

## RISKS AND BENEFITS OF SCREENING FOR INTRACRANIAL ANEURYSMS IN FIRST-DEGREE RELATIVES OF PATIENTS WITH SPORADIC SUBARACHNOID HEMORRHAGE

THE MAGNETIC RESONANCE ANGIOGRAPHY IN RELATIVES OF PATIENTS WITH SUBARACHNOID HEMORRHAGE STUDY GROUP\*

### ABSTRACT

**Background** The first-degree relatives of patients who have subarachnoid hemorrhage from ruptured intracranial aneurysms are themselves at risk for subarachnoid hemorrhage. We studied the benefits and risks of screening for aneurysms in the first-degree relatives of patients with sporadic subarachnoid hemorrhage.

**Methods** We screened 626 first-degree relatives (parents, siblings, or children) of 160 patients with sporadic subarachnoid hemorrhage, from a prospective series of 193 consecutive index patients. Magnetic resonance angiography was the screening tool, and conventional angiography was used as the reference test in subjects thought to have aneurysms. Six months after elective operation, outcome was assessed by means of the modified Rankin scale of neurologic function. This observational study design was combined with a decision-analysis model to estimate the effectiveness of screening. The efficiency of screening was defined by the number of relatives who needed to be screened in order to prevent one subarachnoid hemorrhage.

**Results** Aneurysms were found in 25 of 626 first-degree relatives (4.0 percent; 95 percent confidence interval, 2.6 to 5.8 percent). Eighteen underwent surgery, which resulted in a decrease in function in 11 (disabling in 1). Five had medium-sized aneurysms that were 5 to 11 mm in diameter, 11 had small aneurysms that were less than 5 mm, and 2 had both small and medium-sized aneurysms. On average, surgery increased estimated life expectancy by 2.5 years for these 18 subjects (or by 0.9 month per person screened), at the expense of 19 years of decreased function per person. The number of relatives who would need to be screened in order to prevent 1 subarachnoid hemorrhage on a lifetime basis was 149, and 298 would have to be screened in order to prevent 1 fatal subarachnoid hemorrhage.

**Conclusions** Implementation of a screening program for the first-degree relatives of patients with sporadic subarachnoid hemorrhage does not seem warranted at this time, since the resulting slight increase in life expectancy does not offset the risk of postoperative sequelae. (N Engl J Med 1999;341:1344-50.)

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**T**HE outcome of subarachnoid hemorrhage from a ruptured aneurysm remains poor, with a case fatality rate of 50 percent and a rate of functional dependence of 20 percent.<sup>1</sup> The risk of subarachnoid hemorrhage among first-degree relatives (parents, siblings, and children) of affected patients is three to seven times that in the

general population.<sup>2,3</sup> Magnetic resonance angiography (MRA) has offered a noninvasive method of screening for intracranial aneurysms. The benefits and risks of screening and the associated costs have not been prospectively assessed for persons who have only one affected first-degree relative, although this important issue has recently been discussed.<sup>4-6</sup>

Screening programs targeted at persons with at least two affected relatives have been evaluated. Intracranial aneurysms were found in approximately 8 percent of the subjects, but estimates of the effectiveness of screening were not reported.<sup>7,8</sup> Studies involving decision analysis have suggested that screening followed by surgery might be effective, especially in young people,<sup>9,10</sup> but these studies had to estimate some of the essential variables.

We prospectively screened first-degree relatives of consecutive patients with subarachnoid hemorrhage. We documented the outcome in relatives who underwent surgery for their aneurysms. We also determined the long-term benefits of screening as well as the number of relatives who must be screened in order to prevent one subarachnoid hemorrhage by combining empirical data with a decision-analysis approach.

### METHODS

#### Index Patients and First-Degree Relatives

After approval by the ethics committees, the study was conducted at the University Hospital Utrecht and the Academic Medical Centre of the University of Amsterdam. We included the first-degree relatives of consecutive patients with subarachnoid hemorrhage who were hospitalized between December 1995 and March 1997. The diagnosis of aneurysmal subarachnoid hemorrhage in these index patients was confirmed by the finding of an aneurysmal pattern of hemorrhage on computed tomography (CT). The presence of an aneurysm was confirmed by cerebral angiography, unless the patient died before this procedure could be performed. Patients with nonaneurysmal causes of subarachnoid hemorrhage were excluded.

We asked the index patients (or the next of kin in the case of patients whose clinical condition was poor) whether we could invite all their first-degree relatives to undergo screening. We excluded relatives who were under 20 and over 70 years old, and persons who had relative contraindications to MRA (such as pregnancy, an internal metal device such as a pacemaker, or claustrophobia) or serious conditions that would interfere with the treatment of an unruptured aneurysm. Relatives living outside the Netherlands

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\*Members of the study group are listed in the Appendix.

and those who did not speak Dutch well enough to give informed consent were also excluded.

Eligible relatives received a letter with information about the study. They were subsequently contacted by telephone. Those who responded to the invitation visited our outpatient department to receive more detailed information about the pros and cons of screening and subsequent treatment of unruptured aneurysms. Finally, informed consent to undergo MRA was obtained.

A probabilistic sensitivity analysis based on data from a decision analysis on unruptured intracranial aneurysms<sup>11</sup> indicated that a minimum of 25 relatives with aneurysms would be required for the study. Assuming a 5 percent prevalence of aneurysms among first-degree relatives<sup>12,13</sup> and a sensitivity of MRA of 80 percent,<sup>14-16</sup> we set the target enrollment at 625 participants.

### MRA

MRA was performed on 1.5-T magnetic resonance systems with standard hardware and software. We used a three-dimensional time-of-flight technique with angiographic projections generated with a maximal-intensity projection algorithm. All scans were independently evaluated by three experienced observers: a neurologist and two neuroradiologists (one from each study hospital). Observers categorized the findings as normal (no aneurysm) or as indicating a definite or a possible aneurysm and estimated the size of possible or definite aneurysms. In case of disagreements among the three observers, a decision was reached by consensus.

### Follow-up Assessments and Surgery

No follow-up assessments were performed in relatives with normal findings on MRA. For relatives with a definite aneurysm, conventional angiography was recommended. For relatives with a possible aneurysm, the follow-up consisted of angiography or repeated MRA, 6 to 12 months after the initial MRA. The three independent observers also evaluated angiograms and repeated MRA scans. The results of conventional angiography were used as a reference. Surgery was suggested for subjects with a definite aneurysm.

### Outcome after Angiography and Surgery

The operations were performed by four experienced neurosurgeons. An independent observer assessed the clinical condition of the subjects with definite or possible aneurysms before and after angiography and three and six months after operation. We performed a general and neurologic examination and used the modified Rankin scale to assess neurologic status.<sup>17,18</sup> Scores on the Rankin scale can range from 0 (no neurologic disability) to 5 (severe disability). The Rankin scores before angiography and six months postoperatively were used for data analysis. Any increase in the score was regarded as indicating a decrease in function.

### Effectiveness of Screening

We used a Markov decision model to estimate the long-term effects of screening on health.<sup>19</sup> The effects were expressed in terms of survival and function according to the Rankin score. The decision model distinguished between a screening and a no-screening strategy. Since we assumed that screening itself had no long-term effects on survival or function, the calculations were focused on the subjects who underwent angiography and surgery.

In the screening strategy, we assumed that after the operation, subjects would die only from causes other than subarachnoid hemorrhage. The annual probabilities of dying were derived from national life-tables, with exclusion of deaths related to subarachnoid hemorrhage.<sup>20</sup> The long-term effects of screening on functional health were extrapolated from the Rankin scores measured six months after operation; we assumed that no changes in the scores would occur after that time.

In the absence of screening, we assumed that the unruptured aneurysms would not have been found. Therefore, these subjects would have faced the risk of subarachnoid hemorrhage in addition to the risk of death from other causes. The risk of rupture

was based on a review of previous studies.<sup>21-30</sup> The annual risk of rupture was estimated to be 0.46 percent for asymptomatic aneurysms that were less than 5 mm in maximal diameter, 0.95 percent for aneurysms between 5 and 12 mm, and 6.8 percent for aneurysms that were larger than 12 mm. We did not use more recent estimates,<sup>5</sup> because they relied on retrospective research. Similarly, estimates of survival and function after subarachnoid hemorrhage in the absence of screening were based on previously published data.<sup>1</sup>

The benefit of screening was calculated as the difference in average life expectancy between the screening and the no-screening strategy. We also calculated the difference in the expected number of years of life without impaired function as a result of either subarachnoid hemorrhage or the aneurysm operation.

### Efficiency of Screening

The decision-analysis model was used to calculate the efficiency of screening, defined as the number of relatives who would need to be screened in order to prevent one subarachnoid hemorrhage within a five-year period<sup>31</sup> and over a lifetime. We also calculated the number of relatives who would have to be screened in order to prevent one fatal subarachnoid hemorrhage.

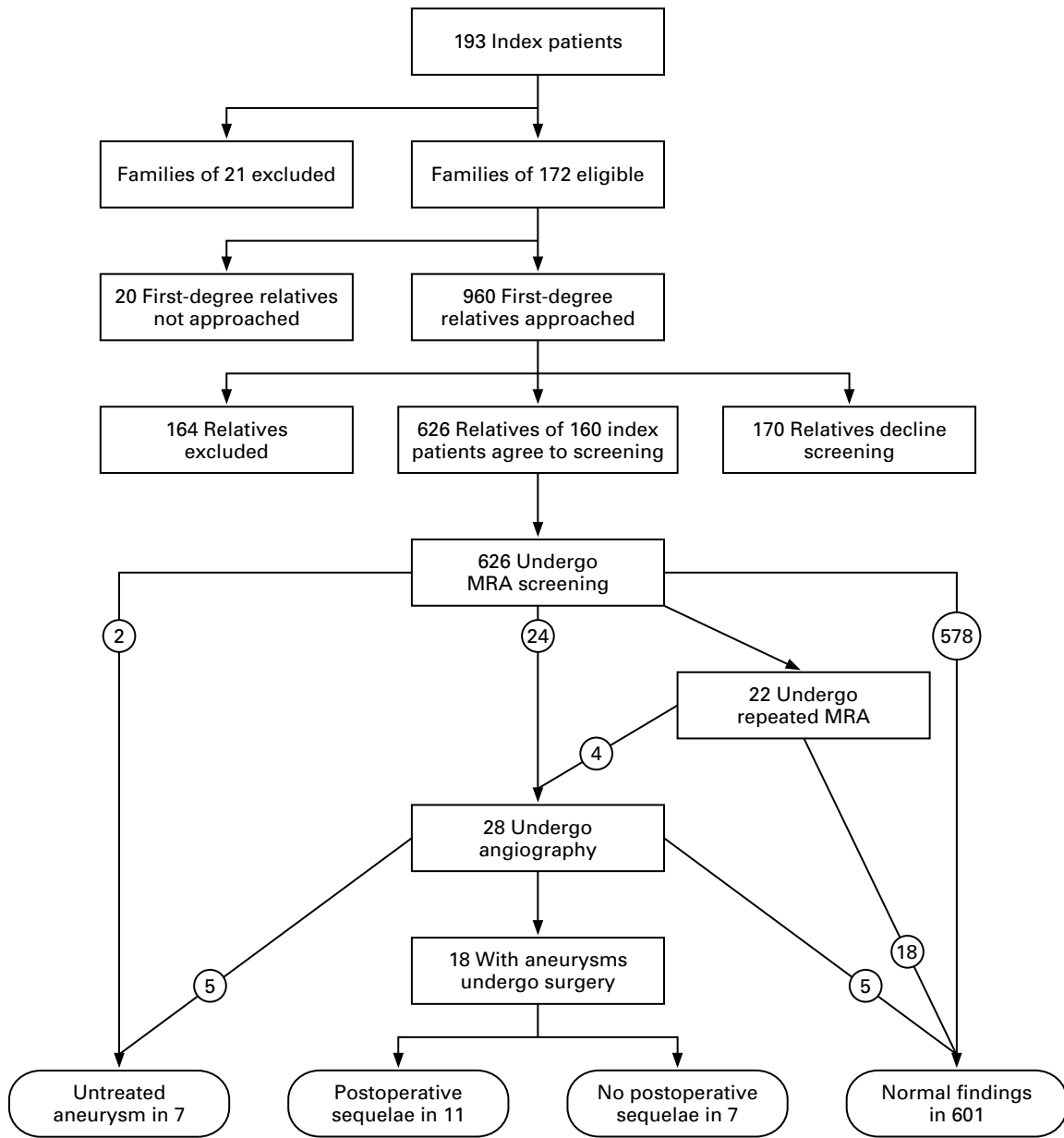
## RESULTS

### Index Patients and Participating First-Degree Relatives

Figure 1 shows the numbers of index patients and first-degree relatives who were included in the study and the reasons for exclusion. We identified 193 consecutive index patients with subarachnoid hemorrhage. The mean ( $\pm$ SD) age of the patients was  $52 \pm 14$  years (range, 24 to 87); 134 of the patients were women. The relatives of 21 index patients were not invited to participate: 12 index patients declined to allow us to contact their relatives, 6 had no first-degree relatives, and the relatives of 3 patients were excluded because of a language barrier. Of the remaining 172 index patients, 4 had one first-degree relative with confirmed subarachnoid hemorrhage (i.e., familial cases); the other 168 had sporadic cases. There were 980 first-degree relatives in these 172 families. The addresses of 20 relatives were unknown. Another 164 were excluded for the following reasons: 68 were younger than 20 years, 60 were older than 70 years, 6 were half-brothers or half-sisters of the index patients, 1 had a relative contraindication to MRA, 8 had serious underlying conditions, 13 lived outside the Netherlands, 2 had been screened elsewhere, 5 did not complete MRA, and 1 died in an accident before screening could be scheduled. A total of 170 relatives declined to participate in the study: 93 were "not interested," 43 were afraid to undergo MRA or surgery, 23 regarded themselves as too old, and 11 had other reasons. A total of 626 first-degree relatives of 160 index patients completed the MRA screening. Their mean age was  $41 \pm 12$  years; 325 were women. Thirty participants were the parents of index patients, 250 were children, and 346 were siblings.

### Results of MRA and Conventional Angiography

On the initial MRA scan, we found one or more definite aneurysms in 18 of the subjects, possible an-



**Figure 1.** Design of the Study.

The numbers of index patients and their relatives are shown, as are reasons for exclusion from the study and outcomes of screening for intracranial aneurysms with the use of magnetic resonance angiography (MRA).

aneurysms in 30, and no aneurysms in 578 (Fig. 1). Two subjects, both of whom had a definite aneurysm, declined further assessment. Twenty-four subjects (16 with definite aneurysms and 8 with possible aneurysms) underwent conventional angiography, and 22 subjects who had small, possible aneurysms underwent repeated MRA. The second MRA was followed by angiography in 4 subjects and did not show an aneurysm in 15 subjects. In three subjects there was

still uncertainty about whether a very small aneurysm was present, and further follow-up MRA was scheduled (data not shown). In 23 of the 28 subjects who underwent angiography, the presence of one or more aneurysms was confirmed.

Including the 2 subjects with definite aneurysms who declined angiography, we found 33 unruptured aneurysms in 25 of 626 first-degree relatives (4.0 percent; 95 percent confidence interval, 2.6 to 5.8 per-

**TABLE 1.** CHARACTERISTICS OF 18 FIRST-DEGREE RELATIVES WHO UNDERWENT SURGERY FOR UNRUPTURED INTRACRANIAL ANEURYSMS AND ESTIMATED BENEFITS OF SURGERY.

PATIENT No.	SEX/AGE (YR)	ANEURYSM*		RANKIN SCORE†		RISK OF SUBARACHNOID HEMORRHAGE WITHOUT SURGERY‡		LIFE EXPECTANCY	
				BEFORE ANGIOGRAPHY	6 MO AFTER SURGERY	5 YR	LIFETIME	WITHOUT SURGERY	WITH SURGERY
						percent		yr	
1	M/20	ICA	5–11	0	1	5	40	48.5	54.7
2	M/28	ICA	<5	0	1	2	19	44.5	47.0
3	M/34	MCA	<5	0	0	2	17	39.3	41.2
4	F/34	ICA	5–11	0	0	5	36	42.1	46.8
5	F/35	ACA	<5	0	1	2	19	43.5	45.8
6	M/38	ICA	<5	0	0	2	16	35.8	37.4
7	F/40	MCA (1), ACA (1)	<5 (2)	0	0	4	31	37.4	41.0
8	F/40	MCA (3), BA (1)	<5 (MCA, 2; BA, 1), 5–11 (MCA, 1)	0	1	11	60	33.4	41.0
9	F/42	MCA (2)	<5 (2)	0	2	4	31	35.8	39.1
10	F/44	ICA	<5	0	0	2	16	35.6	37.2
11	M/45	ICA (1), MCA (1)	<5 (MCA, 1), 5–11 (ICA, 1)	0	1	7	35	27.7	30.8
12	M/51	MCA	<5	0	1	2	11	24.6	25.4
13	F/53	ICA	<5	0	2	2	13	27.9	28.9
14	M/54	ACA	<5	0	1	2	10	22.1	22.8
15	F/55	MCA	5–11	0	0	5	23	25.4	27.1
16	F/57	MCA	5–11	0	1	5	21	23.8	25.4
17	F/61	PA	<5	0	3	2	10	21.3	21.9
18	F/68	ICA	5–11	0	0	4	14	15.7	16.3

\*Unless otherwise indicated in parentheses, each subject had only one aneurysm. ICA denotes internal carotid artery, MCA middle cerebral artery, ACA anterior communicating artery, BA basilar artery, and PA pericallosal artery.

†A score of 0 on the Rankin scale indicates no symptoms; a score of 1, minor symptoms but no limitations; a score of 2, some restrictions but no help needed to perform activities of daily living; and a score of 3, some help needed to perform activities of daily living, but patient is still able to live independently.

‡The annual risk of rupture was estimated to be 0.46 percent for asymptomatic aneurysms that were less than 5 mm in maximal diameter, 0.95 percent for aneurysms between 5 and 12 mm, and 6.8 percent for aneurysms that were larger than 12 mm.

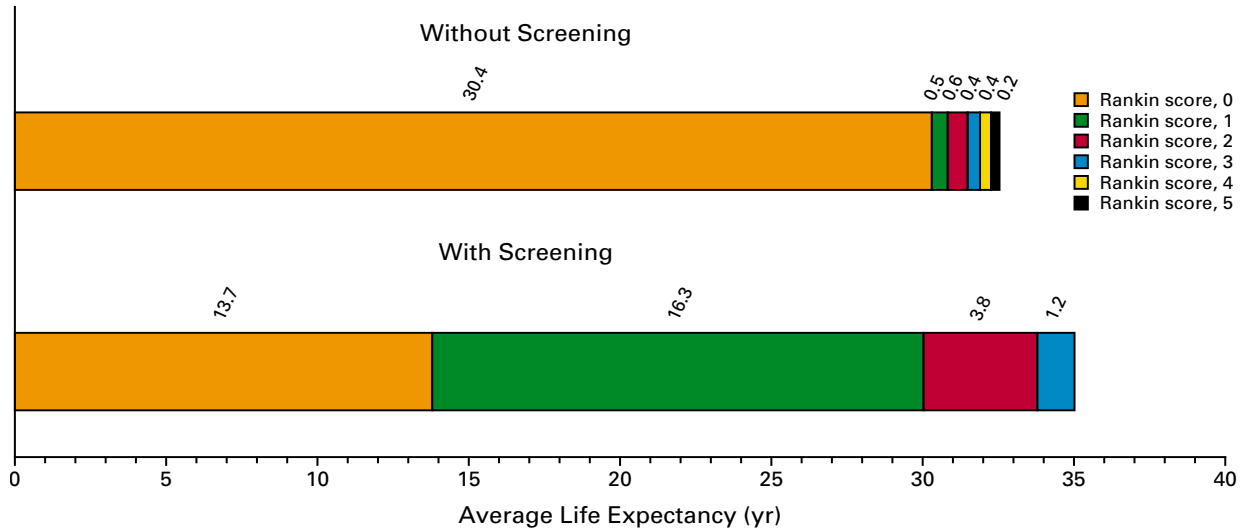
cent). Six relatives had multiple aneurysms. Most of these subjects (22 of 25) were siblings of the index patients. Those with aneurysms were more likely to be older and female than those without aneurysms.

**Outcome**

Of the 23 first-degree relatives who had aneurysms confirmed at angiography, 18 underwent elective surgery. In 5 the aneurysms were 5 to 11 mm in diameter, in 11 the aneurysms were less than 5 mm in diameter, and 2 had both small and medium-sized aneurysms (Table 1). All aneurysms were clipped, except for one aneurysm in the cavernous sinus in a subject with multiple aneurysms. The characteristics of the aneurysms and the subjects are listed in Table 1. The remaining five relatives who did not undergo operation had six aneurysms ranging from 2 to 4 mm in diameter. In three of these relatives the neurosur-

geon recommended follow-up with MRA because of the small diameter of the aneurysm; surgery was not indicated in one, because the aneurysm was in the cavernous sinus; and one patient decided against surgery.

Before conventional angiography none of the relatives with aneurysms had any functional disability (Rankin score, 0). In all five who underwent conventional angiography without subsequent surgery, the Rankin score remained unchanged. In 11 of the 18 subjects who underwent conventional angiography and surgery, the Rankin score had increased six months postoperatively (Table 1). One of these 11 subjects had complications after angiography, resulting in a Rankin score of 3 because of infarcts in the brain stem and cerebellum, leading to ataxia and diplopia. Nevertheless, she decided to undergo surgery, which resulted in occlusion of the aneurysm without



**Figure 2.** Differences in Average Life Expectancy with Screening and without Screening for the 18 First-Degree Relatives Who Underwent Surgery, According to the Rankin Scores. Scores on the Rankin scale can range from 0 (no symptoms) to 5 (severe disability).

additional complications. The remaining 10 subjects had postoperative sequelae, consisting of partial hemianopia (in 1 patient), unilateral visual loss (in 1), anosmia (in 2), and nonspecific symptoms such as headache, fatigue, impaired concentration, and emotional problems (in 6).

**Effectiveness of Screening**

Table 1 summarizes the individual estimates of life expectancy. Since angiography did not affect the function of the first-degree relatives who did not undergo surgery, estimates were calculated for the 18 who did undergo surgery. The subject with an aneurysm in the cavernous sinus was excluded from the analyses, because rupture at this location would not result in subarachnoid hemorrhage. On average, surgery increased life expectancy by 2.5 years (from 32.5 years to 35.0 years). This is equivalent to a gain of 0.9 month (4 weeks) per person screened. Angiography and surgery resulted in impaired function in 11 of the 18 subjects. On average, these sequelae would be present in 21.3 of the expected 35.0 years of life after the operation. In the absence of screening, subarachnoid hemorrhage would account for impaired health in an average of only 2.1 of the 32.5 remaining years. This is a difference of 19 years of decreased function per person. Figure 2 shows this difference in life expectancy with corresponding Rankin scores.

**Efficiency of Screening**

Of the 626 subjects we screened, 18 eventually underwent surgery. We calculated that these operations prevented 4.2 episodes of subarachnoid hemorrhage, of which 0.7 would have occurred within

five years. On the basis of these estimates, 894 first-degree relatives of index patients with subarachnoid hemorrhage would need to be screened in order to prevent 1 subarachnoid hemorrhage within five years, whereas 149 relatives would need to be screened in order to prevent 1 subarachnoid hemorrhage over the course of a lifetime. Assuming a 50 percent fatality rate,<sup>1</sup> we calculated that 1788 relatives would have to be screened to prevent 1 fatal subarachnoid hemorrhage within five years and that 298 would need to be screened to prevent 1 fatal subarachnoid hemorrhage on a lifetime basis.

**DISCUSSION**

We screened 626 first-degree relatives of a consecutive series of patients with subarachnoid hemorrhage and found 33 unruptured aneurysms in 25 of them. Surgery in 18 increased life expectancy, at the expense of a decrease in function in 11, which was disabling in 1. The average gain in life expectancy per person screened was 0.9 month. To prevent 1 subarachnoid hemorrhage over the course of a lifetime, 149 relatives would have to be screened. The aneurysms were 5 to 11 mm in 7 of the relatives who had surgery and less than 5 mm in 11.

Our study design was prospective and observational and was combined with a modeling procedure to calculate the potential benefits of a screening program for unruptured aneurysms. An alternative would have been a prospective and comparative design, with relatives randomly assigned to a screening or a no-screening group. Such a study would have required several decades of follow-up in a large number of subjects. Because estimates for some of the key variables

needed for a calculation of life expectancy, such as the risk of rupture of intact aneurysms and the outcome after subarachnoid hemorrhage, were available from previous studies, the use of decision analysis with extrapolation of our empirical results was considered justified.

The 4.0 percent prevalence of unruptured aneurysms in our study group is almost twice the prevalence of 2.3 percent in the general population, on the basis of available evidence from autopsy and angiographic studies.<sup>30</sup> Yet the prevalence in our study population is much lower than the 8 percent prevalence among persons who have at least two relatives with subarachnoid hemorrhage.<sup>7,8</sup> Our result may be an underestimation because MRA has a sensitivity of between 74 and 100 percent.<sup>14-16</sup> Most first-degree relatives had small aneurysms, for which the sensitivity of MRA is even more limited.

A systematic review showed a clear association between the rates of rupture and the size of aneurysms.<sup>30</sup> Small aneurysms have a low risk of rupture. Our estimate of an 0.46 percent annual risk of rupture for aneurysms smaller than 5 mm is lower than that used in several decision analyses,<sup>9,10,32-35</sup> but it is substantially higher than the recently reported rate of less than 0.05 percent per year for aneurysms that are less than 10 mm in diameter.<sup>5</sup> Yet that result was based on retrospectively identified cases, with a possible underestimation of the risk of rupture, and needs to be confirmed in a prospective study, which is now under way. The risk of rupture may be higher among persons with familial cases, given that the rate of subarachnoid hemorrhage is three to seven times as high among first-degree relatives of patients with sporadic subarachnoid hemorrhage as in the general population,<sup>2</sup> whereas the frequency of aneurysms in our study was not quite twice that in the general population. This suggestion is supported by a recent finding that asymptomatic aneurysms are more likely to rupture in relatives of patients with subarachnoid hemorrhage than in relatives of patients with unruptured aneurysms.<sup>36</sup>

Angiographic evaluation and surgical treatment of intracranial aneurysms have substantial risks. In the literature, the estimated risk of persistent complications from angiography is 0.5 percent.<sup>37</sup> The rate of complications in our study (1 of 28 relatives) is therefore within the expected range. None of our subjects died postoperatively, but six months after surgery, 11 of the 18 had decreased function, which was disabling in 1. In a recent meta-analysis of published studies, we found a mortality rate of 2.6 percent and a 10.9 percent rate of permanent sequelae among patients who underwent elective surgery; aneurysms that were not exceptionally large (i.e., they were less than 25 mm) and that were anterior in location were associated with lower surgical risks.<sup>38</sup> If we consider the risk of death and major complications leading to an im-

paired ability to perform the activities of daily living, our results compare favorably with those from earlier studies.<sup>38</sup>

Data on the risk of rupture<sup>5,21-30</sup> and the risk of preventive surgery<sup>5,38</sup> may lead one to question whether our empirical study was justified. However, information on the prevalence and the site and size of aneurysms in the first-degree relatives of patients with sporadic subarachnoid hemorrhage is essential in assessing the efficiency and effectiveness of a screening program, and these data were not available. Moreover, there is still uncertainty about the risk of rupture of familial aneurysms. Finally, our study has shown that surgical risks are similar for patients with familial aneurysms and those with sporadic aneurysms.

The results of our study cannot be directly applied to members of families that include two or more patients with subarachnoid hemorrhage, since the prevalence of aneurysms is higher in these families,<sup>7,8</sup> rupture rates may be higher, and surgical risks may differ.

Our model showed that screening increased life expectancy. However, the average gain of 0.9 month per person screened is considerably lower than the benefits offered by other preventive programs.<sup>39</sup> Furthermore, this gain in life expectancy cannot be equated with a gain in years of optimal functional health, because of the high risk of complications of angiography and surgery. Our analysis even suggested that screening was associated with fewer morbidity-free years of life than was the no-screening strategy. Similarly, the number of persons who must be screened in order to prevent one fatal subarachnoid hemorrhage within five years of screening (almost 1800) is larger than that for most other strategies for disease screening.<sup>31</sup>

In judging the range of effects of a screening program, the evaluation cannot be limited to patients undergoing elective surgery. Inviting healthy persons to take part in a disease-screening program can in itself affect their well-being. The ambiguous MRA results in some relatives constitute a potential cause for psychological distress. Also, since the sensitivity of MRA is less than 100 percent, the absence of abnormal findings on MRA is not a guarantee that aneurysms are absent. Screening led to the performance of angiography in five subjects who were eventually found not to have an aneurysm. Furthermore, not all detected aneurysms can be managed surgically. In our study, 7 of the 25 relatives who had unruptured aneurysms were not treated surgically. These subjects are now aware that they have an unruptured aneurysm.

All positive and negative effects, as well as costs, must be taken into account when one is making general recommendations about screening programs for unruptured intracranial aneurysms. Despite the small increase in life expectancy with screening, the implementation of a large-scale screening program for the

first-degree relatives of patients with subarachnoid hemorrhage does not seem warranted at this time. Using less detailed<sup>4,5</sup> or entirely theoretical<sup>40</sup> analyses, others have reached a similar conclusion. The gains from screening will increase if safer treatments, such as endovascular therapy, prove effective and become widely available.

Meanwhile, relatives of patients with sporadic subarachnoid hemorrhage may feel threatened by the disease. If these persons seek advice, the physician must weigh the patient's level of anxiety and distress against the evidence of the moderate effectiveness of screening in making recommendations about further diagnostic imaging and elective treatment.

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## APPENDIX

The Members of the Magnetic Resonance Angiography in Relatives of Patients with Subarachnoid Hemorrhage Study Group are as follows: University Hospital Utrecht — *Department of Neurology*: T.W.M. Raaymakers (steering committee, study coordinator), G.J.E. Rinkel (steering committee, principal investigator), J. van Gijn, P. Greebe (steering committee); *Julius Center for Patient-Oriented Research*: A. Algra (steering committee), E. Buskens (steering committee); *Department of Radiology*: P.C. Buys, L.M.P. Ramos, T.D. Witkamp, W.P.T.M. Mali; *Department of Neurosurgery*: C.A.F. Tulleken; Academic Medical Center, Amsterdam — *Department of Neurology*: M. Limburg (steering committee), A. Gorissen (steering committee); *Department of Clinical Epidemiology and Biostatistics*: C.M. Vonk (steering committee), P.M.M. Bossuyt (steering committee), G.J. Bonsel (steering committee); *Department of Radiology*: B. Verbeeten, Jr., E.J. Hulsmans; *Department of Neurosurgery*: K.W. Albrecht.

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