Should We Screen for Familial Intracranial Aneurysm?

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Background and Purpose—The purpose of this study was to establish whether individuals with a family history of \( \geq 2 \) first-degree relatives with intracranial aneurysm should be offered screening for aneurysm.

Methods—We derived 3 theoretical models and calculated the outcomes of screening with magnetic resonance angiography (MRA) followed by digital subtraction angiography (DSA) if MRA was positive (model 1), screening with DSA alone (model 2), and not screening (model 3). Screening was repeated at intervals of 10 years, and aneurysms detected were treated surgically. We assumed a prevalence of aneurysm of 9.8% (95% CI, 8.9% to 10.6%) in the population screened, an annual rupture rate of asymptomatic aneurysm of 0.8% (95% CI, 0.4% to 1.5%), and a 75% chance of poor outcome from rupture. We assumed the sensitivity and specificity of MRA were each 90% and the risk of DSA was 0.1%. The risk of surgery was taken as 5.1%.

Results—Screening 1000 individuals on 3 occasions with MRA and DSA or with DSA alone followed by surgery resulted in poor outcome in 14 and 18 individuals, respectively, over 30 years. Without screening, poor outcome occurred in 15 individuals over the same period of time.

Conclusions—Screening is not an effective way of reducing morbidity and mortality from ruptured intracranial aneurysm in individuals with a history of \( \geq 2 \) affected first-degree relatives with ruptured intracranial aneurysm unless the expected incidence of asymptomatic aneurysm is considerably >10%.

Key Words: familial intracranial aneurysm ■ screening

Subarachnoid hemorrhage from a ruptured intracranial aneurysm is a devastating event. Fifty percent of patients die, 25% are left with disabling sequelae, and only 25% do well.\(^1\) It is accepted that surgery for an unruptured aneurysm is associated with a comparably low risk of stroke or death. It has been suggested that individuals with a family history of intracranial aneurysm should be screened for the condition and offered elective surgery if screening is positive.\(^2\) We have performed an analysis of the utility and cost-effectiveness of screening healthy individuals for cerebral aneurysm using theoretical models.

Subjects and Methods

We chose to model 3 approaches to screening. The first approach we studied was to use magnetic resonance angiography (MRA), followed by digital subtraction angiography (DSA) if MRA suggested an aneurysm (model 1). MRA is increasingly used because of the perception that it is safe. The second approach was to use DSA alone (model 2). It was assumed that if an aneurysm was detected via screening, it would be treated surgically. We compared the outcome of screening with the natural history of the condition (model 3).

To assess the utility of screening, one needs to know the prevalence of the condition in the targeted population. The natural history of the condition must be established. The sensitivity, specificity, and risk of the screening test must be known. Treatment for the condition must be available, and the risk of such treatment must be acceptable. We used the best available figures from the literature to provide this information for our calculations. We chose to use figures in our models appropriate to screening an asymptomatic individual with a strong family history of ruptured cerebral aneurysm.

We assumed a prevalence of asymptomatic aneurysm of 9.8% (95% CI, 8.9% to 10.6%). We took this figure from a recent large population study of the prevalence of asymptomatic intracranial aneurysm in individuals 30 to 70 years of age from 91 different families. Each individual had \( \geq 2 \) first-degree relatives (parent, sibling, or offspring) with intracranial aneurysm.\(^3\) We initially performed calculations using a prevalence of 9.8%. We then repeated the calculations using estimates of the upper and lower 95% CI for prevalence of asymptomatic aneurysm in these families (ie, 8.9% and 10.6%).

We took a figure for average risk for the annual rate of rupture of an asymptomatic aneurysm of 0.8% (95% CI, 0.4% to 1.5%) from a recent meta-analysis of 23 studies totaling 56 304 individuals.\(^4\) We assumed that 75% of patients had a poor outcome (death or severe disability)\(^5\) and therefore used the figure of 0.6% for rupture with poor outcome in our calculations. We repeated the calculations using the upper and lower 95% CI for risk of rupture of asymptomatic aneurysm (ie, 0.4% and 1.5%).

Screening can be performed with either DSA or MRA. We used a risk associated with DSA of 0.1% in our calculations, to favor screening as much as possible. We assumed that the sensitivity and specificity of DSA were each 100% and that MRA was not associated with any risk of stroke or death. We used a figure of 90% for both the sensitivity and specificity of MRA, using a representative favorable figure (nonweighted) from 4 studies.\(^6-7\)

We used a figure of 8.0% for the risk of morbidity resulting in death or dependence in everyday living resulting from surgery for unruptured aneurysms. This figure was taken from a meta-analysis published in 1998 that included 61 studies and 2460 patients.\(^8\) All

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predicted event-free survival. Morbidity and long-term survival rates after intracranial aneurysm surgery are unknown.

In this analysis, the total risk of death or severe morbidity was calculated using cohort data from 5 studies. These studies specified the number of individuals who had surgery-related deaths (2.6%). Forty-seven specified the severity of postoperative morbidity. Overall, some morbidity occurred in 10.9% of individuals; however, this was only severe in half of these patients (5.45%), giving a total risk of death or dependency of 8%.

The “block price” (ie, the charge for a procedure to a regular National Health Service purchaser who has a contract with the hospital) for MRA at our regional neuroscience center in London is £180, for DSA is £900, and for elective aneurysm surgery is £8300.

It is known that intracranial aneurysms are very unusual in the first 2 decades of life and increase steadily after the third. Screening will need to be repeated at least every 10 years. In our model, we assumed that screening would first occur at age 30 and would be repeated every 10 years on 2 additional occasions. Only individuals who remained event-free were included in the models on the second and third occasions.

Results

Figure 1A shows the outcome of initial screening with MRA using the mean estimates of aneurysm prevalence and risk of rupture (model 1). One thousand individuals are screened; 98 of them will actually have an aneurysm, but MRA will fail to detect 10 of these. Over the subsequent 10 years, aneurysm rupture resulting in death or severe morbidity will occur in 0.6 of these 10 individuals. Eighty-eight people will have a true-positive MRA, and 90 will have a false-positive MRA. DSA will cause severe morbidity in 0.2 of these individuals. Surgery in those found to have an aneurysm will result in death or severe morbidity in an additional 8 individuals. Thus, during the initial screening period and subsequent 10 years, a poor outcome will occur in 9 individuals. Figure 2 shows that each successive screening will result in an additional 8 or 9 individuals with poor outcome. If the upper or lower 95% CI for prevalence of intracranial aneurysm and risk of rupture is used, these figures remain unchanged.

Figure 1B shows the outcome of screening 1000 individuals with DSA alone (model 2). DSA will result in 1 stroke. No aneurysms are missed. Severe morbidity or death will occur in an additional 8 individuals as a result of surgery in those patients found to have an aneurysm. Thus, severe morbidity or death will occur in 9 individuals as a result of this screening strategy. Another 9 individuals will have a poor outcome when screening is repeated for each of the second and third times (Figure 2). Again, these numbers are unchanged if the upper or lower 95% CI for prevalence of intracranial aneurysm is used.

Figure 1C shows the outcome of not screening the same 1000 individuals (model 3). Ninety-eight individuals will actually have aneurysms. Over each 10-year period, rupture resulting in death or significant morbidity will occur in 5 individuals. If the upper 95% CIs for prevalence of aneurysm (10.6%) and for risk of rupture per annum (1.5%) are used, aneurysm rupture with poor outcome occurs in 10 individuals in each 10-year interval. If the lower 95% CIs for prevalence of aneurysm (8.9%) and for risk of rupture per annum (0.4%) are used, aneurysm rupture with poor outcome occurs in 2 individuals in each 10-year period. Figure 2 shows the event-free individuals plotted against years using the mean estimate of prevalence of aneurysm and risk of rupture and the upper and lower 95% CIs for these estimates.

If the mean or lower estimates of prevalence of aneurysm and risk of rupture are used, screening for aneurysm with both MRA and DSA or with DSA alone does not prevent death or severe morbidity compared with not screening (Figure 2). The use of MRA followed by DSA (model 1) to screen 1000 individuals on 3 occasions results in 26 individuals with poor outcome. The use of DSA (model 2) to screen 1000 individuals on 3 occasions results in 27 individuals with poor outcome. If screening is not performed over this 30-year period, and the mean estimates of prevalence of aneurysm and risk of rupture are used, 15 individuals have a poor outcome from ruptured intracranial aneurysm.

If the upper 95% CIs for prevalence of intracranial aneurysm and risk of rupture are used, screening by either method does not prevent death or severe morbidity until year 8. By year 30, if no screening is performed, poor outcome has occurred in 28 individuals. Thus, screening 1000 individuals with a strong family history of intracranial aneurysm at 10-yearly intervals on 3 occasions, taking estimates of prev-
rance and risk of aneurysm rupture to make screening as favorable as possible and using the slightly more favorable model of MRA followed by DSA, does not prevent poor outcome.

The cost of screening 1000 individuals with MRA on 3 occasions at 10-year intervals, followed by DSA if MRA was positive, followed by elective surgery if an aneurysm is detected, is £3 177 540. If DSA is used as the initial screening test, the cost is £5 091 000.

Discussion
Screening for familial unruptured intracranial aneurysm using the best-available estimates for prevalence of aneurysm (9.8%) and rate of rupture (0.8% per annum) does not result in a net reduction in severe morbidity or death. Over a 30-year period, the less-expensive strategy of MRA followed by DSA results in severe morbidity or death in 26 individuals per 1000 patients screened. This is in comparison with the estimated natural history in the unscreened population of severe morbidity or death in 15 individuals. Thus, screening at 10-year intervals on 3 occasions causes almost 2 poor outcomes at the time of investigation, and treatment for 1 poor outcome is prevented. These calculations do not support a policy of screening individuals with a high risk of harboring an aneurysm because of a strong family history. The benefits will be even less in individuals without such a strong family history (for example, those with a single first-degree relative with symptomatic aneurysm).

If the most favorable model is used, taking the upper 95% CI for the prevalence of intracranial aneurysm (10.6%) and risk of rupture with poor outcome (1.1%), severe morbidity or death is not prevented until year 8. If these upper estimates are used, by year 30, screening has prevented a maximum of 2 poor outcomes (Figure 2). This is at a cost of almost £1 588 770 per poor outcome prevented, even if the less-expensive option of MRA followed by DSA if MRA is positive, is used.

In our models, we assumed that the prevalence of detectable intracranial aneurysm remains constant on successive screenings. This is unlikely to be the case, and it is probable that the prevalence is less when screening is repeated. This would make repeated screening even less favorable.

We used a mean prevalence of intracranial aneurysm of 9.8% in our calculations. Individuals screened as part of the study on which we base this estimate were aged from 30 to 70 years, and thus the figure of 9.8% may be an overestimation of the prevalence. Other studies have also estimated the prevalence of intracranial aneurysm in individuals with a family history to be ≈10%.9,10 Only 1 study estimates a prevalence significantly higher than 10%;11 this is in a small series of 12 different families. The overall prevalence of intracranial aneurysm in individuals in families who were screened with DSA was 33%. However, in 8 of these families, ≥3 first-degree relatives had ruptured intracranial aneurysms. Thus, the family history was much stronger than in the families screened by Ronkainen et al3 and used in the present calculations.

A recent study12 from Utrecht, Netherlands, screened 626 first-degree relatives of consecutive patients with subarachnoid hemorrhage from ruptured intracranial aneurysm. Patients with subarachnoid hemorrhage did not have a family history of the condition. MRA was used to assess the frequency of unruptured aneurysm in these relatives. Unruptured intracranial aneurysm was found in 24 individuals (3.8%; 95% CI, 2.5% to 5.7%).12 As our models demonstrate, screening for intracranial aneurysm in first-degree relatives of patients such as these without a family history of intracranial

![Figure 2. Screening for intracranial aneurysm at 10-year intervals, commencing with 1000 individuals; number of event-free individuals is shown.](http://stroke.ahajournals.org/)

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aneurysm will not be beneficial, either in terms of stroke/death prevented or of cost.

Estimates of the prognosis of an unruptured cerebral aneurysm vary. We used a figure of 0.8% (95% CI, 0.4% to 1.5%) rupture per annum for asymptomatic aneurysm, based on a meta-analysis of studies of the natural history of asymptomatic aneurysm that involved 1145 patient-years of follow-up. In that meta-analysis, the risk of rupture of aneurysms found incidentally during investigation of individuals with subarachnoid hemorrhage who had already had ≥1 ruptured intracranial aneurysm was higher at 1.4%. The risk of rupture of aneurysms detected because they were producing nonhemorrhagic symptoms was also higher (6.5%), presumably because of their large size. Aneurysms that were larger than 10 mm had a higher risk of rupture than smaller aneurysms. If such aneurysms are detected during radiological investigations, surgery may be more favorable than predicted by our model. It is not clear if familial aneurysms have different characteristics from nonfamilial ones. Familial aneurysms have been described as rupturing at a younger age (42.3 years compared with 50 to 54 years for rupture of nonfamilial aneurysms) and possibly at a smaller size than nonfamilial aneurysms. It has been suggested that aneurysms may grow and rupture soon after formation. If this is the case, they may easily be missed even by repeated screening.

DSA is considered the "gold standard" investigation to identify intracranial aneurysm. If performed and interpreted by an experienced neuroradiologist, it has a sensitivity approaching 100%. We took the risk of stroke from DSA to be extremely low (0.1%). The risk of screening with DSA would be increased if we had used the figure of 0.4% from a prospective series. The risk associated with DSA increases with age, and it might have been more realistic to use an increased risk on successive screenings. This would have altered the calculations in favor of screening with MRA initially. MRA is a noninvasive method to image blood vessels. It is not associated with cerebrovascular complications. We used an estimate of sensitivity and specificity of MRA that corresponds to current experience. An improvement in the sensitivity and specificity of MRA would result in a slight improvement in the overall benefits of screening (avoiding a maximum of 2 poor outcomes over 30 years, mainly from a reduction in the rate of false-negative MRA).

Surgery is the standard treatment for unruptured intracranial aneurysms. We used a large meta-analysis to estimate the risk of surgery for asymptomatic intracranial aneurysm. If the risk of surgery was lower than that estimated from the meta-analysis, screening would become more attractive. Endovascular treatment is a fairly new treatment for intracranial aneurysm. A trial comparing the efficacy of endovascular treatment with traditional surgery is in progress, but it is unlikely that endovascular treatment will prove to be safer than surgery. However, psychological morbidity, not taken into account in our figures, may be less after endovascular treatment than after surgery.

Earlier analyses of the cost-effectiveness of screening for asymptomatic intracranial aneurysm have had to rely on less-recent data on surgical risks. The only previous meta-analysis of surgical risk was published in 1994 and included only 28 series, with 733 patients. The risk of mortality from surgery was calculated as 1%, and the risk of morbidity was 4.1%. These risks are considerably less than the figures from the larger, more-recent meta-analysis used in our models. No other study has produced models based on screening individuals with ≥2 first-degree relatives with intracranial aneurysm. One study on the cost benefit of elective surgery estimated the prevalence of aneurysm from a series of 4 families with a mother and child with ruptured aneurysm. Only other siblings were screened. The prevalence of asymptomatic aneurysm in individuals in the second generation was 29%. The annual rate of aneurysm rupture was also taken from less-recent data than we have used and was assumed to be 2%. Screening the second generation of these families on 1 occasion and offering elective surgery resulted in only 1 extra year of event-free survival. This was seen only in individuals with a life expectancy of 32 years or more. A marginal benefit was found in a Japanese study, but this was influenced by risk of rupture and surgical risk.

The use of a theoretical model to assess the benefit of screening for intracranial aneurysm has limitations. We took figures for the prevalence of aneurysm from a single study, although the prevalence of the condition in most of the other published studies is similar. MRA results in real life may be equivocal, requiring additional individuals to undergo DSA. The risk of intracranial aneurysm may be different in an individual with, for example, 2 siblings with intracranial aneurysm than in an individual with 1 sibling and 1 parent with the condition. Not all individuals in whom screening is positive will want surgery.

When faced with an anxious individual with a family history of intracranial aneurysm, one option is to arrange MRA to reassure the patient. However, if the approach of performing an MRA for reassurance is adopted, the individual will have to be told that the test may miss an aneurysm and that it will need to be repeated in a few years. This may lead to persistent anxiety. We believe that an explanation documenting the chance of actually having an aneurysm (which depends on the individual’s family history), the risks of screening and surgery, and the chance of any aneurysm rupturing based on our figures is a more reassuring approach. Individuals referred for consideration of screening for familial aneurysm who have a history of no more than 2 first-degree relatives with ruptured intracranial aneurysm can be reassured that the small chance of an asymptomatic aneurysm bleeding and the risk of treatment do not warrant screening.

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References
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