# International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion

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## Summary

**Background** Two types of treatment are being used for patients with ruptured intracranial aneurysms: endovascular detachable-coil treatment or craniotomy and clipping. We undertook a randomised, multicentre trial to compare these treatments in patients who were suitable for either treatment because the relative safety and efficacy of these approaches had not been established. Here we present clinical outcomes 1 year after treatment.

**Methods** 2143 patients with ruptured intracranial aneurysms, who were admitted to 42 neurosurgical centres, mainly in the UK and Europe, took part in the trial. They were randomly assigned to neurosurgical clipping (n=1070) or endovascular coiling (n=1073). The primary outcome was death or dependence at 1 year (defined by a modified Rankin scale of 3–6). Secondary outcomes included rebleeding from the treated aneurysm and risk of seizures. Long-term follow up continues. Analysis was in accordance with the randomised treatment.

**Findings** We report the 1-year outcomes for 1063 of 1073 patients allocated to endovascular treatment, and 1055 of 1070 patients allocated to neurosurgical treatment. 250 (23·5%) of 1063 patients allocated to endovascular treatment were dead or dependent at 1 year, compared with 326 (30·9%) of 1055 patients allocated to neurosurgery, an absolute risk reduction of 7·4% (95% CI 3·6–11·2, p=0·0001). The early survival advantage was maintained for up to 7 years and was significant (log rank p=0·03). The risk of epilepsy was substantially lower in patients allocated to endovascular treatment, but the risk of late rebleeding was higher.

**Interpretation** In patients with ruptured intracranial aneurysms suitable for both treatments, endovascular coiling is more likely to result in independent survival at 1 year than neurosurgical clipping; the survival benefit continues for at least 7 years. The risk of late rebleeding is low, but is more common after endovascular coiling than after neurosurgical clipping.

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See Comment page 783

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## Introduction

The International Subarachnoid Aneurysm Trial (ISAT), a randomised trial comparing neurosurgical clipping with endovascular coiling in patients with ruptured intracranial aneurysms, closed recruitment after an interim analysis showed a benefit of endovascular treatment on the primary outcome: death or dependency at 1 year. Our first report[1] of the interim results used the outcome data available at the time of that analysis. These data were incomplete because 1-year follow-up was available for only 1594 of the 2143 patients enrolled. However, the difference between the two treatments was significant: endovascular coiling was associated with an absolute reduction in the risk of death or dependence at 1 year of 6·9% (a relative risk reduction of 22·6%, p<0·001) compared with neurosurgical clipping.[1] The 1-year data are now complete and we report here the primary outcome at 1 year for all patients combined and subdivided by the prespecified subgroups.[2] We also report results for secondary outcomes: epilepsy, rebleeding from the treated aneurysm, deaths during medium-term follow-up (with survival curves to 7 years), and the findings on follow-up angiography. Patients were eligible for enrolment into ISAT if the responsible neurosurgeon and neuroradiologist were uncertain about the best treatment. If there was insufficient uncertainty, the patient could not be randomised.[3]

## Methods

### Patients

The trial protocol and methods, including the randomisation and minimisation criteria, recruiting centres, patient demographics and aneurysm characteristics, have already been published.[1,2] Eligible patients had subarachnoid haemorrhage due to intracranial aneurysm, suitable for either endovascular or neurosurgical treatment. These subgroups were prespecified: World Federation of Neurosurgical Societies (WFNS) grade at randomisation, age groups by decade (<40, 40–49, 50–59, 60–69, ⩾70 years), amount of

blood on CT scan (Fisher grade), and the site and lumen size of the aneurysm. All centres obtained local ethics or institutional review board consent before enrolling patients. Able patients provided written informed consent. However, some ethics committees allowed assent from relatives to enable patients who could not give their own written consent to be enrolled in the trial.

## Procedures

Randomisation procedures have been published elsewhere.[1] The primary objective was to determine whether a policy of endovascular treatment compared with neurosurgical treatment reduced the proportion of patients dead or dependent at 1 year. ISAT also set out to assess any differences between endovascular treatment and neurosurgery in: rebleeding from the treated aneurysm; quality of life at 1 year (assessed with euroqol [EQ5D] measure); epilepsy; cost-effectiveness; and, neuropsychological outcomes in a substudy done in eight centres in the UK, which will be published separately.[2,4] Blinded assessment of definite or suspected rebleeding and intracranial haemorrhage was not possible because clips, coils, and evidence of a craniotomy are readily seen on CT scans. RSCK and AJM (a neurosurgeon and a neuroradiologist, respectively) independently judged all reported instances of definite or suspected rebleeding and intracranial haemorrhage. These were reported to the ISAT office by the investigators or by means of death certificate and of notifications on the hospital readmission reports. The timing of rebleeding was categorised as: before a first procedure, after a first procedure and within 30 days of the subarachnoid haemorrhage, between 30 days and 1 year, and after 1 year. Any disagreement over categorisation was resolved by discussion.

Details of seizures were collected on a separate case record form. There was detailed review of the case record form, the case notes, and, where necessary, information was directly obtained from the patient. Data were extracted from the case records by centre clinicians and coordinators, including: history of epilepsy, anticonvulsant drugs taken or prescribed after seizures, the number and type of seizures, and, if the patient was assigned to endovascular treatment, whether any other neurosurgical procedure (craniotomy or ventricular shunting) was done. The timing of the seizures was defined as: before treatment, after treatment and before initial discharge, after initial discharge to 1 year, and after 1 year. Seizures occurring with the first haemorrhage were not included, those associated with rebleeding were included.

Angiographic follow-up was requested in all patients who had endovascular coiling, because it is standard practice; it was typically done 6 months after treatment, but occasionally was done earlier and, depending on the findings, repeated later. Follow-up was nearly always done by intra-arterial angiography during the period of the trial. Some centres used magnetic-resonance angiography (MRA) because image quality became satisfactory towards the end of the trial. Angiographic follow-up after neurosurgical clipping was not mandatory because this would have been a change in standard clinical practice in many centres. When angiography was done, data on angiographic occlusion were recorded on the case-record forms at discharge, 2 months, 1 year, and thereafter on the annual case record form. At the time of treatment, the investigator assessed (visually during neurosurgery or from the final angiogram for patients who had endovascular coiling) the percentage of occlusion of the aneurysm. On subsequent angiography the investigator was asked to estimate the degree of occlusion within one of three categories: complete aneurysm occlusion, neck remnant or subtotal occlusion, or incomplete occlusion, indicating substantial aneurysm refilling. This method of categorisation has been described previously.[5]

RSCK and AJM assessed survival and long-term outcome by reviewing the certified causes of death, and the case record forms, the clinical records, and post-mortem details, when available. Follow-up data were sought at 1 year and annually thereafter by mailing a postal questionnaire to known surviving patients; the last mail-out for the data reported here was done in November, 2004. Long-term survival data for UK patients is obtained from the Office of National Statistics, so that all deaths of UK patients are reported directly to the ISAT office. This allows us to assume reliably that patients for whom we do not have a death notification are alive, even if they do not return their annual postal questionnaire. Similar mortality data are being collected by all centres in Canada, Sweden, Denmark, and Finland, and several centres in France and Germany. We wish to continue follow-up as long as possible in this cohort of patients, which includes more than 90% of the people who took part in ISAT. The dataset for these analyses was finalised on Nov 30, 2004.

| | Number of patients (%) |
|---|---|
| **Endovascular procedure** | |
| Completed | 1014 (92·6%) |
| Failed to catheterise target aneurysm | 29 (2·6%) |
| Aneurysm catheterised but anatomy unsuitable | 37 (3·4%) |
| Not attempted | 15 (1·4%) |
| Total | 1095 (100%) |
| **Neurosurgical procedure** | |
| Clipped | 977 (96·5%) |
| Wrapped | 13 (1·3%) |
| Not completed (partial clipping or wrapping) | 14 (1·4%) |
| Not attempted | 8 (0·8%) |
| Total | 1012 (100%) |

*The results relate to the first procedure done, not the random treatment assignment.

*Table 1:* **Technical outcome of first procedure** *

### Statistical methods

Data handling and statistical analyses have been described previously.[1] The Kaplan-Meier method was used to analyse time to death, with the log-rank test used to compare mortality between the treatment groups. A statistical test of interaction was done to assess whether the treatment effect was consistent across the prespecified subgroups. Relative risks describe the direction and magnitude of the treatment effect, and relative risk reduction and absolute risk reduction are presented to aid interpretation.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN49866681. The protocol for this study was peer-reviewed and accepted by *The Lancet*: a summary of the protocol was published on the journal's website, and the journal then made a commitment to peer-review the primary clinical manuscript.

### Role of the funding source

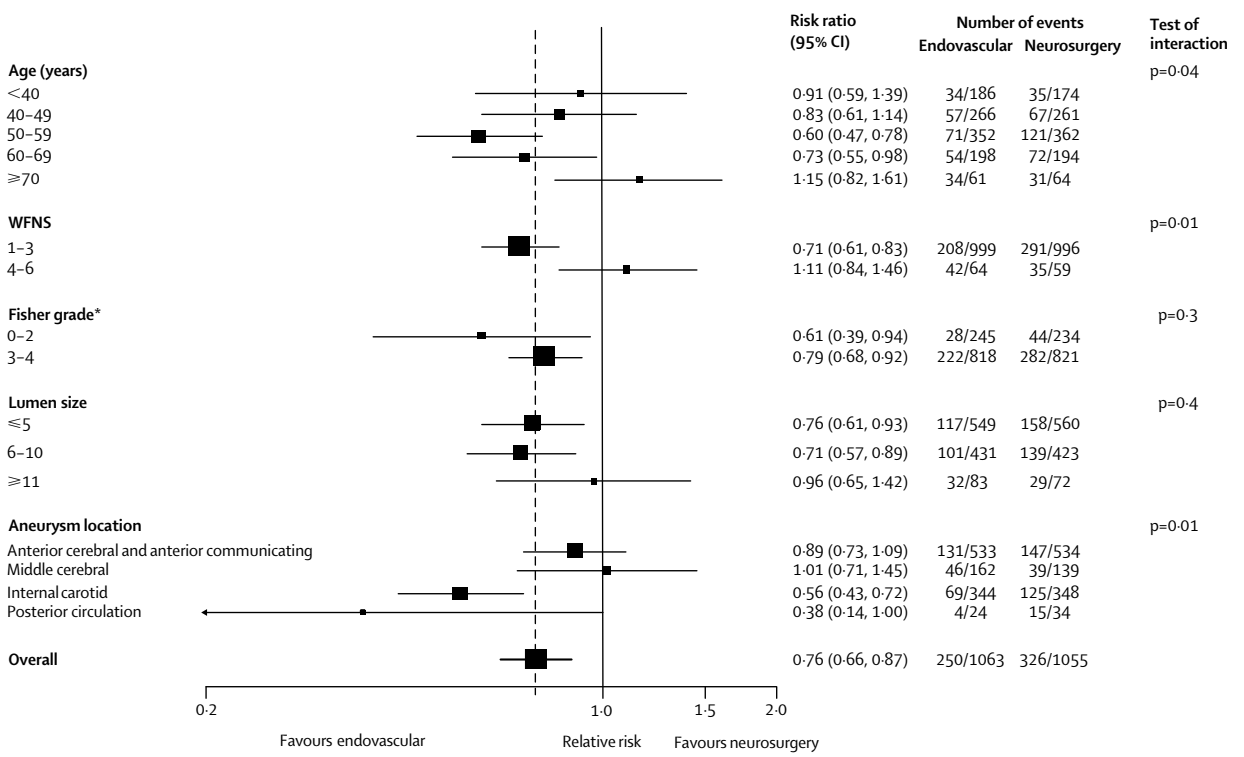
The trial was designed, completed, and analysed independent of the sponsors. The principal investigators (RSCK and AJM) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

| | 2 month outcome | | 1 year outcome | |
|---|---|---|---|---|
| | Endovascular n=1065 | Neurosurgery n=1063 | Endovascular n=1063 | Neurosurgery n=1055 |
| **Modified Rankin Scale** | | | | |
| 0 No symptoms | 203 (19·1%) | 144 (13·6%) | 260 (24·5%) | 187 (17·7%) |
| 1 Minor symptoms | 310 (29·1%) | 273 (25·7%) | 301 (28·3%) | 292 (27·7%) |
| 2 Some restriction in lifestyle | 274 (25·7%) | 254 (23·8%) | 252 (23·7%) | 250 (23·7%) |
| (0-2 inclusive) | 787 (73·9%) | 671 (63·1%) | 813 (76·5%) | 729 (69·1%) |
| 3 Significant restriction in lifestyle | 107 (10·1%) | 189 (17·8%) | 107 (10·1%) | 141 (13·4%) |
| 4 Partly dependent | 34 (3·2%) | 46 (4·3%) | 30 (2·8%) | 42 (4·0%) |
| 5 Fully dependent | 62 (5·8%) | 73 (6·9%) | 28 (2·6%) | 38 (3·6%) |
| 6 Dead | 75 (7·0%) | 84 (7·9%) | 85 (8·0%) | 105 (9·9%) |
| (3-6 inclusive) | 278 (26·1%) | 392 (36·9%) | 250 (23·5%) | 326 (30·9%) |

***Table 2:*** **Clinical outcome at 2 months and 1 year**

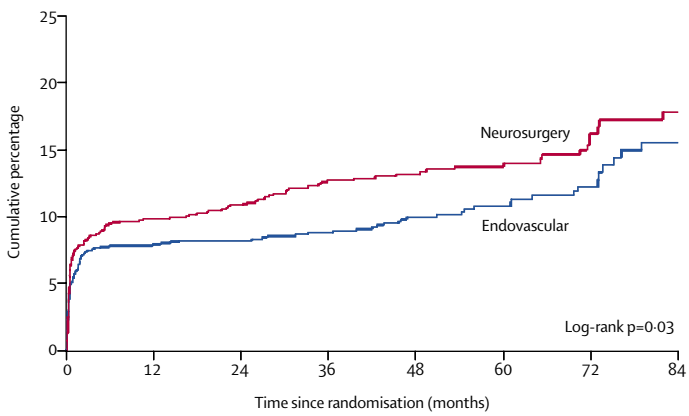
## Results

Baseline characteristics of the enrolled patients were similar between the treatment groups and have been detailed.[1] 88% of patients were in good clinical grade (WFNS 1 or 2) at the time of enrolment, 95% of the aneurysms were in the anterior cerebral circulation, and 90% were smaller than 10 mm. The mean follow-up is now 4 years, with 6542 patient years of follow-up available after 1 year.




* Fisher grade is a measure of the amount of blood on the CT scan.

***Figure 1:*** **Subgroup analyses for death or dependency at 1 year**




**Annual number at risk (deaths):**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Endovascular | 1073 (85) | 974 (3) | 887 (5) | 717 (8) | 541 (4) | 373 (5) | 215 (6) | 103 |
| Neurosurgery | 1070 (105) | 944 (10) | 842 (16) | 663 (3) | 503 (3) | 340 (7) | 192 (3) | 98 |

*Figure 2:* **Kaplan Meier cumulative mortality to 7 years**

1073 and 1070 patients were randomised to endovascular coiling or neurosurgical clipping, respectively. Of the 1073 patients allocated endovascular treatment, seven died before the procedure, and nine underwent clipping as the first procedure. Of the 1070 patients allocated to neurosurgery, 19 died before the first procedure, 39 had coiling as the first procedure, and seven were treated conservatively, and the information is missing for two. Table 1 shows the technical outcome of the first procedure done.

The mRS values at 2 months are missing for eight of the 1073 patients in the endovascular group and seven of the 1070 in the neurosurgery group. At 1 year, eight (0·4%) patients (three endovascular, five neurosurgical) had been lost to follow up, 25 (1%) patients were known to be alive but had missing Rankin data: 10 endovascular and 15 neurosurgical.

278 (26·1%) of 1065 patients allocated endovascular treatment were known to be dead or dependent at 2 months compared with 392 (36·9%) of 1063 allocated neurosurgery (relative risk=0·71, 0·62–0·80; p<0·0001; table 2). 250 (23·5%) of 1063 patients allocated to endovascular treatment were known to be dead or dependent at 1 year compared with 326 (30·9%) of 1055 patients allocated to neurosurgery (0·76, 0·66–0·87); this corresponds to a relative risk reduction at 1 year of 23·9% (12·4–33·9), and an absolute risk reduction of 7·4% (3·6–11·2) in favour of coiling (p=0·0001). Case fatality rates at 1 year were 8·0% (6·4–9·8) and 9·9% (8·2–11·9) among patients allocated endovascular and neurosurgical treatment, respectively.

Figure 1 shows subgroup analyses for death or dependency at 1 year. The treatment effect was heterogeneous and difficult to interpret within these subgroups: age, WFNS grade at baseline, and aneurysm location. For example, of the patients studied, only a small number were older than 70 years or younger than 40 years, and there was no consistent trend for age. Similarly, the number of patients with poor clinical grade (WFNS 4–6) who were randomised was small (<4% of the total).

The advantage of endovascular over neurosurgical treatment varies widely with aneurysm location, but endovascular treatment seems beneficial for all sites. The smallest subgroups were the greatest outliers and also the most subject to chance effects.

Deaths occurring within the first 7 years along with the numbers at risk in each year are shown in figure 2. There were more deaths among patients allocated to neurosurgery than to endovascular treatment (log-rank p=0·03), which seemed to be consistent over time. The causes of deaths after 2 months (and up to 8 years) are shown in table 3, subdivided to show deaths after the first year separately.

Table 4 shows the findings from the first follow-up angiography. Of 988 patients alive at 1 year after endovascular allocation, angiographic follow-up

| | 2–12 months | | After 1 year | |
|---|---|---|---|---|
| | Endovascular | Neurosurgery | Endovascular | Neurosurgery |
| Complication of severe dependent survival (eg, chest or other infections) | 7 | 15 | 1 | 5 |
| Treated aneurysm rebleeding | 1 | 1 | 2 | 2 |
| Probable or definite bleed from another aneurysm | 0 | 0 | 3* | 0 |
| Other intracranial haemorrhage | 0 | 0 | 1† | 0 |
| Ischaemic stroke | 0 | 0 | 2 | 3 |
| Cardiac | 0 | 0 | 5 | 10 |
| Cancer | 0 | 1 | 9 | 12 |
| Suicide | 0 | 1 | 2 | 1 |
| Renal failure | 1 | 0 | 0 | 2 |
| Infections not related to dependent survival | 0 | 1 | 5 | 5 |
| Other causes (eg, trauma, perforated ulcer, pulmonary embolus, neurodegenerative) | 0 | 1 | 2 | 3 |
| Unknown | 1 | 1 | 1 | 2 |
| Total | 10 | 21 | 33 | 45 |

Includes all reported deaths up to November 2004. *See text for details. †Confirmed at autopsy as primary intracerebral haemorrhage.

*Table 3:* **Causes of death**

| | Endovascular, n=988* | Neurosurgery, n=965* |
|---|---|---|
| Number of angiograms performed | 881 (89%) | 450 (47%) |
| Complete occlusion | 584 (66%) | 370 (82%) |
| Neck remnant or subtotal occlusion | 228 (26%) | 55 (12%) |
| Incomplete occlusion | 69 (8%) | 25 (6%) |
| Angiograms not done | 107 (11%)† | 515 (53%) |

* Surviving patients at 1 year. †Reasons for no angiography in endovascular patients: 56 failed initial coiling and had surgery or crossover to neurosurgery, 24 had poor Rankin outcome, 11 refused or did not attend , 2 for a /medical reason, 2 were aged over 70 years, 12 for no reason.

***Table 4:*** **Angiographic occlusion of target aneurysm on first follow-up angiography done after treatment**

| | Endovascular treatment ( n = 1073) | Neurosurgical treatment (n= 1070) | Relative risk (95% CI) |
|---|---|---|---|
| Before first procedure | 17 (7) | 28 (19) | 0·60 (0·33–1·10) |
| After first procedure and before 30 days | 20* (9†) | 8 (4) | 2·46 (1·09–5·57) |
| 30 days to 1 year | 8 (6) | 3 (1)‡ | 2·64 (0·70–9·93) |
| Total during first year | 45 | 39 | 1·15 (0·75–1·75) |
| After 1 year | 7 (2) | 2 (2)§ | |

Numbers in parentheses indicate deaths within 30 days of re-bleeding. *1 patient bled from another aneurysm which was not recognised at the time of the first angiogram. †1 patient reclassified from first paper because date of death >30 days. ‡1 patient reclassified from first paper because date of re-bleed <30 days. §1 patient allocated neurosurgery opted for coiling.

***Table 5:*** **Confirmed rebleeding from target aneurysm**

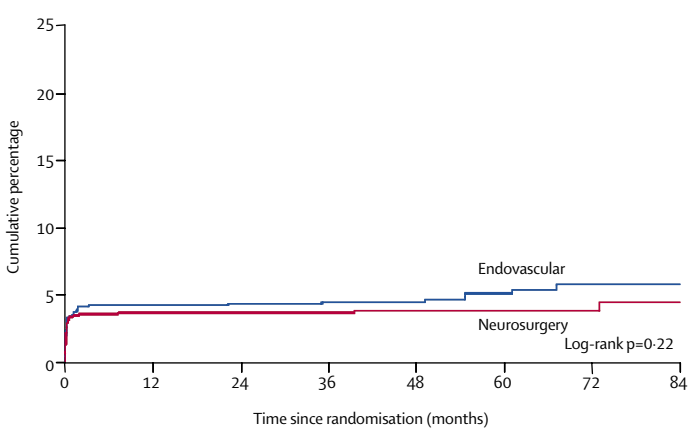
information was available on 881 (89% of surviving patients). Most angiograms (690 of 881) were done between 2 months and 1 year. 28 were done before discharge, 80 before 2 months, 58 from 1 to 2 years, and 25 after 2 years. MRA was used as an alternative to intra-arterial angiography in 47 patients in the endovascular group. In the neurosurgical group, 450 angiograms were done in 965 potentially eligible patients (47%). 142 were done before discharge, 61 before 2 months, 199 from 2 to 12 months, and 48 from 1 to 5 years.

After endovascular coiling, 66% of follow-up angiograms showed complete angiographic occlusion, 26% showed subtotal occlusion or a neck remnant, and 8% showed incomplete occlusion with aneurysm refilling. We have included all angiograms done during the first year as well as those done later when they were the first that a patient had had. Analyses of angiographic data after the first angiogram will be covered in a future paper. In the 450 patients in the neurosurgical group who had follow up angiograms, 82% were completely occluded, 12% had a neck remnant, and 6% were incompletely occluded. This group of neurosurgical patients is probably a selected population because angiography is not routinely done in all centres and was not required by the protocol. In the UK, post-clipping angiography is more likely to be done if there is doubt about whether the aneurysm has been occluded satisfactorily.

We have previously reported part of the data available on rebleeding.[1] These data were mostly for rebleeds during the first year in patients with follow-up to that time point. Rebleeds and patient follow-up beyond that time were few.

Here we report complete data on rebleeding within the first year in almost all patients and additional data beyond 1 year. After the first year there are 3258 patient years of follow-up for the endovascular group and 3107 patient years of follow-up for the neurosurgery group, with a mean follow-up of 4 years. All rebleeding events due to the target aneurysm are shown in table 5 and figure 3. Nine patients (seven allocated endovascular and two allocated neurosurgery) had confirmed rebleeding from the target aneurysm after 1 year (webtable). Rebleeding from another aneurysm was either definite or probable in three patients. A man aged 54 years with a ruptured middle-cerebral aneurysm was randomised to endovascular treatment and had successful coiling. On follow-up angiography he was found to have a new pericallosal aneurysm. This patient died after a further haemorrhage that happened 15 months after his original presentation. Autopsy confirmed haemorrhage from the pericallosal aneurysm. A woman aged 52 years who was randomised to neurosurgery had clipping of a posterior communicating artery aneurysm. She developed a second posterior-communicating aneurysm on the opposite side, which ruptured in year 3, had further clipping, and survived with mRS 1 at follow-up. A woman aged 61 years with a ruptured anterior-cerebral aneurysm who was allocated endovascular treatment had successful coiling. 2 years later her posterior communicating artery aneurysm ruptured and at follow-up her mRS was 4.

See Lancet Online for webtable




**Annual number at risk (rebleeding):**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Endovascular | 1073 (45) | 953 (1) | 865 (1) | 698 (0) | 524 (3) | 360 (2) | 201 (0) | 98 |
| Neurosurgery | 1070 (39) | 926 (0) | 821 (0) | 652 (1) | 495 (0) | 332 (0) | 188 (1) | 95 |

***Figure 3:*** **Cumulative rebleeding risk from target aneurysm**

| | Endovascular n=1073 | Neurosurgery n=1070 |
|---|---|---|
| Before first treatment | 3 (3) | 11 (6) |
| After procedure to before discharge | 16 (2) | 33 (2) |
| Discharge to 1 year | 27 (1) | 44 |
| After 1 year | 14 (1) | 24 |

Figures in parentheses indicate seizures associated with re-bleeding. *Onset of first seizure not associated with first subarachnoid haemorrhage.

***Table 6:*** **Seizure occurrence by treatment allocation***

Two patients died after a further haemorrhage thought to be from another aneurysm: one patient has been previously described,[1] the second patient was a woman aged 69 years who was allocated endovascular treatment and had coiling of a posterior-communicating aneurysm and a good outcome (mRS 1). She is known to have had four further aneurysms and to have died suddenly in year 4; the certified cause of death was intracranial haemorrhage but no CT or autopsy was done.

One patient died of a primary intracerebral haemorrhage (confirmed at autopsy) at age 76 years, 4 years after coiling of a middle cerebral aneurysm.

In summary, among the eight cases of rebleeding from the treated aneurysm after coiling (including one crossover from the neurosurgery group) three patients were independent at follow-up and five were dead or dependent.

Craniotomy or ventricular drainage is known to carry a small risk of later seizures. Table 6 shows the incidence of seizures at various time periods after randomisation in ISAT, by allocated treatment. There was a highly significant reduction in seizures in the endovascular group compared with the neurosurgery group after the first procedure (relative risk 0·52, 0·37–0·74). A separate paper will examine and describe the epilepsy results in more detail.

## Discussion

The final 1-year results presented in this paper reinforce our preliminary findings. Endovascular coiling, compared with neurosurgical clipping, for ruptured intracranial aneurysms that were anatomically suitable for either procedure leads to a significant reduction in the relative risk of death or dependency of 23·9% (12·4–33·9). This equates to an absolute risk reduction of 7·4% (3·6–11·2), which is equivalent to 74 patients avoiding death or dependency at 1 year for every 1000 patients treated.

After publication of the preliminary results of ISAT, there was much controversy and discussion in the worldwide neurosurgical community. Several position statements were issued by groups in neurosurgery and related specialties, including the American Association of Neurological Surgeons, the American Society Neuroradiology (ASNR) and American Society of Therapeutic and Interventional Neuroradiology (ASITN), and the respective German and Japanese societies.[6–8] These statements drew attention to the many questions that the early results did not answer, in particular the durability and long-term efficacy of coil treatment at preventing rerupture, applicability of the results, and possible challenges in the use of ISAT results to inform the treatment of all patients with subarachnoid haemorrhage. Criticisms mostly related to the proportion of eligible patients who were enrolled, which varied very widely between centres, and the expertise of the neurosurgeons who treated patients in ISAT, particularly those in the UK.

We have responded to these criticisms previously[9] but it is worth restating some key points. One of the main successes of ISAT is that it overcame the problems of enrolling patients into randomised trials by recruiting those for whom the best treatment was unclear. This uncertainty clearly also existed during the recruitment period into ISAT in the wider community of clinicians treating patients with subarachnoid haemorrhage. In such circumstances of collective and individual uncertainty, it is ethically justifiable to offer randomisation to the patient (and in fact, when a suitable trial exists it could be deemed unethical not to offer randomisation to such patients).[3] The uncertainties about treatment varied among centres and individual surgeons and interventionists within centres. Thus it was inevitable that enrolment rates for different centres would vary. This variation is a strength of ISAT and justifies large pragmatic trials, not a shortcoming or "fault", because it accommodates the breadth of professional opinion.

Contrary to widespread opinion, observational data cannot objectively and reliably show that one neurosurgeon's results are substantially better than another's for aneurysm clipping. The shortcomings of such data include the small annual volume of cases of aneurysm surgery for an individual neurosurgeon, the objectivity of the collection of outcome data, and the varied case-mix of the treated population (eg, patients' age, clinical grade, location of the aneurysm, timing of presentation, and surgery after the subarachnoid haemorrhage). Comparisons of observational data also ignore the reality of subarachnoid haemorrhage management—ie, that most patients with aneurysms are treated at the neurosurgical unit to which they are first admitted or transferred. Transfer of very sick patients to distant units is hazardous owing to clinical risks during transfer and delay in treatment. Comparisons with other randomised trials are also problematic. We expect that comparisons will be made between ISAT and the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST).[10] In that randomised trial, 1001 patients who had surgery for aneurysm in 30 centres were enrolled. The trial found that 85% of patients had good outcomes (Glasgow outcome score of 1 or 2) at 3 months with 6% mortality, which initially

seems better than ISAT. However, there is an important difference between ISAT and IHAST: in IHAST, randomisation took place in the anaesthetic room immediately before surgery and therefore included a group of patients who had already passed through a period of high risk. If we exclude deaths due to rebleeding before treatment in ISAT, then the mortality at 2 months would be very similar to IHAST: death of 65 (6·1%) of 1063 patients in the neurosurgery group and 68 (6·3%) of 1065 patients in the endovascular group.

After the preliminary results of ISAT were published, practice in the UK and several other countries changed substantially as objectively shown by the National Audit of subarachnoid haemorrhage, Royal College of Surgeons Clinical Effectiveness Unit, (Lindsay K, Langham J, personal communication). However, there are still wide variations in the availability and use of endovascular treatment among countries and within countries. Access to endovascular treatment has been hampered by a lack of trained endovascular operators or adequate neuroangiographic equipment, the cost of coils and other consumables associated with endovascular treatment compared with those for surgery (and the source of payment for these), and logistical barriers (eg, the availability of anaesthesia in neuroradiology departments).

In the subgroup analyses, the relative effects of treatment were heterogeneous by age, WFNS grade, and aneurysm location. However there is no robust evidence that neurosurgical treatment has advantages over endovascular treatment for these subgroups of patients. For example, although there was heterogeneity by age, there was no trend for treatment effect and age. Although the point estimate might suggest that there is less advantage for coiling than clipping in patients older than 70 years and with poor WFNS grade, the estimates of effect are very imprecise because of the relatively small number of such patients in the trial. During ISAT, many patients older than 70 years were not randomised because individual investigators expected that elderly patients would fare worse with surgery. Data from the International Study of Unruptured Intracranial Aneurysms (ISUIA) supported this view.[11] The ISUIA data showed significantly higher morbidity at 1 year among patients older than 50 years who had neurosurgery for an unruptured intracranial aneurysm, with incremental worsening of outcome in each decade after 50.

Dividing the data from any trial into subgroups makes it likely that the results in some subgroups will become non-significant simply because of the reduction in the amount of data and the increased imprecision of the result. Thus, although the effect of the treatments on patients with anterior-cerebral-artery aneurysm was not significant for the primary outcome measure, one of the treatments could still be more beneficial than the other. In addition, for patients with aneurysm of the anterior cerebral artery, there is a greater expectation that they will have cognitive impairment, other deficits of memory and executive functioning, and subtle personality changes, because the surgical techniques used to access the area of the anterior communicating artery might require resection or retraction of frontal lobe structures, such as the gyrus rectus and frontal gyri. A case-matched study of MRI changes and cognitive outcomes after clipping and coiling showed local damage or encephalomalacia exclusively after neurosurgery and more small infarcts in the vascular territory of the aneurysm in the surgical group, with no difference in the incidence of large infarcts.[12] There was also a trend towards poorer cognitive outcome in the surgical group, which was significant on four neuropsychological tests. An ISAT substudy is assessing the neuropsychological effects of the treatments and will be important in detecting subtle deficits that can affect social functioning and return to work.[4]

In summary, the subgroup analyses show no good evidence that the benefit from endovascular treatment does not apply across all the sub-groups.

A crucial issue for endovascular techniques is the uncertainty about the long-term durability of aneurysm occlusion with coils and whether it protects from further aneurysm rupture. ISAT gives the most reliable evidence to date to answer this question. Overall, there was no significant difference in the frequency of rebleeds between the groups. The angiographic outcomes of coil occlusion are not as good as those for surgery either in this study or in the other published large series with follow-up angiography.[5,13] However, the reported risk of rebleeding from the coiled aneurysm after 1 year is low despite several thousand patient years of follow-up. The rebleed rate is 0·2% per patient year with follow-up from 1 to 8 years with a mean of 4 years. Data from Finland have shown that the risk of further haemorrhage continues for up to 30 years after subarachnoid haemorrhage[14] and highlight the importance of the continued follow-up of the ISAT patients.

Patients who have an aneurysmal subarachnoid haemorrhage have a small risk of aneurysm recurrence and new aneurysm formation. The Dutch ASTRA group reported follow-up CT angiography on 610 patients 1–15 years after surgical clipping of a ruptured aneurysm and found an incidence of 16% of new aneurysms.[15] In 24 patients, aneurysms were present at the site of the previous clipping and in three of these, the postoperative angiogram had shown complete aneurysm occlusion. Thus, patients with aneurysmal subarachnoid haemorrhage are at some risk of further subarachnoid haemorrhage. Ronkainen and colleagues[16] reported that patients with a good outcome after subarachnoid haemorrhage who were followed up for up to 21 years (mean 7·5 years) had a standardised mortality rate that was twice that of a matched population. Therefore, it is

unreliable to extrapolate the ISAT results beyond the 7 years for which robust evidence is currently available. Ongoing assessment and follow-up will allow the continued monitoring of this issue for inclusion in future ISAT analyses. The angiographic findings for ISAT reported here are slightly better than those in two other large observational studies:[5,13] the frequency of incomplete treatment at follow-up angiography was 8% and probably reflects two factors that distinguish the ISAT series. First, most (90%) of the aneurysms treated in ISAT were less than 10 mm in diameter and occlusion results are known to be substantially better in patients with aneurysms of this size than in patients with large and giant aneurysms. Second, the ISAT results are more recent than those of the other studies and reflect improvements in the coils available and operator experience.

We have not yet analysed angiographic findings beyond the first follow-up angiogram but such analyses will allow comparison with those of Raymond and colleagues[5] who did angiography 1–3 years after coiling and reported deterioration in the angiographic occlusion. In two cases in ISAT, a coiled aneurysm that was completely occluded on 6-month follow-up angiography reruptured, and there were also several reports of late aneurysm recurrence after complete occlusion. Such late recurrence was also observed in the ASTRA study after surgical clipping.[15] Follow-up imaging, particularly non-invasive MRA might be justified as a routine procedure, particularly for young patients. Even though many patients had subtotal occlusion or neck remnant of the aneurysm at follow-up angiography after coiling, the risk of delayed rerupture seems to be low, at least in the medium term. Patients who have complete aneurysm occlusion on a follow-up angiogram in the first year can therefore be advised that the risk of rerupture is very low. In patients with subtotal occlusion or neck remnant, the risk seems to be low. Thus, any recommendation to retreat the aneurysm needs to be weighed carefully against the risks of further treatment, particularly in older patients.

In patients who had neurosurgical treatment, the likelihood of late rebleeding is extremely low; this event has occurred in only one patient in ISAT, who had a middle cerebral aneurysm after 6 years. This patient had not had follow-up angiography but the very low rate of rebleeds after clipping raises the question of whether patients who have had neurosurgical clipping should have follow-up intra-arterial angiography as routine, unless there are uncertainties at the time of surgery.

All patients enrolled in ISAT in the UK are now noted by the Office of National Statistics, all centres in Scandinavia, centres in Canada and Switzerland, and some French and German centres will continue long-term follow-up of their patients. Therefore, we expect that it will be possible to maintain complete ascertainment of deaths in more than 90% of the ISAT population.

The cumulative mortality curve to 7 years shows slightly more deaths in the neurosurgical group. The effect of rebleeding on death or dependent survival over this period seems small. These findings provide reassurance that late events, in particular late aneurysm rebleeding leading to death or dependency, are uncommon in both treatment groups and are unlikely to reverse the early benefit of endovascular treatment.

The ISAT data now give a reliable estimate of the risk of seizures occurring after allocation to craniotomy and clipping compared with endovascular coiling. The risk of seizures is significantly lower with coiling than with neurosurgery. This finding has important practical implications when seizures occur late after discharge, especially in those for whom the ability to drive is important. The ISAT data on seizures are unique in their scale and reliability and will also provide driving authorities with evidence to formulate advice and policy on whether, and for how long, patients should not drive after subarachnoid haemorrhage and its treatment.

The complete 1-year data from ISAT confirm and reinforce our preliminary findings. Endovascular coil treatment of ruptured intracranial aneurysms, when a patient is in good clinical grade and the aneurysm anatomy is suitable for endovascular treatment, is more likely than neurosurgical treatment to lead to independent survival at 1 year.

Because of a very small risk of late rerupture 1 year after coiling, follow-up to monitor aneurysm reopening might be appropriate.

Continued follow-up of patients in ISAT will give a unique data set of the long-term outcome of subarachnoid haemorrhage and will give even more robust evidence for patients and neuroscience clinicians who advise them.

These new analyses support the conclusion reached in the position statement of the ASNR and the ASITN: "The study data allow us to conclude that for patients with SAH [subarachnoid haemorrhage] and aneurysm anatomy indicating a high likelihood of success by endovascular techniques patients should be offered that option". The new analyses also address their caveat that "this must be tempered by the limited data for long term durability after 1 year", by providing these data. The updated results confirm that the changes in practice seen on the basis of the preliminary findings should have led to substantial reductions in death and dependency for patients with subarachnoid haemorrhage.

**Contributors**

Primary authorship was the responsibility of A J Molyneux and R S C Kerr. P Sandercock and M Clarke provided direct input into the writing, editing and decisions on content, and advice on clinical trial and sub-group analysis interpretation. L-M Yu was responsible for all statistical aspects and analysis. J A Yarold and M Sneade were responsible for data cleaning, editing, table preparation, and checking.

**Conflict of interest statement**

AJM has a consulting and advisory agreement with Micrus Inc, a manufacturer of detachable platinum coils, with stock interest in the company. He has a minor stockholding in Micro Therapeutics Inc and receives salary support from the Medical Research Council. RSCK, AJM, and JAY have received support for travel to meetings from Boston Scientific. No other conflicts of interest by investigators or authors have been notified to the coordinating centre.

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**References**

1 Molyneux AJ, Kerr RSC, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002; **360**: 1267–74.

2 International Subarachnoid Aneurysm Trial (ISAT). http://www.surgery.ox.ac.uk/nvru/isat (accessed Aug 24, 2005).

3 Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; **317:** 141–45

4 Scott RBS, Farmer E, Tovey C, Clarke M, Carpenter K. Methodology of neuropsychological audit in multicentre randomised clinical trials: a model derived from the International Subarachnoid Aneurysm Trial. *Clin Trials* 2004; **1**: 31–39.

5 Raymond J, Guilbert F, Weill A, et al. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke* 2003; **34:** 1398–403.

6 Harbaugh RE, Heros RC, Hadley MN. AANS position statement on the international subarachnoid aneurysm trial (ISAT). *Lancet* 2003; **361:** 783–84.

7 Derdeyn CP, Barr JD, Berenstein A, et al. The International Subarachnoid Aneurysm Trial (ISAT): a position statement from the executive committee of the American Society of Interventional and Therapeutic Neuroradiology and the American Society of Neuroradiology. *Am J Neuroradiol* 2003; **24:** 1404–08.

8 Raabe A, Schmiedek P, Seifert V, Stolke D. German society of neurosurgery section on vascular neurosurgery: position statement on the International Subarachnoid Aneurysm Trial (ISAT). *Zentralbl Neurochir* 2003; **64:** 99–103.

9 Molyneux A, Kerr R. More on ISAT. *Lancet* 2003; **361:** 784.

10 Todd MM, Hindman BJ, Clarke WR, Torner JC. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med* 2005; **352:** 135–45.

11 Wiebers DO, Whisnant JP, Huston J 3rd, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003; **362:** 103–10.

12 Hadjivassiliou M, Tooth CL, Romanowski CA, et al. Aneurysmal SAH: cognitive outcome and structural damage after clipping or coiling. *Neurology* 2001; **56:**1672–77.

13 Murayama Y, Nien YL, Duckwiler G, et al. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. *J Neurosurg* 2003; **98:** 959–66.

14 Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. *J Neurosurg* 2000; **93:** 379–87.

15 Wermer MJH, van der Schaaf IC, Velthius BK, Algra A, Buskens E, Rinkel GJE. Follow-up screening after subarachnoid haemorrhage: frequency and determinants of new aneurysms and enlargement of existing aneurysms. *Brain*; published online July 6, 2005, DOI:10.1093/brain/awh587.

16 Ronkainen A, Niskanen M, Rinne J, et al. Evidence for excess mortality after treated subarachnoid haemorrhage. *Stroke* 2001*;* **32:** 2850.