TITLE: Screening Programs for Asymptomatic Unruptured Intracranial Aneurysms: Review of Clinical Effectiveness, Cost-Effectiveness, and Evidence-Based Guidelines

DATE: 3 May 2010

CONTEXT AND POLICY ISSUES:

Asymptomatic intracranial aneurysms are relatively common with an estimated prevalence of 2% in the general population.\(^1\) When intracranial aneurysms rupture, the resulting subarachnoid hemorrhage (SAH) is associated with high mortality and morbidity rates.\(^2\) The mortality rate in the first 30 days post-rupture is estimated to be approximately 50% and almost half of the survivors will continue to experience a neurological deficit.\(^2\) Screening for patients with unruptured intracranial aneurysms can be accomplished with the use of noninvasive imaging techniques such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA).\(^3\) Prophylactic treatment with surgical clipping and endovascular coiling is used to reduce the risk of future bleeding and neurological damage.\(^4\) However, because only a minority of asymptomatic intracranial aneurysms go on to rupture and the possibility of treatment-related morbidity and mortality,\(^5,6\) screening strategies aim to target populations who are at a high risk for intracranial aneurysm formation and rupture.

This report reviews the evidence for the clinical effectiveness and cost-effectiveness of screening programs in asymptomatic relatives of patients who have experienced intracranial aneurysms. Evidence-based guidelines outlining recommendations for screening strategies will also be reviewed.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of screening programs, such as with computed tomography angiography or magnetic resonance angiography, for asymptomatic relatives of patients who have had intracranial aneurysms?
2. What is the cost-effectiveness of screening programs, such as with computed tomography angiography or magnetic resonance angiography, for asymptomatic relatives of patients who have had intracranial aneurysms?

3. What are the evidence-based guidelines for screening programs for asymptomatic relatives of patients who have had intracranial aneurysms?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID Medline, OVID Embase, The Cochrane Library (Issue 3, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 2005 and March 30, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, economic studies, and guidelines. This search was supplemented by hand searching the bibliographies of selected papers.

SUMMARY OF FINDINGS:

One observational study and one cost-effective analysis assessing outcomes following screening for unruptured intracranial aneurysms were identified. Five observational studies examining the risk factors for intracranial aneurysms and aneurysmal SAH in relatives were identified. One guideline providing recommendations for screening was retrieved. No health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, or controlled clinical trials were identified.

Observational studies

Follow-up of Small Intracranial Aneurysms Detected at Screening

Wermer et al. evaluated the growth and rupture rate of small untreated aneurysms (less than 5mm in diameter) detected using CTA or MRA screening. Patients between the age of 18 years and 70 years with familial intracranial aneurysms (FIA; defined as having two or more first-degree relatives diagnosed with SAH or unruptured intracranial aneurysms) or a personal history of SAH were included in the study. A total of 93 patients (67 with a history of SAH, 16 with FIA, and 10 with a history of both SAH and FIA) underwent follow-up imaging with CTA or MRA (median follow-up time 1.3 years; range 0.7 to 3.8 years). The mean age of the patients was 51 years (range 20 to 69 years) and 75% were women. The mean size of the aneurysms was 3 mm. A slight enlargement of the aneurysm (0.5 mm to 1.5 mm) occurred in 3 (3.2%) patients. Another two (2.2%) patients experienced a SAH. Neither aneurysm enlargement nor rupture occurred in the 16 patients who were screened for FIA but had no previous history of SAH. The only statistically significant risk factor for growth and rupture was a history of both SAH and FIA (relative risk 10.1; 95% CI 1.2 to 81.9). The authors concluded that short-term follow-up of small untreated aneurysms in patients with a history of SAH or FIA is not beneficial and it remains unclear whether follow-up at longer intervals is more effective.
Familial Intracranial Aneurysm Study

The Familial Intracranial Aneurysm (FIA) study was designed to identify the risk factors that underlie the development and rupture of intracranial aneurysms. A total of 26 clinical centers in North America, New Zealand, and Australia are taking part in this ongoing study. Families with affected sibling pairs or with multiple affected relatives were enrolled through retrospective and prospective screening of potential subjects with an intracranial aneurysm. Three separate articles reporting results from this study were identified.

Brown et al. reported preliminary results for the frequency of unruptured intracranial aneurysms in patients enrolled in the FIA study. First-degree relatives of those affected with intracranial aneurysms were screened using MRA. These relatives included the parents, siblings, or children of individuals affected with intracranial aneurysms who belonged to families in which at least two cases of intracranial aneurysms had already been diagnosed; who were 30 years of age or more; who did not have a previous diagnosis of intracranial aneurysms; and who had a history of smoking and/or hypertension. Patients were followed-up once a year from the time of enrollment. Screening the first 303 relatives identified 58 (19.1%) individuals with at least one intracranial aneurysm, 10 (17.2%) of which had multiple lesions. Women were twice as likely as men to harbor an aneurysm (24% versus 11.7%, respectively). Independent predictors of aneurysm detection using MRA included female sex (odds ratio [OR] 2.46 ± 0.290; 95% confidence interval [CI] 1.46 to 4.54; p=0.001), 20 pack-years of cigarette smoking (OR 3.24 ± 0.072; 95% CI 1.81 to 5.79; p<0.001), and 10 years of hypertension (OR 1.26 ± 0.009; 95% CI 1.07 to 1.49; p=0.006). The majority (97.2%) of the aneurysms detected were less than 7 mm in diameter. The authors concluded that among individuals with FIA who are over the age of 30 years, women with a history of smoking or hypertension are at increased risk of intracranial aneurysms and should be strongly considered for screening with MRA.

Broderick et al. reported updated results for the frequency of unruptured intracranial aneurysms in 542 families (n=2,874) enrolled in the FIA study. MRA was performed in 548 family members with no known personal history of intracranial aneurysms. Intracranial aneurysms were detected by MRA in 113 (20.6%) family members, five (0.9%) of which had intracranial aneurysms 7 mm in diameter or greater. Two subjects subsequently had rupture of their intracranial aneurysms (one 3 mm in diameter and one 4 mm in diameter at screening) at 15 months and 17 months after enrollment. Based on these findings, the annual rupture rate was estimated at 1.2 ruptures per 100 subjects (1.2% per year; 95% CI 0.14% to 4.3% per year). The authors noted that this rupture rate is approximately 17 times higher than the rupture rate of aneurysms matched for size and location in the general population. None of the 435 participants who were negative for intracranial aneurysms at screening experienced a ruptured intracranial aneurysm during the follow-up period. The authors concluded that the rupture risk of small intracranial aneurysms was greater in FIA study participants who had a positive history of smoking or hypertension when compared with individuals in the general population who did not have these risk factors.

Woo et al. examined FIA study participants for the age at which intracranial aneurysms rupture in different generations. Of 429 families with ruptured intracranial aneurysms, 54 (12.6%) were found to have parent-offspring (n=35) or aunt/uncle-niece/nephew (n=19) pairs. No significant gender concordance was observed. From these families, all siblings of each generation were included in the analysis (n=1,641). When Kaplan-Meier curves were analyzed, the authors
noted a tendency to have a slightly later rupture rate in the second generation when time to follow-up was accounted for in the analysis model. The authors concluded that rupture of intracranial aneurysms does not appear to occur at a younger age in subsequent generations.

**Risk of SAH According to the Number of Affected Relatives**

Teasdale et al. estimated the risk of experiencing a SAH in a large population study in Scotland. Two population samples were studied: 5478 relatives of patients from the whole of Scotland who had experienced a SAH in during the course of one year and 3213 relatives of patients admitted to the West of Scotland regional neurosurgical unit with a SAH 10 years previously. Overall, 2% of all relatives in each sample had a SAH. Results from the Scotland-wide sample showed that the absolute lifetime risk (from birth to 70 years of age) was higher for first-degree relatives (4.7%; 95% CI 3.1% to 6.3%) than for second-degree relatives (1.9%; 95% CI 1.0% to 2.9%). The estimated relative risk of SAH for first-degree versus second-degree relatives was 2.29 (95% CI 1.36 to 3.87). There was no statistically significant effect of gender on the risk of SAH. Findings from the West of Scotland sample showed that the estimated ten-year prospective risk for SAH increased in an ascending manner depending on the relationship. The risks of SAH over 10 years for relatives of patients who had experienced a SAH were 0.3% (95% CI 0.0 to 0.6) for one affected second-degree relative, 0.8% (95% CI 0.2 to 1.5) for one affected first-degree relative, 1.1% (95% CI 0.0 to 3.3) for at least two affected second-degree relatives, and 7.1% (95% CI 0.2 to 14.0) for at least two affected first-degree relatives. However, none of these results were statistically significant and the wide confidence intervals around these risk estimates reflect the small numbers of SAH events that occur in relatives of index cases, even in large population studies. Based on low absolute risk for SAH among the relatives of patients who have suffered a SAH, the authors concluded that screening is not warranted except for families with two or more first-degree relatives who have experienced a SAH.

Bor et al. reported similar results in a large population base case-control study. A total of 5282 patients diagnosed with SAH in Sweden between 2001 and 2005 were identified from an inpatients register. For each of the 5282 patients, five controls (n=26,402) were identified through a nationwide register. A total of 130,373 first-degree relatives for patients and controls were then assessed for a diagnosis of SAH. Compared with individuals without a family history, the OR was 2.15 (95% CI 1.77 to 2.59) for individuals with one affected first-degree relative and 51.0 (95% CI 8.56 to 11117) for individuals with at least two affected first-degree relatives. Gender, age, and type of kinship (child, sibling, or parent) did not influence the risk for individuals with one or more affected relatives. Based on these findings, the authors concluded that screening should be considered in cases with two or more affected first-degree relatives.

**Economic evaluations**

Takao et al. evaluated the cost-effectiveness of MRA screening for asymptomatic unruptured intracranial aneurysms in family members of patients with a history of aneurysmal SAH. The cost-effectiveness analysis was conducted from a societal perspective. Markov models were used to estimate the probability of different treatments and outcomes following screening or no screening over a lifetime horizon. A 40-year-old family member with two or more first-degree relatives who had aneurysmal SAH was set as the base case. Clinical estimates were derived from multiple published sources including meta-analyses, systematic reviews, cohort studies, and case-control studies. Aneurysm rupture rates and treatment outcomes were based on
results from a large prospective observational study.⁵ The model assumed that aneurysm rupture rates were constant over time. Costs associated with screening, treatment (surgical clipping or endovascular coiling), SAH, and managing long-term disability (including hospital, physician, outpatient, rehabilitation, and nursing home/home care costs) from the published literature were included in the analysis. The price year was 2003.

For patients with two or more affected first-degree relatives, the average cost for patients receiving screening was US$1,900 compared with US$590 for no screening. Screening resulted in 22.43 quality-adjusted life-years (QALYs) compared with 22.40 QALYs for no screening. The incremental cost-effectiveness ratio (ICER) was US$37,400 per QALY gained. A probabilistic sensitivity analysis showed that the 95% CI for the ICER of screening was US$14,800 per QALY to US$90,000 per QALY and that the ICER of screening was equal to or less than US$50,000 in 79.7% of simulations. For patients with one affected first-degree relative, screening resulted in 22.45 QALYs and no screening resulted in 22.44 QALYs. The average cost was US$1,300 for screening and US$290 for no screening. The ICER was US$ 56,500 per QALY gained. A probabilistic sensitivity analysis showed that the 95% CI for the ICER of screening was US$25,000 per QALY to US$142,500 per QALY and that the ICER of screening was equal to or less than US$50,000 in 43.6% of simulations. A one-way sensitivity analysis showed that the ICER was greater than US$50,000 if the age at screening was 50 years or greater, the prevalence of unruptured intracranial aneurysms was less than 4.8%, or the annual rupture rate of 7mm to 12 mm anterior circulation aneurysms was less than 0.30% per year. The authors concluded that MRA screening was cost-effective for family members with two or more affected first-degree relatives depending on the age at screening and assuming a cost-effectiveness threshold of US$50,000 per QALY.

Guidelines and recommendations

A task force of the Stroke Council of the American Heart Association published evidence-based guidelines for the management of aneurysmal SAH in 2009.¹⁴ A systematic review of the literature was used to identify the evidence to support each recommendation. Screening for asymptomatic intracranial aneurysms in the general population or in family members with a single first-degree relative who had experienced a ruptured intracranial aneurysm was not supported in the identified literature. Evidence for the increased risk of intracranial aneurysms in family members with two or more affected first-degree relatives was identified. However, the guidelines state that screening for asymptomatic intracranial aneurysms should be considered on an individual basis as cost-effectiveness had not been evaluated at the time of the literature review. The guidelines indicate that while noninvasive imaging may be used for screening, the optimal imaging technique for initial screening has yet to be established and should be individualized. Based on these findings the guidelines state that screening for unruptured intracranial aneurysms in high-risk populations is of uncertain value (Class IIb, Level of Evidence B).⁶

---

⁵ Class IIb: Usefulness/efficacy is less well established be evidence or opinion;
Level of Evidence B: Data derived from a single grade A study or ≥1 case-control studies or studies using a reference standard applied by an unmasked evaluator
Limitations

- The literature search for this report was limited to studies published within the last five years.
- A single observational study was identified assessing clinical outcomes of untreated intracranial aneurysms following detection at screening. Observational studies are subject to selection bias. Controlled studies assessing different screening strategies in a larger sample of asymptomatic relatives over a longer period of time are needed to assess the effectiveness of screening and to provide more information on the mechanism and risk factors for aneurysm growth and rupture.
- Estimated rupture rates were based on a limited number of events in the study cohorts.
- There is no clear evidence to support optimal imaging technique, age at which to screen, or screening interval for asymptomatic intracranial aneurysms in terms of diagnostic accuracy, cost-effectiveness, and safety. As a result of the limited available evidence, current guidelines state that the benefit of screening is uncertain.
- Although one cost-effectiveness study indicated that screening for unruptured intracranial aneurysms may be a cost-effective option for family members with two or more affected first-degree relatives, these results may not be generalizable to publicly funded healthcare systems in Canada.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In summary, although a genetic predisposition for harboring unruptured intracranial aneurysms has been reported in the literature, few recent studies have assessed the clinical and economic impacts of screening in family members. There is evidence that first-degree relatives of patients who have intracranial aneurysms or have experienced an aneurysmal SAH have a higher risk of harboring unruptured intracranial aneurysms and experiencing an aneurysmal SAH than second-degree relatives. Furthermore, this risk increases when two or more first-degree relatives are affected. Some studies have indicated that among family members over the age of 30 years with two or more affected first-degree relatives, certain risk factors such as female gender and a history of smoking or hypertension further increase the risk of harboring unruptured intracranial aneurysms. Although there is evidence that rupture of intracranial aneurysms does not appear to occur at a younger age in subsequent generations, the optimal age in which to initiate screening in family members is not known. An economic evaluation indicated that MRA screening is cost-effective for family members under the age of 50 years with two or more affected first-degree relatives. It is not clear whether screening for unruptured intracranial aneurysms is cost-effective in a Canadian setting.

The optimal imaging technique for screening has not been established. Previous research indicates that there is no significant difference in the diagnostic performance and test characteristics of MRA and CTA. However, MRA may be preferred over CTA due to the allergic reactions to contrast and the radiation exposure associated with CTA use. The frequency and duration of follow-up imaging for family members receiving both positive and negative screening results is not yet evident. One study indicated that short-term follow-up using MRA imaging of small untreated aneurysms detected at screening is not beneficial but it remains unclear whether follow-up at longer intervals is more effective. There is evidence that individuals with two or more affected first-degree relatives who are negative for intracranial aneurysms with MRA screening have a 7% risk of developing an intracranial aneurysm within 5
years of screening. Based on the limited amount of available evidence, current guidelines state that screening for unruptured intracranial aneurysms should be considered on an individual basis as the benefits of screening are uncertain at this time.

Until further information is available, the benefits versus the risks for the specific patient case, clinical experience, and institution-specific budgets may be a consideration when making policy decisions regarding screening for unruptured intracranial aneurysms in asymptomatic relatives of patients who have had intracranial aneurysms.

PREPARED BY:
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
REFERENCES:


