UNRUPTURED INTRACRANIAL ANEURYSMS

Detection and management

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SUMMARY

Between 3.6 and 6% of the population harbour an unruptured intracranial aneurysm. Risk of rupture is related to aneurysm site and size and whether or not the patient has already had a subarachnoid haemorrhage (SAH) from another aneurysm. In ISUIA 2, the rupture rate for anterior circulation aneurysms <7mm was 0% per year in patients with no prior SAH, and 0.3% per year in patients with previous SAH; 7-12mm aneurysms, 0.5% per year (both groups); 13-24mm aneurysms, 3% per year; and giant aneurysms 8% per year. Rupture rate for posterior circulation aneurysms is higher at all sizes: < 7mm was 0.5% per year in subjects with no prior SAH, 0.7% in those with prior SAH; 7-12mm, 3% per year; 13-24mm, 3.7% per year; and giant aneurysms, 10% per year.

Non-invasive tests like contrast enhanced magnetic resonance angiography (MRA) and multislice computed tomographic angiography (CTA) are alternatives to intra-arterial digital subtraction angiography (IADSA) to detect aneurysms. Although these are promising techniques, the quality of data testing their accuracy remains limited and single slice CTA and time-of-flight MRA are poorer at detecting aneurysms <5mm diameter, which account for up to 1/3 of unruptured aneurysms.

For ruptured aneurysms, the only large scale randomised controlled trial comparing surgical and endovascular treatment (ISAT) by coiling, resulted in an absolute 8.8% reduction (updated figure as of June 2003 for 1888 patients) in death or dependency at 1 year compared with surgical clipping. For unruptured aneurysms, the best available data so far comparing coiling and clipping is from the prospective (but non-randomised) arm of ISUIA. Elective surgical clipping had combined morbidity and mortality at 1 year of 12.2% versus 9.5% for coiling, although the groups were not matched with more high risk patients in the endovascular treatment cohort. Nevertheless these data are encouraging for future randomised trials of elective coiling versus clipping for asymptomatic aneurysms, in particular as the unproven long-term durability of coiling treatment and the fact that complete aneurysm occlusion is not always achieved remain obstacles to its wider use in unruptured aneurysms.

There is an increased risk of SAH in relatives of patients with SAH (highest in those with two or more first degree relatives affected), but most SAH is sporadic and therefore the balance of available evidence indicates that mass screening for aneurysms is not cost effective. There may be a limited role for investigation of high-risk subgroups and ideally such screening should be tested in a randomised trial. The avoidance and active management of vascular risk factors should also be part of the management of at risk subjects.

Key words: unruptured intracranial aneurysm, Magnetic Resonance Angiography, CT Angiography, Screening.

RéSUMÉ

Anévrismes intracrâniens non rompus

La fréquence d’anévrisme intracrânien non rompu dans la population générale est estimée à 3,6 à 6 %. Le risque de rupture est lié à la taille de l’anévrisme, son siège et l’existence éventuelle d’une hémorragie sous-arachnoïdienne (HSA) en rapport avec un autre anévrisme. Dans l’étude ISUIA 2, le taux de rupture pour les anévrismes de la circulation antérieure de moins de 7 mm est de 0 % par an chez les patients sans HSA et de 0,3 % par an chez les patients ayant saigné ; de 0,5 % par an dans les anévrismes de 7 à 12 mm ; de 3 % par an pour les anévrismes de 13 à 24 mm et de 8 % par an pour les anévrismes géants. Le taux de rupture pour les anévrismes de la circulation postérieure est plus important quelque soit la taille : 0,5 % par an chez les sujets sans HSA pour les anévrismes de moins de 7 mm, 0,7 % chez les sujets ayant présenté une HSA ; 3 % par an pour les anévrismes de 7 à 12 mm ; 3,7 % par an pour les anévrismes de 13 à 24 mm et 10 % par an pour les anévrismes géants.

Les méthodes d’imagerie non invasive (ARM, angioscanner) sont susceptibles de remplacer l’angiographie digitalisée pour la détection des anévrismes. Bien qu’il s’agisse de techniques prometteuses, leur sensibilité reste limitée en particulier pour la détection des anévrismes de moins de 5 mm de diamètre qui représentent plus du tiers des anévrismes non rompus.

Pour les anévrismes non rompus, la seule étude randomisée importante comparant chirurgie et traitement endovasculaire (ISAT) montre une réduction de 8,8 % de décès ou de dépendance à un an en cas de traitement endovasculaire. Pour les anévrismes non rompus, les données les plus pertinentes comparant les deux traitements peuvent être tirées de l’étude ISUIA, prospective mais non randomisée. Le traitement chirurgical a une morbidité – mortalité combinée à un an de 12,2 % et le traitement endovasculaire 9,5 %. Cependant le groupe « endovasculaire » comportait plus de patient à risque de complications. Ces données sont encourageantes pour de futurs essais randomisés comparant traitements endovasculaire et chirurgical pour les anévrismes asymptomaticues, en particulier pour apprécier la valeur à long terme du traitement endovasculaire et le fait que l’occlusion anévrismale complète, non toujours atteinte. Ces données restent des obstacles à l’extension des indications du traitement endovasculaire des anévrismes non rompus.

Le risque d’HSA est plus élevé dans les formes familiales mais le plus souvent les HSA sont sporadiques ; le screening de masse est donc peu rentable. Il peut y avoir un intérêt à rechercher un sous-groupe à haut risque et idéalement une telle recherche devrait être évaluée par un essai randomisé. La prévention et le management des facteurs de risque vasculaire devraient faire partie de la prise en charge des sujets à risque.

Mots-clés : anévrisme intracrânien non rompu, angiographie par résonance magnétique, angioscanner, screening.

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UNRUPTURED CEREBRAL ANEURYSMS

INTRODUCTION

Aneurysmal subarachnoid haemorrhage (SAH) accounts for about one-quarter of all cerebrovascular deaths [19] and despite improvements in the management of patients with SAH, the case-fatality rate is still reported at between 25% and 50%, with most patients dying as a result of the initial bleed or its immediate complications [23]. Of the survivors, a third to a half will be left disabled and dependent on others in activities of daily living [22]. SAH is due to rupture of a saccular aneurysm in about 75% of cases, these usually arise from the Circle of Willis or branch artery [77]. With such a poor outcome, there has been interest in the possibility of detection and treatment of intracranial aneurysms prior to rupture.

In order to offer asymptomatic subjects sensible advice, it is necessary to know a) what is their risk of having an aneurysm; b) how best to detect such an aneurysm without exposing the patient to unnecessary stress or risk; c) what is the likely risk of rupture of any aneurysm found; d) having identified an asymptomatic aneurysm what treatment, if any, should be offered. The risk at each stage must be weighed against the risk of not doing anything in that individual. The following article updates a previous article on this topic [91] to summarise systematically the current state of knowledge and highlight where more information is needed.

Symptomatic aneurysms are those causing SAH following rupture, or exerting symptoms by a space occupying effect (most commonly oculomotor nerve palsy produced by a posterior communicating artery aneurysm). Asymptomatic aneurysms may be defined as additional aneurysms found in patients with a symptomatic aneurysm, which are not responsible for the clinical presentation, or those aneurysms found in patients investigated because they are at risk (of harbouring an aneurysm). Incidental aneurysms may be defined as those found unexpectedly in patients undergoing investigation for other suspected pathology.

The relationship between SAH and unruptured intracranial aneurysm:

The overall incidence of SAH (all studies combined) is 10.5 per 100,000 person years, but was 6-8 per 100,000 person years in studies which used CT to confirm the SAH [42]. Spontaneous SAH occurs most commonly between 40 and 60 years, but can occur from childhood to old age. It is about 1.6 times commoner in women than in men, and is associated with physical activity [42, 64].

The risk factors for SAH and for having an unruptured intracranial aneurysm are very similar (table I). Smoking, hypertension, alcohol consumption [81], cocaine and amphetamine abuse [58], oral contraceptive use [30], plasma cholesterol concentration in the highest tertile (>6.3 mmol/l) [1] are all associated with an increased risk of aneurysm formation and/or SAH. The Australian Cooperative Research on Subarachnoid Haemorrhage Study (ACROSS) studied physical exertion, heavy cigarette smoking and binge alcohol consumption in the two hours preceding SAH in 432 patients: moderate to extreme exertion, but not transient heavy cigarette smoking or binge alcohol consumption, was associated with a three-fold increase in the risk of SAH (Odds ratio 2.7, 95% confidence interval 1.6 to 4.6) [3].

Several genetic conditions are associated with SAH and intracranial aneurysms. Aneurysms occur in 10-15% of patients with adult polycystic kidney disease (ADPKD) [63], particularly if there

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk for</th>
<th>Prevalence of aneurysms</th>
<th>Relative risk</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Female gender</td>
<td>+</td>
<td>+</td>
<td>1.6</td>
<td>(Linn et al., 1996)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>+</td>
<td>+</td>
<td>1.9</td>
<td>(Teunissen et al., 1996)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>–</td>
<td>+</td>
<td>2.8</td>
<td>(Teunissen et al., 1996)</td>
</tr>
<tr>
<td>Alcohol (heavy consumption)</td>
<td>–</td>
<td>+</td>
<td>4.7</td>
<td>(Teunissen et al., 1996)</td>
</tr>
<tr>
<td>Oral Contraceptive Pill</td>
<td>?</td>
<td>+</td>
<td>1.5 (low dose)</td>
<td>(Johnston et al., 1998)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>1.9 (high dose)</td>
<td></td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>?</td>
<td>+</td>
<td>2.3</td>
<td>(Rinkel et al., 1998)</td>
</tr>
<tr>
<td>Ischaemic Heart Disease in women</td>
<td>+</td>
<td>+</td>
<td>(4.3)</td>
<td>(Uehara et al., 1998)</td>
</tr>
<tr>
<td>Cholesterol &gt;6.3mmol/l</td>
<td>?</td>
<td>+</td>
<td>10.2 (Odds Ratio)</td>
<td>(Adamson et al., 1994)</td>
</tr>
<tr>
<td>ADPKD</td>
<td>+</td>
<td>+</td>
<td>10-15 %</td>
<td>(Rinkel et al., 1998)</td>
</tr>
<tr>
<td>Familial (2 or more first or second degree)</td>
<td>+</td>
<td>+</td>
<td>9.8 %</td>
<td>(Rinkel et al., 1998)</td>
</tr>
<tr>
<td>First-degree relatives in families with one affected member</td>
<td>+</td>
<td>+</td>
<td>4.5 %</td>
<td>(see Tables 2 and 3 for references)</td>
</tr>
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is a positive family history of aneurysms and/or SAH [24, 70]. Type IV Ehlers-Danlos syndrome [75], possibly pseudoxanthoma elasticum [50]—although a more recent report refutes any association [84]—hereditary haemorrhagic telangiectasia [65], neurofibromatosis type I [48] and alpha1-antitrypsin deficiency [73] are also associated with aneurysm formation. Marfan’s syndrome was thought to be associated with aneurysms but a detailed study of 135 patients average age 21.3 years with Marfan’s syndrome found no evidence of a relationship [85], although these patients may not have been old enough for the aneurysms to be manifest. Aneurysms have also been reported sporadically in other conditions including Klinefelter syndrome, tuberous sclerosis, Noonan’s syndrome and alpha-glucosidase deficiency [85]. Results from studies of aneurysms and HLA-B27, HLA-DR2 [57] HLA-A28 and HLA-B40 [52] are inconclusive [38, 71].

THE FREQUENCY OF INTRACRANIAL ANEURYSMS IN THE GENERAL POPULATION

Incidental aneurysms are commonly found at autopsy. Rinkel et al identified 23 studies between 1955 and 1996 including 56,304 patients (most from retrospective autopsy studies), in which the prevalence of unruptured aneurysms varied considerably: 0.4% and 3.6% (for retro- and prospective autopsy studies respectively), and 3.7% and 6% (for retro- and prospective angiography studies) [63]. Several more recent studies support the higher figures from the prospective studies [36, 67]. 20-25% of patients undergoing angiography following SAH are found to have at least one unruptured aneurysm in addition to the one that has ruptured [43]. Additional aneurysms occur more commonly in females [63]. Both smoking and female gender were important factors in the development of multiple aneurysms in the ISUIA study [25].

So 3.6% to 6.0% of the population aged over 30 harbour an unruptured aneurysm, females more than males. Aneurysms increase in frequency with age, they are associated with smoking, hypercholesterolaemia (at least in women) and possibly with hypertension. As only a small proportion of these aneurysms actually rupture, the key to the management of unruptured intracranial aneurysms is not only to identify those at greatest risk of harbouring an aneurysm but also those aneurysms at greatest risk of rupture.

ARE SPECIFIC GROUPS AT HIGHER RISK OF INTRACRANIAL ANEURYSMS?

SAH may be associated with defined genetic diseases (see above), but SAH may affect several members of a family without any specific genetic “disease”. This was first reported in 1942 [53]. Familial SAH has been defined inconsistently, so it would be preferable to be more precise:

Definition of Familial SAH

Families in which two or more close blood relatives (first or second degree) have a history of aneurysmal SAH without any other known heritable disease.

Note: First degree relatives=parents, siblings, children; Second degree=grandparents, grandchildren, aunts & uncles, nieces & nephews; Third degree=cousins, great grandparents, great grandchildren, etc.

Several families in which numerous members are affected by SAH have been described in detail. These few badly affected families might raise the apparent prevalence of SAH in relatives of index SAH patients in incidence studies [40]. Conversely, many cases of “familial intracranial aneurysms” might simply represent accidental aggregation [80]. On the basis of chance alone, each SAH patient has a 5.6% possibility of having a first- to third- degree relative also affected by SAH [36], and in one study, the proportion of SAH patients with third degree relatives who had had a SAH was the same as the proportion with SAH in the control population [18].

Since 1987, nine studies (table II) have examined the prevalence of unruptured aneurysms and/or SAH amongst relatives of patients with SAH [11, 18, 20, 51, 56, 66, 76, 88, 89]. One additional study in Japan sought family histories of SAH amongst patients self-referred for cranial MRI (including MRA) though they did not sample a defined population [56], and the MARS study screened 626 first-degree relatives of patients presenting with SAH using magnetic resonance angiography (MRA) [45]. Other studies have described small groups of families affected by SAH but were not truly population-based [2].

The studies generally differed somewhat in methodology. The studies varied from population-based screening for SAH amongst asymptomatic family members [88, 89] to case-ascertainment methods which identified cases of SAH and their family members [11, 18, 56]. One study focussed on unruptured aneurysms in first-degree relatives of patients with SAH [20]. In other studies, the cases were defined by the presence of SAH. Since 1987, nine studies (table II) have examined the prevalence of unruptured aneurysms and/or SAH amongst relatives of patients with SAH [11, 18, 20, 51, 56, 66, 76, 88, 89]. One additional study in Japan sought family histories of SAH amongst patients self-referred for cranial MRI (including MRA) though they did not sample a defined population [56], and the MARS study screened 626 first-degree relatives of patients presenting with SAH using magnetic resonance angiography (MRA) [45]. Other studies have described small groups of families affected by SAH but were not truly population-based [2].

In the nine population-based studies, the case ascertainment methods varied considerably, some only included first, some first and second degree, some first to third degree relatives, and furthermore not all the studies analysed the results obtained by relationship to the index case, so the studies were difficult to compare. The studies where it was possible to calculate a relative risk (RR) for SAH in relatives compared with the background population were broadly in agreement: RR of SAH of 4.14 for first degree and 1.6 for second degree [76]; 6.6 for first and second degree combined [11]; 4.7 for first and 2.1 for second degree [18]; 2.9 for first-degree relatives [20]; or Odds Ratio for first degree relatives of 4.0 (95% CI 2.0-8.0) [56]. Whilst the relative risks appear large, it is important to remember the small absolute number of relatives affected: only 156/21054 (0.74%) first-degree relatives were themselves affected by SAH in the studies from which it was possible to extract these data [11, 20, 51, 76, 89]. The prevalence of SAH in relatives of patients with SAH was the same as the proportion with SAH in the control population [18]. The incidence of SAH among family members over the decade after the index case SAH was 1.2% for first-degree and 0.5% for second-degree relatives (some 12 and 5 times background population risk respectively) [89]. So, as the very great majority of
relatives of SAH patients will not have an aneurysmal SAH, screening all relatives for aneurysms would necessitate examination of a very large proportion of people never likely to be affected.

WHICH RELATIONS ARE MORE FREQUENTLY AFFECTED BY SAH AND ANEURYSMS?

In families with more than one person with SAH (table III), the most frequent relationship was index patient to sibling, followed by index patient to parent. Overall a parent was affected in 29% i.e. in only about a third of affected families was there a very clear warning of the potential for SAH from a previous generation. Interestingly, one study found a much stronger familial link to maternal SAH than to paternal or sibling SAH [56] and in another study, the commonest affected first degree relatives were also parents (30%) rather than siblings (24%)[89].

Familial intracranial aneurysms may have distinguishing biological features, including: rupture at a younger age (most frequently in the fifth decade compared to the sixth decade for sporadic SAH) [12]; worse clinical outcome; and an increased prevalence of middle cerebral artery (MCA) aneurysms [12]. It appears there may be a younger age of rupture in subsequent generations, implying possible “anticipation” [12] but familial aneurysms may also have a predilection towards rupture in the same decade in individuals of the same family, particularly in siblings [40].

DETECTING ANEURYSMS

The reference standard for identification of an intracranial aneurysm is an intrarterial digital sub-
traction angiogram (IADSA) with selective cerebral arterial injections and multiple projections particularly with use of 3D DSA technique—see figure I. However IADSA is invasive, requires a stay in hospital, is costly, and not without risk: a meta-analysis found the risk of permanent neurological complication after IADSA in patients with SAH, or suspected aneurysm or arteriovenous malformation was 0.07% [16]. Therefore IADSA is unsuitable for use as a population screening test. Non-invasive tests, like magnetic resonance angiography (MRA), dynamic spiral CT Angiography (CTA) or transcranial doppler sonography (TCDS) might be suitable but have to be extremely accurate to replace IADSA, as an undetected aneurysm is a potentially life-threatening condition, yet one does not want to perform confirmatory IADSA unnecessarily.

A systematic review of studies of non-invasive imaging of aneurysms published between 1988 and 1998 (inclusive) identified 104 studies comparing MRA or CTA, a few of MRA and CTA, and a few of TCDS with IADSA [94]. Most reported apparently excellent results for the non-invasive tests, but many were small studies and had methodological deficiencies, which combined, may have overstated the accuracy of these techniques in clinical practice. Since then, further studies of non-invasive imaging tests in the detection of symptomatic or asymptomatic intracranial aneurysms versus IADSA, as an undetected aneurysm is a potentially life-threatening condition, yet one does not want to perform confirmatory IADSA unnecessarily.

As a result of these methodological limitations, the reported sensitivities, specificities and predictive values must be interpreted with some caution, particularly if one is considering using the non-invasive test to screen for aneurysms in a low prevalence population. Analysis of accuracy per patient rather than per aneurysm is of more clinical relevance to a screening program. Failure to identify any aneurysm by a non-invasive test in a patient where one was actually present could offer false reassurance.

The systematic review [94] found sensitivities, specificities (95% confidence intervals) as follows:

For identification of a patient as having or not having an aneurysm:

- **MRA** (926 subjects in 20 studies) – sensitivity 87% (84-90%); specificity 92% (88-94%)
- **CTA** (677 subjects in 16 studies) – sensitivity 92% (89-95%); specificity 94% (88-99%)
- **TCDS** no studies reported the data per patient.
For identification of an aneurysm correctly:

MRA (1596 aneurysms in 926 subjects) – sensitivity 87% (84-90%); specificity 95% (91-97%)

CTA (1582 aneurysms in 677 subjects) – sensitivity 90% (88-92%); specificity 86% (79-91%)

TCDS (97 aneurysms in 162 subjects – sensitivity 82% (67-92%); specificity 95% (91-97%).

The results for non-invasive imaging methods are significantly poorer for aneurysms <5mm, which constitute as many as a third of aneurysms in asymptomatic patients[36].

Have publications since then changed these figures? The sensitivities and specificities in individual studies have been similar to the above. However, there is more information on the effect of aneurysm size and site on accuracy – smaller aneurysms are much harder to detect with sensitivities of 0.35, 0.57 and 0.35 for aneurysms <5mm diameter for MRA, CTA and TCDS respectively, and ICA aneurysms were harder to detect than those at other sites [92, 95].

Intravenous sonographic-contrast agents improved the visualisation of aneurysms in one study, with sensitivity rising from 40% to 55% but specificity falling from 91% to 83% following contrast [83]. Two small studies suggest that dynamic contrast MRA (rapid MRA during an intravenous injection of gadolinium) may be more accurate than time of flight MRA [47, 78], but these small early studies might be optimistic and do suffer from the methodological problems of the early time of flight MRA studies. Two studies, which looked at the effect of observer experience on aneurysm detection found, not surprisingly, that experts detected substantially more aneurysms, more reliably, than less experienced observers [55, 95]. Finally, White et al examined the accuracy of using combinations of non-invasive tests to detect aneurysms [60]. Two non-invasive tests together were more accurate than one,
CTA in combination with TCDS being best overall (sensitivity 83%) but even the combinations performed poorly for detecting very small aneurysms (CTA plus TCDS sensitivity 43%) with the conclusion that “the addition of power TCDS to either CTA or MRA improved diagnostic performance on a per patient basis, but aneurysms of 5mm or smaller can still not be reliably detected by current standard clinical non-invasive imaging modalities”.

The accuracy of MRA and CTA may depend on how the images were processed and reviewed, though little work has been done in this area [5]. One study found a sensitivity (per patient) of 75% for MRA presented as Maximum Intensity Projection (MIP) reconstructions alone (this type of image resembles an angiogram – figure 2), but sensitivity increased to 95% when axial base and spin echo images were reviewed as well [69]. In a blinded study of 82 patients with two observers Mallouhi et al found greater diagnostic confidence and sensitivity on MRA processed by volume rendering compared with MIP (sensitivity 89% and 71% respectively). Volume rendering particularly helped identify small aneurysms [44].

CTA (figure 2 and 3) has some disadvantages compared to MRA in that it requires an injection of iodine based contrast (which may cause allergic reactions and can cause a deterioration in renal function in vulnerable groups) and is associated with radiation exposure (typically about 2 mSv; equivalent to about one year background radiation in most of Western Europe). The radiation dose is a significant drawback for widespread screening, particularly if this needed to be repeated. However, CTA is more rapid than MRA, and some patients cannot tolerate MR. Colour transcranial Doppler ultrasound became available in the early 1990s, and later Colour Doppler Energy (CDE) or “Power Doppler”, with success reported in the identification of aneurysms [7, 82, 90]. Ultrasound has the advantage of lower capital cost and mobility compared to IADSA, CTA and MRA. Ultrasonic contrast agents and 3-D ultrasound imaging may improve accuracy [83]. Unfortunately about 10% of patients will not have an adequate bone window and the technique is operator dependent.

The practical difficulties of attempting to screen for aneurysms are illustrated by two studies. Ronkainen

![CTA](image1.png)  
![MRA](image2.png)  
![Power Doppler](image3.png)  

**Fig. 2.** Right terminal carotid bifurcation aneurysm (arrow) demonstrated on 2D DSA (a), MRA MIP (b) and CTA “angio-MIP” (c) images. This was a ruptured aneurysm and the associated haematoma results in marked T1 shine through effect on the MRA MIP image- highlighting the location of the aneurysm to an observer. This effect (or the blood distribution on CT) is one of the reasons that diagnostic accuracy studies on SAH patients cannot be readily extrapolated into a screening context.

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et al screened 438 subjects from 85 families of SAH patients using MRA and found 58 aneurysms in 45 subjects. IADSA was performed in 43/45 [68]. Of these 43, 7 did not in fact have an aneurysm (false positives), and the remaining 36 subjects actually had 60 aneurysms (13 had been missed by MRA, i.e. false negatives). 47 aneurysms were found by both MRA and IADSA (true positive rate per aneurysm of 78%, false positive rate of 15%, and a false negative rate of 22%). As 395 patients did not have IADSA, the true negative rate cannot be determined but it is very likely that some aneurysms were missed amongst the 395 MRA negative subjects and indeed one subject suffered an aneurysmal SAH 3 years after a negative MRA. Raaymakers et al used MRA to screen 626 asymptomatic first-degree relatives of 193 SAH patients and found 31 aneurysms in 23 relatives (4%). IADSA confirmed the presence of all 31 aneurysms, but was not performed in the other 603 relatives, so again the number of aneurysms missed is unknown [45].

Imaging technology is improving all the time. Further studies of non-invasive imaging of aneurysms will be required as technology changes, in particular larger studies in patients without SAH but at risk of an aneurysm (and who all have DSA for verification), to eliminate the systematic bias in accuracy assessment of CTA/MRA/TCDS introduced by a preponderance of recent SAH patients. In considering non-invasive screening for aneurysms, as well as the limitations of the tests themselves, one should also consider the need for subsequent follow-up to exclude de novo aneurysm formation or enlargement of any small aneurysms previously detected. How often to do this and for how long? No definite evidence-based answers exist to these questions at this time.

THE RISK OF ANEURYSM RUPTURE

A systematic review in 1998 on the risk of aneurysm rupture identified 9 studies with a total of 3907 patient years of follow up [63], over half of these contributed by one study from Finland [32]. During follow-up, 75/495 (15.2%) patients suffered a SAH, giving an overall annual rupture rate of 1.9% (95% CI 1.5-2.4) – table IV. The median time from diagnosis to rupture in the study by Juvela et al was 9.6 years (range 1.2 to 23.1 years) and this was the only study of the nine included in the systematic review to have a mean or median follow-up of more than nine years. Aneurysms were significantly more likely to rupture in women than in men (RR 2.1, 95% CI 1.1-3.9) and the risk of rupture increased with age. In the group of patients aged 60 to 79 years, RR of rupture was 1.7 (95% CI 0.7-4.0) compared with those aged 40 to 59 years. Symptomatc aneurysms were significantly more likely to rupture than incidental or additional aneurysms (6.5% vs 0.8% vs 1.4% respectively), RR of 8.2. Posterior circulation and large (>10mm) aneurysms were significantly more likely to rupture, RR of 4.4 and 4.0 respectively.
Rinkel et al identified a total of 1145 years of patient follow-up in subjects with asymptomatic aneurysms and no prior SAH (the group applicable to a screening scenario). 93% of the aneurysms in this group of subjects were 10mm or less in size. There were nine ruptures – aneurysmal size could be extracted for 8/9 – and all but one were in aneurysms 10mm or larger [GJE Rinkel, personal communication], thus the annual rupture rate for asymptomatic aneurysms 10mm or less was 0.1%. In Juvela’s study 147/152 patients had had prior SAH [32]. 67% of the aneurysms that later ruptured were less than 6mm in diameter, and the proportion of aneurysm ruptures increased almost constantly according to size (p = 0.03). In a logistic regression model, the only factor significantly related to aneurysm rupture was the size of the aneurysm- 7mm or larger aneurysms had a relative risk of rupture of 2.24 compared with smaller aneurysms [32]. Repeat angiography during follow-up showed, in patients with later SAH, that the size of the aneurysms had increased from the start of follow-up, whereas in those without later SAH the size did not change, and new aneurysms were found which had formed during the study in 19%, giving an approximate rate of formation of 2.2% per year. Some patients later suffered a SAH from these de novo aneurysms.

The largest ever study to follow up unruptured aneurysms is the International Study of Unruptured Intracranial Aneurysms (ISUIA) with 2621 patients in the retrospective arm [26] and 4060 subjects in the prospective arm [27]. ISUIA studied two groups of patients: 1) patients with asymptomatic aneurysms with no prior SAH and 2) those with additional aneurysms who had previously sustained an aneurysmal SAH. The investigators also prospectively studied the risks of treatment of asymptomatic unruptured aneurysms.

The results of the retrospective ISUIA indicated a very small rupture risk of 0.05% per year for small aneurysms (<10mm diameter) in patients who had not had a SAH previously (group 1), and of 0.5% per year for large aneurysms and all aneurysms in patients who had previously sustained a SAH from another aneurysm [71]. The more scientifically robust prospective data indicate a negligible rupture risk for anterior circulation aneurysms <7mm in Group 1 subjects (0%), 0.5% per year for aneurysms 7-12mm but substantially higher risk for larger aneurysms (3-8% per year). The relative rupture risk for

### Tableau IV. – Rupture risk of intracranial aneurysms.

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<th></th>
<th>Rinkel et al.*</th>
<th>ISUIA retrospective</th>
<th>ISUIA Prospective</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>495</td>
<td>1449</td>
<td>1692 (unoperated cohort)</td>
</tr>
<tr>
<td>No. of aneurysms</td>
<td>–</td>
<td>1937</td>
<td>2686</td>
</tr>
<tr>
<td>Duration of follow-up (patient years)</td>
<td>3907 (mean of mean follow-ups 5.5, range 2.1 to 13.7 years)</td>
<td>12023 (mean follow-up 8.3 years)</td>
<td>7587 (mean 4.5 years)</td>
</tr>
<tr>
<td>No. ruptured</td>
<td>75</td>
<td>32</td>
<td>51</td>
</tr>
<tr>
<td>Overall rupture rate (expressed as % pa)</td>
<td>1.9 (1.5-2.4)</td>
<td>0.27 (32 in 12023 years)</td>
<td>0.67</td>
</tr>
<tr>
<td>Rupture rate: &lt;10mm &gt;10mm</td>
<td>0.7 (0.5-1.0)</td>
<td>0.05</td>
<td>&lt;7mm all sites Group 1=-0.07</td>
</tr>
<tr>
<td>Cumulative aneurysm rupture rate</td>
<td>10 % per decade (from Juvela et al.)</td>
<td>0.5-5% per decade</td>
<td>0.7-1.5% per decade**</td>
</tr>
<tr>
<td>Symptomatic aneurysm rupture rate</td>
<td>6.5 (4.4-9.1)</td>
<td>data not extractable</td>
<td>data not extractable</td>
</tr>
<tr>
<td>Asymptomatic aneurysm rupture rate</td>
<td>0.8 (0.4-1.5) but 7/8 ruptures in aneurysms &gt;10mm</td>
<td>data not extractable</td>
<td>&lt;7mm=-0.07</td>
</tr>
<tr>
<td>Additional aneurysm rupture rate</td>
<td>1.4 (0.9-2.0)</td>
<td>data not extractable</td>
<td>-0.36 all sizes</td>
</tr>
<tr>
<td>Posterior circulation aneurysm rupture rate</td>
<td>4.4 (2.7-6.8)</td>
<td>data not extractable</td>
<td>0.5 (&lt;7mm) -10% (&gt;24mm)</td>
</tr>
<tr>
<td>Age: 20-39</td>
<td>0 (0-13)</td>
<td>data not extractable</td>
<td>data not extractable</td>
</tr>
<tr>
<td>40-59</td>
<td>3.5 (1.4-7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-79</td>
<td>5.7 (3.4-9.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*additional data to that published in the systematic review were kindly supplied by Dr Gabriel Rinkel to allow calculation of duration of follow-up in the paper by Juvela et al. (1993) contributed 28% of the patients to the systematic review but almost half the patient-years of follow up. **no difference in rupture rates between groups for larger aneurysms. The rupture rate is much higher than the combined overall figure for the subgroups of posterior circulation aneurysms >7mm and for anterior circulation aneurysms >12mm.
posterior circulation (including posterior communicating) aneurysms was 3-3.2. In Group 2 subjects, rupture risk was 0.3% per year for aneurysms <7mm with no significant difference from Group 1 subjects for larger aneurysms [27]. With a more precise calculation of the rupture risk in the previous literature for incidental aneurysms <10mm of 0.1%, it is apparent that the ISUIA figures for this crucial subgroup are really not substantially different.

In the retrospective arm of ISUIA 32/1449 patients had confirmed aneurysm rupture during follow-up; mean duration of follow-up 8.3 years (12,023 patient-years in total). In the cohort that had not previously had a SAH, only 1/12 aneurysmal ruptures occurred in an aneurysm <10mm in diameter, compared with 17/20 patients in the cohort who had previously had a SAH. The prospective ISUIA had 51 ruptures in 1692 unoperated subjects, mean duration of follow up 4.5 years (7,587 patient years). 49/51 ruptures occurred within 5 years after diagnosis. Only 2/41 ruptures in group 1 subjects were in aneurysms <7mm (both posterior circulation), compared to 7/10 in group 2 subjects.

Recruitment bias may have influenced the ISUIA retrospective results but should be less of a factor in the prospective study – but there are still weaknesses. Most importantly exclusion criteria were wide with no indication of the number of subjects excluded. Furthermore, the regional referral institutions participating in ISUIA should see considerably more eligible patients with newly diagnosed unruptured intracranial aneurysms than are included in the study [41] but data on recruitment rate are omitted. So how truly representative is the recruited study population? Secondly there remains under representation of anterior cerebral/ anterior communicating artery aneurysms in ISUIA compared to the SAH population. Finally, aneurysms <2mm were arbitrarily excluded from both ISUIA studies, though these can rupture. There is clearly a discrepancy between the size of unruptured aneurysms in people with no prior history of SAH which subsequently rupture as opposed to the mean size of aneurysms discovered only after rupture in other studies (>10mm vs 7.5-9mm) [96]. It has been postulated that this may be explained by a propensity for aneurysms that are going to rupture to do so soon after they form, possibly before collagen can form in their walls in significant amounts (D.O. Wiebers, personal communication).

However it may simply be that small aneurysms that despite a much lower rupture risk, ruptures occurring in small aneurysms outnumber those from larger aneurysms.

WHAT SHOULD BE DONE IF AN ANEURYSM IS FOUND – I.E. WHAT ARE THE RISKS OF TREATMENT?

Aneurysms may be treated by surgical clipping or by interventional neuroradiology. Surgical treatment, having been in use for over 40 years, has fairly clearly defined risks and morbidity. There are clear differences in risk between surgery for ruptured and unruptured aneurysms, the risks being higher in patients who have sustained recent SAH [91].

A systematic review of surgical treatment for unruptured aneurysms identified 61 studies published between 1966 and June 1996 including 2460 patients [61]. Only eight studies were prospective, the rest being retrospective. Significantly, in virtually all studies, the neurosurgeon performing the operation was also the observer of outcome. Median follow-up was at only 24 weeks (range 2 – 234 weeks) in the 21 studies that reported the time of outcome assessment. Overall permanent morbidity occurred in 10.9% (95% CI 9.6-12.2%) of patients and mortality was 2.6% (95% CI 2.0-3.3%). The lowest morbidity and mortality was found with small anterior circulation aneurysms (mortality 0.8%, morbidity 1.9%), and the worst with large posterior fossa aneurysms (mortality 9.6%, morbidity 37.9%). In the interpretation of these results, it is important to bear in mind the effect of publication bias - studies that found higher mortality rates than the published literature are much less likely to have been published. The lack of independent outcome assessment would also tend to underestimate the surgical treatment risk. The prospective arm of ISUIA found the surgery-related mortality at 1 year to be 2.7% in patients with no prior SAH and 0.6% in patients who had previously suffered a SAH. Morbidity was 9.9% and 9.8% respectively. A substantial component of the morbidity was ascribed to impaired cognitive status which was not assessed in most previous studies [27]. Age was the only independent predictor of outcome in the ISUIA study: in the retrospective paper the RR of surgery-related morbidity and mortality at one year was approximately 5 in the group >64 years of age compared with patients <45 years of age.

### Table V. – Risk associated with treatment of unruptured aneurysms.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conservative*</th>
<th>Clipping</th>
<th>GDC Coiling</th>
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<tbody>
<tr>
<td>Mortality</td>
<td>0.05^2-5.0^2 (% per decade)</td>
<td>1.5^2-1.8^2%</td>
<td>1.1^1-1.8^1%</td>
</tr>
<tr>
<td>Morbidity</td>
<td>0.02^2-1.0^2 (% per decade)</td>
<td>11.7-15.0^2%</td>
<td>4.0^2-7.3^2%</td>
</tr>
</tbody>
</table>

Figures for morbidity/mortality are at 30 days to allow direct comparison between ISUIA and other studies. 1=ISUIA 1998. 2=Rinkel et al. 1998. 3=Raaymakers et al. 1997. 4=Brilstra et al 1999 *no long term follow-up, procedure related mortality rate quoted. 5=ISUIA 2003. 6=Vinuela et al 1997. *The risks strongly relate to the size of an individual aneurysm. There are patient selection differences between the two ISUIA papers (see text for details).
The effectiveness and risks of aneurysm coiling in unruptured aneurysms are less certain because the technique is newer and still developing. Guigliemi detachable coils (GDC) were introduced in 1991 and revolutionised the endovascular treatment of intracranial aneurysms [21]. A systematic review of aneurysm coiling (all observational studies) identified 48 studies including 1,383 patients [10]. Permanent complications (death/disability) occurred in 3.7% (95% CI 2.7-4.9%). Many studies were retrospective and there was no indication of whether the outcome assessment was independent or not. Only 54% (95% CI 50-57%) of aneurysms were completely occluded after one procedure in the systematic review [10].

The rebleeding rate from partially treated aneurysms is higher and a partial occlusion rate is well recognised to be commoner with coiling than clipping. A more respectable 87.9% were substantially (>90%) coiled though. This partial occlusion problem is reflected in the re-intervention rate in the ISAT trial – 12.7% for coiling versus 3.2% for clipping [28]. This must be borne in mind when examining both the risks and costs of a particular treatment pathway. The technology of coils and coiling assist devices available is constantly improving, so the partial occlusion rate is likely to decline from the levels previously reported. Furthermore a proportion of endovascular procedures are deliberately staged into 2 or 3 treatment sessions.

There is only one large randomised trial – the International Subarachnoid Aneurysm Trial (ISAT) – that has compared coiling with clipping but only in ruptured aneurysms [28]. ISAT enrolled 2143 patients who were matched for age, sex, site & size of aneurysm as well as WFNS and Fisher grades. ISAT demonstrated a relative risk reduction in death/dependency for coiling over clipping of 22.6% (95% CI 8.9-34.2) at 1 year- an absolute risk reduction of 6.9% (2.5-11.3). With data from more patients (1888) who have now completed 12 months of follow-up analysed, the absolute risk reduction for coiling now stands at 8.8% (A Molyneux, personal communication). Most of the ISAT patients had anterior circulation aneurysms <10mm – so the trial was not completely representative of the generality of aneurysms. However, anterior circulation aneurysms <12mm accounted for ~65% of the unoperated subjects and ~67% of the surgically treated subjects in ISUIA [27]. So the aneurysm site/size distribution in ISAT applies to the majority of subjects in the best study of unruptured aneurysms to date. The prospective ISUIA data on treatment outcomes are interesting though directly comparing clipping and coiling treatments is difficult because patient characteristics differ between the cohorts. There were proportionately far more elderly patients, posterior circulation and large aneurysms (all predisposing to poorer outcome) in the endovascular cohort. Nevertheless, for Group 1 subjects combined morbidity and mortality at 1 year was 12.6% for clipping and 9.8% for coiling- a 22.3% relative risk reduction (RRR) for coiling. For Group 2 patients RRR for coiling at 1 year was 29.7% (7.1% versus 10.1%).

In the case of an unruptured aneurysm, should one decide treatment was necessary, the long-term results of coiling (durability) are particularly relevant because coiling provides a less invasive, generally lower short-term risk alternative to surgery. Although the durability of surgical clipping is widely accepted, the literature on rebleeding from a previously clipped aneurysm is actually quite scanty. One centre reported a rebleed incidence in 1170 subjects with completely coiled or clipped aneurysms of 0.9% for completely coiled versus 0.4% for completely clipped aneurysms [4]. Another centre, which treated 466 patients with coiling between 1992 and 2002, found major aneurysm recurrences in 20.7% of treated aneurysms. Three patients rebled from a coiled aneurysm during a mean follow-up of 31 months- an incidence of approximately 0.25%
of aneurysmal SAH in patients on anticoagulants (at least a doubling of the mortality rate) [9], but less evidence for patients on aspirin. Juvela found that the use of non steroidal anti-inflammatory drugs (NSAIDs) preceding aneurysmal SAH did not significantly affect outcome, and that NSAIDs taken after the SAH might actually reduce the risk of secondary ischaemic events [33].

**SCREENING FOR OCCULT INTRACRANIAL ANEURYSMS**

Screening is often complex, of arguably effectiveness and very expensive [37]. To be effective, the screening test must discriminate between those with and without the disease, and not identify self-limiting forms of disease that would not otherwise require treatment (disease likely to remain sub-clinical). Unless a screening test is very sensitive and specific, inexpensive, easy to administer and can be delivered in practice to the appropriate population successfully, it is unlikely to produce worthwhile results (i.e. less impact than expected on cumulative mortality rates) and more likely to increase healthcare costs and stress amongst the population and health-care staff alike [37].

Screening may impact on the ability to obtain life insurance (and mortgages) etc. or to work. We cannot tell when aneurysms are going to rupture or form de novo, so it would be difficult to know who to screen, how to screen, when to screen, which to treat, which to leave alone, etc. The stress of being screened is difficult to quantify but it is not insignificant. McDonald et al. assessed patient reassurance after a normal test result in patients undergoing echocardiography for symptoms or an asymptomatic murmur. All those presenting with symptoms remained anxious despite the normal test result, and over half of those presenting with an asymptomatic murmur became anxious after detection of the murmur despite the normal echocardiogram [46]. The presence of an unruptured asymptomatic aneurysm is considered to be incidental by the UK Driver and Vehicle Licensing Authority for ordinary group I licences, and there are no restrictions imposed. However, for group II licences (i.e. for Heavy Goods Vehicle & Public Service Vehicles licences), the licence will be dependent upon a specialist assessment for the Licensing Authority of the risks on an individual patient basis. This might have considerable employment and financial implications for some patients.

Several groups have recommended screening for intracranial aneurysms in high-risk groups, namely ADPKD patients and those with a strong family history of aneurysmal SAH [13, 36, 68, 96]. The rationale of screening for aneurysms depends crucially on the prevalence and the annual risk of rupture. Analysis of rupture risk is further complicated by the pattern of aneurysm rupture- some aneurysms appear to develop and rupture rapidly whilst others stabilise [9, 32, 74]. Screening will tend to detect the low-risk stable type rather than the high-risk aneurysms. The other critical considerations are the accuracy of screening test(s) and the safety and effectiveness of treatment. Several groups have applied detailed

ARE THERE OTHER WORTHWHILE INTERVENTIONS?

Cessation of smoking, careful control of blood pressure, avoidance of risk factors for atherosclerosis (careful diet, regular exercise etc.), while unproven, may help reduce both the risk of formation of aneurysms and the risk of rupture, as well as improving general health. Avoidance of anticoagulant (and possibly antithrombotic) drugs in patients known to harbour an unruptured aneurysm may reduce the risk of a poor outcome should the aneurysm rupture. There is evidence for a worse outcome
models to the screening decision-analysis process for aneurysms [6, 17, 34, 35, 43, 54, 79, 98] and undertaken cost-effectiveness analyses [6, 98]. The most recent of these papers utilising more up to date information on aneurysm rupture rates, diagnostic test accuracy and treatment morbidity rates have all demonstrated that routine screening is not warranted. The MARS study found surgery-related morbidity occurred in 11/18 (disabling in 1) operated relatives and no ruptures occurred in the un-operated relatives with aneurysms. Overall surgery increased life expectancy by 2.5 years per operation but at the expense of 19 years of decreased function per person treated. The study investigators calculated 298 relatives would need to be screened to prevent 1 fatal SAH [45]. This would not be cost effective at ~€12,000,000 per life saved (taking an institutional cost of treating an unruptured aneurysm of €38,000 [31] plus cost of screening tests [45]). Similar conclusions were reached in two other recent studies [6, 87].

CONCLUSION

Routine screening for unruptured intracranial aneurysms is not warranted and the cost analysis is very unfavourable. Obtaining a careful and complete family history in patients with aneurysmal SAH is mandatory. Asymptomatic subjects with only one family member affected by SAH do not have a sufficiently increased risk to outweigh the risks of screening (and treatment). Those patients with the greatest risk of having an unruptured aneurysm, and if it then rupturing, are those aged over 30 years from families with 2 or more first degree relatives affected by SAH. They are at further increased risk if they have additional risk factors such as smoking and hypercholesterolaemia. Such subjects and ADPKD patients with a family history of SAH should be assessed and counselled on an individual basis- taking all the relevant risk factors into account - for consideration for screening for intracranial aneurysms. Although multislice CTA and CE MRA are promising techniques, IADSA, particularly 3D, should still be regarded as the definitive means to exclude the presence of an intracranial aneurysm.

So what, if anything, should we be doing about asymptomatic unruptured intracranial aneurysms in patients with no prior SAH? The risk of rupture of a small (<7mm) asymptomatic aneurysm is very low and the risk is considerably outweighed by the morbidity and mortality of surgery and the majority of asymptomatic aneurysms will fall into this category. The risk benefit analysis favours treatment for asymptomatic posterior circulation and larger (>7mm) anterior circulation aneurysms if patients are <50 years of age. For patients older than 50 years, bearing in mind the increased treatment risks, only posterior circulation aneurysms >7mm and anterior circulation aneurysms >12mm really should be considered for treatment and then only where the patient has a reasonable life expectancy. The role of coiling in the treatment of unruptured aneurysms is promising, particularly in patients >50 years and for posterior circulation aneurysms.

To resolve some of the issues highlighted, we need more information on the genetic basis for aneurysm formation and randomised trials with long term follow-up to evaluate the risks and effectiveness of best medical therapy compared to surgery and/or coiling for the treatment of asymptomatic unruptured intracranial aneurysms.

RÉFÉRENCES


