Cost-Effectiveness Analysis of Screening for Asymptomatic, Unruptured Intracranial Aneurysms
A Mathematical Model
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Background and Purpose—Subarachnoid hemorrhage (SAH) due to aneurysmal rupture is a major cause of cerebrovascular disease–related death. This problem could be eliminated by diagnosis and successful treatment of aneurysms before rupture. Recent developments in high-resolution imaging technology have made screening for unruptured aneurysms possible in the general population. Such screening has become widespread in Japan (“No Dokku,” or brain checkup). As a result, unruptured aneurysms are being identified with increasing frequency. However, the economic implications of treatment decisions for unruptured aneurysms have not been analyzed. Therefore, we performed such an analysis.

Methods—We used a Markov model to evaluate the cost-effectiveness of screening for asymptomatic, unruptured intracranial aneurysms. The model involved a set of variables describing discrete health states. Each state was assigned a quality of life score and an associated medical cost. A comparison of the expected outcomes was then made between 2 hypothetical cohorts, one receiving screening and the other no screening. A sensitivity analysis was performed by altering the input values within clinically reasonable ranges to reflect uncertainty in the baseline analysis and then assessing the effects on outcomes.

Results—Combining the incremental cost and effectiveness data revealed a cost per quality-adjusted life-year of $7760 for an annual rate of subarachnoid hemorrhage due to unruptured aneurysms (rupture rate) of 0.02; this cost was $39 450 for a rupture rate of 0.01. There was no benefit (negative quality-adjusted life-year benefit) for a rupture rate of 0.005, the rupture rate found in a recently published international cooperative study. The risks of surgery for unruptured aneurysms and the discounting ratio used to assess the impact of timing of costs and benefits on future outcomes also had significant effects on the results. Other variables had little impact on cost-effectiveness.

Conclusions—The cost-effectiveness of screening for an unruptured aneurysm is highly sensitive to the annual rate of subarachnoid hemorrhage due to unruptured aneurysms. The low annual rupture rate seen in the recent large international cooperative study implies that screening asymptomatic populations to identify and treat unruptured aneurysms would not be cost-effective. (Stroke. 1999;30:1621-1627.)

Key Words: aneurysm ■ cost-benefit analysis ■ quality of life ■ subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) due to aneurysmal rupture is a major cause of cerebrovascular disease–related death. The solution to this problem could be to diagnose and treat aneurysms before rupture. Several investigators have tried to devise methods of estimating the risk posed by incidentally discovered aneurysms to guide decisions regarding the need for surgery.2–4 Until the early 1980s, asymptomatic, unruptured aneurysms came to clinical attention only when they were found in SAH patients with multiple aneurysms5–10 or during investigations for other diseases.11 Magnetic resonance angiography12 and 3-dimensional CT angiography have been increasingly used to detect unruptured aneurysms among the general population of Japan (“No Dokku,” or brain checkup).13 As a result, unruptured aneurysms are being identified at an ever-increasing rate.14 Screening followed by surgical repair of unruptured aneurysms has been introduced to reduce the number of patients developing SAH, and many neurosurgeons have reported reasonably good results in several series of patients.9,10,13,15–20 These authors all advocate surgical treatment, but do their results indicate that all asymptomatic, unruptured aneurysms should be repaired? If so, should wide-scale screening be implemented for asymptomatic populations? Although a large-scale, hospital-based, multicenter study was recently published,21 no population-based analysis has been performed.
Such mathematical modeling techniques allow complex problems to be analyzed in an idealized manner. Although some simplification is inevitable, modeling offers the advantage of permitting quantitative exploration of the problem. The present model was defined by a set number of discrete health states (well, well without aneurysm, disabled without aneurysm, and dead). Each state was assigned a quality of life score and an associated medical cost. Transitions between states were assumed to occur at the midpoints of each yearly cycle. The analysis was continued until all individuals in the hypothetical cohort died of their aneurysms or other causes.

We made several simplifying assumptions. Our baseline case considered screening in a cohort of 50-year-old asymptomatic individuals. In our model, surgery was the only treatment available and was assumed to remove permanently the risk of SAH due to aneurysmal rupture. Although endovascular techniques are being developed for the treatment of intracranial aneurysms, their role has yet to be established in long-term follow-up studies; therefore, they were not considered in this study.

**Screening Group**

Screened individuals could be shown to have no unruptured intracranial aneurysms (well without aneurysm) or to have an aneurysm at the beginning of the first cycle. All of the latter group were assumed to undergo aneurysm surgery. They might then die perioperatively (dead), survive with neurological deficits and a repaired aneurysm (disabled without aneurysm), or survive with normal neurological function and a repaired aneurysm (well without aneurysm). In succeeding years, survivors were assumed to live at the postoperative level of functioning until they died of causes other than aneurysmal SAH. We also assumed that the aneurysm would never rupture after surgery and that each patient would have the same death rate as the general population.

**No-Screening Group**

Subjects who did not undergo screening would live without knowing whether they had an intracranial aneurysm. They might die of causes other than aneurysmal SAH or develop SAH. We assumed that all unruptured aneurysms would rupture at a constant rate over time and that all patients who developed aneurysmal SAH and were admitted to hospital would undergo surgical repair of the aneurysm. They might then die, survive with a neurological deficit and a repaired aneurysm (disabled without aneurysm), or survive without a neurological deficit and a repaired aneurysm (well without aneurysm). It was also assumed that patients with a repaired aneurysm would not develop SAH in the future and would have the same death rate as the general population.

**Annual Death Rate of the General Population**

The hazard function \( p(x) \), namely, the annual death rate of the general population at age \( x \), is known to approximate well to an exponential function.\(^24,25\) We plotted yearly death rates for each age group included in the model using Japanese life statistics data from 1990.\(^26\) By regression analysis, the following approximation of \( p(x) \) was obtained:\(^2\)

\[
p(x) = e^{-10.58 + 0.095x}
\]

**Baseline Analyses**

### Probabilities

#### Incidence of Unruptured Aneurysms

In previous autopsy\(^27–32\) and angiographic series\(^11,13,29,33–35\) there has been a wide range in the incidence of unruptured aneurysms in the general population (0.5% to 7.9%). For our baseline analyses, we chose an incidence of unruptured aneurysms of 3.0% in 50-year-old subjects.

#### Annual Rate of SAH Due to Unruptured Aneurysms

Many attempts have been made to clarify the natural history of unruptured aneurysms.\(^3,5,7,21,28,36–42\) Juvela et al\(^37\) followed up 142 patients with 181 aneurysms for an average of 13.9 years (total of 1994 patient-years) and found a yearly rupture rate of 1.4%. This

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**Figure 1.** Decision model. Top, The square on the left symbolizes the choice between 2 options, screening or no screening. “Markov” represents the Markov subtrees for each option. Bottom, The model was defined by 4 discrete health states (well, well without aneurysm, disabled without aneurysm, and dead). Each state was assigned a quality of life score and an associated medical cost. The analysis was continued until all individuals in the hypothetical cohort died of their aneurysm or other causes. An indicates aneurysm; and w/o, without.
Rupture rate was stable over the first, second, and third decades of follow up. Yasui et al\textsuperscript{41} reported results for 234 patients with unruptured intracranial aneurysms, with a mean follow-up period of 75 months, showing an average annual rupture rate of 2.3%.

However, lower annual rupture rates of unruptured intracranial aneurysms were found in a recently reported international cooperative study\textsuperscript{22}: The overall rupture rate for the 1449 patients in this retrospective cohort (12,023 patient-years of follow-up) was 0.5% per year. Because of the range of the above, we chose 3 different annual rupture rates, 0.02, 0.01, and 0.005, for our baseline analyses.

Mortality and Morbidity Due to Aneurysmal SAH

The authors of the International Cooperative Study on Timing of Aneurysm Surgery reported that in their 3521 hospitalized patients, the mortality rate was 26% and the morbidity rate was 16%; 58% of the patients recovered fully.\textsuperscript{43,44} However, more recent articles have reported far higher mortality rates for SAH (52% to 67%).\textsuperscript{21,37,40,41,45}

Thus, we assumed that the mortality rate of SAH would be 50% and that half of the 50% who survived would have some disability and that the remainder would fully recover.

Risks of Surgery for Unruptured Aneurysms

A review and meta-analysis of 28 separate articles reporting the results of elective surgery for unruptured asymptomatic aneurysms in 733 patients found a morbidity rate of 4.1% (95% confidence interval, 2.8% to 5.8%) and a mortality rate of 1% (95% confidence interval, 0.4% to 2.0%).\textsuperscript{46} These data may have been influenced by differing sources of patient referral or selection and/or by publication bias\textsuperscript{47} (ie, the tendency for excellent surgical results to be published more often than average or poor results). A recent prospective international study reported a much higher rate (combined mortality and morbidity, 13.1% to 15.7%).\textsuperscript{21}

Morbidity in that study included cognitive impairment as well as physical disability. We assumed the surgery-related mortality and morbidity rates to be 10% in the baseline analysis. We also assumed that, among those who had surgical complications, 20% died and the rest (80%) survived and had some disability.

Costs

Each health state in the Markov model is associated with one of the following cost considerations: (1) examination costs of screening, (2) hospital costs of surgery for unruptured aneurysms, (3) hospital costs of surgery for ruptured aneurysms and acute care for SAH, and (4) rehabilitation and nursing home costs in subsequent years of survival. We selected magnetic resonance angiography as the screening method because of its noninvasiveness and reliability,\textsuperscript{12} and we set the screening cost at $200 (we are aware of much higher costs in other countries). Thirty percent of SAH patients were assumed to die before admission (prehospital death, zero cost). Accurate data on treatment costs were not available for our baseline analysis; we estimated the cost of a surgical admission for SAH, including acute care, to be $20,000 and that for unruptured aneurysm to be $15,000; these amounts are based on the scale of reimbursement used by the Japanese health insurance system. We estimated the average cost of long-term care for disabled patients after surgery or SAH to be $10,000 per year. Our evaluation included only direct medical costs; indirect costs, such as loss of earnings through inability to work, were omitted.

Quality-Adjusted LifeYears

We expressed the outcome of each treatment strategy in terms of the expected number of quality-adjusted life-years (QALYs) gained. To establish the expected number of QALYs, we identified a “QALY weight” score, ranging between 0.00 and 1.00, for each health state in the model. Lifetime QALYs then equaled the sum of the number of years spent in each health state, multiplied by the QALY weight associated with that state.

Death

By convention, death is assigned a value of zero.

Postoperative or Post-SAH Recovery Period

On the basis of clinical experience, we assigned all patients who underwent surgery for an unruptured aneurysm a postoperative recovery period of 1 month. Three months were assigned for those who underwent surgery after SAH due to a ruptured aneurysm. For the postoperative recovery period, we assumed a quality of life score equal to 60% of the full value.

Postoperative or Post-SAH Deficits

Several methods of measuring the quality of life after stroke have been devised.\textsuperscript{48,49} Previous work in decision analysis has also estimated the value of living with a neurological deficit as 0.50 to 0.75. Thus, we assumed a value of 0.70 for survival with a postoperative or post-SAH neurological deficit.\textsuperscript{50}

Well Without Aneurysm

Normal function without an aneurysm or with a repaired aneurysm was assigned a value of 1.00.

Well Without Screening

Normal function without knowing whether an unruptured aneurysm was present was also assigned a value of 1.00.

Discounting

Benefits and costs are more significant if they occur earlier. To account for this phenomenon, current values for both benefits and costs were calculated by discounting the original values at the rate of 3% per year.

Cost-Effectiveness Ratios

We calculated the expected benefits and costs associated with screening. A treatment strategy that yielded the greatest quality-adjusted survival for the least expensive intervention would obviously become the treatment of choice. However, for a strategy that yielded greater quality-adjusted survival but was more expensive, additional analysis would be necessary to determine whether the longer survival justified the extra costs. This was calculated using the incremental cost-effectiveness ratio: Cost-effectiveness = (Cost A − Cost B)/(Effectiveness A − Effectiveness B), where A and B are 2 different treatment options.

Sensitivity Analysis

The sensitivity analysis was performed by altering the input values for individual variables within a clinically reasonable range to assess the effects of uncertainties in the assumptions made in the baseline analyses. The ranges of variables tested included (1) incidence of unruptured aneurysm (0.01 to 0.10), (2) mortality due to SAH (0.40 to 0.60), (3) overall mortality and morbidity due to surgery for an unruptured aneurysm (0.05 to 0.15), (4) cost of surgery for an unruptured aneurysm ($10,000 to $20,000), (5) cost of surgery for a ruptured aneurysm plus acute care costs ($10,000 to $30,000), (6) cost of long-term care for a disability ($5000 to $15,000 per year), (7) examination costs of screening (magnetic resonance angiography) ($100 to $300), (8) QALY value for postoperative or post-SAH recovery period (0.50 to 0.70), (9) QALY value for living with neurological deficits (0.60 to 0.80), (10) QALY value for living without the knowledge of whether an unruptured aneurysm is present (without having screening) (0.999 or 0.998), (11) subject age (40 to 60 years), and (12) discount rate (0.05).

Results

Baseline Analysis

Screening for asymptomatic aneurysms yielded an additional 0.0690 and 0.0210 QALYs in the first and second analyses, respectively (annual rupture rates of 0.02 and 0.01), for 50-year-old subjects. In the third analysis (annual rupture rate of 0.005), however, the screening strategy proved to be less effective than no screening (ie, there were negative QALY
In all analyses, screening was more expensive than no screening: The average cost per person for individuals who underwent screening was $1121 regardless of the annual rate of SAH from unruptured aneurysms, whereas costs for subjects who did not undergo screening were $583, $293, and $147 in the first, second, and third analyses, respectively. Costs for the unscreened group reflected the weighted average of zero cost plus the discounted costs for patients who developed SAH at some point, followed by death, hospitalization (acute care, including surgery), and/or nursing care.

Combining the incremental cost and effectiveness data in the baseline analyses revealed a cost per QALY of $7760 and $39 450 in the first and second analyses, respectively, which corresponded to the additional cost for the gain in QALYs between the screening and no-screening strategies. In the third analysis, a cost per QALY was undefined because of a negative QALY benefit. Figure 2 shows the effects of annual rate of SAH from unruptured aneurysms on the cost per QALY generated by screening, indicating the marked impact of this variable.

**Sensitivity Analysis**

The sensitivity analyses for other selected model variables are shown in the Table. Overall mortality and morbidity of surgery for unruptured aneurysms had significant effects on the results in all analyses. The relationship between the risks of surgery for unruptured aneurysms and the cost-effectiveness ratio is demonstrated in Figure 3A. As the overall mortality and morbidity rose from 0.05 to 0.15, the cost per QALY rose from $3360 to $13 810 in the first analysis, from $17 290 to $138 200 in the second analysis, and from $73 160 to undefined in the third analysis, indicating a significant impact of this parameter in the second and third analyses. Cost-effectiveness ratios are undefined when screening is less effective than no screening.

**Input values and Sensitivity Analyses for Selected Model Variables**

<table>
<thead>
<tr>
<th>Probability</th>
<th>Input Value</th>
<th>Sensitivity Analysis (Cost per QALY, US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (Best–Worst)</td>
<td>First (RR=0.02) Baseline (Best–Worst)</td>
</tr>
<tr>
<td>Incidence of U-An</td>
<td>0.03 (0.10–0.01)</td>
<td>7760 (5989–13 380)</td>
</tr>
<tr>
<td>Mortality of SAH</td>
<td>0.50 (0.60–0.40)</td>
<td>7760 (7446–8237)</td>
</tr>
<tr>
<td>MM of surgery for U-An</td>
<td>0.10 (0.05–0.15)</td>
<td>7760 (3360–13 810)</td>
</tr>
<tr>
<td>Cost (US$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery for U-An</td>
<td>15 000 (10 000–20 000)</td>
<td>7760 (5596–9925)</td>
</tr>
<tr>
<td>Surgery for R-An, acute care</td>
<td>20 000 (30 000–10 000)</td>
<td>7760 (6581–8940)</td>
</tr>
<tr>
<td>Chronic care for disability per year</td>
<td>10 000 (15 000–5000)</td>
<td>7760 (7390–8131)</td>
</tr>
<tr>
<td>Screening (MR angiography)</td>
<td>200 (100–300)</td>
<td>7760 (6318–9204)</td>
</tr>
<tr>
<td>QALY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>0.00 (—)</td>
<td>7760 (—)</td>
</tr>
<tr>
<td>Postoperative recovery period</td>
<td>0.60 (0.70–0.50)</td>
<td>7760 (7738–7771)</td>
</tr>
<tr>
<td>Disabled after SAH or surgery</td>
<td>0.70 (0.60–0.80)</td>
<td>7760 (7683–7839)</td>
</tr>
<tr>
<td>Well without screening</td>
<td>1.00 (0.999:0.998)</td>
<td>7760 (6022–4925)</td>
</tr>
<tr>
<td>Well without An</td>
<td>1.00 (—)</td>
<td>7760 (—)</td>
</tr>
<tr>
<td>Age, y</td>
<td>50 (40–60)</td>
<td>7760 (4107–15 930)</td>
</tr>
<tr>
<td>Discount rate</td>
<td>0.03 (0.05)</td>
<td>7760 (13 620)</td>
</tr>
</tbody>
</table>

RR indicates rupture rate, the annual rate of SAH from unruptured aneurysms; U-An, unruptured aneurysm; MM, combined mortality and morbidity; and R-An, ruptured aneurysm.

*Screening strategy generates negative QALY benefits.
The effects of the incidence of unruptured aneurysms on the cost-effectiveness relationship are shown in Figure 3B. In the first and second analyses, the costs per QALY were relatively stable for this variable, varying from $5989 to $13,380 and $33,410 to $57,640, respectively. In the third analysis, screening was less effective and more expensive than no screening, regardless of the incidence of unruptured aneurysms.

Age and the discounting ratio also have some influence on the cost per QALY: Older subjects and a high discount ratio (0.05) are less favored for screening. It is to be noted that input QALY scores of 0.999 and 0.998 for being well without screening significantly lowered the cost per QALY even in the third analysis (rupture rate = 0.005). Other variables, including mortality of SAH and all aspects of the cost and QALY scores, had relatively little impact on the cost per QALY in all analyses.

**Discussion**

Although the exact limits for cost-effectiveness are controversial, interventions that cost less than $50,000 to $100,000 per QALY are generally considered acceptable. For example, screening for hypertension costs $8370 to $44,400 per QALY, screening for cervical cancer every 3 years costs $15,500 per QALY, and screening of perimenopausal women for osteoporosis costs $11,700 to $22,100 per QALY. Installation of driver’s side air bags results in net health benefits at an incremental cost of $24,000 per QALY. In contrast, although the Asymptomatic Carotid Atherosclerosis Study showed that carotid endarterectomy was beneficial for symptom-free patients with carotid stenosis of 60% or more, Lee et al reported that a program to identify candidates for endarterectomy by screening asymptomatic populations for carotid stenosis would cost $120,000 per QALY.

In the baseline calculations of our study, screening for unruptured aneurysms produced an incremental cost-effectiveness ratio of $7760 and $39,450 per QALY in the first and second analyses (annual rupture rate of 0.02 and 0.01, respectively), both of which are comparable to those of other widely practiced prophylactic interventions. There was no benefit from screening in our analysis for an annual rupture rate of 0.005.

In sensitivity analyses, we examined other factors that might make screening more or less cost-effective. The risk of surgery for unruptured aneurysms was a significant factor: At the 0.005 annual rupture rate, only extremely low surgical mortality and morbidity would justify screening (Figure 3A). Age had significant effects on the results, as did discount rate. At higher discount rates, screening techniques with early costs and risks (screening and aneurysmal surgery) and delayed benefits (increased quality-adjusted survival and decreased long-term care cost) are less favored. Conversely, screening would be preferable at a lower discount rate.

In contrast, the cost-effectiveness ratio was relatively robust when most other parameters, such as mortality due to SAH, costs of screening and surgery, and QALY scores in each health state, were considered.

The cost-effectiveness of screening was sensitive to the incidence of unruptured aneurysms to some extent (see our second analysis). The effects, however, seem to be limited, because application of higher values resulted in a higher cost as well as a greater QALY gain. This is relevant, because some populations are known to have a greater-than-normal tendency to develop intracranial aneurysms and SAH, eg, patients with polycystic kidney disease and familial aneurysm. Our results do not support elective screening in such populations. We recognized that some of these high-risk individuals have an excessive fear of future SAH, even if they have no clinical symptoms. If such patients have even a slight devaluation of their quality of life (cf Table, QALY score of well without screening: 0.999 or 0.998), the cost-effectiveness analysis of screening is markedly affected, regardless of whether the potentially higher incidence of an
unruptured aneurysm is considered. Screening of such patients might be recommended, because this may ameliorate their psychological distress about the possible future occurrence of SAH. We advocate that the decision of whether to undergo screening should be left to individuals and do not propose the use of public resources for this purpose. Rupture of an aneurysm is a long-term risk over many years, but screening and surgery generate an immediate risk. Some patients may prefer to avoid surgery, even at the cost of a later excess in risk; others may not.4

It must be recognized that the assumptions necessary for the construction of a mathematical model place limitations on the reliability of the conclusions. Thus, we assumed that all patients with unruptured aneurysms would undergo surgery and at the same level of risk. It may be reasonable to repair only aneurysms larger than 10 mm in diameter, because the recently published international study21 suggested that surgical intervention is not likely to improve the natural history of patients with aneurysms smaller than 10 mm. Satisfactory data on the risk of surgery by size of aneurysm would be of value but are not available.

Also, we assumed that SAH did not develop after screening showed no aneurysms or after an aneurysm was obliterated by surgery. This assumption may be false. Because aneurysms are rarely seen in younger subjects,32 it is obvious that they are not congenital but mostly develop during middle age. Therefore, after screening or successful surgery, some de novo aneurysms could grow, enlarge, and eventually rupture. However, to date, no data on the rate of de novo formation of aneurysms have been published. We postulate that the effect of de novo aneurysm formation on our results would be relatively small, because they would develop at the same rate in both the screening and no-screening populations.

Finally, the cost aspect of our study was restricted to direct medical costs.

Conclusion

Our study indicated that the cost-effectiveness of screening for unruptured aneurysms was highly sensitive to assumptions about the annual rate of SAH from an unruptured aneurysm. Screening asymptomatic populations to avoid future SAH might be cost-effective in a population with a high rupture rate (0.01 to 0.02 per year). In contrast, such screening is neither cost-effective nor beneficial if the rupture rate is 0.005 per year (as recently reported21). Under such circumstances, only extremely low rates of surgical mortality and morbidity would make screening justifiable.

References
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Stroke. 1999;30:1621-1627
doi: 10.1161/01.STR.30.8.1621

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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