Unruptured intracranial aneurysms: initial and follow-up screening

Stijntje Bor

Unruptured intracranial aneurysms: initial and follow-up screening

Over het zoeken en vervolgen van ongeruptureerde aneurysmata in het hoofd

(met een samenvatting in het Nederlands)

Proefschrift

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"Je moet altijd het object dat zich aan je waarneming voordoet, voor jezelf definiëren en beschrijven, zodat je ziet wat voor soort ding het eigenlijk is, ontdaan van alle bijkomstigheden, in zijn geheel en in zijn onderdelen, en je moet bij jezelf de namen noemen die het heeft, en de namen van de delen waaruit het is samengesteld en waarin het weer opgelost zal worden."
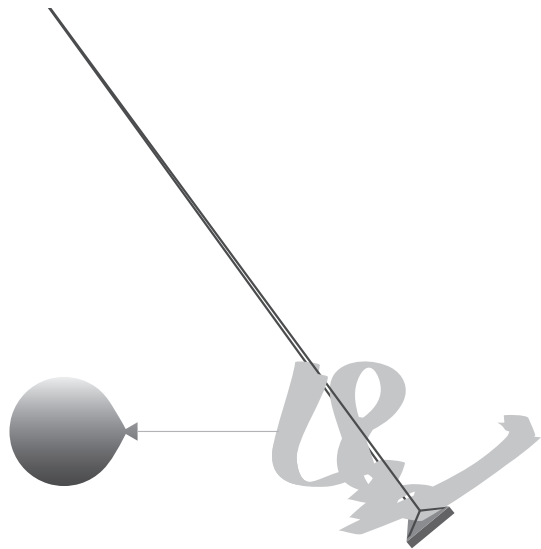
Marcus Aurelius

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Chapter 1

General introduction

Abstract

Subarachnoid haemorrhage (SAH) from a ruptured intracranial aneurysm is a devastating disease that causes death or severe disability in half the patients. Intracranial aneurysms are not present at birth but develop during life. Actively searching and treating intracranial aneurysms before rupture may prevent SAH from some of these aneurysms. The prevalence of intracranial aneurysms is around 3% in the general population, but is higher in certain subgroups such as persons with ≥ 2 first degree relatives with SAH. Screening for intracranial aneurysms should be considered in this subgroup. Some of the intracranial aneurysms detected with screening will be too small to be treated, and will be monitored with repeated imaging. In this general introduction I discuss the current knowledge of screening and follow-up imaging for unruptured intracranial aneurysms, delineate gaps in this knowledge and present the outline of this thesis.

Populations at risk for aneurysmal subarachnoid haemorrhage

The incidence of subarachnoid haemorrhage (SAH) from an intracranial aneurysm has regional differences. In most western populations the risk of SAH is about 9/100,000 person-years (7 to 13/100,000 person-years).[1] The incidence of SAH is higher in Japan (22/100,000 person-years) and Finland (20/100,0000 person-years), and lower in South and Central America (4/100,000 person-years).[1] Incidence of SAH increases with age, ranging from 10/100,000 person-years in persons at 35-45 years old, to 31/100,000 person-years in persons over 85 years old.[1] Although SAH often occurs in young patients, 15–20% of the patients with SAH are over 70 years old.[2, 3] The 28-day case-fatality rate increases with age, from 18% for patients 30–39 years old to 58% for patients over 80 years old.[4] Although mortality from SAH has declined over the last decennia,[5] it is still high. Survivors of SAH often experience cognitive problems, and return to their previous work is often very difficult or impossible.[6,7] Even though SAH only accounts for 5% of all strokes, the effects on society are substantial because it often occurs at a young age and patients have a poor outcome.[8]

Several groups seem to be at a higher risk of aneurysmal SAH than the general population: 1) patients with a previous history of SAH[9,10] 2) patients with hypertension and smoking[11-13] 3) persons with a family history of SAH[14,15] and 4) patients with autosomal dominant polycystic kidney disease (ADPKD).[16,17] The incidence of SAH is markedly increased in patients with a previous SAH (86 to 246/100,000 person-years).[9,10,18] This risk of recurrent SAH is between 10 to 20 times higher than the risk of SAH in the general population.[1,9,10,18] The risk of recurrent SAH is not higher after adequate coiling than after clipping.[9,10,18] Two modifiable risk factors increase the risk of SAH: smoking and hypertension,[12,13] The joint effect of these two risk factors seems larger than the sum of the risk factors.[11] A gene–environment interaction has been suggested for smoking: persons with a smoking history and a family history of SAH had a higher risk of SAH than can be explained by simply adding the risk of smoking to the risk of having a relative affected with SAH.[19] Effects of cessation of smoking or strict hypertension management on aneurysm development and rupture have not been studied. For persons with a positive family history for SAH, it is important to consider both the proximity of the relative affected with SAH and the number of affected relatives, as the risk increases with a higher number of closely related relatives with SAH.[15] Persons with a second degree relative with SAH have a risk of SAH equal to that in the general population.[14,15] Individuals with one first degree relative with SAH have a slightly increased risk of having an SAH.[14,15] Before the studies described in this thesis were done, the risk of having SAH in persons with ≥ 2 first degree relatives with SAH was unknown, although we knew that it was markedly increased,

and screening in persons with ≥ 2 first degree relatives with SAH showed a high yield of unruptured aneurysms.[20,21] To assess the risk of SAH according to the number of affected relatives and to shed more light on the actual risk of SAH in individuals with familial SAH, I performed a population based case control study in the Swedish population (chapter 6) For patients with ADPKD the risk of SAH is increased in comparison to the general population, especially in ADPKD patients with a positive family history.[22] A study in 199 families with ADPKD showed 2% of the relatives with ADPKD to have definite aneurysmal SAH, while none of the relatives without ADPKD had SAH.[22] When definite, probable and possible SAH were considered 5.5% of the relatives with ADPKD versus none of the relatives without ADPKD had SAH. Forty percent of the ADPKD patients with SAH has a family history positive of SAH, showing clustering of SAH in a few of the ADPKD families.[17,22] The characteristics of aneurysms and SAH in ADPKD patients resemble familial SAH patients more than sporadic SAH patients.[23] Although it has been suggested that several other diseases, such as systemic lupus erythematosis and Marfan are associated with SAH, these associations have not been confirmed.[24-27] Ehlers Danlos IV seems to be associated with SAH caused by tearing of the artery wall rather than by saccular intracranial aneurysms.[24,28] Because of arterial wall abnormalities the risks of treatment are reported to be high in this group of patients.[28] We therefore feel that screening for intracranial aneurysms in these possibly associated diseases cannot be recommended.

Yield of screening in different populations

Aneurysms develop during life, and are more prevalent as the population ages.[29] In the general population the probability of finding an aneurysm with screening is around 3%.[29] The wide gap between this relatively high prevalence of unruptured asymptomatic aneurysms, and the low incidence of SAH indicates that most aneurysms never rupture, making screening unattractive in the general population. In a study where 610 patients with a history of SAH were screened for new aneurysms using CTA at a mean follow-up period of 9 years, one out of six patients showed an unruptured aneurysm.[30] A decision analysis on the yield of screening for intracranial aneurysms in patients who have recovered from an episode of SAH showed that this screening is not cost-effective; the risk of aneurysm development and rupture is not high enough to outweigh the risk of screening and preventive aneurysm treatment.[31]

A decision analysis is a reasonable alternative research method if a randomised controlled trial is impossible, for example due to the need for extremely long follow-up. In a decision

analysis a mathematical model (such as a Markov model) is used to simulate certain events, for example aneurysm development and rupture in a specific cohort of patients. Decision models consist of several health states with assigned quality of life (utility) and cost, for example the states 'healthy' (quality of life: 1; cost: 0 euro/year) or 'severely disabled/living in a nursing home' (quality of life: 0.3; cost: 77,000 euro/year). A cohort of hypothetical individuals is followed as they progress in stages of one year through the model, changing health state based on the transition probabilities. Transition probabilities are assigned to possible events, for example the probability that an individual develops a de novo aneurysm or the probability that a developed aneurysm ruptures. Events can be assigned a certain cost, for example the hospital based costs to treat an unruptured aneurysm with coiling. Events can also be assigned a certain utility, to allow individuals to gain happiness or worry by certain events. For example: individuals who have a small untreatable aneurysm detected with screening are bound to have a negative influence of this knowledge on their life, expressed in utility. The simulation stops when all individuals in the model are dead. Outcome is shown as amount of costs made for amount of quality adjusted life years (QALY). After running a baseline scenario, one or more parameters are changed to create a new scenario. The outcome of the new scenario is compared to the baseline scenario. Cost-effectiveness is determined by a cost effectiveness threshold, which is an established amount of money a government has decided to be willing to pay for an additional QALY. This amount of money differs per country. Currently, a cost-effectiveness threshold of €20,000/QALY is applied in the Netherlands, a threshold range of £20,000–£30,000/QALY is applied in the UK, and a threshold range of $50,000–$100,000 is applied in the US.

The sensitivity analysis of a Markov model calculating the yield of screening for intracranial aneurysms in patients who have recovered from an episode of SAH showed that patients with a previous SAH would require at least a twofold increased risk of both aneurysm development and aneurysm rupture to benefit from screening.[30] If only one of these determinants is increased, screening is still not effective. In persons with an increased risk of aneurysm development, but not of rupture, screening will identify many persons with aneurysms that have a low risk of rupture. Treating these aneurysms will cause more complications from preventive treatment, than prevent complications from SAH. Vice versa, in persons with an increased risk of rupture but no increased risk of development, screening will hardly ever detect an aneurysm, yet these persons will continue to have SAHs, because aneurysms develop and rupture in the period between screening intervals. If we discover which persons have an extra increased risk both aneurysm development and aneurysm rupture, screening could be aimed at these persons. The screening interval could be individualised to take

smoking and hypertension into account. Persons with two episodes of SAH are most often women who have had an initial episode of SAH at a young age.[32] Therefore, we discuss the possibility of serial screening at 5 year intervals with young persons who have recovered from an episode of SAH.

For familial SAH, no decision analysis for the yield of screening in persons with ≥ 2 first degree relatives was available at the start of this thesis. In a study using MR angiography to screen 626 persons with only one relative with SAH an aneurysm was revealed in 4% of the screenees.[33] A decision analysis based on data from this screening study showed 150 relatives need to be screened to prevent one episode of SAH.[34] Although screening marginally increased the absolute number of life years, it did not increase the number of quality adjusted life years.[34] Thus screening of persons with only one affected relative could not be recommended on the basis of this study. In a study screening 116 persons with ≥2 first degree relatives with SAH an aneurysm was revealed in 8% of the screenees.[35] After a negative initial screening, a repeated screening five years later revealed a new aneurysm in 7% of the screenees.[21] Before the studies described in this thesis were done, the yield of long term repeated screening in persons with ≥ 2 first degree relatives with SAH was unknown. In an attempt to find the optimal screening strategy for these persons, I assessed the cost-effectiveness of repeated screening in persons with ≥ 2 first degree relatives with SAH in a decision analysis (chapter 7). Next, I analysed the results of twenty years of clinical screening practice in the University Medical Center Utrecht, in terms of number of persons screened, number of aneurysms found and treatment methods for the found aneurysms (chapter 8).

In ADPKD patients, the probability of finding an aneurysm with screening is related to the family history of SAH, as it increases from 6% of the ADPKD patients without a positive family history up to 21% of the ADPKD patients with a positive family history.[36] Aneurysms commonly develop in absence of hypertension in ADPKD patients.[17] The probability of finding an aneurysm with follow-up screening in ADPKD patients is related to previous aneurysms/ SAH, and ranges from 2 out of 76 patients (3%) 10 years after an initial negative screen, up to 5 out of 20 patients (25%) after 15 years in patients with known aneurysms.[36-39] However, follow-up data indicate that rupture of unruptured aneurysms in ADPKD is relatively rare, and resembles the risk of sporadic aneurysms more than familial SAH.[36] It therefore seems reasonable to offer screening to ADPKD patients based on a positive family history of SAH, rather than the mere fact that they have ADPKD.

Screening for unruptured aneurysms

As smoking and hypertension are risk factors for SAH, all patients who are considered for screening for intracranial aneurysms should be recommended to cease smoking and to have their blood pressure checked regularly to enable early treatment of hypertension. A stepwise approach towards screening is shown in Figure 1.1. The risk of elective aneurysm treatment should always be considered when discussing screening for intracranial aneurysms. The risk of treatment of an unruptured aneurysm is influenced directly by age of the patient, aneurysm location, aneurysm size and most likely by aneurysm treatment expertise. Risk of treatment is probably lower in centres with a high volume of aneurysm treatment than in centres with little experience. CTA and MRA are sufficiently accurate for detection of aneurysms with a size that is potentially treatable; with 96–100% sensitivity for aneurysms > 3 mm, and a 92–97% sensitivity for aneurysms < 3 mm.[40,41] The negative predictive value decreases in a screening situation when the chance of finding an aneurysm is much smaller.[42] MRA visualizes aneurysms equally reliable to CTA, without exposing the patient to radiation or contrast material. Non-contrast 3D time-of-flight MRA is thus the preferred method of screening for patients without previously treated aneurysms.[43] In patients with treated aneurysms, the best imaging technique depends on the method used for aneurysm treatment.
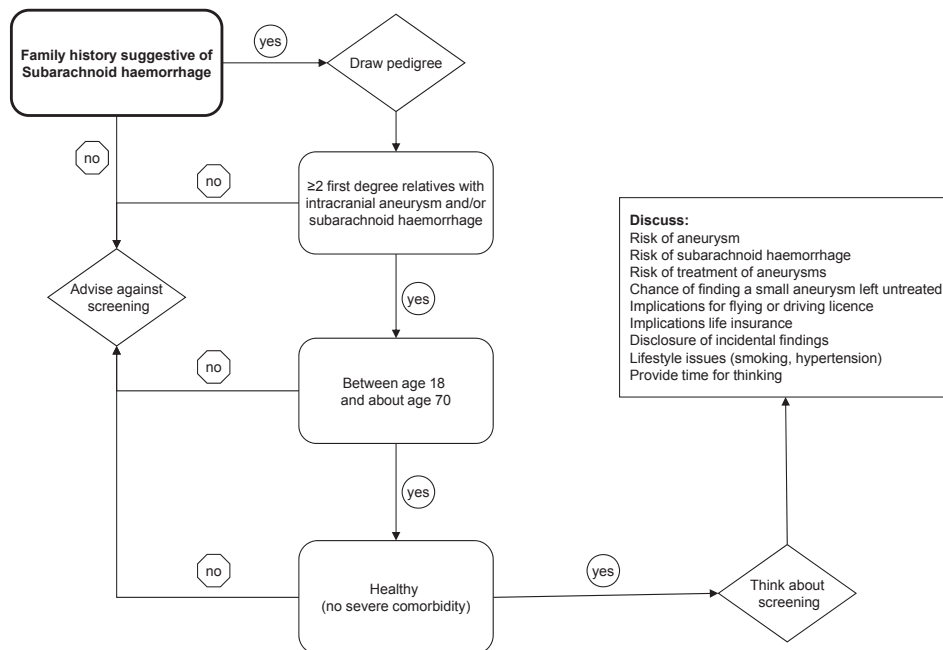

Figure 1.1 Criteria for screening for intracranial aneurysms.

Coiled aneurysms cause much less artefacts on MRA than on CTA.[44] A recent study showed that neither high field strength MRI (3 versus 1.5 Tesla) nor the use of gadolinium contrast agent increases test characteristics in patients with coiled aneurysms.[43] Clipped aneurysms cause less artefacts on CTA than on MRA.[45]

Screening has an important effect on the quality of life. If the screening shows no aneurysms, it probably has a positive or neutral effect, although even relatives with a negative screen had higher mean depression scores than a reference population.[46] A screening positive for intracranial aneurysms has a significant negative effect on patients quality of life.[47-49] The duration of these effects is still unclear, but is probably long lasting. In a follow-up study on the psychosocial impact of screening in 105 relatives with familial SAH, performed years after the initial screening moment 44% of the relatives with a positive screen had stopped working or worked less hours, and 66% reported negative social-emotional changes such as decrease in self-esteem or level of independence.[46] The discovery of a small aneurysm that is not treated but followed in time causes a decrease in the quality of life compared to both patients with a negative screening[49] and patients offered treatment of the newly discovered unruptured aneurysm.[47] This effect of screening on quality of life has an important effect in cost-effectiveness analyses.[48]

Follow-up screening for unruptured aneurysms

If an unruptured aneurysm is found, either as an incidental finding or by screening, the question remains what to do with it. Most incidental aneurysms are smaller than 7 mm, are located in the anterior circulation, and occur in patients without previous SAH or a family history of SAH.[50] Therefore, the immediate risk of complications from preventive aneurysm treatment probably outweighs the possible benefits of preventive aneurysm treatment in terms of minimizing a risk of death and disability due to rupture of the aneurysm at some point later in life. Aneurysm growth probably increases the risk of rupture,[50,51] shifting the balance from conservative treatment towards preventive aneurysm treatment. It is therefore advocated to perform repeated imaging of unruptured aneurysms to monitor aneurysm size. However, the frequency of follow-up and its effectiveness are unknown. At the start of this thesis, very short-term follow-up (1–2 years) seemed inefficient in small aneurysms, as aneurysms grew during the first years of follow-up in only about 2% of the patients.[52-54] A considerable number of aneurysms do grow over the course of 10–20 years of follow-up (Table 1.1).[30,52-60]

Risk factors for aneurysm growth differ per study and confidence intervals are usually wide. Current smoking,[30,30,56,56] aneurysm size,[55,57] multiple aneurysms,[55,57] positive family

history[55] and positive family history in combination with history of SAH[61] were all found as possible risk factors at the start of this thesis, but none of them consistently showed up in all studies, and multivariable analyses were not always possible due to small sample sizes. In chapter 2, 3, and 4 I made an attempt to find more clinical (age, sex, alcohol consumption, hypertension and smoking) and radiological (arterial diameter and bifurcation angles) risk factors for aneurysm growth and rupture. In chapter 5, I analysed a large cohort of patients with untreated, unruptured intracranial aneurysms, using time dependent multivariable analyses, to establish rate of aneurysm growth and identify clinical and radiological risk factors for aneurysm growth in follow-up imaging.

It seems very unlikely that aneurysms grow at a regular pace.[62,63] Aneurysm growth is probably a discontinuous process, where the aneurysm wall remains stable for long periods of time, with short intervals when wall shear stress exceeds the restraining capacities of the aneurysm wall, abruptly causing either aneurysm growth or aneurysm rupture. The implication of this finding is that aneurysm growth and rupture should always be reported in relation to the actual observed period, and not be recalculated to a mean increase in size or mean probability of rupture per observation year. Vice versa, a chance of growth or rupture observed within an observation period cannot simply be multiplied with the number of remaining life years of a patient to calculate his life-time risk of rupture.

Risk of aneurysm rupture

At the start of this thesis, only limited data was available on the rate of aneurysm rupture.[64,65] Since then, several studies on risk of rupture for untreated unruptured aneurysms were published.[60,66-69] Recently, a meta-analysis of six prospective cohort studies on risk of rupture for unruptured aneurysms was published.[50] It found a mean 1 year risk of rupture of 1.4% (95% CI 1.1–1.6), and a 5 year risk of 3.4% (2.9–4.0).[50] Predictors for aneurysm rupture were age, hypertension, history of SAH, aneurysm size, aneurysm location and Finnish or Japanese descent. The majority of the detected aneurysms were <7 mm in size and located in the anterior circulation. The estimated 5 year absolute risk of aneurysm rupture ranged from 0.25% for individuals < 70 years old without vascular risk factors and with a small (< 7 mm) unruptured internal carotid aneurysm, to a rupture risk of > 15% in patients aged > 70 years with hypertension, a history of SAH, and a giant sized (> 20 mm) posterior circulation aneurysm. The rate of rupture declined during the first 5 years of follow-up, indicating that aneurysms prone for rupture were removed from the study population, for example by either aneurysm rupture (natural selection) or elective aneurysm treatment after aneurysm growth

Table 1.1 Studies on aneurysm growth, showing differences in patient population, aneurysm size and period of follow-up

	Juvela 2001	Phan 2002	Miyazawa 2003	Matsubara 2004	Werner 2005	Werner 2006	Burns 2009	Villablanca 2013	Chien 2013	Matsumoto 2013
No. patients	89	57	130	140	46	93	165	165	235	111
No. aneurysms	87	62	159	166	53	125	191	235#	319	136
No. aneurysms < 5 mm	74	?	118	125	?	125	173*	?	258	113^
Average aneurysm size in mm (min–max)	5.1 (2–26)	5 (2–15)	4.2 (2–22)	4.1 (2–20)	?	3 (1–5)	4.9 (2–18)	5.4 (?–?)	3.6 (1–7)	?
Follow-up Mean in yrs (min–max)	18.9 (1.2–38.9)	–	2.4 (0.8–5.8)	1.5 (0.3–4)	8.9 (2.3–18.8)	–	3.9 (2.1–6.1)	2.2 (0.1–8.5)	2.4 (?–?)	? (max 12 yrs)
Follow-up Median (yrs)	–	3.9 (1.4–7.4)	–	–	–	1.3 (0.7–3.8)	–	2.0	?	?
Retrospective/prospective design	Prospective	Retrospective	Retrospective	Prospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective
No. patients with previous SAH	79/89 (88%)	2/57 (3%)	?	8/140 (6%)	46 (100%)	77/93 (82%)	12/165 (7%)	?	0/235 (0%)	8/111 (7%)

Table 1.1 *Continued*

	Juvela 2001	Phan 2002	Miyazawa 2003	Matsubara 2004	Wermer 2005	Wermer 2006	Burns 2009	Villablanca 2013	Chien 2013	Matsumoto 2013
No. patients with positive family history	8/70 (11%)	2/57 (3%)	17/130 (13%)	32/140 (22%)	?	26/93 (28%)	20/163 (12%)	?	9/223 (4%)	?
Growth In 1 yr in aneurysms	?	0/? (0%)	?	3/125 (2%)	?	3/125 (2%)	?	?	?	1 growth 3 rupture
Growth 5/10/15 years	?	?	?	?	5 yrs: 4/18 (22%) 10 yrs: 9/45 (20%)	?	?	?	?	?
Growth total (aneurysms)	39/87 (45%)	4/62 (6%)	16/159 (10%) 9/118 (8%)	10/166 (6%)	13/53 (25%)	3/125 (2%)	20/191 (10%)	39/235 (17%)	42/319 (13%)	13/111 (11%)
Rupture (patients)	2/89 (2.2%)	0/57 (0%)	3/130 (2.3%)	0/166 (0%)	?	2/125 (1.6%)	?	3/235 (1.2%)	0/319 (0%)	6/111 (5.4%)

* < 8 mm.

258 aneurysms in total, of which 235 saccular aneurysms.

^ < 7 mm.

on follow-up imaging.[50,66] It is important to realise that the analysis did not incorporate data on familial SAH, cessation of smoking, and blood pressure management, as information on these subjects was limited in the original studies the meta-analysis was based on. In part I of this thesis, I try to increase our knowledge of risk factors for aneurysm development and rupture. Part II of this thesis is directed specifically at aneurysm development and rupture persons with familial SAH.

Outline of this thesis

Chapter 1: general introduction

Part I: Risk factors for aneurysm development

Chapter 2 studies arterial diameter and bifurcation angles as risk factors for aneurysm development.

Chapter 3 studies anatomic variations as risk factors for aneurysm development and rupture on the anterior and posterior communicating arteries.

Chapter 4 studies the relation between age, sex, alcohol consumption and hypertension, and the site of ruptured aneurysms.

Chapter 5 analyses rate of aneurysm growth and risk factors for aneurysm growth in a follow-up study combining two large cohorts of patients with an untreated, unruptured, aneurysm and at least 6 months of follow-up imaging. Both patient-related risk factors, such as age, sex, hypertension and smoking are considered, as well as aneurysm-related risk factors, such as aneurysm size, site, shape, and bifurcation angles.

Part II: Familial intracranial aneurysms

Chapter 6 assesses the risk of SAH for persons with first degree relatives with SAH in a large population based study in Sweden.

Chapter 7 shows the results of a computer simulation model designed to estimate cost-effectiveness of screening in persons with ≥ 2 first degree relatives with SAH (familial SAH)

Chapter 8 presents the results of the 20 year experience with clinical screening for familial SAH in the Brain Center of the University Medical Center Utrecht.

Chapter 9: general discussion.

References

1   de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry* 2007; **78**: 1365-72.

2   Horiuchi T, Tanaka Y, Hongo K. Surgical treatment for aneurysmal subarachnoid hemorrhage in the 8th and 9th decades of life. *Neurosurgery* 2005; **56**: 469-75.

3   Braun V, Rath S, Antoniadis G, Richter HP, Borm W. Treatment and outcome of aneurysmal subarachnoid haemorrhage in the elderly patient. *Neuroradiology* 2005; **47**: 215-21.

4   Koffijberg H, Buskens E, Granath F et al. Subarachnoid haemorrhage in Sweden 1987-2002: regional incidence and case fatality rates. *J Neurol Neurosurg Psychiatry* 2008; **79**: 294-9.

5   Nieuwkamp DJ, Setz LE, Algra A et al. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol* 2009; **8**: 635-42.

6   Passier PE, Visser-Meily JM, Rinkel GJ, Lindeman E, Post MW. Life satisfaction and return to work after aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis* 2011; **20**: 324-9.

7   Passier PE, Visser-Meily JM, Van Zandvoort MJ et al. Prevalence and determinants of cognitive complaints after aneurysmal subarachnoid hemorrhage. *Cerebrovasc Dis* 2010; **29**: 557-63.

8   Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. *Lancet Neurol* 2011; **10**: 349-56.

9   Wermer MJ, Greebe P, Algra A, Rinkel GJE. Incidence of recurrent subarachnoid hemorrhage after clipping for ruptured intracranial aneurysms. *Stroke* 2005; **36**: 2394-9.

10   Schaafsma JD, Sprengers ME, Van Rooij WJ et al. Long-term recurrent subarachnoid hemorrhage after adequate coiling versus clipping of ruptured intracranial aneurysms. *Stroke* 2009; **40**: 1758-63.

11   Lindekleiv H, Sandvei MS, Romundstad PR et al. Joint effect of modifiable risk factors on the risk of aneurysmal subarachnoid hemorrhage: a cohort study. *Stroke* 2012; **43**: 1885-9.

12   Sandvei MS, Romundstad PR, Muller TB, Vatten L, Vik A. Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway. *Stroke* 2009; **40**: 1958-62.

13   Vlak MH, Rinkel GJ, Greebe P, Greving JP, Algra A. Lifetime risks for aneurysmal subarachnoid haemorrhage: multivariable risk stratification. *J Neurol Neurosurg Psychiatry* 2013; **84**: 619-23.

14   Bromberg JEC, Rinkel GJE, Algra A et al. Subarachnoid haemorrhage in first and second degree relatives of patients with subarachnoid haemorrhage. *BMJ* 1995; **311**: 288-9.

15   Teasdale GM, Wardlaw JM, White PM et al. The familial risk of subarachnoid haemorrhage. *Brain* 2005; **128**: 1677-85.

16   Rinkel GJE, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke* 1998; **29**: 251-6.

17   Gieteling EW, Rinkel GJE. Characteristics of intracranial aneurysms and subarachnoid haemorrhage in patients with polycystic kidney disease. *J Neurol* 2003; **250**: 418-23.

18   Molyneux AJ, Kerr RS, Birks J et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol* 2009; **8**: 427-33.

19   Woo D, Khoury J, Haverbusch MM et al. Smoking and family history and risk of aneurysmal subarachnoid hemorrhage. *Neurology* 2009; **72**: 69-72.

20   Ronkainen A, Hernesniemi J, Puranen M et al. Familial intracranial aneurysms. *Lancet* 1997; **349**: 380-4.

21   Wermer MJ, Rinkel GJE, van Gijn J. Repeated screening for intracranial aneurysms in familial subarachnoid hemorrhage. *Stroke* 2003; **34**: 2788-91.

22   Belz MM, Hughes RL, Kaehny WD et al. Familial clustering of ruptured intracranial aneurysms in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2001; **38**: 770-6.

23   Ruigrok YM, Rinkel GJE, Algra A, Raaymakers TWM, van Gijn J. Characteristics of intracranial aneurysms in patients with familial subarachnoid hemorrhage. *Neurology* 2004; **62**: 891-4.

24   Baizabal Carvallo JF, Cantu BC, Estanol B, Garcia Ramos GS. Subarachnoid Hemorrhage as a Complication of Systemic Lupus Erythematosus. *Cerebrovasc Dis* 2007; **24**: 301-4.

25   Schievink WI, Link MJ, Piepgras DG, Spetzler RF. Intracranial Aneurysm Surgery in Ehlers-Danlos Syndrome Type IV. *Neurosurg* 2002; **51**: 607-13.

26   Conway JE, Hutchins GM, Tamargo RJ. Marfan syndrome is not associated with intracranial aneurysms. *Stroke* 1999; **30**: 1632-6.

27   Wityk RJ, Zanferrari C, Oppenheimer S. Neurovascular complications of marfan syndrome: a retrospective, hospital-based study. *Stroke* 2002; **33**: 680-4.

28   Pepin MG, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000; **342**: 673-80.

29   Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol* 2011; **10**: 626-36.

30   Wermer MJ, van der Schaaf IC, Velthuis BK et al. Follow-up screening after subarachnoid haemorrhage: frequency and determinants of new aneurysms and enlargement of existing aneurysms. *Brain* 2005; **128**: 2421-9.

31   Wermer MJ, Koffijberg H, van dSI. Effectiveness and costs of screening for aneurysms every 5 years after subarachnoid hemorrhage. *Neurology* 2008; **70**: 2053-62.

32   Wermer MJ, Rinkel GJE, Greebe P et al. Late recurrence of subarachnoid hemorrhage after treatment for ruptured aneurysms: Patient characteristics and outcomes. *Neurosurgery* 2005; **56**: 197-204.

33   Raaymakers TWM, MARS study group. Aneurysms in relatives of patients with subarachnoid hemorrhage. Frequency and risk factors. *Neurology* 1999; **53**: 982-8.

34   Raaymakers TWM, Rinkel GJE, van Gijn J et al. Risks and benefits of screening of intracranial aneurysms in first-degree relatives of patients with sporadic subarachnoid hemorrhage. *N Engl J Med* 1999; **341**: 1344-50.

35   Raaymakers TWM, Rinkel GJE, Ramos LMP. Initial and follow-up screening for aneurysms in families with familial subarachnoid hemorrhage. *Neurology* 1998; **51**: 1125-30.

36   Irazabal MV, Huston J, III, Kubly V et al. Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2011; **6**: 1274-85.

37   Schrier RW, Belz MM, Johnson AM et al. Repeat imaging for intracranial aneurysms in patients with autosomal dominant polycystic kidney disease with initially negative studies: a prospective ten-year follow-up. *J Am Soc Nephrol* 2004; **15**: 1023-8.

38   Gibbs GF, Huston J, III, Qian Q et al. Follow-up of intracranial aneurysms in autosomal-dominant polycystic kidney disease. *Kidney Int* 2004; **65**: 1621-7.

39   Belz MM, Fick-Brosnahan GM, Hughes RL et al. Recurrence of intracranial aneurysms in autosomal-dominant polycystic kidney disease. *Kidney Int* 2003; **63**: 1824-30.

40   Li Q, Lv F, Li Y et al. Evaluation of 64-section CT angiography for detection and treatment planning of intracranial aneurysms by using DSA and surgical findings. *Radiology* 2009; **252**: 808-15.

41   Li MH, Cheng YS, Li YD et al. Large-cohort comparison between three-dimensional time-of-flight magnetic resonance and rotational digital subtraction angiographies in intracranial aneurysm detection. *Stroke* 2009; **40**: 3127-9.

42   White PM, Teasdale EM, Wardlaw JM, Easton V. Intracranial aneurysms: CT angiography and MR angiography for detection prospective blinded comparison in a large patient cohort. *Radiology* 2001; **219**: 739-49.

43   Schaafsma JD, Velthuis BK, Majoie CB et al. Intracranial aneurysms treated with coil placement: test characteristics of follow-up MR angiography--multicenter study. *Radiology* 2010; **256**: 209-18.

44   Yamada N, Hayashi K, Murao K, Higashi M, Iihara K. Time-of-Flight MR Angiography Targeted to Coiled Intracranial Aneurysms Is More Sensitive to Residual Flow than Is Digital Subtraction Angiography. *AJNR Am J Neuroradiol* 2004; **25**: 1154-7.

45   van der Schaaf IC, Velthuis BK, Wermer MJ et al. Multislice computed tomography angiography screening for new aneurysms in patients with previously clip-treated intracranial aneurysms: Feasibility, positive predictive value, and interobserver agreement. *J Neurosurg* 2006; **105**: 682-8.

46   Wermer MJ, van der Schaaf IC, Van Nunen P et al. Psychosocial impact of screening for intracranial aneurysms in relatives with familial subarachnoid hemorrhage. *Stroke* 2005; **36**: 836-40.

47   Towgood K, Ogden JA, Mee E. Psychosocial effects of harboring an untreated unruptured intracranial aneurysm. *Neurosurgery* 2005; **57**: 858-6.

23

48   Greving JP, Rinkel GJ, Buskens E, Algra A. Cost-effectiveness of preventive treatment of intracranial aneurysms: new data and uncertainties. *Neurology* 2009; **73**: 258-65.

49   van der Schaaf IC, Wermer MJ, Velthuis BK et al. Psychosocial impact of finding small aneurysms that are left untreated in patients previously operated on for ruptured aneurysms. *J Neurol Neurosurg Psychiatry* 2006; **77**: 748-52.

50   Greving JP, Wermer MJ, Brown RD, Jr. et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014; **13**: 59-66.

51   Chmayssani M, Rebeiz JG, Rebeiz TJ, Batjer HH, Bendok BR. Relationship of growth to aneurysm rupture in asymptomatic aneurysms </= 7 mm: a systematic analysis of the literature. *Neurosurgery* 2011; **68**: 1164-71.

52   Wermer MJ, van der Schaaf IC, Velthuis BK et al. Yield of short-term follow-up CT/MR angiography for small aneurysms detected at screening. *Stroke* 2006; **37**: 414-8.

53   Matsubara S, Hadeishi H, Suzuki A, Yasui N, Nishimura H. Incidence and risk factors for the growth of unruptured cerebral aneurysms: observation using serial computerized tomography angiography. *J Neurosurg* 2004; **101**: 908-14.

54   Phan TG, Huston J, Brown RDJ, Wiebers DO, Piepgras DG. Intracranial saccular aneurysm enlargement determined using serial magnetic resonance angiography. *J Neurosurg* 2002; **97**: 1023-8.

55   Miyazawa N, Akiyama I, Yamagata Z. Risk factors for growth of unruptured intracranial aneurysms: follow-up study by serial 0.5-T magnetic resonance angiography. *Neurosurgery* 2006; **58**: 1047-53.

56   Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms. A long term follow-up study. *Stroke* 2001; **32**: 485-91.

57   Burns JD, Huston J, III, Layton KF, Piepgras DG, Brown RD, Jr. Intracranial aneurysm enlargement on serial magnetic resonance angiography: frequency and risk factors. *Stroke* 2009; **40**: 406-11.

58   Chien A, Liang F, Sayre J et al. Enlargement of small, asymptomatic, unruptured intracranial aneurysms in patients with no history of subarachnoid hemorrhage: the different factors related to the growth of single and multiple aneurysms. *J Neurosurg* 2013; **119**:190-7.

59   Villablanca JP, Duckwiler GR, Jahan R et al. Natural history of asymptomatic unruptured cerebral aneurysms evaluated at CT angiography: growth and rupture incidence and correlation with epidemiologic risk factors. *Radiology* 2013; **269**: 258-65.

60   Matsumoto K, Oshino S, Sasaki M et al. Incidence of growth and rupture of unruptured intracranial aneurysms followed by serial MRA. *Acta Neurochir (Wien)* 2013; **155**: 211-6.

61   Wermer MJ, Buskens E, van der Schaaf IC, Bossuyt PM, Rinkel GJE. Yield of screening for new aneurysms after treatment for subarachnoid hemorrhage. *Neurology* 2004; **62**: 369-75.

62   Koffijberg H, Buskens E, Algra A, Wermer MJ, Rinkel GJ. Growth rates of intracranial aneurysms: exploring constancy. *J Neurosurg* 2008; **109**: 176-85.

63   Mitchell P, Jakubowski J. Estimate of the maximum time interval between formation of cerebral aneurysm and rupture. *J Neurol Neurosurg Psychiatry* 2000; **69**: 760-7.

64   Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. *Stroke* 2007; **38**: 1404-10.

65   Wiebers DO, Whisnant JP, Huston J3 et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003; **362**: 103-10.

66   Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *Stroke* 2013; **44**: 2414-21.

67   Sonobe M, Yamazaki T, Yonekura M, Kikuchi H. Small unruptured intracranial aneurysm verification study: SUAVe study, Japan. *Stroke* 2010; **41**: 1969-77.

68   Ishibashi T, Murayama Y, Urashima M et al. Unruptured intracranial aneurysms: incidence of rupture and risk factors. *Stroke* 2009; **40**: 313-6.

69   Morita A, Kirino T, Hashi K et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med* 2012; **366**: 2474-82.

PART I

Risk factors for aneurysm development

Chapter 2

Configuration of intracranial arteries and development of aneurysms:
a follow-up study

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Abstract

Introduction: The reasons for development of intracranial aneurysms are unknown; hemodynamic factors may play an important role in this process. We performed a cohort study to further elicit the role of intracranial arterial geometry.

Methods: We compared the original CTA/MRA of the circle of Willis of 26 patients who developed an aneurysm during follow-up with those of 78 controls with no aneurysm development who were matched for gender, age and period of follow-up. We assessed hypoplasia of the arteries of the circle of Willis and measured bifurcation angles within and beyond the circle of Willis on three-dimensional CTA/MRA. Bifurcation angles were classified in tertiles for analysis. We used student's t-test for comparison of bifurcation angles and calculated odds ratios (OR) with corresponding 95% confidence intervals (CI) for presence of hypoplasia and bifurcation angles in tertiles.

Results: A hypoplastic branch was found in 5 of 7 (71%) sites with aneurysm development and in 6 of 21 corresponding sites (29%) without aneurysm development (OR 6; 95% CI 0.9–42). The branch angle was sharp (lowest tertile) in 10 of 14 (71%) sites with aneurysm development and in 8 of 42 (19%) sites without aneurysm development (OR 11.3; 95% CI 2.0–64).

Discussion: Bifurcations with a hypoplastic branch and bifurcations with sharper bifurcation angles are risk factors for development of aneurysms. Analysis of the geometry of intracranial arteries might be helpful in detecting persons with increased risk for developing aneurysms.

2

Introduction

Intracranial aneurysms are not present at birth, but develop during life.[1] Besides age, risk factors for the presence or development of aneurysms include gender, familial preponderance of aneurysms, polycystic kidney disease, presence of atherosclerotic disease, smoking and hypertension.[1,2] How these factors contribute to the development of aneurysms is unknown. Hemodynamic risk factors may play an important role in this process.

In cross sectional studies hypoplasia of segments of the circle of Willis and bifurcation angles have been associated with the presence of aneurysms,[3-5] but such an association does not necessarily imply a causal relation. Also, the location of aneurysms has been associated with high shear stress on the artery wall.[4,6-9] Three dimensional (3D) computer simulation programs have shown that arterial curvature, bifurcation angles and branch diameter have a direct relation with wall shear stress.[10,11] Hypoplastic segments in the circle of Willis and the angles of bifurcations and curves may therefore play an important role in aneurysm formation and growth. In a series of patients who underwent serial imaging studies of the intracranial arteries we compared hypoplasia and bifurcation angles of the intracranial arteries on the initial imaging between patients who did develop aneurysms during follow-up and patients who did not.

Methods

Patients

Angiograms were retrieved from patients from one of the following two cohorts of patients: (A) the ASTRA-database, which includes patients with a history of aneurysmal subarachnoid haemorrhage (ho were screened for new aneurysms by means of computed tomography angiography (CTA).[2] The original imaging study in this cohort was a CTA or conventional angiogram acquired to detect the aneurysm causing the SAH. (B) a prospectively collected cohort of patients who were screened for aneurysms because of a positive family history of SAH. These patients were repeatedly screened by means of magnetic resonance angiography (MRA) at the University Medical Center Utrecht between 1993 and 2006, with a screening interval of 3 to 5 years. The original imaging study was considered to be the last study without visualized aneurysm for patients with a newly visualized aneurysm, or the oldest study available for review for patients with an enlarged aneurysm. Aneurysm growth was defined as an increase in size of more than 1mm in at least 2 directions or 2 mm in one

direction. Cases were defined as all patients with a newly visualized or enlarged aneurysm on the latest angiogram (CTA or MRA), for whom the original angiogram (CTA, MRA or conventional angiogram) was available for analysis. Carotid siphon aneurysms below the level of the ophthalmic artery were excluded from this study. All aneurysms were diagnosed by a neuro-radiologist. For every case we retrieved three controls from the same database, matched for gender, age and time of follow-up.

Measurements

For all circles of Willis we assessed the presence of the anterior communicating artery (ACoA), A1 part of the left and right anterior cerebral artery (ACA), P1 part of the left and right posterior cerebral artery (PCA), and the left and right posterior communicating artery (PCoA). We classified each artery or arterial segment in the categories: not visible, diameter < 1 mm, or diameter ≥ 1 mm; hypoplasia was defined as not visible or a diameter < 1 mm. We considered the aneurysms of ACoA, PCoA, carotid T junction and basilar artery (BA) to be part of the actual circle of Willis and determined whether these aneurysms originated from a bifurcation with a hypoplastic branch, by assessing both A1 parts of the ACAs in ACoA-aneurysms, the ipsilateral A1 part of the ACA in carotid T junction aneurysms, the PCoA in PCoA aneurysms, and both P1 parts of the PCAs in BA aneurysms. Bifurcation angles were measured in 3D reconstruction CTA/MRA. In a 3D reconstruction the image can be rotated on the screen for 360° in any plane. The angle was initially marked by dots; thereafter the image was rotated to confirm the correct placement of the dots in the middle of the branch from different views. The bifurcation angles were then measured by connecting the dots. The branch deviating the least from the direction of flow of the parent artery was marked X, the branch deviating the most was marked Y. The bifurcation angles were marked Φx and Φy accordingly (Figure 2.1). This way, the angles of the larger, well visualized bifurcations could be measured in cases and controls. We were not able to measure angles of curves in controls because we could not objectively determine the beginning, middle and ending of the curve. For aneurysms in small branching's it was not possible to find enough matched controls with the similar branching visible, as these small branches are only visible on the newest high quality scans. Many potential control scans were made before these new imaging techniques were available. We analysed the A1–A2 angles of the ACoA-complex separately, because we did not consider the ACoA-complex to be a genuine bifurcation. All aneurysms were reviewed by at least two observers. All measurements were performed by the first author (ASEB) with supervision of an experienced neuroradiologist (BKV or CBM). All 3D measurements were performed with the Philips EasyVision 5.1 software package.
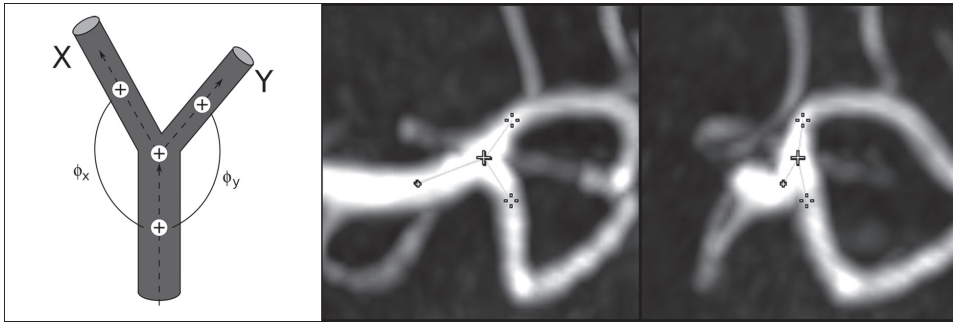
Figure 2.1 Left: Schematic drawing showing the angle measurements we performed on bifurcations. The branch deviating least from the flow of the parent artery is marked X, the branch deviating most is marked Y, the bifurcation angles were marked Φx and Φy accordingly. Center: Example of a bifurcation angle measurement in a 3D MRA. Right: The measurement of 1b slightly rotated to show the 3D characteristics of the measurement.

Baseline characteristics

We found 26 patients with aneurysm development over time (15 patients from database A, 11 patients from database B). In these 26 patients 32 aneurysms had developed (Table 2.1). Seventeen of the 32 aneurysms were newly visualized, 15 had enlarged over time. Eleven of the 15 enlarged aneurysms were only detected in retrospect on the initial imaging study, while four had already been detected on the initial imaging study. The sizes of the aneurysms varied from 1.5 to 9.2 mm. Six aneurysms were smaller than 2.0 mm (1.5 to 1.9 mm), These

Table 2.1 Characteristics of patients and aneurysms

	Cases (n = 26)	Controls (n = 78)
Women (%)	22 (85%)	66 (85%)
Age at time of follow-up angio (mean years, ± SD)	50.3 (± 7.6)	50.8 (± 8.3)
Interval between initial and follow-up imaging (mean years, ± SD)	7.1 (± 2.5)	8.0 (± 3.3)
Site of aneurysm*		
ACoA	2	–
ICA	9	–
BA	1	–
MCA	19	–
Pericallosal	1	–

* Some patients had more than one aneurysm, therefore the total number of aneurysms (n = 32) is larger than the number of patients (n = 26).

aneurysms were all situated in clearly visualized bifurcations (MCA or carotid T-junction), thus at sites where infundibulae do not usually occur. A conventional angiogram confirmed three of these small aneurysms. Of the other three no conventional angiogram was made, they were followed by repeated CTA/MRA.

We matched all patients with gender and matched age with ± 3 years, preferring the controls to be older than the cases. We succeeded in this matching in all but three controls: one was 11 years older than the case, one 13 years older than the case, and one was 14 years younger than the case. This last control was not used for measurement of hypoplasia or bifurcation as the aneurysm of the case was on a curve. We matched time of follow-up with ± 3 years. We measured the bifurcation angles in the original CTA/MRA, but when no 3D reconstruction of the angiogram source data was available for the original scan (16 aneurysms); we measured the bifurcation angles in the follow-up scan. We validated the measuring of the bifurcation angles in the follow-up scan instead of the initial scan as follows. In cases with aneurysm development in a well visualized branching and both an original and follow-up 3D CTA/MRA available (8 cases), we first measured the bifurcation angles of the original scans of these 8 cases twice with a considerable time span; the second measurement was done blinded for the data of the initial measurement. The average difference in the measured angles was 6° (± 19°) in Φx and 7° (± 14°) in Φy. Thus, the intraobserver variation is around 7° (± 15°). Next, we measured the bifurcation angles both in the original angiogram and in the follow-up angiogram. The mean difference in the angle measured was 3.4° (± 12.7°) in Φx and 13.1° (± 11.3°) in Φy. Because the difference between the angles in the first and second angiogram was within the range of the intraobserver variation, we felt justified to perform the measurements on the second angiogram if a 3D reconstruction of the initial angiogram was not available.

Data analysis

We pooled all bifurcations with aneurysms (and their matched controls) in the actual circle of Willis (ACoA, PCoA, carotid T junction and BA) and calculated odds ratios (OR) with corresponding 95% confidence intervals (CI) for the presence of hypoplasia.

We pooled all bifurcations with aneurysms (and their matched controls) and clearly visualized branches (Carotid T-junction, BA T-junction, MCA M1–M2 bifurcation, pericallosal bifurcation and PCoA bifurcation with a well visualized PCoA). Any location with more than 5 cases was also analysed separately; this proved to be the case only for MCA aneurysms. All bifurcations with newly visualized aneurysms were also analysed separately, both for

the pooled bifurcations and the MCA bifurcations. We analysed the angles of bifurcations with and without aneurysm development by means of student's t-test for equality. For comparison all angles were classified in tertiles, subsequently the lowest tertile was compared with the highest tertile and odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated.

Results

Of the 32 aneurysms, 7 developed in the actual circle of Willis (2 located at the ACoA, 1 Carotid T-junction, 3 PCoA, and 1 BA T-junction). Five of these 7 aneurysms (71%) developed on a bifurcation with a hypoplastic branch. Six of 21 control bifurcations (29%) had a hypoplastic branch (OR 6; 95% CI 0.9–42) (Figure 2.2).

Of the 32 aneurysms, 14 developed on a bifurcation (12) or trifurcation (2) with well visualized branches (10 located at the MCA, 1 at the BA T-junction, 1 at the Carotid T junction, 1 at the PCoA, and 1 at the pericallosal artery). Five of the 32 aneurysms developed in the ICA where bone-artefacts made the measurement of angles impossible. 11 aneurysms developed on a curve (4 MCA, 2 PCoA) or near a very small branching (5 MCA), and therefore no control angles could be measured. Two aneurysms developed in the ACoA complex.

The mean ($\pm$ SD) of the least deviating angle (Φx) for the 14 bifurcations with well visualized branches was 124° ($\pm$ 22°) in the 14 cases, and 137° ($\pm$ 16°) in the 42 controls (p = 0.01); the mean of the most deviating angle (Φy) was 88° ($\pm$ 20°) in cases, and 111° ($\pm$ 22°) in controls (p < 0.001). After classification in tertiles, the OR for aneurysm development in the

Figure 2.2 Example of a case (left: MRA 1997 and center: MRA 2002) showing significant growth of a left PCoA aneurysm (arrowhead) over five years. The ipsilateral PCoA (arrow) is hypoplastic. Right: circle of Willis of a control with a normal calibre PCoA (arrow).

lowest tertile (sharper angle) versus the highest tertile (more obtuse angle) was 6.7 (95% CI 0.9–28) for the least deviating angle Φx, and 11.3 (95% CI 2.0–64) for the most deviating angle Φy (Table 2.2).

As there were 10 patients with aneurysm development on the MCA, we could analyse the MCA bifurcation angles separately. The mean ($\pm$ SD) of the least deviating angle (Φx) was 122° ($\pm$ 25°) in the 10 cases, and 139° ($\pm$ 16°) in the 30 controls (p = 0.016); the mean of the most deviating angle (Φy) was 93° ($\pm$ 20°) in cases, and 115° ($\pm$ 19°) in controls (p = 0.003). After classification in tertiles, the OR for aneurysm development in the lowest tertile versus the highest tertile was 10 (95% CI 1.0–104) for the least deviating angle Φx as well as for the most deviating angle Φy (Table 2.2). In the analysis of the subgroup of only the newly visualized aneurysms the effect sizes were in similar direction as in the entire study group, but because the sample sizes were smaller the confidence intervals were wider and the results no longer significant.

Table 2.2 Classification of bifurcation angles in tertiles for all bifurcations and for MCA bifurcations

			Cases (%)	Controls (%)	OR (95% CI)
All bifurcations			n = 14	n = 42	
Φx	1st tertile	(141°–176°)	2 (14)	15 (36)	(reference)
	2nd tertile	(125°–141°)	4 (29)	18 (43)	1.7 (0.3–10.4)
	3rd tertile	(84°–125°)	8 (57)	9 (21)	6.7 (1.2–38.6)
Φy	1st tertile	(117°–144°)	2 (14)	18 (43)	(reference)
	2nd tertile	(93°–117°)	2 (14)	16 (38)	1.1 (0.1–8.9)
	3rd tertile	(51°–93°)	10 (71)	8 (19)	11.3 (2.0–63.6)
MCA bifurcations			n = 10	n = 30	
Φx	1st tertile	(141°–176°)	1 (10)	12 (40)	(reference)
	2nd tertile	(128°–141°)	3 (30)	11 (37)	3.3 (0.3–36.0)
	3rd tertile	(84°–128°)	6 (60)	7 (23)	10.3 (1.0–104.0)
Φy	1st tertile	(122°–143°)	1 (10)	12 (40)	(reference)
	2nd tertile	(103°–122°)	3 (30)	11 (37)	3.3 (0.3–36.0)
	3rd tertile	(70°–103°)	6 (60)	7 (23)	10.3 (1.0–104.0)

The odds ratio for aneurysm development and 95% confidence interval are given. The first tertiles contain obtuse angles, where the bloodstream deviates relatively little from the direction of flow of the parent artery. The third tertiles contain sharp angles, where the bloodstream deviates relatively more from the direction of flow from the parent artery.

Discussion

Aneurysms within the circle of Willis develop more often in bifurcations with a hypoplastic branch than in bifurcations with no hypoplastic branch. Aneurysms develop more often in bifurcations with relatively sharp angles, where the bloodstream deviates significantly from the direction of flow of the parent artery, than in more obtuse bifurcation angles, where the bloodstream deviates relatively little from the direction of flow of the parent artery.

In this study the geometry of intracranial arteries was measured in the original angiogram, before development of an aneurysm. Therefore, the geometry of intracranial arteries found to be associated with the development of aneurysms in this cohort study are actual risk factors, and not the result of the presence of aneurysms, as might be the case in cross sectional studies comparing sites with and without aneurysms. Given the design of the study the number of aneurysms is large, but in absolute numbers the study sample was too small to permit analyses of more than a few variables. Moreover, the different sites where aneurysms developed have different characteristics, which further limited the number of aneurysms to be studied. As a result of the small numbers in absolute sense, we pooled the different bifurcations in one analysis.

Our study has several limitations. We pooled aneurysms that visibly grew with aneurysms that were visible for the first time. In our view, growth of aneurysms is a continuous process, in which wall shear stress exceeds the strength of the vascular muscle wall. In response, this wall segment will weaken and start to bulge in an unknown amount of time. The current imaging techniques make it possible to detect bulging of the wall of 1 mm, or larger.[12] Thus, we see no essential difference between enlargement from an undetectable weak spot to a 1–2 mm aneurysm (which would be classified as a newly visualized aneurysm in this study) and enlargement of a 2x2 mm aneurysm to a 3x3 mm aneurysm (classified as a grown aneurysm). However, some may argue that first appearance and growth of aneurysms are dependent on different factors and influence flow in a different way. A second limitation relates to the test characteristics of CTA and MRA in small aneurysms and hypoplastic vessels. Some of the included aneurysms were smaller than 2 mm. Although with current imaging techniques these small aneurysms can be clearly visualized, the sensitivity and specificity of aneurysms of this size are lower than in larger aneurysms. Not all patients with these small aneurysms had an indication for conventional angiography and therefore not all of these small aneurysms could be confirmed on conventional angiogram. Similarly, test characteristics may have affected our detection of hypoplastic vessels. Although we carefully assessed small aneurysms and hypoplasia in the original source data, reliably assessing hypoplasia can be difficult due to

differences in scan quality, contrast dye loading or flow artefacts. A third limitation of this study is that we cannot exclude the possibility of aneurysm development in the future on branches that did not develop an aneurysm during the current period of follow-up. However, even if aneurysms would develop during prolonged follow-up, our results still hold true for the rate of aneurysm development. A fourth limitation relates to the improvement in scan quality over the years: it proved impossible to find enough matched controls with a scan of such high quality that even the smallest MCA and PCoA branches could be seen. Also, for cases with an original angiogram made before 1996 a 3D reconstruction of the original angiogram was not available. After assessment of the intraobserver measurement error, we considered the difference between original angiogram and follow-up angiogram to be within the measurement error and therefore we analysed bifurcation angles without discriminating measurements in the original CTA/MRA from measurements in the follow-up CTA/MRA. In this cohort of patients only two ACoA aneurysms developed over time, which meant we unfortunately could not analyse the A1–A2 bifurcation angles.

We found that hypoplastic branches are a risk factor for developing aneurysms. Nevertheless many aneurysms develop on non-hypoplastic branches. This observation can at least in part be explained by the risk paradox, as hypoplastic branches are much less common than non-hypoplastic branches. A well-known example of this risk paradox is Down's syndrome. High maternal age (say > 35 years) is a strong risk factor for Down's syndrome. Nevertheless most mothers who give birth to a child with Down's syndrome are younger than 35 years of age. The explanation of this paradox is that there are many more pregnant women younger than 35 years of age than pregnant women older than 35 years of age. In situations where aneurysms of the ACoA develop on the dominant A1 side, or aneurysms of the PCoA on a foetal PCoA origin, or basilar tip aneurysms on bifurcations with bilateral normal P1 segments, high wall shear stress may have been present from high flow. Computer simulation models have shown that high wall shear stress may also be caused by turbulence, such as may exist where a hypoplastic branch detaches from the parent vessel or when a vessel has more acute curve.[10,11] A third explanation for the observation that many aneurysms develop on non-hypoplastic bifurcations despite the increased risk of aneurysm development in hypoplastic bifurcations is the relatively small number of patients in our series, which results in wide confidence. Thus the extent to which hypoplastic branches increase the risk is uncertain.

As bifurcation angles become sharper, the bloodstream has to deviate more from the flow of the parent artery. 3D computer simulation programs showed that it is highly likely that this increase in deviation is directly related to an increase in wall shear stress,[6-11] and cross sectional studies comparing sites with and without aneurysms show that sharper angles

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are associated with the presence of aneurysms.[4,5] Nevertheless, at many sites with sharp bifurcation angles within the circle of Willis no aneurysm develops. Apparently, other factors besides sharp angles play an important role in the aneurysm formation, such as genetic characteristics of the vessel wall, or environmental factors such as smoking or excessive use of alcohol.

Analysis of the configuration of intracranial arteries might be helpful in detecting persons with increased risk for developing aneurysms. Further investigation should clarify which hypoplastic branches exactly pose a risk of aneurysm formation, and enlighten the role of bifurcation angles. The large number of patients to be screened for such an analysis is however not yet available.

References

1	Rinkel GJE. Intracranial aneurysm screening: indications and advice for practice. *Lancet Neurol* 2005; **4**: 122-8.

2	Wermer MJ, van der Schaaf IC, Velthuis BK et al. Follow-up screening after subarachnoid haemorrhage: frequency and determinants of new aneurysms and enlargement of existing aneurysms. *Brain* 2005; **128**: 2421-9.

3	Horikoshi T, Akiyama I, Yamagata Z, Sugita M, Nukui H. Magnetic resonance angiographic evidence of sex-linked variations in the circle of willis and the occurrence of cerebral aneurysms. *J Neurosurg* 2002; **96**: 697-703.

4	Ingebrigtsen T, Morgan MK, Faulder K et al. Bifurcation geometry and the presence of cerebral artery aneurysms. *J Neurosurg* 2004; **101**: 108-13.

5	Kasuya H, Shimizu T, Nakaya K et al. Angeles between A1 and A2 segments of the anterior cerebral artery visualized by three-dimensional computed tomographic angiography and association of anterior communicating artery aneurysms. *Neurosurgery* 1999; **45**: 89-93.

6	Rossitti S. Shear stress in cerebral arteries carrying saccular aneurysms. A preliminary study. *Acta Radiol* 1998; **39**: 711-7.

7	Foutrakis GN, Yonas H, Sclabassi RJ. Saccular aneurysm formation in curved and bifurcating arteries. *AJNR Am J Neuroradiol* 1999; **20**: 1309-17.

8	Shojima M, Oshima M, Takagi K et al. Magnitude and role of wall shear stress on cerebral aneurysm: computational fluid dynamic study of 20 middle cerebral artery aneurysms. *Stroke* 2004; **35**: 2500-5.

9	Mantha A, Karmonik C, Benndorf G, Strother C, Metcalfe R. Hemodynamics in a cerebral artery before and after the formation of an aneurysm. *AJNR Am J Neuroradiol* 2006; **27**: 1113-8.

10	Hoi Y, Meng H, Woodward SH et al. Effects of arterial geometry on aneurysm growth: three-dimensional computational fluid dynamics study. *J Neurosurg* 2004; **101**: 676-81.

11	Oshima M, Kobayashi T, Takagi K. Biosimulation and visualization: effect of cerebrovascular geometry on hemodynamics. *Ann N Y Acad Sci* 2002; **972**: 337-44.

12	Villablanca JP, Jahan R, Hooshi P et al. Detection and Characterization of Very Small Cerebral Aneurysms by Using 2D and 3D Helical CT Angiography. *AJNR Am J Neuroradiol* 2002; **23**: 1187-98.

Development and rupture of anterior and posterior communicating artery aneurysms in relation to anatomic variations

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Abstract

Introduction: Identification of risk factors for aneurysm development and rupture could minimize the risk of subarachnoid haemorrhage (SAH). We analysed the association between anatomic variations of the anterior communication artery (ACoA) and the posterior communicating artery (PCoA) and aneurysm presence and rupture.

Methods: Case-control study including patients with an unruptured ACoA (n = 55) or PCoA (n = 34) aneurysm with sex and age matched ($\pm$ 5 years) controls: patients with a ruptured aneurysm at the same location and with patients without aneurysms. We calculated odds ratios (OR) with corresponding 95% confidence intervals (CI) for the association between A1 asymmetry ($\geq$ 50% diameter difference) and PCoA dominance (PCoA $\geq$ ipsilateral posterior cerebral artery) and aneurysm presence and rupture.

Results: We analysed 165 ACoA aneurysm segments (165 patients), and 203 PCoA aneurysm segments (102 patients). OR for aneurysm presence were 5.1 (95% CI 1.9–13.8) for A1 asymmetry and 2.1 (95% CI 1.1–3.9) for PCoA dominance. OR for ruptured versus unruptured aneurysm were RR 0.7 (95% CI 0.3–1.5) for A1 asymmetry and 2.3 (95% CI 0.9–6.1) for PCoA dominance.

Discussion: A1 asymmetry is associated with ACoA aneurysm development, but not with aneurysm rupture. PCoA dominance is associated with PCoA aneurysm development, and may be associated with PCoA aneurysm rupture. PCoA dominance may explain the increased risk of rupture for PCoA aneurysms compared to other anterior circulation aneurysms.

Introduction

Unruptured intracranial aneurysms are increasingly found with non-invasive imaging techniques. Not all aneurysms rupture and therefore treatment should be directed towards aneurysms at higher risk of rupture.[1] Identification of risk factors for aneurysm development and rupture could help individualize treatment options for new unruptured aneurysms or screening intervals for persons with familial SAH.

Circle of Willis (CoW) hemodynamics probably play an important role in development or rupture of intracranial aneurysms.[2] CoW sites with major anatomic variation and frequent presence of (un)ruptured aneurysms are the anterior (ACoA) and posterior (PCoA) communicating arteries.[3-7] Unruptured aneurysms at these locations have a higher risk of rupture than other anterior circulation aneurysms.[1] Nonetheless, it is unknown whether local ACoA and PCoA anatomic variations contribute primarily to aneurysm development or to rupture or to both. We studied A1 segment anterior cerebral artery asymmetry and PCoA dominance in patients without aneurysms, patients with an unruptured aneurysm, and patients with a ruptured ACoA or PCoA aneurysm. We hypothesized that A1 asymmetry and PCoA dominance are risk factors for both aneurysm development and rupture.

Methods

Data from patients with ruptured and unruptured intracranial aneurysms are prospectively collected in the University Medical Center Utrecht. For this case-control study, we retrieved all patients with unruptured saccular ACoA and PCoA aneurysms. Recurrent aneurysms of previously clipped or coiled aneurysms were excluded. We matched every retrieved patient with two persons with the same gender and comparable age ($\pm$ 5 years): one patient with either an ACoA or PCoA ruptured aneurysm, and one person without aneurysms (from screening or head CTA for minor stroke or transient ischemic attack). Diameters of the following CoW arteries were measured on both sides: A1, PCoA and P1 segment of the posterior cerebral arteries. For patients in het ACoA group, we compared both A1 sizes. For patients in the PCoA group, we analysed both left and a right PCoA segments. A1 asymmetry was considered present if one A1 diameter was $\leq$ 50% of the contralateral A1.[4,7,8] The PCoA was considered dominant if the PCoA diameter exceeded the ipsilateral P1 diameter.[4,6,7]

We calculated odds ratios (OR) with 95% confidence intervals (CI) to analyse the association between A1 asymmetry (ACoA group) or PCoA dominance (PCoA group) and aneurysm presence (ruptured and unruptured aneurysms combined versus no aneurysms), and between

A1 asymmetry (ACoA group) or PCoA dominance (PCoA group) and aneurysm rupture (presence of ruptured aneurysms versus unruptured aneurysms). This study was approved by the institutional review board.

Results

Characteristics of patients

Baseline characteristics of 55 patients with unruptured ACoA aneurysms, 34 patients with unruptured PCoA aneurysms and two controls for each patient are listed in Table 3.1.

Five of the 34 PCoA aneurysm patients had bilateral unruptured PCoA aneurysms and seven had a contralateral ruptured aneurysm. One contralateral ruptured PCoA aneurysm was unassessable due to clip artefacts, and was excluded from analysis. Thus 39 (34 + 5) PCoA segments with an unruptured PCoA aneurysm, 40 (34 + 7 – 1) PCoA segments with a ruptured PCoA aneurysm, and 124 PCoA segments without a PCoA aneurysm were analysed.

Anatomical variations and risk of aneurysm presence

For the ACoA group A1 asymmetry $\leq 50\%$ was present in 37 of 110 (34%) ACoA segments with a (ruptured or unruptured) aneurysm and 5 of 55 (9%) ACoA segments without an

Table 3.1 Baseline characteristics of the patients

ACoA group	No aneurysm n = 55 (100%)	Unruptured aneurysm n = 55 (100%)	Ruptured aneurysm n = 55 (100%)
Mean age (years) ± SD	56.1 ± 11	56.9 ± 11	56.3 ± 11
Women	40 (73%)	40 (73%)	40 (73%)
Hypertension (yes)*	11 (30%)	22 (45%)	14 (28%)
Smoking (current or ever)*	20 (63%)	30 (70%)	26 (68%)
Imaging modality CTA	11 (20%)	29 (53%)	55 (100%)
PCoA group	No aneurysm n = 34 (100%)	Unruptured aneurysm n = 34 (100%)	Ruptured aneurysm n = 34 (100%)
Mean age (years) ± SD	58 ± 10	58 ± 11	58 ± 11
Women	26 (77)	26 (77)	26 (77)
Hypertension (yes)*	8 (38%)	13 (43%)	7 (21%)
Smoking (current or ever)*	9 (50%)	17 (68%)	16 (67%)
Imaging modality CTA	9 (26%)	23 (68%)	34 (100%)

*Numbers do not add up to total due to missing data.

aneurysm (OR 5.1; 95% CI 1.9–13.8). For the PCoA group PCoA dominance was present in 28 of 79 (35%) PCoA segments with a (ruptured or unruptured) aneurysm and in 26 of 124 (21%) PCoA segments without an aneurysm (2.1; 95% CI 1.1–3.9).

Anatomical variations and risk of aneurysm rupture

For the ACoA group A1 asymmetry ≤ 50% was present in 16 of 55 (29%) of ACoA segments with a ruptured aneurysm and in 21 of 55 (21%) ACoA segments with an unruptured aneurysm (OR 0.7; 95% CI 0.3–1.5). For the PCoA group PCoA dominance was present in 18 of 40 (45%) PCoA segments with a ruptured aneurysm and in 10 of 39 (26%) PCoA segments with an unruptured aneurysm (OR 2.3; 95% CI 0.9–6.1).

Discussion

A1 asymmetry and PCoA dominance are associated with aneurysm presence, but not with aneurysm rupture. Our findings suggest that the repeatedly observed association between ruptured ACoA aneurysms and A1 asymmetry is primarily due to an increased rate of aneurysm development near A1 asymmetry, rather than an increased risk of rupture. For PCoA aneurysms the PCoA dominance may also be associated with aneurysm rupture. This should be further investigated in prospective study including more patient, as the increased risk of rupture for unruptured PCoA aneurysms compared to aneurysms elsewhere in the anterior circulation may be (partly) explained by PCoA dominance.[1]

Aneurysms development and aneurysm rupture may be separate processes governed by different causes.[2] Also, anatomic variation may play a different role in different aneurysm locations, as the ACoA is a unique complex with in the CoW, while the PCoA is a 'mere' bifurcation.[2] Previous studies did not distinguish aneurysm development and rupture as separate pathways, or did not differentiate between ACoA and PCoA as aneurysm locations.[3–7] Data from previous studies are in line with our findings. In a randomized trial on aneurysm coiling, A1 asymmetry < 50% was present more often in patients with ACoA aneurysms than in the control group, but in this study ruptured and unruptured aneurysms were grouped together.[8] In a retrospective cohort study on patients with ruptured and unruptured ACoA or PCoA aneurysms, anatomic CoW variation (A1 asymmetry < 50% for ACoA aneurysms and PCoA dominance for PCoA aneurysms) was associated with ruptured aneurysms when ACoA and PCoA aneurysms were grouped together in the analysis, but data on these sites were not given separately.[7] Another retrospective study comparing patients with unruptured

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aneurysms with persons with no aneurysms found an association between non-visualised ACoA and unruptured ACoA aneurysms, and PCoA dominance and unruptured carotid artery aneurysms.[6]

There are limitations to our study. Even though the risk of rupture for unruptured aneurysms is small, the status of unruptured aneurysms may not be definite, and some of the aneurysms may rupture in the future if left untreated. We did not adjust our analysis for possible risk factors as hypertension, smoking, aneurysm size, or flow direction as the CoW configuration itself remains unchanged with these factors.

A1 asymmetry or PCoA dominance may warrant extra vigilance on ACoA or PCoA aneurysm development. Future research should assess the long-term absolute risk of CoW variations for aneurysm development, for example in patients screened for familial SAH. Anatomic variations should not influence management decisions for small unruptured ACoA aneurysms. To what extent PCoA dominance of an unruptured PCoA aneurysm increases the rupture risk is unknown and should be assessed in a prospective study.

References

1 Greving JP, Wermer MJ, Brown RD, Jr. et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014; **13**: 59-66.

2 Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. *Neurosurg Focus* 2009; **26**: E2.

3 Bor AS, Velthuis BK, Majoie CB, Rinkel GJ. Configuration of intracranial arteries and development of aneurysms: a follow-up study. *Neurology* 2008; **70**: 700-5.

4 Velthuis BK, van Leeuwen MS, Witkamp TD et al. Surgical anatomy of the cerebral arteries in patients with subarachnoid hemorrhage: comparison of computerized tomography angiography and digital subtraction angiography. *J Neurosurg* 2001; **95**: 206-12.

5 Songsaeng D, Geibprasert S, Willinsky R et al. Impact of anatomical variations of the circle of Willis on the incidence of aneurysms and their recurrence rate following endovascular treatment. *Clin Radiol* 2010; **65**: 895-901.

6 Horikoshi T, Akiyama I, Yamagata Z, Sugita M, Nukui H. Magnetic resonance angiographic evidence of sex-linked variations in the circle of willis and the occurrence of cerebral aneurysms. *J Neurosurg* 2002; **96**: 697-703.

7 Lazzaro MA, Ouyang B, Chen M. The role of circle of Willis anomalies in cerebral aneurysm rupture. *J Neurointerv Surg* 2012; **4**: 22-6.

8 Tarulli E, Fox AJ. Potent risk factor for aneurysm formation: termination aneurysms of the anterior communicating artery and detection of A1 vessel asymmetry by flow dilution. *AJNR Am J Neuroradiol* 2010; **31**: 1186-91.

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Chapter 4

Differences in risk factors according to the site of intracranial aneurysms

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Abstract

Introduction: Several risk factors for aneurysmal subarachnoid haemorrhage have been identified, but it is unknown whether some sites of aneurysms are linked to a specific risk factor. In a series of patients with aneurysmal subarachnoid haemorrhage, we compared risk factors according to the site of the ruptured aneurysm at the circle of Willis.

Methods: From our prospectively collected database of patients with aneurysmal subarachnoid haemorrhage admitted to our hospital between 2003 and 2007 we retrieved 304 patients with saccular aneurysms on the anterior communicating artery, middle cerebral artery, posterior communicating artery, basilar artery and vertebral artery. Risk factors (age, gender, smoking, no or excessive alcohol intake, hypertension and familial preponderance) were assessed per aneurysm location and compared with the anterior communicating artery as reference. We calculated odds ratios (ORs) and corresponding 95% confidence intervals (CI).

Results: In comparison with aneurysms at the anterior communicating artery, those at the middle cerebral artery were less associated with age > 55 years (OR 0.4; 95% CI 0.2–0.8), those at the posterior communicating artery were less associated with male gender (OR 0.4; 95% CI 0.2–0.9) and those at the basilar artery were more associated with no alcohol consumption (OR 5.8; 95% CI 1.1–29.9).

Discussion: Risk factors differ according to the site of aneurysm. This heterogeneity should be kept in mind in studies on the aetiology of aneurysms, such as genetic studies.

Introduction

Risk factors for intracranial aneurysms and subarachnoid haemorrhage (SAH) include modifiable risk factors such as cigarette smoking, hypertension, excessive alcohol intake, and corticosteroid use; and non-modifiable factors such as age, female gender, positive family history, non-white ethnicity and heritable connective tissue disorder.[1-7] In these studies on risk factors, all sites of intracranial aneurysms have always been considered together. Therefore it is unknown whether some risk factors predispose for aneurysms at a particular location, or whether some sites of aneurysms are linked to a specific risk factor. There are nevertheless indications that risk factors differ per site. Patients with a positive family history have more often an aneurysm at the middle cerebral artery (MCA) than patients without such a family history,[8] and men have been reported to have more often anterior communicating artery aneurysms than women (ACoA).[9] We studied the relation between the prevalence of patient-related risk factors and site of aneurysm at the circle of Willis in patients with aneurysmal SAH.

Methods

Patient selection

From the prospectively collected database of SAH patients admitted to the University Medical Centre Utrecht, we retrieved up to 75 patients per aneurysm location, from the period between January 2003 through December 2007. We had calculated at beforehand that to find an OR of 2 with a confidence interval not including the neutral value (1.0), we needed 75 patients per aneurysm location. We used the following inclusion criteria: 1) SAH confirmed by computed tomography (CT) or lumbar puncture 2) ruptured saccular aneurysm identified on CT-angiography or conventional angiography 3) age at time of the SAH > 18 years 4) ruptured aneurysm located on the ACoA, pericallosal artery, T junction of the internal carotid artery (TCA), MCA, posterior communicating artery (PCoA), basilar artery (BA), and vertebral artery (VA). Posterior inferior cerebellar artery aneurysms were considered VA aneurysms and anterior inferior cerebellar artery aneurysms were considered BA aneurysms.

Patients with non-saccular aneurysms were excluded as well as patients with SAH and multiple aneurysms if there was any doubt about the location of the ruptured aneurysm. Furthermore, locations for which we could retrieve less than 20 patients with ruptured aneurysms were excluded from analysis.

Risk factors

For all patients, information on age, gender, smoking, alcohol consumption, hypertension (> 140/90 mmHg) and familial preponderance was retrieved from the database. If there was no information for a specific risk factor available, patients were excluded for that particular analysis. Former smokers and sporadic alcohol consumers were excluded from the smoking- and alcohol analysis.

Data analysis

Data was analysed using SPSS. We calculated odds ratios (OR) with corresponding 95% confidence interval (CI) for the mentioned risk factors. We compared all locations to the ACoA, which is the most prevalent location for ruptured aneurysms in our database. Subsequently, a multivariate analysis was performed for variables with probability values < 0.20 in the univariate analyses.

Results

We were able to retrieve 75 patients for each of the following locations: ACoA, MCA and PCoA. For the BA only 42- and for the VA only 37 patients could be retrieved (Table 4.1).

Table 4.1 Baseline characteristics

	Total no of patients (%)	ACoA (%)	PCoA (%)	MCA (%)	BA (%)	VA (%)
No of patients	304 (100%)	75 (100%)	75 (100%)	75 (100%)	42 (100%)	37 (100%)
Age > 55 years	164 (53.9%)	47 (62.6%)	50 (66.7%)	30 (40%)	14 (33.3%)	23 (62.2%)
Men	75 (24.7%)	25 (33.3%)	13 (17.3%)	17 (22.7%)	14 (33.3%)	6 (16.2%)
Smoking (n = 245)*						
Never	84 (34.3%)	25 (41.7%)	25 (39.0%)	19 (33.9%)	6 (17.6%)	9 (29.0%)
Former	21 (8.6%)	3 (5.0%)	7 (10.9%)	4 (7.1%)	3 (8.8%)	4 (12.9%)
Current	140 (57.1%)	32 (53.3%)	32 (50.0%)	33 (58.9%)	25 (73.5%)	18 (58.1%)
Alcohol (n = 206)*						
Never	69 (33.5%)	15 (27.8%)	14 (31.1%)	20 (38.5%)	10 (34.5%)	10 (38.5%)
< 1/day	59 (28.6%)	17 (31.4%)	10 (22.2%)	12 (23.1%)	12 (41.4%)	8 (30.8%)
1–3/day	52 (25.2%)	16 (29.6%)	16 (35.6%)	11 (21.2%)	3 (10.3%)	6 (23.1%)
> 3/day	26 (12.6%)	6 (11.1%)	5 (11.1%)	9 (17.3%)	4 (13.8%)	2 (7.7%)
Hypertension (n = 294)*	77 (26.2%)	19 (25.7%)	18 (24.7%)	20 (28.2%)	11 (26.8%)	9 (25.7%)
≥ 1 affected relative (n = 198)*	5 (2.5%)	0 (0.0%)	4 (7.7%)	0 (0.0%)	1 (3.7%)	0 (0.0%)

*Less than 304 because of missing data.

The pericallosal artery and TCA were excluded from the analyses as < 20 patients were found for these locations.

In the univariate analyses (Figure 4.1) and compared with patients with ACoA aneurysms, those with BA aneurysms were less often older than the median age (OR 0.3; 95% CI 0.1–0.7) and smoked more often (OR 3.3; 95% CI 1.2–9.1); those with MCA aneurysms were less often older than the median age (OR 0.4; 95% CI 0.2–0.8), and those with PCoA aneurysms were less often men (OR 0.4; 95% CI 0.2–0.9). Other risk factors had no statistical significant relation with location of the aneurysm. The relation between men and ruptured MCA and VA aneurysms and between no alcohol users (teetotallers) and ruptured BA aneurysms had p-values < 0.2 and were therefore included in the multivariate analysis.

In the multivariate regression analysis, patients with MCA aneurysms were less often older than the median age (OR 0.4; 95% CI 0.2–0.8), those with PCoA aneurysms were less often men (OR 0.4; 95% CI 0.2–0.9), and those with BA aneurysms more often teetotallers (OR 5.8; 95% CI 1.1–29.9). The other associations found in the univariate analyses were no longer significant in the multivariate analysis: patients with MCA aneurysms were less often men (OR 0.6; 95% CI 0.3–13), patients with BA aneurysms were less often older than the median age (OR 0.5; 95% CI 0.2–1.3) en more often smokers (OR 2.8 95% CI 0.8–9.6) and patients with VA aneurysms were less often men (OR 0.4; 95% CI 0.1–1.0).

Discussion

Some risk factors predispose for ruptured aneurysms at a particular location. Within the subset of patients with SAH, MCA aneurysms are less likely to occur in older patients, PCoA aneurysms are less likely to occur in men, and BA aneurysms are more common among teetotallers. Excessive use of alcohol and hypertension did not seem to influence the site of aneurysms.

MCA aneurysms occur more often in patients with a family history of SAH than in patients without a positive family history.[8] Patients with a positive family history are also of a younger age at time of SAH than patients without a positive family history. This may explain why in the current study, patients with MCA aneurysms were more often young than patients with ACoA aneurysms. In the present study, we found no relation between family history and site of aneurysms, possibly because of the small number of patients with a positive family history in our sample. This small number is explained by the fact that in the present sample not all families were scrutinized for a familial occurrence of SAH.[10]

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Our study demonstrates that men have ruptured aneurysms more often at the ACoA compared to the PCoA. This same result was found by Park et al who did a gender comparison study about ruptured aneurysms.[9] We did not find other studies comparing the relation
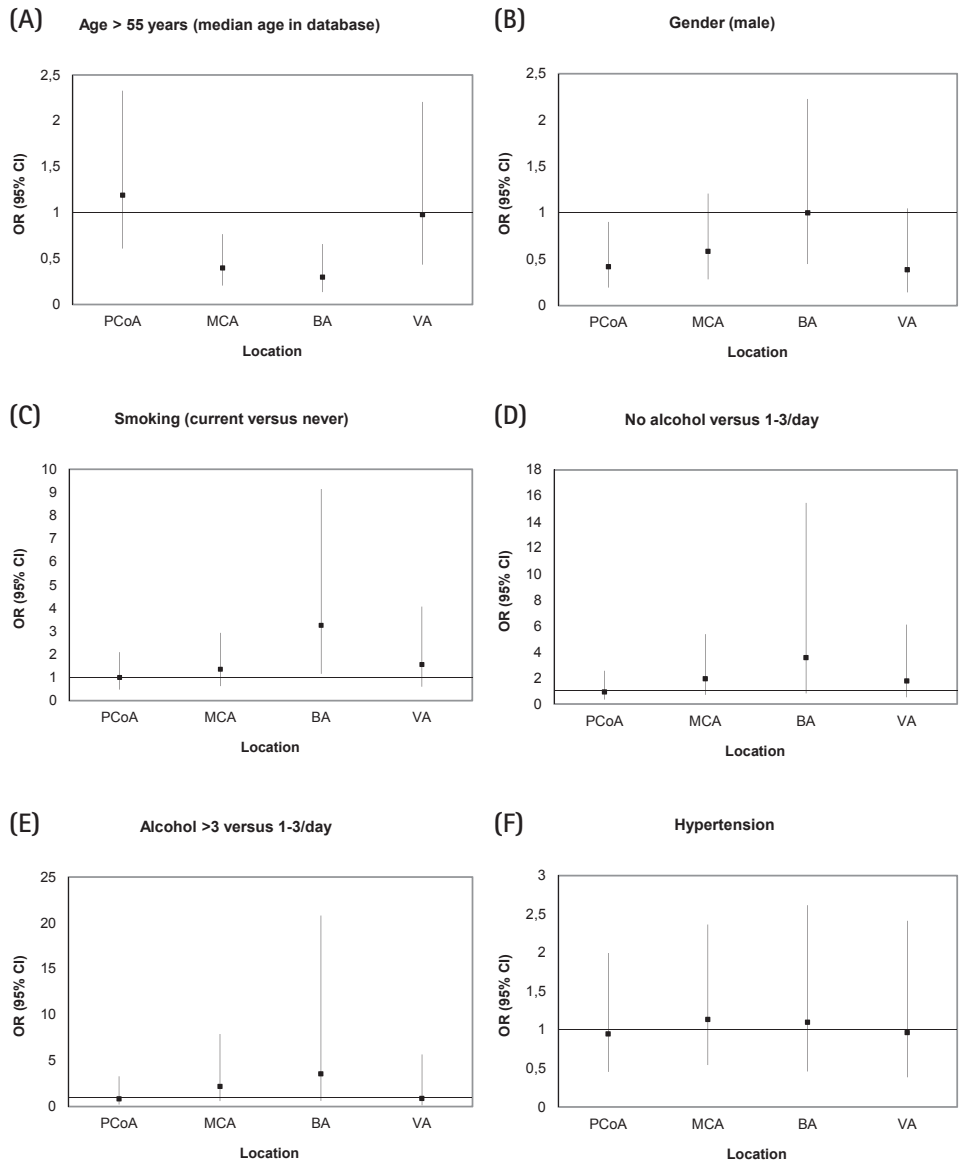
Figure 4.1 A–F Results from univariate analyses showing odds ratios and corresponding 95% confidence intervals for different locations, with the anterior communicating artery as reference. BA = basilar artery. MCA = middle cerebral artery. PCoA = posterior communicating artery. VA = vertebral artery.

between different risk factors and site of aneurysms, so we could not further compare our results to those of the literature.

Some limitations can be noticed for this study. First, the relatively small number of posterior circulation aneurysms has limited the statistical power for posterior circulation aneurysms. Second, the prevalence of familial preponderance is low in our patient group; therefore no clear conclusion can be made about the risk factor familial preponderance and preference for a specific location in this patient cohort.

This study was not designed to assess the influence of the studied risk factors on the development of aneurysms or on the risk of rupture of aneurysms. The conclusion that can be drawn from the results is that risk factors as age, gender and no alcohol consumption influence the site of the aneurysm. In other words, aneurysms at different sites differ not only in site but also in risk factors.

The formation of aneurysms is still a largely unknown process. Although this study shows that risk factors differ per aneurysm location, it should be kept in mind that these differences may not be the same for all genetic populations. Patients in our study were Western-European patients, and the results we found may not be the same for Japanese or Finnish patients. However, it seems likely that there are differences in the occurrence of risk factors per aneurysm location for these populations too. Lumping all aneurysms together may not be appropriate in genetic studies, and should therefore be regarded carefully.

References

1   Feigin VL, Rinkel GJE, Lawes CM et al. Risk Factors for Subarachnoid Hemorrhage. An Updated Systematic Review of Epidemiological Studies. *Stroke* 2005; **36**: 2773-80.

2   Clarke G, Mendelow AD, Mitchell P. Predicting the risk of rupture of intracranial aneurysms based on anatomical location. *Acta Neurochir (Wien)* 2005; **147**: 259-63.

3   Nahed BV, Diluna ML, Morgan T et al. Hypertension, age, and location predict rupture of small intracranial aneurysms. *Neurosurgery* 2005; **57**: 676-83.

4   Rinkel GJE, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke* 1998; **29**: 251-6.

5   Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. *N Engl J Med* 2006; **354**: 387-96.

6   Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJE. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: a meta-analysis. *Stroke* 2007; **38**: 1404-10.

7   Ruigrok YM, Rinkel GJ. Genetics of intracranial aneurysms. *Stroke* 2008; **39**: 1049-55.

8   Ruigrok YM, Rinkel GJE, Algra A, Raaymakers TWM, van Gijn J. Characteristics of intracranial aneurysms in patients with familial subarachnoid hemorrhage. *Neurology* 2004; **62**: 891-4.

9   Park SK, Kim JM, Kim JH et al. Aneurysmal subarachnoid hemorrhage in young adults: a gender comparison study. *J Clin Neurosci* 2008; **15**: 389-92.

10   Greebe P, Bromberg JEC, Rinkel GJE, Algra A, van Gijn J. Family history of subarachnoid haemorrhage: supplemental value of scrutinizing all relatives. *J Neurol Neurosurg Psychiat* 1997; **62**: 273-5.

Chapter 5

Clinical, radiological and flow related risk factors for growth of untreated unruptured intracranial aneurysms
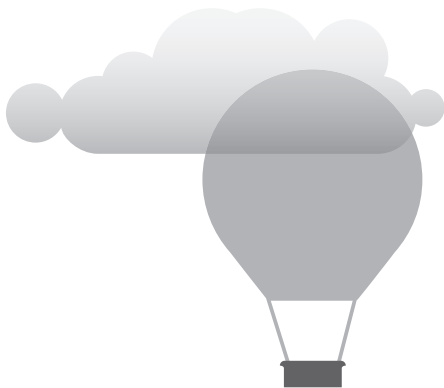
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Abstract

Introduction: Unruptured intracranial aneurysms are frequently followed to monitor aneurysm growth. We studied the yield of follow-up imaging and analyzed risk factors for aneurysm growth.

Methods: We included patients with untreated unruptured intracranial aneurysms and at least 6 months of follow-up imaging from two large prospectively collected databases. We assessed the proportion of patients with aneurysm growth and performed univariable and multivariable Cox regression analyses to calculate hazard ratios (HR) with corresponding 95% confidence intervals (CI) for clinical and radiological risk factors for aneurysm growth. We repeated these analyses for the subset of small (< 7 mm) aneurysms.

Results: Fifty-seven (12%) of 468 aneurysms in 363 patients grew during a median follow-up of 2.1 years (total follow-up 1372 patient-years). In multivariable analysis HRs for aneurysm growth were: 1.08 (1.00–1.16) per each additional mm of initial aneurysm size, 2.7 (95% CI 1.2–6.4) for dome > neck ratio, 2.1 (95% CI 0.9–4.9) for location in the posterior circulation and 2.0 (95% CI 0.8–4.8) for multilobarity. In the subset of aneurysms < 7 mm, 37 of 403 (9%) enlarged. In multivariable analysis HRs for aneurysm growth were 1.09 (0.79–1.49) per each additional mm of initial aneurysm size, 2.2 (95% CI 1.0–4.8) for smoking, 2.9 (95% CI 1.0–8.5) for multilobarity, 2.4 (95% CI 1.0–5.8) for dome > neck ratio and 2.0 (95% CI 0.6–7.0) for location in the posterior circulation.

Discussion: Initial aneurysm size, dome > neck ratio and multilobarity are risk factors for aneurysm growth. Cessation of smoking is pivotal since smoking is a modifiable risk factor for growth of small aneurysms.

Introduction

Approximately 3% of the population has an asymptomatic unruptured intracranial aneurysm.[1] With the increasing availability of non-invasive imaging techniques, unruptured aneurysms are often detected before rupture. Rupture of an intracranial aneurysm causes subarachnoid hemorrhage (SAH), which has a high case fatality and morbidity,[2] and is associated with a high socio-economic burden.[3] Elective occlusion of the unruptured aneurysm to prevent rupture is possible, but the risks of preventive treatment often do not outweigh the risks of rupture for small aneurysms.[4,5] Therefore small unruptured aneurysms are often followed with repeated imaging, with the intention to treat the aneurysm when it increases in size. The effectiveness of this strategy, the optimal interval for repeated imaging, and risk factors for aneurysm growth, other than aneurysm size, are unknown. Identification of clinical or radiological markers for aneurysm growth could tailor follow-up strategies and shed more light on pathogenesis of aneurysm growth and thereby indirectly rupture. The most consistent risk factor for aneurysm growth in the literature is initial aneurysm size.[6-8] In a previous prospective, small, short term follow-up study, previous SAH and familial SAH were also risk factors for aneurysm growth.[9] Suggested risk factors for aneurysm growth include smoking,[10] multiplicity of aneurysms,[11] aneurysm shape,[12] flow direction into the aneurysm,[13] and bifurcation angles.[14] Prospective long term follow-up data on these factors are lacking. Moreover, most studies were too small to perform reliable multivariable analyses.

We combined two large datasets with prospectively collected, consecutive series of patients with an unruptured untreated intracranial aneurysm and follow-up imaging. This international dataset has a uniquely large number of patients, which enables us to study the independence of potential clinical and radiological risk factors for aneurysm growth in untreated, unruptured intracranial aneurysms that are managed with follow-up imaging rather than occlusion.

Methods

Patient inclusion criteria

Data from all patients from the Toronto Western Hospital (Canada) and the University Medical Centre Utrecht (the Netherlands) with an unruptured aneurysm were prospectively collected. From these databases all patient aged 18 years and older with at least one saccular untreated intracranial aneurysm and a minimum of 6 months of radiological follow-up by CTA or MRA were retrieved.

Risk factors

Data on sex, age, smoking, hypertension (previous diagnosis made by a general practitioner or other physician), antihypertensive medication, previous SAH, and family history of SAH at the time of detection of the unruptured aneurysm were retrieved from clinical records. The imaging data were assessed for aneurysm location, maximum aneurysm height, maximum aneurysm dome width, aneurysm neck width, flow direction into the aneurysm, and bifurcation angles. Shape of the aneurysm was scored visually (round, elliptical, multilobar) and calculated as dome-neck ratio (aneurysm dome width divided by aneurysm neck width in mm) and as aspect ratio (aneurysm height divided by aneurysm neck width in mm). An example of some of these measurements is shown in Figure 5.1.
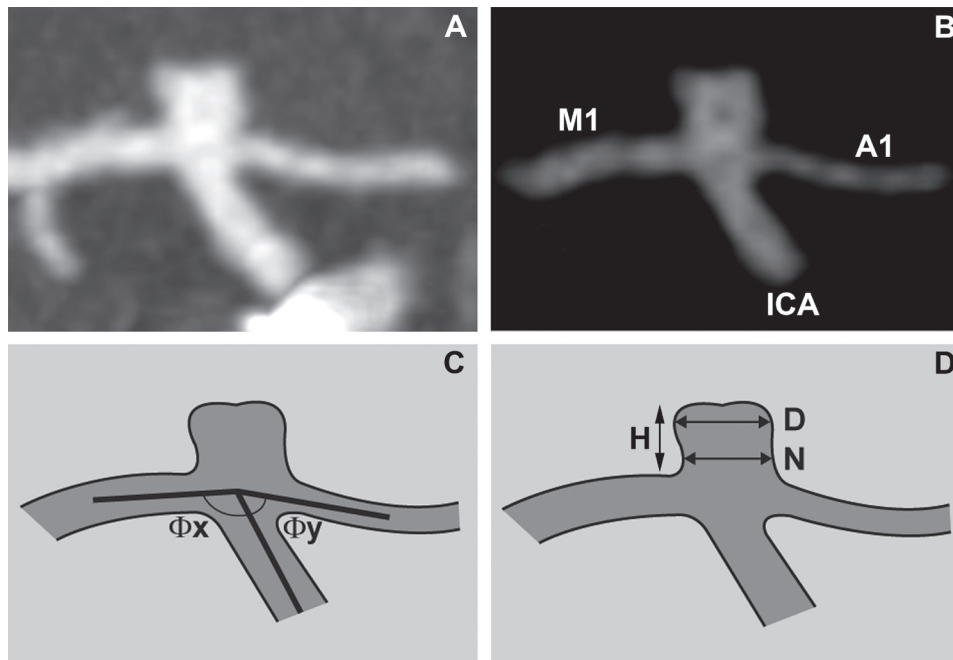
Figure 5.1 Example of aneurysm measurements in an unruptured aneurysm of the right internal carotid artery (ICA) bifurcation. Panel A: asymptomatic unruptured aneurysms on right carotid artery bifurcation. Panel B: aneurysm in the window setting in which we performed all measurements (window width and window level equal the Hounsfield density measurement in the aneurysm), with the surrounding with the surrounding arteries: ICA; M1 = M1 segment middle cerebral artery; A1 = A1 segment anterior cerebral artery. Panel C: measurement of the bifurcation angles with ΦX as the maximum angle and ΦY as the minimum angle. Panel D: measurement of the aneurysm height (H), aneurysm neck (N) and aneurysm dome (D).

Outcome measurement

Initial aneurysm size was measured on the first and last imaging available in two directions: maximum height and maximum dome width. Aneurysm growth was defined as 1) growth ≥ 1 mm in at least one direction for identical or different imaging modalities, 2) growth ≥ 0.5 mm in two directions for identical imaging modalities (CTA or MRA), or 3) undisputable change in shape of the aneurysm, such as change from unilobar to multilobar shape.[15] An example of aneurysm growth is shown in Figure 5.2.
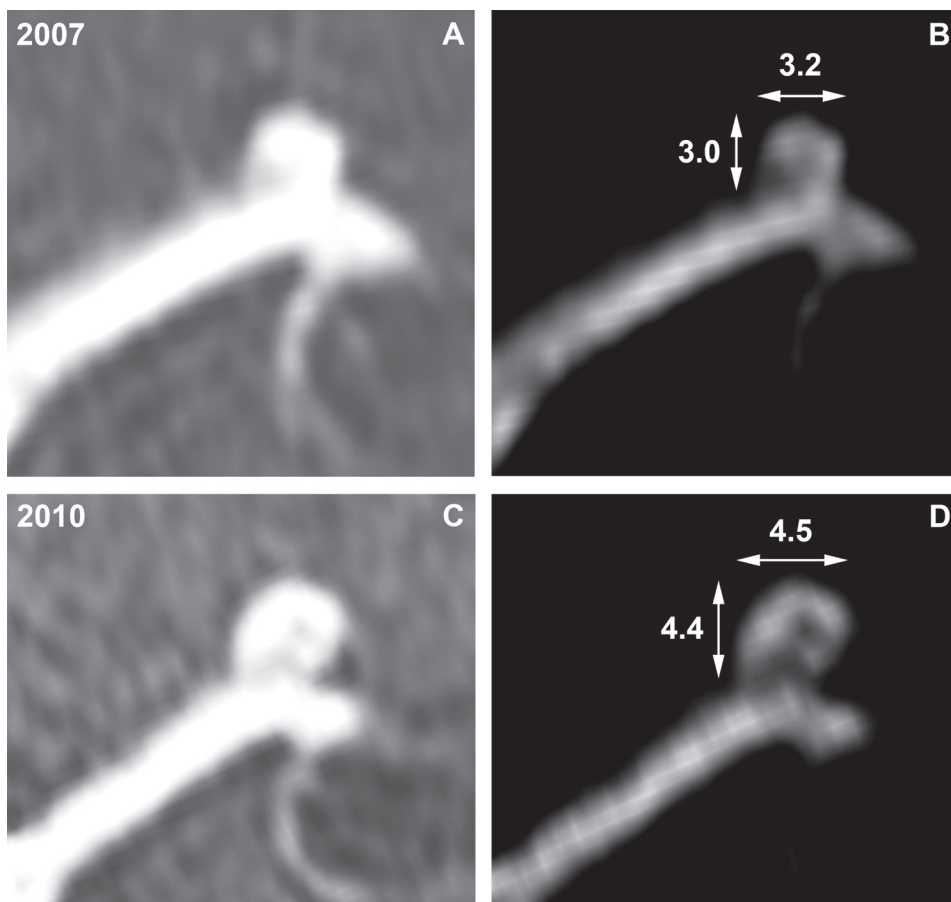
Figure 5.2 Example of a grown unruptured aneurysm of the left middle cerebral artery (MCA), showing the initial MR angiography in 2007 (top row) and a follow-up MR angiography in 2010 (bottom row). Panel A and C: original windowing. Panel B and D: windowing used for measurements (window width and window level equal the Hounsfield density measurement in the aneurysm), with measurement of aneurysm dome and height, showing aneurysm growth.

Radiological assessment

All images were assessed by one of two observers (ASEB or ATTG). Training for this assessment was done under supervision of an experienced neuroradiologist (BKV), and included extensive analyses of a training dataset with scans from both participating academic centers to ascertain identical measurement methods. Assessment was done without knowledge on (presumed) clinical risk factors for aneurysm growth. First and last imaging of each patient was assessed in a single session by the same researcher to avoid interobserver variability and to minimize intra-observer variability. All aneurysms with possible growth were re-evaluated in a consensus meeting with ASEB, ATTG and BKV to confirm aneurysm growth. If consensus on growth was reached, aneurysm size was assessed in all imaging studies performed between the first and the last imaging study. The first follow-up imaging that showed growth and the time that had elapsed between this imaging and the initial imaging were used for further analyses. For aneurysms that ruptured, the last follow-up imaging before rupture was used as endpoint imaging. All radiological measurements were performed in a single center in a single radiological data evaluation program (Philips Intellispace Portal software, Philips Healthcare).

Statistical analysis

We performed univariable Cox regression analyses and calculated hazard ratios (HR) with corresponding 95% confidence intervals (95% CI), and p-values. We performed a multivariable Cox regression analysis including all risk factors related to aneurysm growth in the univariable Cox regression analysis with a p-value < 0.2. All analyses were performed on a per aneurysm basis. As initial aneurysm size is a known strong risk factor for aneurysm growth and rupture, an identical secondary analysis was performed, including only small aneurysms defined as initial aneurysm size < 7 mm. Data are presented in Kaplan Meier survival curves, for all aneurysms, and for aneurysms with initial aneurysm size < 7 mm and ≥ 7 mm separately. We reported the number of aneurysms with and without growth per two years of follow-up.

The following risk factors were entered in the univariable Cox regression analysis: sex, age, smoking and hypertension at the time of diagnosis, previous SAH (SAH predating or at the time of diagnosis), presence of multiple aneurysms (ruptured or unruptured), family history of SAH (two or more first degree relatives with an (un)ruptured intracranial aneurysm), initial aneurysm size (maximum aneurysm height or dome width), aneurysm location (posterior circulation versus anterior circulation), multilobarity (multilobar versus unilobar shape), dome

> neck ratio (aneurysm dome width larger than aneurysm neck width versus aneurysm dome width smaller than aneurysm neck width), aspect ratio ≥ median (aspect ratio larger than the median versus aspect ratio smaller than the median), flow direction into the aneurysm (highest versus lowest tertile) and bifurcation angles (highest versus lowest tertile).

Additionally the following variables were analyzed in categories to increase discrimination: age (< 50, 50–60, > 60 years at initial diagnosis), initial aneurysm size (< 2 mm, 2–4 mm, 4–7 mm, 7–15 mm and > 15 mm), aneurysm location in the anterior circulation: middle cerebral artery versus carotid artery, and anterior communicating/cerebral artery versus carotid artery.

This study was approved by the institutional review board of the University Medical Center Utrecht.

Results

The baseline characteristics of the included 363 patients with 468 unruptured aneurysms are described in Table 5.1. Two hundred seventy eight patients had one aneurysm, 67 patients had two aneurysms, 16 patients had three aneurysms and two patients had four aneurysms. In total 57 aneurysms (12%) increased in size during the total follow-up time of 1372 patient years, with a median follow-up time of 2.1 year (mean follow-up time 2.8 years per aneurysm). None of the aneurysms had indisputable change in shape without simultaneous growth in size. Four patients had an SAH during follow-up; three from a known and followed aneurysm (3/468 aneurysms, 0.6%), one from a de novo aneurysm. One of the three known aneurysms showed growth (largest diameter from 7.3 to 8.5 mm) on the last follow-up imaging 16 months prior to the rupture. The other two known aneurysms that ruptured did not show growth at follow-up imaging at nine (aneurysm size 2.9 mm) and 15 months (aneurysm size 4.0 mm) before rupture.

In multivariable analysis on risk factors for aneurysm growth HR were 1.08 (1.00–1.16) per each additional mm of initial aneurysm size, 2.7 (95% CI 1.2–6.4) for dome > neck ratio, 2.0 (95% CI 0.8–4.8) for multilobarity and 2.1 (95% CI 0.9–4.9) for location in the posterior circulation (Table 5.2). In the subset of aneurysms < 7 mm, 37 of 403 aneurysms (9%) enlarged. In multivariable analysis on risk factors for growth HR in these small aneurysms were: smoking 2.2 (95% CI 1.0–4.8), multilobarity 2.9 (95% CI 1.0–8.5), dome > neck ratio 2.4; (95% CI 1.0–5.8) location in the posterior circulation 2.0 (95% CI 0.6–7.0) and presence of multiple aneurysms 0.3 (95% CI 0.1–0.9) (Table 5.3). Kaplan Meier's survival curves show aneurysm growth for all aneurysms (Figure 5.3A) and for aneurysms with initial size < 7 mm

Table 5.1 Baseline characteristics of patients and aneurysms

Patient characteristics	Utrecht n = 174	Toronto n = 189	All patients n = 363
Median follow-up in years (range)	3.5 (0.5–9.3)	1.8 (0.5–7.1)	2.1 (0.5–9.3)
Female	133 (76%)	147 (78%)	280 (77%)
Age (years)			
< 50	57 (33%)	56 (29%)	113 (31%)
50–60	68 (40%)	68 (36%)	136 (38%)
> 60	49 (28%)	65 (34%)	114 (31%)
Smoking*	72 (53%)	59 (31%)	131 (40%)
Hypertension*	60 (44%)	78 (42%)	138 (43%)
Family history of SAH*	30 (25%)	42 (29%)	72 (27%)
Previous SAH*	69 (42%)	29 (16%)	98 (28%)
Multiple aneurysms	94 (54%)	69 (37%)	163 (45%)
Patients with a grown aneurysm	23 (13%)	32 (17%)	55 (15%)
Aneurysm characteristics	Utrecht n = 222	Toronto n = 246	All aneurysms n = 468
Aneurysm location			
ICA	67 (30%)	116 (47%)	183 (39%)
MCA	89 (40%)	67 (27%)	156 (33%)
ACA	40 (18%)	32 (13%)	72 (15%)
Posterior circulation	26 (12%)	31 (13%)	57 (12%)
Initial aneurysm size (mm)			
< 2	18 (8%)	15 (6%)	33 (7%)
2.0–3.9	125 (56%)	111 (45%)	236 (50%)
4.0–6.9	63 (28%)	71 (29%)	134 (29%)
7.0–14.9	16 (7%)	36 (15%)	52 (11%)
≥ 15.0	0 (0%)	13 (5%)	13 (3%)
Aneurysm rupture during FU	2 (1%)	1 (0.4%)	3 (0.6%)
Aneurysms growth during FU	25 (11%)	32 (13%)	57 (12%)

*Variable not known for all patients.
ICA: internal carotid artery. MCA: middle cerebral artery. ACA: anterior cerebral artery.

and aneurysm size ≥ 7 mm separately (Figure 5.3B). Rate of aneurysm growth per year of follow-up is shown in Table 5.4. Aneurysmal growth was seen in 15 of 188 aneurysms (8%; 95% CI 5–13%) with follow-up ≥ 3 years, and five of 77 (6%; 95% CI 2–5%) aneurysms with follow-up ≥ 5 years.

(A) Aneurysm growth including all 468 aneurysms

(B) Aneurysm growth in 65 aneurysms with initial size ≥ 7 mm and 403 aneurysms with initial size < 7 mm
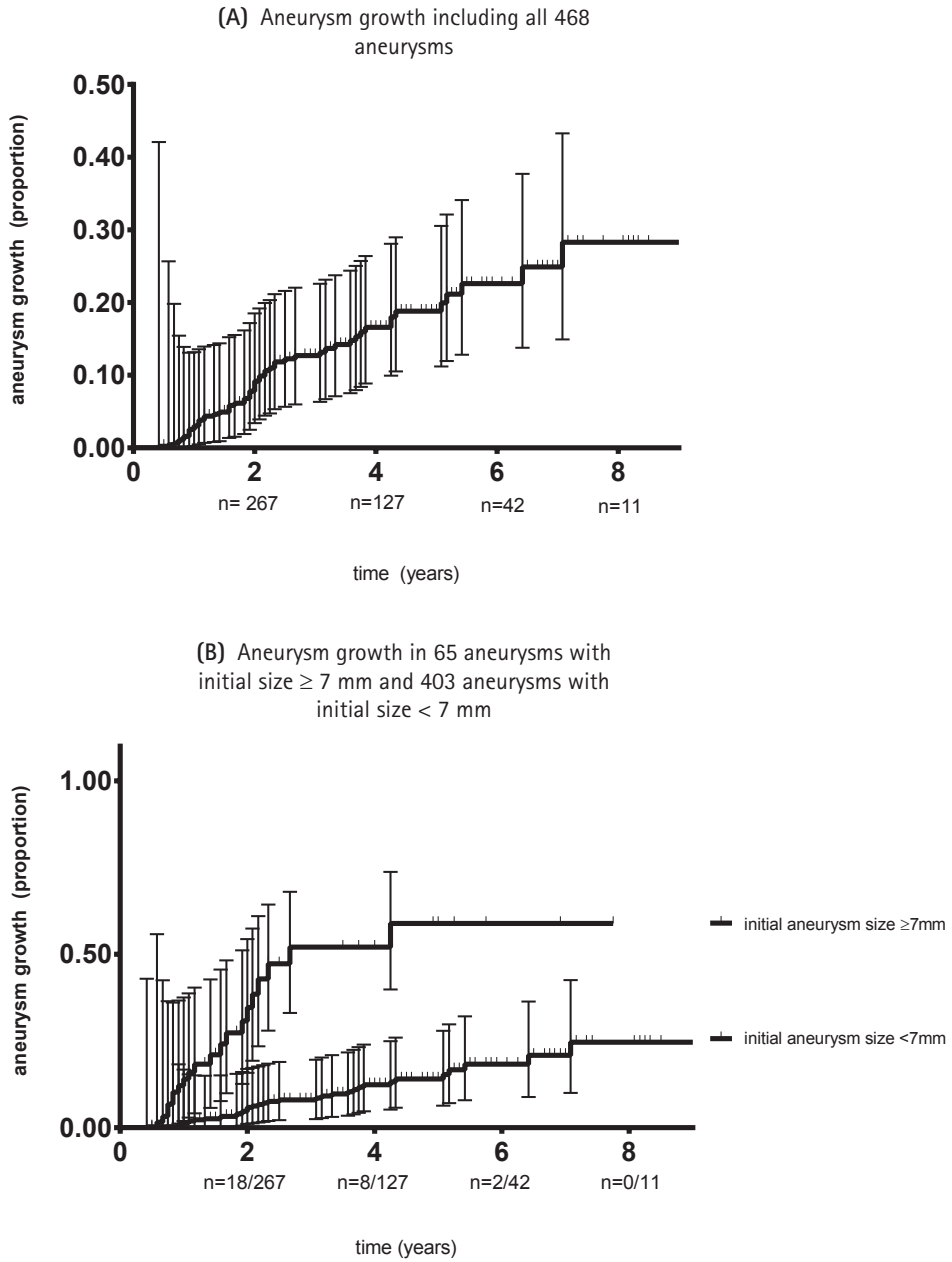
Figure 5.3 Kaplan Meier survival curves for aneurysm growth in all aneurysms **(A)** and for aneurysms with initial aneurysm size ≥ 7 mm and aneurysms with initial aneurysm size < 7 mm separately **(B)**.

Table 5.2 Results of univariable and multivariable Cox regression analyses of clinical and radiological risk factors in hazard ratios (HR) with 95% confidence intervals (95% CI)

Risk factor	Stable aneurysms n = 411	Grown aneurysms n = 57	Univariable analyses HR (95% CI)	Univariable analyses p-value	Multivariable analysis HR (95% CI)	Multivariable analyses p-value
Age						
Mean (in years)	55	55	1.0 (1.0–1.0)	0.39		
< 50 year	123 (30%)	19 (33%)	1.2 (0.6–2.1)	0.60		
50–60 year	158 (38%)	20 (35%)	1.3 (0.7–2.5)	0.40		
> 60 year	130 (32%)	18 (32%)	Ref			
Female	329 (80%)	43 (75%)	0.7 (0.4–1.2)	0.19	1.1 (0.4–2.7)	0.86
Smoking	153 (42%)	26 (50%)	1.3 (0.7–2.2)	0.39		
Hypertension	155 (43%)	27 (52%)	1.3 (0.7–2.2)	0.36		
Family history of SAH	95 (32%)	7 (18%)	0.5 (0.2–1.1)	0.09	0.6 (0.2–1.6)	0.31
Previous SAH	123 (31%)	7 (13%)	0.3 (0.1–0.6)	0.00	0.9 (0.3–2.7)	0.92
Multiple aneurysms	240 (58%)	28 (49%)	0.6 (0.3–0.9)	0.03	0.6 (0.3–1.2)	0.14
Initial aneurysm size						
Mean (in mm)	4.3	7.7	1.12 (1.09–1.15)	0.00	1.08 (1.00–1.16)	0.07
< 2 mm	31 (8%)	2 (4%)	0.9 (0.2–3.9)	0.89		
2–3.9 mm	220 (54%)	16 (28%)	Ref			
4.0–6.9 mm	115 (28%)	19 (33%)	2.7 (1.4–5.3)	0.00		
7.0–14.9 mm	39 (9%)	13 (23%)	6.9 (3.3–14.5)	0.00		
≥ 15.0 mm	6 (1%)	7 (12%)	23.4 (9.4–58.3)	0.00		
Aneurysm anterior circulation						
ICA	161 (39%)	22 (39%)	Ref			
MCA	141 (34%)	15 (26%)	0.7 (0.4–1.4)	0.29		
ACA	63 (15 %)	9 (16%)	0.8 (0.4–1.7)	0.57		

Risk factor	Stable aneurysms n = 411	Grown aneurysms n = 57	Univariable analyses HR (95% CI)	Univariable analyses p-value	Multivariable analysis HR (95% CI)	Multivariable analyses p-value
Aneurysm posterior circulation	46 (11%)	11 (19%)	2.1 (1.1–4.1)	0.03	2.1 (0.9–4.9)	0.12
Multilobar aneurysm	43 (11%)	13 (23%)	3.9 (2.1–7.5)	0.00	2.0 (0.8–4.8)	0.13
Size ratio						
Dome > neck	152 (40%)	33 (64%)	2.9 (1.7–5.1)	0.00	2.7 (1.2–6.4)	0.02
Aspect ratio ≥ median (1.0)	176 (46%)	33 (64%)	2.3 (1.3–4.1)	0.00	0.8 (0.4–1.9)	0.64
Flow into aneurysm						
1st tertile (54–112°)	136 (33%)	21 (37%)	Ref			
2nd tertile (112–143°)	140 (34%)	13 (23%)	0.7 (0.3–1.4)	0.30		
3rd tertile (143–180°)	135 (33%)	23 (40%)	1.2 (0.7–2.3)	0.47		
Bifurcation, largest angle						
1st tertile (133–178°)	83 (36%)	7 (22%)	Ref			
2nd tertile (112–133°)	72 (31%)	10 (31%)	1.5 (0.6–3.9)	0.41		
3rd tertile (57–112°)	78 (34%)	15 (47%)	1.9 (0.8–4.7)	0.16		
Bifurcation, smallest angle						
1st tertile (90–139°)	75 (33%)	15 (47%)	Ref			
2nd tertile (71–90°)	75 (33%)	6 (19%)	0.5 (0.2–1.2)	0.10		
3rd tertile (26–71°)	79 (35%)	11 (34%)	0.5 (0.8–1.6)	0.47		

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Table 5.3 Results of univariable and multivariable Cox regression analyses of clinical and radiological risk factors in hazard ratios (HR) with 95% confidence intervals (95% CI), in 403 aneurysms with initial aneurysm size < 7 mm

Risk factor	Stable aneurysms n = 366	Grown aneurysms n = 37	Univariable analyses HR (95% CI)	Univariable analyses p-value	Multivariable analysis HR (95% CI)	Multivariable analyse p-value
Age (years)						
< 50	116 (32%)	16 (43%)	1.3 (0.6–2.6)	0.49		
50–60 year	141 (39%)	15 (41%)	Ref			
> 60 year	109 (30%)	6 (16%)	0.7 (0.3–1.8)	0.43		
Female	297 (81%)	28 (76%)	0.6 (0.3–1.2)	0.16	1.1 (0.4–3.0)	0.77
Smoking	143 (44%)	19 (58%)	1.6 (0.8–3.2)	0.19	2.2 (1.0–4.8)	0.04
Hypertension	140 (44%)	14 (42%)	0.8 (0.4–1.6)	0.60		
Familial history of SAH	93 (34%)	7 (25%)	0.7 (0.3–1.7)	0.42		
Previous SAH	118 (34%)	7 (21%)	0.4 (0.2–0.8)	0.02	0.8 (0.3–2.4)	0.66
Multiple aneurysms	226 (62%)	16 (43%)	0.4 (0.2–0.7)	0.00	0.3 (0.1–0.9)	0.02
Initial aneurysm size						
Mean (in mm)	3.4	4.1	1.43 (1.16–1.77)	0.00	1.09 (0.79–1.49)	0.61
< 2 mm	31 (9%)	2 (5%)	0.9 (0.2–3.9)	0.87		
2–3.9 mm	220 (60%)	16 (43%)	Ref			
4.0–6.9 mm	115 (31%)	19 (51%)	2.7 (1.4–5.3)	0.00		
Aneurysm anterior circulation						
ICA	143 (43%)	12 (38%)	Ref			
MCA	133 (40%)	11 (34%)	0.9 (0.4–2.0)	0.79		
ACA	58 (17 %)	9 (28%)	1.4 (0.6–3.4)	0.44		

Risk factor	Stable aneurysms n = 366	Grown aneurysms n = 37	Univariable analyses HR (95% CI)	Univariable analyses p-value	Multivariable analysis HR (95% CI)	Multivariable analyse p-value
Aneurysm posterior circulation	32 (9%)	5 (14%)	1.9 (0.7–4.8)	0.19	2.0 (0.6–7.0)	0.29
Multilobar aneurysm	27 (7%)	5 (14%)	3.0 (1.2–7.9)	0.02	2.9 (1.0–8.5)	0.05
Size ratio						
Dome > neck	117 (34%)	19 (53%)	2.3 (1.2–4.4)	0.01	2.4 (1.0–5.8)	0.06
Aspect ratio ≥ median (0.9)	171 (50%)	19 (53%)	1.7 (0.9–3.4)	0.10	0.7 (0.3–1.8)	0.5
Flow into aneurysm						
1st tertile (54–112°)	136 (33%)	21 (37%)	Ref			
2nd tertile (112–137°)	140 (34%)	13 (23%)	0.9 (0.4–2.2)	0.85		
3rd tertile (137–180°)	135 (33%)	23 (40%)	1.4 (0.7–3.0)	0.37		
Bifurcation, largest angle						
1st tertile (136–178°)	83 (36%)	7 (22%)	Ref			
2nd tertile (114–136°)	72 (31%)	10 (31%)	1.8 (0.6–5.5)	0.31		
3rd tertile (67–114°)	78 (34%)	15 (47%)	1.7 (0.6–5.1)	0.31		
Bifurcation, smallest angle						
1st tertile (90–139°)	75 (33%)	15 (47%)	Ref			
2nd tertile (71–90°)	75 (33%)	6 (19%)	0.5 (0.2–1.6)	0.25		
3rd tertile (26–71°)	79 (35%)	11 (34%)	0.8 (0.3–2.1)	0.69		

Table 5.4 Growth per number of aneurysms with follow-up screening, presented per year of follow-up

Duration of follow-up	All aneurysms growth/total (%)	Initial aneurysm size < 7 mm growth/total (%)
0–1 year	11/468 (2%)	4/403 (1%)
1–2 years	18/393 (5%)	11/347 (3%)
2–3 years	13/267 (5%)	8/249 (3%)
3–4 years	7 /188 (4%)	7/178 (4%)
4–5 years	3/127 (2%)	2/119 (2%)
5–6 years	3/77 (4%)	3/72 (3%)
6–7 years	1/41 (2%)	1/39 (3%)
7–8 years	1/24 (4%)	1/23 (4%)
> 8 years	0/11 (0%)	0/11 (0%)

Discussion

In this large dataset more than one out of ten aneurysms increased in size during a mean follow-up time of almost 3 years. Initial aneurysm size and dome > neck ratio were risk factors for aneurysm growth for all aneurysms combined, and dome > neck ratio, multilobarity and smoking were risk factors for growth in small aneurysms. Aneurysm location in the posterior circulation was a risk factor in the univariable analyses for all aneurysms combined and for small aneurysms, but was not shown to be an independent risk factor in the multivariable analyses. We found no relation between aneurysm growth and patient age, female sex, hypertension, familial history of SAH, previous SAH, and flow direction into the aneurysm or bifurcation angles.

There have been several previous studies on aneurysm growth, however our study is the largest study performed so far, data have been collected prospectively rather than retrospectively, and this is the first study to do a time dependent multivariable regression analysis.[6-8,11,15,16] Also, previous studies focused on patient-related risk factors, such as age, hypertension, and smoking, and usually included only aneurysm size and aneurysm location as aneurysm-related risk factors. This is the first study to include multiple aneurysm-related risk factors for aneurysm growth in the analysis, such as dome > neck ratio, multilobarity, and bifurcation and inflow angles.

When we compare the proportion aneurysm enlargement per year of follow-up, the 4% per year of follow-up we found is in agreement with previous studies, which found rates of 2–5% per year of follow-up.[6-8,11,16] Initial aneurysm size was a risk factor for aneurysm growth in our study, which is in agreement with previous studies.[6-9,11] For small aneurysms

(< 7 mm) size was not related to aneurysm growth in the multivariable analysis. This finding is supported by a recently published study on small aneurysms.[16]

Aneurysm location in the posterior circulation is an established risk factor for aneurysm rupture,[5] and is therefore a probable risk factor for aneurysm growth. In this study aneurysm location in the posterior circulation was not an independent risk factor for aneurysm growth, although the effect size with a doubled risk was rather large. The lack of statistical significance is probably caused by small numbers, as posterior circulation aneurysms are relatively rare.[6,8,9,16]

We found multiplicity of aneurysms to be related to a decreased risk of aneurysm growth for small aneurysms, which may be explained by the choice to perform analyses per aneurysm rather than per patient. In a *post hoc* patient-based analysis with the largest aneurysm per patient included in patients with multiple aneurysms, multiplicity of aneurysms was no longer related to aneurysm growth.

Strengths of our study are the meticulous measurements of the aneurysms and adjacent vessels and the unique size of our international dataset, which enabled performing multivariable analyses for many factors and even multivariable analyses for the subset of small aneurysms only. A post hoc analysis including exclusively the 46 aneurysms with growth ≥ 1 mm showed similar results in univariable and multivariable analyses, with HR 1.1 (95% CI 1.0–1.2) per mm increase in aneurysm size for initial aneurysm size and 4.1 (95% CI 1.5–11.2) for dome > neck ratio in the multivariable analysis.

Limitations of our study include the selection bias of patients and aneurysms, as we included only aneurysms that were left untreated for at least 6 months and followed with repeated imaging. Aneurysms that were deemed fit for immediate treatment by the treating neurologist, neurosurgeon or radiologist, and aneurysms in patients who were deemed unfit for repeated imaging because of their medical condition or age, are therefore not included in this study. We found previous SAH and family history of SAH not to be risk factors for aneurysm growth, in contrast to previous studies.[6,8,9,11,16] This may be due to selection bias, as persons with a positive family history or previous SAH may be inclined to treat unruptured aneurysms at a smaller aneurysm size. We did not correct our analysis for multiple comparisons. We did not have data on blood pressure management and smoking status during follow-up, so no conclusions can be drawn about the effects of management of hypertension and smoking on risk of aneurysm growth.

We consider growth of aneurysms to be a marker for increased risk of rupture in follow-up studies, because size is the most important risk factor for rupture. Therefore, an aneurysm

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that increased in size has a higher risk of rupture than before growth.[5] Aneurysm growth is probably an irregular and discontinuous process, with long periods of aneurysm wall stability interjected with short periods of aneurysm wall instability, temporarily allowing aneurysm growth or aneurysm rupture.[17,18] Increase in aneurysm size at follow-up should therefore not be interpreted as instability of the aneurysm wall at the time of imaging. From the three patients with SAH from a known aneurysm during follow-up in this study, only one showed aneurysm growth on the follow-up imaging preceding the rupture.

The similarity in risk factors for aneurysm growth and aneurysm rupture supports the hypothesis that aneurysm growth and aneurysm rupture are both signs of aneurysm wall instability.[5] Aneurysm size, dome > neck ratio and multilobarity should be validated in an external dataset as predictors for aneurysm growth and/or rupture, so that they may be incorporated in treatment decisions for newly diagnosed unruptured intracranial aneurysms. Since smoking at the time of diagnosis is a modifiable risk factor for aneurysm growth, patients with an unruptured intracranial aneurysm should be urged to stop smoking. The optimal interval of follow-up imaging is still uncertain, as is the duration of follow-up. Recent literature suggests a decrease in the risk of rupture after five years, which may indicate that unstable aneurysms disappear from the research population, lowering risk of rupture for the remaining aneurysms.[5,19]

References

1   Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol* 2011; **10**: 626-36.

2   Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. *Lancet Neurol* 2011; **10**: 349-56.

3   Rivero-Arias O, Gray A, Wolstenholme J. Burden of disease and costs of aneurysmal subarachnoid haemorrhage (aSAH) in the United Kingdom. *Cost Eff Resour Alloc* 2010; **8**: 6.

4   McDonald JS, McDonald RJ, Fan J, Kallmes DF, Lanzino G, Cloft HJ. Comparative Effectiveness of Unruptured Cerebral Aneurysm Therapies: Propensity Score Analysis of Clipping Versus Coiling. *Stroke* 2013; **44**: 988-94.

5   Greving JP, Wermer MJ, Brown RD, Jr., Morita A, Juvela S, Yonekura M, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014; **13**: 59-66.

6   Burns JD, Huston J, III, Layton KF, Piepgras DG, Brown RD, Jr. Intracranial aneurysm enlargement on serial magnetic resonance angiography: frequency and risk factors. *Stroke* 2009; **40**: 406-11.

7   Matsubara S, Hadeishi H, Suzuki A, Yasui N, Nishimura H. Incidence and risk factors for the growth of unruptured cerebral aneurysms: observation using serial computerized tomography angiography. *J Neurosurg* 2004; **101**: 908-14.

8   Miyazawa N, Akiyama I, Yamagata Z. Risk factors for growth of unruptured intracranial aneurysms: follow-up study by serial 0.5-T magnetic resonance angiography. *Neurosurgery* 2006; **58**: 1047-53.

9   Wermer MJ, van der Schaaf IC, Velthuis BK, Majoie CB, Albrecht KW, Rinkel GJ. Yield of short-term follow-up CT/MR angiography for small aneurysms detected at screening. *Stroke* 2006; **37**: 414-8.

10   Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms. A long term follow-up study. *Stroke* 2001; **32**: 485-91.

11   Matsumoto K, Oshino S, Sasaki M, Tsuruzono K, Taketsuna S, Yoshimine T. Incidence of growth and rupture of unruptured intracranial aneurysms followed by serial MRA. *Acta Neurochir (Wien)* 2013; **155**: 211-6.

12   Ryu CW, Kwon OK, Koh JS, Kim EJ. Analysis of aneurysm rupture in relation to the geometric indices: aspect ratio, volume, and volume-to-neck ratio. *Neuroradiology* 2011; **53**: 883-9.

13   de Rooij NK, Velthuis BK, Algra A, Rinkel GJ. Configuration of the circle of Willis, direction of flow, and shape of the aneurysm as risk factors for rupture of intracranial aneurysms. *J Neurol* 2009; **256**: 45-50.

14   Bor AS, Velthuis BK, Majoie CB, Rinkel GJ. Configuration of intracranial arteries and development of aneurysms: a follow-up study. *Neurology* 2008; **70**: 700-5.

15   Villablanca JP, Duckwiler GR, Jahan R, Tateshima S, Martin NA, Frazee J,et al. Natural history of asymptomatic unruptured cerebral aneurysms evaluated at CT angiography: growth and rupture incidence and correlation with epidemiologic risk factors. *Radiology* 2013; **269**: 258-65.

16   Chien A, Liang F, Sayre J, Salamon N, Villablanca P, Vinuela F. Enlargement of small, asymptomatic, unruptured intracranial aneurysms in patients with no history of subarachnoid hemorrhage: the different factors related to the growth of single and multiple aneurysms. *J Neurosurg* 2013;**119**:190-7.

17   Koffijberg H, Buskens E, Algra A, Wermer MJ, Rinkel GJ. Growth rates of intracranial aneurysms: exploring constancy. *J Neurosurg* 2008; **109**: 176-85.

18   Chmayssani M, Rebeiz JG, Rebeiz TJ, Batjer HH, Bendok BR. Relationship of growth to aneurysm rupture in asymptomatic aneurysms </= 7 mm: a systematic analysis of the literature. *Neurosurgery* 2011; **68**: 1164-71.

19   Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *Stroke* 2013; **44**: 2414-21.
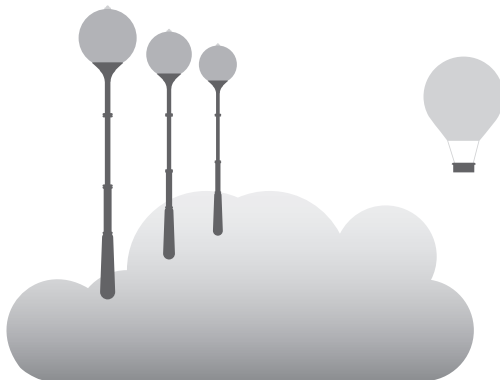
PART II

Familial intracranial aneurysms

Chapter 6

Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case control study

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Abstract

Introduction: Relatives of patients with aneurysmal subarachnoid haemorrhage (SAH) have an increased risk of SAH. In a population-based study we analysed individualised risks of SAH according to the number of affected first degree relatives.

Methods: From the Swedish Inpatient Register we retrieved all patients diagnosed with SAH in 2001–2005. For each of the 5,282 patients we identified 5 controls (total 26,402) through the nationwide Register of Total Population. Through the Multi-generation Register we retrieved all first degree relatives for patients and controls, and checked whether these 130,373 relatives had been diagnosed with SAH. By means of conditional logistic regression, we calculated odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for the risk of SAH according to the number of affected relatives, and to the gender, age and type of kinship of the patient and affected relative.

Results: The OR of SAH for individuals with one affected first-degree relative was 2·15 (95% CI 1·77–2·59). For individuals with two affected first-degree relatives OR was 51·0 (95% CI 8·56–1117). Gender, age, and type of kinship did not influence the risk of SAH for individuals with one or more affected relatives.

Discussion: The risk of SAH is slightly increased in case of one, but strongly increased in case of two or more affected first-degree relatives. The strongly increased risk in case of two affected relatives corresponds to a considerable absolute life-time risk of SAH, and underscores the need to consider screening for aneurysms in these individuals.

Introduction

Subarachnoid haemorrhage (SAH) from a ruptured aneurysm is a rare, but devastating subset of stroke,[1-5] which occurs at relatively young age. Individuals have an increased risk of SAH if a first degree relative has had SAH.[6-11] The prevalence of unruptured aneurysms in individuals with one first degree relative with SAH is slightly increased compared to individuals without first degree relatives with SAH.[12] The prevalence of unruptured aneurysms is even higher in individuals with two or more affected relatives.[13,14] However, the actual risk of SAH in individuals with two or more relatives with SAH is unknown, since families with two or more affected first degree relatives are very rare. Moreover, individuals from these families may nowadays ask for screening and preventive treatment of asymptomatic aneurysms, which may affect the natural history. A study on the familial risk of SAH in Scotland found a trend towards an increasing risk of SAH as more, and more closely related, relatives experienced an SAH.[9] However, the increased risk was not statistically significant, probably because of the small number of patients with two or more affected first degree relatives with SAH. Recently the risk of SAH in siblings was studied in the Swedish population.[11] A risk ratio of SAH of 2.75 was found for siblings of SAH patients. However, this study was too small to assess the risk of multiple affected relatives with SAH. We performed a population based case-control study in the Swedish population to assess the risk of SAH according to the number of affected relatives and type of kinship.

Methods

Cases and controls

The patients in this patient-control study were identified in the Swedish Inpatient Register 1964–2006[15] which contains individual-based information on discharges from inpatient care coded according to International Classification of Diseases (ICD) [versions 7–10] with a population-based (county-wise) coverage that encompassed 80% of Sweden in the mid 1970s and 100% since 1987. We included patients admitted to a hospital between 2001 and 2005 with SAH as the primary diagnosis who were 15 years or older, and who had no prior admission with SAH as either primary or secondary diagnosis in the Inpatient Register. Through the nationwide Register of Total Population, which since 1969 comprises the Swedish Census Register, we matched 5 controls to each case based on sex, year of birth, marital status and county of residence in the year of the index patients' admission with SAH. This selection yielded 5,282 cases and 26,402 controls. For 8 cases we were not able to fulfil the number of five controls.

Relatives

The Swedish Multi-generation Register[16] includes information on parent-offspring relations for Swedish citizens born in 1932 or later. For both cases and controls we retrieved all first degree relatives (parents, children and siblings). For patients and controls born before 1932 the family history could only be defined through children and siblings. This selection yielded 21,724 relatives for cases and 108,649 relatives for controls, in total 130,373 first degree relatives.

Assessing family history

For all 130,373 identified relatives, all records were retrieved from both the Swedish Inpatient Register and the Cause of Death Register. This latter register includes also causes of death from patients who died without being admitted to the hospital. A relative was defined as being affected by SAH when either an admission to a hospital with a primary or secondary diagnosis of SAH was recorded, or when the underlying or contributing cause of death of the relative was SAH. We only considered events that occurred before the date of the SAH of a case or the corresponding time for the controls.

Data analysis

By means of conditional logistic regression we calculated odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for the risk of SAH according to the family history. Due to small observed numbers exact mid-p corrected 95% confidence intervals were calculated when assessing the risk associated with having more than one affected relative. We aggregated counties into three regions for analysis: northern, central and southern Sweden. Risk associated with family history in relation to the individual's sex, age at diagnosis, and region was assessed by means of stratification.

Results

Table 6.1 and 6.2 show the baseline characteristics of the 5,282 patients and the 26,402 controls.

The OR of SAH for individuals with one or more affected first-degree relatives was 2·28 (95% CI 1·89–2·74). Compared to individuals without family history the risk ratio was 2·15 (95% CI 1·77–2·59) for individuals with only one affected relative, and 51·0 (95% CI

8.56–1117) for individuals with two or more affected relatives (Table 6.1). The risk associated with family history was approximately the same irrespective of type of kinship between the person at risk and the affected relative (Table 6.1). The effect of family history was not significantly modified by sex and age of the person at risk, or by geographical region (Table 6.2).

Table 6.1 Risk ratio of SAH according to number and type of affected relatives

	SAH patients n = 5,282	Controls n = 26,402	Odds ratio	95% confidence interval
Number of relatives with SAH				
No affected relative	5,116 (96·86%)	26,030 (98·59%)	1	(reference)
1 relative	156 (2·95%)	371 (1·41%)	2·15	(1·77–2·59)
≥ 2 relatives	10 (0·19%)	1 (0·00%)	51·0	(8·56–1117)*
Affected relative				
No affected relative	5,116 (96·86%)	26,030 (98·59%)	1	(reference)
Child	92 (1·74%)	181 (0·69%)	2·02	(1·31–3·10)
Sibling	46 (0·87%)	104 (0·39%)	2·40	(1·72–3·34)
Parent	27 (0·51%)	64 (0·24%)	2·35	(1·82–3·03)

* Exact confidence interval using the mid-P correction for discreteness of the distribution.

Table 6.2 The odds ratio for having family history, defined as one or more affected first degree relatives, compared to no family history in relation to characteristics of the person at risk

	SAH patients n = 5,282	Controls n = 26 402	Odds ratio	95% confidence interval
Gender				
Male	2,169 (41%)	10,834 (41%)	1·84	(1·33–2·53)
Female	3,113 (59%)	15,568 (59%)	2·56	(2·04–3·22)
Age (yrs)				
15–49	1,251 (24%)	6,250 (24%)	1·92	(1·33–2·76)
50–59	1,318 (25%)	6,592 (25%)	2·27	(1·64–3·15)
60–69	1,131 (21%)	5,654 (21%)	2·64	(1·86–3·74)
≥ 70	1,582 (30%)	7,906 (30%)	2·40	(1·44–3·99)
Geographical region				
Northern	603 (11%)	3,013 (11%)	2·64	(1·55–4·49)
Central	2,132 (40%)	10,659 (40%)	2·33	(1·75–3·10)
Southern	2,547 (48%)	12,730 (48%)	2·14	(1·64–2·83)

Discussion

In this large population-based study, we found that having a relative with SAH increases the risk of SAH, and that this risk is highly dependent on the number of affected relatives. Although the OR exceeded two, with one affected relative, the absolute risk of SAH remains limited. With two or more affected relatives a steep rise in risk was observed. This increased risk of SAH is independent of the age and gender of the person at risk, independent of the relation with the affected relative, and independent of the gender of the affected relative. The high risk ratio for SAH in individuals with two affected relatives implies a considerable absolute risk of SAH for such individuals. If we assume a 0·7 % life-time risk of SAH in the general population,[5,17] the data in this study would suggest an absolute life-time risk of SAH for individuals with two or more affected relatives of 26%, with a lower confidence limit of 6%.

The increased risk of SAH in first degree relatives of SAH patients we found in this population-based study is in line with the findings of other studies.[6-10,18] In previous studies the risk of SAH in first degree relatives was in general somewhat higher than in our study, but confidence intervals in these previous studies were wide and included the risk ratios found in the present study.[6-10,18] A recent study in Sweden on the risk of subarachnoid haemorrhage in siblings, found a similar risk for one affected relative.[11] Our current study includes data on more individuals and is taking into account a longer period of observation. Therefore we were able to analyse the effect of multiple affected relatives on the risk of SAH. Although we used the same databases as the previous study, overlap between these studies was limited to affected sib-pairs with one sibling affected during the year 2001. We are not aware of any studies regarding the risk of SAH in families with two or more affected relatives. As the cause of SAH is most likely multifactorial in familial as well as sporadic SAH, the risk and familial risk ratio of SAH may vary between different populations.[17] In contrast to previous studies,[7,12] we found the risk of SAH to be equally increased for siblings, parents and children of SAH patients.

A strength of the current study is the large number of patients with SAH and controls that could be included in the study. As families with two or more affected relatives are very rare, very large databases with diagnoses of hospital admissions and causes of death are needed to provide enough data to assess the risk of SAH in a population-based study. The database with information of all first degree relatives of Swedish residents born after 1932 allowed us to assess the prevalence of SAH in relatives of affected patients. We included cases and controls from 2001–2005, but recorded SAH in their relatives in a much larger time span

(1964–2005). Although this study provides information on the prevalence of SAH in first degree relatives of SAH patients, it does not give any information about the incidence or prevalence of SAH in Sweden, as we identified index patients through the Swedish Inpatient Register only, and not through the Cause of Death Register. Because most data in our study originate from a time before screening and preventive treatment may have been introduced, it is highly unlikely that the introduction of screening for intracranial aneurysms in familial SAH affected our results. Notably, had screening and preventive treatment of detected aneurysms played a role, this would have led to an underestimation of the risk in families with two or more affected relatives. To further exclude the role of influence of screening we have only included patients with a diagnosis of SAH, and not patients with a diagnosis of aneurysm, because an unruptured aneurysm may have been detected through screening. The current study is probably a last chance to study the risk of SAH in relatives of families with two or more SAH patients, because nowadays screening and preventive treatment is usually performed in such families. This will obviously alter the natural history in such families.

A potential weakness of our study could be the diagnosis of SAH, which was based on ICD coding. Since the index patients with SAH were selected in 2001 through 2005, the coding will have been stable over time and the diagnosis will have been accurate, as CT scans were widely available in Sweden in these years. However, for the relatives who had an SAH in earlier years, diagnosis and coding ICD coding could be less reliable, because CT scans were not always available in the eighties of the previous century, and were not available before the eighties. There is however no reason to believe that the inaccuracy of the diagnosis would be different between relatives of cases and relatives of controls, the more so since familial aggregation of SAH has been recognized only since the mid-nineties of the previous century.[6,7,14] Another issue is that we probably have not excluded all instances of perimesencephalic nonaneurysmal subarachnoid haemorrhage, not only because with older ICD coding systems it was more difficult to separate this diagnosis, but also because the diagnosis was not recognized before 1985.[19] However, we do not feel this will have influenced our results, firstly because perimesencephalic SAH constitutes only 5% of all SAHs,[20] and secondly because familial perimesencephalic haemorrhage is very rare if it exists at all. In the literature, only one family with two relatives with perimesencephalic haemorrhage has been reported,[21] which may very well be a chance finding

Another potential weakness inherent to population based studies is that not all databases are 100% complete. If diagnoses are missing, it is possible that we have underestimated the risk of SAH due to affected first degree relatives. On the contrary, the risk might be overestimated if the diagnosis of SAH is better recognised in case of a positive family

history. However, as SAH causes very severe and sudden symptoms, it seems unlikely that a diagnosis of SAH would go unnoticed, either in patients with or without family history. We therefore feel that although we cannot entirely exclude the possibility that the risk we found is overestimated by this effect, it is not very likely.

We found 2% less parents for the cases than for the controls. This could be caused by early death of the parents of the cases, such as one would expect in familial SAH. Also it is possible that we missed index cases, as we identified our index cases trough the Swedish Inpatient Register, and we did not use the Cause of Death Register for index patient identification.[22] Since familial SAH may have a worse prognosis than incidental SAH[6] we might have missed relatively more patients with familial SAH than with sporadic SAH. Therefore, our estimates of the increased risk of SAH due to affected first-degree relatives might even be conservative.

Although people with one relative with SAH have an increased risk of SAH, the absolute risk of SAH is still low. This low absolute risk underscores current recommendations that, in general, screening for aneurysms is not indicated in case of one affected relative.[23] The high risk ratio that we found for individuals with two or more affected first degree relatives has a wide confidence interval, and provides no exact certainty about the life time risk of SAH of these individuals. Yet the risk ratio clearly shows that the absolute life-time risk of SAH in case of two or more affected relatives is considerable, and screening for aneurysms should definitely be considered in such individuals. Because aneurysms develop during life, and can also develop after an initial screening, screening for aneurysms should be repeated.[13] The optimal screening interval should be assessed in future studies, taking into account the irregular pattern of aneurysm development over time.[24]

References

1   Hop JW, Rinkel GJE, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. *Stroke* 1997; **28**: 660-4.

2   Inagawa T. Trends in incidence and case fatality rates of aneurysmal subarachnoid hemorrhage in Izum City, Japan, between 1980-1989 and 1990-1998. *Stroke* 2001; **32**: 1499-507.

3   Hackett ML, Anderson CS, ACROSS study. Health outcomes 1 year after subarachnoid hemorrhage. An international population-based study. *Neurology* 2000; **55**: 658-62.

4   Stegmayr B, Eriksson M, Asplund K. Declining mortality from subarachnoid hemorrhage: changes in incidence and case fatality from 1985 through 2000. *Stroke* 2004; **35**: 2059-63.

5   Koffijberg H, Buskens E, Granath F et al. Subarachnoid haemorrhage in Sweden 1987-2002: regional incidence and case fatality rates. *J Neurol Neurosurg Psychiatry* 2008; **79**: 294-9.

6   Bromberg JEC, Rinkel GJE, Algra A et al. Subarachnoid haemorrhage in first and second degree relatives of patients with subarachnoid haemorrhage. *BMJ* 1995; **311**: 288-9.

7   Schievink WI, Schaid DJ, Michels VV, Piepgras DG. Familial aneurysmal subarachnoid hemorrhage: a community based study. *J Neurosurg* 1995; **83**: 426-9.

8   Ronkainen A, Hernesniemi J, Ryynanen M. Familial subarachnoid hemorrhage in east Finland, 1977-1990. *Neurosurgery* 1993; **33**: 787-96.

9   Teasdale GM, Wardlaw JM, White PM et al. The familial risk of subarachnoid haemorrhage. *Brain* 2005; **128**: 1677-85.

10   Gaist D, Vaeth M, Tsiropulos I et al. Risk of subarachnoid haemorrhage in first degree relatives of patients with subarachnoid haemorrhage: follow up study based on national registries in Denmark. *BMJ* 2000; **320**: 141-5.

11   Sundquist J, Li X, Sundquist K, Hemminki K. Risks of Subarachnoid Hemorrhage in Siblings: A Nationwide Epidemiological Study from Sweden. *Neuroepidemiology* 2007; **29**: 178-84.

12   Raaymakers TWM, MARS study group. Aneurysms in relatives of patients with subarachnoid hemorrhage. Frequency and risk factors. *Neurology* 1999; **53**: 982-8.

13   Wermer MJ, Rinkel GJE, van Gijn J. Repeated screening for intracranial aneurysms in familial subarachnoid hemorrhage. *Stroke* 2003; **34**: 2788-91.

14   Ronkainen A, Hernesniemi J, Puranen M et al. Familial intracranial aneurysms. *Lancet* 1997; **349**: 380-4.

15   Anonymous. Patientregistret 1987-1996: Kvalitet och innehåll (Swedish). EpC, National Board of Health and Welfare. 1998.

16   Anonymous. Multi-generation register 2005 - A description of content and quality. Statistics Sweden, Population and Welfare Statistics. 2006.

17   de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry* 2007; **78**: 1365-72.

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18   Okamoto K, Horisawa R, Kawamura T et al. Family history and risk of subarachnoid hemorrhage: a case-control study in Nagoya, Japan. *Stroke* 2003; **34**: 422-6.

19   van Gijn J, van Dongen KJ, Vermeulen M, Hijdra A. Perimesencephalic hemorrhage: a nonaneurysmal and benign form of subarachnoid hemorrhage. *Neurology* 1985; **35**: 493-7.

20   Flaherty ML, Haverbusch M, Kissela B et al. Perimesencephalic Subarachnoid Hemorrhage: Incidence, Risk Factors, and Outcome. *J Stroke Cerebrovasc Dis* 2005; **14**: 267-71.

21   Tieleman AA, van der Vliet TA, Vos PE. Two first-degree relatives with perimesencephalic nonaneurysmal hemorrhage. *Neurology* 2006; **67**: 535-6.

22   Huang J, Van Gelder JM. The Probability of Sudden Death from Rupture of Intracranial Aneurysms: A Meta-analysis. *Neurosurg* 2002; **51**: 1101-7.

23   MARS study group. Risks and benefits of screening for intracranial aneurysms in first-degree relatives of patients with sporadic subarachnoid hemorrhage. *N Engl J Med* 1999; **341**: 1344-50.

24   Koffijberg H, Buskens E, Algra A, Wermer MJ, Rinkel GJ. Growth rates of intracranial aneurysms: exploring constancy. *J Neurosurg* 2008; **109**: 176-85.

Chapter 7

Optimal screening strategy for familial intracranial aneurysms: a cost-effectiveness analysis

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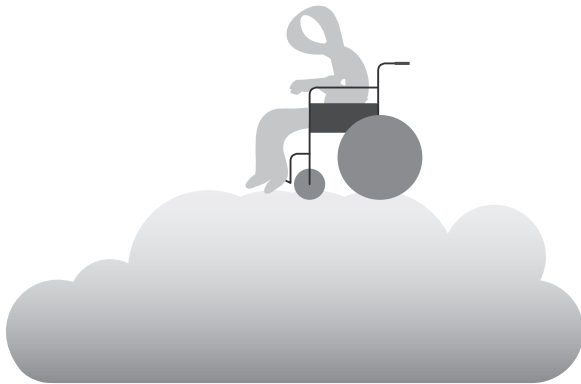
Abstract

Introduction: Individuals with a family history of subarachnoid haemorrhage (SAH), defined as 2 or more affected first-degree relatives, have an increased risk of aneurysm formation and rupture. Screening such individuals for intracranial aneurysms is advocated, but its effectiveness and cost-effectiveness are unknown, as are the optimal age ranges and interval for screening.

Methods: With a Markov model and Monte Carlo simulations we compared screening with no screening in individuals with a family history of SAH. We varied age ranges (starting screening at 20, 30, or 40 years old, ending screening at 60, 70, or 80 years old) and screening intervals (2-, 3-, 5-, 7-, 10-, and 15-year interval), and analysed the impact in costs and quality-adjusted life years (QALY).

Results: Screening individuals with a family history of SAH is cost-effective. The strategy with the lowest costs per QALY was to screen only twice, at 40 and 55 years old. Sequentially lengthening the screening period and decreasing the screening interval yielded additional health benefits at acceptable costs up to screening from age 20 to 80 every 7 years. More frequent screening within this age range still provided extra QALYs, with an incremental cost-effectiveness ratio more favourable than €26,308/QALY ($38,410/QALY).

Discussion: This study provides evidence for recommendations to screen individuals with 2 or more first-degree relatives with subarachnoid haemorrhage. The optimal screening strategy according to our model is screening from age 20 until 80 every 7 years given a cost-effectiveness threshold of €20,000/quality-adjusted life year (QALY) ($29,200/QALY).

Introduction

Individuals with a positive family history of subarachnoid haemorrhage (SAH) have an increased risk of aneurysm development and rupture.[1-3] The risk of SAH is increased slightly in individuals with 1 affected relative, but considerably in those with 2 or more affected first-degree relatives.[1] Screening for aneurysms is therefore often recommended for individuals with 2 or more affected first-degree relatives.[4,5] As aneurysms are not present at birth, but develop during life, such individuals should be screened repeatedly.[2] The benefits of screening for intracranial aneurysms have been addressed before with decision models; however, the necessity of repeated screening,[6,7] or the availability of coiling as treatment option,[8,9] were not included in these models. Consequently, the overall benefits of screening and the optimal screening strategy regarding age ranges and screening interval are unknown for individuals with 2 or more affected first-degree relatives. Using a Markov model and Monte Carlo simulation we analysed the effectiveness and costs of screening with magnetic resonance angiography (MRA) for several screening intervals, and for several ages to start and stop screening.

Methods

Markov model

We used a Markov model to simulate aneurysm development and rupture in a cohort with familial SAH, defined as individuals with 2 or more first-degree relatives with SAH. Markov decision models consist of several health states with an assigned quality of life and cost.[10] In our model, individuals enter the model at 15 years old, in the state "healthy without aneurysm." They progress in cycles of 1 year through the model, changing health state based on the transition probabilities in the decision model. The 5 health states incorporated in this model are healthy without aneurysm, healthy with aneurysm, healthy with small known aneurysm, disabled, and dead (Figure 7.1).

Patients may become disabled or die because of SAH, complications of digital subtraction angiography (DSA), or complications of preventive aneurysm treatment. Each cycle patients have an age-related risk of dying from all other causes combined, based on the mortality in the general Dutch population. The model does not apply to patients with polycystic kidney disease or to patients with Ehlers-Danlos type IV disease, because these patients have different life expectancies. The simulation stops when all individuals in the model are dead.

We compared 2 strategies: 1 simulating natural history without screening, the other simulating regular screening for aneurysms with treatment of the detected, treatable aneurysms. Screening was performed with MRA. If an aneurysm was suspected on MRA, a DSA was performed to identify false positives. Aneurysms confirmed by DSA were either treated with clipping or coiling, or considered too small to treat, in which case the patient entered the state "healthy with small known aneurysm." Total costs and quality adjusted life years (QALYs) were calculated in 54 simulations with 200 cohorts each containing 5,000 individuals. Each simulation assessed a particular screening scenario, defined by the age to start screening, the age to stop screening, and the screening interval. The first screening was performed exactly on the age to start screening; the last screening was performed before or on the age to stop screening.

The Markov model was built using the TreeAge Pro (version 2009, TreeAge software, Williamstown, MA).

Transition probabilities

Values were assigned to model variables using data available from the literature, and uncertainty about exact values was translated into distributions and ranges (Table 7.1).

Incidence of aneurysm development and aneurysm rupture

Literature on the rate of aneurysm development and rupture is limited for the population with familial SAH. Based on the available data, we decided to use a probability of aneurysm development of 0.3%–0.7% per annum,[11-15] and a probability of aneurysm rupture of 1.0%–2.0% per annum.[3,13,16] Of *de novo* aneurysms, 63%–67% were considered too small for treatment (< 3–5 mm).[2] These small aneurysms were assigned a rupture rate of 0.5%–1.0% per annum, and they encountered an annual risk of aneurysm enlargement (increase in size > 1 mm) of 2.2%–4.9%.[11,17,18] Small aneurysms were imaged every 2 years until they either enlarged or ruptured. Enlarged small aneurysms changed the next cycle to rupture rate 1.0%–2.0%, and were always treated following the next imaging moment. With these probabilities, approximately 27% of the study population would develop 1 or more aneurysms during their lifetime, and approximately 10% of the study population would develop SAH during their lifetime in the natural history scenario. We considered these to be realistic values as a 10-year risk of SAH in individuals with a family history of SAH is estimated at 7%,[20] and as lifetime risk of SAH in individuals with 2 affected first-degree relatives is as large as 26%.

Figure 7.1 Markov Monte Carlo model: a simplified version of the tree.

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Costs

Costs were derived from the Dutch health care system (Table 7.1).[19-21] Costs for coiling an unruptured aneurysm included 6 and 18 months follow-up imaging. Complications from recoiling were not included in this analysis, as the risk of complications from recoiling is very low.[22] All costs were updated using Dutch inflation indices from the date of publication to December 2007. We incorporated a discount rate of 1.5% per annum for both costs and effects.

Utilities

QALYs were used to measure health benefits. According to convention, death was given a utility of 0. We anticipated the screened and unscreened healthy individuals to have the same quality of life, but assumed a positive effect from a screening negative for aneurysms, and a negative effect from a screening that revealed a small untreatable aneurysm (Table 7.1).[23,24] We considered this psychological effect to be fading in time, and assumed the change in utility to be present only during the first 3 months after screening. As in our model small untreatable aneurysms were repeatedly screened every 2 years, these individuals kept a recurring negative influence from their knowledge of the untreated aneurysm. As it is unknown how soon the effect of screening on utility fades in time, we also evaluated the model with an effect of screening lasting 1 month and 12 months. Patients who returned in the healthy state after SAH received a lower utility than patients without previous SAH.

Assumptions

We made the following assumptions: the rate of aneurysm development is constant throughout life and the rate of rupture is constant in time. The rate of rupture increases linearly with the number of aneurysms an individual carries. If an individual is treated for 1 aneurysm (electively or after SAH) we considered all aneurysms to be treated during that procedure. We assumed treated aneurysms never to reopen again, and considered the risk of re-growth to be incorporated in the lifetime risk of aneurysm development. We considered MRA to be performed without any complications, because MRA screening for aneurysms does not necessitate contrast enhancement, and complications of MRA are mainly related to contrast administration.[25,26] All individuals directed to a nursing home were assumed to stay there until they died.

Table 7.1 Probabilities and distributions

Variable	Cases-population	Probability/ year or Probability/ event	Type of distribu-tion	95% CI (beta distribution) min–max (triangular distribution)	Source
Risk aneurysm development	–	0.003–0.007	uniform	–	[11–15]
Risk aneurysm is a 'small aneurysm'	–	0.333–0.667	uniform	–	[2]
Risk aneurysm rupture for all but 'small aneurysms'	–	0.01–0.02	uniform	–	[3,13,16]
Risk aneurysm rupture for 'small aneurysms'	–	0.005–0.01	uniform	–	[17]
Risk aneurysm growth for 'small aneurysms'	9–45 in ten years 4–18 in five years	0.022–0.049	uniform	–	[11,18,27,28]
Risk death nursing home		0.10–0–30	uniform	–	[29–31]
Risk death other causes	age dependent	age dependent	5 years	age dependent	[32]
Risk death SAH	age dependent	age dependent	10 years	age dependent	[33]
Risk disability SAH	168–1,838	0.096	beta	0.083–0.110	[34,35] Combined data
Risk death preventive coiling	5–880	0.006	beta	0.002–0.012	[36,37]
Risk disability preventive coiling	6–550	0.011	beta	0.004–0.021	[36,37]
Risk death preventive clipping	16–2,253	0.007	beta	0.004–0.011	[9,38–44] Combined data
Risk disability preventive clipping	17–774	0.022	beta	0.013–0.033	[38–40,43] Combined data
Risk death DSA	12–19,826	0.0006	beta	0.0003–0.0010	[45]
Risk disability DSA	27–19,826	0.0014	beta	0.0009–0.0019	[45]
Risk MRA false-negative	62–486	0.128	beta	0.099–0.159	[46]
Risk MRA false-positive	30–364	0.082	beta	0.056–0.113	[46]
Risk/probability aneurysm can be coiled	55–74	0.743	beta	0.639–0.835	[47]
Utility unscreened population	–	0.83	triangular	0.76–0.90	[23,24]
Utility screen negatives	–	0.87	triangular	0.82–0.93	[23]
Utility screen positives	–	0.73	triangular	0.63–0.83	[23]
Utility after SAH	–	0.64	triangular	0.52–0.71	[24]
Utility nursing home resident	–	0.31	triangular	0.29–0.34	[24]
Cost DSA*	–	603	–	–	[20]
Cost MRA*	–	267	–	–	[20]
Cost nursing home per year*	–	77,490	–	–	[19]
Cost treatment SAH*	–	26,561	–	–	[21]
Cost preventive clipping*	–	8,611	–	–	[20]
Cost preventive coiling*	–	10,046	–	–	[20]

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Univariate sensitivity analysis

This Markov model could be improved for future studies by reducing the uncertainty in model outcomes. This could be done by reducing the uncertainty (confidence intervals) in the model input variables, preferably directing our efforts toward input variables that have a large influence on the model outcomes. To identify which input variables influence model outcomes most, we performed an analysis of covariance (ANCOVA). The results of the ANCOVA analysis are only relevant for models which are highly linear. The linearity of our model is expressed in the R^2 value, where an R^2 value close to 1 indicates the model is highly linear, and an R^2 value close to zero indicates the model is highly nonlinear.

Results

We found screening for intracranial aneurysms in individuals with 2 or more first-degree relatives with SAH to be cost-effective (< €20,000/ QALY; < $29,200/QALY), irrespective of the interval of screening (Table 7.2). The most cost-effective screening strategy in terms of the lowest costs per QALY was screening every 15 years from age 40 to 60, which means screening only twice, at ages 40 and 55 years (€1,914/QALY; $2,794/QALY). This screening strategy is relatively inexpensive, but results in only a small health benefit. The largest health benefits in terms of yield of QALYs are gained using a strategy with a short interval and a long time span, in this case screening every 2 years from age 20 to 80 (€13,704/QALY; $20,008/QALY).

Table 7.2 Estimated costs and effects of screening compared to not screening in both euro per QALY (€/Q) and dollar per QALY ($/Q), classified by screening age (age to start screening-age to stop screening) and screening interval. We stated costs per QALY to facilitate comparison, followed by actual cost and effect of screening.

Screening Start-stop Age, y	2 cost/QALY (cost/effect)	5 cost/QALY (cost/effect)	10 cost/QALY (cost/effect)	15 cost/QALY (cost/effect)
20–60, €	13,018 (4,166/0.32)	6,875 (1,581/0.23)	3,639 (619/0.17)	1,992 (239/0.12)
$	19,006 (6,082/0.32)	10,037 (2,308/0.23)	5,312 (904/0.17)	2,908 (349/0.12)
20–70, €	13,093 (4,975/0.38)	7,336 (1,907/0.26)	4,911 (884/0.18)	2,987 (448/0.15)
$	19,116 (7,264/0.38)	10,711 (2,784/0.26)	7,170 (1,291/0.18)	4,361 (654/0.15)
20–80, €	13,704 (5,619/0.41)	8,215 (2,300/0.28)	5,092 (1,069/0.21)	3,663 (623/0.17)
$	20,008 (8,204/0.41)	11,994 (3,358/0.28)	7,434 (1561/0.21)	5,348 (910/0.17)
30–60, €	11,595 (2,899/0.25)	5,960 (1,013/0.17)	4,006 (521/0.13)	2,742 (302/0.11)
$	16,929 (4,233/0.25)	8,702 (1,479/0.17)	5,849 (761/0.13)	4,003 (441/0.11)
30–70, €	12,030 (3,609/0.30)	6,838 (1,436/0.21)	3,640 (546/0.15)	3,247 (487/0.15)

We found screening to be very effective in preventing SAH and the rate of SAH prevention to be highly dependent on the screening interval (Figure 7.2).

The health effect in QALYs was also dependent on screening interval (Table 7.2). As all screening strategies we assessed were cost-effective (< €20,000/QALY; <$29,200/QALY), we derived the most effective strategy. Figure 7.3 shows the cost-effectiveness frontier, i.e., the red line connecting the most efficient strategies that provide increasingly more QALYs at the lowest possible cost. All strategies above this cost- effectiveness frontier can be considered inefficient and are excluded based on the existence of alternative strategies that achieve more health benefits at lower costs. The slope of the cost-effectiveness frontier at any point reflects the incremental cost-effectiveness ratio, which is the additional cost at which additional health benefits can be obtained. If a threshold of €20,000/QALY ($29,200/ QALY) is applied, the optimal screening strategy would be screening from age 20 to 80, every 7 years, as this strategy has both an absolute cost-effectiveness below €20,000/QALY (€6,391/QALY; $9,331/QALY) and an incremental cost-effectiveness ratio below €20,000/ QALY (€13,216/QALY; $19,295/QALY) (Figure 7.3B).
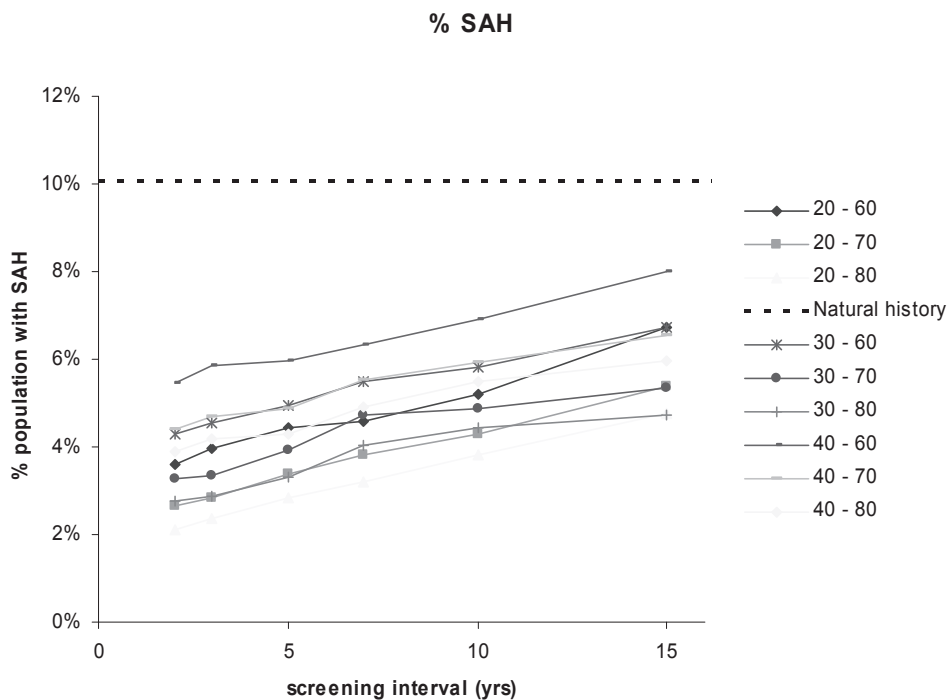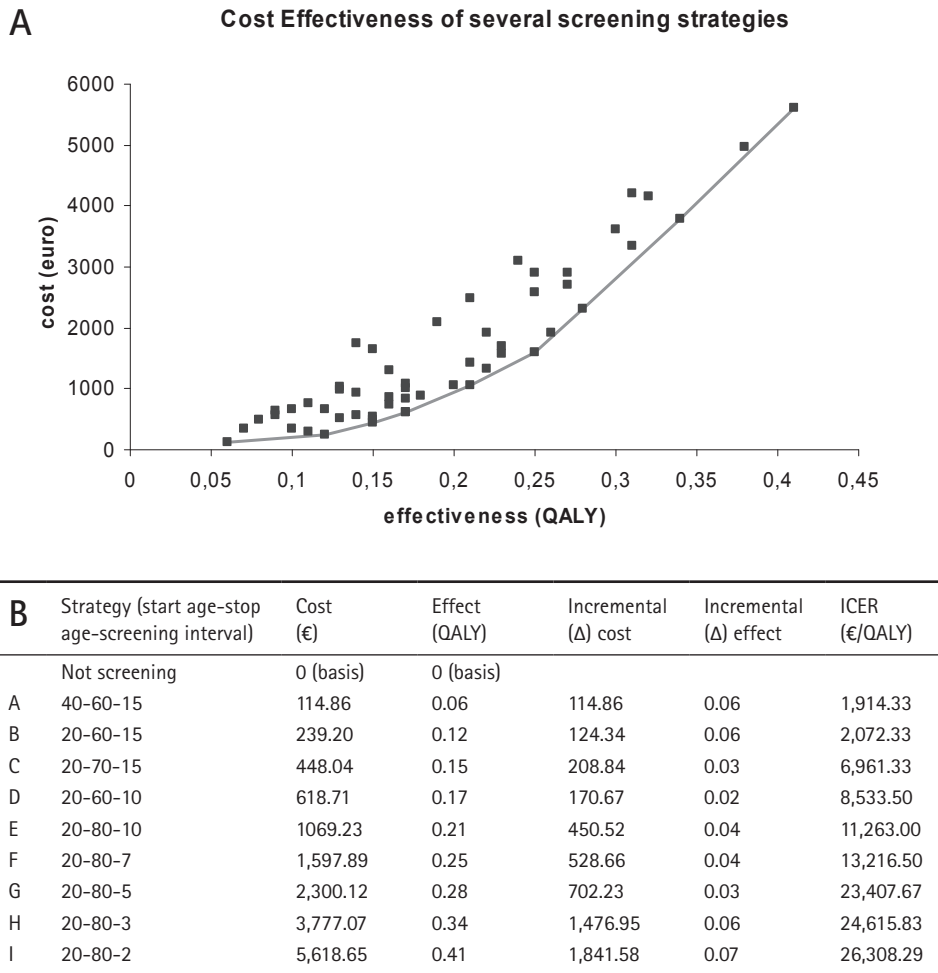
% SAH

Figure 7.2 Effectiveness of screening expressed as percentage of the population having subarachnoid haemorrhage.

A

Cost Effectiveness of several screening strategies

B

	Strategy (start age-stop age-screening interval)	Cost (€)	Effect (QALY)	Incremental (Δ) cost	Incremental (Δ) effect	ICER (€/QALY)
	Not screening	0 (basis)	0 (basis)			
A	40–60–15	114.86	0.06	114.86	0.06	1,914.33
B	20–60–15	239.20	0.12	124.34	0.06	2,072.33
C	20–70–15	448.04	0.15	208.84	0.03	6,961.33
D	20–60–10	618.71	0.17	170.67	0.02	8,533.50
E	20–80–10	1069.23	0.21	450.52	0.04	11,263.00
F	20–80–7	1,597.89	0.25	528.66	0.04	13,216.50
G	20–80–5	2,300.12	0.28	702.23	0.03	23,407.67
H	20–80–3	3,777.07	0.34	1,476.95	0.06	24,615.83
I	20–80–2	5,618.65	0.41	1,841.58	0.07	26,308.29

Figure 7.3 Incremental (additional) costs and effects and incremental cost-effectiveness ratio (ICER) for the efficient screening strategies on the cost-effectiveness frontier. Here the ICER denotes the cost per quality-adjusted life year (QALY) of moving from 1 efficient strategy to the next efficient strategy that provides additional health benefits, which means traveling along the red line from left to right.

Figure 7.4 shows the effect on cost-effectiveness when varying the duration of the psychological effects of screening on the utility of the screened population.

The ANCOVA indicates that our model is highly linear as far as the health effects are concerned (R^2 0.95), but mostly nonlinear as far as the costs are concerned (R^2 0.37). Therefore, ANCOVA can only be used to identify the input variables having an important effect on the health effectiveness outcomes. The input variables predominantly influencing
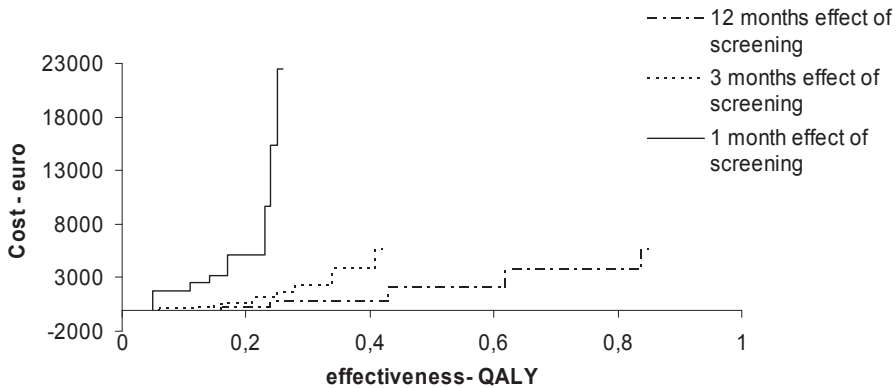
Figure 7.4 Cost-effectiveness ratio for screening compared to not screening, for the duration of the psychosocial effects of screening on utility of 12 months, 3 months and 1 month.

health effectiveness are utility of individuals who were not offered screening and did not experience SAH and utility of individuals having a negative screening. If we were to decrease the uncertainty in these 2 input variables, for example by conducting a study on quality of life in patients with a positive family history, then the uncertainty of the effectiveness outcome of our model would be reduced, and the Markov model could be further improved (Figure 7.5).

Discussion

The optimal strategy according to this model is screening from age 20 to 80, every 7 years. This screening strategy maximizes the health benefits given a cost-effectiveness threshold of €20,000/QALY ($29,200/QALY). In general, randomized controlled trials (RCT) are considered to be the most accurate research method to determine treatment efficacy. However, RCTs are not always feasible as they may require a long period of follow-up, and can only assess a limited number of strategies at the same time. As familial SAH is rare, and the risk of aneurysm development and rupture is a continuous risk during the total lifespan of patients, assessment of the optimal screening strategy in an RCT would take decades of follow-up in a research population that is difficult to acquire. In addition to these difficulties, an RCT with natural history as basic strategy of intervention and screening as alternate strategy of intervention seems problematic, because most individuals with 2 or more relatives with SAH ask for screening, and are unwilling to await the natural history. When an RCT is not feasible, a simulation model may provide a reasonable alternate research method.[48] In a

Estimated importance of individual model variables

ANCOVA analysis of the proportion of sum of squares explained by uncertainty in the model input variables: for incremental costs, effects, and cost-effectiveness
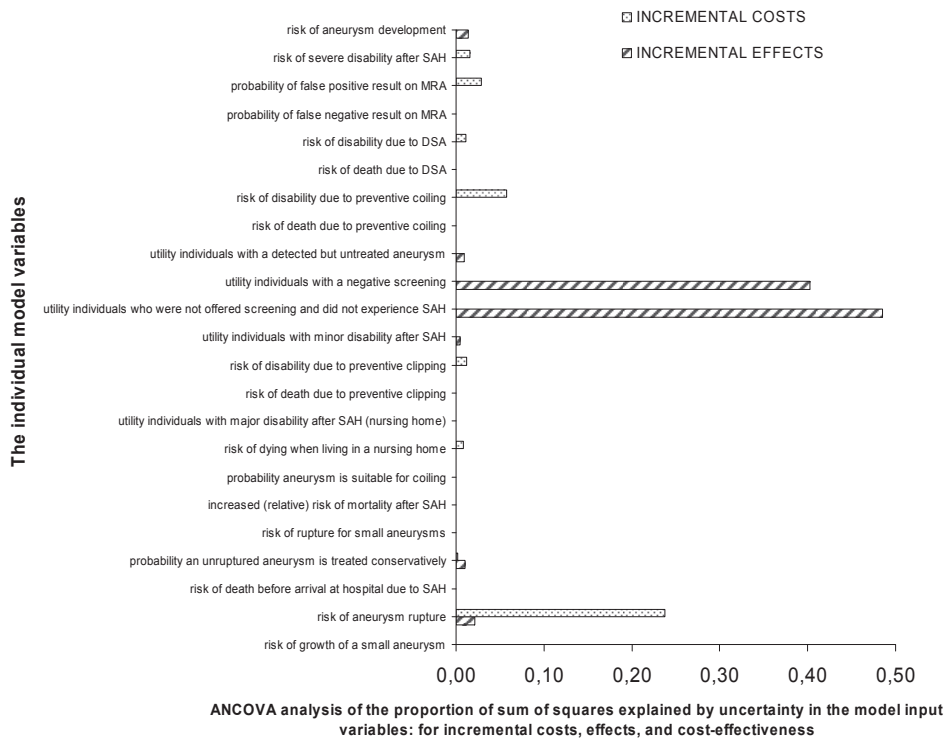
Figure 7.5 Covariance analysis: the amount of variation in the model outcomes (i.e. costs and effects) that can be contributed to uncertainty in the individual input variables. All input variables combined could explain 37% of the variation in costs of screening and 95% of the variation in effects of screening. Thus the sum of the lengths of the dotted bars equals 0.37 whereas the sum of the lengths of the striped bars equals 0.95. The length of the individuals bars indicate the relative importance of the individual input variables, i.e. the degree to which uncertainty in that particular input variable is related to uncertainty in the model outcomes (i.e. costs and effects). The longest bars point towards variables for which it is most relevant to reduce uncertainty as such a reduction would result in less variation in model outcomes.

context of constantly evolving medical technology, efficient expenditure of the national health care budget is required. Cost-effectiveness of a new intervention is therefore often compared to a cost-effectiveness threshold to decide whether the new intervention has an acceptable efficiency. This acceptability of cost-efficiency is taken into account when making policy decisions, such as deciding on reimbursements or incorporation of the new intervention into medical guidelines. Currently, a cost-effectiveness threshold of €20,000/

QALY is applied in the Netherlands, a threshold range of £20,000–£30,000/QALY is applied in the United Kingdom, and a threshold range of $50,000–$100,000/QALY is applied in the United States. Costs of clipping and coiling of ruptured and unruptured aneurysms differ throughout the world.[20,49-52] We added an analysis of our preferred screening strategy (screening from age 20 to 80 every 7 years) reverting the costs of our model to US dollars, using the following costs: MRA $596, DSA $1,520, major disability/nursing home $15,203 per annum, therapy SAH (66% coiling) $79,762, preventive clipping unruptured aneurysm $43,227, preventive coiling $19,915.[49,53] After adjusting our model to US dollars, screening from 20 to 80 every 7 years would have a cost-effectiveness of $10,749/QALY.

Only limited data are available on rate of aneurysm development and time interval between development and rupture. We assumed a constant rate of development throughout life, although an irregular and discontinuous growth rate is more likely.[54] Also, we did not incorporate additional risk factors for aneurysm development and rupture such as smoking, hypertension, and excessive use of alcohol in our analysis. It is possible that more frequent screening is more cost-effective in persons with both a positive family history and exposure to these additional risk factors. However, the amount of risk that these risk factors individually and concomitantly contribute to development and to rupture of aneurysms is un- known, especially in patients with a positive family history. In addition, as far as we know, no studies have been performed on the effect of strict medical management of these risk factors. The lack of accurate evidence made it impossible to enter these data in the simulation model. Finally, it is unknown whether the rate of aneurysm development changes according to age. We assumed this rate to be stable after the age of 15 years. Under this assumption, screening is cost-effective between ages 20–80. However, if for example the rate of development is very low before the age of 30, is high between ages 30 to 60, and then levels off again, cost effectiveness deteriorates under the age of 30 and above the age of 65.

We consider familial aneurysms to be different from sporadic aneurysms in rate of development, growth, and rupture, with higher risks of growth and rupture for familial than sporadic aneurysms.[1,3] This is why rupture rates in the model are higher than those reported by the ISUIA group. We have specifically searched for literature on familial aneurysms for input data in the model. Size and site specific risks could not be incorporated in the model because of a lack of data on this subject for familial aneurysms.

An increasing number of first-degree relatives with SAH may be associated with an increasing risk of aneurysm development or rupture, and therefore have an effect on the efficiency of screening. However, since familial SAH is a rare disease, it will be very difficult to gather

enough data to ever enter family size and number of relatives with SAH as input variables in a Markov model.

The benefits of screening are dependent on the complication rate of elective coiling and clipping. Since this is an elective procedure, we considered all patients to be redirected to a medical center with ample expertise in treating aneurysms, with corresponding low complication rates. Although it is known that increasing age increases the risk of complications of SAH and elective coiling and clipping, data quantifying this effect are scarce[17,33] and insufficiently available to incorporate an age-dependent complication risk in our analysis. The actual cost-effectiveness of screening above the age of 50 may therefore be less than we found with our model. A similar lack of data on gender specific aneurysm development and rupture prohibited an analysis of differences in optimal screening strategy for men and women. The benefits of screening are also dependent on the emotional burden on the families to be screened. Covariance analysis of our model showed that the health benefits of screening depend foremost on the quality of life of individuals as they perceive it, while living with an untreated aneurysm or while not offered screening. Other factors such as the quality of life in individuals with actual SAH were less important in our model.

Although several models have been published to assess cost-effectiveness of screening for unruptured intracranial aneurysms, none of these assessed repeated screening or the optimal screening strategy in repeated screening.[6-9,55] The results of our study show that effectiveness of screening increases with higher frequency of screening and longer screening period, and that even screening every 2 years during a 60-year period may be cost-effective. The Markov model constructed here allows us to reassess the benefits of aneurysm screening strategies and to redetermine the optimal screening strategy once new evidence on familial SAH becomes available. Based on this model, we cannot say anything about cost-effectiveness of screening in individuals with 1 first-degree relative with SAH. However, it might well be that a single moment of screening in the fourth or fifth decade of life is cost-effective in these individuals.

Based on this study on cost-effectiveness, we advise screening for all patients with 2 or more affected first-degree relatives, as the cost-effectiveness of any screening strategy is likely to be acceptable. The preferred screening strategy according to our model is to start screening at age 20 and to repeat screening every 7 years up to the age of 80, or as long as the biologic age of the patient allows it. Although we found that the cost-effectiveness of screening every 2 years may still be acceptable, screening this often may put a significant burden on a patient, and may therefore lead to early abandonment of this screening strategy

by patient and doctor. In contrast to our model, in clinical practice screening every 2 years might therefore be less advantageous than a wider screening interval. Further studies on the emotional impact of regular screening are needed. Further studies for relatives with only 1 first-degree relative with SAH may reveal subgroups of persons within this domain who might benefit from screening.

References

1   Bor AS, Rinkel GJ, Adami J et al. Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case-control study. *Brain* 2008; **131**: 2662-5.

2   Wermer MJ, Rinkel GJE, van Gijn J. Repeated screening for intracranial aneurysms in familial subarachnoid hemorrhage. *Stroke* 2003; **34**: 2788-91.

3   Broderick JP, Brown RD, Jr., Sauerbeck L et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. *Stroke* 2009; **40**: 1952-7.

4   Rinkel GJ. Intracranial aneurysm screening: indications and advice for practice. *Lancet Neurol* 2005; **4**: 122-8.

5   Bederson JB, Awad IA, Wiebers DO et al. Recommendations for the management of patients with unruptured intracranial aneurysms. A statement for healtcare professionals from the Stroke Council of the American Heart Association. *Stroke* 2000; **31**: 2742-50.

6   Yoshimoto Y, Wakai S. Cost-effectiveness analysis of screening of asymptomatic, unruptured intracranial aneurysms. A mathematical model. *Stroke* 1999; **30**: 1621-7.

7   Takao H, Nojo T, Ohtomo K. Screening for familial intracranial aneurysms: decision and cost-effectiveness analysis. *Acad Radiol* 2008; **15**: 462-71.

8   Crawley F, Clifton A, Brown MM. Should we screen for familial intracranial aneurysm? *Stroke* 1999; **30**: 312-6.

9   King JT, Jr., Glick HA, Mason TJ, Flamm ES. Elective surgery for asymptomatic, unruptured, intracranial aneurysms: a cost-effectiveness analysis. *J Neurosurg* 1995; **83**: 403-12.

10   Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993; **13**: 322-38.

11   Wermer MJ, van der Schaaf IC, Velthuis BK et al. Follow-up screening after subarachnoid haemorrhage: frequency and determinants of new aneurysms and enlargement of existing aneurysms. *Brain* 2005; **128**: 2421-9.

12   David CA, Vishteh AG, Spetzler RF et al. Late angiographic follow-up review of surgically treated aneurysms. *J Neurosurg* 1999; **91**: 396-401.

13   Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms. A long term follow-up study. *Stroke* 2001; **32**: 485-91.

14   Juvela S, Porras M, Heiskanen O. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *J Neurosurg* 1993; **79**: 174-82.

15   Tsutsumi K, Ueki K, Morita A, Usui M, Kirino T. Risk of aneurysm recurrence in patients with clipped cerebral aneurysms. Results of long-term follow-up angiography. *Stroke* 2001; **32**: 1191-4.

16   Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJE. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: a meta-analysis. *Stroke* 2007; **38**: 1404-10.

17   Wiebers DO, Whisnant JP, Huston J3 et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003; **362**: 103-10.

18   Miyazawa N, Akiyama I, Yamagata Z. Risk factors for growth of unruptured intracranial aneurysms: follow-up study by serial 0.5-T magnetic resonance angiography. *Neurosurgery* 2006; **58**: 1047-53.

19   Anonymous. College Voor Zorgverzekeringen kostenhandleiding 2004. 2004.

20   Halkes PH, Wermer MJ, Rinkel GJE, Buskens E. Direct costs of surgical clipping and endovascular coiling of unruptured intracranial aneurysms. *Cerebrovasc Dis* 2006; **22**: 40-5.

21   Roos YBWEM, Dijkgraaf MG, Albrecht KW et al. Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis. *Stroke* 2002; **33**: 1595-9.

22   Slob MJ, Sluzewski M, Van Rooij WJ, Roks G, Rinkel GJE. Additional coiling of previously coiled cerebral aneurysms: clinical and angiographic results. *AJNR Am J Neuroradiol* 2004; 25: 1373-6.

23   Wermer MJ, van der Schaaf IC, Van Nunen P et al. Psychosocial impact of screening for intracranial aneurysms in relatives with familial subarachnoid hemorrhage. *Stroke* 2005; **36**: 836-40.

24   Dorman P, Dennis M, Sandercock P. Are the modified "simple questions" a valid and reliable measure of health related quality of life after stroke? United Kingdom Collaborators in the International Stroke Trial. *J Neurol Neurosurg Psychiatry* 2000; **69**: 487-93.

25   Niendorf HP, Dinger JC, Haustein J et al. Tolerance data of Gd-DTPA: a review. *Eur J Radiol* 1991; **13**: 15-20.

26   Murphy KP, Szopinski KT, Cohan RH, Mermillod B, Ellis JH. Occurrence of adverse reactions to gadolinium-based contrast material and management of patients at increased risk: a survey of the American Society of Neuroradiology Fellowship Directors. *Acad Radiol* 1999; **6**: 656-64.

27   Burns JD, Huston J, III, Layton KF, Piepgras DG, Brown RD, Jr. Intracranial aneurysm enlargement on serial magnetic resonance angiography: frequency and risk factors. *Stroke* 2009; **40**: 406-11.

28   Matsubara S, Hadeishi H, Suzuki A, Yasui N, Nishimura H. Incidence and risk factors for the growth of unruptured cerebral aneurysms: observation using serial computerized tomography angiography. *J Neurosurg* 2004; **101**: 908-14.

29   van Dijk PT, Mehr DR, Ooms ME et al. Comorbidity and 1-year mortality risks in nursing home residents. *J Am Geriatr Soc* 2005; **53**: 660-5.

30   Kimura K, Minematsu K, Kazui S, Yamaguchi T. Mortality and cause of death after hospital discharge in 10,981 patients with ischemic stroke and transient ischemic attack. *Cerebrovasc Dis* 2005; **19**: 171-8.

31   Slot KB, Berge E, Dorman P et al. Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. *BMJ* 2008; **336**: 376-9.

32   Anonymous. Centraal Bureau voor de Statistiek, Voorburg/Heerlen. 14-1-2008.

33   Koffijberg H, Buskens E, Granath F et al. Subarachnoid haemorrhage in Sweden 1987-2002: regional incidence and case fatality rates. *J Neurol Neurosurg Psychiatry* 2008; **79**: 294-9.

7

34   Ronkainen A, Niskanen M, Piironen R, Hernesniemi J. Familial subarachnoid hemorrhage. Outcome study. *Stroke* 1999; **30**: 1099-102.

35   Hop JW, Rinkel GJE, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. *Stroke* 1997; **28**: 660-4.

36   Lanterna LA, Tredici G, Dimitrov BD, Biroli F. Treatment of unruptured cerebral aneurysms by embolization with guglielmi detachable coils: case-fatality, morbidity, and effectiveness in preventing bleeding--a systematic review of the literature. *Neurosurgery* 2004; **55**: 767-75.

37   Van Rooij WJ, Sluzewski M. Procedural morbidity and mortality of elective coil treatment of unruptured intracranial aneurysms. *AJNR Am J Neuroradiol* 2006; **27**: 1678-80.

38   Gerlach R, Beck J, Setzer M et al. Treatment related morbidity of unruptered intracranial aneurysms - Results of a prospective single centre series with an interdisciplinary approach during a 6 year period (1999- 2005). *J Neurol Neurosurg Psychiatry* 2007; **78**: 864-71.

39   Krisht AF, Gomez J, Partington S. Outcome of surgical clipping of unruptured aneurysms as it compares with a 10-year nonclipping survival period. *Neurosurgery* 2006; **58**: 207-16.

40   Moroi J, Hadeishi H, Suzuki A, Yasui N. Morbidity and Mortality from Surgical Treatment of Unruptured Cerebral Aneurysms at Research Institute for Brain and Blood Vessels-Akita. *Neurosurgery* 2005; **56**: 224-31.

41   Ogilvy CS, Carter BS. Stratification of outcome for surgically treated unruptured intracranial aneurysms. *Neurosurgery* 2003; **52**: 82-7.

42   Orz YI, Hongo K, Tanaka Y et al. Risks of surgery for patients with unruptured intracranial aneurysms. *Surg Neurol* 2000; **53**: 21-7.

43   Solomon RA, Fink ME, Pile-Spellman J. Surgical management of unruptured intracranial aneurysms. *J Neurosurg* 1994; **80**: 440-6.

44   Raaymakers TWM, Rinkel GJE, Limburg M, Algra A. Mortality and morbidity of surgery for unruptured intracranial aneurysms: a meta-analysis. *Stroke* 1998; **29**: 1531-8.

45   Kaufmann TJ, Huston J, III, Mandrekar JN et al. Complications of diagnostic cerebral angiography: evaluation of 19 826 consecutive patients. *Radiology* 2007; **243**: 812-9.

46   White PM, Wardlaw JM, Easton V. Can noninvasive imaging accurately depict intracranial aneurysms? A systematic review. *Radiology* 2000; **217**: 361-70.

47   Nilsson OG, Saveland H, Ramgren B, Cronqvist M, Brandt L. Impact of coil embolization on overall management and outcome of patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2005; **57**: 216-24.

48   Schaafsma JD, van der GY, Rinkel GJ, Buskens E. Decision analysis to complete diagnostic research by closing the gap between test characteristics and cost-effectiveness. *J Clin Epidemiol* 2009; **62**: 1248-52.

49   Hoh BL, Chi YY, Dermott MA, Lipori PJ, Lewis SB. The effect of coiling versus clipping of ruptured and unruptured cerebral aneurysms on length of stay, hospital cost, hospital reimbursement, and surgeon reimbursement at the university of Florida. *Neurosurgery* 2009; **64**: 614-9.

50   Wolstenholme J, Rivero-Arias O, Gray A et al. Treatment pathways, resource use, and costs of endovascular coiling versus surgical clipping after aSAH. *Stroke* 2008; **39**: 111-9.

51   Javadpour M, Jain H, Wallace MC et al. Analysis of cost related to clinical and angiographic outcomes of aneurysm patients enrolled in the international subarachnoid aneurysm trial in a North American setting. *Neurosurgery* 2005; **56**: 886-94.

52   Bairstow P, Dodgson A, Linto J, Khangure M. Comparison of cost and outcome of endovascular and neurosurgical procedures in the treatment of ruptured intracranial aneurysms. *Australas Radiol* 2002; **46**: 249-51.

53   Post PN, Kievit J, van Baalen JM, van den Hout WB, van Bockel JH. Routine duplex surveillance does not improve the outcome after carotid endarterectomy: a decision and cost utility analysis. *Stroke* 2002; **33**: 749-55.

54   Koffijberg H, Buskens E, Algra A, Wermer MJ, Rinkel GJ. Growth rates of intracranial aneurysms: exploring constancy. *J Neurosurg* 2008; **109**: 176-85.

55   Wermer MJ, Buskens E, van der Schaaf IC, Bossuyt PM, Rinkel GJE. Yield of screening for new aneurysms after treatment for subarachnoid hemorrhage. *Neurology* 2004; **62**: 369-75.

Chapter 8

Long-term, serial screening for intracranial aneurysms in individuals with a family history of aneurysmal subarachnoid haemorrhage: a cohort study
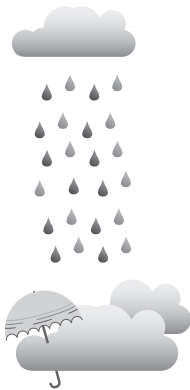
A.S.E. Bor
G.J.E. Rinkel
J. van Norden
M.J.H. Wermer

Abstract

Introduction: Individuals with two or more first-degree relatives who have had aneurysmal subarachnoid haemorrhage (SAH) have an increased risk of aneurysms and SAH. We investigated the yield of long-term serial screening for intracranial aneurysms in these individuals.

Methods: In a cohort study, we reviewed the results of screening of individuals with a positive family history of SAH (two or more first-degree relatives who had had SAH or unruptured intracranial aneurysms) done at the University Medical Centre Utrecht (Utrecht, Netherlands) between April 1, 1993, and April 1, 2013. Magnetic resonance angiography or CT angiography was done from age 16–18 years to 65–70 years. After a negative screen, we advised individuals to contact us after 5 years, but did not actively call them for repeated screening. We recorded familial history of ruptured and unruptured intracranial aneurysms, smoking history, hypertension, previous aneurysms, screening dates, and screening results. We identified risk factors for positive initial and follow-up screens with univariable and multivariable regression analysis.

Results: We identified aneurysms in 51 (11%; 95% CI 9–14) of 458 individuals at first screening, in 21 (8%, 5–12) of 261 at second screening, in seven (5%; 2–11) of 128 at third screening, and three (5%; 1–14) of 63 at fourth screening. Five (3%; 95% CI 1–6) of 188 individuals without a history of aneurysms and with two negative screens had a *de novo* aneurysm in a follow-up screen. Smoking (odds ratio 2.7; 95% CI 1.2–5.9), history of previous aneurysms (3.9; 1.2–12.7), and familial history of aneurysms (3.5; 1.6–8.1) were significant risk factors for aneurysms at first screening in the multivariable analysis. History of previous aneurysms was the only significant risk factor for aneurysms at follow-up screening (hazard ratio 4.5; 1.1–18.7). Aneurysms were identified in six (5%; 95% CI 2–10) of 129 individuals who were screened before age 30 years. One patient developed a *de novo* aneurysm that ruptured 3 years after the last negative screen.

Discussion: In individuals with a family history of SAH, the yield of long-term screening is substantial even after more than 10 years of follow-up and two initial negative screens. We advocate long-term serial screening in these individuals, although the risk of SAH within screening intervals is not eliminated.

Introduction

Individuals with two or more first-degree relatives who have had aneurysmal subarachnoid haemorrhage (SAH) have an increased lifetime risk of an unruptured intracranial aneurysm and SAH.[1,2] However, although the risk of unruptured intracranial aneurysms is roughly tripled in these individuals, the relative risk of SAH is even higher.[1,2] Therefore, individuals with familial SAH not only have an increased risk of aneurysm development, but also have an increased risk of aneurysm rupture compared with individuals without familial SAH. The Familial Intracranial Aneurysm study[3] showed that the frequency of rupture was 17-times higher for individuals with a family history of intracranial aneurysms than for those who had a sporadic aneurysm when matched for age, sex, site, and size of aneurysms.

Because SAH has high case fatality and morbidity,[4] the risks of elective treatment of unruptured aneurysms in people with a family history of SAH are often deemed to be lower than the lifetime risk of rupture.[5] Screening for intracranial aneurysms should be considered in individuals with at least two first-degree relatives with SAH, according to guidelines from the European Stroke Organisation and the American Heart Association.[6,7] Screening should be repeated, because aneurysms can develop at any point.[8] However, the yield (i.e., proportion of positive screens) of long-term serial screening is unknown. In this study, we analysed the yield of repeated screening in individuals with a family history of SAH.

Methods

Cohort

All individuals who are screened at the University Medical Center Utrecht (Utrecht, Netherlands) for intracranial aneurysms because of familial SAH are recorded in a database. Screening at this centre began in April, 1993. We reviewed the results of screening done between April 1, 1993, and April 1, 2013. All patients with SAH who were admitted to the tertiary referral centre or individuals with an unruptured aneurysm who visited the outpatient clinic at University Medical Center Utrecht were routinely asked for details about their family history. If other family members had had SAH, we suggested that they extend an invitation to their relatives to visit the clinic to learn about screening for unruptured aneurysms. People were also referred for screening by their general practitioner or neurologist.

Screening was offered to individuals with a positive family history of SAH after careful and extensive discussions about the possible consequences of screening, including those on

flying, driving licences, life insurance, and quality of life. All potential screenees were advised about modifiable risk factors for SAH, such as smoking and hypertension. A positive family history was defined as two or more first-degree relatives (parents, siblings, or children) who had had definite or probable SAH, or unruptured intracranial aneurysms. Definite SAH must have been identified in a hospital, and probable SAH was defined as an episode suspected to be SAH in a person younger than 70 years, such as stroke with a second ictus within 4 weeks followed by death.[9] All unruptured intracranial aneurysms in first- degree relatives had to have been diagnosed with MRI, CT, or conventional angiogram. The cause of familial clustering of SAH is probably multifactorial, with both environmental and genetic risk factors having a role.[10-16] We defined familial SAH as familial clustering, without any assumption about genetic or environmental risk factors or their interaction. When reviewing the family history, we noted that when an individual had relatives who had had probable SAH, their family already had a positive history of intracranial aneurysms (i.e., probable SAH did not shift family history from negative to positive for SAH).

This study was approved by the institutional review board of the University Medical Center Utrecht. Participants provided oral informed consent before screening.

Procedures

Screening was usually started at age 18 years in individuals who agreed to proceed, but in families with a history of SAH at ages younger than 20 years, screening could begin at age 16 years. The standard screening modality was magnetic resonance angiography. In case of claustrophobia or a previously clipped aneurysm, we did CT angiography. After a negative screen, we advised people to contact us after 5 years for repeated screening.[8] We did not actively call individuals to repeated screening because the effectiveness of screening for prevention of SAH is unknown. We discontinued screening in individuals older than 65–70 years, with the precise cutoff dependent on their state of health, because after this age the risk of rupture of aneurysms left untreated will not outweigh the risks associated with elective aneurysm treatment. Because the screening interval reflected clinical practice and was not dictated by a study protocol, screening intervals shorter and longer than the advised 5 years could occur.

We obtained information about smoking status and hypertension (previous diagnosis made by a general practitioner or other physician) at time of first screening, familial and personal history of SAH and unruptured intracranial aneurysms (including SAH after the first screening), and history of autosomal dominant polycystic kidney disease. We reviewed date

and modality for all vascular imaging. We deemed that an individual had begun screening when the first imaging was done with the purpose to screen for intracranial aneurysms. To assess adherence to screening, we calculated the expected next screening date for all individuals who had no known reason to stop screening. If more than 1 year had lapsed after the expected date of follow-up screening, we classified the person as a non-attendant.

If a new aneurysm was recorded during follow-up screening, it was classified as either a newly identified aneurysm (located at a site without a previously reported aneurysm) or a regrowth aneurysm (located at the site of a previously treated aneurysm). We reviewed all available previous imaging for that individual as part of our analysis, and the aneurysm was classified as truly *de novo* (a newly developed aneurysm at a site that previously showed no aneurysm) or visible in retrospect (an aneurysm that was not reported before, but was present retrospectively on previous imaging). We deemed small lesions (< 2 mm) to be aneurysms only if the first follow-up imaging confirmed them as aneurysms. We obtained information about the method of management (clipping, coiling, or follow-up imaging) and complications of treatment for all aneurysms identified during screening.

Statistical analysis

Yield of screening is reported as the proportion of positive screenings with corresponding 95% CIs for each screening. We included shorter and longer screening intervals than the advised 5-year screening interval in the analysis.

To identify risk factors for aneurysm presence at initial screening, we used univariable logistic regression to calculate odds ratios and p values. To identify risk factors for aneurysm development during follow-up screening (all follow-up screening combined, excluding aneurysms retrospectively visible on the first screening), we used univariable Cox regression analysis to calculate hazard ratios and p values. We did a multivariable logistic and Cox regression analysis including all risk factors with a p value of less than 0.2 in the univariable regression analysis. We calculated risk factors for aneurysms present at the first screening (including aneurysms detected at follow-up screening but retrospectively visible on the first screening) and for those present at follow-up screening (all follow-up screening combined, excluding aneurysms retrospectively visible on the first screening). We entered several risk factors in the univariable regression analyses: age (age at first screening and at last follow-up screening), sex, smoking status at first screening, history of hypertension at first screening, history of previous aneurysms (previous aneurysm vs no previous aneurysm), high familial burden of aneurysms (three or more first-degree relatives with ruptured or unruptured

aneurysms vs two first-degree relatives with ruptured or unruptured aneurysms), and low familial burden of SAH (one first-degree relative with SAH and at least one first-degree relative with an unruptured aneurysm vs two or more first-degree relatives with SAH). Survival curves are shown for all individuals participating in screening and for individuals with and without a previous aneurysm (including aneurysms identified at initial screening). We assessed yield of follow-up screening for two subgroups: individuals with no aneurysms (i.e., at least one negative screen) at age 50 years and all individuals with at least two negative screens. Additionally, we analysed a subgroup of our study population consisting of individuals who fulfilled the inclusion criteria of the Familial Intracranial Aneurysm study[3] – i.e., individuals with a known history of smoking or hypertension, or both, and who had not had an aneurysm before the first screening.

Results

458 individuals were screened at least once, more than half of whom were women (Table 8.1).

138 individuals (30%, 95% CI 26–34) were classified as non-attendants, 95 of whom (69%, 60–76) did not return after the first screening. 114 aneurysms were identified in 82 positive screens of 72 individuals (16%, 95% CI 13–19). The yield was highest in the first screening cycle (Table 8.2), but did not differ significantly between follow-up screenings (second vs third screening: p = 0.9; second vs fourth screening: p = 0.6; third vs fourth screening: p = 1.0).

21 of the 114 aneurysms (18%, 12–27) were visible retrospectively: five were visible on imaging done before screening (i.e., patients with previous imaging because of previous

Table 8.1 Baseline characteristics at first screening

	All persons (n = 458)
Women	265 (58%)
Age at first screening (years)	38 (29–48)
Smoker at first screening*	70 (34%)
Hypertension at first screening[†]	76 (36%)
ADPKD at first screening	4 (1%)
History of previous aneurysms before first screening	43 (9%)
High familial burden of aneurysms	241 (53%)
Low familial burden of SAH	100 (22%)

Data are n (%) or median (IQR). * Information available for 205 individuals. [†] Information available for 210 individuals.

Table 8.2 Positive screens and characteristics of the aneurysms identified

	First screening	Second screening	Third screening	Fourth screening	Total
Positive screening (%)	51/458 (11%, 9–14)	21/261 (8%, 5–12)	7/128 (5%, 2–11)	3/63 (5%, 1–14)	82/910 (9%, 7–11)
Screening interval in years* median (min;max)	–	5 (1;16)	10 (4;16)	14 (6;18)	–
Woman (%)	31/265 (12%, 8–16)	18/158 (11%, 7–17)	4/70 (6%, 2–14)	1/37 (3%, 0–15)	54/530 (10%, 8–13)
Man (%)	20/193 (10%, 7–16)	3/103 (3%, 1–9)	3/58 (5%, 1–15)	2/26 (8%, 1–25)	28/380 (7%, 5–10)
No previous aneurysms (%)**	40/414 (10%, 7–13)	11/200 (6%, 3–10)	3/92 (3%, 1–10)	2/41 (5%, 0–17)	56/747 (7%, 6–10)
Previous aneurysms (%)**	11/44 (25%, 14–40)	10/61 (16%, 9–28)	4/36 (11%, 4–26)	1/22 (5%, 0–24)	26/163 (16%, 11–22)
Number of aneurysms found (total)	73	28	9	4	114
Newly visualized aneurysm	70 (96%, 88–99)	27 (96%, 81–100)	9 (100%, 66–100)	4 (100%, 45–100)	110 (96%, 91–99)
Regrowth aneurysm	3 (4%, 0–12)	1 (4%, 0–19)	–	–	4 (4%, 1–9)
Revision					
Truly de novo	4 (5%, 2–14)	8 (29%, 15–47)	3 (33%, 12–65)	3 (75%, 29–97)	18 (16%, 10–24)
Visible in retrospect	5 (7%, 3–15)	14 (50%, 33–67)	1 (11%, 0–46)	1 (25%, 3–71)	21 (18% 12–27)
No previous imaging available	64 (88%, 78–94)	6 (21%, 10–40)	5 (56%, 27–81)	–	75 (66%, 57–74)
Aneurysm location					
ICA	34 (47%, 36–58)	8 (29%, 15–47)	3 (33%, 12–65)	–	45 (39%, 31–49)
MCA	26 (36%, 26–47)	12 (43%, 26–61)	4 (44%, 19–73)	2 (50%, 15–85)	44 (39%, 30–48)
ACA	10 (14%, 7–24)	4 (14%, 5–32)	2 (22%, 5–56)	2 (50%, 15–85)	18 (16%, 10–24)
Posterior circulation	3 (4%, 0–12)	4 (14%, 5–32)	–	–	7 (6%, 3–12)
Aneurysm size					
< 2 mm	18 (25%, 16–36)	14 (50%, 33–67)	3 (33%, 12–65)	2 (50%, 15–85)	37 (32%, 25–42)
2–5 mm	37 (51%, 39–62)	11 (39%, 24–58)	5 (56%, 27–81)	2 (50%, 15–85)	55 (48%, 39–57)
> 5 mm	18 (25%, 16–36)	3 (11%, 3–28)	1 (11%, 0–46)	–	22 (19%, 13–27)

* Time interval between follow-up screening and first screening.

** History of previous aneurysms was determined per screening cycle: if an aneurysm was found in a person in the "no previous aneurysm" group, the person was transferred from the "no previous aneurysm" to the "previous aneurysm" group for the next screening cycle.

SAH), 14 had been visible on the first screen (six had grown and eight were unchanged), and two (one each in screening cycle three and four) were visible at a previous follow-up screen but not the first screen. Ten (5%, 95% CI 3–9) of 200 individuals without a history of aneurysms and with a negative first screen had a *de novo* aneurysm in a follow-up screen. Five (3%, 1–6) of 188 individuals without a history of aneurysms and with two negative screens had a *de novo* aneurysm in a follow-up screen. Smoking (past or present), history of previous aneurysms, and a high familial burden of aneurysms were significant risk factors for aneurysms at first screening in the multivariable logistic regression analysis (Table 8.3). History of previous aneurysms was the only significant risk factor for aneurysms at follow-up screening in multivariable Cox regression analysis (Table 8.3).

An aneurysm was identified in more than 20% of individuals who were screened again at least 10 years after the first screening, and risk of an aneurysm was higher in individuals who had had a previous aneurysm (ruptured or unruptured) than in those who had not (Figure 8.1). An aneurysm was identified during screening in six (5%, 95% CI 2–10) of 129 individuals who were screened before age 30 years (Figure 8.2). In five, the aneurysm was identified in the first screen (Figure 8.2). Two of these aneurysms were treated with clipping. An aneurysm was identified with screening in 12 (18%, 4–49) of 61 individuals aged at least 60 years at the time of screening. In eight, the aneurysm was present in the first screen (Figure 8.2). Of 44 individuals who had never had an aneurysm by age 50 years, *de novo* aneurysms were detected in one (3%, 0–14%) at follow-up screening (mean additional follow-up time 7 years, SD 4). 44 aneurysms were treated (42 initially, two after growth) in 35 patients (Table 8.4). 23 patients were treated without complications. Six patients experienced temporary deficits: one had fever; one had pulmonary problems; one had one seizure; one had temporary dysphasia; one had a seizure and delirium; and one had CSF leakage, meningitis, and seizures. In three patients, deficits were still present 6 months or more after treatment: one patient had partial loss of vision in the right eye, one had anosmia after clipping of a second aneurysm, and one was admitted to a rehabilitation facility. Three patients were treated in other hospitals more than 10 years ago, and we have little data on their treatment complications. However, two of these patients were in good clinical condition at our outpatient clinic several years after treatment when they returned for further screening. For the third patient, no information from after the procedure was available.

One woman aged 42 years developed a *de novo* aneurysm that ruptured during a screening interval. She had SAH from a truly *de novo* aneurysm of the anterior communicating artery 3 years after the first screen. A second woman aged 52 years had two small posterior

Table 8.3 Risk factors for aneurysms at the first screening and at follow-up screening. Aneurysms that were in retrospect visible on the first screening are included in the first screening and excluded from the follow-up screening.

	No aneurysm	Aneurysm	Univariable analysis	Multivariable analysis
FIRST SCREENING			OR (95% CI)	OR (95% CI)
Total (in persons)	399 (100%)	59 (100%)		
Age 1st screening Mean (standard deviation)	38 (± 13)	45 (± 11)	1·05 (1·02–1·07)	1·01 (0·98–1·05)
Age < 30 years	124 (31%)	5 (9%)	0·2 (0·1–0·5)	–
Age 30–39 years	103 (26%)	12 (20%)	0·5 (0·2–1·1)	–
Age 40–49 years	98 (25%)	22 (37%)	ref	–
Age ≥ 50 years	74 (19%)	20 (34%)	1·2 (0·6–2·4)	–
Women	227 (57%)	38 (64%)	1·4 (0·8–2·4)	–
Hypertension	55 (33%)	21 (49%)	1·9 (1·0–3·8)	1·5 (0·7–3·5)
Smoking	49 (30%)	21 (49%)	2·2 (1·1–4·4)	2·7 (1·2–5·9)
History of previous aneurysms	31 (8%)	13 (22%)	3·4 (1·6–6·9)	3·9 (1·2–12·7)
High familial burden in aneurysms	202 (51%)	39 (66%)	1·9 (1·1–3·4)	3·5 (1·6–8·1)
Low familial burden in SAH	86 (22%)	14 (24%)	1·1 (0·6–2·1)	–
FOLLOW-UP SCREENING			HR (95% CI)	HR (95% CI)
Total (in persons)	242 (100%)	19 (100%)		
Age at censure/event Mean (standard deviation)	47 (± 12)	51 (± 10)	1·02 (0·99–1·07)	–
Age < 30 years	24 (10%)	1 (5%)	0·7 (0·3–2·0)	–
Age 30–39 years	55 (23%)	1 (5%)	1·2 (0·1–9·4)	–
Age 40–49 years	59 (24%)	5 (26%)	ref	–
Age ≥ 50 years	104 (43%)	12 (63%)	0·2 (0·3–1·5)	–
Women	144 (60%)	14 (74%)	2·4 (0·9–6·7)	1·1 (0·3–4·5)
Hypertension	40 (40%)	6 (43%)	0·7 (0·2–2·1)	–
Smoking	34 (33%)	5 (50%)	3·2 (0·8–11·8)	3·7 (0·9–16·0)
History of previous aneurysms	52 (22%)	9 (47%)	3·6 (1·5–9·0)	4·5 (1·1–18·7)
High familial burden in aneurysms	133 (55%)	13 (68%)	0·6 (0·2–1·6)	–
Low familial burden in SAH	47 (19%)	7 (37%)	1·7 (0·7–4·3)	–

circulation aneurysms (2 mm and 4 mm in diameter) on the first screen, which were left untreated because of their size. Both aneurysms were stable in size at repeated imaging after 12 months. 8 months later, she had SAH from one of these aneurysms and died. A third woman aged 48 years had no aneurysms on the first screen and did not return for follow-up screening. She presented with SAH from a 3 mm basilar tip aneurysm 14 years after the first
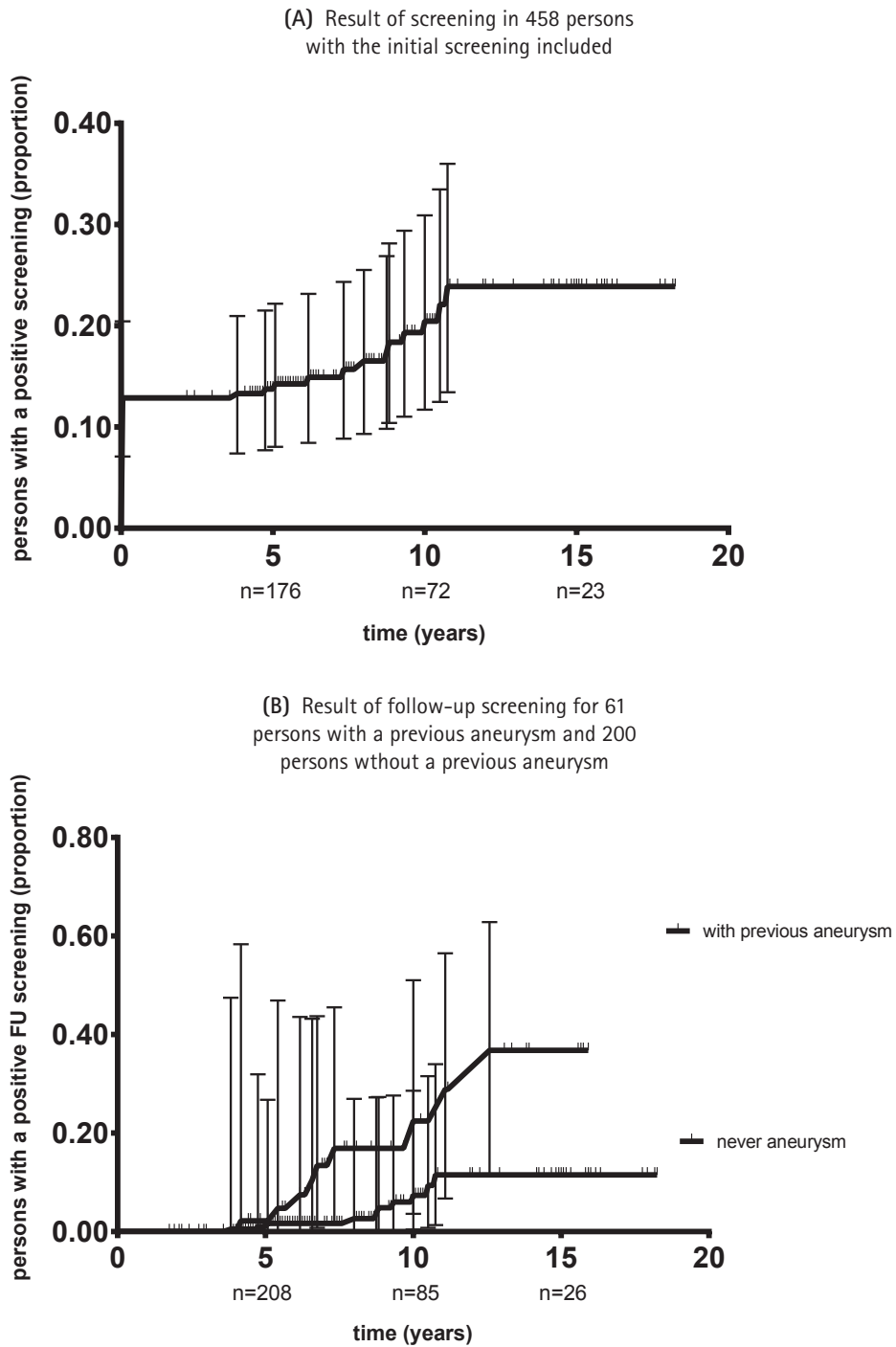
(A) Result of screening in 458 persons with the initial screening included

(B) Result of follow-up screening for 61 persons with a previous aneurysm and 200 persons wthout a previous aneurysm
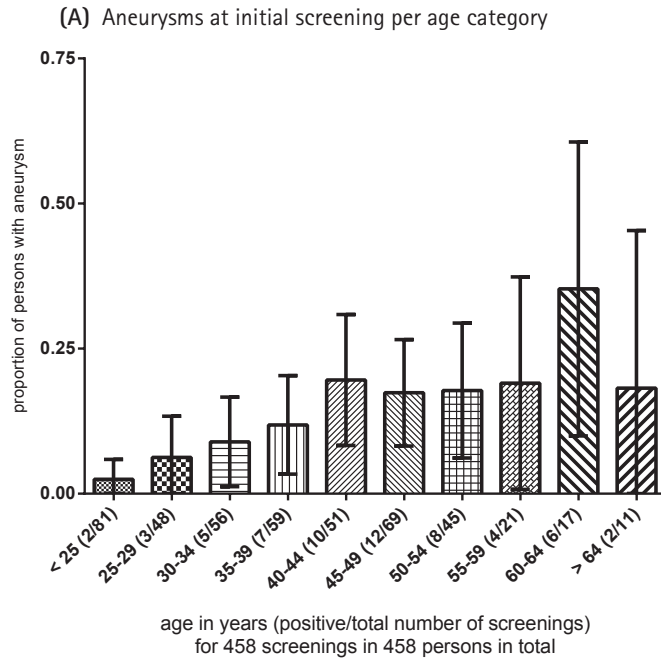
Figure 8.1 Kaplan Meier curve of individuals for whom an aneurysm was identified. **(A)** Any screening. **(B)** Follow-up screening. Error bars show 95% CIs. Vertical lines indicate censoring.

(A) Aneurysms at initial screening per age category

(B) Aneurysms at follow-up per age category
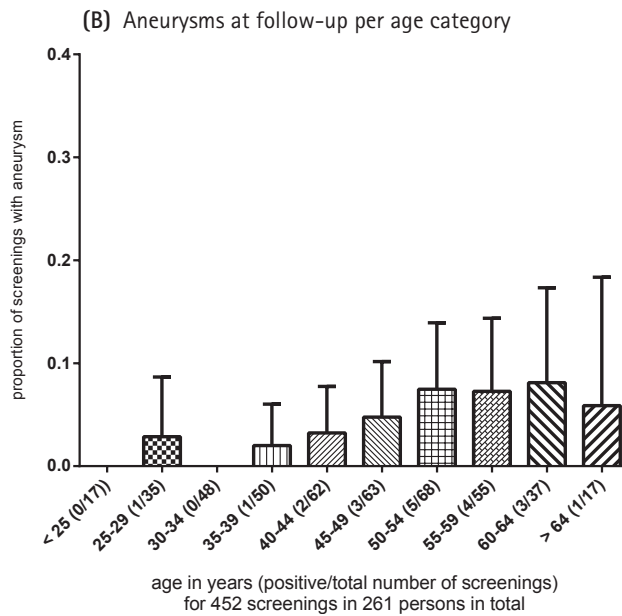
Figure 8.2 Aneurysms identified during screening, by age. **(A)** Individuals with one or more aneurysms at first screen. Aneurysms that were retrospectively visible on the first screening are included. **(B)** Screenings with one or more de novo aneurysms at follow-up. Aneurysms that were retrospectively visible on the first screening are excluded. Numbers above bars show number of positive screenings/ total number of screenings. Error bars show 95% CIs.

Table 8.4 Management of the 114 aneurysms found with screening, presented per aneurysm size

Aneurysm size	< 2 mm n = 37 (100%)	2–5 mm n = 55 (100%)	> 5 mm n = 22 (100%)
Initial management: clipping	0 (0%)	19 (35%)	14 (64%)
Initial management: coiling	0 (0%)	4 (7%)	5 (23%)
Initial management: follow-up	37 (100%)	32 (58%)	3 (14%)
Follow-up: growth*	3 /37 (8%)	3 /32 (9%)	0 /3 (0%)
Follow-up: treatment (clipping or coiling)	1 /37 (3%)	1 /32 (3%)	0 /3 (0%)

* Including aneurysms treated after growth.

screening. The films from the first screening could not be retrieved because of transition to new software (films were not supported by new programs). In the subgroup analysis of individuals who fulfilled the inclusion criteria of the Familial Intracranial Aneurysm study,[3] the first screening identified a *de novo* aneurysm in 23 (23%) of 98 individuals, which is a result similar to the 21% in the previous study.[3] Additionally, in the subgroup resembling the Familial Intracranial Aneurysm study, eight (14%) of 59 individuals had a *de novo* aneurysm at follow-up screening, again underlining the importance of repeated screening.

Discussion

We have shown that the yield of screening for intracranial aneurysms in individuals with a family history of SAH remains at about 5% for each follow-up screening in more than 10 years of follow-up, even after several negative screens. Individuals who have had a previous aneurysm, smoke (past or present), and have three or more first-degree relatives with aneurysms have an increased risk of aneurysms at first screening. Individuals who have had a previous aneurysm also have an increased risk of *de novo* aneurysms at follow-up screening. Sex and hypertension at time of first screening were not risk factors for aneurysm development. One individual in our cohort developed a *de novo* aneurysm that ruptured between screenings, which emphasises that a screening programme will not completely eliminate the risk of SAH.

We cannot compare our findings for serial screening with previous data, because we have not identified other studies of serial long-term follow-up screening for familial aneurysms (panel). In previous studies of the result of one screen in individuals with a family history of SAH,[17-21] the proportions of individuals with aneurysms at first screening was higher than in our study, with yields of up to 20%. Indeed, in our subgroup analysis of individuals

who fulfilled the inclusion criteria of the Familial Intracranial Aneurysm study,[18] the first screening identified a *de novo* aneurysm in more than 20% of individuals. The increased proportions of individuals with aneurysms in previous studies may thus be explained by patient selection, such as an overrepresentation of individuals with modifiable risk factors, such as smoking.[18,19] In the general population, aneurysms are more prevalent in women than in men.[1] However, we recorded no difference in the risk of aneurysm formation between men and women. This finding is in agreement with previous studies of familial aneurysms, in which the number of affected women equalled that of men[22] or the preponderance of women was less obvious for familial than for sporadic aneurysms.[23]

Our study had several strengths. First, the data we used were from one centre and encompassed the entire period that our centre has offered screening for familial SAH. Second, we excluded all individuals with an ambiguous familial history of intracranial aneurysms or SAH. We defined familial SAH as at least two first-degree relatives with intracranial aneurysms, rather than ruptured aneurysms. Although this definition could have affected the results of our study because of dilution of true familial aneurysms because the prevalence of unruptured aneurysms in the general population is already around 3%, this would only weaken the effect of screening (i.e., diminish the yield). However, our results cannot be extrapolated to individuals with only one first-degree relative with SAH or intracranial aneurysms.

Some weaknesses of our study were the variation in screening interval and the number of non-attendants, which were caused by the data being derived from clinical practice and not from a standardised study protocol. For the same reason, we could not analyse the effect of smoking cessation and hypertension treatment for separate screening cycles. We did not call individuals to return for screening, because of a scarcity of evidence from randomised trials for effectiveness of screening. As a result of this policy, natural selection of patients could have affected the results of long-term screening, because the motivation for repeated long-term screening could be higher in individuals who have previously had aneurysms, a higher family burden of aneurysms or SAH, or additional risk factors for SAH (eg, smoking). Therefore, our results are applicable to individuals who return for repeated screening; we cannot be sure that they would be relevant for individuals who did not return. Additionally, because we did not scrutinise causes of death of individuals who did not return for follow-up screening, the number of individuals with SAH despite screening could be an underestimation. Imaging techniques have improved substantially in the past two decades. Some of the newly identified, small aneurysms discovered with follow-up screening might have been present but not seen at the previous screening. Most aneurysms identified were smaller than 5 mm in diameter, and therefore not all aneurysms identified with screening

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were preventively treated. The risk of rupture for unruptured intracranial aneurysms in familial SAH is unknown, and a pooled analysis of prospective studies of risk of rupture[24] did not incorporate familial history as a risk factor because data were sparse. Risk of rupture is probably higher for unruptured aneurysms in familial SAH than in sporadic aneurysms,[2,3] and previous studies[3,23,25] have shown that ruptured aneurysms in familial SAH are often smaller than 5 mm. Small aneurysms (< 2 mm) could be monitored for growth, because an increase in size could justify treatment. Our study provides data for the number of unruptured aneurysms identified at screening and so we cannot tell how many (if any) instances of SAH were prevented by this screening programme. However, a randomised controlled trial to assess the effectiveness of screening by comparing no screening with repeated screening in individuals with familial SAH would not be feasible, because many individuals from families with familial SAH insist on screening and preventive aneurysm treatment. Additionally, such a trial would need decades of follow-up. Therefore, modelling has been used instead.[5] Results of our study are compatible with the estimated rate of aneurysm development used in previous modelling and therefore underline the conclusions about cost-effectiveness of screening in individuals with a family history of SAH.[5,7]

Because we have shown that smoking is a clear risk factor for aneurysms at the first screening, prevention of smoking is crucial in individuals with familial SAH. Genetic factors have a role in the development of intracranial aneurysms[10-12] and are probably implicated in familial clustering of SAH,[13,26] but environmental risk factors such as smoking and hypertension also play a part in familial clustering, and these environmental risk factors could interact with the genetic risk factors.[14-16] Many screens in individuals younger than 30 years were positive, and a *de novo* aneurysm could develop during additional follow-up even in individuals who had reached the age of 50 years without aneurysm development. Therefore, we recommend that screening for familial SAH should be started at about age 18 years and should be continued until the age at which risk of rupture for aneurysms that are left untreated will probably not outweigh the risk of elective aneurysm treatment. Screening should be continued irrespective of the number of previous negative screens. Our finding that SAH can occur from *de novo* aneurysms despite regular screening and that SAH can occur from previously detected but very small aneurysms favours an increased screening frequency and an aggressive approach to treatment of small aneurysms (< 5 mm) for individuals with a family history of SAH. However, such a strategy should be carefully considered, because such an aggressive approach will also increase the financial costs of screening and the number of patients who might have complications from preventive aneurysm treatment.

References

1   Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol* 2011; **10**: 626-36.

2   Bor AS, Rinkel GJ, Adami J et al. Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case-control study. *Brain* 2008; **131**: 2662-5.

3   Broderick JP, Brown RD, Jr., Sauerbeck L et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. *Stroke* 2009; **40**: 1952-7.

4   Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. *Lancet Neurol* 2011; **10**: 349-56.

5   Bor AS, Koffijberg H, Wermer MJ, Rinkel GJ. Optimal screening strategy for familial intracranial aneurysms: a cost-effectiveness analysis. *Neurology* 2010; **74**: 1671-9.

6   Steiner T, Juvela S, Unterberg A et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis* 2013; **35**: 93-112.

7   Connolly ES, Jr., Rabinstein AA, Carhuapoma JR et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke* 2012; **43**: 1711-37.

8   Wermer MJ, Rinkel GJE, van Gijn J. Repeated screening for intracranial aneurysms in familial subarachnoid hemorrhage. *Stroke* 2003; **34**: 2788-91.

9   Bromberg JEC, Rinkel GJE, Algra A et al. Validation of family history in subarachnoid hemorrhage. *Stroke* 1996; **27**: 630-2.

10 Alg VS, Sofat R, Houlden H, Werring DJ. Genetic risk factors for intracranial aneurysms: a meta-analysis in more than 116,000 individuals. *Neurology* 2013; **80**: 2154-65.

11 Bae JS, Cheong HS, Park BL et al. Genome-wide association analysis of copy number variations in subarachnoid aneurysmal hemorrhage. *J Hum Genet* 2010; **55**: 726-30.

12 Yasuno K, Bilguvar K, Bijlenga P et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. *Nat Genet* 2010; **42**: 420-5.

13 Kissela BM, Sauerbeck L, Woo D et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. *Stroke* 2002; **33**: 1321-6.

14 Connolly ESJr, Choudhri TF, Mack WJ et al. Influence of smoking, hypertension, and sex on the phenotypic expression of familial intracranial aneurysms in sibling. *Neurosurg* 2001; **48**: 64-8.

15 Rasing I, Nieuwkamp DJ, Algra A, Rinkel GJ. Additional risk of hypertension and smoking for aneurysms in people with a family history of subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 2012; **83**: 541-2.

16 Woo D, Khoury J, Haverbusch MM et al. Smoking and family history and risk of aneurysmal subarachnoid hemorrhage. *Neurology* 2009; **72**: 69-72.

17   Ronkainen A, Hernesniemi J, Puranen M et al. Familial intracranial aneurysms. *Lancet* 1997; **349**: 380-4.

18   Brown RD, Jr., Huston J, Hornung R et al. Screening for brain aneurysm in the Familial Intracranial Aneurysm study: frequency and predictors of lesion detection. *J Neurosurg* 2008; **108**: 1132-8.

19   Miller TD, White PM, Davenport RJ, Al-Shahi SR. Screening patients with a family history of subarachnoid haemorrhage for intracranial aneurysms: screening uptake, patient characteristics and outcome. *J Neurol Neurosurg Psychiatry* 2012; **83**: 86-8.

20   Leblanc R, Worsley KJ, Melanson D, Tampieri D. Angiographic screening and elective surgery of familial intracranial aneurysms: a decision analysis. *Neurosurg* 1994; **35**: 9-19.

21   Obuchowski NA, Modic MT, Magdinec M. Current implications for the efficacy of non-invasive screening for occult aneurysms in patients with a family history of aneurysms. *J Neurosurg* 1995; **83**: 42-9.

22   Wills S, Ronkainen A, Van D, V et al. Familial Intracranial Aneurysms. An Analysis of 346 Multiplex Finnish Families. *Stroke* 2003; **34**: 1370-4.

23   Ruigrok YM, Rinkel GJE, Algra A, Raaymakers TWM, van Gijn J. Characteristics of intracranial aneurysms in patients with familial subarachnoid hemorrhage. *Neurology* 2004; **62**: 891-4.

24   Greving JP, Wermer MJ, Brown RD, Jr. et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014; **13**: 59-66.

25   Kleinloog R, van 't Hof FN, Wolters FJ et al. The association between genetic risk factors and the size of intracranial aneurysms at time of rupture. *Neurosurgery* 2013; **73**: 705-8.

26   Cannon Albright LA, Camp NJ, Farnham JM et al. A genealogical assessment of heritable predisposition to aneurysms. *J Neurosurg* 2003; **99**: 637-43.

Chapter 9

General discussion

This chapter summarizes the main results of this thesis and puts them put into perspective, discusses strengths and limitations, and outlines future perspectives for research and clinical practice.

Unruptured intracranial aneurysms in itself cause little harm, with exception of unruptured aneurysms that cause damage through a mechanical pressure effect. Such effects can be seen in aneurysms of unusually large size (giant aneurysms), and aneurysms at a distinctly disadvantageous location (third nerve palsy caused by a posterior communicating artery aneurysm). However, if an unruptured aneurysm ruptures, it causes a subarachnoid haemorrhage (SAH), often with devastating effect.[1,2] Elective treatment of unruptured aneurysms is available at tertiary referral centres and can prevent rupture, but at a certain treatment risk.[3] The majority of unruptured aneurysms do not rupture,[4,5] and in the ideal situation we would selectively treat the unruptured aneurysms destined to rupture, and leave the stable unruptured aneurysms untouched. Research is thus directed at the identification of risk factors for aneurysm rupture, with the aim to accurately and timely predict rupture for unruptured aneurysms. Aneurysm growth is considered a risk factor for aneurysm rupture, and is sometimes used as a substitute marker for rupture in research studies on risk factors for rupture.[6–11] Both aneurysm growth and rupture have a complex and probably multifactorial pathogenesis, with roles for genetic causes, for patient-related risk factors such as hypertension, age, sex, and smoking and for aneurysm-related risk factors such as site and size, shape, inflow- and bifurcation-angles and arterial diameter of the surrounding arteries.[4,12-14] Interactions between these risk factors are likely.[15-19]

Part I: Risk factors for aneurysm development

In part one of this thesis I focused on risk factors for growth and rupture of intracranial aneurysms.[13] Aneurysms of the anterior and posterior communicating artery are frequent and have an increased risk of rupture compared to aneurysms elsewhere in the anterior circulation.[4,20] It is hypothesized that hemodynamic risk factors play a role in this phenomenon, as it has long been known that ruptured ACoA aneurysms are related to A1 segment asymmetry.[21-23] The geometry of branching in the arterial network is complex.[24] In bifurcations the arterial diameters of the branching arteries and the bifurcation angles are most likely interrelated to minimize the hemodynamic stress caused by branching.[24-27] In chapter 2, I thus hypothesized that arterial diameter and bifurcation angles are a risk factor for aneurysm development. I compared 26 patients with aneurysm development during follow-up to 78 patients without aneurysm development. Arterial hypoplasia and sharp

bifurcation angles were found to be a risk factor for aneurysm development. The major limitation in this study was the small number of aneurysms, which necessitated grouping different locations of aneurysms in the analysis. Chapter 3 focuses on two locations where ruptured aneurysms are often found and arterial asymmetry is common; the anterior and posterior communicating artery.[21,22,28] This could be due to an increased risk of aneurysm development near asymmetry (more aneurysms, thus also more ruptured aneurysms) or to an increased risk of aneurysm rupture near asymmetry. We compared patients with an unruptured ACoA or PCoA aneurysm to patients with a ruptured aneurysm in the same location and patients without an aneurysm, after matching the patients for age and sex. Asymmetry of the ACA-A1 was found to be a risk factor for aneurysm development, but not for aneurysm rupture. Dominance of the PCoA seems to be a risk factor for aneurysm development as well as aneurysm rupture. Anatomic variation may therefore (partly) explain the increased risk of rupture found for unruptured PCoA aneurysms compared to aneurysms elsewhere in the anterior circulation.

At first glance, the results of chapter 3 and chapter 2 may seem confusing regarding arterial size of the posterior communicating artery. Hyperplasia of the PCoA was a risk factor for both aneurysm development and rupture in chapter 3, while in chapter 2 hypoplasia was found to be a risk factor for aneurysm development. The difference may be explained by the study design; in chapter 2 I pooled the analysis for 7 unruptured aneurysms at different locations, including only 2 aneurysms on the ACoA and 3 aneurysms on the PCoA , while in chapter 3 I analysed aneurysms located at the ACoA and PCoA separately, analysing a much larger number of aneurysms per site. This seeming controversy of hypoplasia versus hyperplasia does not arise for ACoA, since an asymmetry always incorporates both a hypoplastic and a hyperplastic A1. It may be that arterial diameter plays a different role in different aneurysm locations, as the anterior cerebral arteries connect with the ACoA to form a unique complex within the circle of Willis, while the internal carotid artery forms a bifurcation with the PCoA, which is a much 'simpler' form of branching than the ACoA-complex.[28-30] Another explanation would be that arterial size may have to be interpreted in relation to bifurcation angles or aneurysm morphology.[24-26] Recent studies using image-based computational fluid dynamics studies show equally conflicting and complex results, with for example both high wall shear stress and low wall shear stress being related to aneurysm development and rupture.[31] Larger clinical studies, including more (un)ruptured aneurysms may offer the opportunity to analyse arterial diameter size in multivariable analyses.

Patient-related risk factors such as age, hypertension and smoking also play a role in aneurysm development and rupture.[4,15,19,32] In patients with familial SAH the MCA seems

to be at a higher risk of aneurysm formation compared to other aneurysm locations.[33] I hypothesized that patient related risk factors such as age, hypertension, smoking and alcohol use do not just influence aneurysm development, but specifically influence the location of aneurysm development. To test this hypothesis, in chapter 4, I compared the presence of patient-related risk factors in ruptured aneurysms at different sites. In comparison to patients with a ruptured anterior communicating artery aneurysm, patients with a ruptured middle cerebral artery are generally younger, patients with a ruptured posterior communicating artery aneurysm are more often female and patients with a ruptured basilar artery aneurysm are more likely to be a teetotaller (a person that does not drink alcohol). Excessive use of alcohol, hypertension and smoking did not seem to influence the site of aneurysms. This finding underscores the complexity of the pathways leading to aneurysm development and rupture, and should be kept in mind when contemplating prediction of aneurysm growth and rupture.

For small aneurysms, the risk of rupture is modest, and the best course of action usually seems to be watchful waiting.[4] Recent studies analysing the risk of aneurysm growth show a rate of 2–5% risk of aneurysm growth per year of follow-up.[6-11] In chapter 5, I analysed a large dataset of patients with an untreated unruptured intracranial aneurysm and at least 6 months of radiological follow-up available, and assessed the relation between aneurysm growth and patient-related risk factors such as age, sex and hypertension, as well as aneurysm-related risk factors characteristics such as site, size, shape, inflow and bifurcation angles. I found that 12 % of the aneurysms (57/468 aneurysms) grew during a median follow-up of 2.1 years, and that independent risk factors for growth were aneurysm size and an aneurysm dome wider than the aneurysm neck. A location in the posterior circulation and multilobarity were risk factors in the univariable analyses, but did not reach statistical significance in the multivariable analysis. Because large aneurysms generally have a treatment indication based on size alone, I performed a subgroup analysis for small (< 7 mm) aneurysms only, as these are the aneurysms for which the choice between treatment and follow-up imaging is usually made. This subgroup analysis showed that 9% (37/403 aneurysms) of the small aneurysms grew with smoking and multilobarity as independent risk factors for aneurysm growth, and location in the posterior circulation and an aneurysm dome wider than the aneurysm neck as possible risk factors that did not reach statistical significance in the multivariable analysis. Size was not an independent risk factor for growth for small aneurysms.

Clinical implications and future research

Future research should focus on two pathways, a clinical path that will lead to a better prediction of aneurysm growth and treatment advices, and a pre-clinical path to elucidate the pathogenesis of aneurysm formation, development and rupture.

Recently, several studies including unruptured aneurysms with follow-up imaging have become available,[6-11] and a joint analysis of these data could provide enough information for a large multivariable analysis. Aneurysm growth is a risk factor for rupture in follow-up imaging studies.[6,34] It is unclear whether aneurysm growth leads to a higher risk of rupture merely through an increase in aneurysm size (as size is an important risk factor for rupture) or that aneurysm growth is a marker for aneurysm wall instability, with the wall instability leading to either growth or rupture, depending on unknown circumstances at the time of wall instability. After the large multivariable analysis, efforts should be direct towards design and validation of a prediction model for aneurysm growth based on characteristics such as patient age, hypertension, smoking, aneurysm site and size; the same characteristics that were available for the prediction model for aneurysm rupture.[4] The prediction model could also incorporate simple geometric data of the aneurysm, such as dome-neck ratio and multilobarity, which are measurements that can easily be performed in the current standard imaging for unruptured aneurysms with CTA or MRA. Such a prediction model could improve decision making when discussing treatment options for (small) unruptured aneurysms.

Simultaneously, imaging techniques are developing fast, and complex software is becoming available to measure the aneurysm and perianeurysmal environment at acceptable speed per measurement.[35] The accuracy and standardization of radiological measurements (now by hand) will probably be greatly enhanced, with the possibility of new markers for aneurysm growth or rupture surfacing. Technical improvements make it possible to image aneurysms as never before; with 7T MRI it is possible to analyse aneurysm wall thickness, and to visualize movement of the aneurysm with the heart cycle. Hypotheses involving differences in wall thickness and elasticity as explanations for aneurysm growth and rupture may be put to the test very soon.[14,31] Image based computational fluid dynamic studies have become more complex, and may thus resemble the actual situation in the arteries more and more. As these models become able to analyse large numbers of aneurysms at a high reproducibility, they could provide insight in the hemodynamics behind the geometric indices that we measure (such as dome-neck ratio or multilobarity). Ultimately, the risk factors for rupture that these programmes show may be put to the test in clinical trials as predictors of growth and rupture, hopefully improving a clinical prediction model based on the current imaging techniques.

Genome analysis should be combined with patient related risk factors, as smoking and hypertension seem to have an additive effect on genetic risk factors for aneurysm development and/or rupture.[16-18] At this point, only for a minority of the aneurysms with a probable genetic component in their formation/rupture, the exact DNA mutation is known.[36] When new data on genetics and aneurysm formation and/or rupture become available, DNA information could be added to the prediction model. Naturally, with every addition to the model, it should be tested whether this is an improvement to the previous prediction model. With the arrival of big data analysis, new ways to look at data analysis are being explored, and may provide us with new insights on how to look at these complex interrelated data.

Last but not least, future studies should be directed towards the here and now: studies are needed that assess the effect of smoking prevention or cessation, treatment for hypertension, the use of aspirin, and the effects of regular exercise on the risk of aneurysm development and rupture.[15,19,37-39] These are risk factors that can actually be influenced today and tomorrow for every individual that seeks counselling, and as these factors seem to play a role in many fields of health and society, efforts to effectively influence these factors will probably have a large effect on the well-being of patients (or keep persons from becoming patients).

Part II: Familial intracranial aneurysms

In the second part of the thesis, I gathered information on screening for unruptured aneurysms in familial SAH. Persons with ≥ 2 first degree relatives with SAH (familial SAH) have an increased risk of SAH themselves, and screening for unruptured aneurysms is often advocated.[40-44] However, it is still not well known how high this risk of SAH actually is, as it is very difficult to assess due to the scarcity of familial SAH. In chapter 6, I performed a large population based case-control study in Sweden, comparing the occurrence of SAH in all relatives of 5,282 patients with SAH between 2001–2005, and the occurrence of SAH in all relatives of 26,402 controls, with the controls matched for sex, age, marital status and county of residence. I found that the risk of SAH is slightly increased in individuals with one first degree relative with SAH (OR 2.2; 95% CI 1.8–2.6), but strongly increased in individuals with ≥ 2 first degree relatives with SAH (OR 51.0; 95% CI 8.6–1117). To stress the scarcity of familial SAH (which is also reflected in the large confidence interval!): I found only 11 persons with ≥ 2 first degree relatives with SAH (10/5,282 SAH patients and 1/26,402 controls). If I assume a life time risk of SAH of 0.7% for the general population,[45] the data in this study would suggest an absolute life time risk of SAH of 26% for individuals with ≥ 2 first degree relatives with SAH, with a lower confidence limit of 6%.

With this high life time risk of SAH for familial SAH, circumstantial evidence has become available that patients with an unruptured aneurysm and a positive family history have a higher risk of rupture than patients with an unruptured aneurysm without a positive family history. It should be noted that although both the risk of aneurysm development and the risk of SAH are increased for individuals with familial SAH compared to the general population, the risk of SAH is excessively higher than the risk of aneurysm development.[20] This suggests that persons with familial SAH do not just have an increased risk of aneurysm development, but also an increased risk of aneurysm rupture. Second, in the familial intracranial aneurysm (FIA) study, patients with familial SAH and an unruptured aneurysm had a 17 times increased risk of rupture compared to a group of patients with a sporadic aneurysm of a similar size and location.[46] Although aneurysm size is a risk factor for aneurysm rupture, the majority of ruptured aneurysm in familial SAH are small (< 10 mm), and four of five ruptured aneurysms in the FIA study were ≤ 5 mm in size.[46-48]

This data suggests that an aggressive approach with early treatment of familial aneurysms at small aneurysm sizes could be warranted, supporting the idea of screening for unruptured intracranial aneurysms in persons with ≥ 2 first degree relatives with SAH.[43,44,49] Since aneurysms develop during life, screening should be repeated.[44] However, the effectiveness and cost-effectiveness of screening for unruptured aneurysms is unknown, as are the optimal screening strategy in age ranges and screening interval. In chapter 7, I therefore built a Markov model to simulate risks and benefits of screening for individuals with familial SAH. I found that screening was cost effective in persons with familial SAH, with the lowest costs per QALY if individuals were screened twice, at 40 and 55 years old. The optimal cost–benefit screening strategy (highest yield in QALY for an acceptable cost in euro) was screening from age 20–80 years old every 7 years. The sensitivity analysis showed that the best (easiest) way to improve the model would be to improve the input information on the quality of life of persons who were not offered screening and the effect of a negative screening on the quality of life in persons who were offered screening.

The University Medical Center Utrecht has offered repeated screening, with an advised 5 year screening interval, to persons with familial SAH since 1993. In chapter 8, I analysed the results of 20 years of this clinical practice, including 458 individuals with at least one screening. In total, 114 aneurysms were identified in 82 positive screens in 72 individuals. I found that the yield of screening is stable at about 5% for each follow-up screening during two decades of follow-up. Five (3%; 95% CI 1–6) of 188 persons without a history of aneurysms and with two negative screenings had a *de novo* aneurysm in further follow-up screening. History of previous aneurysms was a risk factor for positive initial and follow-

up screening. Smoking and ≥ 3 first degree relatives with intracranial aneurysms were risk factors for positive initial screening only. In a subgroup analysis including only patients with familial SAH and smoking or hypertension, 23% of the individuals had a positive first screening. Aneurysms were identified in six (5%; 95% CI 2–10) of 129 individuals who were screened before aged 30 years. One patient developed a *de novo* aneurysm that ruptured 3 years after the last negative screening, and one patient with two small (2 and 4 mm) unruptured aneurysms found with screening and left untreated, had SAH from one of these aneurysms 8 months after a stable follow-up imaging. This underscores that screening may lower the risk of SAH, but cannot completely eradicate this risk.

Clinical implications and future research

As smoking is so far the only modifiable risk factors for positive screening, families with familial SAH should be counselled to prevent smoking. Screening should start at a young age (around 20 years old), be repeated every few years (every 3 to 7 years) and should be continued regardless of the results of previous screening. The natural history of familial SAH will probably not be studied anymore, as relatives with familial SAH ask for screening and treatment of unruptured aneurysms. It would be very valuable to check the occurrence of SAH in the individuals who did not return for screening in the cohort of chapter 8, and in the individuals who decided not to proceed to imaging after the initial counselling interview. Gathering additional data on smoking and (treatment of) hypertension could provide more insight in the effects of intervention in smoking prevention and blood pressure management in familial SAH.[16-18] The rate of aneurysm development found in chapter 8 is compatible with the estimated rate of aneurysm development used in the Markov model in chapter 7. With the additional data of chapter 8 it would be possible to improve the input in the Markov Model, with new data on aneurysm development, decisions on aneurysm treatment, and growth of small untreated aneurysms. With even more data, for example on the actual risks of aneurysm development and/or rupture in patients that smoke and in patients with previous aneurysms, it would be possible to extend the model and incorporate these risk factors in the risk analysis, for example by giving a higher risk of *de novo* aneurysm formation to individuals who smoke and have a previous aneurysm than to individuals who do not smoke and have never had an aneurysm. However, it is very difficult to incorporate this extension into the model at this point, as, even with the data of chapter 8, absolute risks are still very difficult to calculate. The current model does not include individuals with only one first degree relative with SAH, even though these individuals have a slightly increased risk.[50,51] A previous study showed screening in individuals with only one first degree relative with

SAH not to be cost-effective, but the improvement in technique seen in the previous years has made both screening and elective aneurysm treatment more effective, and with the new data on the increased risk of SAH the cost-benefit analysis of screening for aneurysms in individuals with one first degree relative with SAH could be reconsidered.[52] This model could also be adjusted to individualize screening strategies for patients with and without smoking, and with and without hypertension. The most ambiguous data incorporated in cost-benefit models are the estimates of quality of life. It is very difficult to grasp quality of life for any person, and it is even more difficult for individuals to draw conclusions on the effects of screening on their personal quality of life, as can be shown by the lowered QALY in individuals who agreed to screening compared to a reference population (regardless of the outcome of screening), who would still perform the screening.[53] The arrival of smartphones and big data analysis may open a new field of data, with new possibilities to assess quality of life for all kinds of life events, including diagnosis and follow-up of unruptured aneurysms.

References

1   Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. *Lancet Neurol* 2011; **10**: 349-56.

2   Nieuwkamp DJ, Setz LE, Algra A et al. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol* 2009; **8**: 635-42.

3   Wiebers DO, Whisnant JP, Huston J3 et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003; **362**: 103-10.

4   Greving JP, Wermer MJ, Brown RD, Jr. et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014; **13**: 59-66.

5   Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *Stroke* 2013; **44**: 2414-21.

6   Villablanca JP, Duckwiler GR, Jahan R et al. Natural history of asymptomatic unruptured cerebral aneurysms evaluated at CT angiography: growth and rupture incidence and correlation with epidemiologic risk factors. *Radiology* 2013; **269**: 258-65.

7   Burns JD, Huston J, III, Layton KF, Piepgras DG, Brown RD, Jr. Intracranial aneurysm enlargement on serial magnetic resonance angiography: frequency and risk factors. *Stroke* 2009; **40**: 406-11.

8   Matsubara S, Hadeishi H, Suzuki A, Yasui N, Nishimura H. Incidence and risk factors for the growth of unruptured cerebral aneurysms: observation using serial computerized tomography angiography. *J Neurosurg* 2004; **101**: 908-14.

9   Miyazawa N, Akiyama I, Yamagata Z. Risk factors for growth of unruptured intracranial aneurysms: follow-up study by serial 0.5-T magnetic resonance angiography. *Neurosurgery* 2006; **58**: 1047-53.

10   Matsumoto K, Oshino S, Sasaki M et al. Incidence of growth and rupture of unruptured intracranial aneurysms followed by serial MRA. *Acta Neurochir (Wien)* 2013; **155**: 211-6.

11   Chien A, Liang F, Sayre J et al. Enlargement of small, asymptomatic, unruptured intracranial aneurysms in patients with no history of subarachnoid hemorrhage: the different factors related to the growth of single and multiple aneurysms. *J Neurosurg* 2013; **119**: 190-7.

12   Ruigrok YM, Rinkel GJE, Wijmenga C. Genetics of intracranial aneurysms. *Lancet Neurol* 2005; **4**: 179-89.

13   Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. *Neurosurg Focus* 2009; **26**: E2.

14   Sforza DM, Putman CM, Cebral JR. Hemodynamics of Cerebral Aneurysms. *Annu Rev Fluid Mech* 2009; **41**: 91-107.

15   Vlak MH, Rinkel GJ, Greebe P, Algra A. Independent risk factors for intracranial aneurysms and their joint effect: a case-control study. *Stroke* 2013; **44**: 984-7.

16   Rasing I, Nieuwkamp DJ, Algra A, Rinkel GJ. Additional risk of hypertension and smoking for aneurysms in people with a family history of subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 2012; **83**: 541-2.

17   Woo D, Khoury J, Haverbusch MM et al. Smoking and family history and risk of aneurysmal subarachnoid hemorrhage. *Neurology* 2009; **72**: 69-72.

18   Connolly ESJr, Choudhri TF, Mack WJ et al. Influence of smoking, hypertension, and sex on the phenotypic expression of familial intracranial aneurysms in sibling. *Neurosurg* 2001; **48**: 64-8.

19   Lindekleiv H, Sandvei MS, Romundstad PR et al. Joint effect of modifiable risk factors on the risk of aneurysmal subarachnoid hemorrhage: a cohort study. *Stroke* 2012; **43**: 1885-9.

20   Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol* 2011; **10**: 626-36.

21   Kwak R, Niizuma H, Suzuki J. Hemodynamics in the anterior part of the circle of Willis in patients with intracranial aneurysms: a study of cerebral angiography. *Tohoku J Exp Med* 1980; **132**: 69-73.

22   Velthuis BK, van Leeuwen MS, Witkamp TD et al. Surgical anatomy of the cerebral arteries in patients with subarachnoid hemorrhage: comparison of computerized tomography angiography and digital subtraction angiography. *J Neurosurg* 2001; **95**: 206-12.

23   Tarulli E, Fox AJ. Potent risk factor for aneurysm formation: termination aneurysms of the anterior communicating artery and detection of A1 vessel asymmetry by flow dilution. *AJNR Am J Neuroradiol* 2010; **31**: 1186-91.

24   Li J. Dynamics of the vascular system. 2004.

25   Rossitti S, Lofgren J. Optimality principles and flow orderliness at the branching points of cerebral arteries. *Stroke* 1993; **24**: 1029-32.

26   Rossitti S, Lofgren J. Vascular dimensions of the cerebral arteries follow the principle of minimum work. *Stroke* 1993; **24**: 371-7.

27   Farnoush A, Avolio A, Qian Y. Effect of bifurcation angle configuration and ratio of daughter diameters on hemodynamics of bifurcation aneurysms. *AJNR Am J Neuroradiol* 2013; **34**: 391-6.

28   Jou LD, Lee DH, Mawad ME. Cross-flow at the anterior communicating artery and its implication in cerebral aneurysm formation. *J Biomech* 2010; **43**: 2189-95.

29   Castro MA, Putman CM, Sheridan MJ, Cebral JR. Hemodynamic patterns of anterior communicating artery aneurysms: a possible association with rupture. *AJNR Am J Neuroradiol* 2009; **30**: 297-302.

30   Baek H, Jayaraman MV, Karniadakis GE. Wall shear stress and pressure distribution on aneurysms and infundibulae in the posterior communicating artery bifurcation. *Ann Biomed Eng* 2009; **37**: 2469-87.

31   Meng H, Tutino VM, Xiang J, Siddiqui A. High WSS or Low WSS? Complex Interactions of Hemodynamics with Intracranial Aneurysm Initiation, Growth, and Rupture: Toward a Unifying Hypothesis. *AJNR Am J Neuroradiol* 2014; **35**: 1254-62.

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32   Sandvei MS, Romundstad PR, Muller TB, Vatten L, Vik A. Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway. *Stroke* 2009; **40**: 1958-62.

33   Mackey J, Brown RD, Jr., Moomaw CJ et al. Unruptured intracranial aneurysms in the Familial Intracranial Aneurysm and International Study of Unruptured Intracranial Aneurysms cohorts: differences in multiplicity and location. *J Neurosurg* 2012; **117**: 60-4.

34   Chmayssani M, Rebeiz JG, Rebeiz TJ, Batjer HH, Bendok BR. Relationship of growth to aneurysm rupture in asymptomatic aneurysms </= 7 mm: a systematic analysis of the literature. *Neurosurgery* 2011; **68**: 1164-71.

35   Cebral JR, Mut F, Weir J, Putman CM. Association of hemodynamic characteristics and cerebral aneurysm rupture. *AJNR Am J Neuroradiol* 2011; **32**: 264-70.

36   Yasuno K, Bilguvar K, Bijlenga P et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. *Nat Genet* 2010; **42**: 420-5.

37   Vlak MH, Rinkel GJ, Greebe P, Algra A. Risk of Rupture of an Intracranial Aneurysm Based on Patient Characteristics: A Case-Control Study. *Stroke* 2013; **44**: 1256-9.

38   Shiue I, Arima H, Hankey GJ, Anderson CS. Modifiable lifestyle behaviours account for most cases of subarachnoid haemorrhage: a population-based case-control study in Australasia. *J Neurol Sci* 2012; **313**: 92-4.

39   Hasan DM, Mahaney KB, Brown RD, Jr. et al. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. *Stroke* 2011; **42**: 3156-62.

40   Bromberg JEC, Rinkel GJE, Algra A et al. Subarachnoid haemorrhage in first and second degree relatives of patients with subarachnoid haemorrhage. *BMJ* 1995; **311**: 288-9.

41   Connolly ES, Jr., Rabinstein AA, Carhuapoma JR et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke* 2012; **43**: 1711-37.

42   Steiner T, Juvela S, Unterberg A et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis* 2013; **35**: 93-112.

43   Ronkainen A, Hernesniemi J, Puranen M et al. Familial intracranial aneurysms. *Lancet* 1997; **349**: 380-4.

44   Wermer MJ, Rinkel GJE, van Gijn J. Repeated screening for intracranial aneurysms in familial subarachnoid hemorrhage. *Stroke* 2003; **34**: 2788-91.

45   de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry* 2007; **78**: 1365-72.

46   Broderick JP, Brown RD, Jr., Sauerbeck L et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. *Stroke* 2009; **40**: 1952-7.

47   Ruigrok YM, Rinkel GJE, Algra A, Raaymakers TWM, van Gijn J. Characteristics of intracranial aneurysms in patients with familial subarachnoid hemorrhage. *Neurology* 2004; **62**: 891-4.

48   Kleinloog R, van 't Hof FN, Wolters FJ et al. The association between genetic risk factors and the size of intracranial aneurysms at time of rupture. *Neurosurgery* 2013; **73**: 705-8.

49   Brown RD, Jr., Huston J, Hornung R et al. Screening for brain aneurysm in the Familial Intracranial Aneurysm study: frequency and predictors of lesion detection. *J Neurosurg* 2008; **108**: 1132-8.

50   Bor AS, Rinkel GJ, Adami J et al. Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case-control study. *Brain* 2008; **131**: 2662-5.

51   Teasdale GM, Wardlaw JM, White PM et al. The familial risk of subarachnoid haemorrhage. *Brain* 2005; **128**: 1677-85.

52   Raaymakers TWM, Rinkel GJE, van Gijn J et al. Risks and benefits of screening of intracranial aneurysms in first-degree relatives of patients with sporadic subarachnoid hemorrhage. *N Engl J Med* 1999; **341**: 1344-50.

53   Wermer MJ, van der Schaaf IC, Van Nunen P et al. Psychosocial impact of screening for intracranial aneurysms in relatives with familial subarachnoid hemorrhage. *Stroke* 2005; **36**: 836-40.

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Summary

Unruptured intracranial aneurysms may rupture, causing subarachnoid haemorrhage (SAH). SAH is a devastating subtype of stroke, resulting in death or severe disability in half the patients, and therefore is best prevented. Intracranial aneurysms are not present at birth, but develop during life. Larger aneurysms have a higher risk of rupture than small aneurysms, however what determines whether aneurysms grow or remain stable over time is unclear. Therefore, more distinct risk factors would be welcome to separate small aneurysms that will most likely never rupture, from small aneurysms that are likely to grow and/or rupture. Part I of this thesis aims to find risk factors for aneurysm growth and/or rupture. Persons with two or more first degree relatives with SAH have an increased risk of SAH themselves, and screening for unruptured aneurysms may be warranted in these persons. Part II of this thesis aims to provide more information on screening for unruptured aneurysms in persons with two or more first degree relatives with SAH.

Part I: Risk factors for aneurysm development

Chapter 2 describes a cohort study analysing the relation between aneurysm development during follow-up and arterial configuration, being arterial diameter and bifurcation angles. For this study, aneurysms from several sites were analysed en bloc. A hypoplastic branch in a bifurcation and sharp bifurcation angles were both related to aneurysm development. To gain more insight in aneurysm development and rupture per aneurysm site, chapter 3 describes a case-control study focusing specifically on two sites: the anterior and posterior communicating artery. Two separate analyses were performed for each site: arterial diameter in relation to aneurysm presence (including ruptured as well as unruptured aneurysms), and arterial diameter in relation to presence of a ruptured rather than an unruptured aneurysm. In this study, asymmetry of the anterior cerebral arteries is related to aneurysm presence at the ACoA, and larger diameter of the posterior communicating artery is related to aneurysm presence at the PCoA, though not to aneurysm rupture. A trend was observed towards a relation between dominance of the posterior communicating artery and aneurysm rupture. In chapter 4 a case control study was performed, in which patient- related risk factors such as smoking, hypertension and gender were compared between aneurysm sites. In comparison to persons with an ACoA aneurysm, persons with an aneurysm at the middle cerebral artery (MCA) were younger, persons with a PCoA aneurysm were more often female, and persons with an aneurysm of the basilar artery (BA) were more often teetotaller. This indicates that patient-related risk factors do not merely increase the risk of aneurysm development and

rupture in general, but may influence the actual location of the aneurysm that ruptures. In chapter 5, data from Toronto and Utrecht was combined to create a large follow-up study including 363 patients with 468 unruptured aneurysms. Risk factors for aneurysm growth were analysed, showing aneurysm size, shape of the aneurysm (multilobarity and dome-neckratio) and smoking to be risk factors for aneurysm growth.

Part II: Familial intracranial aneurysms

Chapter 6 analyses the risk of SAH according to the number of first degree relatives with SAH. In this large population-based case-control study, the incidence of SAH is compared between persons without a relative with SAH, with one relative with SAH and with two or more relatives with SAH (familial SAH). In this study, the increased risk of SAH in familial SAH is clearly shown, as persons with one first degree relative with SAH have a slightly increased risk of SAH (OR 2.2; 95% CI 1.8–2.6), whereas persons with two or more first degree relatives with SAH have a markedly increased risk of SAH (OR 51; 95% CI 9–1117). This markedly increased risk of SAH is equal to a substantial life time risk of SAH, and thus makes preventive screening for unruptured aneurysms in these persons an attractive alternative. In chapter 7, the theoretical optimal screening strategy is calculated, using a Markov model to calculate cost-effectiveness of 54 screening strategies. With the data available at this point, any form of screening is cost effective in persons with familial SAH, with repeated screening every 3–7 years, from age 20–80 as the most cost effective strategy. Chapter 9 shows the results of the clinical screening programme that the University Medical Center Utrecht has been offering to persons with familial SAH for the past 20 years, from 1994 to 2014. In this programme, persons are offered screening with the advice to repeat screening every 5 years. In total 458 persons decided to have at least one screening angiography, and 114 aneurysms were found in 82 angiographies in 72 persons. Per screening cycle around 5% of the angiographies show a newly diagnosed intracranial aneurysm. Risk factors for an aneurysm at the initial screening are smoking and three or more first degree relatives with SAH (as opposed to exactly two first degree relatives with SAH). Persons with a previous aneurysm have an increased risk of a new aneurysm at the initial screening, as well as at follow-up screening. Nonetheless, five (3%; 95% CI 1–6) of 188 persons without a history of aneurysms and with two negative screenings had a *de novo* aneurysm in further follow-up screening. The results of this clinical study support repeated screening from an early age (20 years old) until an age at which the risks of preventive treatment of an (possible) aneurysm do not outweigh the risks of natural history of a (possible) aneurysm (usually at age 65–70 years old). Two patients had SAH despite adherence to the screening programme:

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one patient developed a *de novo* aneurysm that ruptured 3 years after the last negative screening, and one patient with two small (2 and 4 mm) unruptured aneurysms found with screening and left untreated, had SAH from one of these aneurysms 8 months after a stable follow-up imaging. This underscores that screening may lower the risk of SAH, but cannot completely eradicate this risk.

With this thesis, some new information has been gathered on initial and follow-up screening of unruptured intracranial aneurysms. As often in an interesting field of research, new questions arise more quickly than that they can be answered. I therefore conclude this summary with the everlasting wisdom that more research is needed, to build a prediction model for development and growth of unruptured intracranial aneurysms, and to find the optimal screening strategy for persons with familial SAH.

Samenvatting

Intracraniële aneurysmata zijn uitstulpingen in de slagaders van de hersenen. Deze uitstulpingen (aneurysmata) kunnen in de loop van het leven ontstaan, groeien, en knappen (ruptureren). Bij ruptureren van een aneurysma ontstaat een subarachnoïdale bloeding (SAB). Een SAB is een ernstig type beroerte die met name jonge mensen treft; de helft van de mensen met een SAB overlijdt of houdt een ernstige handicap. Met de huidige beeldvormende technieken kunnen de slagaders van de hersenen eenvoudig worden afgebeeld met een (CT- of MR-) angiografie. Met het toenemend aantal angiografiën werd duidelijk dat ongeruptureerde aneurysmata vrij frequent voorkomen, in ongeveer 3% van de bevolking. SAB's zijn daarentegen zeer zeldzaam, slechts (±) 0.5% van de mensen krijgt gedurende zijn/haar leven een SAB. Hieruit kan worden geconcludeerd dat kennelijk slechts een beperkt deel van de gevonden (ongeruptureerde) aneurysmata uiteindelijk knapt en een SAB veroorzaakt. Er zijn mensen die een sterk verhoogd risico hebben op een SAB, bijvoorbeeld mensen met een familiaire aanleg voor het ontwikkelen van SAB's. Hoe hoog het absolute risico op een SAB is voor iemand met een familiaire belasting voor SAB's is onbekend, maar SAB's komen in deze families zo vaak voor, dat zoeken naar (screenen op) ongeruptureerde aneurysmata voor deze families zinvol wordt geacht.

Het is namelijk mogelijk om ongeruptureerde aneurysmata preventief te behandelen om te voorkomen dat ze een SAB veroorzaken, door ze af te sluiten van de circulatie met een operatie (middels clippen of coilen). Operaties aan slagaders van de hersenen zijn echter niet zonder risico. Bij voorkeur wordt preventieve behandeling daarom alleen toegepast op gevaarlijke aneurysmata met een grote kans op ruptureren. Omdat met de huidige angiografiën frequent ongeruptureerde aneurysmata gevonden worden, is het belangrijk om accuraat onderscheid te kunnen maken tussen gevaarlijke aneurysmata (die ruptureren) en onschuldige aneurysmata (die stabiel blijven). Aan het begin van dit proefschrift was reeds aannemelijk dat de grootte van een aneurysma een positieve relatie heeft met de kans op ruptuur (hoe groter het aneurysma, des te hoger de kans op ruptuur). De meeste aneurysmata die gevonden worden zijn echter klein, en hebben een daarmee een klein risico op ruptuur. Deze kleine aneurysmata worden over het algemeen periodiek (bijvoorbeeld jaarlijks) vervolgd met een angiografie, met de gedachte dat de kleine aneurysmata die groeien op een vervolgangiografie een hoger risico hebben om te ruptureren, en dus behandeld dienen te worden. In dit proefschrift wordt gekeken naar twee onderwerpen: (I) is het mogelijk om bij ongeruptureerde aneurysmata onderscheid te maken tussen gevaarlijke en ongevaarlijke aneurysmata, en (II) wat is de plaats van screening bij mensen met een familiaire belasting voor SAB's.

Deel I: risicofactoren voor de ontwikkeling van aneurysmata

In hoofdstuk 2 werd een vergelijking gemaakt tussen 26 mensen bij wie zich gedurende follow-up-onderzoek een aneurysma ontwikkelde en 78 mensen die geen aneurysma kregen. Het verband tussen de anatomie van de vertakkingen in de vaatboomstructuur en de ontwikkeling van aneurysmata werd geanalyseerd, waarbij hoeken en diameters van de vaten werden vergeleken tussen vaatsplitsingen die wel of niet een aneurysma ontwikkelden. Er lijkt een verhoogd risico op aneurysmaontwikkeling te zijn voor vaatsplitsingen waarbij een van de afsplitsende vaten opvallend klein is (hypoplastisch), en voor vaatsplitsingen waarbij de afsplitsende vaten scherp afbuigen van de eerdere stroomrichting.

Aneurysmata komen doorgaans voor op specifieke voorkeurslocaties in de intracraniële vaatboomstructuur (de cirkel van Willis). Voor het onderzoek in hoofdstuk 2 werden al deze locaties gezamenlijk geanalyseerd. In hoofdstuk 3 werd een selectie gemaakt van twee veel voorkomende aneurysmalocaties: de vertakking van de arteria cerebri anterior (ACA) ter plaatse van de arteria communicans anterior (ACoA) en de vertakking van de arteria carotis interna (ICA) ter plaatse van de arteria communicans posterior (PCoA). Voor deze twee vertakkingen werden de vaatdiameters vergeleken in mensen zonder aneurysma, mensen met een ongeruptureerd aneurysma, en mensen met een geruptureerd aneurysma. De aanwezigheid van aneurysmata op de ACoA en PCoA blijkt gerelateerd aan een grotere vaatdiameter van de vertakkende arterie (respectievelijk de ACA en de PCoA). Daarnaast blijkt de aanwezigheid van een geruptureerd PCoA aneurysma mogelijk geassocieerd met een grotere vaatdiameter van de PCoA, maar dit kon niet met zekerheid worden aangetoond. Concluderend lijkt een abnormaal grote vaatdiameter van de ACA en de PCoA eerder een risicofactor voor het ontstaan van een aneurysma op de aangrenzende vertakking (ACoA en PCoA), dan een risicofactor voor ruptureren van een aneurysma op deze plek.

Hoofdstuk 2 en 3 beschreven variaties ter plaatse in de cirkel van Willis waar een aneurysma kan ontstaan: de lokale risicofactoren. Ook patiëntgebonden risicofactoren, zoals leeftijd, hoge bloeddruk en roken, spelen een rol bij de ontwikkeling en ruptuur van aneurysmata. In hoofdstuk 4 werd onderzocht of deze patiëntgebonden risicofactoren geassocieerd waren met specifieke aneurysmalocaties. Omdat aneurysmata op de ACoA in deze studie het meest voorkwamen, werden mensen met aneurysmata op deze locatie als norm genomen. Vergeleken met mensen met een ACoA aneurysma waren mensen met een aneurysma op de arteria cerebri media jonger, waren mensen met een PCoA aneurysma vaker vrouwen en waren mensen met aneurysma op de arteria basilaris vaker geheelonthouder. Hoge bloeddruk, roken en alcoholmisbruik lijken niet geassocieerd met een specifieke voorkeurslocatie.

Deze bevindingen onderstrepen de complexiteit van de ontwikkeling en ruptuur van aneurysmata.

Hoofdstuk 5 bevat de resultaten van een follow-up-studie, waarbij aneurysmata die (uiteindelijk) groeiden vergeleken werden met aneurysmata die stabiel bleven in grootte. In totaal 363 patiënten met een ongeruptureerd aneurysma ondergingen herhaaldelijk een angiografie. Patiëntgebonden risicofactoren zoals hoge bloeddruk, roken, geslacht en leeftijd, werden genoteerd. In de eerste angiografie werden diverse lokale risicofactoren gescoord, zoals locatie, grootte en vorm van het aneurysma en vaathoeken van de afsplitsing van de vaatboom nabij het aneurysma. Uiteindelijk groeide 12% (57 van 468) van de ongeruptureerde aneurysmata gedurende een mediane follow-up-tijd van 2 jaar. Van alle mogelijke risicofactoren die waren gescoord bleken twee lokale risicofactoren geassocieerd met groei: de grootte en de vorm van het aneurysma (dome-neck-ratio: verhouding tussen de breedte van het aneurysma en de breedte van de hals van het aneurysma). De locatie van het aneurysma in de cirkel van Willis en de vorming van een uitstulpsel op het aneurysma (multilobariteit) bleken mogelijk geassocieerd met groei. Omdat met name bij kleine aneurysmata onduidelijk is welke aneurysmata zullen ruptureren, werd een subanalyse gedaan met alleen kleine aneurysmata (< 7 mm op de eerste angiografie). Van de kleine aneurysmata bleek 9% (37 van 403) gegroeid. Roken en multilobariteit bleken hierbij risicofactoren voor groei. *Mogelijke* risicofactoren voor groei waren locatie en de vorm van het aneurysma (dome-neck-ratio). Voor kleine aneurysmata bleek grootte geen onafhankelijke risicofactor voor groei; klein of heel klein maakt kennelijk niet uit voor de kans op groei.

Deel II: familiaire intracraniële aneurysmata

Uit eerder onderzoek was reeds bekend dat mensen met twee of meer eerstegraads familieleden met een SAB een verhoogd risico hebben om zelf ook een SAB te krijgen. Hoe hoog het absolute risico op een SAB is voor iemand met een belaste familieanamnese, is niet bekend. In hoofdstuk 6 werd gekeken naar het risico op een SAB afhankelijk van het aantal eerstegraads verwanten met SAB. Dit case-control-onderzoek werd uitgevoerd door Zweedse landelijke databases met informatie te koppelen: patiënten die tussen 2001 en 2005 de diagnose SAB kregen (5.282 patiënten), werden ieder gematched met 5 controlepersonen (26.402 personen). Vervolgens werden alle eerstegraads verwanten van deze mensen achterhaald via een geboorteregister (130.373 verwanten). Daarna werd gekeken of deze verwanten de ziekenhuisdiagnose SAB hadden. Uit deze analyse bleek dat

mensen met 1 eerstegraads familielid met een SAB een iets verhoogd risico lopen om zelf een SAB te krijgen (OR 2.2; 95% CI 1.8–2.6). Opvallend genoeg lopen mensen met twee of meer eerstegraads familieleden met een SAB een excessief veel hoger risico op een SAB (OR 51; 95% CI 9–1117). De aanzienlijke breedte van het betrouwbaarheidsinterval, ondanks de eveneens aanzienlijke grootte van de databases, illustreren de zeldzaamheid van familiaire subarachnoïdale bloedingen, wat het bepalen van absolute risico's bemoeilijkt. Zeker is dat het risico op een SAB voor een individu met twee of meer eerstegraads familieleden met een SAB substantieel is, terwijl het voor de normale bevolking en voor mensen met een enkel familielid met een SAB beschouwd mag worden als een verwaarloosbaar risico.

Eerdere studies toonden aan dat het niet kosteneffectief is om te screenen bij mensen die een laag risico op een SAB hebben. Doordat mensen met twee of meer eerstegraads familieleden met SAB een substantieel risico op een SAB hebben gedurende hun leven, wordt screenen op ongeruptureerde aneurysmata relevant(er) voor deze mensen met familiaire SAB. Als ongeruptureerde aneurysmata worden opgespoord en behandeld voordat ze ruptureren, zullen waarschijnlijk minder SAB's optreden in deze families, en is het waarschijnlijk kosteneffectief om te screenen. Ter onderbouwing van deze theorie werd in hoofdstuk 8 een computersimulatiemodel gebouwd, dat de kosteneffectiviteit van screenen in verschillende screeningsstrategieën afzette tegen het natuurlijke beloop bij personen met twee of meer eerstegraads familieleden met een SAB. Uit de analyses bleek dat screenen in iedere vorm kosteneffectiever is dan afwachten voor mensen met familiaire SAB. De meest kosteneffectieve strategie is om iedere 5–7 jaar te screenen bij personen tussen 20 tot 80 jaar oud.

Het UMC Utrecht biedt sinds 1994 screening aan voor mensen met twee of meer eerstegraads familieleden met een SAB, met het advies de screening iedere 5 jaar te herhalen. De resultaten van 20 jaar screenen werden omschreven in hoofdstuk 8. In deze 20 jaar ondergingen 458 personen minimaal 1 screenende angiografie. Hierbij werden in totaal 114 ongeruptureerde aneurysmata gevonden. In iedere screeningsronde laat ongeveer 5% van de angiografieën een nieuw, niet eerder gediagnosticeerd aneurysma zien. Risicofactoren voor een aneurysma bij de eerste screening waren roken en het hebben van 3 of meer (in tegenstelling tot exact 2) eerstegraads familieleden met een SAB. Mensen met een eerder aneurysma hebben een hogere kans op een nieuw aneurysma bij screening. Desondanks werd bij 5 van 188 personen (3%; 95% CI 1–6) die nooit een aneurysma hadden gehad, inclusief een 1e en 2e screeningsronde zonder aneurysmata, een nieuw aneurysma gevonden in verdere follow-up-screening (3e of 4e screeningsronde). De bevindingen van deze studie laten zien dat screenen in principe herhaald moet worden tot het natuurlijk beloop van een (eventueel) aneurysma

opweegt tegen (eventueel) preventief ingrijpen indien een aneurysma bij screening gevonden wordt (gewoonlijk tot een persoon 65–70 jaar oud is, bij gezondheidsproblemen eerder). Screenen en indien nodig behandelen kan het risico op een SAB wel verkleinen, maar niet volledig wegnemen. Dit werd duidelijk door twee patiënten die tijdens (ondanks) het screeningprogramma een SAB kregen.

Met dit proefschrift zijn enkele substantiële stappen gezet in het denken over het zoeken naar en vervolgen van ongeruptureerde intracraniële aneurysmata. Hierbij worden, zoals niet geheel ongebruikelijk, nieuwe vragen sneller opgeworpen dan ze beantwoord kunnen worden. Ik besluit deze samenvatting dan ook graag met de stelling dat meer onderzoek van essentieel belang is, opdat een predictiemodel gebouwd kan worden dat groei en ruptuur voor kleine ongeruptureerde aneurysmata accuraat voorspelt, en opdat screeningstrategiën voor mensen met een verhoogd risico op subarachnoïdale bloedingen worden geoptimaliseerd.

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Dankwoord

Dit proefschrift is tot stand gekomen dankzij de hulp en ondersteuning van veel mensen. Graag wil ik op deze plaats een aantal mensen persoonlijk bedanken.

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* "If you understand me correctly, I can say that choosing depends not so much on making the right choice as on the energy, the gravity, and the passion with which one chooses. In this the Personality announces itself in its inner endlessness, and thereby again the Personality is consolidated. Even then, if a man made the wrong choice, exactly because of the energy with which he chose, he could come to the awareness that he made the wrong choice." (S. Kierkegaard)

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maakt dat ik me altijd welkom voel, ook tijdens spitsuur in een gezin met (inmiddels drie!) superenthousiaste kiddo's, waarvoor dank!

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Lieve Annemieke. Vanaf de eerste dag dat we elkaar ontmoetten in het Goois Jeugd Orkest hadden we de grootste lol. Als combinatie altviool-cello hebben we eindeloos samengespeeld. Ook toen we niet meer samenspeelden, bleven we in eenzelfde toonsoort en maat door het leven lopen, waardoor de muziek tussen ons vaak verrassend goed klopt. Nu sta je achter mij, binnenkort sta ik hopelijk achter jou. De laatste loodjes zijn in zicht!

Lieve Nienke. Wij ontmoetten elkaar in Groningen bij de start van de geneeskundestudie en zijn sindsdien bij vlagen onafscheidelijk. Ik denk nog geregeld aan je vrolijke en geduldige lessen in onderhandelen in Marokko en India, en de cursus 'overtuigend autorijden' in Italië en Spanje. Wat hebben we veel mensen gesproken en wat hebben we veel mooie dingen gezien samen. Ik ben blij jou achter me te weten bij dit onderdeel van mijn wetenschappelijke reis. Ook voor jou is de bestemming bijna bereikt!

Tenslotte: Joost. Jij kwam in mijn leven op een moment dat ik me begon te realiseren dat er meer is in het leven dan alleen werken. Je opende het inzicht dat het genoeg is om te zijn, in plaats van te worden. Met jou ben ik meer mij dan alleen, in jou ontmoet ik de schoonheid van gedeelde waarden als rechtvaardigheid, oprechtheid, compassie en vriendschap. Jij maakt de wereld tot een mooiere plaats en maakt me trots en blij met jou te zijn. Ik kan niet wachten om samen met jou de wereld nog mooier te maken, en hoop, nu dit boekje af is, de vrijheid te krijgen en te nemen om met jou nog vele avonturen te beleven.

Curriculum Vitae

Stijntje Bor was born on the 1st of May 1981 in Amsterdam, the Netherlands. After gradu-ating from the Comenius College in Hilversum in 1999, she moved to Groningen to study Greek and Latin Languages and Cultures. During her first year, she discovered that these ancient languages would probably not fulfil her expectations for a life-long occupation.* She analysed the drawbacks in the choice for GLLC, and then searched for their opposites: a field with ever-expanding knowledge, challenging visions, impact on society, interdisciplinary communication, ethical questions, and human interest. She thus transferred her studies to medicine in Groningen in 2000. During her study she enrolled in the Junior Scientific Masterclass, and participated in some research projects. In 2006 she came to Utrecht for a 6-month scientific internship under the direct supervision of prof. dr. G.J.E. Rinkel. This project resulted in a published article and was rewarded with the Frits the Waard Award in 2008. In February 2007 she obtained her medical degree and started her training to become a neurologist at the University Medical Center Utrecht under supervision of prof. dr. J. Van Gijn and prof. dr. J.H.J. Wokke. The article that resulted from the scientific internship became the first chapter of this thesis, under supervision of prof. dr. G.J.E. Rinkel, dr. M.J.H. Wermer and dr. B.K. Velthuis. Stijntje received the Junior Investigators Award at the European Stroke Conference twice; in 2008 in Nice for the study described in chapter 6, and in 2012 in Lisbon for the study described in chapter 8 of this thesis. She expects to finish her neurology training in August 2016.

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*This epiphany came when she discovered a 10 cm thick book in the library that contained every single mention of the word "εκ" in every single ancient Greek text, with the sole purpose to clarify the exact meaning of this two-letter word for every specific sentence. She acknowledged that it was unlikely that she would be the one to add any knowledge to this beautiful field of science that is static (being "the dead languages") and has been studied this thoroughly and lovingly by scholars before her time.

List of publications

This thesis

Bor AS, Velthuis BK, Majoie CB, Rinkel GJ. Configuration of intracranial arteries and development of aneurysms: a follow-up study. *Neurology* 2008; **70**: 700-5.

Bor AS, Wermer MJ, Velthuis BK, Rinkel GJ. Development and rupture of anterior and posterior communicating artery aneurysms in relation to anatomic variations. *Submitted.*

Lindner SH, Bor AS, Rinkel GJ. Differences in risk factors according to the site of intracranial aneurysms. *J Neurol Neurosurg Psychiatry* 2010; **81**: 116-8.

Bor AS, Tiel Groenestege AT, terBrugge KG, Agid R, Velthuis BK, Rinkel GJ, Wermer MJ. Clinical, radiological and flow related risk factors for growth of untreated unruptured intracranial aneurysms. *In revision.*

Bor AS, Rinkel GJ, Adami J et al. Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case-control study. *Brain* 2008; **131**: 2662-5.

Bor AS, Koffijberg H, Wermer MJ, Rinkel GJ. Optimal screening strategy for familial intracranial aneurysms: a cost-effectiveness analysis. *Neurology* 2010; **74**: 1671-9.

Bor AS, Rinkel GJ, van NJ, Wermer MJ. Long-term, serial screening for intracranial aneurysms in individuals with a family history of aneurysmal subarachnoid haemorrhage: a cohort study. *Lancet Neurol* 2014; **13**: 385-92.

Other publications

Bor AS, Wermer MJ, Rinkel GJ. Unruptured intracranial aneurysms:initial and follow-up screening. *Future Neurology* 2010; **5**: 4211-431

Bor AS, Niemansburg SL, Wermer MJ, Rinkel GJ. Anosmia after coiling of ruptured aneurysms: prevalence, prognosis, and risk factors. *Stroke* 2009; **40**: 2226-8.

Backes D, Vergouwen MD, Velthuis BK et al. Difference in aneurysm characteristics between ruptured and unruptured aneurysms in patients with multiple intracranial aneurysms. *Stroke* 2014; **45**: 1299-303.