* 1997).

When procedural thromboembolic occlusion occurs in eloquent brain areas, thrombus disruption (either mechanical or pharmacologic) is mandatory to reestablish arterial blood flow in the absence of collateral circulation (Mounayer *et al.* 2003). The purpose of mechanical disruption is two-fold: to establish flow beyond the thrombus, permitting passage of the fibrinolytic drug, the heparin, and the intrinsic fibrinolytic factors into the occluded area and to increase the surface of the clot accessible to the drug (Barnwell *et al.* 1994). Intra-arterial thrombolysis with fibrinolytics has been widely used to disrupt the complicating clot either alone or combined with mechanical disruption. By intra-arterial administration of urokinase, complete arterial recanalization was attained in 53% of the cases, while in 47% of the cases the effect was partial (Cronqvist *et al.* 1998). In cases of insufficiently coiled, ruptured aneurysms, the use of urokinase may lead to rebleeding from the aneurysm. Cronqvist *et al.* (1998) reported urokinase-related hemorrhage in three out of 19 patients (16%). Two of these patients had aneurysm rerupture, and the third developed ICH, probably due to hemorrhagic transformation of an ischemic lesion. The authors thus concluded that fibrinolytics should only be administered to patients with sufficiently packed aneurysms. Abciximab (glycoprotein IIb/IIIa inhibitor) has been demonstrated to be a safe and effective first-line treatment for patients with ruptured aneurysms and procedural thrombotic complications (Mounayer *et al.* 2003, Aviv *et al.* 2005). Following intravenous bolus administration of abciximab (5-10 mg in 92% of the treatments) to 13 patients, Aviv *et al.* (2005) found complete or partial recanalization of the thrombus in 92% of the cases. They had one bleeding complication following additional coiling after the administration of abciximab, while in three other cases additional coiling did not have any clinical sequelae. In the study of Mounayer *et al.* (2003), the investigators administered an intra-arterial bolus of abciximab (4-10 mg) to 13 patients suffering a procedural thrombotic complication and reported total recanalization of the thrombus in 92% of the treatments with no hemorrhagic complications.

2.5.3.3 Iatrogenic aneurysmal rupture

Aneurysmal rupture during endovascular treatment is one of the most feared complications of endovascular aneurysm treatment. The reported percentage of aneurysmal rupture in clinical series varies between 2.0% and 8.8% (Guglielmi *et al.* 1992, Valavanis *et al.* 1996, Raymond & Roy 1997, Vinuela *et al.* 1997, Cognard *et al.* 1998, McDougall *et al.* 1998, Ricolfi *et al.* 1998, Vanninen *et al.* 1999, Doerfler *et al.* 2001, Ng *et al.* 2002, Henkes *et al.* 2004b, Cronqvist *et al.* 2005, Norbäck *et al.* 2005). In the meta-analysis by Brilstra *et al.* (1999), the calculated procedural perforation rate was 2.4%

Rupture may occur during any stage of the treatment procedure. Komiyama *et al.* (1993) reviewed the aneurysmal ruptures during angiography and found that rebleeding occurred most often when the examination was performed on the day when the initial bleeding occurred, and the risk was highest during the first 6 hours from the onset of SAH. Fluctuations in blood pressure resulting from pain, anxiety, or anesthesia may be contributing factors (McDougall *et al.* 1998). The pressure wave of an injection of contrast material may overcome the weak walls of an aneurysm (Saitoh *et al.* 1996). Perforation may be caused by the guidewire as it is steered into the aneurysm or subsequently by the microcatheter as it is advanced over the guidewire into the aneurysm. The coil itself or the delivery wire to which the coil is attached may perforate the aneurysm. Excessive packing of the aneurysm with coils for sealing the neck of the aneurysm may also result in its rupture. The alterations in flow dynamics inside the aneurysm after the introduction of coils may divert the flow toward the weak point of the aneurysm, resulting in bleeding either during the procedure or afterwards (McDougall *et al.* 1998). In the series of Doerfler *et al.* (2001), one of the five (20%) ruptures was due to the microguidewire, while the microcatheter perforated the aneurysm in two of the cases (40%), and two of the ruptures (40%) occurred during the placement of the first coil. One of these patients died as a result of aneurysmal rupture, while all of the others recovered without long-term effects (mortality 20%, morbidity 0%). Vanninen *et al.* (1999) reported aneurysm perforation during the endovascular procedure in three out of 52 patients (5.8%). In one of them the coiling was completed after the rupture, and two of them, who did not receive general anesthesia, had subsequent surgery. All of the patients had uneventful recovery (mortality 0%, morbidity 0%). Raymond & Roy (1997) reported six perforations among 103 endovascular procedures (5.8%). Three of these patients died due to a bleeding complication, and another three suffered no clinical deterioration (mortality 50%, morbidity 0%). Because five of the iatrogenic ruptures occurred in small aneurysms, the authors suggested that this complication could be minimized if acutely ruptured aneurysms smaller than 3 mm were not treated by endovascular coiling. Ricolfi *et al.* (1998) also reported increased fragility of smaller aneurysms and presented two possible explanations: 1) The surface area of the initial rupture is proportionally larger for small aneurysms than for larger aneurysms, and 2) small coils 2-3 mm in diameter have more effective shape memory and may therefore tend to cause damage to the weakened site of the ruptured aneurysm. Raymond & Roy (1997) expected, on the basis of their experience, that the incidence of intraprocedural rupture would decrease with increasing experience. However, other investigators have had opposite experiences (McDougall *et al.* 1998, Doerfler *et al.* 2001, Norbäck *et al.* 2005). According to a meta-analysis of 17 publications, the risk of perforation was significantly higher in patients with a ruptured aneurysm compared to patients with an unruptured aneurysm (4.1% vs. 0.5%, $p<0.001$). The combined risk of permanent neurological disability and death among patients having iatrogenic aneurysm rupture was 38% for patients experiencing ruptured aneurysms and 29% for those having unruptured aneurysms (Cloft & Kallmes 2002).

The basic management of iatrogenic aneurysm rupture involves immediate reversion of anticoagulation therapy by protamin sulfate and continuation of the embolization procedure (McDougall *et al.* 1998, Ricolfi *et al.* 1998). In a case of microcatheter perforation, Willinsky & terBrugge (2000) described a salvage maneuver including the use of a second microcatheter, with which the aneurysm was packed with coils, while the

first microcatheter was temporarily left in place. If the balloon remodeling technique is used, the neck of the ruptured aneurysm can also be temporarily sealed by the balloon to control the bleeding (Phatouros *et al.* 1999, Cronqvist *et al.* 2005). Aneurysm rupture during embolization may be accompanied by severe intracranial hypertension, which causes either a decrease or an arrest of cerebral perfusion, the duration of which determines the clinical outcome. Ricolfi *et al.* (1998) addressed the value of emergency ventriculostomy (which should be done in the angiographic suite) to reduce intracranial pressure.

2.5.3.4 Other technical complications

In addition to thromboembolic and hemorrhagic complications, there are many other possible hazards that may complicate the endovascular treatment of aneurysms. The patient is exposed to puncture site complication risks in every endovascular procedure. Complication risks related to anesthesia, contrast media, and radiation are also present. These complications are not reviewed in detail here.

In the largest clinical series published, other than thromboembolic or hemorrhagic complications occurred during the treatment of 4.7 % of the 1811 aneurysms (overall complication rate 17.4%) (Henkes *et al.* 2004b). Coils may protrude from the aneurysm sac into the parent artery and, if already detached, migrate distally with the arterial blood flow. Protruding coil loops in the aneurysm neck increase the risk for thrombus formation. Inadvertent parent artery or branch artery occlusion may result from coil malposition and additional thrombosis. Henkes *et al.* (2004b) found the incidence of complications related to coil malposition to be 2.7%. Coils can get damaged ("stretched") during the procedure, or premature coil detachment may occur. Vessel wall dissection may occur during any stage of the procedure and at any site of the arterial tree from the puncture site to the target lesion. Vasospasm can be induced or increased due to irritation by the guiding catheter or the microcatheter. Endovascular packing of an aneurysm may result in an increased mass effect. Kirollos *et al.* (2002) reported a case of brain abscess where an endovascularly treated aneurysm acted as a foreign-body nidus. Two cases of chemical meningitis after cerebral aneurysm treatment using two 2nd generation aneurysm coils (one case with Hydrocoil and another with Matrix) have been reported as well (Meyers *et al.* 2004).

2.5.4 Clinical outcome after endovascular treatment

The clinical outcome after endovascular treatment depends on the preprocedural clinical state of the patient, likewise in aneurysm surgery. The follow-up clinical outcomes of selected endovascular series are summarized in Table 6. The series of Vanninen (1999) and Koivisto (2000) include the same group of patients with different length of follow-up. The follow-up length varies from 1 to 26 months in the presented series. The real management outcome can relevantly be established from series having the follow-up time at least 12 months.

Table 6. Summarized follow-up clinical outcomes in endovascular series. The H&H, GOS and rebleeding figures represent percentages of patients. The figures in parenthesis represent patients with unruptured aneurysms, while all the other patients have had subarachnoid hemorrhage prior to the treatment. The results of the study by Molyneux et al. *(2005) have been modified according to H&H and GOS.*

Study	Number of patients	Follow-up months	H&H 1- 2 (%)	H&H 3 (%)	H&H 4-5 (%)	GOS 4-5 (%)	GOS 2-3 (%)	GOS 1 (%)	Rebleed-ings (%)
Raymond& Roy 1997	75	6	41	40	19	72	5	23	5
Byrne *et al.* 1999	317	22	76	13	11	81	14	5	1,6
Kähärä *et al.* 1999b*	34 (15)	26	48	17	35	79 (93)	6 (7)	15 (0)	0,0 (0,0)
Vanninen *et al.* 1999	52	3	60	23	17	81	8	11	1,9
Koivisto *et al.* 2000	52	12	60	23	17	79	8	13	1,9
Ng *et al.* 2002	73 (63)	2	65	22	13	63 (92)	4 (0)	23 (8)	1,4 (1,6)
Friedman *et al.* 2003	83	19	57	24	19	77	11	12	0,0
Henkes *et al.* 2004	1034 (777)	1	51	21	24	75 (90)	14 (7)	11 (3)	NA NA
Molyneux *et al.* 2005	1063	12	88 WFNS	6 WFNS	5 WFNS	77 mR S0-2	15 mRS 3-5	8 mRS 6	3,2 (f-u 4 y)
Norbäck *et al.* 2005	239	6	42	25	33	57	30	13	NA

H&H = Hunt & Hess grade, GOS = Glasgow outcome scale, NA = data not applicable, WFNS = World Federation of Neurological Surgeons grading scale (Johnson *et al.* 2001), mRS = modified Rankin scale (Rankin 1957), f-u = follow-up, y = years

* five patients with lethal outcome included contrary to original publication

2.5.4.1 Rebleedings

The natural course of a ruptured intracranial aneurysm is unfavorable. Early rebleeding, within hours of the initial hemorrhage, occurs in at least 15% of the patients (Kassell & Torner 1983, Hijdra *et al.* 1987, Fujii *et al.* 1996, Hillman *et al.* 2002). After the first day of bleeding, the risk of recurrent hemorrhage is more or less evenly distributed over the next four weeks (Hijdra *et al.* 1987). The estimated total risk of rebleeding without any intervention during the first four weeks after the first day of aneurysm rupture has been 35-40% (Hijdra *et al.* 1987). Between one and six months, the risk of rebleeding gradually decreases from the initial level of 1-2% a day to a constant level of approximately 3% a year (Winn *et al.* 1977). At present, it is virtually impossible to

prevent early rebleedings possibly occurring before admission into hospital, but later rebleedings can be prevented by surgical or endovascular interventions (van Gijn & Rinkel 2001). In a randomized multicenter study by Hillman *et al.* (2002), a reduction in the ultra early rebleeding rate from 10.8% to 2.4% during the period from the SAH diagnosis to a surgical or endovascular intervention could be achieved by immediate administration of tranexamic acid. Tranexamic acid treatment resulted in an 80% reduction in the mortality rate from early rebleeding (Hillman *et al.* 2002).

The percentages of rebleeding aneurysms after endovascular treatment are represented in Table 6. In the ISAT study, the rebleeding rates after treatment during a mean follow-up of four years were 1.2% in the surgical group and 3.2% in the endovascular group (Molyneux *et al.* 2005). A retrospective analysis of endovascularly treated ruptured aneurysms in a single center revealed a 1.4% incidence of early rebleeding (at 30 days after treatment) and a 1.27% incidence of late rebleeding (>30 days after treatment) during a mean follow-up time of 18.7 months (Sluzewski & van Rooij 2005b, Sluzewski *et al.* 2005). The combined risk of rebleeding is thus approximately 2.7%. The risk factors for early rebleeding were aneurysm location in AcomA, incomplete aneurysm occlusion, and poor clinical condition at the time of treatment (Sluzewski & van Rooij 2005b).

2.5.4.2 Symptomatic unruptured aneurysms

Kazekawa *et al.* (2003) treated 12 ICA aneurysms associated with cranial nerve dysfunction by coil embolization preserving the parent artery. In follow-up, 33% of the patients had complete resolution of symptoms, 33% had significant improvement of symptoms, and 33% had symptoms that had remained unchanged. Gonzalez *et al.* (2004) reported follow-up data of 32 coil-embolized symptomatic aneurysms, and they observed clinical improvements in 47% of the cases, especially in cases of cranial nerve palsies. Stiebel-Kalish *et al.* (2003) followed up 11 patients with oculomotor paresis due to PcomA aneurysms, which were embolized by GDC. Complete resolution did not occur in any of the patients, but in 10/11 of the patients, diplopia and ptosis were no more evident in follow-up. Lubicz *et al.* (2004) treated 13 patients (9 of them with symptoms of a mass effect) with giant VBA aneurysms by parent artery occlusion. Endovascular treatment resulted in clinical improvements in 67% and worsening in 33% of the patients having symptoms of a mass effect. In a recent series of aneurysms treated with Onyx, 80% of the patients treated due to a mass effect either improved or remained stable symptomatically, while 20% of them had aggravation of symptoms (Lubicz *et al.* 2005b). In another series of unruptured aneurysms treated with Onyx, 50% of the patients with cranial nerve dysfunction showed improvement of symptoms and another 50% remained unchanged (Weber *et al.* 2005).

2.5.5 Learning curve

Only a few publications on the learning curve for endovascular treatment of intracranial aneurysms were found in a literature search. Turjman *et al.* (1998) investigated whether operator experience corresponded to the degree of endovascular occlusion in the period immediately after treatment. The chronological sequence in which the aneurysms were treated was used as a measure of operator experience. The early chronological order of treatments predicted unsatisfactory angiographic results in a retrospective review of 72 patients treated with GDC embolization (Turjman *et al.* 1998). In a study by Singh *et al.* (2002), 94 patients who underwent coil embolization of an unruptured intracranial aneurysm were analyzed in terms of complications. For the first five procedures performed by each of three operators the complication rate was 53%, and for the later cases it was 10% ($p<0.001$), while the total complication rate for all cases was 17%. The authors concluded that, because all of the three operators in this study were highly experienced in other endovascular techniques at the study onset, the rate of learning may not be as fast in less experienced centers (Singh *et al.* 2002). In an analysis of first and second 100 intracranial aneurysms treated with GDC in a single center, the overall morbidity/mortality dropped from 14% to 7%, the rate of lethal complications from 2% to 1%, the need for multiple treatment sessions from 27% to 10%, and the need for subsequent surgery from 20% to 6% (Malisch *et al.* 1997).

2.6 Comparative studies of endovascular and surgical treatment

Accurate comparison of endovascular and surgical treatment methods is possible only in a prospective, randomized study. By now, two studies comparing endovascular and surgical management of ruptured intracranial aneurysms fulfil that criterion. In a single-center study performed in Kuopio University Hospital, Finland, 109 patients (52 in the endovascular and 57 in the surgical group) were included (Vanninen *et al.* 1999, Koivisto *et al.* 2000). The international subarachnoid aneurysm trial (ISAT) consisted of 2143 patients (1073 in the endovascular and 1070 in the surgical group) treated in 42 centers, mainly in the United Kingdom and elsewhere in Europe (Molyneux *et al.* 2002, Molyneux *et al.* 2005).

In the Kuopio study (Vanninen *et al.* 1999, Koivisto *et al.* 2000), 46% of the patients experiencing aneurysmal SAH during the study period were randomized. The most important reasons for exclusion were a large hematoma (27%) and aneurysm morphology unsuitable for coiling (25%). The initial angiographic results were significantly better after surgery in the patients with ACA aneurysms and after endovascular treatment in those with posterior circulation aneurysms. In MCA or ICA aneurysms, no significant differences were seen. The procedural mortality rate was 2% in the endovascular group and 4% in the surgical group. Clinical outcome at 3 months or at 1 year was not significantly different between the groups. One patient (2%) in the endovascular group had early rebleeding, while no rebleedings were detected in the surgical group. The patients eligible for neuropsychological analysis did not differ in their test scores. In postprocedural MRI, superficial brain retraction deficits and ischemic lesions in the

territory of the treated aneurysm were more common in the patients treated with surgical clipping than in those who had undergone endovascular treatment. Kaplan-Meier analysis revealed equal survival in both groups. (Vanninen *et al.* 1999, Koivisto *et al.* 2000).

In the ISAT study (Molyneux *et al.* 2002, Molyneux *et al.* 2005), only 22.4% of the patients experiencing acute SAH during the study period could be randomized. The 1-year outcome in terms of survival free of disability turned out to be significantly better in the patients allocated to endovascular coiling (76.5%) compared to those allocated to neurosurgical clipping (69.1%). The absolute risk reduction in dependency or death in the endovascular versus surgical groups was 7.4% (95% CI 3.6-11.2, p=0,0001). The early survival advantage was maintained for up to seven years and was statistically significant (p=0.03). The risk of seizures after the treatment procedure was substantially lower in the patients allocated to endovascular treatment. The risk for rebleeding was higher among the patients allocated to endovascular treatment (3.2%) than in the surgical group (1.2%). However, the results of the ISAT study reflect only the subgroup of SAH patients eligible for either of the two treatment options. (Molyneux *et al.* 2002, Molyneux *et al.* 2005).

In an international study of unruptured intracranial aneurysms (ISUIA), patients with unruptured aneurysms were enrolled by multiple centers in North America and Europe for prospective assessment (Wiebers *et al.* 2003). The authors assessed the morbidity and mortality associated with either endovascular procedures or open surgery of the aneurysm. The patients were not randomized. The endovascular group consisted of 451 patients and the surgical group of 1917 patients. The overall morbidity and mortality rates at 30 days were 7.3% and 1.8% for the endovascular group and 11.8% and 1.5% for the surgical group, respectively. The characteristics of the patients in the endovascular cohort differed significantly from those in the surgical group, including older patients with larger aneurysms and a higher proportion of posterior circulation aneurysms, which made direct comparison between the groups impossible, as any such comparison would have overestimated the rates in the endovascular group. Despite that difference, the morbidity rate was lower in the endovascular group (7.3% vs. 11.8%). The authors reported that, in endovascular treatment, morbidity and mortality seem to be less dependent on the patient's age, indicating that this treatment might have advantages for elderly patients. (Wiebers *et al.* 2003).

In a case-matched study by Hadjivassiliou *et al.* (2001), the authors found local damage or encephalomalasia exclusively in patients who underwent surgery compared to those having endovascular treatment. There were more small infarcts in the vascular territory of the treated aneurysm in the surgical group, but no difference was detected with large infarcts. There was also a trend toward a poorer cognitive outcome in the surgical group, which was significant on four neuropsychological tests. The authors concluded that endovascular treatment may cause less structural brain damage than surgery and have a more favorable cognitive outcome, but the cognitive outcome appears to be dictated primarily by the complications of SAH (Hadjivassiliou *et al.* 2001). In the study by Koivisto *et al.* (2002), cerebral perfusion was detected by SPECT before and after endovascular or surgical treatment of acutely ruptured intracranial aneurysms. The study revealed significant decreases in cortico-cerebellar perfusion ratios (in the right frontobasal cortex, right frontal cortex, and right pericallosal area) in the surgical group. The findings suggest that surgery has a greater impact on cerebral perfusion than endovascular treatment (Koivisto *et al.* 2002). In the study by Kivisaari *et al.* (2001),

MRI revealed infarction in the frontal lobe in 48% of the patients who had undergone early surgery for a ruptured aneurysm.

Only a few reports were found in the literature comparing the economic aspects of endovascular and surgical treatments of intracranial aneurysms. In a retrospective study by Sturaitis *et al.* (2000), the authors investigated the impact of GDC therapy on the overall management outcome of intracranial aneurysms by comparing consecutive cases managed by a single multidisciplinary neurovascular team two years before and after the introduction of GDC in a single center. The results of the study did not demonstrate any significant impact of integration of the GDC modality on the clinical or economic outcome (Sturaitis *et al.* 2000). Le Feuvre & Taylor (2004) calculated total treatment costs in a subgroup of 17 patients who had undergone either endovascular or surgical treatment of PcomA aneurysms. The groups were comparable for age, sex, and clinical condition. The average cost for endovascular treatment was 16% less than that for surgical treatment (Le Feuvre & Taylor 2004). In another analysis, a subgroup of patients randomized to the ISAT study (10 patients in the endovascular and 12 patients in the surgical group) was analyzed by cost and outcome in a single center (Bairstow *et al.* 2002). While the endovascular procedure tended to be the more expensive in terms of the cost of consumables, this expense was more than compensated for by savings in staffing costs and the period and cost of hospitalization. Endovascularly treated patients returned to normal activity or paid employement sooner and had a favorable functional outcome compared with patients scheduled for a neurosurgical procedure (Bairstow *et al.* 2002). Niskanen *et al.* (2002) compared resource use after endovascular treatment (68 patients) and surgical clipping (103 patients) of ruptured intracranial aneurysms. In 12-month follow-up, the modality of treatment did not seem to affect resource use, and both of the two treatment options required a similar amount of intensive care resources (Niskanen *et al.* 2002). In general, the length of stay in the intensive care unit is the most important factor influencing the management costs of patients with aneurysmal SAH. By using activity-based cost analysis, the average cost of endovascular embolization of intracranial aneurysms in 1999 was 4472 Euros, and coils accounted 63.3% of the total costs (Rautio *et al.* 2003).

3 Aims of the study

The purpose of this study was to analyze the outcomes of the patients allocated to endovascular treatment of intracranial aneurysm(s) in Oulu University Hospital between December 1993 and July 2004. Specifically, the study aimed:

1. to determine the technical feasibility of the endovascular treatment of intracranial aneurysms,
2. to analyze the angiographic results and clinical outcomes of the patients after endovascular treatment of intracranial aneurysms,
3. to identify predictors of angiographic and clinical outcomes after endovascular treatment of intracranial aneurysms,
4. to determine whether the outcomes of endovascular treatment of intracranial aneurysms improved over a long period.

4 Patients and methods

4.1 Patients

Between December 1993 and July 2004, a consecutive series of 416 patients (201 males, 48.3% and 215 females, 51.7%) underwent endovascular treatment for intracranial aneurysm(s) in Oulu University Hospital. In digital subtraction angiography (DSA), a total of 630 aneurysms were detected in these patients. 467 (74.1%) of the 630 aneurysms were selected for endovascular treatment, and they constituted the study series analyzed here. The remaining 163 (25.9%) aneurysms were treated surgically or remained untreated during the period of data collection (Fig.1). The age distribution of the patients with saccular aneurysms with or without a history of SAH is represented in Fig.2.

The patient selection for endovascular treatment was made by a multidisciplinary team consisting of neurointerventional radiologist(s) and neurosurgeon(s). The treatment decision was made on the basis of the location, size, and shape of the aneurysm and the patient's clinical status and comorbidities. The patient and his/her relatives were informed about the disease, the treatment options available, and the risks included in the treatment. Endovascular treatment was usually chosen if it seemed feasible. There were no absolute exclusion criteria for endovascular treatment, but surgical treatment was favored on the following occasions: 1) a large ICH in a poor-grade patient necessitating emergency craniotomy and hematoma evacuation, 2) a very wide-necked aneurysm, and 3) one or more parent artery branches originating from the aneurysm sac. In cases of acutely ruptured aneurysms, the availability of endovascular treatment and the experience of the neurosurgeon and/or endovascular interventionist also had an impact on the treatment decision. During the study period, a total of 466 intracranial aneurysms were surgically clipped in Oulu University Hospital, and approximately 50% of the intracranial aneurysm operations were thus performed by using endovascular techniques and approximately 50% by using neurosurgical techniques.

Among the 416 patients included in the study, 12 patients had a dissecting aneurysm, and this group of patients was analyzed separately. However, there is some overlap between the groups, since three of the patients with a ruptured dissecting aneurysm also had an additional saccular aneurysm treated. These three patients were included in both groups. One of the 12 dissecting cases included in this study has been previously

published as a case report (Tikkakoski *et al.* 1997). The mean age of the patients was 51 years (range 14–81 years). The patient characteristics in the group with dissecting aneurysms are presented in Table 29 (chapter 4.6).

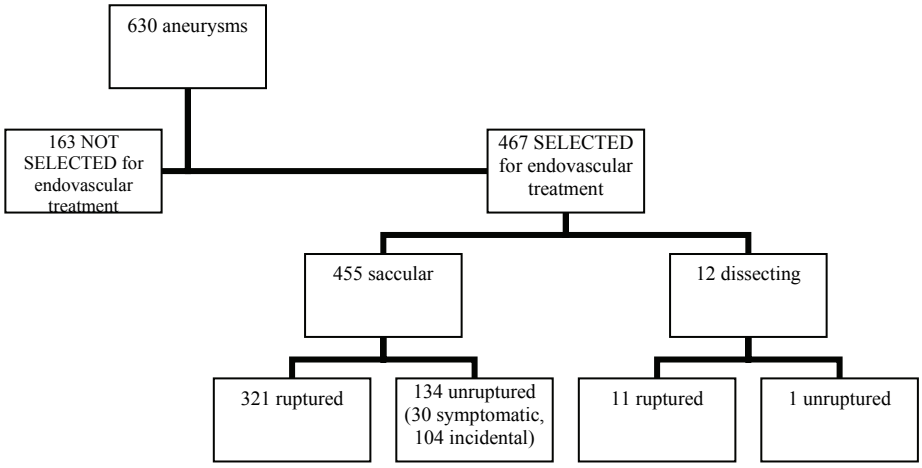

Fig. 1. Characteristics of the aneurysms detected in 416 patients.

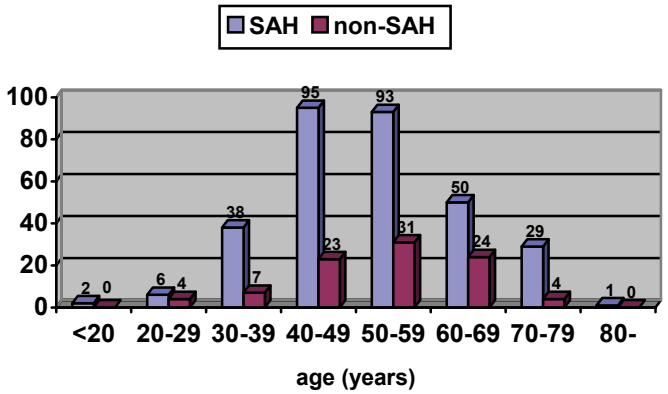

Fig. 2. Age distribution of 407 patients with saccular aneurysm(s).

All the angiographic and CT/MRI images available were retrospectively analyzed by two neurointerventional radiologists (M.I. and T.S.) in consensus. Within the group of 314 patients with subarachnoid hemorrhage due to a ruptured saccular aneurysm, the amount of blood visible in CT images was graded using Fisher grading scale (Fisher *et al.* 1980) (Table 7). Two patients (0.6%) did not undergo CT scanning (Grade 0), and 20 patients (6.2%) had CT findings negative for SAH (Grade 1), which was, however, evident in lumbar puncture. In 96 patients (30.6%) with SAH detected by CT, grading was not possible, because they had been scanned outside our hospital, and the (CT) images were not available for retrospective analysis.

Table 7. Severity of bleeding in 314 patients with subarachnoid hemorrhage graded by Fisher grading scale.

Grade	Description	No. of patients	% of patients
0	No CT scan	2	0,6
1	No SAH	20	6,4
2	Diffuse SAH, less than 1 mm thick	38	12,1
3	Localized clots of layers of hemorrhage 1mm or thicker	34	10,8
4	IVH or ICH with or without SAH	124	39,5
5	SAH, unknown grade	96	30,6
Total		314	100

No. = number

Patients' clinical status was retrospectively analyzed from patient records by one radiologist (M.I.). The H&H (Hunt & Hess 1968) grading system was used in the evaluation of the pre-embolization clinical status of the 314 patients with ruptured aneurysms (Table 8). Four of the patients (1.2%) had a ruptured aneurysm which was not treated in the acute phase, and they were classified as H&H 0. In 21 patients (6.7%), classification could not be done retrospectively from the patient files. For statistical analysis, the H&H groups 1 and 2 as well as the groups 4 and 5 were combined.

Table 8. Pre-treatment clinical status of 314 patients with ruptured saccular aneurysms graded by the Hunt & Hess grading scale.

Grade	Description	Number of patients	% of patients
0	No bleeding	4	1,3
1	Asymptomatic or minimal headache and slight nuchal rigidity	120	38,2
2	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy	39	12,4
3	Drowsiness, confusion, or mild local deficit	60	19,1
4	Stupor, moderate to severe hemiplegia, possibly early decerebrate rigidity, and vegetative disturbances	50	15,9
5	Deep coma, decerebrate rigidity, moribund appearance	20	6,4
	Unknown grade	21	6,7
Total		314	100

The pre-embolization clinical condition of the patients with ruptured dissecting aneurysms is represented in Table 29 (chapter 4.6).

4.2 Aneurysmal features

All the aneurysms visible in DSA images were analyzed by location, size, shape, rupture, and etiology. If the patient had had SAH, and multiple aneurysms were found, the ruptured one was judged according to the location of hemorrhage in CT images and the

size and shape of the aneurysms in DSA images (i.e. secondary pouch or sharp edge in the aneurysm margin).

The etiology of the aneurysm was dissecting in 12 cases and flow-related in four cases (AVM in one case, moyamoya in three cases), while the remaining 451 aneurysms were saccular. The 12 dissecting aneurysms were analyzed separately, while the four flow-related aneurysms were included among saccular aneurysms because the aneurysm morphology and treatment strategies were similar to those of saccular aneurysms. Nine of the saccular aneurysms included in the present study had been operated on prior to the endovascular treatment (seven clipped, one wrapped, and one carotid ligation).

The anatomic locations of the 455 saccular aneurysms are shown summarized in Table 9. Altogether 384 (84.4%) of the aneurysms were located in the anterior circulation and 71 (15.6%) in the posterior circulation. The most common locations were *AcomA* (25.7%), *MCA bifurcation* (17.1%), *PcomA* (16.7%), and *BA tip* (9.7%).

The size of the aneurysm was measured directly from 3DRA reconstruction images, when available, or from 2D DSA images calibrated to the extracranial markers. Radiopaque rings 10 mm in diameter were used for calibration, and they were taped on the patient's skin on at least two opposite sites of the head. The maximum diameter of the treated aneurysms ranged from 2 mm to 35 mm, and the average (± SD) was 7.1 mm (± 5.1 mm). Aneurysms were graded by size as follows (Byrne & Guglielmi 1998): small (maximal diameter < 10mm), large (maximal diameter 10-25mm), and giant (maximal diameter > 25mm). The sizes of the 455 saccular aneurysms are shown summarized in Table 10. There were 336 (73.8%) small, 105 (23.1%) large, and 14 (3.1%) giant aneurysms. The aneurysm neck width ranged from 1 mm to 10 mm (median 3 mm). The dome-to-neck ratio (dnr) was calculated by dividing the maximal aneurysm diameter by the neck width. The dnr ranged from 1.00 to 7.00 with a median of 1.43.

321 (70.5%) of the saccular aneurysms had ruptured before the treatment, and 134 (29.5%) were unruptured. Nine patients with SAH were diagnosed with two potentially ruptured aneurysms, and they were both judged as ruptured in this study. Of the unruptured aneurysms, 30 were symptomatic. The main presenting symptom was oculomotor palsy in 12 cases, other cranial nerve palsy in four cases (optic nerve in three cases, trochlear nerve in one case), seizures in six cases, thromboembolic events in five cases, and headache in three cases. The remaining 104 aneurysms were either discovered incidentally or detected in SAH patients with multiple aneurysms.

Table 9. Anatomic locations of the 455 saccular aneurysms selected for endovascular treatment.

Aneurysm location	Total	%	Ruptured	%	Unruptured	%
ICA	151	33.2	107	33.3	44	32.8
Cavernous	8	1.8	2	0.6	6	4.5
OphtA	21	4.6	12	3.7	9	6.7
Carotid cave	5	1.1	0	0.0	5	3.7
PcomA	76	16.7	64	19.9	12	9.0
AChorA	16	3.5	14	4.4	2	1.5
SHypA	3	0.7	3	0.9	0	0.0
Bifurcation	18	4.0	10	3.1	8	6.0
Other	4	0.9	2	0.6	2	1.5
ACA	148	32.5	125	38.9	23	17.2
A1	9	2.0	4	1.2	5	3.7
AcomA	117	25.7	105	32.7	12	9.0
A2 and beyond	22	4.8	16	5.0	6	4.5
MCA	85	18.7	50	15.6	35	26.1
M1	7	1.5	3	0.9	4	3.0
Bifurcation	78	17.1	47	14.6	31	23.0
VBA	71	15.6	39	12.1	32	23.9
VA	1	0.2	1	0.3	0	0.0
PICA	2	0.4	1	0.3	1	0.7
AICA	1	0.2	0	0.0	1	0.7
SCA	16	3.5	8	2.5	8	6.0
BA trunk	2	0.4	2	0.6	0	0.0
BA tip	44	9.7	26	8.1	18	13.4
P1	2	0.4	0	0.0	2	1.5
P2 and beyond	3	0.7	1	0.3	2	1.5
Total	455	100	321	100	134	100

The details of the 12 dissecting aneurysms are represented in Table 29 (chapter 4.6).

Table 10. Sizes of 455 saccular aneurysms.

Size	Ruptured		Unruptured				Total	
			Symptomatic		Incidental			
	n	%	n	%	n	%	n	%
Small	238	74.1	9	30.0	89	85.5	336	73.8
Large	77	24.0	14	46.7	14	13.5	105	23.1
Giant	6	1.9	7	23.3	1	1.0	14	3.1
Total	321		30		104		455	100

4.3 Endovascular treatment

4.3.1 Treatment sessions

Of the 455 saccular aneurysms, 369 (81.1%) underwent one treatment session, 54 (11.9%) two sessions, and 32 (7.0%) three or more sessions. In nine patients two aneurysms were treated during a single session, and in one patient three aneurysms were treated during one session. The total number of treatment sessions was 583. The time intervals between the onset of SAH and the initial treatment for ruptured saccular aneurysms are summarized in Fig.3. Two of the 12 dissecting aneurysms (16.7%) were treated in two sessions, while the remaining 10 aneurysms (83.3%) were treated in a single session (total of 14 treatment sessions).

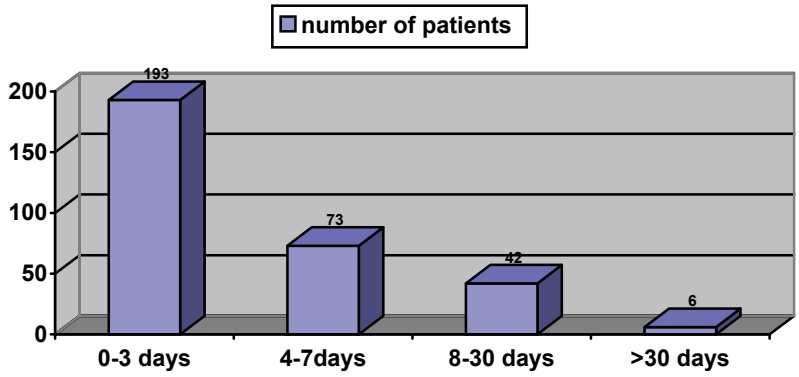

Fig. 3. Time interval between the onset of SAH and the initial treatment among patients with ruptured saccular aneurysms (314 patients).

4.3.2 Angiographic equipment

At the beginning of the study period, cerebral angiographies and endovascular treatments were performed on a Siemens Neurostar (Erlangen, Germany) monoplane angiographic unit. A biplane angiographic unit (Siemens Biplane Neurostar, Erlangen, Germany) was installed in September 1994, and most of the embolizations and angiographies included in this study were performed on this unit. A 3D rotational angiography unit (Philips Integris Allura, Best, the Netherlands) was installed in July 2003, and thereafter all cerebral angiographies and neurointerventional procedures have been performed in this suite.

4.3.3 Anesthesia and periprocedural medication

Between December 1993 and January 1998, 62 of the 205 treatments were performed under local anaesthesia with or without intravenous conscious sedation, and 143 treatments were done under general anesthesia. Since February 1998, all the 392 embolizations were performed under general anesthesia.

Systemic heparinization was used routinely. Initially, 5000 units of heparin were usually administered intravenously. When treating acutely ruptured aneurysms, heparinization was often delayed until the first coil had been successfully deployed into the aneurysm. Heparinization was individually decided by the treating radiologist case by case. Since May 1998 (after having appropriate equipment), the level of heparinization was monitored by measuring activated clotting time (ACT) values (target 200-300 seconds) during the procedure, and additional doses of heparin were given as needed. At the end of the procedure, heparinization was partially reversed by intravenous protamine sulphate, if needed.

4.3.4 Embolization methods and devices

Transfemoral catheterization (via unilateral or bilateral femoral artery puncture) was used in all but one case. In one treatment, catheterization was done via direct common carotid artery puncture.

The sizes of the transfemorally deployed introducer sheaths ranged from 5 to 7 French (F). Guiding catheters (range, from 5F to 7F) were used, except in the single case with direct common carotid artery puncture, where a 4F introducer sheath was used. At the beginning of this study period, Tracker-10 or Tracker-18 (Target Therapeutics, Boston Scientific, Fremont, CA, USA) microcatheters were exclusively used, but later on, a large variety of microcatheters and microguidewires were used to catheterize aneurysms.

Until the year 2003, only GDC-10 and GDC-18 (Boston Scientific, Target Therapeutics, Fremont, CA, USA) were used for the coiling procedure. Since 2003, TruFill (Cordis, Miami, FL, USA), Matrix (Boston Scientific, Target Therapeutics, Fremont, CA, USA) and Sapphire coils (MTI, Bochum, Germany) were also used. In one retreatment procedure, the Onyx liquid embolic agent (MTI, Irving, CA, USA) was used as an embolic agent.

A vast majority (395/455, 86.8%) of the successful and unsuccessful procedures to treat saccular aneurysms involved the use of the standard coiling technique. The balloon remodeling technique was used in 48 (10.5%) and the stent remodeling technique in 8 (1.8%) treatments of wide-necked saccular aneurysms. The first treatment using the balloon remodeling technique in Oulu University Hospital was performed in December 1997, and the stent remodeling technique has been used since April 2001. Among saccular aneurysms, parent artery occlusion was used in the treatment of 4 aneurysms (0.9%). Among dissecting aneurysms, parent artery occlusion was used in 5/12 aneurysms (41.7%) and the stent remodeling technique in one aneurysm (8.3%).

4.3.5 Embolization procedure

Prior to the embolization procedure, cerebral angiography (including both internal carotid and both vertebral arteries, with only few exceptions) was performed with a 4F diagnostic catheter, if it had not been done previously. Otherwise, the appropriate ICA or VA was directly catheterized with a guiding catheter, and angiographies were repeated in frontal and lateral views and in additional views if indicated. A 3DRA run was always done after the 3DRA equipment became available (Fig. 4). Nonionic contrast medium was used; iohexol (Omnipaque 300mgI/ml, Amersham Health AS, Oslo, Norway), iopromid (Ultravist 300mgI/ml, Schering, AG, Berlin, Germany), iobitridol (Xenetix 300mgI/ml, Guerbet, Aulnay sous Bois, France), or ioversol (Optiray 300mgI/ml, Mallinckrodt Inc., St Louis, MO, USA) in the early experience, and isosmolar iodixanol (Visipaque 270mgI/ml, Amersham Health AS, oslo, Norway) was used later on most occasions.

Before the introduction of microcatheters, the guiding catheter was connected to continuous saline flush (containing 5000 IU of heparin in 1000 ml of saline) using an Y-connector. The microcatheter was then navigated into the aneurysm with help of a microguidewire under fluoroscopic control (“road map”). Thereafter, the embolization procedure was performed by deploying platinum coils into the aneurysm through the microcatheter. Whenever feasible, the size of the first coil was selected to be equivalent to the diameter of the aneurysm sac, in order to create a “basket” inside the aneurysm. After that, the aneurysm was packed more tightly with smaller coils. Prior to the detachment of each coil, an angiographic run or a “road map” image was obtained to check the angiographic status of the aneurysm, including the position of the coil loops within the aneurysm, and also to detect any other angiographic findings outside the aneurysmal sac that could affect the treatment. If the position of coil loops was unsatisfactory, the coil was retrieved and repositioned. If the result seemed satisfactory, the coil was detached. At the end of the coiling procedure, angiographic runs were obtained in working projections to determine the angiographic end result.

The degree of aneurysm occlusion was visually graded using modified Raymond classification, where the “dog ear” and “residual neck” groups were combined as “neck remnant” (Raymond *et al.* 1997) (Fig. 5). Frontal and lateral projections (whole skull in field of view) were also routinely obtained at the end of the treatment. The standard coiling procedure is demonstrated in Figure 6.

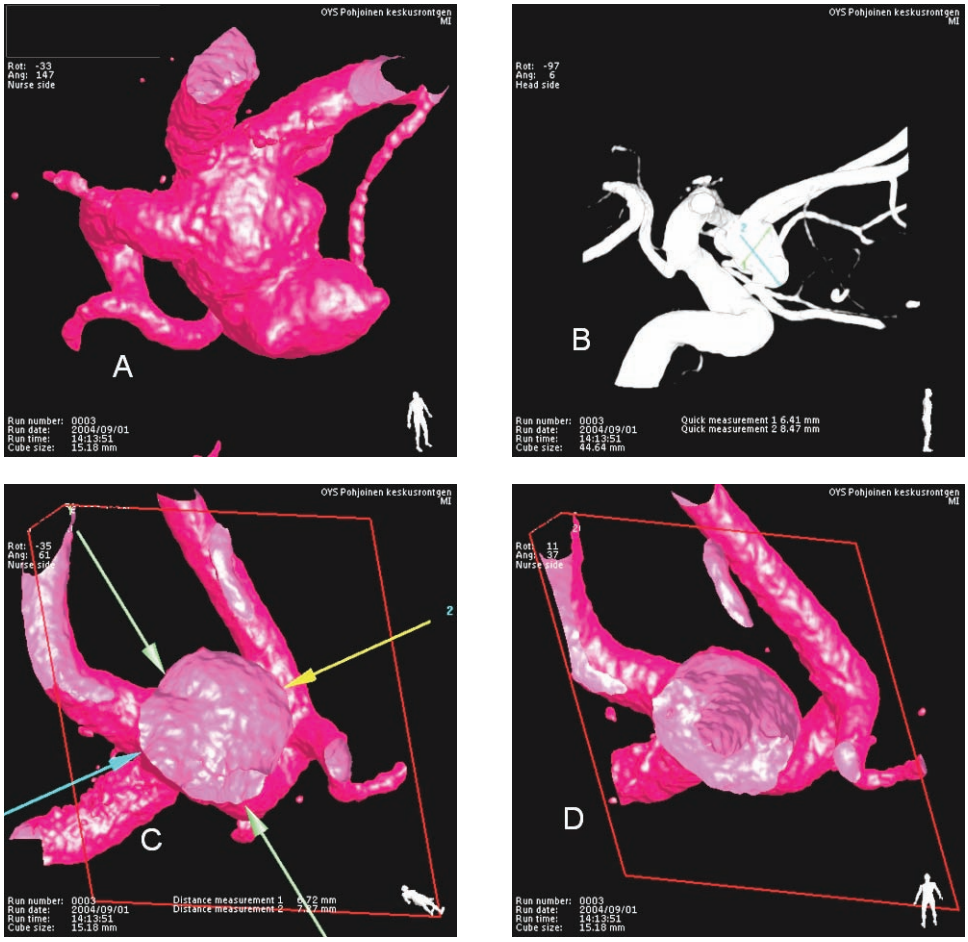

Fig. 4. An 3DRA reconstruction image of an irregular, ruptured AcomA aneurysm (A). Measurements can be made directly from a volume-rendered image (B) or, more accurately, from a cross-sectional surface-shaded reconstruction image (C). 3DRA reconstruction images allow an inside view into the aneurysm, demonstrating the origins of the parent arteries (D).

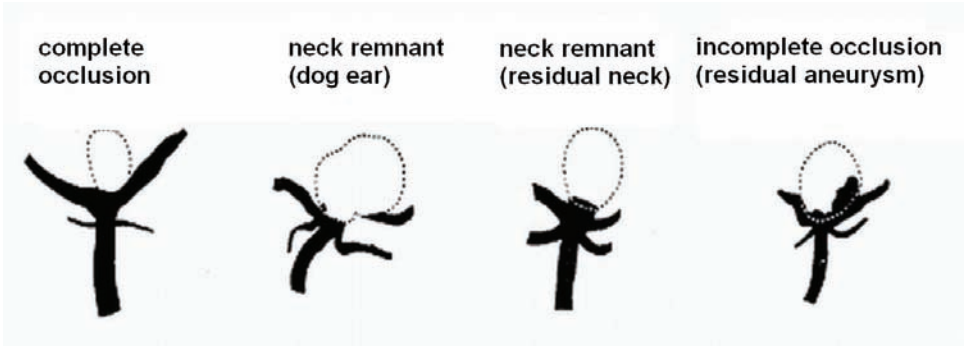

Fig. 5. Grading for aneurysm occlusion according to modified Raymond classification. The original Raymond classification is represented in parenthesis.

In cases where the balloon remodeling technique was used, both femoral arteries were punctured. The balloon catheter was introduced through a 6F guiding catheter to an appropriate position in the parent artery at the level of the aneurysm neck prior to aneurysm catheterization. The coiling procedure was performed in the way described by Moret *et al.* (1997). When the stent remodeling technique was used: the stent was deployed first, and the aneurysm was subsequently catheterized through the stent interstiches with a microcatheter and packed with coils (except in one case, where only a stent was deployed). In cases of parent artery occlusion, the balloon occlusion test was performed in 6 of the 9 cases prior to permanent occlusion of the parent artery. Permanent occlusion was accomplished with a detachable balloon in one case and with coils in eight cases. In one treatment, where liquid embolic (Onyx) was used, the procedure was performed in the way described by Molyneux *et al.* (2004).

After the embolization procedure, the patient was transferred to the postoperative recovery unit (routine practice), where his/her clinical status was continuously monitored until the next morning. Alternatively, the patient could be transferred to the intensive care unit, if indicated. Systemic heparinization was discontinued postoperatively after discharge from the angiographic suite. If a thromboembolic complication occurred or the coil protruded into the parent vessel, antithrombotic therapy was individually scheduled by the attending neurointerventional radiologist. If the patient recovered without any clinical complication, he/she was transferred to the neurosurgical ward on the morning following the endovascular treatment.

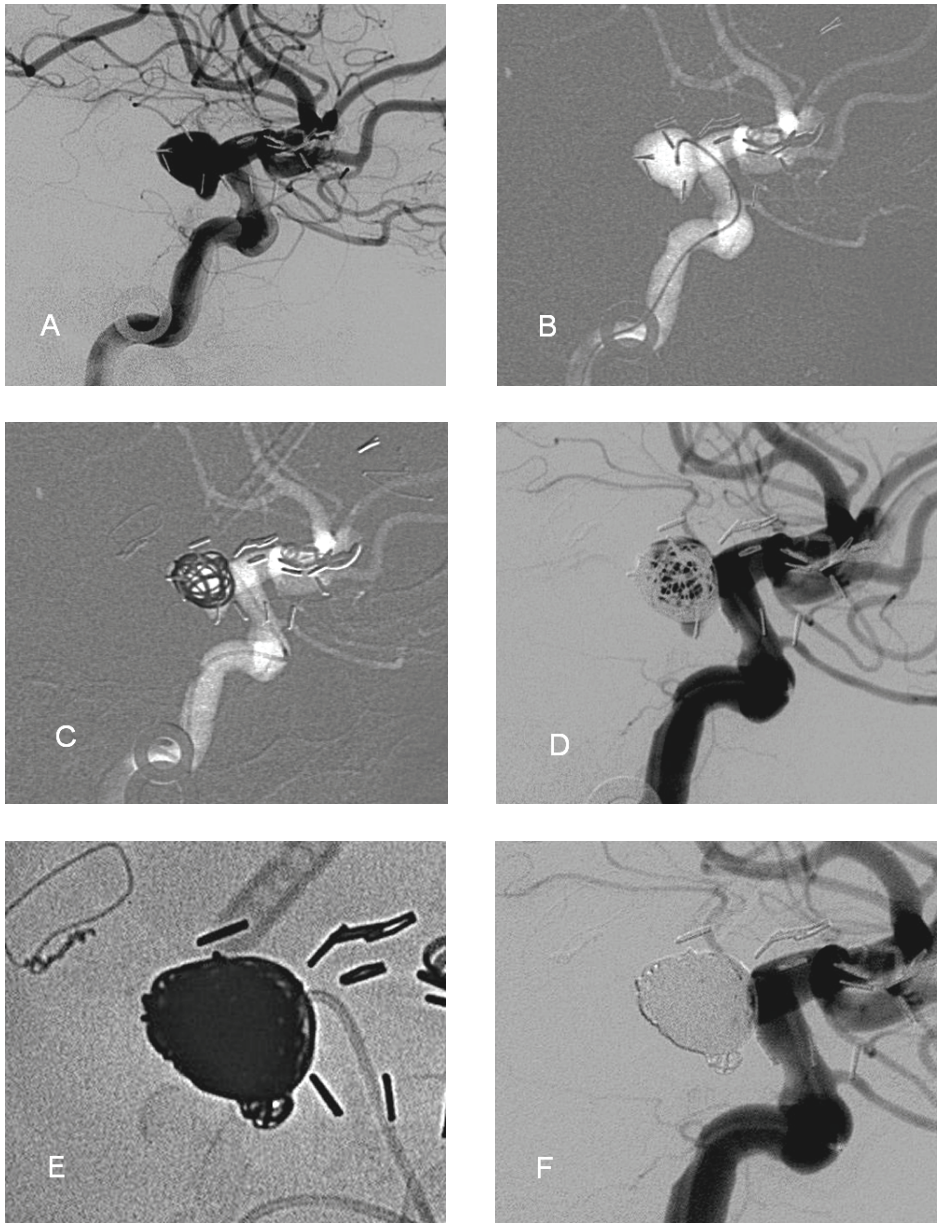

Fig. 6. Standard coiling procedure of an acutely ruptured PcomA aneurysm in a 76-year-old female who had undergone surgical clipping of an MCA aneurysm on the contralateral side 23 years earlier. DSA revealed a 10 mm aneurysm with a rupture site (secondary pouch) inferiorly (A). A microcatheter has been advanced inside the aneurysm sac (B). The first coil has been deployed and forms a "basket" (C). Control angiography after the deployment of the second coil demonstrates residual filling in the aneurysm sac and the secondary pouch. After deployment of 8 additional coils (total length of coils 186 cm), the coil mesh is dense (E), and the final angiogram (F) shows the aneurysm to be completely occluded.

4.3.6 Complications, morbidity and mortality

All procedural complications, both transient and permanent, were verified and recorded. Post-procedural complications were also verified and recorded, if they could be related to the endovascular treatment. Subclinical complications were recorded if found on imaging examinations performed in response to various indications. Because only a minority of the patients had undergone neuropsychologic examinations, and many of these examinations had been done outside hospitals and not in Oulu University Hospital, the results of neuropsychological examinations were not analyzed.

Lethal procedure-related complications were included in procedural mortality. All procedure-related complications causing clinical symptoms were included in procedural morbidity, if the symptoms persisted until discharge.

4.4 Time of treatment

The numbers of patients, aneurysms, and treatment sessions in each year during the study period are represented in Figure 7.

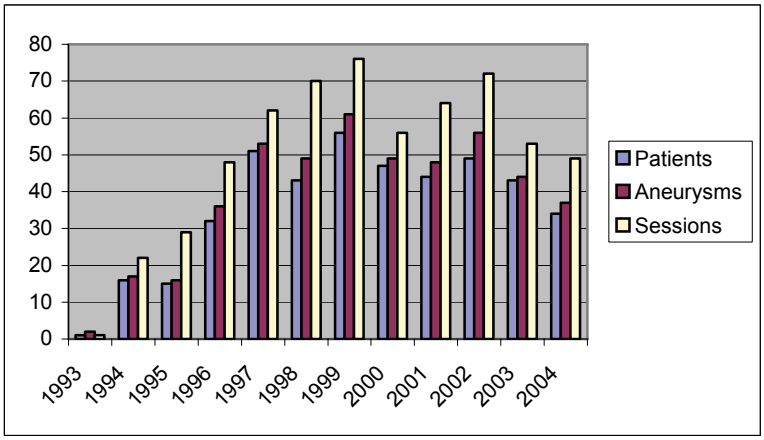

Fig. 7. Numbers of patients, aneurysms, and treatment sessions per year.

For a statistical analysis of possible improvement in outcomes during a long period, the data set was divided into three shorter periods: the years 1993-1997, 1998-2000, and 2001-2004. If an aneurysm was treated in multiple sessions, which were performed during different periods, the aneurysm was coded according to the initial treatment.

4.5 Technical feasibility

The treatment was considered technically feasible if at least one coil, stent, or detachable balloon could be detached; otherwise it was categorized as technical failure. Technical failures were not included in angiographic or clinical follow-up, and they were excluded from the statistics of the initial angiographic results. Because failed treatment attempts tend to involve procedural complications, morbidity, and mortality, the technical failures are included in these statistics.

4.6 Follow-up

4.6.1 Angiographic follow-up

The angiographic follow-up protocol was individualized for each patient, and there is thus lots of interindividual variation. The patient's age and clinical condition were taken into account, as were also the initial angiographic result at the end of the treatment. In the case of ruptured aneurysms, the protocol usually included DSA at 6 months and 3 years after the treatment. If the initial angiographic result was not satisfactory, the first follow-up examination was done within 2-3 months after the treatment. Unruptured aneurysms were usually checked at least once in 1-3 years after the endovascular treatment. Longer follow-up was scheduled if considered indicated.

If the primary treatment result was not satisfactory, or the aneurysm showed recidivous filling or regrowth in follow-up, the case was re-evaluated by the same multidisciplinary team, and further treatment options were considered. Ruptured aneurysms were usually followed up for at least three years. The same grading scale as at the initial treatments was used in the angiographic analysis of follow-up angiograms (Figure 5).

Angiographic follow-up was discontinued if the aneurysm was subsequently operated.

4.6.2 Clinical follow-up

The clinical status of the patients was retrospectively recorded from the patient files of Oulu University Hospital. All hospital visits were analyzed. The patient outcomes were graded using the Glasgow Outcome Scale (Table 3) (Jennet & Bond 1975). The end points of clinical follow-up were death and surgical treatment of an endovascularly treated aneurysm.

4.7 Data collection

All collected data were entered into an electronic database similar to the published versions (Sohn & Byrne 2000), but customized to meet our specific needs. The following significant parameters related to patient history, aneurysm features, endovascular treatment, and follow-up findings were included:

Patient history:

- Name, gender, and date of birth
- Referring unit
- History of intracranial bleedings and previous endovascular or surgical interventions
- Clinical presentation of the aneurysm(s)
- Pre-procedural clinical findings of the patient (H&H)
- CT findings on Fisher grading scale

Aneurysm features:

- Location and size (length and width)
- Neck width and dome-to-neck ratio
- Involvement of parent artery
- Aneurysm margin (regular/irregular, secondary pouch)
- Date when found and imaging method used (DSA/MRA/CTA)
- Ruptured/unruptured
- Etiology (saccular/dissecting/flow-related)

Endovascular treatment:

- Date of first treatment
- Time interval from rupture to treatment
- Dates of retreatments
- Number, type, and manufacturer of device used
- Techniques used (single catheter/ balloon remodeling/ stent remodeling/ parent artery occlusion)
- Procedural and delayed complications
- Angiographic result
- Clinical outcome (GOS)
- Treatment abandonment and reason for abandonment

Follow-up findings:

- Date
- Angiographic result and imaging method (DSA/MRA)
- Clinical recovery (GOS)
- Indication for additional treatment
- Need and time for further follow-up

4.8 Statistical analysis

SPSS for Windows version 11.01 (SPSS Inc., Chicago Ill., USA) was used for statistical analysis. Descriptive parameters were evaluated for the entire data set. For specific variables of interest, correlative analysis was also done. Fisher's exact test was used to test two categorical variables with two independent samples and Pearson χ^2-test to test two categorical variables with more than two independent samples.

Differences were considered to be statistically significant if the two-tailed p-value was less than 0.05 and very significant if the two-tailed p-value was below 0.01.

5 Results

5.1 Technical feasibility

In 416 of the 455 saccular aneurysms (91.4%) at least one coil or some other embolic device (stent or detachable balloon) could be deployed and detached, and endovascular treatment was considered feasible. There were 39 treatment failures: 25 occurred in the treatment of ruptured aneurysms and 14 with unruptured aneurysms (failure rate 7.8% among ruptured and 10.4% among unruptured aneurysms). In eight aneurysms (1.8%) the first treatment attempt failed, but embolization could be performed at the second attempt, and these aneurysms were not recorded as technical failures.

In the case of wide-necked aneurysms (dnr $\leq$ 1.5), technical failures were significantly more common than among aneurysms with a narrow neck (11.6% vs. 3.9%, $p<0,05$). The technical feasibility of endovascular treatment was very significantly higher among posterior circulation aneurysms than among anterior circulation aneurysms (98.6% vs. 90.1%, $p<0.01$). Among anterior circulation aneurysms, feasibility was higher among ICA (93.1%) aneurysms than among aneurysms located in either MCA or ACA (87.7%), but the difference was not statistically significant. Previous rupture of the aneurysm had no statistical significance for technical feasibility.

The reasons for technical failures are shown summarized in Table 11.

Table 11. Reasons for technical failures in 39 aneurysms.

Reason	Number of aneurysms
Aneurysm neck too wide to retain coils	22
Unable to catheterize aneurysm	11
Aneurysm diameter too small	1
Instability of the first coil	1
Vasospasm	1
Thromboembolic complication	2
Inadvertent ethanol injection	1
Total	39

The most common reason for technical failure (22 cases) was a wide aneurysm neck, which did not allow the coils to remain inside the aneurysm sac. The dome-to-neck ratio was 1.5 or less in all but one of these cases (range from 1.0 to 1.71; mean 1.19, SD 0.21). In two cases the balloon remodeling technique was used, but the first coil prolapsed into the parent vessel after deflation of the balloon in both patients, and none of the coils could be detached. In one of these two cases an MCA aneurysm had been previously clipped. Follow-up angiography was done upon recurrent SAH, and it revealed residual aneurysm after clipping.

The aneurysm could not be catheterized in 11 cases, mostly due to tortuous vessels. Among these cases, there were four small AcomA aneurysms, four MCA bifurcation aneurysms (one giant, one large, and two small), one large OphtA aneurysm, one small PcomA aneurysm, and one small distal ACA aneurysm.

These 39 unsuccessful treatment attempts included 6 procedural complications (15.4%) with 5.1 % morbidity (two patients) and 2.6% mortality (one patient). The single case with a fatal outcome is presented in detail in Appendix (cases of procedural mortality). Twenty-seven of these 39 aneurysms were later surgically clipped, while 12 of them remained untreated (unruptured 6, ruptured 6). One of these ruptured aneurysms had been previously clipped (partial occlusion with rebleeding) prior to the attempt at endovascular treatment (resulting in technical failure), and no further surgical treatment was attempted in this case. Four of the patients with a ruptured aneurysm that did not allow endovascular treatment were in a poor clinical condition (H&H 4 or 5), obviating surgical treatment, and one of them died due to a complication of attempted endovascular treatment.

5.2 Initial angiographic results

The initial angiographic results of 416 saccular aneurysms (with 39 technical failures excluded) according to the location, size, and neck width of the aneurysm are summarized in Table 12. In Table 13, the initial angiographic results are presented separately for the three treatment periods. The results according to the treatment method used are summarized in Table 14.

In terms of complete occlusion, no statistically significant difference was seen between ruptured and unruptured aneurysms (25.7% vs. 25.8%). The difference between the location of the aneurysm in the territory of anterior or posterior circulation had no statistical significance, either (26.3% vs. 22.9%). Complete occlusions were significantly more common among small than large aneurysms (28.4% vs. 16.5%). Giant aneurysms were too few to allow statistical analysis. There was no statistically significant difference between wide (dnr=1.5 or less) and narrow-necked (dnr>1.5) aneurysms (26.7% vs. 24.3%) in the rate of complete occlusions. Complete occlusions among aneurysms treated with the balloon remodeling technique were significantly less common than among the cases where standard coiling was used (13.0% vs. 26.5%, Table 14). The percentages of complete occlusion among the aneurysms treated with parent artery occlusions (75.0%) or stent remodeling (37.5%) were higher than those of standard coiling (26.5%) or

balloon remodeling technique (13.0%), but there were too few cases for statistical analysis.

Table 12. Initial angiographic results of 416 aneurysms according to the location, size, and neck width of the aneurysms.

Aneurysm characteristics	Occlusion grade						Total	
	Complete		Neck remnant		Incomplete			
	n	%	n	%	n	%	n	%
Location								
ICA	35	21.7	98	60.9	28	17.4	161	100
MCA	18	24.3	44	59.5	12	16.2	74	100
ACA	38	34.2	58	52.3	15	13.5	111	100
VBA	16	22.9	41	58.6	13	18.6	70	100
Size								
Small	87	28.4	164	53.6	55	18.0	306	100
Large	16	16.5	70	72.2	11	11.3	97	100
Giant	4	30.8	7	53.9	2	15.4	13	100
Neck width (dnr)								
≤1.5	65	26.7	130	53.5	48	19.8	243	100
>1.5	42	24.3	111	64.1	20	11.6	173	100

Table 13. Initial angiographic results of 416 saccular aneurysms (with 39 technical failures excluded). The results were divided into three cathegories according to the time of treatment. The results of the entire data set are shown at the bottom. The percentages represent the percentages of treated aneurysms on each row.

Time period (No. of aneurysms)	Occlusion grade					
	Complete		Neck remnant		Incomplete	
	n	%	n	%	n	%
1993-1997 (91 aneurysms)						
Total	15	16.5	48	52.7	28	30.8
Ruptured	12	19.4	29	46.8	21	33.9
Unruptured	3	10.3	19	65.5	7	24.1
1998-2000 (152 aneurysms)						
Total	35	23.0	91	59.9	26	17.1
Ruptured	27	22.7	69	58.0	23	19.3
Unruptured	8	24.2	22	66.7	3	9.1
2001-2004 (173 aneurysms)						
Total	57	32.9	102	59.0	14	8.1
Ruptured	37	32.2	68	59.1	10	8.7
Unruptured	20	34.5	34	58.6	4	6.9
1993-2004 (416 aneurysms)						
Total	107	25.7	241	57.9	68	16.3
Ruptured	76	25.7	166	56.1	54	18.2
Unruptured	31	25.8	75	62.5	14	11.7

Table 14. Initial angiographic results of saccular aneurysms treated with standard coiling, parent artery occlusion, balloon remodeling or stent remodeling.

Treatment technique	Occlusion grade						Total	
	Complete		Neck remnant		Incomplete			
	n	%	n	%	n	%	n	%
Standard coiling	95	26.5	203	56.7	60	16.8	358	100
PA occlusion	3	75.0	1	25.0	0	0.0	4	100
Balloon remodeling	6	13.0	33	71.7	7	15.2	46	100
Stent remodeling	3	37.5	4	50.0	1	12.5	8	100

In terms of incomplete occlusion, no statistically significant difference was detected between ruptured and unruptured aneurysms (18.2% vs. 11.7%), between small and large aneurysms (18.0% vs. 11.3%) or between aneurysms located in the territory of anterior or posterior circulation (15.9% vs. 18.6%). Wide-necked (dnr 1.5 or less) aneurysms resulted significantly more often in incomplete occlusion than aneurysms with a narrow neck (19.8% vs. 11.6%). No statistically significant difference was found between aneurysms treated with the balloon remodeling technique or standard coiling (15.2% vs. 16.8%).

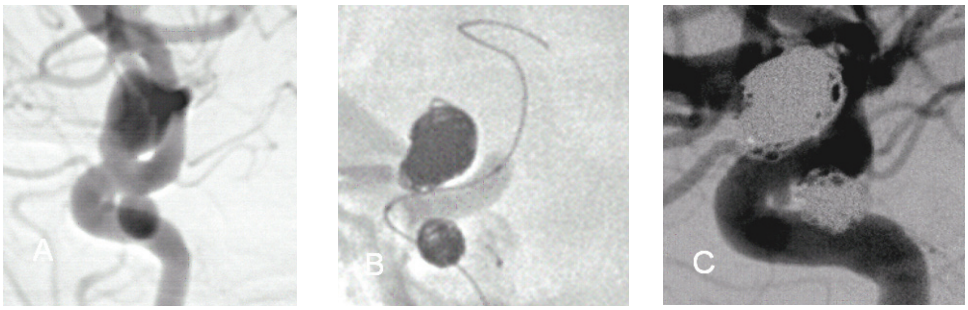

Fig. 8. Multiple ICA aneurysms incidentally found in a 57-year-old female. Initial angiography revealed 3 aneurysms in left ICA (A). Two of the aneurysms were successfully treated with the balloon remodeling technique (B), while the third (located extradurally) was too small for coil embolization. Follow-up angiography 3 years after the treatment shows complete occlusion in both treated aneurysms, while the third has remained unchanged (C).

5.3 Follow-up angiographic results

At least one follow-up angiography was performed on 330 treated saccular aneurysms (79.3 % of treated aneurysms, 85.0 % of survivors). The lengths of angiographic follow-up for 416 saccular aneurysms are summarized in Table 15. For 86 aneurysms (20.7%), there was no angiographic follow-up available. The causes for missing angiographic follow-up are summarized in Table 16. Long-term (at least 3 years) angiographic follow-up was available for 214 of the 330 saccular aneurysms eligible for follow-up (64.8%).

Table 15. Lengths of angiographic follow-up.

Months	Number of aneurysms	% of aneurysms
≥60	88	21.2
36-59	126	30.3
12-35	54	13.0
<12	62	14.9
None	86	20.7
Total	416	100

Table 16. Reasons for missing angiographic follow-up.

Reason	Number of aneurysms
Patient died before follow-up angiography	29
Follow-up angiography scheduled later than 2005	12
Patient's poor clinical condition	16
Patient lost to follow-up	12
Follow-up in another hospital	9
Patient too old	3
Patient refused	3
Aneurysm was operated	2
Total	86

In Table 17, the follow-up angiographic results are separately represented according to aneurysm location and size. The follow-up angiographic occlusion rates are summarized in Table 18 separately for each of the three treatment periods. In Table 19, the follow-up angiographic results are represented according to the treatment method used. Follow-up angiography data was available for all of the four aneurysms treated with PA occlusion, for 38 of the 46 (82.6%) aneurysms treated with the balloon remodeling technique, and for 6 of 8 (75.0%) aneurysms treated with the stent remodeling technique.

In terms of complete occlusion, no statistically significant differences emerged between ruptured and unruptured aneurysms (34.8% vs. 44.3%) or between small and large aneurysms (39.9% vs. 32.9%). Giant aneurysms were too few to allow statistical analysis. When posterior circulation aneurysms were compared to anterior circulation aneurysms, complete occlusions were significantly less common among posterior circulation aneurysms (25.4% vs. 40.2%). There was no statistically significant difference in complete occlusions between wide and narrow-necked aneurysms (38.8% vs. 35.9%) or between aneurysms treated with the balloon remodeling technique or standard coiling (31.6% vs. 37.0%). All of the four aneurysms treated with parent artery occlusion and 57.1% of the aneurysms treated with the stent remodeling technique were completely occluded in follow-up (not enough cases for statistical analysis).

In terms of incomplete occlusion, no statistically significant differences were detected between ruptured and unruptured aneurysms (14.6% vs. 8.2%) or between small and large aneurysms (14.3% vs. 8.9%). Giant aneurysms were too few to allow statistical analysis, as were also posterior circulation aneurysms. Incomplete occlusions were highly significantly more common among wide-necked aneurysms compared to aneurysms with a narrow neck (17.6% vs. 6.3%). The difference in incomplete occlusions between

aneurysms treated with the balloon remodeling technique or standard coiling was not statistically significant (23.7% vs. 11.7%).

Table 17. Follow-up angiographic results of 330 saccular aneurysms according to the location and size of the aneurysm.

Aneurysm characteristics	Occlusion rate						Total	
	Complete		Neck remnant		Incomplete			
	n	%	n	%	n	%	n	%
Location								
ICA	52	40.3	56	43.4	21	16.3	129	100
MCA	21	41.2	26	51.0	4	7.8	51	100
ACA	36	39.6	42	46.2	13	14.3	91	100
VBA	15	25.4	40	67.8	4	6.8	59	100
Size								
Small	95	39.9	109	45.8	34	14.3	238	100
Large	26	32.9	46	58.2	7	8.9	79	100
Giant	3	23.1	9	69.2	1	7.7	13	100
Neck width (dnr)								
≤ 1.5	73	38.8	82	43.6	33	17.6	188	100
> 1.5	51	35.9	82	57.7	9	6.3	142	100

Table 18. Follow-up angiographic results of 330 saccular aneurysms.

Time period (No. of aneurysms)	Occlusion grade					
	Complete		Neck remnant		Incomplete	
	n	%	n	%	n	%
1993-1997						
(80 aneurysms)						
Total	36	45.0	26	32.6	18	22.5
Ruptured	21	39.6	18	33.9	14	26.4
Unruptured	15	55.6	8	29.6	4	13.8
1998-2000						
(122 aneurysms)						
Total	36	29.5	68	55.7	18	14.8
Ruptured	26	27.4	54	56.9	15	15.8
Unruptured	10	37.0	14	51.8	3	11.1
2001-2004						
(128 aneurysms)						
Total	52	40.6	69	53.9	7	5.5
Ruptured	34	39.5	46	53.5	6	7.0
Unruptured	18	42.9	23	54.8	1	2.4
1993-2004						
(330 aneurysms)						
Total	124	37.6	164	49.7	43	12.7
Ruptured	81	34.8	118	50.6	35	14.6
Unruptured	43	44.3	46	47.4	8	8.2

Table 19. Follow-up angiographic results of saccular aneurysms treated with standard coiling, parent artery occlusion, balloon remodeling, or stent remodeling.

Treatment technique	Occlusion rate						Total	
	Complete		Neck remnant		Incomplete			
	n	%	n	%	n	%	n	%
Standard coiling	104	37.0	144	51.2	33	11.7	281	100
PA occlusion	4	100	0	0.0	0	0.0	4	100
Balloon remodeling	12	31.6	17	44.7	9	23.7	38	100
Stent remodeling	4	57.1	3	42.9	0	0.0	7	100

The follow-up angiographic results according to the initial angiographic occlusion grades are represented in Table 20, where the angiographic results of the aneurysms that underwent endovascular retreatment are represented as prior to retreatment. During follow-up, the initial angiographic occlusion grade spontaneously changed in 46.1% of the aneurysms (improved in 24.8% and deteriorated in 21.2%). When compared with the initial occlusion grades (Table 13), the difference in occlusion grades is statistically highly significant.

During follow-up, endovascular retreatment was performed on 79 (20.4%) of the treated aneurysms. The pre-existing occlusion grade improved in 44.3% of the retreatments. Among neck remnants, occlusion grade improved to complete occlusion in 25.0% of the aneurysms, while in 75.0% the classification of occlusion did not change. Among incomplete occlusions, in 60.5% of the aneurysms the occlusion grade improved (to complete occlusion in 14.0% and to neck remnant in 46.5%), and 39.5% of them resulted in unchanged classification of occlusion grade. (Table 21).

Subsequent surgical clipping was performed on 19 (5.0%) of the aneurysms. In the case of 4 aneurysms, endovascular retreatment was performed prior to surgical clipping, and thus either endovascular or surgical (or both) retreatment was done on 94 aneurysms (22.6% of the treated aneurysms). The pre-existing angiographic classification among these clipped aneurysms was neck remnant in 7 and incomplete occlusion in 12 cases.

Table 20. Spontaneous evolution of angiographic occlusion grade in 330 saccular aneurysms.

Initial angiographic result	Follow-up angiographic result (prior to possible retreatment)						Total	
	Complete occlusion		Neck remnant		Incomplete occlusion			
	n	%	n	%	n	%	n	%
Complete occlusion	40	51,9	34	44,2	3	3,9	77	100
Neck remnant	62	31,0	105	52,5	33	16,5	200	100
Incomplete occlusion	6	11,3	14	26,4	33	62,3	53	100
Total	108	32,7	153	46,4	69	20,9	330	100

Table 21. Follow-up angiographic results of the 79 aneurysms that underwent endovascular retreatment.

Pretreatment angiographic result	Follow-up angiographic result after retreatment						Total	
	Complete occlusion		Neck remnant		Incomplete occlusion			
	n	%	n	%	n	%	n	%
Neck remnant	9	25.0	27	75.0	0	0.0	36	100
Incomplete occlusion	6	14.0	20	46.5	17	39.5	43	100
Total	15	19.0	47	59.5	17	21.5	79	100

5.4 Treatment complications

Ninety-six of the 583 (16.5%) treatment procedures were complicated. Seventy-nine of the complications occurred during the procedure (Fig. 9 and 10) and 17 of them were delayed (Fig. 11). Four patients with multiple embolization procedures each had 2 treatment sessions that included a complication. There were procedural complications in the treatment of 92 out of 455 aneurysms (20.2% of all aneurysms, 19.9% of ruptured aneurysms, and 20.9% of unruptured aneurysms, with no statistically significant difference).

Among 583 treatment procedures, there were 10 lethal complications (mortality rate 1.7%) and 39 clinically symptomatic complications at discharge (morbidity rate 6.7%). In 47 cases, the complication did not cause any clinical symptoms, or the symptoms had completely resolved by the time of discharge. Eighty-two of the complications occurred during the initial treatment (complication rate 18.9%) and 14 during retreatment (complication rate 9.4%). The difference between the complication rates between initial and retreatments was statistically very significant. The procedural mortality and morbidity rates for initial treatments were 2.3% and 8.3% and those for retreatments 0.7% and 2.0%, respectively. The difference in the morbidity rate of initial treatments compared to retreatments was statistically very significant. The cases of procedural mortality were too few to allow statistical analysis.

The complications, mortality, and morbidity of the treatments based on standard coiling of saccular aneurysms are summarized in detail in Table 22. The detailed results on complications associated with the parent artery occlusion and remodeling techniques are presented in Table 23. The treatments with the balloon remodeling technique were associated with a significantly higher complication risk than standard aneurysm coiling. There were not enough cases to allow relevant statistical analysis of parent artery occlusions or stent remodeling techniques. No mortality was associated with any of these three techniques. The procedural morbidity rates for parent artery occlusion, balloon remodeling, and stent remodeling were 25.0%, 9.8%, and 25.0%, respectively. One retreatment was performed uneventfully using a liquid embolic agent (Onyx).

Ten complications had a lethal outcome, and the overall procedural mortality rate was 1.7%. The most common reason for procedural mortality was aneurysm rupture (four

cases). In all of these cases, the aneurysm was small and had already bled with a clinical manifestation of SAH. Detailed information of the cases of procedural mortality is presented in Appendix (cases of procedural mortality).

Table 22. Treatment-related complication, mortality, and morbidity rates in 519 treatments of saccular aneurysms with standard coiling.

Complication type	Complications		Mortality		Morbidity	
	n	%	n	%	n	%
Procedural						
Aneurysm rupture	11	2.1	4	0.8	2	0.4
Thromboembolic event	34	6.6	1	0.2	19	3.7
Parent artery occlusion	4	0.8	0	0.0	2	0.4
Coil in parent artery	8	1.5	1	0.2	1	0.2
Coil migration	2	0.4	0	0.0	1	0.2
Coil broke	4	0.8	1	0.2	0	0.0
Parent artery dissection	1	0.2	0	0.0	0	0.0
Vasospasm	5	1.0	1	0.2	0	0.0
Ethanol injection	1	0.2	1	0.2	0	0.0
Anesthetic complication	1	0.2	0	0.0	0	0.0
Total	69	13.3	9	1.7	24	4.6
Delayed						
Cerebral ischemia	5	1.0	0	0.0	5	1.0
Increased mass effect	3	0.6	1	0.2	0	0.0
Increased cranial nerve compression	2	0.4	0	0.0	2	0.4
Total	10	1.9	1	0.2	7	1.4
Total	79	15.2	10	1.9	31	6.0

n = number of aneurysms

Table 23. Complications associated with treatments with the parent artery occlusion and remodeling techniques

Complication type	Parent artery occlusion (n=4)		Balloon remodeling (n=51)		Stent remodeling (n=8)	
	n	%	n	%	n	%
Thromboembolism	0	0.0	5	9.8	0	0.0
Vasospasm	0	0.0	0	0.0	0	0.0
Coil in parent artery	0	0.0	2	3.9	1	12.5
Parent artery occlusion	0	0.0	1	2.0	0	0.0
Parent artery dissection	0	0.0	0	0.0	1	12.5
Delayed cerebral ischemia	1	25.0	3	5.9	0	0.0
Increased mass effect	0	0.0	3	5.9	0	0.0
Total	1	25.0	14	27.5	2	25.0

n = number of aneurysms

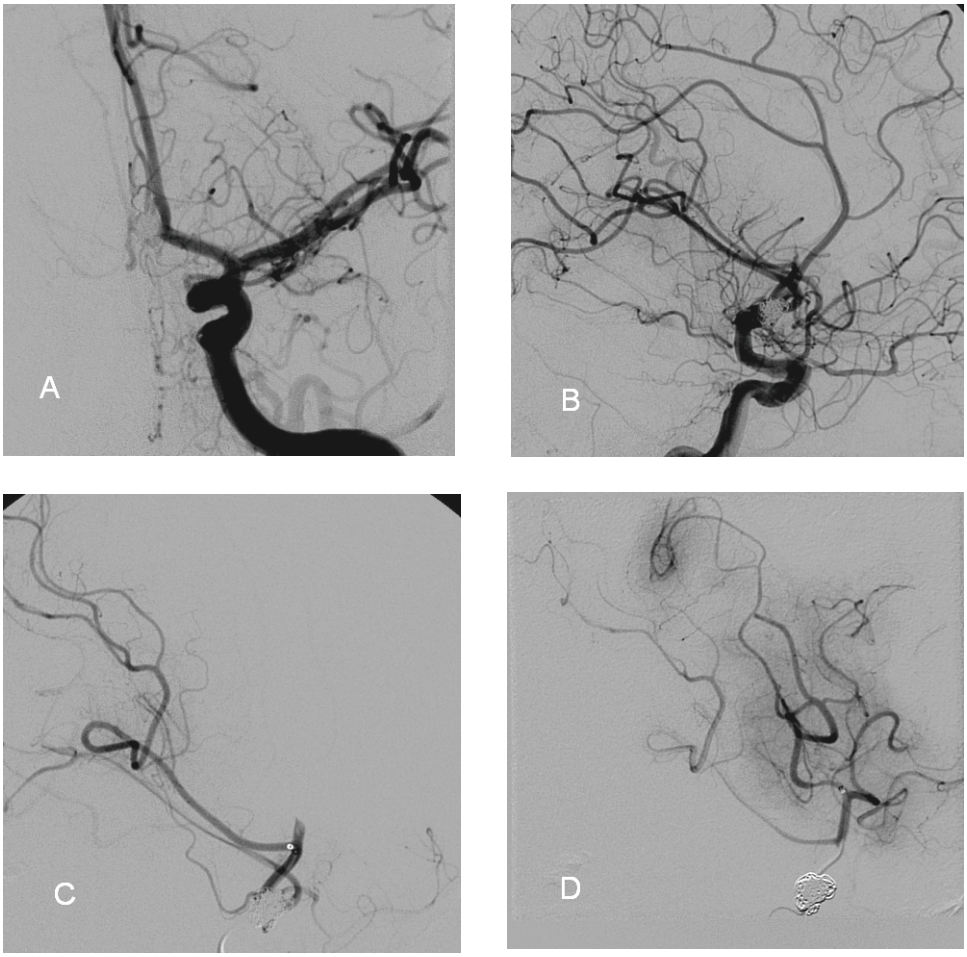

Fig. 9. Thromboembolic complication in the treatment of an acutely ruptured AcomA aneurysm. The aneurysm was coiled, resulting in minimal neck remnant (A). Postprocedural DSA revealed thromboembolic occlusion in the ipsilateral frontotemporal branch of MCA (B), which is clearly demonstrated in the superselective angiogram performed after selective catheterization with a microcatether (C). After recanalization and intra-arterial thrombolysis, the distal branches are well opacified (D). Clinically, the patient recovered without any deficits.

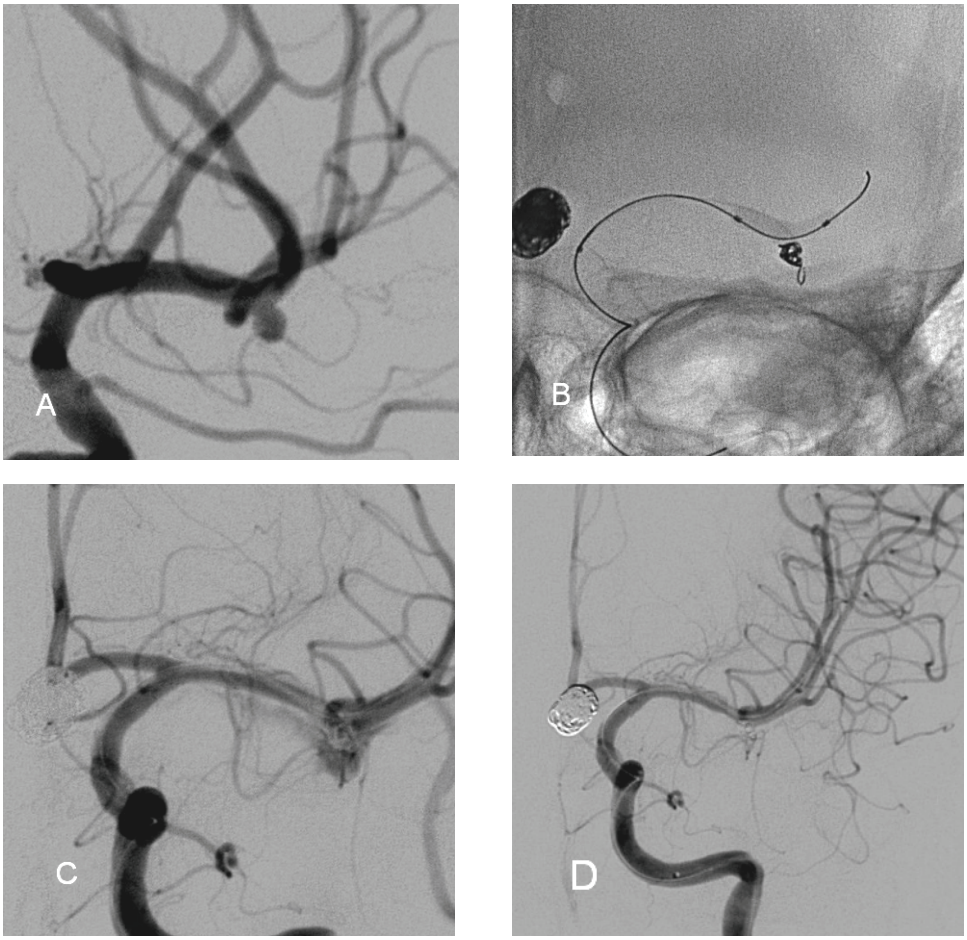

Fig. 10. Procedural aneurysmal rupture in the treatment of an unruptured MCA aneurysm. DSA revealed an incidental MCA aneurysm (A) in a patient, who had previously undergone endovascular treatment of a ruptured BA tip aneurysm. The balloon remodeling technique was applied. While deploying an ultrasoft coil, a coil loop ruptured the aneurysm wall (B). Subsequent angiography demonstrated extravasation of contrast into the ipsilateral Sylvian fissure (C). Heparinization was immediately reversed, and the balloon inflated across the aneurysm neck to control the bleeding. The final angiogram demonstrates complete occlusion of the aneurysm without extravasation (D). Clinically, the patient had moderate headache for a few days but recovered without any permanent sequelae.

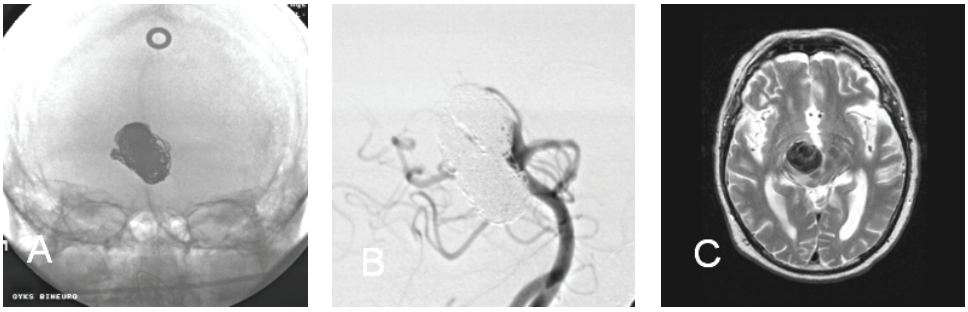

Fig. 11. A giant BA aneurysm was coiled in a 68-year-old male with ischemic symptoms probably due to embolies originating from the aneurysm. The patient underwent endovascular treatment of the aneurysm, and due to coil compaction, two retreatments were performed. The angiogram after the last treatment demonstrates a large coil mesh (A) and a small neck remnant (B). After the last treatment, the patient had new symptoms due to an increased mass effect. MRI showed that the size of the aneurysm had increased to 30mm (initially 25mm), and the aneurysm was compressing the midbrain (C).

5.5 Clinical follow-up

5.5.1 Clinical outcome

Clinical follow-up was possible for 356 patients with treated saccular aneurysm(s). Clinical follow-up data were missing due to technical failure of the treatment in the case of 31 patients (Table 24).

Table 24. Causes of death during follow-up.

Cause of death	Number of patients	Percents of deaths
Procedural complication	10	29.4%
Initial disease (SAH)	13	38.2%
Rebleeding	6	17.6%
Increased mass effect	2	5.9%
Cancer	2	5.9%
Pneumonia	1	2.9%
Total	34	100%

In seven cases, the patient was lost to follow-up, and in six cases, the patient's permanent place of residence was abroad or in another university hospital district, and follow-up was thus performed elsewhere. In four cases, the scheduled follow-up had not yet been performed by the time of data analysis. Two patients were excluded from follow-up due to either refusal or early surgery of the endovascularly treated aneurysm. In one case, no clinical follow-up was scheduled. The mean follow-up time (± SD) was 38.2 ± 27.1 months (39.8 ± 27.3 months among 278 patients with a history of SAH and 32.6 ± 25.4

months among 78 patients with no history of SAH). A total of 34 patients (9.6%) died during the follow-up. The clinical follow-up results are summarized in Table 25.

Table 25. Clinical follow-up results in 356 patients.

Patient	GOS								Pearson
	4-5		2-3		1		total		χ^2-test
	n	%	n	%	n	%	n	%	p-value
Gender (n=356)									
male	135	79.4	15	8.8	20	11.8	170	100	>0.05
female	154	82.8	18	9.7	14	7.5	186	100	
Age (n=356)									
<20 years	1	50.0	0	0.0	1	50.0	2	100	
20-29 years	7	87.5	1	12.5	0	0.0	8	100	
30-39 years	31	86.1	1	2.8	4	11.1	36	100	
40-49 years	92	86.8	5	4.7	9	8.5	106	100	0.01
50-59 years	91	80.5	10	8.8	12	10.6	113	100	
60-69 years	49	79.0	8	12.9	5	8.1	62	100	
70-79 years	18	64.3	7	25.0	3	10.7	28	100	
80 years or older	0	0.0	1	100.0	0	0.0	1	100	
SAH (n=356)									
yes	217	78.1	31	11.2	30	10.8	278	100	<0.05
no	72	92.3	2	2.6	4	5.1	78	100	
H&H (n=256)									
1-2	128	91.4	4	2.9	8	5.7	140	100	
3	43	81.1	6	11.3	4	7.5	53	100	<0.01
4-5	27	42.9	20	31.7	16	25.4	63	100	
Fisher (n=189)									
1	15	100.0	0	0.0	0	0.0	15	100	
2	29	87.9	1	4.0	3	13.0	33	100	<0.01
3	27	90.0	2	6.7	1	3.3	30	100	
4	70	63.1	22	19.8	23	12.2	111	100	
Treatment									
Complication (n=356)									
yes	62	72.9	9	10.6	14	16.5	85	100	<0.05
no	227	83.8	24	8.9	20	7.4	271	100	
Timing (n=278)									
0-3 days	137	78.7	17	9.8	20	11.5	174	100	
4-7 days	52	78.8	6	9.1	8	12.1	66	100	>0.05
8-30 days	25	75.8	6	18.2	2	6.1	33	100	
>30 days	3	60.0	2	40.0	0	0.0	5	100	
Total (n=356)	289	81.2	33	9.3	34	9.6	356	100	

In statistical analysis, good clinical outcome was highly significantly associated with the patients' younger age and better pretreatment clinical condition (lower H&H grade) and with less abundant bleeding (lower Fisher grade) seen in the CT scan. History of SAH

and complicated treatment (any procedural complication) were significantly associated with a poorer outcome. The patient's gender and the timing of the treatment did not have statistically significant impacts on outcome. (Table 25)

5.5.2 Rebleedings

Thirteen (3.7%) of the 356 patients eligible for clinical follow-up experienced intracranial hemorrhage after aneurysm treatment. The intervals between the initial endovascular treatment and the rebleeding ranged from 0 days to 57 months (mean ± SD, 17.2 ± 19.6 months). The cases are presented in detail in Appendix (cases of recurrent bleeding).

In further analysis, three patients were excluded from the cohort of recurrent bleedings because the treated aneurysm was not the source of bleeding in these cases. In one patient (patient 152, Appendix), the source of recurrent bleeding was verifiably another untreated aneurysm. In another case (patient 185, Appendix), the previously treated aneurysm was completely occluded, and the recurrent bleeding originated from a *de novo* aneurysm. In the third case (patient 304, Appendix), the source of recurrent bleeding was judged to be located inside the ventricle, where ventriculostomy catheters had been replaced several times. After these corrections, the number of patients with intracranial bleeding from an endovascularly treated aneurysm was ten (2.8% of the patients eligible for follow-up). The cases are summarized in Table 26.

Table 26. Characteristics of the aneurysms showing bleeding during clinical follow-up. The figures in parenthesis indicate the total number of aneurysms within the cell. Statistical analysis was done for a combination of ruptured and unruptured aneurysms.

Aneurysm characteristics	Recurrent bleeding									p-value
	Ruptured (n=286)			Unruptured (n=112)			Total (n=398)			
	n		%	n		%	n		%	
Size										<0.01
Small	4	(211)	1.9	0	(79)	0.0	4	(290)	1.4	
Large	3	(69)	4.3	1	(26)	3.8	4	(95)	4.2	
Giant	2	(6)	33.3	0	(7)	0.0	2	(13)	15.4	
Location										>0.05
ICA	3	(115)	2.6	1	(41)	2.4	4	(156)	2.6	
MCA	2	(43)	4.7	0	(27)	0.0	2	(70)	2.9	
ACA	2	(92)	2.2	0	(14)	0.0	2	(106)	1.9	
VBAs	2	(36)	5.6	0	(30)	0.0	2	(66)	3.0	
Occlusion grade										<0.01
Complete	0	(72)	0.0	0	(28)	0.0	0	(100)	0.0	
Neck remnant	2	(160)	1.3	0	(70)	0.0	2	(230)	0.9	
Incomplete	7	(54)	13.0	1	(14)	7.1	8	(68)	11.8	
Total	9	(286)	3.1	1	(112)	0.9	10	(398)	2.5	

There were 398 endovascularly treated aneurysms (with the technical failures excluded) among the patients eligible for clinical follow-up. Nine of the bleedings occurred from

previously ruptured aneurysms, and in one case a previously unruptured aneurysm bled 51 months after the initial treatment (Fig.12). Two of the patients with ruptured aneurysm(s) (0.7%) showed early rebleeding (within 30 days after treatment), while in seven cases (2.4%) the recurrent bleeding occurred more than 30 days after the treatment.

The risk for further bleeding from a treated aneurysm was 3.1% in previously ruptured aneurysms and 0.9% in previously unruptured aneurysms. The bleeding risk was highly significantly associated with large aneurysm size and the pre-existing occlusion grade of the treated aneurysm. There was no statistically significant difference in further bleedings between aneurysms located in the territories of ICA, MCA, ACA, or VBA. (Table 26)

The annual bleeding risks after endovascular treatment of intracranial saccular aneurysms are represented in Table 27. The overall annual bleeding risk per treated aneurysm during follow-up was 0.79 % (0.95 % for ruptured aneurysms, 0.33 % for unruptured aneurysms).

Table 27. Annual bleeding risk after aneurysm embolization among the patients included in clinical follow-up (n=356).

Follow-up	Total	Ruptured	Unruptured
Number of patients	356	278	78
Number of aneurysms	398	286	112
Bleedings	10	9	1
Range (months)	1-138	1-138	2-110
Mean (months)	38.2	39.8	32.6
Total (months)	15204	11382	3651
Total (years)	1267.0	948.6	304.3
Annual bleeding risk /aneurysm	0.79%	0.95%	0.33%

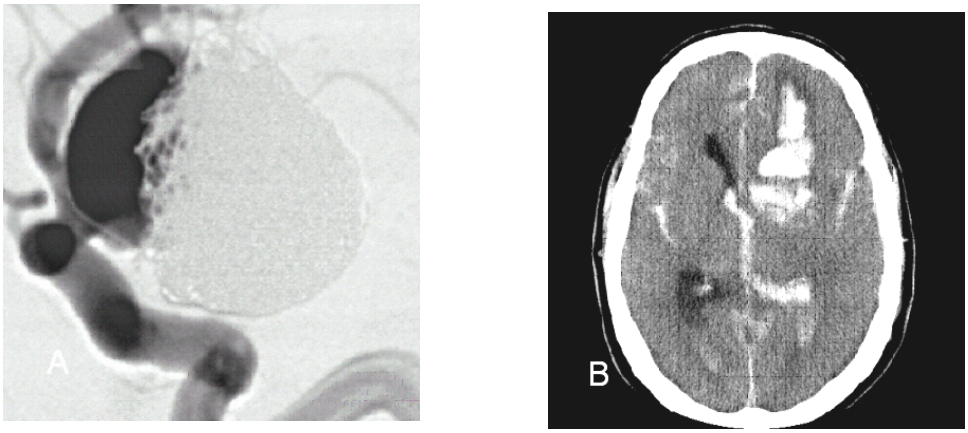

Fig. 12. A 39-year-old male experienced oculomotor nerve paresis, and a large unruptured OphtA aneurysm was treated with coil embolization. Residual filling in the aneurysm sac was detected in follow-up angiography (A). CT revealed bleeding due to aneurysm rupture (B) 51 months after the initial treatment and 3 months after the last angiographic follow-up. (case 147, Appendix, cases of recurrent bleeding)

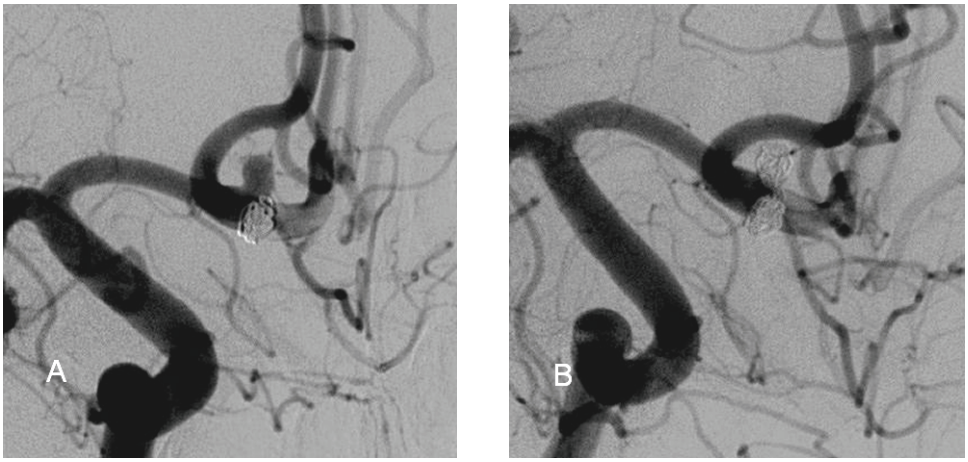

Fig. 13. A 36-year-old male had recurrent bleeding 57 months after initial SAH. A completely occluded AcomA aneurysm and a *de novo* aneurysm opposite to the previously coiled aneurysm are demonstrated in DSA (A). Follow-up angiography one month after the endovascular treatment of the *de novo* aneurysm shows complete occlusion of both aneurysms (B). (case 185, Appendix, cases of recurrent bleeding)

5.5.3 Symptomatic unruptured aneurysms

The outcomes of 30 patients treated for a symptomatic unruptured aneurysm are summarized in Table 28. Four of the aneurysms (13.3%) were treated by parent artery occlusion, and in the rest of the cases, the aneurysm sac was packed with coils, preserving the parent artery. One patient with trochlear nerve paresis died due to a procedural complication, and the effect of the treatment could not be assessed. Epilepsy was considered to be cured, if antiepileptic medication was discontinued and the patient remained seizure-free during the follow-up.

Table 28. Outcomes of 30 patients treated due to symptomatic unruptured aneurysms.

Symptom	Cured		Improved		Unchanged		Worse		Dead		Total
	n	%	n	%	n	%	n	%	n	%	n
3rd nerve palsy	4	33.3	4	33.3	3	25.0	1	8.3	0	0.0	12
Other cranial nerve palsy	0	0.0	1	25.0	2	50.0	0	0	1	25.0	4
Epilepsy	2	33.3	0	0.0	3	50.0	1	16.7	0	0.0	6
Embolic events	3	60.0	0	0.0	0	0.0	2	40.0	0	0.0	5
Headache	2	66.7	0	0.0	1	33.3	0	0.0	0	0.0	3
Total	11	36.7	5	16.7	9	30.0	4	13.3	1	3.3	30

5.6 Dissecting aneurysms

There were 12 dissecting aneurysms among the 467 aneurysms included in this study. The cases are summarized in Table 29.

Female gender was overrepresented in this subgroup of dissecting aneurysms (83%). The patients' ages ranged from 23 to 72 years (median 49.3 years). The aneurysms were exclusively located in the territory of posterior circulation, and PICA was the most common site (67%). All except one patient experienced SAH prior to embolization. The presenting symptom in patient 365 was headache.

Table 29. Details of the 12 patients who had dissecting aneurysms treated.

Patient number	Sex/age	Aneurysm location	SAH	H&H	Treatment method	Initial angiographic result	Follow-up angiographic result	Follow-up time, months	GOS
8	F/46	PICA	yes	4	Std.coiling	failure	-	-	-
28	F/34	PICA	yes	1	PAO	complete	complete	63	5
106	F/23	PCA	yes	1	PAO	complete	complete	3	5
143	M/64	PICA	yes	1	PAO	complete	complete	49	5
188	F/60	PICA	yes	3	Std. coiling	incomplete	neck	18	5
207	F/45	VA	yes	5	Std. coiling	complete	complete	27	3
308	F/47	VA	yes	1	Stent	neck	complete	33	5
324	F/72	AICA	yes	2	Std. coiling	incomplete	incomplete	23	5
346	F/52	PICA	yes	2	PAO	incomplete	complete	1	5
347	F/42	PICA	yes	5	Std. coiling	neck	-	0.5	1
365	F/46	PICA	no	0	PAO	incomplete	complete	8	5
406	M/60	PICA	yes	1	PAO	failure	-	-	-

SAH = subarachnoid hemorrhage, H&H = Hunt & Hess grading for preprocedural clinical condition, GOS = Glasgow outcome scale, F = female, M = male, PICA = posterior inferior cerebellar artery, PCA = posterior cerebral artery, VA = vertebral artery, AICA = anterior inferior cerebellar artery, Std. = standard, PAO = parent artery occlusion.

Five of the 12 aneurysms were treated, and one aneurysm was scheduled for treatment with parent artery occlusion (6/12, 50%). The technical feasibility of PAO in the treatment of intracranial dissecting aneurysms was 83.3%. In the case of technical failure (case 406), the intention was to glue the parent artery (a distal very narrow branch artery of PICA) via a 1,2F microcatheter, but the branch appeared to be too small even for the smallest microcatheter available (Magic 1.2, Balt, France). This aneurysm was subsequently successfully clipped. Four of the treated aneurysms were located in PICA and one in distal PCA. Vascular anatomy was evaluated angiographically prior to treatment, to ensure the presence of potential collateral vessels. Test occlusion was performed in two cases prior to permanent occlusion of the vessel. In initial angiography after the procedure, 2/5 (40%) of the aneurysms demonstrated residual filling of the aneurysm sac, while 3/5 (60%) of them were completely occluded. In follow-up, all the 5 aneurysms showed complete occlusion. One of the treatments was complicated by external iliac artery dissection without clinical consequences, and another had a small

asymptomatic lacunar cerebellar infarct in postprocedural MRI (Fig.14). One additional patient had mild symptoms of hemisensory loss, which, however, resolved within two days. The procedural complication, morbidity, and mortality rates among these six dissecting aneurysms treated (or scheduled for treatment) with parent artery occlusion were 50.0%, 0%, and 0%, respectively.

The stent remodeling technique was applied in one case, where a dissecting VA aneurysm was embolized. Initial angiography revealed slight residual filling into the aneurysm sac, which was no more evident in angiographic follow-up (complete occlusion). The procedure was uncomplicated.

Standard coiling of the aneurysm sac was the method of choice in five dissecting aneurysms. One treatment resulted in technical failure (patient 8) due to procedural aneurysm rupture while catheterizing the aneurysm (technical feasibility 80%). This occurred very early in our experience, and the patient was transferred to emergency craniotomy according to the prevailing treatment policy. The patient did not survive. Among the four aneurysms treated with standard coiling, one VA aneurysm resulted in complete occlusion and no visible recurrence during angiographic follow-up. Two of these aneurysms were located in PICA. One of them was initially graded as incomplete occlusion, which, however, spontaneously improved to a neck remnant during follow-up. Another PICA aneurysm had a neck remnant in initial angiography, and no follow-up was performed in this case, because the patient died due to her disease (SAH). One dissecting AICA aneurysm was treated with standard coiling, and the angiographic result in this case was an incomplete occlusion, which did not change during follow-up despite one retreatment.

In summary, there were 4 procedural complications in 14 treatment sessions (patients 324 and 365 underwent two treatments), and the procedural complication rate was 28.6%. Procedural morbidity was 0% and mortality 7.1% (one patient). Nine of the patients (75.0%) had good clinical recovery, one patient (8.3%) was severely disabled, and two (16.7%) died. One death occurred due to iatrogenic aneurysm rupture, and one patient (patient 347) died due to the disease (SAH, initially H&H grade 5). One patient (patient 207) had persistent neurological deficits (hemiparesis, dysphasia, and cranial nerve deficits) due to the disease and was graded as GOS 3 (severely disabled). There were no recurrent SAHs among the patients who underwent endovascular treatment of dissecting aneurysms during follow-up.

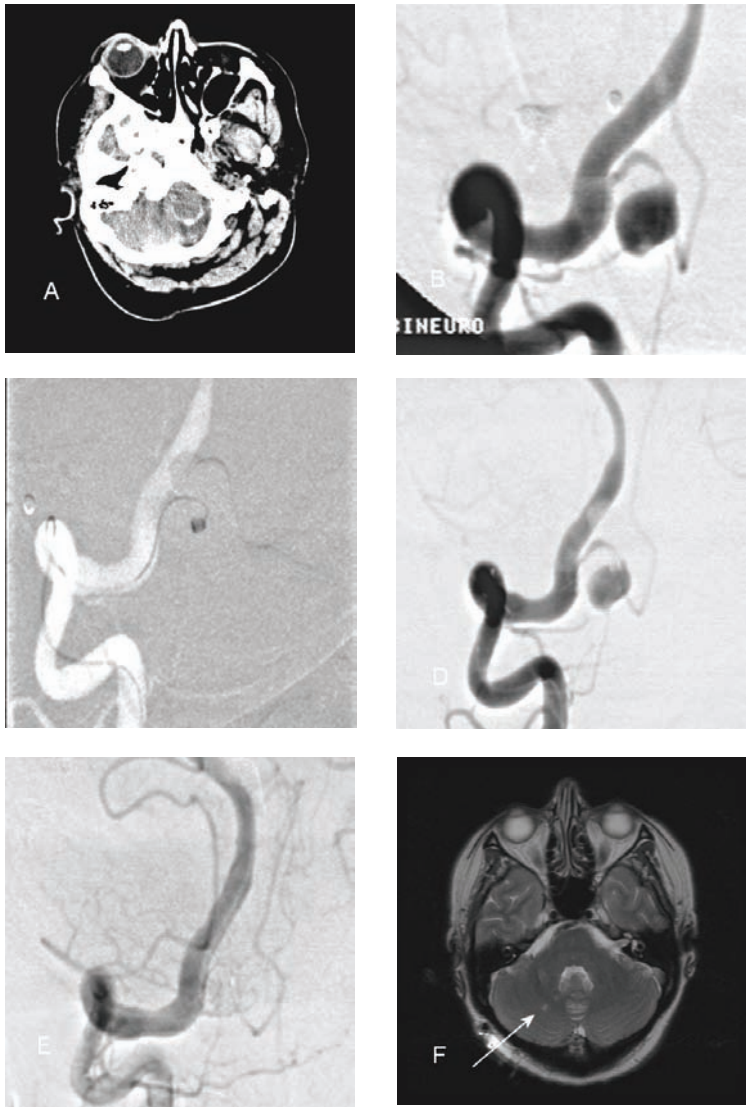

Fig. 14. Case 346. A 55-year-old female experienced acute headache, and CT scan revealed basal SAH with blood accumulation around the brain stem (A). Initial angiography was negative. The patient recovered and was discharged without follow-up angiography. Three weeks later she had recurrent bleeding, and repeat angiography revealed a dissecting aneurysm in left PICA (B). The aneurysm was treated by occluding the proximal PICA with one coil (GDC-10 2mm x 6cm SOFT) anchored to the aneurysm neck and the PICA origin in VA (C). Angiography immediately after the procedure showed residual flow in proximal PICA and aneurysm filling (D). Follow-up angiography revealed complete occlusion of proximal PICA and a dissecting aneurysm, while distal PICA was filling retrogradely by collateral flow from ipsilateral SCA (E). Postprocedural MRI revealed a small lacunar cerebellar infarct (arrow) without any clinical consequences (F).

5.7 Long-term improvement of treatment outcomes

When the overall study period is divided into three subperiods, we can see that the technical failure rate was 15.7% from 1993 to 1997, 9.0% from 1998 to 2000, and 3.9% from 2001 to 2004. The differences in failure rates between the three periods are statistically very significant ($p<0.01$). The percentages of failed treatment attempts among treated aneurysms per year are represented in Figure 15.

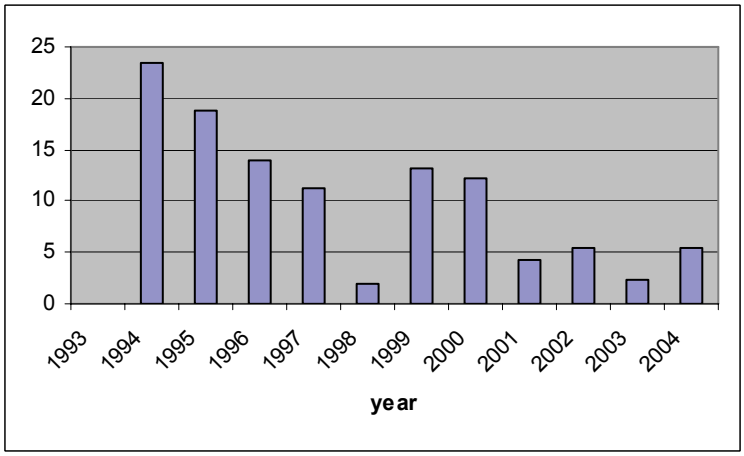

Fig. 15. Percentage of technical failures among treated aneurysms per year.

The angiographic occlusion grades are presented separately for the three periods in Table 13 for the initial results and in Table 18 for the follow-up results. The improvement of the initial angiographic occlusion grades in terms of complete (16.5%, 23.0%, and 32.9% during the first, second, and third periods, respectively) and incomplete (30.8%, 17.1%, and 8.1% during the first, second, and third periods, respectively) occlusion between the three treatment periods was statistically very significant (Table 13). In follow-up, the differences between complete occlusions (45.0%, 29.5%, and 40.6% during the first, second, and third periods, respectively) had no statistical significance, but in terms of incomplete occlusion (22.5%, 14.8%, and 5.5% during the first, second, and third periods, respectively), the improvement was very significant (Table 18).

Endovascular retreatment was performed on a total of 79 saccular aneurysms. The percentages of retreated aneurysms were 35.2%, 20.4%, and 12.7% for the first, second, and third treatment periods, respectively. The difference between the periods is statistically very significant.

According to the time of treatment, the complication rates were 15.2% during the first period, 15.8% during the second period, and 18.4% during the third period. The differences between the complication rates within the treatment periods are not statistically significant. The procedural mortality rate was 2.5% during the first period, 1.5% during the second period, and 1.3% during the third period. There were not enough cases for statistical analysis. The morbidity rates for the three treatment periods were

5.1%, 6.9%, and 7.6%, respectively (no statistically significant difference). The combined morbidity and mortality rates were 7.6%, 8.4%, and 9.0% during the first, second, and third time periods, respectively (no statistically significant difference).

6 Discussion

The present study consisted of a consecutive series of 416 patients treated or admitted for treatment of intracranial aneurysm(s) with endovascular embolization in Oulu University Hospital between December 1993 and July 2004. Oulu University Hospital is the only neurovascular center in Northern Finland (its catchment area comprising a population of 725,000), and there is thus no referral bias in the study population. The mean annual case flow during the study period was approximately 40 aneurysms per year, which means that Oulu University Hospital can be classified as a high-volume hospital in terms of endovascular treatment of intracranial aneurysms (Hoh *et al.* 2003). In many previous reports, the study population has been recruited based on aneurysm characteristics (location, size, previous rupture, etiology), patient characteristics (age, clinical condition), or embolization technique (aneurysm occlusion, parent artery occlusion). Unlike most previous reports, this study included all the intracranial aneurysms treated or admitted for treatment during the time of data collection without selection. Our very early experience from the very first case onward was included. The number of patients (416) and aneurysms (467) in this study is the largest so far reported from the Scandinavian countries (Kähärä *et al.* 1999b, Vanninen *et al.* 1999, Rodriquez-Catarino *et al.* 2003, Cronqvist *et al.* 2005, Norbäck *et al.* 2005) and one of the largest among single-center studies worldwide. The present study included 12 dissecting aneurysms, all of them located in the posterior circulation and eight of them specifically in PICA. This is the largest single-center series of isolated dissecting PICA aneurysms reported so far (Maimon *et al.* 2006). The average clinical follow-up time (38.2 months) is relatively long compared to other published series.

Most of the data of the present study was collected retrospectively, which resulted in limitations considering about the unstrict protocols of patient selection, angiographic follow-up, and clinical follow-up. There was no systematic postprocedural imaging (CT, MRI, or DWI), which means that clinically silent brain complications may have remained undetected. Neither neuropsychologic examination nor subsequent epilepsy was included in this study due to the heterogeneity of the information available retrospectively from patient records.

6.1 Technical feasibility of treatment

In the present study, endovascular treatment was technically feasible in 91.4% of the saccular aneurysms. The percentage of technical failures significantly decreased during the ten years of experience, and during the last four years of this study, the technical feasibility rate exceeded 96%. The results are in accordance with other published endovascular series, in which the technical feasibility rates range from 84% to 97% (Raymond & Roy 1997, Vanninen *et al.* 1999, Molyneaux *et al.* 2002, Ng *et al.* 2002, Murayama *et al.* 2003b, Henkes *et al.* 2004b, Norbäck *et al.* 2005). Direct comparison between series is, however, difficult or impossible due to the variation in patient selection and other factors.

A wide aneurysm neck was by far the most important reason for technical failure. Among aneurysms with a narrow neck, the technical failure rate was only 3.9%. Another important reason for technical failures was the inability to catheterize the aneurysm. Due to anatomical reasons, aneurysms in the territory of VBA can usually be catheterized without difficulties, and no catheterization failures occurred concerning saccular VBA aneurysms in the present series. In the territory of the anterior circulation, catheterization failures occurred more often among more distally located ACA and MCA aneurysms compared to more proximally located ICA aneurysms, which can be explained by anatomical reasons.

6.2 Angiographic results

In the present study, complete aneurysm occlusion was initially achieved in 25.7% of the saccular aneurysms and in follow-up in 37.6%. In terms of the percentage of complete occlusions, the initial angiographic results are slightly inferior to the majority of results from previously published endovascular series, and the follow-up angiographic results are at the lower limit of the published series, where complete occlusion has been achieved initially in 33-66% of the treated aneurysms and in follow-up in 35-77% (Table 5). The results obtained during the last four years of the follow-up of the present series (complete occlusion initially in 32.9% of saccular aneurysms) are significantly better than the overall results, being comparable to the lower limit of the published series (Friedman *et al.* 2003, Cronqvist *et al.* 2005). In terms of incomplete occlusions, the results of the present study (16.3% initially and 12.7% in follow-up) are in the range of the other published series (5-38% initially and 2-16% in follow-up). The overall angiographic results in the present series are significantly influenced by the unselected study population, which also makes direct comparison to other series with selected patient groups impossible.

Several factors may explain the low percentage of completely occluded aneurysms in the present study. The estimation of aneurysm occlusion is subjective. According to the ACTIVE study (*Matrix* newsletter 2003), interobserver error was huge between the doctors performing the treatment and the independent core lab (consensus result of three independent fellowship-trained angiographers). While the centers performing the procedures reported 54% of the aneurysms to be completely occluded, the core lab

approved only 15% of the aneurysms to be completely occluded. Some authors have also defined at least 98% occlusion as complete (Sluzewski *et al.* 2003). In the present study, all angiograms were retrospectively analyzed by two reviewers in consensus. Strict criteria for the classification of complete occlusion were used, and in several cases the initially reported complete occlusion was re-evaluated to have a neck remnant. Therefore, we were most likely to be even stricter than the average in accepting occlusions as complete.

In the present study, a higher percentage of aneurysms were located in MCA (18.7%) compared to most other published series, where the percentage of MCA aneurysms has varied from 3.6% to 14.4% (Raymond & Roy 1997, Kuether *et al.* 1998, Byrne *et al.* 1999, Vanninen *et al.* 1999, Ng *et al.* 2002, Friedman *et al.* 2003, Murayama *et al.* 2003b, Henkes *et al.* 2004b, Cronqvist *et al.* 2005, Norbäck *et al.* 2005). MCA aneurysms are typically bifurcation type aneurysms, and their anatomy has often been considered unfavorable for endovascular treatment. The neck of an MCA aneurysm is often wide and incorporates MCA branches (Iijima *et al.* 2005). On the other hand, the anatomy of MCA aneurysms is usually favorable for neurosurgical clipping (Rinne *et al.* 1996). Surgery has thus remained the preferred treatment option for MCA aneurysms in many institutions. In the present series, complete occlusion was achieved in 24.3 % of all MCA aneurysms and specifically in 20.9% of MCA bifurcation aneurysms, which is slightly less than the average for aneurysms of other locations (27.0%), but the difference is not statistically significant. However, the small percentage of completely occluded aneurysms can be only partially explained by the overrepresentation of MCA aneurysms in the present series. The recent literature has demonstrated that MCA aneurysms can also be successfully treated with endovascular techniques. In one of the most experienced centers in the field of neurointerventional radiology, a 77.2% complete occlusion rate among 149 endovascularly treated MCA aneurysms was reported (Iijima *et al.* 2005).

There were a few cases in the present series where the aneurysm neck was intentionally left open to secure the patency of the parent artery or the arterial branches originating from the aneurysm neck. Complete occlusion of the aneurysm would have resulted in ischemic complications in these cases, and partial aneurysm occlusion was considered a better option for the patient than sacrificing the branch artery.

Parent artery occlusion was performed in the treatment of four saccular aneurysms in this study. Of these aneurysms, 75.0% were completely occluded initially and all in follow-up. In one case (25.0%) the parent artery and the aneurysm showed slight residual filling at the end of the embolization procedure, and complete occlusion was demonstrated in follow-up angiography. Parent artery occlusion is only feasible in cases where sufficient collateral flow is maintained by collateral arteries. Despite a passed occlusion test, higher complication and morbidity rates have been reported with parent artery occlusion compared to the reported rates with aneurysm packing with coils (Higashida *et al.* 1991, Brilstra *et al.* 1999, Vanninen *et al.* 1999, Henkes *et al.* 2004b, Molyneux *et al.* 2005). The present cases were too few to allow statistical analysis. All of the parent artery occlusions among the treatments of saccular aneurysms were performed early in our experience, and the single ischemic complication was delayed and occurred a few days after the treatment of an acutely ruptured aneurysm. This delayed complication was due to vasospasm, which caused a significant decrease in initially sufficient collateral flow.

Since the visual grading of aneurysm occlusion is more or less subjective and subject to limitations, as previously discussed, more objective and reliable methods for evaluating aneurysm occlusion should be developed. Measurement of the embolized volume of the aneurysm lumen, defined as the ratio of coil volume to aneurysm volume, could be useful in addition to angiographic assessment (Tamatani *et al.* 2002, Sluzewski *et al.* 2004). The volume of inserted coils can be accurately measured, whereas accurate calculation of aneurysm volume from 2D angiographic images is more complex (Sluzewski *et al.* 2004). Using 3D imaging and volume measurement software, aneurysm volume can also be accurately measured. In an experimental study, Piotin *et al.* (2003b) found that 3DRA is the most precise method to assess aneurysm volume, and CTA is more accurate than MRA. At present, 3DRA is performed in all cases of intracranial aneurysms in our practice.

Because aneurysm recurrence, coil compaction, and enlargement of the residual neck may occur after endovascular treatment of intracranial aneurysms, long-term angiographic follow-up is generally considered necessary (Thornton *et al.* 2002). A recurrence rate of 33% was reported in a large single-center study (Raymond *et al.* 2003b). Compaction of the coil mesh due to the "water hammer effect" of the pulsatile blood flow is believed to be the most important contributing factor for aneurysm recurrences (Sluzewski *et al.* 2004). A significant correlation between embolized volume and stability of embolized aneurysms has been reported (Tamatani *et al.* 2002, Sluzewski *et al.* 2004). Sluzewski *et al.* (2004) found that, if the aneurysm volume was packed by at least 24%, compaction did not occur in aneurysms with a volume of <600 mm^3. In small aneurysms (volume <200 mm^3), compaction did not occur when more than 20% of the aneurysm volume was packed. In large aneurysms (volume >600 mm^3), high volumetric packing could not be achieved, resulting in compaction in most cases (Sluzewski *et al.* 2004). Volumetric analysis was not used in the present study due to the difficulty of reliable measurement of aneurysm volume from 2D DSA images.

In the present study, 330 saccular aneurysms had angiographic follow-up (79.3% of all treated saccular aneurysms), and 64.8% of them were followed up for at least 3 years. The length of angiographic follow-up was less than one year in 62 cases (14.9% of all aneurysms). This short-term follow-up is not sufficient to predict the natural course of the aneurysm, unless parent artery occlusion has been performed. Most of these aneurysms were treated during the last two years of the study, and follow-up angiograms were not yet available during the data collection. For 86 aneurysms (20.%), angiographic follow-up was not available, mostly due to the patient's death or poor clinical condition. During the follow-up, only 53.9% of the aneurysms remained stable (angiographic occlusion grade did not change), while the initial occlusion grade improved in 24.8% of the cases and deteriorated in 21.2%. These figures are well in line with the findings of Ng *et al.* (2002), but huge variation in the stability of coiled aneurysms has generally been reported in the literature (Thornton *et al.* 2002). The initial occlusion grades improved due to spontaneous subsequent thrombosis after treatment, while coil compaction explains the majority of decrease. The instability of the angiographic results in follow-up underlines the need for angiographic follow-up to detect the aneurysms requiring further treatment. In the present study, either endovascular or surgical retreatment was performed in 22.6% of the treated aneurysms. In the series of Raymond *et al.* (2003b), 20.7% of the aneurysms presented with major recurrences indicating retreatment after a mean period of

16.5 months. In view of the substantially longer follow-up time in the present study, the retreatment/major recurrence rates are comparable. Endovascular retreatment improved the angiographic occlusion grade in 25.0% of the neck remnants and in 60.5% of the incompletely occluded aneurysms. In fact, at least minor improvement in aneurysm occlusion occurred in all retreatments, if any coil could be deployed, but the amount of improvement did not necessarily change the occlusion grade determined by a modified Raymond scale.

Complete occlusions were significantly more common among small than large aneurysms in initial angiography, but the difference in follow-up results was not statistically significant. It is usually technically easier to achieve complete occlusion of a small aneurysm, where less coils are needed, and the neck is more often suitable to retain the smaller filling coils needed to finish the coiling procedure successfully. No significant difference was detected between wide and narrow-necked aneurysms in the number of complete occlusions in either initial or follow-up angiography, but wide-necked lesions resulted in incomplete occlusions significantly more commonly than those with a narrow neck. It might be assumed that complete occlusions were more common among narrow-necked aneurysms. In the present study, neck width was determined by the ratio of the length of the aneurysm dome to the diameter of the neck, and the absolute neck width was not taken into account. By using this dome-to-neck ratio, many large aneurysms with an absolute neck width of more than 4 mm were classified as narrow-necked aneurysms (dnr>1.5), which most probably explains the findings on complete occlusions.

The percentage of complete occlusions in follow-up was significantly lower among posterior circulation aneurysms than among those located in the anterior circulation. Almost two thirds of posterior circulation aneurysms were located at the tip of the basilar artery. BA tip aneurysms are bifurcation aneurysms with direct inflow from the basilar artery and outflow into the P1 arteries branching off at a relatively steep angle. Thus, for anatomical reasons, these aneurysms are more prone to coil compaction due to the water hammer effect. On the other hand, posterior circulation aneurysms are poor candidates for surgery, and practically all posterior circulation aneurysms were treated with endovascular coiling during the present series, despite the width of the aneurysm neck, which was not optimal for endovascular treatment in many cases.

Angiographic follow-up examinations in the present study were exclusively performed using DSA. DSA is an invasive study carrying an inherent, though low risk for complications (Willinsky *et al.* 2003), and hospitalization of the patient is necessary. In many institutions, noninvasive MRA has replaced DSA as an imaging method in follow-up studies (Kähärä *et al.* 1999a, Cronqvist *et al.* 2005, Molyneux *et al.* 2005). MRA has a capability for 3D imaging and pontential advantages over 2D DSA in showing small remnants, which can be masked by coil mesh in routinely obtained projections in DSA. Recently, we performed 3DRA in follow-up angiographies for acquiring 3D images for better estimation of the complex vascular anatomy. However, 3DRA images must always be confirmed by traditional 2D DSA in selected projections because, especially in large aneurysms, high coil volume causes artefacts in volume-rendered 3D reconstruction images. In practice, MRA may replace DSA in long-term follow-up if it has been "calibrated" to DSA by performing the initial follow-up angiography using both methods. Subsequent follow-up examinations can thereafter be performed by using MRA, and further DSA may be indicated only if the occlusion state deteriorates.

6.3 Complications

The present procedural complication rate among treatments of saccular aneurysms was 16.7%, which is in the range of the complication rates (from 8.4% to 23%) in other published endovascular series (Brilstra *et al.* 1999, Vanninen *et al.* 1999, Ng *et al.* 2002, Friedman *et al.* 2003, Murayama *et al.* 2003b, Henkes *et al.* 2004b, Cronqvist *et al.* 2005, Norbäck *et al.* 2005). The procedural mortality and morbidity rates were 6.7% and 1.7%, respectively. The procedural morbidity and mortality rates are comparable with those in other endovascular series, the variation in morbidity rates being 3.7-9.1% and that in mortality rates 1.5-7.8%, respectively (Raymond & Roy 1997, Kuether *et al.* 1998, Brilstra *et al.* 1999, Vanninen *et al.* 1999, Ng *et al.* 2002, Murayama *et al.* 2003b, Henkes *et al.* 2004b).

Treatments with the balloon remodeling technique were associated with a significantly higher complication risk than standard coiling (25.2% versus 15.2%), and the majority of complications associated with the balloon remodeling technique were ischemic. Soeda *et al.* (2004) reported the balloon remodeling technique to be an independent prognostic factor for ischemic complications. The present results support this finding. Direct comparison between the balloon remodeling technique and standard coiling is impossible, however, because the remodeling techniques were used in the present study only in cases of wide-necked aneurysms considered untreatable by standard coiling, or in cases where standard coiling had been attempted but failed. Use of the remodeling technique makes the procedure more time-consuming and complex.

Contrary to balloons, stents are foreign bodies that will be permanently implanted inside the vessel lumen. Use of the stent remodeling technique carries an increased risk for thrombosis due to the thrombogenity of the stent material. Optimal antithrombotic medication (acetylsalic acid and clopidrogel) is thus required whenever the stent remodeling technique is used. Aggressive antithrombotic medication is contoversial in the treatment of an acutely ruptured intracranial aneurysm. When the stent has been deployed, the patient must be on antithrombotic therapy even if the subsequent coiling of the aneurysm is not successful. Without antithrombotic medication, the risk for in-stent thrombosis and subsequent parent artery occlusion is significant. In the present series, we had one fatal rebleeding after a stent remodeling procedure in the treatment of an acutely ruptured wide-necked PcomA aneurysm, where the stent was deployed but subsequent coiling was postponed due to migration of the stent (case 312, Appendix, cases of recurrent bleeding). Nowadays, many authors consider the stent remodeling technique contraindicated in the treatment of acutely ruptured aneurysms due to the risks associated with antithrombotic medication. My personal opinion is that stents should be avoided in the treatment of acutely ruptured aneurysms if any safer option (i.e. surgery, balloon remodeling, staged procedure) is feasible to secure the aneurysm. For example, in the case of a wide-necked and large aneurysm, where the site of bleeding (secondary pouch) is located in the fundus, it might be better to initially occlude the aneurysm sac as well as possible with the standard coiling or balloon remodeling technique and to leave the neck intentionally open. The neck can thereafter be coiled in a second session with the help of a stent after the patient has recovered from the bleeding.

A significantly lower complication rate was associated with retreatments compared to initial treatments. Similar findings have been reported by other authors (Friedman *et al.* 2003, Henkes *et al.* 2004b). By the time of retreatment of a ruptured aneurysm, the patient has most probably already recovered from the acute SAH and is no longer at a hypercoagulative stage, which situation resembles more or less the treatment of unruptured aneurysms. However, this theory cannot explain the finding, because no significant difference emerged between the complication rates of the treatments of ruptured or unruptured aneurysms in the present series or has been reported in the literature (Brilstra *et al.* 1999, Henkes *et al.* 2004b). The risk for iatrogenic aneurysm rupture is most probably lower in retreatments, where the fundus (usually the weakest portion of the aneurysm and the site of rupture) is usually well packed with coils, and the treatment is focused on the neck. Because aneurysm ruptures can explain only approximately 10% of all procedural complications, this is not enough to explain the significant reduction in complication rates. On the basis of our experience, we could not find any explanation or even sufficient theory for this phenomenon, which has also remained unsolved in previous studies (Brilstra *et al.* 1999, Henkes *et al.* 2004b).

All non-neurologic complications were also recorded in the present study, as were temporary and clinically asymptomatic complications. Systematic postprocedural CT or MRI imaging was not done, but when, in postprocedural imaging studies done for any clinical indication, a new ischemic lesion was detected, it was recorded as a procedural complication if it was not clinically clearly related to any other abnormality, such as vasospasm secondary to SAH. Procedural thromboembolic events were the most common complication in the present study, occurring in 6.5% of the treatments, which is well in line with the other published endovascular series (Malich *et al.* 1997, Kuether *et al.* 1998, Pelz *et al.* 1998, Brilstra *et al.* 1999, Murayama *et al.* 1999, Henkes *et al.* 2004b). In 46.2% of the treatments complicated by thromboembolic events in the present study, the complication did not cause clinical symptoms, or the symptoms ceased before discharge. In most of these cases, the embolus either dissolved spontaneously or by successful thrombolysis. In our practice, intra-arterial thrombolysis was avoided in the treatment of acutely ruptured aneurysms until sufficient occlusion of the aneurysm had been achieved. Earlier during the present series, thrombolysis was performed by intra-arterial infusion of urokinase, but we have later used intravenous boluses of abciximab (2-10 mg) with good results. In a few cases, sufficient collateral flow into the territory of the occluded vessel prevented infarctation or decreased the size of infarction resulting in only minor or no clinical symptoms. Some small clinically silent infarcts might have remained undetected due to missing systematic postprocedural imaging. Procedural thromboembolic complications caused morbidity in 51.3% of the cases and accounted for 50% of the overall procedural morbidity. Mortality was associated with procedural thromboembolies only in one case (2.6%). The morbidity rate of 51.3% for thromboembolic complications in the present study is slightly lower than that reported by Pelz *et al.* (1998), in whose series 58.8% of the thromboembolic complications resulted in stroke.

Procedural aneurysm ruptures occurred in 2.0% of all treatments in the present study, which is at the lower limit of the reported endovascular series (Guglielmi *et al.* 1992, Valavanis *et al.* 1996, Raymond & Roy 1997, Vinuela *et al.* 1997, Cognard *et al.* 1998, McDougall *et al.* 1998, Ricolfi *et al.* 1998, Vanninen *et al.* 1999, Doerfler *et al.* 2001, Ng

et al. 2002, Henkes *et al.* 2004b, Cronqvist *et al.* 2005, Norbäck *et al.* 2005). One explanation for the low percentage of procedural aneurysm ruptures in the present study might be the relatively loose level of aneurysm packing (and the lower stress against the aneurysmal wall while deploying the coils), especially in our early experience, which in turns resulted in less complete angiographic occlusion.In the present study, iatrogenic aneurysm ruptures (n=11) had a lethal outcome in 36.4% of the cases and a morbidity rate of 18.2%. Procedural aneurysm ruptures accounted for 45.5% of all procedural mortality. The treatment of procedural aneurysm ruptures improved during the present study period, as did the outcome of the patients. In our early experience, patients were referred to emergency craniotomy at such an incidence of procedural aneurysm rupture (two cases resulting in lethal outcome). Later on, the treatment consisted of immediate reversal of heparinization by protamine sulfate, control of blood pressure, and continuation of the embolization procedure, which in turns resulted in better outcomes (mortality and morbidity rates of 22.2% and 22.2%, respectively). In a meta-analysis of 17 publications, a combined risk of permanent neurological disability or death among patients with procedural aneurysm rupture was 38% (Cloft & Kallmes 2002). If the two cases in our early experience are excluded, the present results are comparable with those reported by Cloft & Kallmes (2002).

Eighteen of the treatment procedures (3.1%) resulted in inadvertent positioning of coil(s) or coil loop(s) outside the aneurysm cavity. The coil loop(s) protruded into the parent artery in 14 cases, of which in 5 cases resulted in subsequent occlusion of the parent artery. In two cases the coil migrated distally from the aneurysm. The incidence of such technical complications is well comparable with the large series by Henkes *et al.* (2004b), where coil malpositioning was reported in 3.0% of the treated aneurysms. Protrusion of a coil loop into the parent artery occurs commonly during coil deployment, but in most cases the coil can be retrieved into the microcatheter and redeployed into a sufficiently good position. Sometimes a loop of a previously detached coil may protrude into the parent vessel while additional coils are being deployed, and in this situation it may not be possible to retrieve the protruded coil. Occasionally it may be possible to reposition the protruding loop into the aneurysm sac with the help of a balloon or a stent (Lavine *et al.* 2000). One coil loop in the parent artery does not usually restrict the flow unless it is associated with thrombus formation. The risk of subsequent thrombosis is increased if larger coil segments protrude into the parent artery. In cases where the diameter of the detached coil is smaller than the length of the aneurysm neck, the entire coil may escape into the parent artery and migrate distally with the arterial blood flow. It may be possible to catch and retrieve a migrated coil by means of a specific coil retrieval device (snare). There were two cases of coil migration in the present series where the coil could not be retrieved. In the first case, a small 2mm coil migrated into distal PCA and was trapped in a small branch. Due to the small caliber of the vessel, retrieval was not attempted. In the second case, the migrated coil was caught by the snare, but retrieval failed, and the migrated coil was subsequently surgically removed at craniotomy from the MCA bifurcation, where it was trapped. If any coil or coil loop(s) remain inside the vessel lumen, good heparinization continued for few days has been our treatment policy during this series. Due to subsequent thrombosis, 38.9% (7/18) combined morbidity and mortality was, however, associated with the complications of permanent coil malposition.

Delayed (hours or days after the procedure) ischemic events occurred after 10 procedures (1.7%) in the present study. Pelz *et al.* (1998) reported as high as 12% incidence of delayed ischemic complications in their series of 59 patients. In most endovascular series, no delayed ischemic complications have been reported. The mechanism of delayed ischemic complications has been postulated to involve extension of the thrombus from the aneurysm sac into the parent vessel or fragments of a clot breaking free from the coiled aneurysm with residual flow in the coil interstices (Derdeyn *et al.* 2002). With patients having acute SAH, it is difficult or sometimes impossible to differentiate postprocedural ischemic complications from sequelae of vasospasm, although the highest incidence for vasospasm occurs 4 to 10 days after the hemorrhage. Without routine postprocedural imaging, clinically asymptomatic delayed ischemic complications may remain undetected. Delayed postprocedural ischemia has been reported to occur as late as nine weeks after embolization (Studley *et al.* 2002). In such cases, the clot inside the coiled aneurysm should be well organized, and the mechanism is probably different from that previously described. One explanation could be perianeurysmal inflammation causing parent artery stenosis. Coil embolization and subsequent thrombosis of an aneurysm may cause up to 15% aneurysm enlargement (Wanke *et al.* 2004). Transient enlargement of the aneurysm cavity may occur due to increased capillary permeability of the neovessels within the evolving thrombus (Wanke *et al.* 2004). The increased mass effect may compress the adjacent structures and cause morbidity and mortality. An increased mass effect was detected after six endovascular treatments in the present series (1.0%), causing morbidity in one case and mortality in another. Recently, we have used periprocedural corticosteroid therapy when treating giant or very large aneurysms to decrease perianeurysmal inflammation after the treatment. However, the benefit of this therapy is unproven (Wanke *et al.* 2004).

6.4 Clinical outcome

The mean follow-up time in the present series was 38.2 months for saccular aneurysms, which is substantially longer than in most published endovascular or surgical series (Tables 4 and 6). Of the patients who experienced SAH due to aneurysm rupture, 78.1% recovered to resume independent life (GOS 4-5), 11.2% remained dependent (GOS 2-3), and 10.8% died (GOS 1). These results are well in line with the clinical results of other endovascular and surgical series, represented in the Tables 4 and 6. The present results are also well comparable with the results of the ISAT study, where 76.5% of the patients in the endovascular group were independent at one-year follow-up, while only 69.1% of the surgically treated patients recovered enough to resume independent life (Molyneux *et al.* 2005). Of the patients with an unruptured aneurysm treated, 92.3% resumed independent life, 2.6% remained dependent, and 5.1% died during the follow-up. The present results are in the range of the two endovascular series reporting unruptured aneurysms (Ng *et al.* 2002, Henkes *et al.* 2004b) (Table 6).

The present study confirmed that older patients and patients with a ruptured aneurysm, a worse preprocedural clinical stage, a larger amount of blood in the CT scan, or a procedural complication have significantly worse outcomes than younger patients and

patients with an unruptured aneurysm, a better preprocedural clinical condition, less bleeding in the CT scan, and/or an uncomplicated procedure.

The functional status of the present patients was assessed retrospectively from the patient files using the Glasgow Outcome Scale (GOS, Jennet & Bond, 1975). GOS provides summary measures of outcome and is considered relevant to clinicians and patients undergoing intervention for any kind of stroke (Kasner 2006). However, GOS is a relatively coarse indicator of the patient's functional status, but more delicate tests, such as modified Rankin Scale (mRS, Rankin 1957), Karnofsky Scale (KS, Karnofsky & Burchenal 1949), or Barthel Index (BI, Mahoney & Barthel 1965), were not considered to be useful in the present study due to the difficulties of retrospective classification and, on the other hand, the difficulty of comparing the results with other endovascular or surgical series, where GOS has most commonly been used. GOS, mRS, KS, and BI are based on the patient's self-report or proxy report (given by a spouse, partner, or caregiver) and may lead to overreporting of functional status (King *et al.* 2006). Another limitation of these tests is the ceiling effect (i.e. clustering of the patients at the high end of the scale), which was also evident in the present study as well as in the other endovascular or surgical series. To overcome these shortcomings, more precise tests, such as the Physical Performance Test (PPT), have been created. PPT is based on determination of functional status based on direct observation by trained personnel and may differentiate between patients better than GOS, mRS, KS, or BI. The PPT test has proven to be a valid and reliable instrument for measuring functional status in patients with intracranial aneurysms. (King *et al.* 2006)

In a series of 30 symptomatic unruptured aneurysms, the treatment was efficient in 53% of the cases (resulting in either complete resolution or alleviation of the symptoms). The best results were achieved in aneurysms causing oculomotor nerve palsy, embolic symptoms, or headache. The results are well comparable to those of other published endovascular series, where embolization was performed with either coils or Onyx, and with or without parent artery occlusion (Kazekawa *et al.* 2003, Rodriguez-Catarino *et al.* 2003, Stiebel-Kalish *et al.* 2003, Gonzalez *et al.* 2004, Lubicz *et al.* 2004, Lubicz *et al.* 2005b, Weber *et al.* 2005) and slightly better than the average in surgical reports, where 26-56% of the patients showed resolution or improvement of their symptoms (Drake 1979b, Peris & Ross Russell 1980, Ferguson & Drake 1981, Heros *et al.* 1983). Althought there are a few reports of aneurysms that spontaneously decrease in size or occlude, the majority of aneurysms increase in size, and the natural course of symptomatic unruptured aneurysms is not favorable (Kazekawa *et al.* 2003). To become symptomatic, the aneurysm has to grow, and the more it grows, the bigger is the risk for rupture (Wiebers *et al.* 2003). Growth may occur within a short time, resulting in a risk of rupture (Yonekura 2004). This underlines the fact that, in cases of symptomatic unruptured aneurysms, the treatment is not targeted only to resolve or improve the symptoms, but also to prevent rupture. In a study by Hashimoto & Handa (1982), the authors studied the outcome of untreated symptomatic unruptured aneurysms and reported that, in all cases, neurological symptoms persisted or slowly progressed over a long time, often resulting in aneurysm rupture and SAH.

Aneurysm swelling shortly after the procedure may result in transient aggravation of the mass effect. Later on, after the organization of the intra-aneurysmal thrombus, the aneurysm will shrink, and the mass effect gradually decreases (Wanke *et al.* 2004). Even

if the size of the aneurysm does not decrease, the decrease of pulsatility may improve the symptoms (Rodriguez-Catarino *et al.* 2003).

6.5 Rebleedings

The goal of our treatment is to prevent intracranial aneurysms from bleeding. In the present study, the risk of aneurysm rupture after endovascular treatment was 2.5% among all treated aneurysms, 3.1% among ruptured aneurysms, and 0.9% among unruptured ones. The annual bleeding risk after endovascular treatment was 0.79% for all aneurysms, 0.95 % for ruptured aneurysms, and 0.33 % for unruptured aneurysms. Compared to the natural course of untreated ruptured aneurysms described previously (a 35-40% rebleeding rate for 1-30 days after treatment), the value of endovascular treatment in preventing rebleedings is clear. The 3.1 % bleeding rate during a mean follow-up time of 39.8 months is in the range of the rates reported in other endovascular series (0-5%, Table 6). In the ISAT study, the rebleeding rate among ruptured aneurysms treated endovascularly was 3.3% during a mean follow-up time of four years (annual bleeding risk 0.83%)(Molyneux *et al.* 2005).

Larger aneurysm size and incomplete embolization are associated with an increased risk for aneurysm (re)rupture. As represented in Table 25, only two of the ten ruptured aneurysms in this series had neck remnants, while all the other ones were incompletely occluded. Actually, one aneurysm with a neck remnant after the initial treatment (case 286, Appendix, cases of recurrent bleeding) had progressed to incomplete occlusion, but this was missed because the follow-up angiography was canceled. According to our ongoing treatment policy, this would have indicated retreatment, and rebleeding could most likely have been avoided. This case underlines the importance of angiographic follow-up. In three cases (cases 58, 147 and 259, Appendix, cases of recurrent bleeding), endovascular or surgical retreatment was indicated, but was not performed due to the patient's poor clinical condition in two cases and the patient's refusal in one case. One patient (case 312, Appendix, cases of recurrent bleeding) refused to stay in bed despite the risk of rebleeding after stent deployment (coiling of the aneurysm was scheduled to be performed later), and by following the orders might have avoided this rebleeding. In a retrospective summary, five out of ten (50%) bleedings could possibly have been avoided.

Only two of the bleedings occurred within 30 days after the procedure (early rebleedings), two of them occurred between 30 days and one year after the procedure, and in six cases the interval between the procedure and the bleeding was more than one year. In the ISAT study, among the first 30 days after the treatment, the rebleeding rate was 1.9%, being 0.7% between 30 days and one year and 0.7%after one year (Molyneux *et al.* 2005). In their retrospective analysis, Sluzewski *et al.* found a 1.4% incidence of early rebleeding and a 1.27% incidence of late rebleeding (Sluzewski *et al.* 2005, Sluzewski & van Rooij 2005). Compared to these two series, the incidence of bleedings was more or less equal in the present study. However, more late rebleedings and fewer early rebleedings were detected in this study. The difference may be explained by our conservative approach to postprocedural anticoagulant and antithrombotic medication

(anticoagulant or antithrombotic medication was administrated only in response to specific indications, i.e. coil protrusion or stent deployment), which decreased the rebleeding risk in the early stage in cases of insufficient aneurysm occlusion. However, some of these incompletely occluded aneurysms ruptured later.

Interestingly, three of the rebled aneurysms (30%) had undergone previous surgery. The endovascular retreatment resulted in insufficient occlusion of all these aneurysms. This indicates that it is extremely problematic to sufficiently prevent some difficult lesions from further bleeding by either of these treatment options.

6.6 Dissecting aneurysms

The etiology of the treated aneurysm was dissecting in 12 of the present cases. All of these aneurysms were located in the posterior circulation, and in 8 cases (67%) specifically in PICA. Isolated dissecting aneurysms of PICA are reported to be rare (Locksley 1966, Kanou *et al.* 2000). Surgical treatment of dissecting PICA aneurysms carries a high risk of neurological complications due to the proximity of the aneurysm to the brain stem and the lower cranial nerves (Al-khayat *et al.* 2005). In endovascular treatment of PICA aneurysms, manipulation of these structures can be avoided. According to a recent report by Maimon *et al.* (2006), in addition to their series of 6 patients, only 4 case reports exist in the literature concerning the endovascular treatment of dissecting PICA aneurysms.

The technical feasibility of endovascular treatment of dissecting aneurysms in this series was 83.3% (two technical failures), which is less than in the case of saccular ones. However, cases of dissecting aneurysms are very few compared to saccular ones, and the figures are thus not strictly comparable. One patient with a distal PICA aneurysm died due to procedural aneurysm rupture, which occurred in our very early experience of the series (patient 8) while catheterizing the aneurysm in order to treat it with the standard coiling technique. The endovascular procedure was interrupted when the rupture occurred, and the patient was transferred to the operation room for emergency craniotomy. In retrospective evaluation of this case, parent artery occlusion might have been a better option to treat this lesion. On the other hand, continuation of aneurysm coiling instead of conversion to surgery might also have resulted in a more favorable outcome. Another technical failure was due to inability to catheterize a distal PICA branch of very small diameter, where a dissecting aneurysm was located. In this case, the smallest microcatheter available did not fit into this very narrow branch, and surgery was considered a better option than more proximal occlusion. Later on, this aneurysm was successfully trapped by a neurosurgeon.

Dissecting aneurysms are commonly more or less fusiform in shape, and in these cases, endovascular treatment can consist of parent artery occlusion, stenting, or stent-assisted coiling. Parent artery occlusion was successfully performed in 5 cases in the present series (PICA in 4 cases and distal PCA in 1 case). Vascular anatomy was evaluated by angiography prior to treatment to ensure the presence of potential collateral vessels. Test occlusion was performed in 2 cases prior to permanent occlusion of the parent vessel. According to the literature, anatomical studies and surgical and

endovascular experience indicate that, in most patients with PICA or distal PCA dissection, good collateral flow exists and bypass surgery is not necessary (Ali *et al.* 2002, Hallacq *et al.* 2002). In one of these 5 cases treated with parent artery occlusion, a small asymptomatic lacunar cerebellar infarct was detected in postprocedural MRI, and in another case transient symptoms of hemisensory loss were evident. No morbidity or mortality was associated with this technique.

One dissecting aneurysm located in the vertebral artery was treated with the stent remodeling technique without complications and with a good angiographic outcome (complete occlusion in follow-up). Standard coiling of the aneurysm sac was performed in 4 cases in the present study. Only one of these aneurysms (located in VA) resulted in complete occlusion, while two had neck remnants (both of them located in PICA), and one remained incompletely occluded (located in AICA). According to the present results, parent artery occlusion is a safe and effective method in the treatment of dissecting PICA aneurysms, and angiographic results are superior to those achieved with standard coiling of the aneurysm sac. These results confirmed the findings of Maimon *et al.* (2006), who reported 6 own cases and 4 additional cases from the literature (altogether 10 isolated dissecting PICA aneurysms) treated with parent artery occlusion with excellent angiographic results and without permanent morbidity.

In the present study, the procedural complication rate was higher among dissecting aneurysms than among saccular ones, but the combined morbidity-mortality rates and clinical outcomes were about equal. Cases of dissecting aneurysms were very few compared to saccular ones, which most probably explains the difference in complication rates. Clinically, the treatment was effective, since no rebleedings occurred during the follow-up among these patients.

6.7 Long-term improvement of treatment outcomes

Very limited data exist in the literature concerning the learning curve in endovascular treatment of intracranial aneurysms. According to three previous publications, the angiographic results are expected to improve and the complication rate to decrease following increased operator experience in endovascular embolization of intracranial aneurysms with coils (Malisch *et al.* 1997, Turjman *et al.* 1998, Singh *et al.* 2002).

The technical feasibility of the treatment significantly improved during the study period. Wide aneurysm neck and inability to catheterize the aneurysm were by far the most important reasons for technical failures in endovascular treatment of intracranial aneurysms. Most of the catheterization failures occurred in the early years of our experience. The improvement of microcatheters and guidewires as well as the increased experience of the operators have practically solved this problem, and nowadays failures of catheterization of the target aneurysm occur very seldom. Most of the failures associated with a wide aneurysm neck occurred before the introduction of remodeling techniques in Oulu University Hospital (balloon remodeling technique in December 1997 and stent remodeling technique in April 2001). By now, many of the wide-necked aneurysms unsuitable for conventional coiling can be treated with balloon or stent remodeling techniques. Only in two out of 48 cases (4.2%) where the balloon remodeling

technique was used did the treatment end in technical failure. There were no technical failures involved in the stent remodeling technique or parent artery occlusions in this series.

Several factors may explain the improvement of technical feasibility over time. In addition to the technical development of the tools available, the operators' skills have improved through increased experience. The selection criteria of aneurysms eligible for endovascular treatment have become better defined, and the preprocedural imaging of the aneurysm and the adjacent vessels has become more accurate due to increased experience and especially 3DRA imaging, which has been very valuable when making a decision on the treatment strategy. The possibilities and limitations of endovascular treatment have become better understood. In addition, the change in the anesthesia methods (general anesthesia exclusively used since February 1998) have most probably improved the feasibility of treatment.

The present results showed that the number of completely occluded aneurysms in initial angiography increased and the number of incompletely occluded aneurysms decreased significantly during the study period. In angiographic follow-up, the percentage of incomplete occlusions decreased very significantly due to increasing experience. The percentage of aneurysms that required retreatment also significantly decreased over time. There was no improvement in angiographic follow-up in terms of complete occlusions, most probably due the rate of retreatments among the aneurysms treated during the early years.

Contrary to previous reports (Malisch *et al.* 1997, Singh *et al.* 2002), no significant differences were detected in the total complication rates between the three periods of treatment. Many aneurysms were not packed very densely during the early years of the present study, when less tight packing or even partial occlusion (loose packing) was commonly accepted as the initial treatment result. Loose aneurysm packing made the procedure technically easier and quicker. The angiographic occlusion grades were poor, and many of the treated aneurysms had to be retreated later. Later on, the treatment strategy changed, and aneurysms have been more recently packed as tightly as possible. This has most likely been the main reason for the improvement of occlusion grades both initially and at follow-up. Dense packing is, however, technically more demanding and time-consuming compared to packing the aneurysm more loosely with coils. This is most likely one of the reasons explaining the fact that the total complication rate has not decreased over the years. The growing use of remodeling techniques has increased the risk for thromboembolic complications, but has otherwise decreased the incidence of inadvertent parent artery occlusions. Four radiologists were involved in the endovascular treatment of intracranial aneurysms during the present study. Thus, the series includes the learning curves of all the four operators, which may also explain the stability of the complication rates over time.

The impact of a single variable on the evolution of the results of endovascular treatment of intracranial aneurysms cannot be reliably determined, because so many variables influencing the results have changed or developed within a relatively short time. This also makes direct comparison of older endovascular series with more recent series difficult or downright impossible.

6.8 Future prospects of endovascular treatment

Initially, endovascular treatment was usually used only in cases that were poor candidates for surgery, especially in patients in a poor clinical condition or with posterior circulation aneurysms. By now, in many centers, including Oulu, endovascular treatment is considered the primary method in most cases that would also be suitable for surgery.

The most important limitations of endovascular treatment have been the inability to treat wide-necked aneurysms and the durability of the treatment. The introduction of balloon and stent remodeling techniques has enabled the treatment of most wide-necked aneurysms by endovascular coiling, but there are still important shortcoming especially in the stent technology that need to be solved. The development in stent technology is expected to provide more flexible stents with better navigability in the intracranial vessels in the near future to enable stent-assisted treatment in more distal aneurysms. The rigidity of stent-grafts has limited their use in lesions otherwise optimal for this kind of embolization device in ICA and VA aneurysms. It would also be interesting to design "customized" drug-eluting stents to decrease the risk of thrombotic complications in the parent artery as well as to increase the durability of the thrombosis at the neck of the aneurysm.

After the introduction of GDC, rapid development in the coil technology has taken place in the recent years. The development has gone towards 3D coils, which can be used throughout the procedure for excentric filling of the aneurysm sac (Cloft *et al.* 2000, Piotin *et al.* 2003a, Lubicz *et al.* 2005b). The coils have also become softer, enabling better accommodation to the complex shapes of aneurysms with a decreasing risk of rupture. Bare platinum coils have been increasingly replaced with coils having surface modifications aiming at better volumetric filling of the aneurysm (Hydrocoil, Micro Vention, Aliso Viejo, CA) or more stable occlusion of the aneurysm neck (Matrix, Boston Scientific, Fremont, CA and radioactive coils) (Murayama *et al.* 2003a, Raymond *et al.* 2003b, Cloft & Kallmes 2004, *Matrix newsletter* 2004). The rapid evolution of the technology for endovascular treatment of intracranial aneurysms has also raised some important ethical questions. New devices are coming and have already come on to the market without sufficient preclinical and clinical tests and proven safety or efficacy compared to the previous devices (Raymond *et al.* 2004b). Controlled clinical trials with comparison to the standard technique may not be possible in the evaluation of devices designed to assist the treatment of rare or previously untreatable cases (Moret *et al.* 1997, Raymond *et al.* 2001, Mawad *et al.* 2002, Higashida *et al.* 2005, Lylyk *et al.* 2005). The safety and efficacy of standard platinum coils have been proven, and endovascular procedures performed with them have yielded good clinical results (Molyneux *et al.* 2005). Before new type of coils with surface modifications are used to replace the standard platinum coils, they should be tested in large clinical trials with a control group of patients treated with standard platinum coils, to prove their safety and efficacy over the standard technique (Raymond *et al.* 2004b). Unfortunately, so far, only pilot studies have been published about the clinical use of these second-generation coils (Raymond *et al.* 2003b, Cloft & Kallmes 2004, *Matrix newsletter* 2004).

At the present, endovascular interventions address the structural consequences of the pathology rather than its biological basis. Combination of gene therapy and endovascular

techniques, used as a tool to deliver active molecules or living cells, will offer many interesting therapeutic possibilities in the future. Promoters, such as growth factors, may be transported to the aneurysm by a stent or coils. The current advances in gene therapy also include the potential use of circulating progenitor cells, which can be delivered after *ex vivo* genetic manipulations (Ribourtout & Raymond 2004). Several receptors associated with the remodeling of saccular intracranial aneurysm walls have already been identified, making them potential targets for bioactive endovascular implants or drug therapy to reinforce the aneurysm wall (Frösen *et al.* 2006). Many technical and conceptual problems will have to be solved, however, before this technology will become reality in the clinical practice.

As demonstrated by Wermer *et al.* (2005b) and also confirmed in the present study, aneurysmal SAH is not a single event in the lifetime. Recurrences occur even after initially completely occluded aneurysms. In addition, up to one third of patients harbor multiple aneurysms, and the formation of *de novo* aneurysms is possible. Imaging follow-up is mandatory after treatment to identify the patients who should undergo further treatment and thus to minimize the risk for further bleedings. The question remains – which method should be used and for how long?

7 Conclusions

In the present study, the angiographic and clinical results of 416 consecutive patients and 467 intracranial aneurysms allocated for endovascular treatment in Oulu University Hospital were analyzed.

1. Technical feasibility was mostly restricted by the wide aneurysm neck and the inability to catheterize the aneurysm. Increased experience and the development of devices caused technical feasibility to exceed 96%.
2. Only one fourth of saccular aneurysms showed complete occlusion in initial angiography, while neck remnant was the most common result (58%). Angiographic follow-up is mandatory, because occlusion grade spontaneously changed in almost half of the cases. Treatment was associated with 6.7% morbidity and 1.7% mortality, which must be taken into account when considering the treatment of an unruptured aneurysm. Almost four fifths of the patients treated for ruptured aneurysms recovered to resume independent life. By endovascular therapy, the rebleeding risk among ruptured aneurysms could be decreased below 1% per year.
3. Better angiographic results were associated with aneurysms of small size, with a narrow neck, and located in the anterior circulation. Young age, good pre-treatment clinical condition, no history of SAH, small amount of blood in the pretreatment CT scan, and uncomplicated procedure predicted a good clinical outcome. The risk for recurrent bleeding was associated with larger aneurysm size and incomplete occlusion.
4. During a long period in a single center, the technical feasibilty of treatment and the angiographic occlusion grades were improved, and fewer aneurysms needed retreatment. Procedural complication and combined morbidity/mortality rates did not significantly change.

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Appendices

Appendix 1 Cases of procedural mortality
Appendix 2 Cases of recurrent bleeding

Appendix 1 Cases of procedural mortality

Case 10. A 46-year-old female, who had previously been diagnosed with Fabry's disease, had acute SAH. A ruptured, giant basilar artery aneurysm was detected at the origin of the left SCA. Endovascular coiling was performed two days later. The aneurysm was wide-necked, and only partial occlusion was initially achieved. The patient had good clinical recovery. The aneurysm was retreated three times during the next two years due to coil compaction and regrowth, but the neck of the aneurysm could not be completely sealed. About four years after the initial treatment the patient experienced recurrent hemorrhage. At that time, dissection of the left intracranial vertebral artery was diagnosed (eccentric stenosis without pseudoaneurysm), and that might have been the origin of bleeding as well as the aneurysm. The aneurysm was further packed with coils, but residual filling of the neck was still evident after retreatment. Clinically, the patient was moderately disabled after the recurrent bleeding. In follow-up eight years after the initial treatment, recurrent filling of the aneurysm due to coil compaction and regrowth was noted again, and one additional retreatment was performed. A few hours after the treatment, the patient became unconscious and unresponsive. CT scan showed ischemic lesions in the brain stem and in both cerebellar hemispheres and obstructive hydrocephalus due to compression of the fourth ventricle. Despite ventriculostomy, the patient did not recover but died ten days later. Autopsy confirmed the mass effect of the treated aneurysm compressing the fourth ventricle and the brain stem as the cause of death.

Case 26. A 65-year-old female had acute SAH, and DSA revealed a ruptured left-sided 9mm OpthA aneurysm and an additional 3mm aneurysm in AcomA, which was not considered to have ruptured. The patient was clinically of H&H grade 1, and a embolization procedure was performed 3 days after the onset of bleeding. The patient was not under general anesthesia. While the first coil was being deployed into the OpthA aneurysm, the patient had a sudden onset of severe headache and seizures. No additional coils were deployed, and the procedure was abandoned. CT revealed recurrent massive bleeding. The patient developed right-sided hemiparesis and a few hours later lost consciousness and subsequently died. Autopsy revealed rupture of both aneurysms. However, due to the patient's clinical course during the embolization procedure, the death was judged to be due to iatrogenic aneurysm rupture.

Case 31. A 71-year-old male had acute SAH, and DSA revealed a small wide-necked AcomA aneurysm. The patient was clinically in a good condition (H&H 1), and endovascular treatment of the aneurysm was performed 3 days after the onset of SAH. While doing control angiography ("road map") after the deployment of the first coil, 99% ethanol was inadvertently injected through the guiding catheter into ICA. At that time (1995), ethanol was used for cleaning the connecting cables to improve contact with the coil wire. Accidentally, the syringes containing ethanol and contrast were mixed, and ethanol was injected instead of contrast. In control angiography, arterial flow in ipsilateral MCA and ACA appeared markedly slowed down, and the procedure was interrupted. The patient developed a large infarctation of the ipsilateral cerebral hemisphere and died 3 days later.

Case 49. In a 61-year-old female, an unruptured 9mm wide-necked basilar tip aneurysm was treated due to trochlear nerve paresis. The first coil prolapsed partially into

the parent artery after detachment, and it could not be retrieved. Thrombus formation was evident in angiography close to the aneurysm neck, and thromboembolic complications were also detected in the posterior cerebral and superior cerebellar arteries. Thromboembolic changes were treated with intra-arterial thrombolysis, but multiple hemorrhagic infarcts in the posterior circulation were evident in a postprocedural CT scan. Regardless of temporary improvement of her clinical condition, the patient did not survive.

Case 68. DSA revealed two small incidental aneurysms (left MCA and left PcomA) in a 68-year-old female, who underwent DSA due to ischemic symptoms. An attempt was made to embolize the wide-necked MCA aneurysm first. The first coil was deployed into the aneurysm sac, but the location of the coil was not satisfactory, and retrieval and replacement of the coil were attempted. However, the coil stretched, and it was not possible to pull it back into the microcatheter. An attempt was made to pull back the microcatheter together with the coil, but it turned out to be impossible to pull them through the narrow M1 segment. Severe vasospasm resulted, and the coil finally had to be pushed back into the aneurysm. The microcatheter was left in place and cut at the groin. The patient developed a large MCA infarct and died a few days later.

Case 112. An 8 mm BA tip aneurysm was detected by DSA in a 55-year-old female with acute SAH. Clinically, the patient was of H&H grade 3. An embolization procedure was performed 5 days after the onset of SAH. While the aneurysm sac was being filled with coils, an iatrogenic aneurysm rupture occurred. Heparinization was immediately reversed by administering 50mg of protamin sulfas intravenously, and the coiling procedure was thereafter completed with complete occlusion of the aneurysm. Subsequent ventriculostomy was done, but the patient did not survive the recurrent bleeding.

Case 129. Iatrogenic vasospasm was the cause of the lethal outcome of a 60-year-old male. He had acute SAH due to a ruptured, large MCA bifurcation aneurysm. Four days after the bleeding, the aneurysm was completely occluded with coils, but vasospasm developed during the procedure, possibly secondary to irritation by the catheter. The patient developed a large infarct in the ipsilateral MCA territory, which he did not survive.

Case 148. A 37-year-old female had acute SAH due to a ruptured 3mm aneurysm located at the right ICA bifurcation. The patient was clinically of H&H grade 1, and the aneurysm was embolized 5 days after the onset of bleeding. Iatrogenic aneurysm rupture occurred while the 2nd coil was being deployed. Heparinization was reversed by protamin sulfas, and the procedure was completed. Control angiogram showed the flow of contrast to be very slow, and decreaced intracranial circulation was detected. Ventriculostomy was performed, but the patient died 2 days later.

Case 367. A large, ruptured MCA bifurcation aneurysm with a wide neck was completely occluded with coils in a 57-year-old female, but at the end of the procedure, thromboembolic occlusions in both MCA branches distal to the neck of the aneurysm were detected. Intra-arterial thrombolysis was unsuccessful. A large cerebral infarct developed, and the patient died two days thereafter. The patient was in a moribund condition on admission (H&H 5), and vasospasm was also evident in initial angiography. However, her death was classified as being related to the procedural complication.

Case 392. A 14-year-old boy suddenly lost consciousness and had seizures due to massive SAH. Clinically, the patient was graded as H&H 5. Two days earlier he had visited the hospital due to severe headache, which had, however, subsided. and CT had not been performed at that time. Ventriculostomy was performed prior to DSA, which revealed a 9mm AcomA aneurysm with a narrow neck and additional severe vasospasm. Endovascular treatment was performed immediately after the diagnostic angiography. At the beginning of the procedure, 2mg of nimodipine was slowly (10 minutes) injected through a microcatheter into distal ICA to release the vasospasm (tightly stenosed A1 segment) prior to the catheterization of the aneurysm. Heparin was not administrated. After the administration of nimodipine, extravasation of contrast media into the subarachnoid space was evident in a control angiogram. The aneurysm was thereafter immediately catheterized and completely occluded with coils. At the end of the procedure, intracranial circulation was significantly decreased in the final angiogram. On the next day, the patient was tested to be brain-dead and active treatment was discontinued. Autopsy did not reveal any additional aneurysms or other rupture sites except the AcomA aneurysm, which was completely packed with coils.

Appendix 2 Cases of recurrent bleeding

Case 10.This case is represented in the chapter on cases of procedural mortality (Appendix).

Case 13. A 57-year-old female was initially operated on for a ruptured PcomA aneurysm. One month postoperatively, the patient experienced recurrent SAH, and angiography showed residual filling of the aneurysm sac. The aneurysm was retreated with endovascular coiling, but the treatment resulted in incomplete occlusion because of the wide neck of the aneurysm. Two months after the embolization, the patient had a second episode of rebleeding. Endovascular retreatment was performed, but the neck remained unsealed again. In follow-up, the aneurysm was unstable, showing recurrent filling due to regrowth and coil compaction. Three more endovascular retreatments were performed, but complete occlusion was not achieved. Follow-up angiographies revealed recurrent filling time after time, and the initially 9mm aneurysm was measured to have a maximal diameter of 27mm in MRI. Parent artery occlusion was not possible due to insufficient collateral flow, and the remodeling technique was not available at that time. Surgical retreatment was considered, but neurosurgeons refused to reoperate the aneurysm, unless rebleeding would occur. Clinically, the patient was severely disabled after her recurrent SAHs.

Case 58. A 60-year-old male was initially examined for cerebral ischemia and seizures. He suffered from severe pulmonary problems, cardiac insufficiency, renal insufficiency, and colitis. A giant AcomA aneurysm was detected by CT. The treatment was initially conservative due to his comorbidities. Seven years later, the patient experienced a small ICH. In angiography, the aneurysm appeared mostly thrombosed, and the open portion of the aneurysm sac was subsequently packed with coils, leaving only a small portion of the neck unsealed. However, in six months' follow-up angiography the aneurysm sac showed recurrent filling due to coil compaction. Retreatment was impossible due to the concurrent diseases, which did not allow general anesthesia. Two and a half years after the endovascular treatment, the patient suffered a fatal rebleeding.

Case 102. A large ICA bifurcation aneurysm was surgically wrapped, and the ipsilateral CCA was ligated in a 29-year-old female suffering from SAH in the 1970's. Twenty years later, the patient had a recurrent episode of SAH. The aneurysm was then treated with endovascular coiling by navigating the microcatheter from the contralateral vertebral artery through the PcomA into the aneurysm. The angiographic result was incomplete, and rebleeding occurred three months later. Angiography showed a new secondary pouch at the neck of the aneurysm. On retreatment, the aneurysm was completely occluded. In follow-up, minimal coil compaction and filling of the aneurysm neck were detected six months after the last treatment. Clinically, the patient recovered well, and no other deficits except ipsilateral oculomotor nerve paresis remained.

Case 147. A 39-year-old male experienced oculomotor nerve paresis, and imaging revealed a large OphtA aneurysm. The aneurysm had a wide neck, and only partial occlusion was achieved with residual filling of the neck and the sac. During the following ten months, the aneurysm was retreated twice with the balloon remodeling technique, but the treatments resulted in insufficient occlusion due to the wide neck. Further treatment with either Onyx or stent remodeling was suggested, but the patient refused because his

oculomor nerve function had significantly improved and he did not consider further treatments necessary. Fifty-one months after the initial treatment the patient suffered a lethal SAH (Fig. 11).

Case 152. A 47-year-old female had an acute SAH, and two aneurysms were detected by DSA (in the right pericallosal artery and at the left MCA bifurcation). The pericallosal aneurysm was judged to be ruptured, and it was coiled two days after the bleeding with a satisfactory outcome (only a small neck remnant remained). However, two weeks later the patient experienced headache and right-sided hemiparesis, and CT scan revealed ICH in the left temporal lobe. Later on, the MCA aneurysm was surgically clipped. The operation was complicated by intraoperative bleeding, and the patient did not survive. Autopsy was not performed.

Case 185. A 36-year old male had an acute onset of SAH. A small AcomA aneurysm was revealed by DSA, and it was completely occluded by GDC embolization 3 days after the onset of bleeding. The patient had excellent recovery, and the aneurysm remained completely occluded at two-year follow-up angiography. However, 57 months after the initial bleeding the patient had recurrent SAH. DSA showed the previously coiled aneurysm to be completely occluded, but there was a new small aneurysm in the same AcomA located opposite to the previously treated aneurysm. This aneurysm had not been evident in the previous angiograms, and it was classified as a *de novo* aneurysm. This aneurysm was also treated by coil embolization. Regardless of loose packing, the aneurysm underwent spontaneous thrombosis and appeared to be completely occluded in the first follow-up angiography one month after the treatment (Fig. 12). The patient recovered from the recurrent bleeding without deficits.

Case 255. A 66-year-old female had an acute SAH due to a ruptured AcomA aneurysm. The aneurysm was endovascularly treated during the same day. There were technical problems, and only one coil was detached, and the aneurysm remained incompletely occluded. The patient's clinical condition deteriorated four hours after the treatment, and CT revealed recurrent hemorrhage. Retreatment was performed after two months, and the aneurysm was ultimately completely occluded. In three years' follow-up, a small recurrence was detected at the neck of the aneurysm, but no further treatments were indicated. Clinically, the patient had good recovery.

Case 259. A 51-year-old male had an acute SAH and ICH and was clinically in a moribund condition (H&H 5). An emergency operation was done to evacuate the ICH, but clipping of the aneurysm failed. On the next day, angiography revealed a large MCA aneurysm, and endovascular coiling was performed during the same session. Only partial occlusion was achieved. Further treatments were abandoned because of the patient's poor neurological condition (vegetative survival). Thirteen months later the patient died due to rebleeding of the aneurysm.

Case 282. A 44-year-old male experienced acute SAH due to rupture of a large, wide-necked BA tip aneurysm. The initial treatment was complicated by spontaneous thrombosis of the aneurysm and left P1. Recurrent filling of the aneurysm was seen in follow-up, and the aneurysm was retreated twice. The last treatment was performed with the balloon remodeling technique, and the aneurysm was nearly completely occluded. Clinically, the patient had good recovery without any deficits. Despite this, he died 10 months after the last treatment (48 months after the initial treatment) due to massive rebleeding.

Case 286. A 73-year-old female was treated due to a ruptured MCA bifurcation aneurysm. The treatment outcome was satisfactory with only minimal residual filling at the neck. The patient had good clinical recovery. Unfortunately, angiographic follow-up was canceled by a neurosurgeon, because it was not considered necessary. The patient had recurrent SAH 17 months after the treatment, and angiography revealed recurrent filling of the aneurysm sac due to coil compaction. Endovascular retreatment was performed, and the sac was packed with coils, but a small neck remnant was left. In follow-up, the aneurysm remained stable, and the patient recovered without deficits.

Case 304. A 53-year-old female was referred to DSA five days after the onset of acute SAH. The patient was in a poor clinical condition (H&H 5). DSA revealed the typical appearance of moyamoya disease with bilateral ICA occlusions. At the tip of the basilar artery, a ruptured small aneurysm was detected. The aneurysm was coiled, and complete occlusion was achieved. The patient recovered only to vegetative stage, and she needed a permanent ventriculoperitoneal shunt. The shunt had to be removed and replaced several times because of infection. Two months after the treatment, a control CT scan revealed intraventricular bleeding. In DSA, the aneurysm occlusion was good and there was no need for retreatment. The origin of the bleeding was most likely in the ventricular wall and induced by the shunt catheter. The patient remained in a vegetative stage, and no further follow-up angiographies were scheduled.

Case 312. A 39-year-old male had an acute SAH and a small wide-necked aneurysm was detected at the PcomA junction in ICA by DSA. Because of the wide neck, coil embolization was not possible even with the help of balloon remodeling. A balloon-expandable stent was placed across the neck of the aneurysm. There were technical problems with the stenting procedure because of stent migration, and further coiling was planned to be performed after a few weeks, when the stent would be more stable. The patient was ordered to absolute bed rest in the ward, but against all orders, he left the ward to smoke a cigarette, had a rebleeding while smoking, and died.

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