# Subarachnoid haemorrhage and the life after

# Subarachnoid haemorrhage and the life after

Leven na een subarachnoïdale bloeding
(met een samenvatting in het Nederlands)

**Proefschrift**

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door

**Jannetje Greebe**

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**Promotor**: Prof.dr A. Algra

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***Voor hen die ik lief heb***

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# Contents

# Chapter 1

# General introduction

**Subarachnoid haemorrhage** (SAH) is a subset of stroke: the incidence is approximately 9 per 100.000 person-years.[1] Causes for SAH are rupture of an intracranial aneurysm (80%), a so called perimesencephalic nonaneurysmal haemorrhage (10%), intracranial artery dissection, and miscellaneous rare causes. It often occurs at a relatively young age: half of the patients are younger than 55 years old. A majority of the patients is women (66%). Most instances of SAH are sporadic, but in 10% there is a positive family history.[2, 3] The overall prognosis after SAH from rupture of an intracranial aneurysm is poor: 35% of the patients dies within the initial 4 weeks after the haemorrhage[4] and 30% of the survivors remains dependent for activities of daily life.[5] Because of the young age at onset and the poor prognosis, the loss of productive life years from aneurysmal SAH (ASAH) in the general population is as large as that from brain infarcts, the most common type of stroke.[6] Furthermore life expectancy is reduced after ASAH, probably from an excess of cardiovascular diseases.[4] Patients with a good outcome, still have symptoms and a reduced quality of life (QoL) on both physical and psychosocial domains.[5] A common disabling factor after an aneurysmal SAH is anosmia. The presumed cause of anosmia after ASAH is spurting of blood under arterial pressure or treatment by clipping.[7-9]

In contrast with ASAH the prognosis after a perimesencephalic subarachnoid haemorrhage (PMH) is good.[10] This haemorrhage does not reduce quality of life or capacity to work.[11] However it is unknown if life expectancy is reduced and if anosmia occurs in this type of haemorrhage.

This thesis describes a series of observational studies on the long–term outcome and life-expectancy in ASAH patients or a PMH. In all studies the follow-up was done by one research nurse.

To determine the proportion of ASAH in patients with a positive family history we contacted all first and second degree relatives in a consecutively admitted cohort of patients with a SAH from a ruptured aneurysm (***Chapter 2***).

Serial follow-up after ASAH is not easy to perform. In outpatient clinic follow-up is time-consuming and expensive. Since part of the former patients resumes daily

work, many of those cannot be contacted by telephone during office hours. We therefore assessed the feasibility of follow-up through e-mail (***Chapter 3***).

Prognosis after PMH is good in terms of risk of recurrence, working capacity and quality of life. Life expectancy is reduced after ASAH, probably because of an excess of cerebro- and cardiovascular diseases. Whether life expectancy is reduced after PMH is unknown. We performed a long term follow-up study to assess life expectancy after PMH (***Chapter 4***).

Anosmia frequently occurs after ASAH not only after clipping, but also after coiling; however, it does not occur after coiling of an unruptured aneurysm. It is unknown whether anosmia is related to the presence of blood in de basal cisterns or to rupture of the aneurysm with sudden increase in intracranial pressure. Although the cause of PMH has not yet been identified, the invariably good clinical condition at onset, the often more gradual onset of headache and the localized nature of the blood on computed tomography (CT) all argue against spurting of blood under arterial pressure and favour a venous oozing of blood.[12] A venous source is further supported by the normal arteriogram and often abnormal findings in venous drainage in PMH patients.[13] We studied anosmia in PMH to determine whether anosmia is related to the sudden increase of the intracranial pressure during aneurysmal rupture or to the presence of blood. ***Chapter 5*** describes the prevalence of anosmia after PMH.

Of the patients who survive an episode of SAH from a ruptured aneurysm approximately 8% is discharged to a nursing home. In general, most patients admitted to nursing homes are elderly patients often with degenerative diseases and comorbidity, and their life expectancy is usually short. In a retrospective cohort study, 35% of nursing home residents had died within one year.[14] Because patients with SAH are generally young, they may improve, become functionally independent and eventually resume independent living. In ***Chapter 6*** we describe the long-term outcome of patients admitted to a nursing home after SAH and their chances of recovery to a state enabling living independently.

Patients without disability after an ASAH often have neuropsychological and psychosocial sequellae that impair quality of life, but this may improve over years. In

***Chapter 7*** we describe a long-term follow-up study on functional outcome and quality of life in patients 5 and 12.5 years after the haemorrhage.

***Chapter 8*** (general discussion) describes the main conclusions from the studies in this thesis, their implications for clinical practice and recommendations for future studies.

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# Chapter 2

# Family history of subarachnoid haemorrhage: supplemental value of scrutinising all relatives

P. Greebe RN, J.E.C. Bromberg MD, G.J.E. Rinkel MD, A. Algra MD,
J. van Gijn MD, FRCPE.

*J Neurol Neurosurg Psychiatry 1997;62:273-275*

# Abstract

### Objective and methods

To assess the validity of the family history obtained at the bedside of patients with recent subarachnoid haemorrhage by subsequently contacting all first and second degree relatives, with verification from medical record data.

### Results

In a prospectively collected series of 163 patients with recent subarachnoid haemorrhage we assessed the history or cause of death could be ascertained in 1259 (98%) of the first degree relatives and in 3038 (85%) of the second degree relatives. For first degree relatives only, the sensitivity of the family history at the bed-side was 0.75 (95% CI 0.35-0.97) and the positive predictive value was 0.55 (95% CI 0.23-0.83); for first and second degree relatives together the sensitivity was 0.58 (95% CI 0.28-0.85) and the positive predictive value 0.64 (95% CI 0.31-0.89).

### Conclusion

The accuracy of the family history taken at the bedside is modest; a more thorough collection of data is crucial if the decision is taken to screen relatives based on the family history.

## Introduction

In 6% to 9% of patients with subarachnoid haemorrhage (SAH) the disorder is familial,[1] and in these familial cases outcome is worse.[2] If screening for and treatment of aneurysms in asymptomatic relatives is considered, it is important to be accurately informed about the family history. The most exact method to ascertain the number of relatives and the nature of any illnesses is to construct a pedigree for each patient to subsequently interview all relatives personally and to then verify this information with medical documents.

Because it is unknown whether this time-consuming process yields more accurate information than a simple family history obtained at the bedside, we compared the two strategies in a prospective, hospital based series of patients with subarachnoid haemorrhage.

## Patients and methods

A series of 163 patients with aneurysmal subarachnoid haemorrhage established by CT, admitted to the University Hospitals in Utrecht and Rotterdam and the Academic Medical Center in Amsterdam, was prospectively collected from September 1991 to October 1992. In the same period 50 other patients with subarachnoid haemorrhage were admitted and excluded for the following reasons: three patients because a cause other than a ruptured aneurysm was found for the subarachnoid haemorrhage; 36 patients because the patient or the next of kin refused to participate; 10 patients because most relatives lived outside Europe; and one patient because she was adopted and knew nothing of her biological relatives.

Soon after admission patients were asked whether any of their relatives had had a subarachnoid haemorrhage or a stroke. For patients with a depressed level of consciousness, the family history was obtained from the partner, the next of kin or in some instances from both at the same time. These data represent the standard strategy of collecting the 'family history at the bedside'. Our experimental and

extensive strategy was as follows. A pedigree was drawn up for each family and all living relatives known to us were interviewed by telephone, by means of a standard questionnaire. For deceased relatives a next of kin was interviewed about the cause of death. If this informant mentioned a stroke or any other brain disease, all available medical documents were retrieved, including those from abroad. All histories and all medical documents with any relation to subarachnoid haemorrhage were classified independently by two observers (JECB and GJER) as definite subarachnoid haemorrhage, probable subarachnoid haemorrhage, or possible subarachnoid haemorrhage, according to criteria decided on in advance (table 1).

Table 1: Criteria for the diagnosis of SAH in relatives.

| | **medical documents** | **history** |
|---|---|---|
| **definite SAH** | - clinical features<br>*and* blood in basal cisterns on CT<br>*or* xanthochromic CSF<br>*or* aneurysm on angiogram or autopsy | - |
| **probable SAH** | - sudden severe headache<br>*and* normal neurologic examination<br>*and* hemorrhagic CSF<br>*and* sudden deterioration and death within 4 weeks | - in first 4 weeks after "stroke" second ictus followed by death<br>*and* age < 70 |
| **possible SAH** | - sudden severe headache<br>*and* normal neurologic examination<br>*and* angiography not performed<br>*and* haemorrhagic CSF<br>*or*<br>- sudden severe headache<br>*and* focal abnormalities and/or decreased consciousness<br>*and* haemorrhagic or xanthochromic CSF<br>*and* age < 70<br>*or*<br>- sudden death *and* age < 40 | - "stroke", no details<br>*and* age < 50<br>*or*<br>- in first 4 weeks after "stroke" second ictus followed by death<br>*and* age > 70<br>*or*<br>- sudden severe headache necessitating bed rest<br>*and* death within 4 weeks<br>*and* age < 70<br>*and* no medical examination<br>*or*<br>- sudden severe headache followed by loss of consciousness and death<br>*and* age < 70<br>*and* no medical examination |

A diagnosis of definite subarachnoid haemorrhage could be made only from medical records. In five cases the observers did not agree and in these instances the data were classified by a third observer (JvG) after which a decision was made by majority vote.

For the analysis we recorded as positive for the family history at the bedside all episodes classified as probable or possible subarachnoid haemorrhage; most likely these include all instances of definite subarachnoid haemorrhage if records could be retrieved for these relatives. For the extensive search strategy we recorded as positive only episodes classified as definite or probable subarachnoid haemorrhage. The family history given by the patient or the next of kin at the bedside was compared with the information obtained by the extensive strategy; the extensive strategy was considered the "gold standard".

The 163 patients had 1290 first degree and 3588 second degree relatives. The medical history or cause of death could be confirmed in 1259 (98%) first degree relatives and in 3038 (85%) second degree relatives.

## Results

The family history obtained at the bedside identified 11 families in which subarachnoid haemorrhage had previously occurred in one of the relatives (table 2).

Table 2. Number of families with or without familial subarachnoid haemorrhage.

| | interview of all | relatives + | medical data | |
|---|---|---|---|---|
| standard | | SAH | no SAH | |
| fam. history | SAH | 7 (6) | 4 (5) | 11 |
| at bed-side | no SAH | 5 (2) | 147 (150) | 152 |
| | | 12 (8) | 151 (155) | 163 |

The numbers between brackets represent the data when only first degree relatives are taken into account

In seven cases this was correct: in six of these patients it concerned a first degree, in one a second degree relative. In five of these seven patients the relative had died.
For four of the 11 relatives purported to have had a subarachnoid haemorrhage this diagnosis could not be confirmed: one (first degree) relative proved to have had a pontine haemorrhage, another had had a "stroke" but no details could be retrieved. In the other two instances our search strategy did not confirm a subarachnoid haemorrhage in any of the relatives.
In the remaining 152 families the history at the bedside was negative for familial subarachnoid haemorrhage. In five of these 152 families scrutinising the relatives disclosed unreported instances of subarachnoid haemorrhage: in one family a sister, in another family a half brother; and in three families a second degree relative. Three of these five relatives had died. Apart from the 12 relatives with definite or probable subarachnoid haemorrhage there were 12 relatives with possible episodes of subarachnoid haemorrhage that could not be confirmed because medical records were no longer available.
For first degree relatives only, the predictive value of a bedside history positive for familial subarachnoid haemorrhage was 0.55 (95% CI: 0.23-0.83) and the sensitivity was 0.75 (95% CI: 0.35-0.97). For the first and second degree relatives combined the predictive value of a positive family history of subarachnoid haemorrhage was 0.64 (95% CI: 0.31-0.89) and the sensitivity was 0.58 (95% CI: 0.28-0.85).

## Discussion

In our study one quarter of the families with a positive history for subarachnoid haemorrhage in a first degree relative would have been undetected without the information provided by scrutinising all individual relatives; if second degree relatives are also taken into account, the proportion of undetected families rose to almost a half. The poor sensitivity of family history for subarachnoid haemorrhage shows that the frequency of "familial subarachnoid haemorrhage" in other studies has probably

been underestimated as in none of these studies were the relatives contacted systematically.[3,4,5]

Because subarachnoid haemorrhage is a dramatic event it should be easily remembered by relatives, but apparently it is not. In a recent study on the reliability of the family history for myocardial infarction, sensitivity was comparably poor, but in that study the family history was verified only by contacting the general practitioners of the living relatives.[6] Even when the analysis was restricted to deceased relatives, sensitivity for family history of stroke in general proved to be low.[7] These data corroborate our present finding that the sensitivity of the family history is low, even for well known emergencies, and that an accurate family history requires verification of the family history by medical record data.

Several factors may have influenced our results. Firstly, in a minority of the relatives who had died, the cause of death could not be retrieved. In some families relatives were no longer in contact with one another and their whereabouts or even their being alive could not be ascertained. In other families relatives declined to cooperate, including one family in which the index patient had died and one first degree relative had previously had a subarachnoid haemorrhage. In addition, when relatives were willing to provide information, medical reports had sometimes been destroyed if the event had occurred more than five or 10 years previously so that the information could not be verified. Thus, even by contacting all relatives we probably have still underestimated the familial occurrence of subarachnoid haemorrhage. Secondly, this study has been carried out in centers specializing in care of patients with subarachnoid hemorrhage. Attending physicians in these centers may obtain the family history more accurately than physicians in general hospitals; the family history may have been collected more thoroughly than usual as some attending physicians were aware of our study being in progress, but we do not think these two phenomena have had a major influence on our results. Thirty six families (18%) could not be included because the patient or next of kin refused participation in the study. In most instances the reason for refusal was that the patient had died; we consider it unlikely that this has introduced an important bias. A third factor that should be taken into account in the interpretation of our results is that we accepted

even the slightest suspicion of a subarachnoid haemorrhage as a positive family history at the bedside, whereas for the extensive strategy only episodes of definite and probable subarachnoid haemorrhage were counted as positive. The sensitivity of the bedside history decreases even further if only highly suggestive histories are considered positive.

In conclusion, our study shows that a considerable proportion of familial cases of subarachnoid haemorrhage will be missed if the medical history of all relatives is not scrutinised. Family history has become important in subarachnoid haemorrhage, because non-invasive imaging methods allow screening of asymptomatic relatives in familial subarachnoid haemorrhage. If screening is based on a positive family history, we advise a more thorough collection of data than a routine conversation at the bedside.

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# Chapter 3

# Feasibility of follow-up through e-mail in patients discharged after subarachnoid haemorrhage

P. Greebe, RN and G.J.E. Rinkel, MD

*Cerebrovasc Dis 2006;21:363-366*

# Abstract

## Background

Long term follow-up in patients with a subarachnoid haemorrhage (SAH) can be important in patients care and for clinical research, but outpatients' visits or telephone interviews are time consuming.

## Methods

We studied the feasibility of follow-up through e-mail in a prospectively collected series of patients with aneurysmal SAH.

## Results

Of the 97 patients who were discharged 58 (60%; 95% CI 49 - 70%) had e-mail, and all 58 provided their e-mail address. At one year 37 patients (64%; 95% CI 50 – 76%) responded to the first questionnaire sent by e-mail, 6 did so after an e-mail reminder. Fifteen responded after a telephone call, of which 12 had a new e-mail address.

## Conclusions

E-mail follow-up after SAH is feasible and for patients acceptable, but the proportion of patients with no or with changing e-mail address is considerable. The validity of the responses via e-mail has to be assessed in further studies.

## Introduction

Half the patients with a subarachnoid haemorrhage (SAH) from a ruptured aneurysm die within the first few weeks after the event. One third of the patients who survived the initial weeks are still dependent on help half a year after the haemorrhage and those who have resumed independent living at that time often have physical, emotional and social problems.[1] Recovery from SAH continues for several years,[2] and therefore long term follow-up is important. Another reason necessitating long-term follow-up after SAH is the uncertainty of durability of aneurysm occlusion after coiling. Usually follow-up is done in the outpatients' clinic or by telephone. These methods of follow-up are time consuming and therefore expensive. E-mail is a new method of corresponding, but it is unknown how many patients who survived an episode of SAH have an e-mail address and are still able to use it. Moreover, e-mail addresses tend to change regularly, which may impede the response rate.
We assessed the feasibility of follow-up by e-mail in patients who have survived an episode of SAH

## Methods

We studied a prospectively collected series of patients with aneurysmal SAH, admitted to our hospital between July 2002 and July 2003.
As routine practice all patients with SAH are contacted by a stroke research nurse 3 months and 1 year after the SAH to assess outcome. During the study period a research nurse asked patients who were in good clinical condition shortly before discharge consent to follow-up by e-mail. Patients who were discharged in a poor condition to their referring hospital or to a rehabilitation hospital were asked for an e-mail address during the standard telephone interview at 3 months. If patients still resided in a nursing home at the 3 months follow-up, we asked the relative for his or her e-mail. During the study period a trial was performed with outcome assessment

by telephone at 3 months. Patients participating in this trial were asked for an e-mail address during this outcome assessment at 3 months. Patients with no e-mail address of their own could use an e-mail address of a relative or an e-mail address at work. Patients without an e-mail address were contacted by telephone at 3 months and 1 year as usual.

The follow-up questions asked by e-mail were adapted from the “simple questions” on outcome after stroke.[3] We also asked consent for another follow-up after 1 year, and asked for additional questions of the patients.

If a patient did not respond to the e-mail, we sent a reminder 2 weeks later. If patients did not respond after this reminder or if the e-mail was sent back with the notification that the address was unknown, we contacted the patient by telephone to ask for the correct e-mail address. If patients could not be contacted by telephone, we contacted the general practitioner to check if the patient was still alive and lived at the same address.

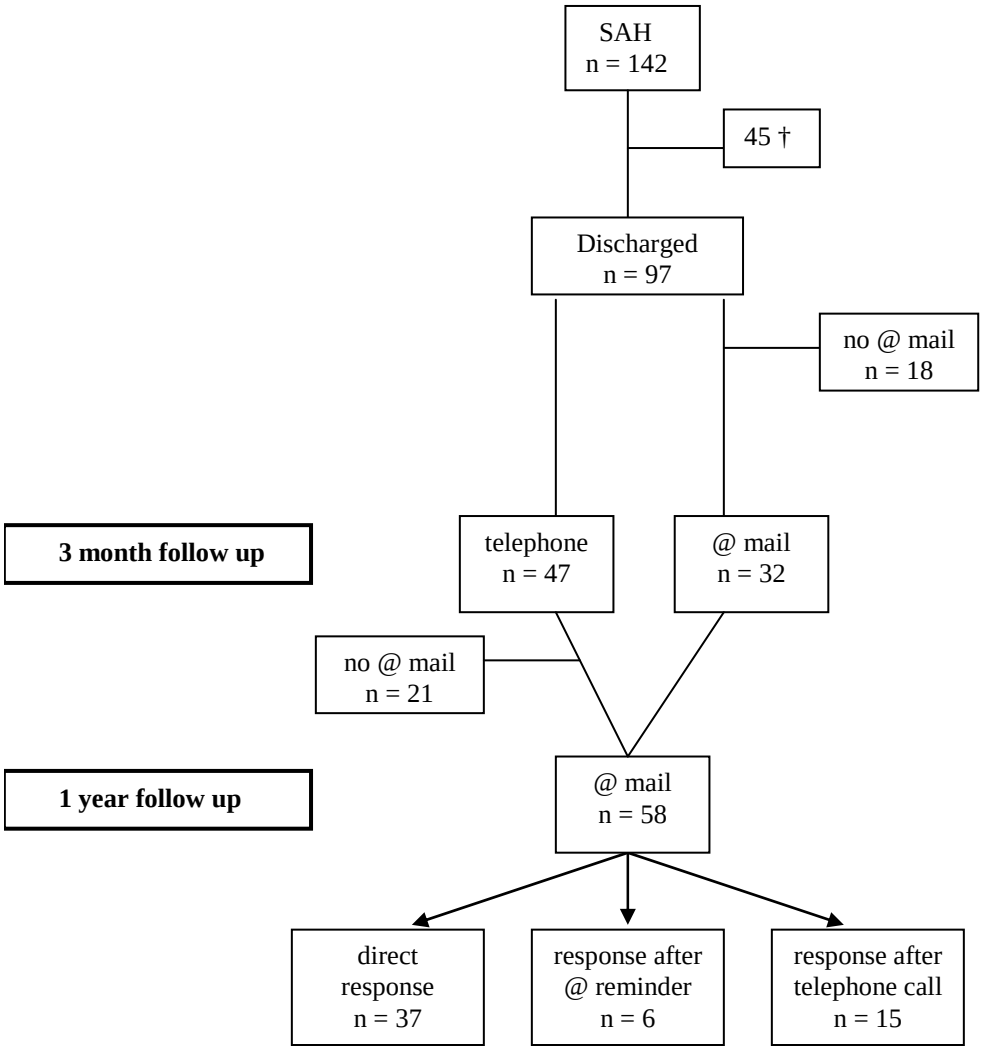
**Data-collection and analyses**

We assessed feasibility in terms of the proportion with corresponding 95% confidence intervals (CI) of patients who reported to have an e-mail-address, the proportion of patients with an e-mail address who responded to the e-mail spontaneously, and the proportion of patients who responded to the e-mail after a telephone call. Moreover, we recorded how often patients asked questions when returning the e-mail questionnaire.

## Results

During the 12 months inclusion period, 142 patients (85 women) had been admitted with an aneurysmal SAH (fig 1).

Figure 1. Data from the 12 months follow-up period.




Of the 97 patients who were discharged alive, 58 (60%; 95% CI 49 - 70%) had e-mail, and all provided their e-mail address. The proportion of women was similar between the patients without (62%; 95% CI 45 – 77%) and with (57%; 95% CI 43 - 70%) e-mail. The patients without e-mail address were slightly older (mean age 56 years; range 20 to 86) than those with an e-mail address (mean age 49 years; range 22 to 76 years). Of the 58 patients with an e-mail address, 49 had an e-mail address of their own, 5 patients provided an e-mail address of a relative, and 4 patients an e-mail address at work. Seven patients provided two e-mail addresses.

At 3 months, an e-mail was sent out to 32 patients. We received an e-mail response for 29 of these patients (88%; 95% CI 71 – 97%). Two additional patients responded after a telephone call, one of these patients had changed his e-mail address. One patient did not respond at all at the 3 months follow-up, and did not respond to telephone calls. The general practitioner informed us that she had moved. She could be contacted at her new address and provided her new e-mail address for the 1 year follow-up. Of the 31 patients who responded, 2 were dependent on help for daily activities (response by relative), 29 were independent, and 10 of these answered to have made a complete recovery.

At 3 months 47 patients or relatives were contacted by telephone, 12 because they were participating in a trial with follow-up obligatory by telephone and 35 because they had been discharged to their referring hospital, a rehabilitation facility or a nursing home. During the telephone interview these patients or their relatives were asked for e-mail follow up at 1 year. Of these 47 patients, 26 had e-mail and all consented to e-mail follow-up at 1 year. These 26 patients and the 32 patients with e-mail follow-up at 3 months were followed-up by e-mail at 1 year. Of these 58 patients, 37 (64%; 95% CI 50 – 76%) responded spontaneously, and six after an e-mail reminder. Fifteen responded after a telephone call; 12 (21%; 95% CI 11 – 33%) of them had a new e-mail address. One of these patients also had changed the e-mail address between discharge and 3 months follow-up. None of the patients had died after discharge. Of the 58 patients who responded, 9 were dependent on help for daily activities (response by relative), 49 patients were independent, and 25 of these answered to have made a complete recovery.

All 58 patients consented to another follow-up 1 year later. Twenty-four patients asked additional questions by e-mail, 10 after 3 months follow-up and 14 after 1 year follow-up. In 8 instances the questions were about physical or cognitive complaints, in 2 instances about trials patients had been involved in and in 14 instances about information on the disease and its consequences. All questions were answered by a research nurse, in 6 instances after consulting a neurologist. Answers were given by e-mail to 21 patients and by telephone to 3 instances. In none of the patients was the e-mail follow-up followed by an additional outpatient contact.

## Discussion

Patients who are discharged after being treated for aneurysmal SAH are willing to cooperate with follow-up through e-mail for study purposes. For those patients who have internet access follow up through e-mail is feasible, willingness to participate in e-mail follow-up is high, and the majority of these patients responded promptly. However, follow-up through e-mail can not replace other forms of follow-up entirely given the considerable proportions of patients with no, or with changing e-mail address.

We have not found other studies that evaluated follow-up through e-mail and very few studies on e-mail in medicine at all. E-mail was used to send individually timed educational messages in an Internet smoking cessation intervention, and in that study these e-mail messages increased the effectiveness of the intervention.[4] Obviously, the patient population is different from our population, and having internet access was a prerequisite in this study, which makes comparisons with our study difficult. The overall age of the patients with an e-mail address was younger than patients without an e-mail address. Patients with SAH in general are younger than patients with other types of stroke; therefore our results cannot be extrapolated to all patients with stroke.

The proportion of patients with internet is expected to increase, but whether this will increase the feasibility of e-mail follow-up is uncertain, given the high proportion of changing e-mail addresses. Even within a relatively short time frame of 1 year, the proportion of patients with a changed e-mail address was considerable. Probably with longer periods of follow-up this proportion increases, with decreasing feasibility as a result. In a similar way, however, the feasibility of follow-up through telephone may decline, because the number of people with only mobile phone numbers, which are also changing frequently, is increasing.

E-mail follow-up is less time consuming than follow-up by telephone. Many patients who survive an episode of SAH resume working or other outdoor activities, and therefore often several telephone calls, including calls at out of office hours have to be made before a former patient can be contacted. Another advantage of e-mail

follow-up is that patients can chose a proper time to respond. A disadvantage may be that it is less easy to ask questions, but the results show that almost half the patients did ask questions, even though many of these patients also had outpatient contacts with their treating neurologist or neurosurgeon during the study period. We have not assessed whether the patients who did not ask questions in fact had questions, but felt uneasy to ask these questions by e-mail or to contact the study nurse through the telephone number provided. Also, we did not study the validity of the answers provided by e-mail, which should be done in a following study.

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# Chapter 4

# Life expectancy after perimesencephalic subarachnoid haemorrhage

P. Greebe, RN and G.J.E. Rinkel, MD

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## Abstract

### Background and Purpose

Patients with a perimesencephalic nonaneurysmal subarachnoid hemorrhage are not at risk for rebleeding in the initial years after the hemorrhage. Nevertheless, uncertainty remains on the long-term prognosis after perimesencephalic hemorrhage, and former patients are often considered high-risk cases for health insurance or are denied life insurance. We performed a very long-term follow-up study of a large consecutive series of such patients and compared mortality in this cohort with that in the general population.

### Methods

All patients with a perimesencephalic hemorrhage (defined by pattern of hemorrhage on computed tomography within 72 hours after onset and absence of aneurysm) admitted between 1983 and 2005 to our service were followed-up by telephone. For patients who had died, we retrieved age and cause of death. We compared the age- and sex-specific mortality of this cohort with that of the general population by means of standardized mortality ratios with corresponding
95% confidence intervals.

### Results

The cohort consisted of 160 patients, with a total number of patient-years of 1213. No new episodes of subarachnoid hemorrhage had occurred. During follow-up 11 patients had died; the expected number of deaths based on mortality rates in the general population (adjusted for age and gender) was 18.1. The standardized mortality ratio was 0.61 (95% confidence interval, 0.34 to 1.1).

### Conclusions

Patients with perimesencephalic hemorrhage have a normal life expectancy and are not at risk for rebleeding. No restrictions should be imposed on these patients by physicians or health or life insurance companies.

## Introduction

Patients with a perimesencephalic subarachnoid hemorrhage are not at risk for rebleeding in the first years after the initial bleeding and have no reduced quality of life.[1] Nevertheless; uncertainty remains on the long-term prognosis after a perimesencephalic hemorrhage. Perimesencephalic hemorrhage is a subset of subarachnoid hemorrhage; in recent years, evidence has become available that patients with an aneurysmal subarachnoid hemorrhage have a reduced life expectancy. This reduced life expectancy is not only caused by new episodes of subarachnoid hemorrhage from newly developed or previously undetected aneurysms[2] but also by a higher risk of cardiovascular disease than that of healthycontrols.[3] The explanation for the excess mortality from cardiovascular diseases is the finding that smoking and hypertension are important risk factors for subarachnoidhemorrhage.[4,5] Some studies also found a higher occurrence of hypertension and smoking in patients with perimesencephalic hemorrhage than in the general population,[6] which suggests that these patients may be at increased risk for other cardiovascular diseases. Given these uncertainties, many patients who have had a perimesencephalic hemorrhage are denied life insurances and are considered high-risk cases for health insurance. We performed a very long-term follow-up study of a large consecutive series of patients with perimesencephalic hemorrhage and compared mortality in this cohort with that in the general population.

## Methods

### Patients

From a prospectively collected database of patients admitted to the University Medical Center Utrecht with subarachnoid hemorrhage, we retrieved all patients admitted between 1983 and 2005 who met the following criteria: computed tomography scan performed within 72 hours after the onset of headache showing a

perimesencephalic pattern of hemorrhage,[7] and absence of a saccular aneurysm on computed tomographic angiography or conventional angiography. Patients who lived outside the Netherlands were excluded.

**Follow-up**

First, we contacted the general practitioner of all eligible patients to find out if the patient was still alive. If a patient had died, we asked for the date and cause of death. If death occurred in a hospital or other facility, we reviewed the medical records. Subsequently, we sent a letter to all patients who were still alive. In this letter we announced a telephone call. If a patient had no phone number or an ex-directory one, we sent a letter asking the patient to contact us. During the telephone interview we asked the patients about new episodes of hemorrhage and new vascular events by means of a standardized interview. We assessed functional outcome by means of 2 simple questions. The first question was whether patients need help from another person for everyday activities. For patients who do not need help, the next question was whether patients feel they have made a complete recovery from their stroke. These questions are practical and accurate, and have reasonable reliability and validity when administered by telephone.[8,9]

**Data Analysis**

We registered the number of patients in our cohort who had died during follow-up. We used standardized mortality ratios to investigate possible excess mortality in patients with perimesencephalic hemorrhage compared with the general population. Population based statistics of The Netherlands were used as reference for the calculation of the total expected number of deaths.[10] Mortality ratios were standardized in an indirect manner according to age and sex. Person-years of our cohort were calculated for sex and age (5-year) strata. Because of the long-term follow-up, many patients changed from age stratum during follow-up, for which we adjusted. For example, a patient 37 years of age at time of the hemorrhage and a 12-year follow-up counted for 2 years in the stratum 35 to 39, 5 years in the stratum 40 to 44, and 4 years in the stratum 45 to 49. This adjustment is necessary, because

mortality increases with each stratum; therefore, unadjusted calculations would lead to an underestimation of the expected number of deaths in the cohort. The expected number of deaths was calculated by totalling the number of patient-years in each stratum and by multiplying this cumulative number of patient-years per stratum with the age- and sex-specific mortality rates of the reference population in this stratum. The sum of expected deaths per stratum yielded the total number of expected deaths in our cohort. For the reference population, we used mortality rates from 2000, which was the median year of hemorrhage in our cohort. The standardized mortality ratio is the ratio of the observed number of deaths in our cohort to that of the expected number deaths based on the general population. A standardized mortality ratio >1 means excess mortality in the study cohort compared with the reference population. Ninety-five percent confidence intervals were calculated based on the Poisson distribution. We performed a sensitivity analysis for those patients who were excluded because they resided outside the Netherlands. In a worst-case analysis, these patients were considered to have died in the first year after the hemorrhage.

## Results

During the study period, 162 patients with a perimesencephalic hemorrhage had been admitted. One of these patients was a UK resident spending his vacation in the Netherlands; he returned to the UK after discharge. Another patient emigrated soon after the hemorrhage to Australia. Both patients were excluded from the cohort. Therefore, the cohort consisted of 160 patients, 65 (41%) of whom were women. The mean age at time of the hemorrhage was 54.8 years (range, 24 to 90 years). Mean follow-up was 7.5 years (range, 1 to 23 years); the total number of patient-years was 1213. No new episodes of subarachnoid hemorrhage had occurred (0%; 95% confidence interval, 0% to 0.3%). During follow-up 11 patients had died. Causes of death were myocardial infarction (n=2), cardiac failure (n=1), cerebral infarction (n=1), hepatic failure (n=1), gastric cancer (n=2), colon carcinoma (n=1),

and infection at old age (n=3). In this cohort the expected number of deaths based on mortality rates in the general population (adjusted for age and gender) was 18.1. The standardized mortality ratio was 0.61 (95% confidence interval, 0.34 to 1.1). In the worst-case scenario with the 2 patients living abroad entered as death within the first year after the hemorrhage, the standardized mortality ratio was 0.72 (95% confidence interval, 0.42 to 1.24). Of the 149 patients who were alive at time of follow-up, one patient, a woman aged 80 years at time of the hemorrhage, had an ischemic stroke at age 86, and was admitted to a nursing home thereafter. A second patient, who had insulin-dependent diabetes and was 74 years of age at time of the hemorrhage, had recovered completely from the hemorrhage but had been admitted to a nursing home at 80 years of age after a humerus fracture. All other 147 patients were independent on activities for daily living, but 39 had symptoms including headaches or dizziness (n=7), fatigue (n=7), forgetfulness (n=12), and irritability (n=5).

## Discussion

This study shows that patients with perimesencephalic hemorrhage have no excess in mortality compared with the general population. Moreover, even on very long-term follow-up no episodes of rebleeding occurred, and all patients regained independence for activities of daily life. After treatment of a ruptured aneurysm, patients with aneurysmal subarachnoid hemorrhage have a small but definite risk of new episodes after treatment of the ruptured aneurysm from newly developed aneurysms or regrowth aneurysms at the site of the treated aneurysm.[11] The development of new aneurysms indicates that having an aneurysm is not a single lifetime event, but a vessel disease that continues during life if patients survive an episode of aneurysmal subarachnoid hemorrhage. In a study from our center, the cumulative risk of a new episode in the first 10 years after the initial hemorrhage was 3.2% and the incidence rate was 286/100 000 patient-years.[2] Others have found similar estimates.[12] If patients with perimesencephalic hemorrhage would have a

similar risk, 3.5 episodes of aneurysmal subarachnoid hemorrhage could have been expected during the follow-up of this cohort. The absence of any episode of aneurysmal subarachnoid hemorrhage indicates that our patients with perimesencephalic hemorrhage are not “missed aneurysm,”[13] and that patients with perimesencephalic hemorrhage have a disease process other than intracranial aneurysms. One of every 4 patients had non-specific symptoms such as headaches, dizziness, fatigue, and forgetfulness. Unfortunately, we do not have reliable data on the prevalence of such symptoms in the general population. Therefore, we cannot directly compare the prevalence of these symptoms in our cohort with that of the general population, but the impression is that the prevalence in our cohort is higher. Previous studies found similar high rates of non-specific symptoms and minor cognitive deficits, although none used a proper control group.[14,15] The occurrence of these symptoms has been linked to the presence of depression.[14] Whether a strategy of strict surveillance for depression and treating it decreases the rate of non-specific symptoms and minor cognitive deficits remains to be seen. Our series is the largest with the longest period of follow-up; previous studies have included fewer patients and shorter periods of follow-up, and did not compare long-term outcome with that in the general population.[1,14-16] The large number of included patients enabled reliable estimates of the standardized mortality ratio. Another strength of the current study is that patients were prospectively collected into our database; thus, no retrieval bias can have occurred. We did not take into account the first year of follow-up. The total number of follow-up years in our calculation is therefore an underestimation of the total number of follow-up years, which leads to an underestimation of the number of expected deaths, and thus to an overestimation of the mortality ratio. Most patients in our cohort had only computed tomographic angiography to rule out an aneurysm, and repeated studies were not performed unless the initial examination was technically unsatisfactory. In a formal decision analysis that included the risk of angiography and the risk of missing an aneurysm with computed tomographic angiography alone, we found that in patients with a perimesencephalic hemorrhage, computed tomographic angiography alone is the best diagnostic strategy.[17] Other studies have confirmed the high negative predictive

value of computed tomographic angiography for an aneurysm is patients with a perimesencephalic hemorrhage,[18] and the low yield of repeated angiography in these patients.[19] Therefore, we feel confident about our diagnostic approach. The absence of catastrophes during the clinical course and long-term follow-up confirms the safety of our strategy. Because patients with perimesencephalic hemorrhage have a normal life expectancy and are not at risk for rebleeding, no restrictions should be imposed on these patients by physicians or health or life insurance companies.

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# Chapter 5

# Anosmia after perimesencephalic nonaneurysmal haemorrhage

P. Greebe RN, G.J.E. Rinkel MD and A. Algra MD

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## Abstract

### Background

Anosmia frequently occurs after aneurysmal subarachnoid hemorrhage (SAH), not only after clipping but also after endovascular coiling. Thus, at least in part anosmia is caused by the hemorrhage itself and not only by surgical treatment. However, it is unknown whether anosmia is related to rupture of the aneurysm with sudden increase in intracranial pressure or to the presence of blood in the basal cisterns. Therefore we studied the prevalence of anosmia in patients with nonaneurysmal perimesencephalic hemorrhage (PMH).

### Methods

We included all patients admitted to our hospital with PMH between 1983 and 2005. Patients were interviewed with a structured questionnaire. We calculated the proportion of patients with anosmia with corresponding 95% CI's.

### Results

Nine of 148 patients (6.1%; 95% CI:2.8-11%) had noticed anosmia shortly after the PMH. In two the anosmia had disappeared after 8 to12 weeks, in the other 7 it still persisted after a mean period of follow up of 9 years.

### Conclusions

Anosmia occurs in one of every sixteen patients with PMH, which is lower than previously reported rates after coiling in patients with SAH, but higher than rates after coiling for unruptured aneurysms. These data suggest that blood in the vicinity of the olfactory nerves plays a role in the development of anosmia.

## Introduction

Patients with an aneurysmal subarachnoid hemorrhage (SAH) often report a loss of smell, not only after clipping, but also after coiling and this has an important impact on quality of life.[1] Anosmia can occur after intracranial surgery[1, 2] and after SAH it often has been attributed to the operative treatment of the aneurysm. Recent studies have shown that anosmia also occurs in patients with SAH and endovascular occlusion of the aneurysm. Thus, at least in part the anosmia is caused by the hemorrhage itself.

Although the cause of perimesencephalic hemorrhage (PMH) has not yet been identified, the invariably good clinical condition at onset, the often more gradual onset of headache and the localized nature of the blood on computed tomography (CT) all argue against spurting of blood under arterial pressure and favor a venous oozing of blood.[3] A venous source is further supported by the normal arteriograms and often abnormal findings in venous drainage in PMH patients.[4] We therefore studied the prevalence of anosmia in patients with PMH.

## Methods

### Patients

From a prospectively collected database of patients admitted to the University Medical Center Utrecht with subarachnoid hemorrhage, we retrieved data on all patients admitted between 1983 and 2005 who met the following criteria: CT scan performed within 72 hours after the onset of the headache showing a perimesencephalic pattern of hemorrhage,[5] and absence of a saccular aneurysm on CT angiography or conventional angiography. Hydrocephalus was defined as a bicaudate index exceeding the upper limit for age.[6] The study was approved by the Medical Ethics Committee of our hospital.

### Follow-up

We contacted the general practitioner of eligible patients to find out if the patient was still alive. Subsequently, we sent a letter to all patients who were still alive to announce a telephone call. If the patient's phone number was unknown, we sent a letter asking the patient to contact us. Patients were interviewed by telephone with a standardized, previously used questionnaire.[1] The questionnaire comprised questions on whether or not patients had noticed any degree of loss of smell or taste after the hemorrhage. If so, the patients were asked if there had been some recovery and after what time the improvement had occurred.

For all included patients we retrieved the following data: age, sex, smoking, hypertension and hydrocephalus. For description of these baseline characteristics we used descriptive statistics. To assess the relationship between presence of hydrocephalus and anosmia we calculated risk factors with corresponding 95% confidence intervals (CI).

## Results

During the study period 164 patients were admitted with perimesencephalic nonaneurysmal hemorrhage. We excluded 16 patients: thirteen patients had died during the follow-up period, one patient was a UK resident, another was imprisoned, and one had emigrated. Therefore, the cohort consisted of 148 patients, 61 (41.2%) of whom were women. The mean age at time of the hemorrhage was 54 years (range, 24 to 81 years). Table 1 describes baseline characteristics of the patients.

Tabel 1: Baseline characteristics of the 148 patients

| | |
|---|---|
| Women | 61 (41%) |
| Age at time of hemorrhage | 54 (24 – 81) |
| Age at time of interview | 62 (34 – 88) |
| Smoking | 38 (26%) |
| Hypertension | 40 (27%) |
| Hydrocephalus | 19 (13%) |

None of the patients had symptoms or signs of Parkinson's disease or had developed Parkinson's disease during follow up. Mean follow-up was 7.5 years (range, 1 to 23 years). None of the patients had had a severe head trauma or intracranial surgery during follow up.

Nine (five women and four men) of the 148 patients (6.1%; 95% CI:2.8-11%) had noticed a loss of smell after the hemorrhage; all had noticed the loss of smell already during the clinical course, which typically lasted a few days. Two reported a complete recovery after 8 to 12 weeks. The mean period of follow up was 9 years. None of the 19 patients with hydrocephalus had anosmia; the corresponding RR is 0.0 (95% CI 0.0 - 3.5).

## Discussion

In patients with a perimesencephalic nonaneurysmal hemorrhage the prevalence of anosmia is one in sixteen. The prevalence in patients with endovascular treatment of the aneurysm after SAH is one in six,[7] but in patients with endovascular treatment of an unruptured aneurysm the prevalence of anosmia is negligible.[8] Therefore the anosmia should be attributed, at least in part, to the hemorrhage itself, and is related not only to the suddenly increased intracranial pressure from a ruptured aneurysm, but also to the presence of blood in the basal cisterns. This finding that

subarachnoid blood is related to anosmia is further supported by case reports of patients with hemosiderosis of the central nervous system and anosmia.[9, 10]

As in a previous study, we found no relation between anosmia and risk factors such as age, sex and hydrocephalus, but the power of our study was limited.

The study population was retrieved from a large cohort of patients admitted since 1983 and none of the patients was lost. The data were collected retrospectively and the prevalence of anosmia might therefore have been underestimated, because patients might have forgotten about temporary loss of smell. Moreover, the diagnosis of anosmia was based on an interview by telephone and was not verified with smelling tests. Nevertheless, all nine patients were confident that the anosmia had not been present before the hemorrhage and had started shortly after the PMH.

Our cohort of patients with PMH is a good setting to study whether the occurrence of anosmia should be attributed to aneurysmal rupture or to the presence of blood in the basal cisterns. Our data suggest that blood in the vicinity of the olfactory nerves contributes to the development of anosmia.

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# Chapter 6

# Long-term follow-up in patients with a subarachnoid haemorrhage after discharge to a nursing home

P. Greebe RN, G.J.E. Rinkel MD and A. Algra MD

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## Abstract

### Background

In general, life expectancy is short and chances of discharge are small after admission to a nursing home. We studied long-term outcome in patients with aneurysmal subarachnoid hemorrhage (SAH), who are relatively young.

### Methods

From all SAH patients admitted in 1996-2006 we included those who were discharged to a nursing home and followed them until July 2008. We retrieved causes of death and determined functional status of patients who were still alive. We analyzed survival and discharge rates with survival analysis and assessed the influence of baseline characteristics on outcome with Cox regression analysis.

### Results

Of the 92 included patients 45 had died after a median of 1.1 years (range 0.0-8.5), 35 were discharged to home, a sheltered housing or rehabilitation centre after a median of 0.6 years (range 0.1-9.6) and 12 still remained in a nursing home after a median of 4.8 years (range 2.2-12.0). Forty-four (43%) had survived longer than five years, and 29 (31%) had regained functional independence within the initial two years after admission to the nursing home. Early discharge tended to occur more often in patients admitted in 2001 - 2006 than in those admitted in 1996 - 2001 (HR 1.8;95%CI 0.9-3.7) and in those with an aneurysm not in the anterior communicating artery (HR 1.9;95%CI 0.9-3.9).

### Conclusions

The prognosis for SAH patients after admission to a nursing home is not gloomy. The type of rehabilitation that offers best chances to these patients needs to be investigated.

## Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating disease that occurs at a relatively young age. Around half the patients die within a month after SAH and about 15 % of the patients are functionally dependent at 3 to 12 months after the SAH.[1] Some of these functionally dependent patients are admitted to a nursing home. In general, most patients admitted to nursing homes are elderly patients often with degenerative diseases and co morbidity, and their life expectancy is usually short. In a retrospective cohort study 35% of nursing home residents had died within one year after assessment performed because of admission or change in clinical status.[2] Patients with SAH are generally young, with a mean age of 55 years,[3] and have a tendency to improve in functional outcome and quality of life within the first two years after the hemorrhage.[4] Thus, patients admitted to a nursing home after SAH might become functionally independent and eventually resume independent living, but follow-up data on such patients are lacking. We therefore performed a long-term follow-up study in patients admitted to a nursing home after SAH to assess survival rates, length of stay in the nursing home, and probability of recovering to a functionally independent state. An additional question was whether there is a time period after which recovery to a functionally independent state no longer occurs. Finally we studied whether there were baseline characteristics that were related to survival and discharge from the nursing home.

## Methods

Patients were selected from our prospectively collected database of patients admitted with an SAH to the University Medical Center Utrecht. We selected those patients with SAH from a ruptured aneurysm who had been admitted in 1996 - 2006 and discharged to a nursing home. Aneurysmal SAH was diagnosed if CT scanning confirmed the presence of subarachnoid blood and if an aneurysm was found on

conventional, CT- or MR-angiography. In the initial years of the study conventional or CT angiography was only performed if treatment of the aneurysm was considered. We therefore also included patients with an aneurysmal pattern of hemorrhage on CT in whom no conventional or CT angiography was performed because their clinical condition precluded treatment of the aneurysm. Patients with a non-aneurysmal cause of the SAH were excluded. Patients transferred from our service to a referring hospital and discharged from that hospital to a nursing home were included too. Day care facility in a nursing home was not considered an admission to a nursing home. Patients who had an in-hospital course longer than 3 months and who died in hospital after this period of three months were considered to have died in a nursing home. We excluded three patients who were living abroad and were discharged from our hospital to a hospital or other facility abroad. The study had been approved by the medical ethics committee of our institution

During the study period, 1149 patients had been admitted to our hospital with an aneurysmal SAH. Of these 1149 patients, 366 had died within three months (32%; 95% CI 29-35%) after admission. Of the remaining 783 patients, 92 (8.0%; 95% CI 6.5 – 9.7%) had been discharged to a nursing home (mRankin 4 = moderately severe or mRankin 5 = severe disability): 37 had been discharged directly to a nursing home and another 55 patients to a nursing home after initial transferal to their referring hospital. For these 92 patients we retrieved all discharge letters from the referring hospitals and the nursing homes and if these were not available we contacted the general practitioner. If the nursing home could or would not provide data whether the patient had died or had been discharged and if we could not contact the general practitioner to assess whether the patient was still alive, we retrieved data from the municipality register.

For all included patients we retrieved the following data: sex, age, location of the ruptured aneurysm (anterior communicating artery (AcomA) including anterior cerebral artery (ACA) and pericallosal artery, middle cerebral artery (MCA), internal carotid artery (ICA) including posterior communicating artery (PcomA) and aneurysm

on the vertebrobasilar arteries), type of aneurysm treatment, living status before SAH (alone or with partner) and length of stay in our hospital and if discharged to a referring hospital length of stay in the referring hospital. For the period after admission to the nursing home we collected: length of stay in the nursing home, discharge destination (home, sheltered housing, rehabilitation centre, and death), functional status at time of discharge and cause of death if applicable. For cause of death we assumed it to be a direct consequence of the SAH if the patient had died in the nursing home without recovery in functional status with no new event or after a new infection. If patients died from infections after discharge from the nursing home, the cause of death was categorized as infection. To assess functional status we contacted all patients who were still alive in the nursing home or, after discharge, in another facility or at home. Functional status was assessed by means of the modified Rankin scale (mRankin).[5]

### Data analysis

For baseline characteristics we used descriptive statistics. Outcome measures were death and discharge from the nursing home. We used survival analysis to analyze risk of death and chance of discharge. For this latter analysis, patients were censored in case of death. Survival and chance of discharge were depicted with Kaplan Meier curves. We used Cox regression analysis to calculate hazard ratios (HR) and corresponding 95% confidence intervals (95% CI's) to describe the relationship between baseline characteristics and outcome. The hazard ratios may be interpreted as relative risk. We also analyzed whether chances of survival and discharge were different between the first (1996 to 2001) and second half (2001 to 2006) of the study period, because reactivation in nursing homes may have been improved last decade.

## Results

The baseline characteristics of the 92 included patients are listed in table 1.

Table 1: Baseline characteristics and follow-up data of the 92 patients who had been discharged to a nursing home after SAH

| **Baseline characteristics** | |
|---|---|
| Women | 69 (75%) |
| Age (mean + Std. Deviation) ) | 66.8 (12.3) |
| Location of the ruptured aneurysm | |
| Acom | 37 (40.2%) |
| ICA | 27 (29.3%) |
| MCA | 16 (17.4%) |
| Vertebrobasilar | 7 (7.6%) |
| No angio | 5 (5.4%) |
| Treatment of the aneurysm | |
| No treatment | 20 (21.7%) |
| Clipping | 52 (56.5%) |
| Coiling | 14 (15.2%) |
| Clip + EC/IC bypass | 6 (6.5%) |
| Living status before SAH | |
| Alone | 37 (40%) |
| Living with partner | 55 (60%) |
| **Follow-up data** | |
| Follow-up (mean + Std. Deviation) | 4.1 (3.3) |
| Status at end of follow-up | |
| Death | 56 |
| Discharged | 24 |
| Still in nursing home | 12 |
| m Rankin | |
| 0 (no symptoms at all) | 4 |
| 1 (no significant disability despite symptoms) | 0 |
| 2 (slight disability) | 5 |
| 3 (moderate disability) | 3 |
| 4 (moderately severe disability) | 14 |
| 5 (severe disability) | 9 |
| death | 56 |

Acom / ACA = Anterior Communicating Artery / Anterior Cerebral Artery / pericallosa

ICA = Internal Carotid Artery

MCA = Middle Cerebral Artery

Vertebrobasilar = Arteries of the vertebrobasilar system

The median age was 69.5 years; 69 (75%) were women. The total duration of follow-up was 349 patient-years with a median period of follow-up of 3.3 years (range 0.0 – 12.0 years). During this follow-up 56 of the 92 patients (60%; 95% CI 50-71%) had died after a median period of follow-up of 3.7 years. Forty-five of these patients had died in the nursing home after a median of 1.1 years and another 11 after discharge from the nursing home after a median of 4.9 years (range 1.3-10.6). Figure 1 shows the time to event curves for death and for discharge to home.

Figure1A: Kaplan Meier curve for death

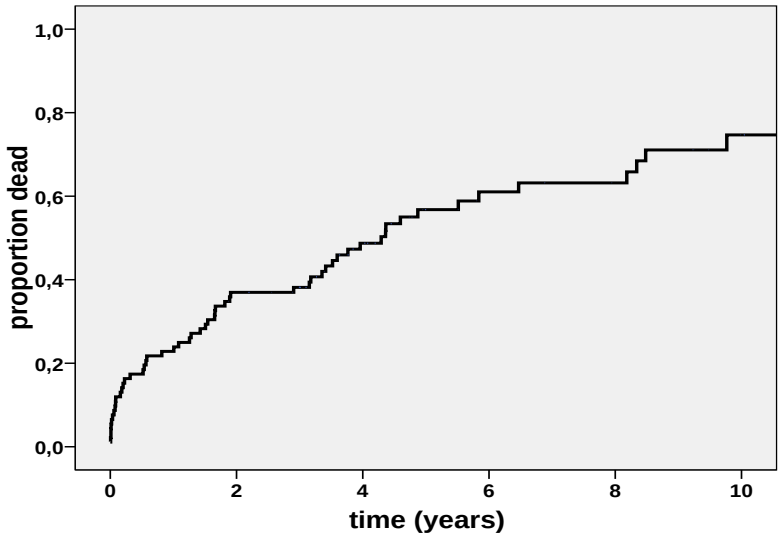
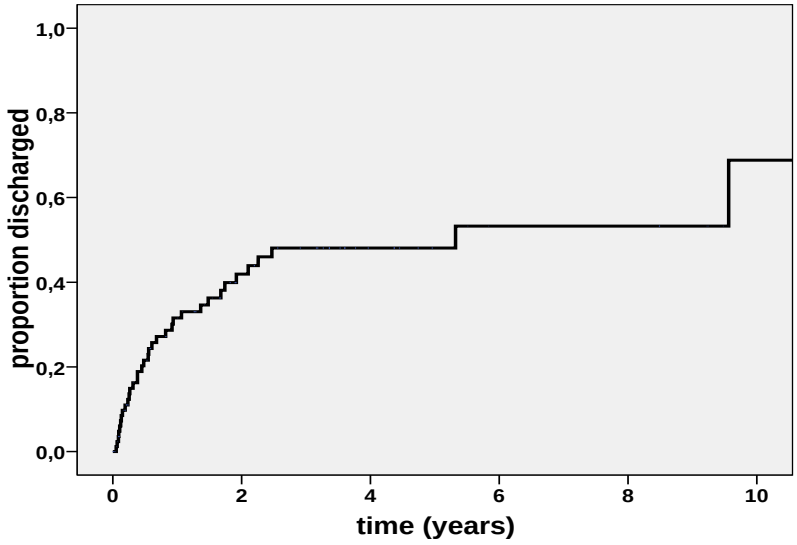



Figure 1B: Kaplan Meier curve for discharge home, censored for death



Causes of death were: direct consequence of SAH (25), recurrent SAH (n=1), other stroke (n=6), sudden death (n=4), cancer (n=3), cardiac causes (n=1), infections (n=2) and miscellaneous causes including renal failure (n=10). For four patients cause of death could not be retrieved. At close out from the study 12 patients still resided in a nursing home (mRankin score 4 or 5). Twenty-one patients were discharged home and fourteen patients had been discharged to another facility. Table 2 provides a detailed description of the status of the patients over time.

Table 2: Change in status of the 92 patients over time

| | Time after admission in nursing home | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 m | 3 m | 6 m | 1 y | 2 y | 5 y | 10y |
| | N=92 | N=92 | N=92 | N=92 | N=91 | N=77 | N=71 |
| in nursing home | 92 | 67 | 59 | 47 | 29 | 17 | 12 |
| discharged and alive | 0 | 10 | 17 | 24 | 28 | 12 | 4 |
| death in nursing home | 0 | 15 | 16 | 21 | 33 | 42 | 45 |
| death after discharge | 0 | 0 | 0 | 0 | 1 | 6 | 10 |
| follow-up ended | 0 | 0 | 0 | 0 | 1 | 15 | 21 |

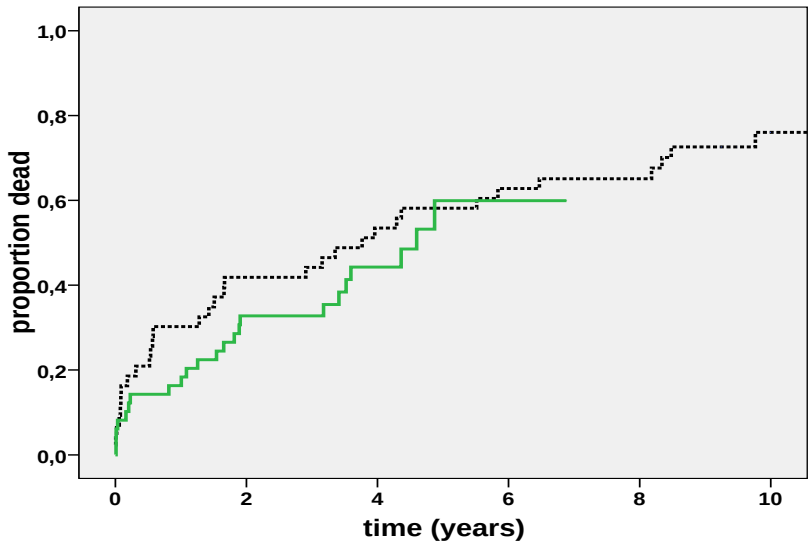
m, month; y, year

Because some patients had been discharged less than five years ago, the number of patients available for follow-up more than five years is less than 92.

At two years follow-up 29 (31%) of the patients had been discharged home or to another facility and 29 (31%) still remained in a nursing home. Between two and five years follow-up three patients had been discharged home or to another facility. After more than five years one other patient had been discharged to a protecting habitat. Forty-four (43%; 95% CI 32-54%) of the patients who were admitted to a nursing home were still alive after five years follow-up. During the second half of the study

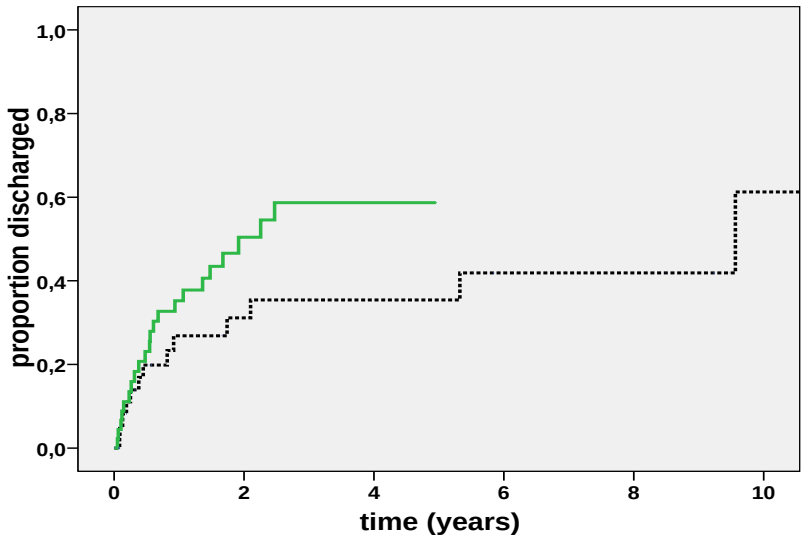
(2001 - 2006) patients were discharged home earlier than in the first half of the study (Figure 2); the hazard ratio was 1.8 (95%CI 0.8 - 3.6) (Table 3), and case fatality tended to be lower (HR 0.9; 95%CI 0.5 – 1.5). These results remained essentially the same after adjustment for age and sex. Patients with an aneurysm not in the AcomA tended to be discharged more often than those with AcomA aneurysm.

Figure 2A: Kaplan Meier curve for death 1996-2001 and 2001-2006




…… 1996 – 2001 _____ 2001 – 2006

Figure 2B: Kaplan Meier curve for discharge home 1996-2001 and 2001-2006, censored for death




…… 1996 – 2001 _____ 2001 - 2006

Table 3: Determinants of death and discharge from nursing home

| | Case fatality<br>Hazard ratio (95% CI) | Discharge<br>Hazard ratio (95% CI) |
|---|---|---|
| Male sex | 1.3 (0.7 – 2.4) | 1.3 (0.6 – 3.0) |
| Age (per year)* | 1.017 (0.994 – 1.041) | 0.994 (0.968 – 1.022) |
| Location of the ruptured aneurysm | | |
| Acom / ACA | Ref | Ref |
| ICA (incl Pcom) | 0.7 (0.4 – 1.4) | 1.6 (0.7 – 3.8) |
| MCA | 0.7 (0.3 – 1.6) | 2.0 (0.8 – 5.2) |
| Vertebrobasilar | 1.6 (0.6 – 3.9) | 2.3 (0.6 – 8.5) |
| No angio | 0.4 (0.1 – 1.7) | 2.3 (0.6 – 8.6) |
| Acom /ACA vs.other | 0.8(0.5 – 1.3) | 1.9(0.9 – 3.9) |
| Treatment of the aneurysm | | |
| No treatment | Ref | Ref |
| Clipping | 1.1 (0.6 – 2.2) | 0.7 (0.3 – 1.6) |
| Coiling | 0.5 (0.2 – 1.6 | 0.8 (0.3 – 2.4) |
| Clip+EC/IC | 0.8 (0.2 – 2.7) | 0.9 (0.2 – 3.3) |
| Living status before SAH | | |
| Living with partner | 1.3 (0.7 – 2.1) | 1.0 (0.5 – 2.0) |
| Study period | | |
| 2001-2006 vs 1996-2001 | 0.9(0.5 – 1.5) | 1.8(0.9 - 3.7) |

Acom / ACA = Anterior Communicating Artery / Anterior Cerebral Artery

ICA = Internal Carotid Artery

MCA = Middle Cerebral Artery

Vertebrobasilar = Arteries of the vertebrobasilar system

* The hazard ratio denotes the change of risk per year of increasing age.

## Discussion

Almost half the patients admitted to a nursing home after SAH survive longer than five years and more than one-third regained independence for activities of daily living, mostly within the initial two years after admission to the nursing home.

We also found a tendency for a better prognosis for patients discharged to a nursing home in the second study period than in the first one. This might be explained by the implementation of reactivation facilities in nursing homes in the more recent years in the Netherlands.[6] These reactivation facilities within nursing home result in better survival and higher discharge rates.[7] In contrast to our assumption we found no higher discharge rates to the community in patients with a partner than in those without. In patients with ischemic stroke the presence or absence of a partner is an important determinant of community discharge.[8] We do not have a good explanation for our finding that the presence of a partner is not related to the chance of being discharged home. It might be related to the relatively young age of our study population. Partners (more often men than women) will have more or less the same age and will therefore often still have a job, which precludes them from staying home and taking care of their disabled partner. This idea is partly substantiated by the high divorce rate between former SAH patients and their partners.[9] Another explanation is that our result is a chance finding, because the confidence interval is rather wide and includes an importantly increased chance of being discharged home in case a partner is present.

In our 10-year cohort of patients with SAH from a ruptured aneurysm, around 10% had been discharged to a nursing home, and the proportion of patients discharged to a nursing home remained stable throughout the study period. In population-based studies, the proportion of patients who are dependent on help in activities of daily living in the first year after the SAH varies between 10 and 20%.[1] The similar proportion of patients discharged to a nursing home in our study suggests that we have not deliberately discharged many patients, including those with a relatively good prognosis beforehand, to a nursing home. Therefore our study results can probably be generalised to other cohorts of SAH patients from facilities treating large

numbers of patients with SAH per year. Another factor favoring the generalisability of our data is our case fatality rate of around 30%, which is in line with case fatality rates of other cohorts of SAH patients.[10-12] We found no other studies on long-term follow-up after discharge to a nursing home in SAH patients, thus we cannot compare our data with those from other studies. The study population is retrieved from a very large cohort of patients seen over a 10 year period, it includes 92 patients with mRankin 4 or 5 (moderately severe or severe disability) at time of admission to the nursing home. Another strong point of the study is that despite the long period of follow-up, none of the patients was lost.

Our study had the following limitations. First, our results may not be generalisable to countries with different discharge policies such as South European countries where discharge to nursing homes is much less common than in Western European countries.[13] Second, functional status at discharge after the SAH was measured with the modified Rankin, which is a global measure of disability and is not very specific to true functional status. A more specific index reflecting functional performance on ADLs, IADL's or possibly physical performance would provide a more appropriate reflection of the patients' abilities at discharge. Third, we did not collect information on quality of life of the patients during the long-term follow-up, because we considered this not to be feasible. Finally even when this series is large in its kind, the total of number of 92 may be viewed as too small to obtain precise results.

The relatively high proportion of patients with community discharge after admission to a nursing home because of persisting deficits from SAH shows that patients and partners should be informed on the possibility of improvement in the long-term. Further studies are needed, for example on quality of life, to assess which type of rehabilitation offers the best chances to discharge home for these patients.

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# Chapter 7

# Functional outcome and quality of life 5 and 12.5 years after aneurysmal subarachnoid haemorrhage

P. Greebe RN, G.J.E. Rinkel MD, J.W. Hop MD,
A.J.M. Visser-Meily MD and A. Algra MD

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## Abstract

### Background

Patients who recover after aneurysmal subarachnoid hemorrhage (SAH) often remain disabled, have persisting symptoms and a reduced quality of life (QoL). We assessed functional outcome and QoL 5 and 12.5 years after SAH.

### Methods

In a consecutive series of 64 patients, mean age at SAH 51 years, initial outcome assessments had been performed at 4 and 18 months after SAH. At the initial and current outcome assessments functional outcome was measured with the modified Rankin Scale (mRS) and QoL with the SF-36 and a visual analogue scale (VAS). We studied the change in outcome measurements over time. We used the non-parametric Wilcoxon test and calculated differences in the domain scores of the SF-36 and the VAS.

### Results

After 5 years seven patients had died; for five patients data were missing. Compared with the 4 month follow-up the mRS had improved in 29 of the 52 patients, in 19 patients the mRS did not change, in 11 it worsened and in five data were missing. The overall QoL (SF-36 domains and VAS score) were better. At 12.5 year an additional six patients had died. In 25 of the 46 patients the mRS was better, compared with 4 months, in 12 the mRS unchanged and in 9 patients the mRS decreased. Between the 5 and the 12.5 years follow-up the improvement in mRS had decreased, but patients reported overall a better quality of life.

### Conclusions

Among long-time survivors QoL may improve over more than a decade after SAH.

## Introduction

Subarachnoid hemorrhage (SAH) from a ruptured aneurysm carries a poor outcome. Within the first months after the hemorrhage a third of the patients dies.[1] Of those who survive the initial weeks, a third is disabled in the first months after the hemorrhage,[1, 2] but recovery continues after this period. In a cohort study 4 and 18 months after the hemorrhage half the patients showed an improvement on the modified Rankin scale (mRS) with at least one point.[2, 3] Of the patients who were independent (mRS<4) at 18 months after the hemorrhage, many experienced a reduced quality of life. Because most patients are between 40 and 60 years old at the time of the hemorrhage, functional disability and quality of life may further improve. If disability and quality of life remain reduced in the long term, this can have considerable impact for patients and for health economics. We assessed the extent of changes in functional outcome and quality of life after five and 12.5 years in a prospectively collected cohort of patients with aneurysmal SAH.

## Methods

We studied a prospectively collected, consecutive series of 98 patients with aneurysmal SAH, admitted to the University Medical Center Utrecht between September 1995 and September 1996. Aneurysmal SAH was diagnosed if CT scanning confirmed the presence of subarachnoid blood and if an aneurysm was found on conventional, CT- or MR-angiography. Patients with a non-aneurysmal cause of the SAH were excluded. Thirty of the 98 enrolled patients had died during their clinical course, two had been excluded from the previous study because they did not speak Dutch and two patients had declined participation in the study. Thus our study consisted of 64 patients. Between 4 months and 18 months three patients had died;[3] their deaths were not directly related to the SAH.

For the five and 12.5 year outcome assessment we first contacted the general practitioner of the patient to find out if the patient was still alive. If not, we asked for

the date and cause of death. If unknown to the general practitioner, we verified the address of the patient via the municipal archives. Patients who had no telephone were sent a letter and asked to call us. We asked the patient by telephone to answer the same questionnaire as after 4 and 18 months follow-up.

**Instruments**

For assessment of disability we applied the modified Rankin scale (mRS)[4], a frequently used functional outcome instrument in stroke. The mRS is a 6-point handicap scale that focuses on restrictions in lifestyle. The Rankin scale is easy to administer, available in a validated Dutch version and reliable in terms of interobserver agreement.[4] This Dutch version is also validated for telephone assessment.[5] For assessment of QoL we used the Medical Outcome Study Short Form 36 (SF-36), a validated instrument to assess general QoL and a visual analogue scale (VAS). The SF-36 is brief (5 to 10 minutes) and measures 8 health-related domains: physical functioning (10 items), role limitations because of physical health problems (4 items), bodily pain (2 items), general health perceptions (5 items), vitality (4 items), social functioning (2 items), role limitations because of emotional problems (3 items) and general mental health (5 items). The SF-36 scores are calculated by assignment of predefined weights to the different items and range per domain from 0 (maximum reduction in QoL) to100 (no reduction in QoL). The validity and reliability of the SF-36 have been studied extensively, also for the Dutch version.[6-9] The VAS ranged from 0 (poor) to 100 (excellent) just by asking the patient to put a mark on this scale for overall well-being.

**Data collection**

All questionnaires were administrated in a semi-structured interview by telephone by one experienced research nurse (PG). We started the interview with a short introduction and reminder of the 4 and 18 months quality of life studies. If the patient was not able to answer the questionnaires because of severe cognitive deficits, we only recorded the Rankin grade of the patient based on information obtained from the partner.

### Data analyses

To compare differences in Rankin grades and quality of life scores between 4 months and 5 years, 4 months and 12.5 years, and 5 years and 12.5 years we used the non-parametric Wilcoxon test. We calculated differences in the domain scores of the SF-36 and of the VAS; the corresponding 95% confidence intervals (95%CI) were based on the paired T-test.

## Results

At time of the 18 months follow-up the study population consisted of 61 patients.

For the 5 years outcome assessment, the mean period of follow-up was 5.5 years after the SAH (range 5.3 – 5.7 years). Four patients (three women, one man) had died between the 18 months and five years outcome assessment. In one patient the general practitioner said that the cause of death was an unverified SAH that occurred abroad, and in three it was cancer. We could no longer contact another four patients, because no telephone number was available and the patients did not respond to our letter. Another patient could be retrieved and contacted by telephone, but was too deaf to be interviewed. The remaining 52 patients could be contacted and none declined participation for the five years outcome assessment.

For the 12.5 years follow-up the mean follow-up was 13.3 years after SAH (range 12.8 – 13.5 years). An additional six patients had died between the 5 and 12.5 years outcome assessment. Four of the five patients who were not interviewed at time of the 5 years outcome assessment were again not interviewed, but were known to be alive. One patient declined further participation. The remaining 46 patients, 34 women and 12 men, could be contacted by telephone for the 12.5 years outcome assessment.

### *Functional outcome*

Figure 1A provides an overview of the proportions of the patients still alive at outcome assessment with distribution of mRS grades, together with the proportions of patients who had died and patients whose data were missing at the four moments at which we assessed outcome. Figure 1B shows the proportions of the patients still

alive at outcome assessment with distribution of mRS grades, together with the proportions of patients who had died and Figure 1C displays the proportions only for the surviving patients at outcome assessment with distribution of mRS grades.

Figure 1A. Proportions of surviving patients with distribution of mRS grades, dead and missing patients

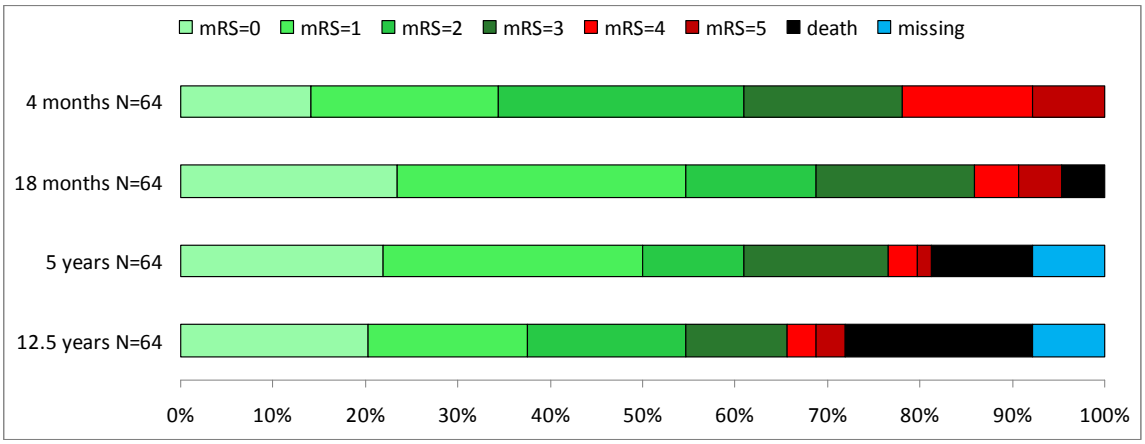



Figure 1B. Proportions of surviving patients with distribution of mRS grades, dead patients

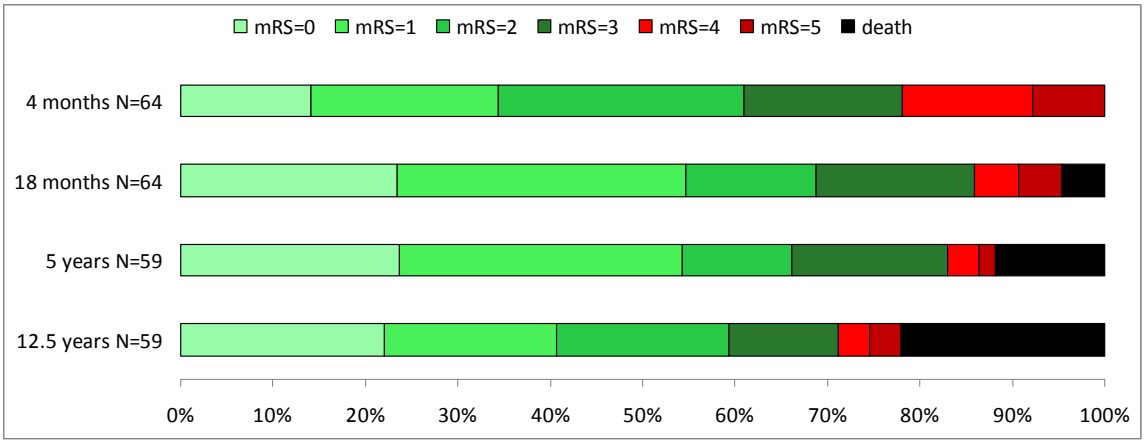
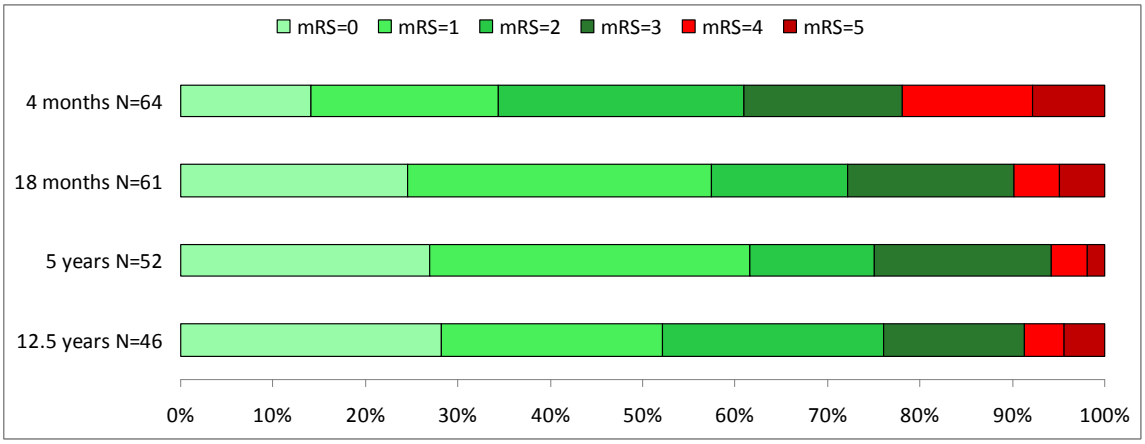



Figure 1C. Proportions of surviving patients with distribution of mRS grades



The changes and corresponding Wilcoxon tests of mRS grades between 4 months - 5 years, 4 months - 12.5 years, 5 and 12.5 years are shown in Tables 1A - 1C.

Table 1A. Modified Rankin grades at 4 months and 5 years follow-up

| | | 5 years | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | dead | missing | total |
| 4 months | 0 | 7 | 2 | - | - | - | - | - | - | 9 |
| | 1 | 3 | 5 | 1 | 2 | - | - | 1 | 1 | 13 |
| | 2 | 3 | 6 | 3 | - | - | - | 4 | 1 | 17 |
| | 3 | 1 | 5 | 2 | 2 | - | - | - | 1 | 11 |
| | 4 | - | - | 1 | 5 | 1 | - | - | 2 | 9 |
| | 5 | - | - | - | 1 | 1 | 1 | 2 | - | 5 |
| total | | 14 | 18 | 7 | 10 | 2 | 1 | 7 | 5 | 64 |

Table 1B. Modified Rankin grades at 4 months and 12.5 years follow-up

| | | 12.5 years | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | dead | missing | total |
| 4 months | 0 | 4 | 2 | - | - | - | - | 2 | 1 | 9 |
| | 1 | 4 | 2 | 3 | 1 | - | - | 2 | 1 | 13 |
| | 2 | 4 | 4 | 3 | 2 | - | - | 4 | - | 17 |
| | 3 | 1 | 2 | 5 | 1 | - | - | 1 | 1 | 11 |
| | 4 | - | 1 | - | 2 | 1 | 1 | 2 | 2 | 9 |
| | 5 | - | - | - | 1 | 1 | 1 | 2 | - | 5 |
| total | | 13 | 11 | 11 | 7 | 2 | 2 | 13 | 5 | 64 |

Table 1C. Modified Rankin grades at 5 and 12.5 years follow-up

| | | 12.5 years | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | dead | missing | total |
| 5 years | 0 | 9 | 1 | - | 1 | - | - | 2 | 1 | 14 |
| | 1 | 4 | 9 | 4 | 1 | - | - | - | - | 18 |
| | 2 | - | 1 | 6 | - | - | - | - | - | 7 |
| | 3 | - | - | 1 | 4 | 1 | - | 4 | - | 10 |
| | 4 | - | - | - | - | 1 | 1 | - | - | 2 |
| | 5 | - | - | - | - | - | 1 | - | - | 1 |
| dead | | - | - | - | - | - | - | 7 | - | 7 |
| missing | | - | - | - | 1 | - | - | - | 4 | 5 |
| total | | 13 | 11 | 11 | 7 | 2 | 2 | 13 | 5 | 64 |

Wilcoxon tests for comparisons of mRS: 4 m - 5 y, p = 0.12; 4 m - 12.5 y, p = 0.58; 5 y - 12.5 y, p = 0.01

m Rankin scale: 0 (no symptoms at all)
1 (no significant disability despite symptoms)
2 (slight disability)
3 (moderate disability)
4 (moderately severe disability)
5 (severe disability)

In 19 patients the mRS was the same at the 4 months and 5 years follow-up, in 29 patients the mRS was better. In 18 of these patients 29 patients the mRS had improved 1 point, in 10 it had improved 2 points, and in one patient it had improved 3 points. In 12 patients the mRS grade was the same at the 4 months and the 12.5 years follow-up. In 25 patients the mRS grade was better; of these patients 16 had improved 1 point, seven had improved 2 points, and two patients had improved 3 points. Between the 5 and the 12.5 years follow-up the improvement had decreased: one patient reported a heart operation and one a myocardial infarction. Another patient had a colon cancer. In 30 patients the mRS grade was the same.

### *Quality of life in patients*

Table 2 shows the differences for the domains of the SF-36 and the VAS score between 4 months and 5 years, 4 months and 12.5 years, and 5 and 12.5 years.

Table 2: Differences over time in SF-36 and VAS

| | 4 m | 5 y | 12.5 y | 4 m – 5 y* | 4 m – 12.5 y# | 5 y – 12.5 y# |
|---|---|---|---|---|---|---|
| | | means | | | differences (95%CI) | |
| SF-36 | | | | | | |
| PF | 68.7 | 74.7 | 77.2 | 6.5 (0.6 – 12.4) | 5.9 (-0.3 – 11.4) | -1.7 (-8.0 – 4.6) |
| RP | 24.6 | 62.5 | 91.3 | 34.8 (18.9 – 50.6) | 64.0 (50.9 – 77.1) | 25.0 (7.9 – 42.1) |
| BP | 75.1 | 85.9 | 92.2 | 7.6 (1.2 – 13.9) | 14.4 (6.3 – 22.6) | 6.0 (-1.7 – 13.6) |
| GH | 70.7 | 73.4 | 71.9 | 0.5 (-6.4 – 7.4) | -1.2 (-8.2 – 5.8) | -4.1 (-9.4 – 1.1) |
| VT | 60.1 | 59.8 | 65.3 | -2.2 (-7.9 – 3.5) | 3.4 (-2.5 – 9.4) | 3.9 (-0.5 – 8.3) |
| SF | 66.3 | 80.7 | 90.4 | 12.0 (2.9 – 21.0) | 22.6 (13.1 – 32.0) | 6.4 (-3.0 – 15.8) |
| RE | 59.5 | 81.3 | 96.9 | 18.8 (3.3 – 34.4) | 39.0 (25.9 – 52.1) | 13.8 (1.4 – 26.3) |
| MH | 70.1 | 70.4 | 73.8 | 0.4 (-5.0 – 5.9) | 4.5 (-1.3 – 10.3) | 2.8 (-1.2 – 6.8) |
| PCS | 42.8 | 48.6 | 51.1 | 4.7 (2.1 – 7.4) | 6.7 (3.8 – 9.6) | 1.5 (-1.2 – 4.2) |
| MCS | 47.2 | 49.4 | 52.7 | 1.5 (-1.8 – 4.9) | 5.9 (2.7 – 9.1) | 2.8 (0.2 – 5.8) |
| VAS | 59 | 72 | 76 | 11 (5 – 17) | 16 (9 – 23) | 3 (-6 – 7) |

* 46 pairs; # 41 pairs;

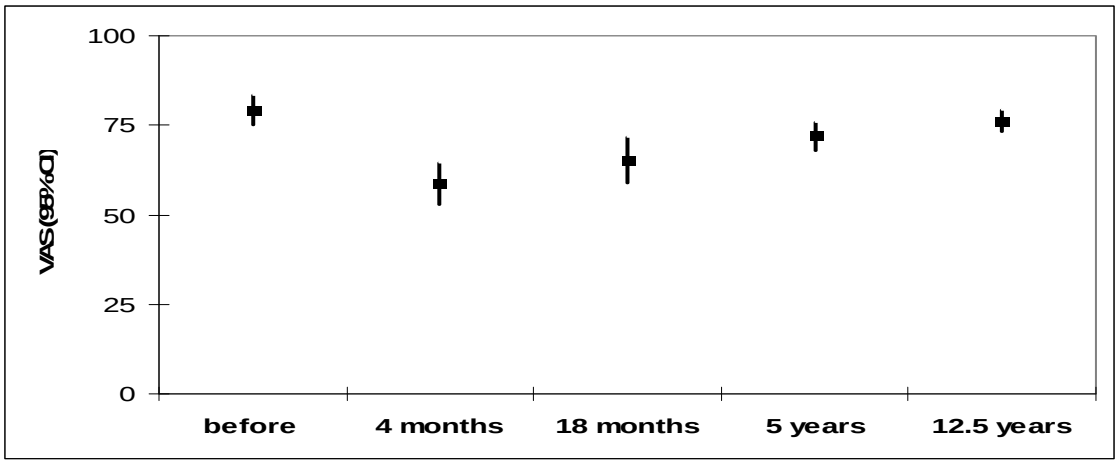
SF-36:

PF = physical functioning
RP = role limitations because of physical health problems
BP = bodily pain
GH = general health perceptions
VT = vitality
SF = social functioning
RE = role limitations because of emotional problems
MH = general mental health
PCS = physical summary scale
MCS = mental summary scale

In the SF-36 the domains role limitations because of physical health problems and role limitations because of emotional problems the scores are clearly higher (improvement) after 5 years than at 4 months and further increased after 12.5 years follow-up. On the contrary the physical functioning and general mental health scores worsened.

Figure 2 shows VAS scores after 4 months, 18 months, 5 and 12.5 years follow-up.

Figure 2: VAS score according to time




Also at very long-term follow-up the surviving patients reported improvement in their wellbeing compared with their score at 4 months. At 5 year follow-up most patients reported their functional, social and physical problems as SAH-related: persistent tiredness, slowness, impairment of memory, change in personality, headache and concentration problems.

## Discussion

This study shows that recovery among patients who have survived an episode of SAH continues in the long-term. Between 4 months and 5 years after the hemorrhage half the surviving patients showed an improvement on the modified Rankin scale (mRS) with at least one point. Between 5 and 12.5 years follow-up there was no further improvement but even a slight decrease in functional outcome.

At 12.5 years follow-up patients reported the functional status to be “normal for my age”, despite a decline in physical functioning because they attributed this reduced physical functioning to other diseases they had, such as osteoporosis, emphysema, cancer, diabetes, heart failure, and impairment of vision and hearing. Despite a reduced physical functioning between 5 and 12.5 years outcome assessment, QoL had improved over this period. This suggests that patients continue to adapt and improve coping with restrictions in functioning. Psychological adaptation has been described also in other chronic diseases.[10] The overall good QoL indicates an improved appreciation of life also long after recovery of a life-threatening illness. Similar observations have been done in long-term survivors of TIA or minor ischemic stroke who have an overall QoL not much different the norm population.[11]

Some limitations of the current study have to be mentioned. To assess disability in terms of functional outcome and quality of life we used the mRS, the SF-36 and a VAS, because these outcome measurements had also been used at the 4 and 18 months follow-up, before the current study was developed. The Sickness Impact Profile (SIP) was also used in the initial outcome assessments, but had similar outcomes at 4 and 18 months and did not discriminate between patients with improved and unchanged Rankin grades.[3] The SIP contains 136 items and is very time-consuming. For both reasons we decided not to continue using the SIP during the 5 year and the 12.5 year follow-up. A disease specific quality of life list was not used in 1995. Therefore we cannot distinguish between disability remaining from the SAH and disability as a result of other, age-related diseases. Another limitation is that the initial cohort of 64 patients is relatively small and all interviews were administered by telephone. However, we demonstrated that telephone assessment of the mRS with a structured interview has good agreement with face-to-face assessment.[5] Strong points are that at 12.5 years outcome there was no loss to follow-up and all interviews were performed by the same research nurse. As far as we know this is the first attempt to assess of functional outcome and QoL over more than a decade in SAH patients. Therefore we could not compare our results with those from other studies. We conclude that it is important for patient care to inform patients and their partners that QoL may improve over more than a decade after

SAH. In further studies the relationship between functional outcome and QoL at long-term follow-up should be assessed, as well as determinants of a good outcome long after the SAH.

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# Chapter 8

# General discussion

The incidence of spontaneous subarachnoid haemorrhage (SAH) in Western Europe is 9 per 100.000 per year which means that in the Netherlands each year approximately 1400 persons have an SAH.[1] The most common cause of an SAH is rupture of an aneurysm of one of the intracranial arteries. These aneurysms are not present at birth but develop during life.[2] Most aneurysms are sporadic, but in around 10% of patients there is a familial preponderance.[3] Other risk factors are smoking, hypertension and excessive use of alcohol.[2, 4] Rupture of an intracranial aneurysm results in a sudden increase in intracranial pressure, with often a cessation of intracranial circulation.[5] Clinically, this cessation of intracranial circulation is expressed in a loss of consciousness and is usually short lasting, but is irreversible in around 10% of patients.[6] These are the patients who die early after the haemorrhage, usually before admission to hospital. Patients who reach hospital alive are at risk of several complications. The most feared complication is rebleeding, which leads to poor outcome in around 80% of patients.[7] To prevent rebleeding, the aneurysm is occluded by means of endovascular coiling or neurosurgical clipping. Besides rebleeding, other complications are delayed cerebral ischaemia, hydrocephalus and cardiopulmonary complications. The impact of the initial haemorrhage and the complications result in a poor short-term outcome in patients with ASAH: one-third of the patients dies in the first weeks after the haemorrhage and one-third of the patients remains dependent on help from others for daily activities.[8, 9] This does not apply to patients with a perimesencephalic haemorrhage (PMH), a non-aneurysmal form of SAH; short-term outcome in these patients is good.[10] In contrast to the extensively studied short-term outcome, data on long-term follow-up are scarce. In this thesis we studied long-term follow-up in patients after an aneurysmal or perimesencephalic SAH.

**Aneurysmal subarachnoid haemorrhage**

To inform and advise patients better about the long-term effects after SAH it is important to follow them in time. However, regular and long-term follow-up is not easy to perform. In outpatient clinics follow-up is time-consuming and expensive. An

alternative is regular follow up by telephone interviews. At first glance this seems easier to perform. However, a considerable proportion of patients resumes some kind of work, and thus cannot be reached during office hours. Another drawback is the increasing proportion of patients with a mobile phone only, with frequently changing numbers. Because more and more patients now have internet access, follow up through internet or e-mail may also be an option for regular and long-term follow-up. We found that e-mail is easy and acceptable for patients after an SAH. Patients can chose a proper time to respond and e-mail follow-up is less time-consuming than telephone calls. Another strong point is that if the patient has moved, the e-mail address remained the same. However, the proportion of patients with no or with a changing e-mail address is also considerable, thus, till now follow-up through e-mail cannot replace other forms of follow-up entirely. The development of a Dutch website for SAH patients admitted to our hospital has to be explored. An SAH website has additional benefits: patients can obtain information about SAH and options for treatment, patients can fill out a yearly questionnaire and they can ask questions. If patients forget to use the website it will be easy to send a reminder by regular mail.

The most frequently used outcome measurements for patients with SAH are case-fatality rates, functional outcome in terms of handicap and quality of life. To assess changes over time in functional outcome we used the modified Rankin scale (mRS)[11] and for changes in quality of life we used the SF-36[12-14] and a visual analogue scale (VAS). Overall we observed improvement between 4 months and 5 years. Only in the SF-36 domain general mental health (psychological distress and psychological well-being) the score was worse after 5 years follow-up compared to 4 months. In the domains role limitations because of physical heath problems and role limitations because of emotional problems the scores were twice as good after 5 years. In the follow-up 12.5 years after the SAH (mean age of the patients 63.5 years) the scores for the functional status in the long-term survivors worsened, probably as a result of age-related problems, whereas quality of life improved.

Patients who are partly or completely dependent on help for daily activities (mRS 4 = moderately severe handicap, or 5 = severe handicap) after an SAH are usually

discharged to a nursing home. The prognosis for patients after an ischaemic stroke who are admitted to a nursing home is poor; 35% of the patients die within the first year.[15] Patients who have had an SAH have a tendency to improve over time, mostly within 2 years, after admission to a nursing home. Our long-term follow-up study shows that one-third of SAH patients admitted to a nursing home was discharged home or to another facility and became independent for daily activities. Another finding is that those patients who were admitted to a nursing home in the most recent study period did better than those admitted in the first part of the study. The information of this study can help to explore which type of rehabilitation offers the best chances for SAH patients admitted to a nursing home. It also can give other healthcare professionals motivation to provide high quality of care to this patient population. Half of the SAH patients survived more than five years after admission to a nursing home. The search for determinants of recovery needs further attention.

To study familial occurrence of SAH it is important to obtain accurate information about history of SAH in families. The family history obtained at the bedside may not be sufficient if a decision has to be taken for familial screening. Most cerebro-vascular accidents in families are just known as “a stroke” or patients do not know all their family members and their health status. In a series of 163 patients with SAH we interviewed all first and second degree relatives, with verification of medical record data to assess the validity of the family history. We found that one quarter of the families with a positive history for SAH in a first degree relative would have been undetected without the information provided by contacting all relatives systematically. In first and second degree relatives together the proportion of undetected families rose to almost a half. Thus, scrutinising all family members is pivotal for a more thorough collection of data if decisions are to be taken based on the family history. Genetic research has become important. For genetic studies it is important matters to study the family history extensively and then the accuracy of the family history taken at the bedside only is insufficient.

**Perimesencephalic haemorrhage**

In 10% of SAH's the cause is a PMH. This benign, non-aneurysmal subset of spontaneous subarachnoid haemorrhage is presumed to have venous source: the invariably good clinical condition at onset, the often more gradual onset of headache and the localized nature of the blood on computed tomography (CT)[16] all argue against spurting of blood under arterial pressure and favour a venous oozing of blood.[17] Patients who have had an SAH or cerebro-vascular accident are considered high-risk cases for drivers licence in the first six months after the stroke or for health and life insurance in later years. In patients with a PMH the outcome in short-term follow-up is good in terms of working capacity and quality of life. Patients have no risk for rebleeding in the initial months after the haemorrhage and have no persisting neurological deficits. However, no data were available for long-term outcome. In our long-term follow-up study we conducted a telephone interview in a cohort of 160 patients with a PMH admitted to our hospital between 1983 and 2005. During follow-up none of these 160 patients had had another episode of SAH, and overall 11 patients had died, whereas the expected number of deaths based on mortality rates in the general population was 18. Thus patients with a PMH have no reduced life expectancy. No restrictions should be imposed on these patients by physicians. Health or life insurance companies and authorities regulating drivers' licences no longer should regard patients after a PMH as high risk cases.

Anosmia (loss of smell) frequently occurs after ASAH not only after clipping, but also after endovascular coiling.[18-20] Thus, at least in part, anosmia is caused by the haemorrhage itself and not only by surgical treatment. However, it is unknown whether anosmia is related to rupture of the aneurysm with sudden increase in intracranial pressure or to the presence of blood in the basal cisterns. Therefore, we studied the proportion of patients with anosmia after nonaneurysmal perimesencephalic haemorrhage. Nine of 148 patients had noticed anosmia shortly after the PMH, so anosmia occurs in one of every 16 patients with PMH, which is lower than previously reported rates after coiling in patients with SAH, but higher than rates after coiling for unruptured aneurysms.[18-20] These data suggest that blood in the basal cistern (in the vicinity of the olfactory nerves) plays a role in the

development of anosmia. Loss of smell has an important impact on quality of life and patients have to be informed about occurrence and prognosis of anosmia after a PMH.

**Strengths and limitations**

All studies were embedded within the infrastructure of a large research group specialised in the treatment of SAH patients with an aneurysmal or perimesencephalic haemorrhage in the University Medical Center Utrecht. Our database contains a prospectively collected, consecutive series of more than 3100 SAH patients since 1983. As little as 15 patients are lost to follow-up, in 35 of the patients who are living abroad it is unknown if they are alive. These studies are performed by a dedicated nurse and therefore the results may not be generalisible. The very long-term follow-up in these studies is unique and not feasible within the context of a regular PhD study.

Some limitations have to be mentioned. First, in our study of functional outcome and quality of life we only used the modified Rankin scale (mRS), the SF-36 and a visual analogue scale (VAS), because these instruments were applied at the 4 and 18 months follow-up. A disease specific list was not yet validated at that time. This is the first attempt to study long-term functional outcome and QoL in SAH patients and therefore we could not compare our study with that of others. Secondly, we studied the long-term prognosis of those patients with SAH and an mRS 4 or 5 who were admitted to a nursing home. We did not study the reason why they were discharged to the nursing home, but used the mRS as a global measure of disability that is not very specific to true functional status. A more specific index reflecting functional performance on activities on daily living (ADL) or possibly physical performance would provide a more appropriate reflection of the patient's abilities at discharge, but such data were not collected in our study.

**Implications of this thesis for patient care and future research**

Patients who had an SAH are relatively young (age 40 – 60) and the impact on everyday life for family, work and social functioning, is high. Not only disability, but also neuropsychological and psychosocial problems impair their quality of life. To inform patients better after discharge it is important to see them once in a multi-disciplinary team at the outpatient clinic for a check-up by a specialised team six weeks after the haemorrhage. In one visit they see a dedicated nurse, a neuropsychologist for a short neuropsychological screening and a rehabilitation physician. This SAH-Rehabilitation aftercare includes: inventory symptoms, information about risk factors as smoking, hypertension and family history, risk of a new event and limitations in functional outcome and QoL. SAH patients in whom the aneurysm was treated by means of neurosurgical clipping are also seen by the neurosurgeon. All SAH patients should yearly be followed by means of a very short questionnaire. A special website for SAH patients has to be developed for serial follow-up and to inform and advise SAH patients better. Patients who are discharged to a nursing home have to be reactivated as soon as possible after admission and these patients and their partners have to be informed on the possibility of improvement in the long-term. The type of rehabilitation that offers best chances to these patients has to be investigated.

From my personal experience of interviewing many SAH patients, stress and major life events as death, divorce or to be dismissed, may very well be triggers to develop SAH – the relation of these factors with the onset of SAH should be further investigated.

The impact of the initial haemorrhage and the complications result in a poor short-term outcome in patients with an aneurysmal SAH, but these patients may improve in the long-term with regard to functional outcome and quality of life. Other important issues that need to be addressed in future studies are: persisting tiredness immediately after the SAH and the years thereafter and determinants for recovery after initial poor outcome. Patients who are depressed could may benefit from a diet or antidepressants. Recent studies have shown anosmia after SAH, but hearing loss and hypersensitivity of hearing also occur after SAH, but little is known about their prevalence and risk factors.

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# Chapter 9

## Summary

Samenvatting

List of publications

Dankwoord

Curriculum Vitae

Of all stroke patients 5% has a subarachnoid haemorrhage (SAH). An SAH is a bleed in the so-called subarachnoid space, which is the very small space between the brain and the skull that contains blood vessels that supply the brain. Every year 9 per 100.000 patients have an SAH and half the patients are younger than 55 years old. In most instances (80%) the cause of the bleeding is a ruptured aneurysm, in 10% a perimesencephalic nonaneurysmal haemorrhage (PMH) and in the remainder intracranial artery dissection and miscellaneous rare causes. SAH from a ruptured intracranial aneurysm has a poor outcome: 35% of the patients dies in the first 4 weeks after the haemorrhage and 20% remains dependent for activities of daily life. Life expectancy is reduced after aneurysmal SAH (ASAH), probably from an excess of other heart and vessel diseases. A disabling factor after SAH from a ruptured intracranial aneurysm is anosmia. The presumed causes of anosmia are the haemorrhage itself, the treatment by clipping or coiling or the rupture of the aneurysm with sudden increase in intracranial pressure.

Patients with a perimesencephalic nonaneurysmal haemorrhage have a good outcome in terms of recurrence, working capacity and quality of life. The cause of a perimesencephalic haemorrhage favours a venous source, supported by normal arteriograms and absence of arterial haemorrhage.

**Chapter 2** describes the supplemental value of scrutinising the history of all first and second degree relatives to detect SAH and heart and vessel diseases in a consecutively collected cohort of patients with ASAH admitted to our hospital. A pedigree was drawn up for 163 families and all living relatives over 18 years were interviewed by telephone, by means of a standard questionnaire. The included 163 patients had 1290 first degree and 3588 second degree relatives. Almost a half of the families with a positive history for SAH in a first or second degree relative would have been gone undetected without the information provided by scrutinising all individual relatives.

Serial follow-up by telephone of all patients with a ruptured ASAH is time-consuming, since part of them resumes daily work and cannot be contacted during office hours. In **Chapter 3** we studied the feasibility of follow-up through e-mail in patients discharged after a ruptured aneurysmal SAH. E-mail follow-up was easy to

perform, comfortable for the patient or relative and less time-consuming than follow-up by telephone. However, only 60% of all included patients had an e-mail address and 21% of those patients changed once or more the e-mail address.

Life expectancy is reduced after aneurysmal SAH. Patients with a PMH have a good outcome and there is no risk of recurrence, but whether life expectancy is reduced after the haemorrhage is unknown. In **Chapter 4** we describe a long-term follow-up study to assess life expectancy in 160 patients with a PMH with a total number of patients-years of 1213. At time of follow-up (range 1 – 23 years) 149 patients were still alive. The study shows that patients with PMH have no excess in mortality compared with the general population. Even on very long-term follow-up no episodes of rebleeding occurred and all patients regained independence for activities of daily life.

In **Chapter 5** we studied anosmia after PMH. The presumed causes of anosmia after a ruptured aneurysmal SAH are the sudden intracranial arterial pressure or the presence of blood in itself. The cause of a PMH has not yet been identified but favours a venous source. It is unknown whether anosmia can develop after a PMH. In our study nine of 148 included patients had noticed a loss of smell already during the clinical course. Two patients reported a complete recovery after 8 to 12 weeks. We found no relation between anosmia and risk factors such as age, sex or hydrocephalus.

In general, life expectancy after admission to a nursing home is short and chances of discharge are small. Most patients are elderly, and often have degenerative diseases or comorbidity. Patients with an SAH are relatively young and tend to improve in functional outcome and quality of life. **Chapter 6** describes long-term outcome of patients discharged to a nursing home after SAH. Of 1149 SAH patients admitted to our hospital, 92 (8%) were discharged to a nursing home. After 2 years 28 (30%) of these patients were discharged home or to another facility and forty-four patients (43%) lived longer than 5 years.

**Chapter 7** is a continuation to a former study of quality of life after 4 and 18 months in patients after a SAH. In that cohort of patients there was improvement of functional outcome measured in modified Rankin scale and quality of life measured

in SF-36 and a VAS score. We performed a long-term follow-up study after 5 and 12.5 years. Overall there was still an improvement in quality of life, while functional outcome worsened between 5 and 12.5 years follow-up.

## Chapter 9

Summary

**Samenvatting**

List of publications

Dankwoord

Curriculum Vitae

Van alle patiënten met een beroerte heeft 5% een subarachnoïdale bloeding. Een subarachnoïdale bloeding is een bloeding tussen de hersenvliezen, de ruimte tussen de hersenen en de schedel. Jaarlijks krijgen in Nederland 9 op de 100.000 mensen, dat is ongeveer 1400 mensen, een dergelijke bloeding en de helft van de patiënten is jonger dan 55 jaar. Bij 80% wordt een subarachnoïdale bloeding veroorzaakt door een gebarsten intracranieel aneurysma, en bij10% door een zogenaamde perimesencephale bloeding, die niet uit een aneurysma ontstaat. Het restant ontstaat uit verschillende zeldzame oorzaken. Een subarachnoïdale bloeding uit een gebarsten aneurysma is een ernstige aandoening: 35% van de patiënten overlijdt in de eerste 4 weken na de bloeding en van de overige patiënten blijft 20% geïnvalideerd en afhankelijk van anderen. De levensverwachting van deze patiënten is verminderd ten opzichte van die in de open bevolking ten gevolge van een hogere kans op andere hart en vaatziekten. Een andere invaliderende factor na een subarachnoïdale bloeding uit een geruptureerd aneurysma is anosmie (onvermogen om te ruiken). De vermoedelijke oorzaken van anosmie zijn de aanwezigheid van bloed in de basale cisternen, het spuiten van arterieel bloed in de subarachnoïdale ruimte en de behandeling van het geruptureerde aneurysma door middel van clippen (het chirurgisch afklemmen van het aneurysma) of coilen (het neuroradiologisch opvullen van het aneurysma door middel van coils).

Patiënten met een perimesencephale bloeding herstellen goed en hebben geen slechtere kwaliteit van leven of een verminderde geschiktheid voor werk. De oorzaak van een perimesencephale bloeding lijkt niet van arteriële, maar van veneuze aard, maar het is onbekend of anosmie ook na een dergelijke bloeding op kan treden.

In **hoofdstuk 2** wordt bij een opeenvolgende groep patiënten met een geruptureerd aneurysma een onderzoek beschreven naar het optreden van aneurysmata en hart- en vaatziekten bij alle eerste en tweede graads familieleden. Voor dit onderzoek werd van alle 163 patiënten een stamboom gemaakt. De 163 geïncludeerde patiënten hadden 1290 eerstegraads en 3588 tweedegraads familieleden. Bij alle in leven zijnde familieleden boven de 18 jaar werd telefonisch een vragenlijst afgenomen. Door het uitgebreide familie onderzoek werden bij eerste- en

tweedegraads familieleden bijna de helft meer familieleden gevonden met een subarachnoïdale bloeding. In de dagelijkse praktijk zal het maken van een stamboom en het benaderen van elk familielid afzonderlijk te veel tijd kosten, maar bij onderzoek naar familiaire risicofactoren is het zinvol om een uitgebreide familie stamboom te maken, omdat een patiënt zelf meestal niet op de hoogte is van de ziektegeschiedenis van alle familieleden.

Follow-up van alle patiënten met een subarachnoïdale bloeding is tijdrovend, omdat veel patiënten weer geheel of gedeeltelijk hun werk hervatten en dus niet op kantooruren bereikbaar zijn. In de studie beschreven in **hoofdstuk 3** wordt gekeken naar de haalbaarheid van follow-up door middel van e-mail. E-mail follow-up bleek eenvoudig uitvoerbaar, gemakkelijk voor de patiënt en minder tijdrovend dan een telefonische follow-up. Een nadeel is dat maar 60% van alle geïncludeerde patiënten een e-mail adres had of vaak van e-mail adres wisselde (21%). Een voordeel is dat de patiënt of een familielid zelf het tijdstip kan bepalen om te antwoorden.

In **hoofdstuk 4** beschrijven we de levensverwachting op de lange termijn bij patiënten die een perimesencephale bloeding hebben gehad. Van de 160 geïncludeerde patiënten waren er op het moment van follow-up (range 1 - 23 jaar) nog 149 in leven. Geen van de patiënten had een nieuwe perimesencephale bloeding gehad. Hoewel het ook hier gaat om een subarachnoïdale bloeding hadden deze patiënten geen beperkte levensverwachting in vergelijk met de open bevolking.

In **hoofdstuk 5** wordt gekeken naar het voorkomen van anosmie (niet kunnen ruiken) bij patiënten met een perimesencephale bloeding. De vermoedelijke oorzaken van anosmie bij een subarachnoïdale bloeding zijn de initiële druk door het barsten van het aneurysma of de aanwezigheid van bloed. De oorzaak van een perimesencephale bloeding is waarschijnlijk van veneuze aard en dus anders dan bij een subarachnoïdale bloeding uit een gebarsten intracranieel aneurysma. Negen van de 148 patiënten met een perimesencephale bloeding (6.1%) konden minder goed ruiken na de bloeding. Bij 2 patiënten herstelde de reuk zich binnen 8 tot 12 weken. We vonden geen relatie tussen anosmie en risicofactoren zoals leeftijd, geslacht en hydrocephalus.

Doorgaans hebben patiënten die opgenomen worden in een verpleeghuis een korte levensverwachting en weinig kans op herstel. Vaak zijn het oudere patiënten die naast een ziekte ook algemene klachten van achteruitgang en comorbiditeit hebben. In een retrospectieve cohort studie was binnen 1 jaar 35% van de patiënten overleden. Patiënten met een subarachnoïdale bloeding zijn relatief jong en mogelijk is er wel een kans op verder herstel. In **hoofdstuk 6** beschrijven we de lotgevallen op lange termijn van patiënten die na een subarachnoïdale bloeding ontslagen zijn naar een verpleeghuis. Van de 1149 patiënten die opgenomen werden in ons ziekenhuis met een subarachnoïdale bloeding werden 92 patiënten (8%) ontslagen naar een verpleeghuis. 28 van deze patiënten (30%) waren na 2 jaar uit het verpleeghuis ontslagen naar huis of naar een andere woonvoorziening en 44 patiënten (48%) leefden langer dan 5 jaar.

In een eerdere studie naar de kwaliteit van leven op 4 en 18 maanden bij patiënten met een subarachnoïdale bloeding is een duidelijk herstel te zien, gemeten in functionaliteit en kwaliteit van leven. In **hoofdstuk 7** wordt hetzelfde cohort patiënten beschreven na 5 en 12.5 jaar. Ook na 5 en 12.5 jaar gaat de kwaliteit van leven bij patiënten na een subarachnoïdale bloeding nog steeds vooruit.

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**List of publications**

Dankwoord

Curriculum Vitae

## This thesis

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**Het Trial Bureau Neurologie** is een kleine wereld, maar mijn leefwereld is groot.

Dank voor iedereen die, bewust of onbewust, mij gevormd en gevolgd heeft in die wereld.

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**Prof.dr Ale Algra**: vanaf mijn eerste werkdag op het Trial Bureau Neurologie, een eigen wereldje in de keet op het grasveld voor het AZU, was je mijn vraagbaak voor alles wat ik niet wist over computers en dataverzameling en ik wist er echt helemaal niets van. Verder maakte je me enthousiast voor een epidemiologie cursus, een cursus over trials, en het zelf SPSS-en. Daaruit volgt dan eigenlijk als vanzelf een eerste artikel en daarna nog een en nog een. Ik waardeer het dan ook bijzonder dat je nu, door mijn promotor te zijn, mij de mogelijkheid biedt te promoveren.

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**Curriculum Vitae**

Paut (Jannetje) Greebe was born in Groningen and after one year she moved to Zweeloo, Drenthe. She finished high school at the Gemeentelijk Lyceum in Emmen.
In Haarlem she attended nursing school at the St. Elisabeth's of Groote Gasthuis and graduated as a nurse. The year after her graduation she specialized in Child care. After obtaining her degree in child nursing in 1972, she was appointed as head of the department for children between four and six years old in the Medisch Kleuterdagverblijf Margriet te Haarlem.
In 1975 she moved to Velsen and started as project manager for a dental health care education project (Tandheelkundig Gezondheids Voorlichting en Opvoedingsproject (TGVO) in the community of Velsen.
From 1977 on she raised three daughters and meanwhile she taught playing the flute and served as board member of several committees.
When her daughters went to high school she started a management course in Haarlem and graduated in 1991. Meanwhile she was appointed as research nurse, later on also as coordinator, in the Trial Office Neurology in the University Hospital in Utrecht. The first study she was involved in, Familial Subarachnoid Haemorrhage, raised her enthusiasm for research and analyzing data. Therefore she attended a Clinical Trial Course in Edinburgh, Scotland and an epidemiology Course at the Julius Centre in Utrecht. This resulted in a first article that was published in 1997. Besides her daily business as research nurse in large national and international trials as the European / Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), the Magnetic resonance Angiography in Relatives of patients with Subarachnoid haemorrhage study (MARS), the International Study of Unruptured Intracranial Aneurysms (ISUIA) and Aneurysm Screening after Treatment of Ruptured Aneurysms (ASTRA), her steering and writing committee membership in some of these and other trials and the daily work in the Trial Office, she steadily worked at the research based on this thesis. The stimulating environment of work and marriage has contributed to the final results.