Brain (2000), **123,** 205–221

INVITED REVIEW

The detection and management of unruptured intracranial aneurysms

J. M. Wardlaw[1] and P. M. White[1,2]

[1]*Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh and* [2]*University Department of Neurosurgery, Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK*

Correspondence to: J. M. Wardlaw, Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK
E-mail: jmw@skull.dcn.ed.ac.uk

Summary

The incidence of subarachnoid haemorrhage (SAH) is 6–8 per 100 000 person years, peaking in the sixth decade. SAH, mostly due to rupture of an intracranial aneurysm, accounts for a quarter of cerebrovascular deaths. Aneurysms increase in frequency with age beyond the third decade, are 1.6 times more common in women and are associated with a number of genetic conditions. Prospective autopsy and angiographic studies indicate that between 3.6 and 6% of the population harbour an intracranial aneurysm. Studies have found an increased rate of SAH in first degree relatives of SAH patients (relative risk 3.7–6.6). In affected families, the most frequent relationship between sufferers is sibling to sibling. The rupture rate of asymptomatic aneurysms was thought to be 1–2% per annum, but the recent International Study of Unruptured Intracranial Aneurysms found that the rupture rate of small aneurysms was only 0.05% per annum in patients with no prior SAH, and 0.5% per annum for large (>10 mm diameter) aneurysms and for all aneurysms in patients with previous SAH. Non-invasive tests such as magnetic resonance angiography (MRA), computed tomographic angiography (CTA) and transcranial Doppler (TCD) have been advocated as alternatives to intra-arterial digital subtraction angiography to screen for aneurysms. Although all are promising techniques, the quality of data testing their accuracy is limited. Overall reported sensitivity for CTA and MRA (TCD is poorer) was 76–98% and specificity was 85–100%, but many subjects had an aneurysm or recent SAH, which could overestimate accuracy. CTA and MRA are much poorer methods for the detection of aneurysms <5 mm diameter, which account for up to one-third of unruptured aneurysms. Elective surgical clipping of asymptomatic aneurysms has a morbidity of 10.9% and mortality of 3.8%. Treatment of aneurysms by Guglielmi coils, for which there is less long-term follow-up available, has a 4% morbidity and 1% mortality, but only achieves complete aneurysm occlusion in 52–78% of cases. There has been interest in screening for aneurysms, but the indication for, and cost effectiveness of screening are unclear because aneurysm prevalence varies, rupture rate is low, non-invasive imaging tests are not yet accurate enough to exclude small aneurysms and the morbidity and mortality for elective surgical treatment of unruptured aneurysms is high. There may be a limited role for investigation of high risk subgroups. Ideally, screening in such subgroups should be tested in a randomized trial. The avoidance of risk factors for aneurysms such as smoking, hypertension and hypercholesterolaemia should be part of the management of at-risk subjects.

Keywords: unruptured intracranial aneurysm; magnetic resonance angiography; CT angiography; transcranial ultrasound; screening

Abbreviations: ADPKD = adult polycystic kidney disease; CI = confidence interval; CTA = computed tomographic angiography; GDC = Guglielmi detachable coils; IADSA = intra-arterial digital subtraction angiography; ISUIA = International Study of Unruptured Intracranial Aneurysms; MRA = magnetic resonance angiography; NSAID = non-steroid anti-inflammatory drug; RR = relative risk; SAH = subarachnoid haemorrhage; TCD = transcranial Doppler

Introduction

Subarachnoid haemorrhage (SAH), due to rupture of an intracranial aneurysm, is a serious disorder with a high mortality and morbidity. It accounts for about one-quarter of cerebrovascular deaths and, despite improvements in the management of patients with SAH (Fogelholm *et al.*, 1993), the case-fatality rate is still reported as between 25 and 50%, with most patients dying as a result of the initial bleed or its immediate complications (Hop *et al.*, 1997). Of the survivors, ~50% will be left disabled and dependent on others in activities of daily living (Hijdra *et al.*, 1987). SAH is due to rupture of a saccular aneurysm in ~75% of cases, which usually arise from the circle of Willis or branch artery (Sengupta and McAllister, 1986).

In recent years, there has been increasing interest in the possibility of detection and treatment of intracranial aneurysms prior to rupture. Patients increasingly are being referred to neurological and neurosurgical clinics, concerned that they may have an aneurysm themselves following an SAH in a relative. In order to offer asymptomatic subjects reasonable advice, it is necessary to know what their risk of having an aneurysm is, and should they have one what the likely risk of rupture is, how one might go about detecting such an aneurysm without exposing the patient to unnecessary stress or risk, and 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 present review summarizes the current state of knowledge and highlights where more information is needed. In the preparation of this review, we have drawn heavily on evidence from systematic reviews of the available evidence performed by others (supplemented by more recent evidence where appropriate) and our own systematic reviews where others had not already applied this technique.

The relationship between SAH and unruptured intracranial aneurysm

In a recent systematic review of 18 studies worldwide, the overall incidence of SAH in all studies was 10.5 per 100 000 person years, but 6–8 per 100 000 person years in the most recent studies (with more frequent use of CT to confirm the diagnosis) and was greater for women than for men (Linn *et al.*, 1996). SAH is associated with physical activity, but the formation of aneurysms *per se* is not (Schievink *et al.*, 1989). Spontaneous SAH occurs most commonly in subjects aged between 40 and 60 years, but can occur from childhood to old age. It is ~1.6 times more common in women than in men (van Gijn, 1996; Rinkel *et al.*, 1998).

The risk factors for SAH and for having an unruptured intracranial aneurysm are very similar (see Table 1). Smoking, hypertension, alcohol consumption (particularly binge drinking) (Teunissen *et al.*, 1996), cocaine and amphetamine abuse (Oyesiku *et al.*, 1993), oral contraceptive use (Johnston *et al.*, 1998) and plasma cholesterol concentration in the highest tertile (>6.3 mmol/l) (Adamson *et al.*, 1994) are all associated with an increased risk of aneurysm formation and/or SAH.

Genetic conditions associated with SAH and intracranial aneurysms include adult polycystic kidney disease (ADPKD) (Rinkel *et al.*, 1998)—aneurysms occur in 10–15% of ADPKD patients (Hughes *et al.*, 1996) and recur frequently in ADPKD patients with known aneurysms, particularly if there is a positive family history (Ruggieri *et al.*, 1994; Hughes *et al.*, 1996). Less common hereditary conditions associated with intracranial aneurysms include type IV Ehlers–Danlos syndrome (Schievink *et al.*, 1990), possibly pseudoxanthoma elasticum (Munyer and Margulis, 1981) [although a very recent report refutes any association (van den Berg *et al.*, 1999)], hereditary haemorrhagic telangiectasia (Roman *et al.*, 1978), neurofibromatosis type I (Morooka and Waga, 1983; Mulvihill *et al.*, 1990) and α1-antitrypsin deficiency (Schievink *et al.*, 1996). Marfan's syndrome was thought to be associated with aneurysms, but a recent detailed study of 135 patients with Marfan's syndrome (classified as such using standard criteria) found no evidence of a relationship (van den Berg *et al.*, 1996). The authors suggested that previous case reports indicating an association may have been based on a doubtful or inconclusive diagnosis of Marfan's. The only caveat to this assertion (about the lack of an association) is that the average age in this large series was 21.3 years, whereas the median age of case reports in the literature was 41.3 years and, even in association with genetic disorders, aneurysms are rare below 20 years of age. Predilection to aneurysm formation has also been reported sporadically in other conditions including Klinefelter syndrome, tuberous sclerosis, Noonan's syndrome and α-glucosidase deficiency (King, 1997). While some studies have shown a relationship between aneurysms and HLA-B27, HLA-DR2 (Ostergaard and Hog, 1985) HLA-A28 and HLA-B40 (Norrgard *et al.*, 1987*b*), other studies have failed to confirm these associations (Schievink *et al.*, 1988; Leblanc *et al.*, 1989).

What is the frequency of intracranial aneurysms in the general population?

Incidental aneurysms are found commonly at autopsy in patients dying of unrelated conditions, and the answer to the question 'How common are unruptured aneurysms?' depends on the method of case ascertainment (e.g. autopsy or angiography), whether the study is retro- or prospective, the population studied and—most importantly—how hard you look!

'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).

Table 1 *Risk factors for aneurysm formation and rupture*

Risk factor	Risk for		Prevalence of aneurysms	Relative risk	Reference
	aneurysm	SAH			
Female gender	+	+		1.6	Linn *et al.* (1996)
Current smoking	+	+		1.9	Teunissen *et al.* (1996)
Hypertension	–	+		2.8	Teunissen *et al.* (1996)
Alcohol (heavy consumption)	–	+		4.7	Teunissen *et al.* (1996)
Oral contraceptive pill	?	+		1.5 (low dose) 1.9 (high dose)	Johnston *et al.* (1998)
Atherosclerosis	?	+		2.3	Rinkel *et al.* (1998)
Ischaemic heart disease in women	+	+		(4.3)	Uehara *et al.* (1998
Cholesterol >6.3 mmol/l	?	+		10.2 (odds ratio)	Adamson *et al.* (1994)
ADPKD	+	+	10–15%	4.4	Rinkel *et al.* (1998)
Familial (two or more first or second degree)	+	+	9.8%	4.0	Rinkel *et al.* (1998)
First degree relatives in families with one affected member	+	+	4.5%	1.8	(see Tables 2 and 3 for references)

'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.

Prior to the 1970s, several autopsy studies suggested that the overall prevalence of unruptured aneurysms in adults was as low as 0.3%, but was as high as 9% in studies which looked specifically for aneurysms (Bannerman *et al.*, 1970). Studies using angiography are confounded by the underlying disease for which the angiogram was done (e.g. tumour, stroke, intracranial haemorrhage), and the images may be suboptimal for detection of aneurysms, thereby underestimating frequency. Rinkel *et al.*'s systematic review of all studies (published between 1955 and 1996) of the frequency of aneurysms identified 23 studies including a total of 56 304 patients (Rinkel *et al.*, 1998). The majority of these (78%) were retrospective autopsy studies, 5% were retrospective angiography studies, and 11 and 7% were prospective autopsy and angiography studies, respectively. 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, respectively).

Subsequent data support the figures derived from earlier prospective studies. A recent prospective Japanese study of 8680 'normal' people investigated with magnetic resonance angiography (MRA) found that 5.6% of men and 8.5% of women had intracranial aneurysms (Kojima *et al.*, 1998). Another Japanese study found that 3.4% of men and 15.4% of women (out of a total of 120 patients) with ischaemic heart disease (but no neurological symptoms) had one or more asymptomatic aneurysms, compared with 2.6 and 3.6%, respectively in a control group (Uehara *et al.*, 1998). A prospective autopsy study of unruptured intracranial aneurysms performed in East Finland (Ronkainen *et al.*, 1998) found 33 incidental unruptured aneurysms in 29 of 532 patients (4.7%) aged 30–70 years, of which 21 aneurysms in 18 patients (2.9%) were 3 mm or greater in diameter. In this study, only a quarter of subjects were female, so it may have underestimated the true prevalence of unruptured aneurysms. An important technical point to note is that the size of an aneurysm at autopsy is significantly less than its size in life when it is distended by transmural (arterial minus intracranial) pressure. Perfusion of aneurysms identified at autopsy with saline at 70 mmHg increased aneurysm diameter by 30–60% and volume by up to 400% (see Fig. 1) (McCormick and Acosta-Rua, 1970).

Of patients undergoing angiography following SAH, 20–25% are found to have at least one unruptured aneurysm in addition to the one which has ruptured (Lozano and Leblanc, 1987). Additional aneurysms occur more commonly in females (Rinkel *et al.*, 1998). Both smoking and female gender were important factors in the development of multiple aneurysms in the International Study of Unruptured Intracranial Aneurysms (ISUIA) study (International Study of Unruptured Intracranial Aneurysms Investigators, 1996).

Thus it would appear that 3.6–6.0%, of the population aged over 30 years harbour an unruptured aneurysm, that these are commoner in females than in males, and increase in frequency with age; they are associated with smoking and alcohol consumption, possibly with hypertension, oral contraceptive use and hypercholesterolaemia. However, clearly only a modest proportion of these aneurysms actually rupture, so the key to the management of unruptured intracranial aneurysms is to identify (i) those at greatest risk of harbouring an aneurysm and (ii) which of those aneurysms are at greatest risk of rupture.

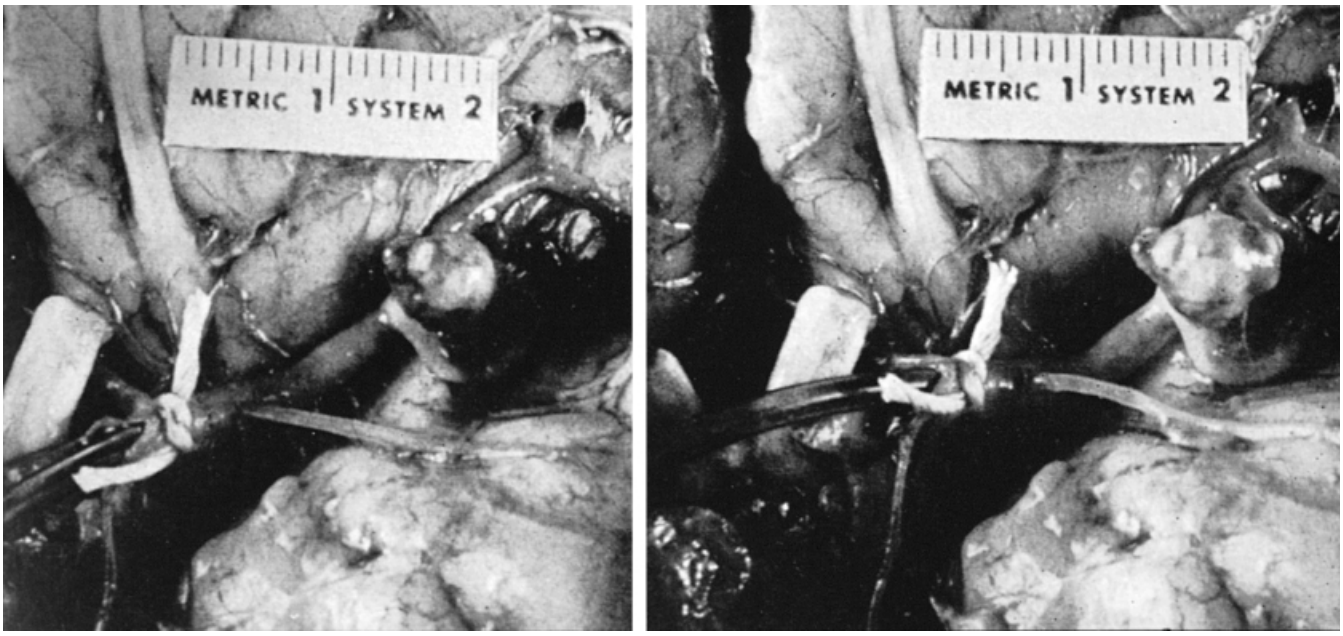

Fig. 1 The size of an aneurysm as seen at autopsy (left) and the effect of perfusion of the aneurysm with saline at 70 mmHg (right). Note the approximate doubling in size of the aneurysm when perfused at a pressure equivalent to normal transmural pressure in life. Reproduced from McCormick and Acosta-Rua (1970) with the permission of the publishers.

Can we identify specific groups at higher risk of intracranial aneurysms?

The association of SAH and aneurysms with specific genetic diseases and risk factors such as smoking has been mentioned earlier. SAH may affect several members of a family without any specific genetic 'disease'. The first report of intracranial aneurysms affecting several members of the same family was made in 1942 (O'Brien, 1942), and the association is now well described. Familial SAH has been defined inconsistently, including as 'families in which two or more members have had an SAH', which does not take account of the degree of relationship. Therefore, it would be preferable to use a more precise definition of familial SAH as given below. Some studies of the familial incidence of SAH included first to third degree relatives, and others only first and second degree, leading to potentially confusing results. Several examples of families in which numerous members are affected by SAH have been described in detail, and it may be that several of these badly affected families are raising the apparent prevalence of SAH in relatives of index patients with SAH in incidence studies (Leblanc, 1997). Though there is concern about the possibility of increased risk of intracranial aneurysms in families where only one member has had an SAH, it has been suggested that many cases of seeming 'familial intracranial aneurysms' might simply represent accidental aggregation (ter Berg *et al.*, 1992). ter Berg *et al*. calculated that if each SAH patient had on average 17.5 relatives (first to third degree), and the prevalence of intracranial aneurysms in the general population was 1% and the annual rupture rate of aneurysms was also 1%, then each SAH patient had, on the basis of chance alone, a 5.6% possibility of having a first to third degree relative also affected by SAH. This is consistent with data from a case–control study by De Braekeleer and colleagues in Quebec, in which each SAH patient was matched with controls from the same geographical population (De Braekeleer *et al.*, 1996). The proportion of SAH patients with third degree relatives who had had a SAH was the same as the proportion in the control population (14%). The difference occurred in the proportion of second degree (9.6% versus 4.6%, SAH versus control) and first degree relatives (9.0% versus 1.9%) also affected by SAH (De Braekeleer *et al.*, 1996). So is the risk of SAH in relatives of SAH patients truly increased in all cases or just in occasional families?

Familial SAH should, therefore, be defined as 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 that first degree relatives are parents, siblings and children; second degree relatives are grandparents, grandchildren, aunts and uncles, and nieces and nephews; and third degree relatives are cousins, great grandparents, great grandchildren, etc.

Six studies since 1987 (Table 2) have examined the prevalence of unruptured aneurysms and/or SAH amongst relatives of patients with SAH (Norrgard *et al.*, 1987*a*; Bromberg *et al.*, 1995*a*; Schievink *et al.*, 1995; Wang *et al.*, 1995; De Braekeleer *et al.*, 1996; Ronkainen *et al.*, 1997). A further recent Japanese study sought family histories of SAH amongst patients self-presenting for cranial MRI (including MRA) though they did not sample a defined population (Kojima *et al.*, 1998). Other studies have described small groups of families affected by SAH but were not truly population-based (Alberts *et al.*, 1995; Leblanc, 1997). In

Table 2 *Summary of population-based studies of familial SAH*

Study	No. of index subjects	Country	No. of relatives surveyed			No. of relatives with SAH			% 1° with SAH	Comment
			1°	2°	3°	1°	2°	3°		
Norrgard *et al.* (1987)	485	Umea, Sweden	1352 (sibs only)	–	–	22	–	–	4.7	Sibs only surveyed—average six per index case
Wang *et al.* (1995)	149/171*	Washington, USA	N/S	N/S	N/S	18	16	–	11.4	OR for SAH in 1° relative = 1.8, 2° = 2.4, P = NS
Shievink *et al.* (1995)	76/81*	Rochester, USA	608	N/S	N/S	11	5	–	1.8	RR of SAH in 1° relative = 4.14 (2.06–7.4), 2° = 1.6
Bromberg *et al.* (1995)	163	Utrecht, The Netherlands	1290	3588	N/S	10 + 7†	4 + 12†	–	1%	RR of SAH in 1° relative = 6.6 (95% CI 2–21) definite and 2.7 (95% CI 1.4–5.5) possible SAH
De Braekeleer *et al.* (1996)	533 (+1599 controls)	Quebec, Canada	N/S	N/S	N/S	48	51	77	–	RR of SAH in 1° relative = 4.7, 2° = 2.1, 3° = 1.1
Ronkainen *et al.* (1997) ‡	91	Kuopio, E. Finland	716 relatives in total (1°, 2° and 3°)			76	37 in total		10.6§	

OR = odds ratio; RR = relative risk; N/S = not stated. *No. surveyed/total sample available; †definite + possible SAH; ‡relatives with SAH or aneurysm; §percentage of all relatives not just first degree.

the six population-based studies, four were retrospective (studying families of patients who had had their SAH in a defined prior time period) and two prospective (studying families of patients presenting with SAH during the study period). Two were case-controlled and the others primary observational studies. Two were Scandinavian, two American, one Dutch and one Canadian. Four used a hospital-admitted population of SAH patients, and two were community-based. Three excluded patients known to have ADPKD. Four used a questionnaire or interview to determine the family history (which was validated only in the study by Bromberg *et al*., 1995*a*) and two used centralized health data alone without contacting the patient or relatives at all. The six studies did not include similar groups of relatives, i.e. some only included first, some first and second degree, and some first to third degree relatives, and furthermore not all the studies analysed the results obtained by relationship to the index case.

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: Schievink *et al*. found an RR for SAH of 4.14 for first degree and 1.6 for second degree relatives; Bromberg *et al*. found an RR of 6.6 for first and second degree relatives combined; and De Braekeleer *et al*. found an RR of 4.7 for first and 2.1 for second degree relatives. Whilst the relative risks appear large, it is important to bear in mind the small absolute number of relatives affected: Norrgard *et al*. found that 22 of 1352 (1.6%) siblings had had an SAH; Schievink *et al*. found that 11 of 608 (1.8%) first degree relatives had had an SAH; and Bromberg *et al*. found that 17 of 1290 (1%) first degree relatives had had a definite or probable SAH, giving a total of only 50 out of 3250 (1.5%) first degree relatives affected by SAH in studies from which it was possible to extract these data.

Some of the differences between studies in the number of relatives with SAH per index case may be due to case ascertainment bias; e.g. in the study by Ronkainen and colleagues, only two-thirds of those invited to participate actually did so, and those who did may have been motivated by a positive family history, whereas the third who declined may have been less interested in a disease which did not appear to affect their family. Other possible sources of bias include recall bias, patients missed from hospital-based studies, lack of knowledge about family history, failure to recognize SAH, etc. In addition, some of the studies are relatively small and geographically localized, so that a few families with many affected members amongst a large number of families with no affected relatives could raise the overall average considerably. Despite these methodological problems, on the evidence available so far, somewhere between 1 (Bromberg *et al.*, 1995*a*) and 11.4% (Wang *et al.*, 1995) of SAH patients will have at least one first degree relative with SAH, and between 16 (Ronkainen *et al.*, 1997) and 29.8% (De Braekeleer *et al.*, 1996) will have at least one first to third degree relative with SAH. Nevertheless, the great majority of relatives of SAH patients will not have had an aneurysmal SAH, which implies that the prevalence of aneurysms likely to become symptomatic is also small. Therefore, screening all relatives for aneurysms would necessitate examination of a very large proportion of unaffected people.

Are any particular relations affected more frequently by SAH and aneurysms?

Most of the above studies reported detailed family trees of the families in which two or more subjects were affected (including the index SAH case) (Table 3). The most frequent relationship was index patient to sibling only (44%), followed by index patient to second or third degree relative only (25%), followed by index patient to parent (18%). Overall, a parent was affected in 24% of cases, i.e. in only a quarter of affected families was there a clear warning of the potential for SAH from a previous generation. The quarter of cases in which only a second or third degree relative has been affected offers an even more difficult target for screening as it would

Table 3 *Breakdown of familial SAH by degree of relationship to index case*

Study	No. of index patients	Affected relatives (%)							
		Parent no sib.	Sib. no parent	Parent + sib.	Offspring only	Sib. + other	Offspring + other	Parent + other	Other only
Norrgard *et al*. (1987	23	17	52	0	0	0	0	0	30
Leblanc *et al*. (1997)	17	23	42	6	0	18	0	0	12
Wang *et al*. (1995)	17	36	12	3	0	0	0	0	48
Bromberg *et al*. (1995)*	17	24	71	5	N/S	N/S	N/S	N/S	N/S
Shievink *et al*. (1995)	15	20	47	0	0	7	0	0	27
De Braekeleer *et al*. (1996)*	48	4	26	N/S	N/S	N/S	N/S	N/S	N/S
Ronkainen *et al*. (1997)	91	15	40	1	5	10	1	3	24
Kojima *et al*. (1998)*	20	5	55	20	5	5	0	10	N/S
Average (%)		16	44	5	3	3	0.2	3	25

Sib. = sibling; N/S= not stated or data not extractable from the paper. *Studies which did not document detailed family histories for second or third degree relatives affected by SAH.

be difficult to know whom to screen. As siblings are the most frequently affected relatives (affected in 52% of cases overall), these would be the obvious group of relatives towards whom any screening effort should be targeted.

Familial intracranial aneurysms are reported to have distinguishing biological features, including rupture on average at a younger age than non-familial [most frequently in the fifth decade compared with the sixth decade for sporadic SAH (Kassell *et al.*, 1990)], worse clinical outcome (after matching for age and sex with non-familial cases) and an increased prevalence of middle cerebral artery aneurysms (Bromberg *et al.*, 1995*b*; Kojima *et al.*, 1998). From published case series of familial aneurysms, it appears there may be a younger age of rupture in subsequent generations (Bromberg *et al.*, 1995*b*), implying possible anticipation. Familial aneurysms are also reported to have a predilection towards rupture in the same decade in individuals of the same family, particularly in siblings (Leblanc, 1997). Familial asymptomatic aneurysms are more likely to rupture in families having members with a history of SAH than in those without (Kojima *et al.*, 1998), though this finding might be due, at least in part, to case ascertainment bias.

What is the frequency of aneurysm rupture?

A systematic review of the literature on the risk of rupture of aneurysms identified nine studies with a total of 3907 patient years of follow-up (Rinkel *et al.*, 1998), over half of these contributed by one study from Finland (Juvela *et al.*, 1993). During follow-up, 75 of 495 (15.2%) patients suffered an SAH, giving an annual rupture rate of 1.9% [95% confidence interval (CI) 1.5–2.4] (Table 4). 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, e.g. in the group of patients aged 60–79 years, RR of rupture was 1.7 (95% CI 0.7–4.0) compared with those aged 40–59 years. Symptomatic aneurysms were significantly more likely to rupture than asymptomatic or additional aneurysms (6.5% versus 0.8% versus 1.4%, respectively); RR of 8.2. Posterior circulation and large ($>$10 mm) aneurysms were significantly more likely to rupture; RR of 4.4 and 4.0, respectively. The median time from diagnosis to rupture in the study by Juvela and colleagues was 9.6 years (mean 9.4 years, range 1.2–23.1 years), but this was the only study of the nine included in the systematic review to have a mean or median follow-up of $>$9 years.

The initial size of the aneurysm and subsequent rupture rate is a complex issue. In Juvela's study, there was no disparity in the size of the aneurysm on intra-arterial digital subtraction angiography (IADSA) at the start of follow-up between patients who later had a SAH and those who did not (median 4 mm, range 2–25 mm in those with later SAH versus median 4 mm, range 2–26 mm in those without). Of the aneurysms which later ruptured, 67% were $<$6 mm in diameter, although the proportion of aneurysm ruptures increased almost constantly according to size ($P = 0.03$). Aneurysm size was not associated with the interval to rupture. In a logistic regression model, the only factor significantly related to aneurysm rupture was the size of the aneurysm, i.e. aneurysms of $\geqslant$7 mm had a relative risk of rupture of 2.24 compared with smaller aneurysms (Juvela *et al.*, 1993). Although the threshold size critical for SAH is not certain, most studies indicate minimal risk of rupture for incidental aneurysms measuring 3 mm or less (McCormick and Acosta-Rua, 1970; Wiebers *et al.*, 1987). A proportion of the patients in the study of Juvela and colleagues had a repeat angiogram during follow-up: in patients with later SAH, the size of the aneurysms had increased from the start of follow-up, whereas in those without later SAH the size did not change. In addition, in patients undergoing angiography during follow-up, 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 an SAH from these *de novo* aneurysms.

The largest ever study to follow-up unruptured aneurysms is the ISUIA with 2621 patients (International Study of Unruptured Intracranial Aneurysms Investigators, 1998). This studied two groups of patients retrospectively: (i) patients

Table 4 *Summary of data on risk of aneurysmal rupture*

	Rinkel *et al.* (1998)	ISUIA (1998)
No. of subjects	495	1449
No. of aneurysms	0150	1937
Duration of follow-up (patient years)	3907 (mean of mean follow-ups 5.5, range 2.1–13.7 years)	2 023 (mean follow-up 8.3 years)
No. ruptured	75	32
Overall rupture rate (expressed as % per annum)	1.9 (1.5–2.4)	0.27 (32 in 12 023 years)
Rupture rate		
<10 mm	0.7 (0.5–1.0)	0.05
>10 mm	4.0 (2.7–5.8)	0.5
Cumulative aneurysm rupture rate	10% per decade (from Juvela *et al*., 1993)	0.5–5% per decade
Symptomatic aneurysm rupture rate	6.5 (4.4–9.1)	Data not extractable
Asymptomatic aneurysm rupture rate	0.8 (0.4–1.5)	Data not extractable
Additional aneurysm rupture rate	1.4 (0.9–2.0)	Data not extractable
Posterior circulation aneurysm rupture rate	4.4 (2.7–6.8)	Data not extractable
Age (years)		
20–39	0 (0–13)	Data not extractable
40–59	3.5 (1.4–7.0)	
60–79	5.7 (3.4–9.0)	

Data additional to those published in the systematic review were kindly supplied by Dr Gabriel Rinkel to allow calculation of duration of follow-up; 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.

with asymptomatic aneurysms with no prior SAH and (ii) those with multiple aneurysms who previously had sustained an aneurysmal SAH. The investigators also studied prospectively the risks of treatment of asymptomatic unruptured aneurysms. The results of the ISUIA indicate a tiny rupture risk, compared with previous estimates, of 0.05% per annum for small aneurysms (<10 mm diameter) in patients who have not had an SAH previously, and of 0.5% per annum for large aneurysms and for all aneurysms in patients who previously have sustained an SAH from another aneurysm. Of the 1449 included patients with 1937 unruptured saccular aneurysms ⩾2 mm diameter, 32 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 previously had not had an SAH, only one of 12 aneurysmal ruptures occurred in an aneurysm <10 mm in diameter, compared with 17 of 20 patients in the cohort who previously had had an SAH. This study also found that the only significant predictors of rupture were the size and location of the aneurysm: aneurysms ⩾10 mm diameter had an RR of rupture of 11.6; for posterior circulation aneurysms the RR was 13.8 and 13.6 for basilar tip and vertebrobasilar locations, respectively, and 8.0 for posterior communicating artery aneurysms. The follow-up of patients in ISUIA is continuing until 2001. 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 [>10 mm versus 7.5–9 mm (Wiebers *et al.*, 1987)]. 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 are so much more frequent than large aneurysms that despite a much lower rupture risk, ruptures occurring in small aneurysms outnumber those from large aneurysms.

The discrepancy in aneurysmal rupture rates between the systematic review (Rinkel *et al*., 1998) and the ISUIA requires explanation. Annual rupture rate was 0.5% (ISUIA) versus 1.4% per annum (Rinkel *et al*.) for unruptured additional aneurysms in patients with a prior history of aneurysmal SAH; and 0.05% (ISUIA <10 mm) versus 0.8% (Rinkel *et al*., all sizes) per annum for asymptomatic aneurysms. Although the mean follow-up in the nine studies included in the systematic review ranged from 2.1 to 13.7 years, compared with 8.3 years for the ISUIA, ISUIA follow-up was significantly shorter than the 13.7 years of Juvela *et al*. (which contributed substantially to the systematic review data), who found a median time to aneurysm rupture of 9.4 years (Juvela *et al*., 1993). ISUIA data from 1999 to 2001 should clarify whether the duration of follow-up is a significant factor in explaining this discrepancy. Recruitment bias may have influenced the results. The majority of ISUIA patients were identified retrospectively from hospital records (1981 onwards, with the identification process commencing in 1992) and only survivors with persistently asymptomatic aneurysms, in whom a complete set of angiograms could be traced, were eligible for inclusion. These patients might not be entirely representative of the natural history of all aneurysms: e.g. subjects who had suffered a fatal episode of SAH, or where an asymptomatic aneurysm had been treated since 1981, or who had incomplete angiograms could not be included in the ISUIA. The patients with asymptomatic aneurysms identified and followed up prospectively from 1992 to 1998 provide less biased data but there were fewer

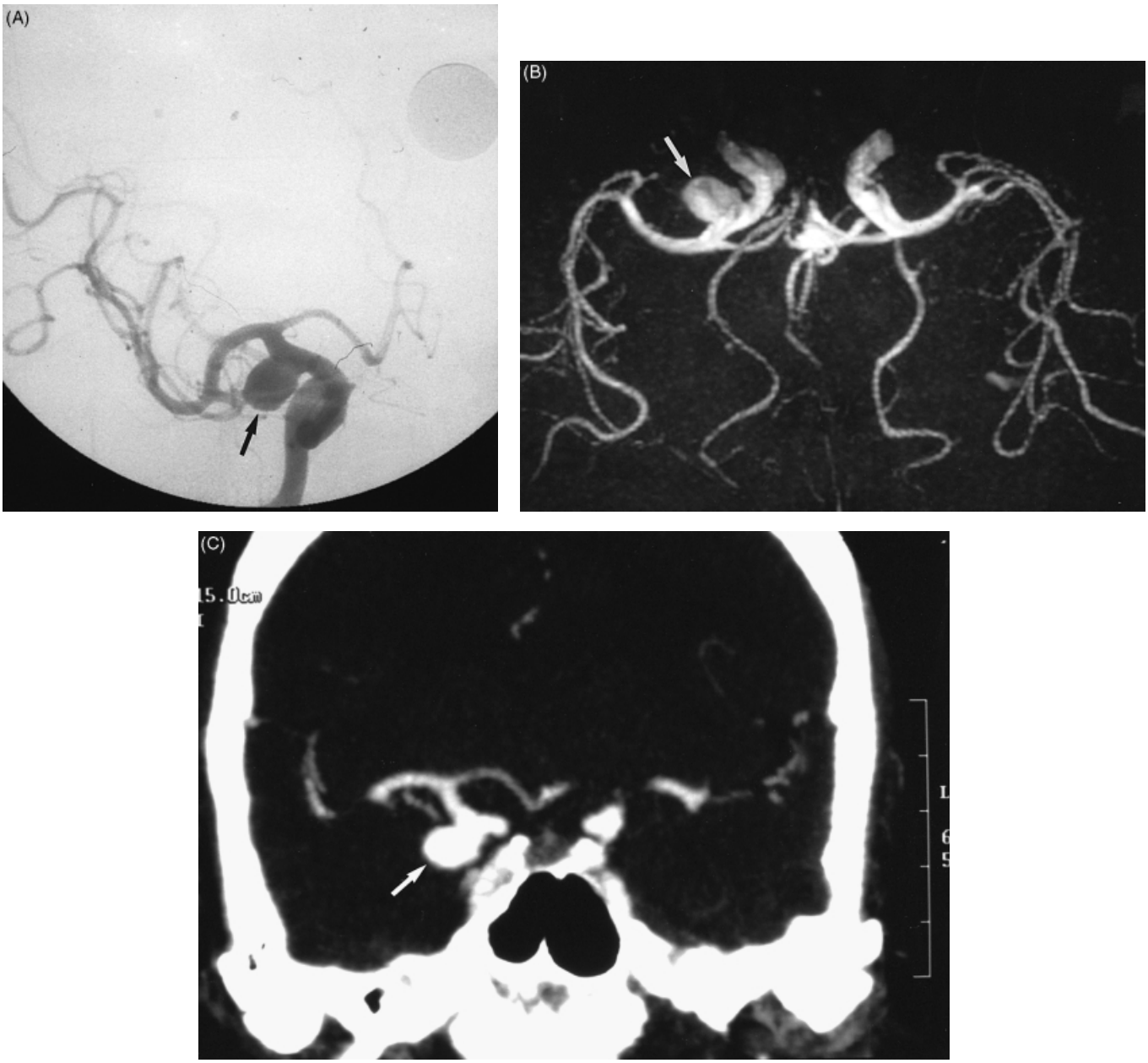

Fig. 2 Imaging of a right posterior communicating artery aneurysm (arrow) with the gold standard intra-arterial digital subtraction angiography (**A**), and two non-invasive techniques, i.e. magnetic resonance angiography (**B**) and computed tomographic angiography (**C**). The aneurysm is large and readily identified by both non-invasive techniques.

of them, and 6 years of follow-up is too short. Finally, one also needs to bear in mind the relatively small numbers of ruptured aneurysms in the studies from which the rupture rates were calculated (32 in the ISUIA and 75 in the systematic review by Rinkel *et al*.) and the potential for the influence of chance.

How should one search for aneurysms?

The gold standard for identification of an intracranial aneurysm is an IADSA with selective cerebral arterial injections and multiple projections (Mayberg *et al.*, 1994) (see Figs 2A and 3A). However, IADSA is invasive, requires a stay in hospital, is costly and carries a risk of complications. Modern IADSA has an overall 1% risk of transient and 0.5% risk of permanent neurological complication (Warnock *et al.*, 1993); but a recent meta-analysis indicated that the risk in SAH patients and patients with an aneurysm or arteriovenous malformation but no SAH is much lower at 0.07%, and the risks of either transient or permanent neurological complication were greater in the SAH group than in the non-SAH group (Cloft *et al.*, 1999).

Due to these problems, IADSA is unsuitable for use in large numbers of subjects as a screening test. Intravenous digital subtraction angiography has inadequate resolution to replace IADSA (Atlas, 1994). Hence the increasing interest

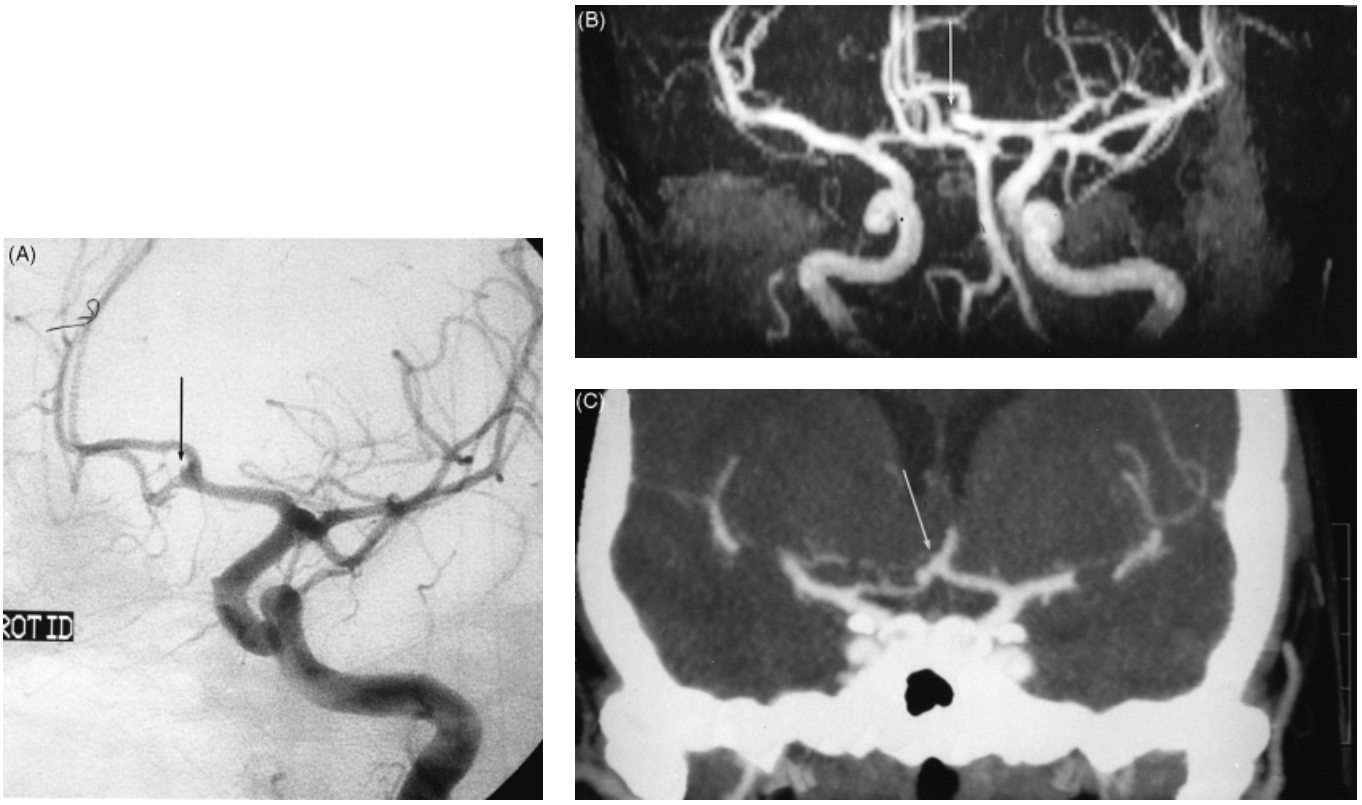

Fig. 3 Imaging of a left anterior communicating artery aneurysm (arrow) with the gold standard intra-arterial digital subtraction angiography (**A**), and two non-invasive techniques, i.e. magnetic resonance angiography (**B**) and computed tomographic angiography (**C**). The aneurysm is small and very difficult to identify with certainty using the MRA or CTA.

in using non-invasive tests such as MRA, dynamic spiral CT angiography (CTA) or transcranial Doppler ultrasound (TCD), all of which can be performed on out-patients. Any test aiming to replace IADSA in the detection of asymptomatic aneurysms has to be extremely sensitive because an undetected ('missed') aneurysm is a potentially life-threatening circumstance, yet one does not want to perform confirmatory IADSA (or, even worse, surgery) unnecessarily; therefore, specificity also has to be excellent.

A systematic search of the English and non-English language literature to identify all studies of non-invasive imaging of aneurysms was performed by the authors. Over 100 studies published between 1988 and 1998 (inclusive) have compared non-invasive imaging methods with IADSA. Most of these studies have been of MRA or CTA, a few of MRA and CTA, and a few of TCD. Most report apparently excellent results, but many are small studies and have methodological deficiencies, which combined may have led to an overestimation of the accuracy of these techniques in clinical practice. We identified 104 studies (to the end of 1998) which met initial eligibility criteria (White and Wardlaw, 1999), i.e (i) comparison of a non-invasive method with IADSA (the gold standard); (ii) at least 10 subjects in the study; (iii) and published from January 1988 to December 1998 inclusive. Two readers independently reviewed all these papers against a pre-defined set of inclusion criteria using an intrinsically weighted scoring system.

The major methodological problems (summarized in Table 5) included lack of clear and definite blinding (50%), failure to list exclusion criteria and/or number excluded (79%) and failure to present data in a way that enabled recalculation of the imaging test sensitivity, specificity, predictive values per aneurysm and/or per patient. The average sample size was only 37 (even though all studies were of $\geqslant$10 subjects) and most studies were in patients with recent SAH so the aneurysm prevalence was high. A summary of the methodological weaknesses with studies comparing MRA, CTA or TCD with IADSA identified by our systematic review is given in Table 5.

Studies testing MRA, CTA or TCD accuracy in patients with recent SAH are likely to have overestimated 'accuracy' were these tests to be used for screening for the following reasons. (i) The prevalence of aneurysms was higher than it would be in asymptomatic individuals to be screened. It was thought that disease prevalence did not affect the sensitivity and specificity of diagnostic tests (Sackett *et al.*, 1991), but there is statistical mathematical modelling to support the concept that, in addition to the effect of prevalence upon predictive values, increasing prevalence also improves the sensitivity and specificity of a test (Brenner and Gefeller, 1997). (ii) The observer looks harder for aneurysms if there is a high probability of one being present (i.e. observer expectation bias). The addition of control groups without SAH has been used in some studies to reduce this bias but, as these control groups have not had corroborative IADSA,

Table 5 *Methodological problems identified in studies of non-invasive imaging of aneurysms*

	CTA	MRA	TCD
No. of adequate studies/no. meeting initial inclusion criteria*	17/45 (38%)	20/48 (42%)	4/11 (36%)
Mean assessment score of adequate studies†	6.8	6.5	6.3
No. of subjects (patients in adequate studies/total)	681/1678 (41%)	929/1802 (52%)	162/380 (43%)
Not definitely blinded	25 (56%)	20 (42%)	7 (64%)
Inclusion and/or exclusion criteria not stated	40 (89%)	34 (71%)	8 (73%)
Limited information on methodology (examination and/or review)	28 (62%)	29 (60%)	7 (64%)
Unable to extract relevant data from results presented	22 (49%)	25 (52%)	6 (55%)
Interobserver variability not assessed	39 (87%)	42 (88%)	10 (91%)

*Initial inclusion criteria were a study of a non-invasive imaging modality for aneurysms versus IADSA including $\geqslant$10 subjects.
†A score was derived for each paper from an aggregate of two independent reviewers' assessments against a list of predefined quality criteria. A score of >5 was determined as indicating adequate quality.

caution must still be employed in the interpretation of the results. (iii) The presence of subarachnoid blood can help to draw attention to the aneurysm. (iv) Publication bias: studies showing greater accuracy are more likely to be submitted (and published) than those with poorer accuracy.

As a result of these methodological issues, 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 programme where the detection of any aneurysm in a patient would lead to definitive IADSA, which would then detect any aneurysms missed by the non-invasive screening investigation. However, failure to identify any aneurysm by MRA (or any other imaging test) in a patient where one was actually present could offer false reassurance.

For 18 adequate quality blinded-reader studies of MRA, the sensitivity for detection of at least one aneurysm per patient ranged from 69% (Huston *et al.*, 1994) to 100% (Futatsuya *et al.*, 1994) and the specificity from 75% (Gasparotti *et al.*, 1994) to 100% (Futatsuya *et al.*, 1994). For the detection of all aneurysms, sensitivity ranged from 70% (Huston *et al.*, 1994) to 97% (Aprile, 1996) and specificity from 75% (Gasparotti *et al.*, 1994) to 100% (Wilcock *et al.*, 1996). In many papers, it was not possible to extract the precise numbers of false-negative and false-positive results per patient and per aneurysm from the data presented. There is a trend towards a correlation between the results reported and the prevalence of aneurysms in the study population. The lower the prevalence, in general, the poorer the reported results: for the MRA studies with aneurysm prevalence $\geqslant$75% (12/18), median sensitivity for the detection of all aneurysms was 91% (range 70–97%), whereas for studies with aneurysm prevalence $<$75%, median sensitivity was 82% range (77–95%).

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 (Atlas *et al.*, 1997). One study found a sensitivity (for identification of at least one aneurysm per patient) of 75% for MRA presented as Maximum Intensity Projection reconstructions alone (this type of image resembles an angiogram; see Figs 2B and 3B), but sensitivity increased to 95% when axial base and spin-echo images were reviewed as well (Ross *et al.*, 1990). Aneurysm size is an important factor in aneurysm detection, with studies of MRA consistently indicating sensitivity rates of $>$95% for aneurysms $>$6 mm diameter but much less for smaller aneurysms (Atlas *et al.*, 1997). For aneurysms $<$5 mm, detection rates as low as 56% have been reported (Korogi *et al.*, 1996). With the standard time-of-flight MRA technique, flow-related artefacts may obscure some of the anatomical detail that is available with other methods such as CTA (Brown *et al.*, 1997), but time-of-flight techniques have a greater sensitivity for aneurysm detection than phase-contrast techniques (Atlas, 1997).

CTA (see Fig 2C and 3C for examples) has some disadvantages compared with 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 ~2 mSv, equivalent to ~1 years background radiation in the UK). The radiation dose would be a significant drawback in using CTA for community screening, particularly if this needed to be repeated several times during an individual's lifetime. However, CTA is more rapid than MRA, and some patients have a contraindication to MRI or suffer from claustrophobia and cannot tolerate the MRI examination. Spiral CT technology allows the acquisition of a volumetric data set which markedly improves the image data reconstruction techniques and allows the whole area of interest to be examined rapidly during peak arterial contrast concentration. CTA has been studied less extensively than MRA, but published data of CTA versus IADSA indicate that spiral CTA is at least as good, if not more accurate than MRA, with overall aneurysm detection rates of 85–98% (Alberico *et al.*, 1995; Hope *et al.*, 1996). In our systematic review, we identified 16 adequate quality blinded-reader studies of CTA versus IADSA (of $\geqslant$10 subjects, published 1988–1998). The prevalence of aneurysms was $\geqslant$75% in 13 of 16 studies and $>$60% in all cases. It should be borne in

mind that these are relatively early reports of spiral CTA, and the early results reported for MRA were often better than those reported in later years.

Colour TCD ultrasound became available in the early 1990s, with apparent success at identification of aneurysms (Tsuchiya *et al.*, 1991; Becker *et al.*, 1992). Ultrasound has the advantage of lower capital cost and mobility compared with IADSA, CTA and MRA. A recent technological development of colour Doppler called Colour Doppler Energy or Power Doppler, offers significantly greater sensitivity to flowing blood than standard colour flow imaging (Wardlaw and Cannon, 1996). Using this technique, one of the authors found an overall sensitivity for detection of aneurysms of 80% but a sensitivity of 91% for detection of at least one aneurysm in patients harbouring aneurysm(s) who had an adequate temporal bone window. Specificity was 87.5% (Wardlaw and Cannon, 1996). Unfortunately, ~10% of patients will not have an adequate bone window and the technique is very operator dependent. For our systematic review, we identified 11 papers comparing TCD with IADSA, of which only three were prospective blinded-reader studies, and aneurysm prevalence was >78% in all three. Ultrasonic contrast agents and 3D ultrasound imaging may improve accuracy. A very recent paper has combined these two technical advances together, and in a series of 30 patients with known aneurysms the authors reported a sensitivity for aneurysm detection of 87% and specificity of 100%, although in this particular study the ultrasonographer was not fully blinded (Klotzsch *et al.*, 1999). Nevertheless, the technology is improving and these results are encouraging.

The results for non-invasive imaging methods are significantly poorer for smaller (<5 mm) aneurysms, which constitute as many as a third of aneurysms in asymptomatic patients (Kojima *et al.*, 1998). These aneurysms cannot necessarily be ignored just because their current rupture risk is low. An example of the problems of current non-invasive imaging of aneurysms is the study by Ronkainen and colleagues who screened 85 families of patients with SAH using MRA (Ronkainen *et al.*, 1997), and found 58 aneurysms in 45 of 438 subjects with MRA and performed IADSA in 43 of these 45. Of these 43, seven did not in fact have an aneurysm (false positives), and the remaining 36 subjects actually had 60 aneurysms (13 of these had been missed by MRA, i.e. false negatives). Forty-seven aneurysms were found by both MRA and IADSA, giving a true positive rate per aneurysm of 78%, a false-positive rate of 15% and a false-negative rate of 22%. Data per patient could not be extracted. The positive predictive value was 87% but, as 395 patients did not have IADSA, the true negative rate and negative predictive value rates cannot be calculated for the whole study. It is 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. Despite these limitations, MRA is being used to screen for aneurysms in some neuroscience centres in Europe and extensively in Japan (Kojima *et al.*, 1998). MRA is also being used in studies to identify the frequency of aneurysms in families of SAH patients (Ronkainen *et al.*, 1995; Kojima *et al.*, 1998; J. van Gijn, personal communication).

Imaging technology is improving all the time, and recent developments such as contrast-enhanced subtraction MR techniques and 3D contrast-enhanced transcranial power Doppler sonography should lead to an improvement in diagnostic accuracy. Further studies of non-invasive imaging of aneurysms are ongoing, but what is particularly required is a larger study in patients without SAH but at risk of an aneurysm (and who all have digital subtraction angiography for verification), to eliminate the systematic bias in accuracy assessment of CTA/MRA/TCD 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, which raises the question of how often to do this and for how long? No definite evidence-based answers exist to these questions at present.

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 wrapping) or by interventional neuroradiology. Surgical treatment, having been in use routinely for >40 years, has fairly clearly defined risks and morbidity. There are clear and important differences in risk between surgery for ruptured and unruptured aneurysms, the risks being much higher in patients who have sustained an aneurysmal SAH. A systematic review of surgical treatment for unruptured aneurysms was performed by Raaymakers and colleagues who identified 61 studies including 2460 patients and at least 2568 aneurysms published between 1966 and June 1996 (Raaymakers *et al.*, 1998). Only studies in which at least 90% of patients were treated by clipping (as opposed to wrapping or other surgical techniques) were included. Unfortunately, only eight of the studies were prospective, the rest being retrospective, and, 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 which 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%), with large anterior circulation aneurysms (mortality 7.4%, morbidity 26.9%) and small posterior fossa aneurysms (mortality 3.0%, morbidity 12.9%) being intermediate. To some extent, the higher mortality of posterior fossa (than anterior fossa) operations was due to confounding by aneurysm size, giant

Table 6 *Risks associated with treatment of unruptured aneurysms*

	Management		
Outcome	Conservative	Clipping	GDC coiling*
Mortality	0.5[†]–5.0[‡] (% per decade)	2.6[§]–3.8[†]%	1.0[¶]–1.1[#]%
Morbidity	0.1[†]–1.0[‡] (% per decade)	10.9[§]–12.1[†]%	3.7[¶]–4.0[#]% (22[¶]–48[#]% partially coiled)

*No long term follow-up, procedure-related mortality rate quoted; [†]ISUIA (1998); [‡]Rinkel *et al*. (1998); [§]Raaymakers *et al*. (1997); [¶]Vinuela *et al*. (1997); [#]Brilstra *et al*. (1999).

aneurysms being more frequent in the posterior fossa in patients included in these studies. In the interpretation of these results, it is important to bear in mind the effect of publication bias. Studies which found higher mortality rates than the published literature of the time are less likely to have been published because, as Raaymakers *et al*. point out, public awareness of these results might be disadvantageous to the neurosurgeon or the hospital.

The prospective arm of the ISUIA also addressed the issue of risks of surgical intervention in unruptured aneurysms. This enrolled 1172 patients (211 of whom had a history of previous SAH) and 996 underwent surgery. The surgery-related mortality at 1 year was 3.8% (95% CI 2.4–5.4) in patients with no prior SAH and 2% (0–2.6) in patients who previously had suffered an SAH from a different aneurysm, already treated. Morbidity was 12.0 and 12.1%, respectively. These figures are based on current surgical practice and indicate higher mortality and morbidity than the overall figures quoted in the systematic review by Raaymakers and colleagues, although it must be noted that the 95% confidence intervals for these two papers overlap. The increased morbidity was ascribed largely to impaired mental status, which was not assessed in most previous studies (International Study of Unruptured Intracranial Aneurysms Investigators, 1998). The mortality figures at 1 month in the ISUIA study were similar to those in the systematic review at a median of 24 weeks, 2.3% versus 2.6%, respectively. Age was the only independent predictor of outcome in the ISUIA study: the RR of surgery-related morbidity and mortality at 1 year was ~5 in the group >64 years of age compared with patients <45 years of age. These data are summarized in Table 6.

The effectiveness and risks of aneurysm coiling are less certain because the technique is newer and still developing. Currently, interventional neuroradiology treatment would usually be with Guglielmi detachable coils (GDC), which were introduced in 1991 and revolutionized the endovascular treatment of intracranial aneurysms (Guglielmi *et al.*, 1991). The USA Multicenter Study Group identified a 1% mortality and a 4% morbidity for unruptured aneurysm treatment, with 78% of aneurysms being completely occluded. The rupture rate of partially coiled aneurysms was 0.5% per annum from the limited follow-up data available (Vinuela *et al.*, 1997). There is some evidence that even partial treatment by GDC confers benefit in the early post-rupture period; post-GDC treatment haemorrhage occurred in only nine of 403 patients, although the length of follow-up was very limited in many patients (Vinuela *et al.*, 1997). A systematic review of aneurysm coiling (all observational studies) identified 48 studies including 1383 patients (Brilstra *et al.*, 1999). Permanent complications of coiling occurred in 3.7% (95% CI 2.7–4.9%), but only 54% (95% CI 50–57%) of aneurysms were completely occluded. Many included studies were retrospective and there was no indication of whether the outcome assessment was by an independent assessor or not. There is only one randomized trial—the International Subarachnoid Haemorrhage Trial—which is comparing coiling with clipping (though only in ruptured aneurysms) and that is ongoing. Coiling has not been utilized for long enough to know what the long-term success rate will be in preventing SAH or what other long-term complications might develop. It is difficult to make much sense of the morbidity and mortality data in observational case series (and hence in the systematic review) because the type of patients treated may be 'worse' than those in surgically treated observational series, they may get more (or less) intensive after-care, and there are numerous other sources of bias and confounding which make it impossible to say more than that the coiling technique appears very promising but needs to be evaluated against surgery in randomized trials.

In the case of an unruptured aneurysm, should one decide treatment was necessary, the long-term results of coiling are particularly relevant because coiling could provide a less invasive alternative to surgery. It is worth noting that the published rupture rate of partially coiled aneurysms is the same as that reported from the ISUIA study for *untreated* unruptured aneurysms >10 mm diameter or for any unruptured aneurysm in a patient with a previous SAH. The regrowth rate of partially coiled aneurysms is still being defined, thus there are considerable uncertainties about the long- and short-term effectiveness of coiling. Current evidence suggesting an overall rupture rate of asymptomatic untreated unruptured aneurysms in the range 0.27% (International Study of Unruptured Intracranial Aneurysms Investigators, 1998) to 1.9% (Rinkel *et al*., 1998) means that the cost effectiveness of GDC treatment or surgery is decidedly uncertain. If the ISUIA rupture rate of 0.05% per annum (for aneurysms <10 mm in diameter) is correct (and it is the most rigorous large study to address this issue to

date), then neither coiling nor surgery seems sufficiently safe to justify intervention in most patients with unruptured aneurysms. A randomized trial of best medical therapy versus intervention with long-term follow-up is required.

Are there other worthwhile interventions?

Apart from direct treatment of the aneurysm, it is likely that there are other ways of reducing the risk of rupture, which collectively could have a useful effect. 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 of aneurysmal SAH in patients on anticoagulants (at least a doubling of the mortality rate) (Rinkel *et al.*, 1997), but less evidence for patients on aspirin. With the widespread use of aspirin, there must be a reasonable proportion of patients who happen to rupture an aneurysm while on aspirin and the prolonged bleeding time in patients on aspirin or other non-steroidal anti-inflammatory drugs (NSAID) theoretically might result in a similar poor outcome to that found with anticoagulant drugs. However, a study on this subject has not confirmed the hypothesis. In fact, Juvela found that the use of 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 (Juvela, 1995).

Screening for occult intracranial aneurysms

There is a popular belief that screening to detect and so prevent disease 'must' be beneficial as well as straightforward, effective and cost effective; in fact it is often complex, of arguable effectiveness and very expensive (*Lancet* Editorial, 1998). To be effective, the screening test must discriminate between those with and without the disease, and not identify any self-limiting forms of disease which would not otherwise require treatment. A large administration infrastructure is required to deliver and maintain a national quality-assured screening programme. Some of the problems with screening as highlighted in the above-mentioned *Lancet* editorial may be illustrated further by the following examples. Screening for congenital dislocation of the hip failed to detect the condition in 70% of those children who subsequently required corrective surgery for it (Godward and Dezateux, 1998). In Japan, screening of children at 6 months of age for neuroblastoma found that screening at this age detects numerous cases that would have otherwise regressed spontaneously, and misses the more aggressive cases, in whom neuroblastoma develops later (Kudo *et al.*, 1998). A trial of screening for colorectal cancer (Kronberg *et al.*, 1996) randomized 61 933 subjects to screening or no screening with faecal occult blood tests twice yearly for 10 years to demonstrate a 0.1% absolute reduction in deaths from colorectal cancer. The calculated cost for each colorectal cancer death prevented in a UK study of 152 580 patients (Hardcastle *et al.*, 1996) was $200 000 (Wagner *et al.*, 1996).

Unless a screening test is very highly 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 and is more likely to increase health care costs and stress amongst the population and health care staff alike (*Lancet* Editorial, 1998). Furthermore, unless one can differentiate between disease likely to remain sub-clinical and that likely to cause significant symptoms, the treatment of disease following on from a screening programme may have less impact than expected on cumulative mortality rates. In the case of intracranial aneurysms, because we cannot yet tell when aneurysms are going to rupture or form *de novo*, it would be difficult to know which to treat, which to leave alone, how often to screen, etc. The stress of being screened is difficult to quantify and probably depends in part upon the seriousness (in the mind of the screened population) of the disease being sought. McDonald *et al*. assessed patient reassurance after a normal test result in patients undergoing echocardiography for symptoms or an asymptomatic murmur (McDonald *et al.*, 1996). All those presenting with symptoms remained anxious despite the normal test result, and 39 of 52 people (75%) presenting with an asymptomatic murmur became anxious after detection of the murmur. Over half of these (21/39) remained anxious despite the normal echocardiogram result.

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 (Levey, 1990; Wiebers and Torres, 1992; Ronkainen *et al.*, 1995; Butler *et al.*, 1996; Kojima *et al.*, 1998). The efficacy of screening for aneurysms depends crucially on certain parameters relating to the natural history of aneurysms, particularly the prevalence and the annual risk of rupture. Analysis of rupture risk is complicated further by the pattern of aneurysm rupture—some aneurysms appear to develop and rupture rapidly whilst others stabilize (Schievink *et al.*, 1991; Juvela *et al.*, 1993; Black, 1994; International Study of Unruptured Intracranial Aneurysms Investigators, 1998). 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 models to the screening decision analysis process for aneurysms (ter Berg *et al.*, 1988; Leblanc *et al.*, 1994; King *et al.*, 1995; Obuchowski *et al.*, 1995; Kallmes *et al.*, 1998; Crawley *et al.*, 1999), and only the most recent of these papers came out against screening, the others suggesting it was justified in the at-risk populations identified. This may be because the earlier studies assumed higher aneurysm rupture rates, higher MRA accuracy and a lower morbidity

rate from treatment than are apparent in the more recent and rigorous evidence now available.

Are there other considerations of screening for unruptured aneurysms?

As with any screening exercise, multiple factors need to be considered, such as raising anxieties in the patient or the patient's family, confidentiality issues, 'the right not to know', the problems raised by false-positive and false-negative diagnoses, what age to start investigating patients, how often to repeat the investigations, etc. For intracranial aneurysms, many of these factors remain uncertain. There may be financial costs for the individuals who are screened (e.g. through insurance costs and employment implications). If conservative management is advised, the knowledge of the presence of an aneurysm may be worrying to the individual concerned (and to his/her family and employer). The question of whether any genetic test results should be used for actuarial purposes by insurance companies is highly controversial and unresolved (Morrison, 1998; Thomson, 1998). Even defining a 'genetic test' is fraught with difficulty (Harper, 1997), and this may well prevent legislative attempts to prevent discrimination on the grounds of genetic heritage from succeeding in Europe and the USA (Council of Europe, 1996; Thomson, 1998). UK financial institutions will not (at present) charge higher premiums for life assurance simply because investigations have been done, provided the results are negative. Bearing all these factors in mind, ignorance (of the presence or absence of an aneurysm) may actually be the best course of action for an individual at present.

As regards driving, 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 and Public Service Vehicle licences), the licence will be refused or revoked pending a specialist assessment for the DVLA of the risks on an individual patient basis. This might have considerable financial implications for some patients.

Conclusion

In summary, the indications for, and the cost effectiveness of, screening for unruptured intracranial aneurysms is unproven because the range of values reported for aneurysm prevalence and rupture rates are wide, the imaging tests are not accurate enough and the risks of surgical treatment are high compared with the risk of aneurysm rupture, and these values are critical to the cost–benefit analysis. We should be wary of introducing any screening programme which may lead to the detection and treatment of cases which would never have caused clinical disease and which equally might miss cases, including those arising *de novo*, after screening.

So what, if anything, should we be doing at present about unruptured intracranial aneurysms? Clearly, the weight of evidence is against routine screening of all relatives of SAH patients. However, obtaining a careful and complete family history in patients with aneurysmal SAH should be mandatory. In general, 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 of it then rupturing, are females aged over 30 years from families with two or more first or second degree relatives affected by SAH. They are particularly at risk if they have additional identifiable risk factors such as smoking, excess alcohol consumption or hypercholesterolaemia, hypertension or are using the oral contraceptive pill. Such subjects (and patients from the rare families with many affected members, and ADPKD patients) should be assessed on an individual basis taking all the relevant risk factors into account before offering screening for intracranial aneurysms. Until the accuracy of non-invasive tests is better defined, IADSA should be still be regarded as the only way definitively to exclude the presence of an intracranial aneurysm. The risk of rupture if an asymptomatic aneurysm is present is low ($<0.5\%$ per annum) and the risk of most aneurysms (small, non-posterior circulation aneurysms) is considerably outweighed by the morbidity and mortality of surgery, the role of coiling being as yet unproven, but known risk factors for aneurysm rupture should be stringently avoided. To resolve some of the issues highlighted above, we need more information on the genetic basis for aneurysm formation and randomized trials with long-term follow-up to evaluate the risks and effectiveness of best medical therapy compared with surgery and/or coiling for the treatment of asymptomatic unruptured intracranial aneurysms.

Acknowledgements

P.M.W. is funded by the British Brain and Spine Foundation as a Research Fellow on the Davie Cooper Scottish Aneurysm Study, a joint project between the Institute of Neurosciences in Glasgow and the Department of Clinical Neuroscience in Edinburgh.

References

Adamson J, Humphries SE, Ostergaard JR, Voldby B, Richards P, Powell JT. Are cerebral aneurysms atherosclerotic? Stroke 1994; 25: 963–6.

Alberico RA, Patel M, Casey S, Jacobs B, Maguire W, Decker R. Evaluation of the circle of Willis with three-dimensional CT angiography in patients with suspected intracranial aneurysms. AJNR Am J Neuroradiol 1995; 16: 1571–8.

Alberts MJ, Quinones A, Graffagnino C, Friedman A, Roses AD. Risk of intracranial aneurysms in families with subarachnoid hemorrhage. Can J Neurol Sci 1995; 22: 121–5.

Aprile I. Evaluation of cerebral aneurysms with MR-angiography. Riv Neuroradiol 1996; 9: 541–50.

Atlas SW. MR angiography in neurologic disease. [Review]. Radiology 1994; 193: 1–16.

Atlas SW. Magnetic resonance imaging of intracranial aneurysms. Neuroimaging Clin N Am 1997; 7: 709–20.

Atlas SW, Sheppard L, Goldberg HI, Hurst RW, Listerud J, Flamm E. Intracranial aneurysms: detection and characterization with MR angiography study with use of an advanced postprocessing technique in a blinded-reader study. Radiology 1997; 203: 807–14.

Bannerman RM, Ingall GB, Graf CJ. The familial occurrence of intracranial aneurysms. Neurology 1970; 20: 283–92.

Becker G, Perez J, Krone A, Demuth K, Lindner A, Hofmann E, et al. Transcranial color-coded real-time sonography in the evaluation of intracranial neoplasms and arteriovenous malformations. Neurosurgery 1992; 31: 420–8.

Black WC. Intracranial aneurysm in adult polycystic kidney disease: is screening with MR angiography indicated? [editorial]. Radiology 1994; 191: 18–20.

Brenner H, Gefeller O. Variation of sensitivity, specificity, likelihood ratios and predictive values with disease prevalence. Stat Med 1997; 16: 981–91.

Brilstra EH, Rinkel GJ, van der Graaf Y, van Rooij WJ, Algra A. Treatment of intracranial aneurysms by embolization with coils: a systematic review. [Review]. Stroke 1999; 30: 470–6.

Bromberg JE, Rinkel GJ, Algra A, Greebe P, van Duyn CM, Hasan D, et al. Subarachnoid haemorrhage in first and second degree relatives of patients with subarachnoid haemorrhage. Br Med J 1995a; 311: 288–9.

Bromberg JE, Rinkel GJ, Algra A, Limburg M, van Gijn J. Outcome in familial subarachnoid hemorrhage. Stroke 1995b; 26: 961–3.

Brown JH, Lustrin ES, Lev MH, Ogilvy CS, Taveras JM. Characterization of intracranial aneurysms using CT angiography. AJR Am J Roentgenol 1997; 169: 889–93.

Butler WE, Barker FG, Crowell RM. Patients with polycystic kidney disease would benefit from routine magnetic resonance angiographic screening for intracerebral aneurysms: a decision analysis [abstract]. Stroke 1996; 27: 1137.

Cloft HJ, Joseph GJ, Dion JE. Risk of cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation: a meta-analysis. Stroke 1999; 30: 317–20.

Council of Europe. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the application of Biology and Medicine. ETS 164. Strasbourg: Council of Europe; 1996.

Crawley F, Clifton A, Brown MM. Should we screen for familial intracranial aneurysm? Stroke 1999; 30: 312–6.

De Braekeleer M, Perusse L, Cantin L, Bouchard J-M, Mathieu J. A study of inbreeding and kinship in intracranial aneurysms in the Saguenay-Lac Saint-Jean region (Quebec, Canada). Ann Hum Genet 1996; 60: 99–104.

Fogelholm R, Hernesniemi J, Vapalahti M. Impact of early surgery on outcome after aneurysmal subarachnoid hemorrhage: a population-based study. Stroke 1993; 24: 1649–54.

Futatsuya R, Seto H, Kamei T, Nakashima A, Kakishita M, Kurimoto M, et al. Clinical utility of 3-dimensional time-of-flight magnetic resonance angiography for the evaluation of intracranial aneurysms. Clin Imaging 1994; 18: 101–6.

Gasparotti R, Bonetti M, Crispino M, Pavia M, Chiesa A, Galli G. Subarachnoid hemorrhage: assessment in the acute phase with angiography, with high-resolution magnetic resonance (angio-MR). [Italian]. Radiol Med (Torino) 1994; 87: 219–28.

Godward S, Dezateux C. Surgery for congenital dislocation of the hip in the UK as a measure of outcome of screening. Lancet 1998; 351: 1149–52.

Guglielmi G, Vinuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach: Part 2. Preliminary clinical experience. J Neurosurg 1991; 75: 8–14.

Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996; 348: 1472–77.

Harper PS. What do we mean by genetic testing? J Med Genet 1997; 34: 749–52.

Hijdra A, Braakman R, van Gijn J, Vermeulen M, van Crevel H. Aneurysmal subarachnoid hemorrhage: complications and outcome in a hospital population. Stroke 1987; 18: 1061–7.

Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. [Review]. Stroke 1997; 28: 660–4.

Hope JK, Wilson JL, Thomson FJ. Three-dimensional CT angiography in the detection and characterization of intracranial berry aneurysms. AJNR Am J Neuroradiol 1996; 17: 439–45.

Hughes R, Chapman A, Rubinstein D, Stears J, Johnson A, Gabow P. Recurrent intracranial aneurysms (ICA) in autosomal dominant polycystic kidney disease (ADPKD) [abstract]. Stroke 1996; 27: 178.

Huston J 3rd, Nichols DA, Luetmer PH, Goodwin JT, Meyer FB, Wiebers DO, et al. Blinded prospective evaluation of sensitivity of MR angiography to known intracranial aneurysms: importance of aneurysm size. AJNR Am J Neuroradiol 1994; 15: 1607–14.

International Study of Unruptured Intracranial Aneurysms (ISUIA) Investigators. Factors related to the development and detection of single versus multiple unruptured intracranial aneurysms [abstract]. Stroke 1996; 27: 178.

International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. N Engl J Med 1998; 339: 1725–33.

Johnston SC, Colford JM Jr, Gress DR. Oral contraceptives and the risk of subarachnoid hemorrhage: a meta-analysis. Neurology 1998; 51: 411–8.

Juvela S. Aspirin and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. J Neurosurg 1995; 82: 945–52.

Juvela S, Porras M, Heiskanen O. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. J Neurosurg 1993; 79: 174–82.

Kallmes DF, Kallmes MH, Cloft HJ, Dion JE. Guglielmi detachable coil embolization for unruptured aneurysms in nonsurgical candidates: a cost-effectiveness exploration. AJNR Am J Neuroradiol 1998; 19: 167–76.

Kassell NF, Torner JC. Aneurysmal rebleeding: a preliminary report from the Cooperative Aneurysm Study. Neurosurgery 1983; 13: 479–81.

Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part I: overall management results. J Neurosurg 1990; 73: 18–36.

King JT Jr. Epidemiology of aneurysmal subarachnoid hemorrhage. [Review]. Neuroimaging Clin N Am 1997; 7: 659–68.

King JT Jr, Glick HA, Mason TJ, Flamm ES. Elective surgery for asymptomatic, unruptured, intracranial aneurysms: a cost-effectiveness analysis. J Neurosurg 1995; 83: 403–12.

Klotzsch C, Bozzato A, Lammers G, Mayfrank D, Mull M, Noth J. 3D-transcranial color-coded sonography of intracranial aneurysms [abstract]. Cerebrovasc Dis 1999; 9 Suppl 1: 79.

Kojima M, Nagasawa S, Lee YE, Takeichi Y, Tsuda E, Mabuchi N. Asymptomatic familial cerebral aneurysms. Neurosurgery 1998; 43: 776–81.

Korogi Y, Takahashi M, Mabuchi N, Nakagawa T, Fujiwara S, Horikawa Y, et al. Intracranial aneurysms: diagnostic accuracy of MR angiography with evaluation of maximum intensity projection and source images. Radiology 1996; 199: 199–207.

Kronberg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal occult-blood test. Lancet 1996; 348: 1467–71.

Kudo K, Arai Y, Kondo Y. Japanese mass screening for neuroblastoma [letter]. Lancet 1998; 352: 1316.

Lancet Editorial. The screening muddle [editorial]. Lancet 1998; 351: 459.

Leblanc R. Familial cerebral aneurysms. [Review]. Can J Neurol Sci 1997; 24: 191–9.

Leblanc R, Lozano AM, van der Rest M, Guttmann RD. Absence of collagen deficiency in familial cerebral aneurysms. J Neurosurg 1989; 70: 837–40.

Leblanc R, Worsley KJ, Melanson D, Tampieri D. Angiographic screening and elective surgery of familial cerebral aneurysms: a decision analysis. Neurosurgery 1994; 35: 9–18.

Levey AS. Screening for occult intracranial aneurysms in polycystic kidney disease: interim guidelines [editorial]. J Am Soc Nephrol 1990; 1: 9–12.

Linn FH, Rinkel GJ, Algra A, van Gijn J. Incidence of subarachnoid haemorrhage. Role of region, year, and rate of computed tomography: a meta-analysis. Stroke 1996; 27: 625–9.

Lozano AM, Leblanc R. Familial intracranial aneurysms. J Neurosurg 1987; 66: 522–8.

Mayberg MR, Batjer H, Dacey R, Diringer M, Haley EC, Heros RC, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 1994; 25: 2315–28.

McCormick WF, Acosta-Rua GJ. The size of intracranial saccular aneurysms. An autopsy study. J Neurosurg 1970; 33: 422–7.

McDonald IG, Daly J, Jelinek VM, Panetta F, Gutman JM. Opening Pandora's box: the unpredictability of reassurance by a normal test result. Br Med J 1996; 313: 329–32.

Morooka Y, Waga S. Familial intracranial aneurysms: report of four families. Surg Neurol 1983; 19: 260–2.

Morrison PJ. Implications of genetic testing for insurance in the UK. Lancet 1998; 352: 1647–8.

Mulvihill JJ, Parry DM, Sherman JL, Pikus A, Kaiser-Kupfer MI. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. [Review]. Ann Intern Med 1990; 113: 39–52.

Munyer TP, Margulis AR. Pseudoxanthoma elasticum with internal carotid artery aneurysm. AJR Am J Roentgenol 1981; 136: 1023–4.

Norrgard O, Beckman G, Beckman L, Cedergren B, Fodstad H, Angquist KA. Genetic markers in patients with intracranial aneurysms. Hum Hered 1987a; 37, 255–9.

Norrgard O, Angquist K, Fodstad H, Forsell A, Lindberg M. Intracranial aneurysms and heredity. Neurosurgery 1987b; 20: 236–9.

O'Brien JG. Subarachnoid haemorrhage in identical twins. Br Med J 1942; 1: 607–9.

Obuchowski NA, Modic MT, Magdinec M. Current implications for the efficacy of noninvasive screening for occult intracranial aneurysms in patients with a family history of aneurysms. J Neurosurg 1995; 83: 42–9.

Ostergaard JR, Hog E. Incidence of multiple intracranial aneurysms: influence of arterial hypertension and gender. J Neurosurg 1985; 63: 49–55.

Oyesiku NM, Colohan AR, Barrow DL, Reisner A. Cocaine-induced aneurysmal rupture: an emergent factor in the natural history of intracranial aneurysms? Neurosurgery 1993; 32: 518–26.

Raaymakers TW, Rinkel GJ, Limburg M, Algra A. Mortality and morbidity of surgery for unruptured intracranial aneurysms: a meta-analysis. Stroke 1998; 29: 1531–8.

Rinkel GJ, Prins NE, Algra A. Outcome of aneurysmal subarachnoid hemorrhage in patients on anticoagulant treatment. Stroke 1997; 28: 6–9.

Rinkel GJ, Djibuti M, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke 1998; 29: 251–6.

Roman G, Fisher M, Perl DP, Poser CM. Neurological manifestations of hereditary hemorrhagic telangiectasia (Rendu–Osler–Weber disease): report of 2 cases and review of the literature. Ann Neurol 1978; 4: 130–44.

Ronkainen A, Puranen MI, Hernesniemi JA, Vanninen RL, Partanen PL, Saari JT, et al. Intracranial aneurysms: MR angiographic screening in 400 asymptomatic individuals with increased familial risk. Radiology 1995; 195: 35–40.

Ronkainen A, Hernesniemi JA, Puranen M, Niemitukia L, Vanninen

R, Ryynanen M, et al. Familial intracranial aneurysms. Lancet 1997; 349: 380–4.

Ronkainen A, Miettinen H, Karkola K, Papinaho S, Vanninen R, Puranen M, et al. Risk of harboring an unruptured intracranial aneurysm. Stroke 1998; 29: 359–62.

Ross JS, Masaryk TJ, Modic MT, Ruggieri PM, Haacke EM, Selman WR. Intracranial aneurysms: evaluation by MR angiography. AJNR Am J Neuroradiol 1990; 11: 449–55.

Ruggieri PM, Poulos N, Masaryk TJ, Ross JS, Obuchowski NA, Awad IA, et al. Occult intracranial aneurysms in polycystic kidney disease: screening with MR angiography. Radiology 1994; 191: 33–9.

Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. Boston: Little Brown; 1991.

Schievink WI, De Waal LP, Hageman LM, Van der Werf DJ. Intracranial aneurysm and HLA-DR2. J Neurol Neurosurg Psychiatry 1988; 51: 883.

Schievink WI, Karemaker JM, Hageman LM, Van der Werf DJ. Circumstances surrounding aneurysmal subarachnoid hemorrhage. [Review]. Surg Neurol 1989; 32: 266–72.

Schievink WI, Limburg M, Oorthuys JW, Fleury P, Pope FM. Cerebrovascular disease in Ehlers–Danlos syndrome type IV. Stroke 1990; 21: 626–32.

Schievink WI, Limburg M, Dreissen JJ, Peeters FL, ter Berg HW. Screening for unruptured familial intracranial aneurysms: subarachnoid hemorrhage 2 years after angiography negative for aneurysms. [Review]. Neurosurgery 1991; 29: 434–8.

Schievink WI, Schaid DJ, Michels VV, Piepgras DG. Familial aneurysmal subarachnoid hemorrhage: a community-based study. J Neurosurg 1995; 83: 426–9.

Schievink WI, Katzmann JA, Piepgras DG, Schaid DJ. Alpha-1-antitrypsin phenotypes among patients with intracranial aneurysms. J Neurosurg 1996; 84: 781–4.

Sengupta RP, McAllister VL. Subarachnoid haemorrhage. Berlin: Springer-Verlag; 1986.

ter Berg HW, Dippel DW, Habbema JD, Bijlsma JB, van Gijn J, Tulleken CA, et al. Treatment of intact familial intracranial aneurysms: a decision-analytical approach. Neurosurgery 1988; 23: 329–34.

ter Berg HW, Dippel DW, Limburg M, Schievink WI, van Gijn J. Familial intracranial aneurysms: a review. [Review]. Stroke 1992; 23: 1024–30.

Teunissen LL, Rinkel GJ, Algra A, van Gijn J. Risk factors for subarachnoid hemorrhage: a systematic review. Stroke 1996; 27: 544–9.

Thomson B. Time for reassessment of use of all medical information by UK insurers. Lancet 1998; 352: 1216–8.

Tsuchiya T, Yasaka M, Yamaguchi T, Kimura K, Omae T. Imaging of the basal cerebral arteries and measurement of blood velocity in adults using transcranial real-time color flow Doppler sonography. AJNR Am J Neuroradiol 1991; 12: 497–502.

Uehara T, Tabuchi M, Mori E. High frequency of unruptured intracranial aneurysms in female patients with ischaemic heart disease. J Neurol Neurosurg Psychiatry 1998; 64: 536–8.

van den Berg JS, Limburg M, Hennekam RC. Is Marfan syndrome associated with symptomatic intracranial aneurysms? [Review]. Stroke 1996; 27: 10–2.

van den Berg JS, Limburg M, Hennekam RC, Cruysberg JR, Steijilen PM, Limburg M. Prevalence of symptomatic intracranial aneurysm and ischaemic stroke in pseudoxanthoma elasticum [abstract]. Cerebrovasc Dis 1999; 9 Suppl 1: 3.

van Gijn J. What caused this subarachnoid haemorrhage? In: Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PA, Bamford JM, et al, editors. Stroke: a practical guide to management. Oxford: Blackwell Science; 1996. p. 322–59.

Vinuela F, Duckwiler G, Mawad M. Guglielmi detachable coil embolization of acute intracranial aneurysm: perioperative anatomical and clinical outcome in 403 patients. J Neurosurg 1997; 86: 475–82.

Wagner Jl, Tunis S, Brown M. Cost-effectiveness of colorectal cancer screening in average-risk adults. In: Young GP, Rozen P, Levin B, editors. Prevention and early detection of colorectal cancer. London: W.B. Saunders; 1996. p. 321–56.

Wang PS, Longstreth WT, Koepsell TD. Subarachnoid hemorrhage and family history: a population-based case–control study. Arch Neurol 1995; 52: 202–4.

Wardlaw JM, Cannon JC. Color transcranial 'power' Doppler ultrasound of intracranial aneurysms. J Neurosurg 1996; 84: 459–61.

Warnock NG, Gandhi MR, Bergvall U, Powell T. Complications of intraarterial digital subtraction angiography in patients investigated for cerebral vascular disease. Br J Radiol 1993; 66: 855–85.

White PM, Wardlaw JM. How reliable is the non-invasive imaging of intracranial aneurysms? [abstract]. Cerebrovasc Dis 1999; 9 Suppl 1: 51.

Wiebers DO, Torres VE. Screening for unruptured intracranial aneurysms in autosomal dominant polycystic kidney disease [editorial]. N Engl J Med 1992; 327: 953–5.

Wiebers DO, Whisnant JP, Sundt TM Jr, O'Fallon WM. The significance of unruptured intracranial saccular aneurysms. J Neurosurg 1987; 66: 23–9.

Wilcock D, Jaspan T, Holland I, Cherryman G, Worthington B. Comparison of magnetic resonance angiography with conventional angiography in the detection of intracranial aneurysms in patients presenting with subarachnoid haemorrhage. Clin Radiol 1996; 51: 330–4.

Received May 25, 1999. Revised August 12, 1999.
Accepted August 23, 1999