Articles

International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial

*International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group**

Summary

Background Endovascular detachable coil treatment is being increasingly used as an alternative to craniotomy and clipping for some ruptured intracranial aneurysms, although the relative benefits of these two approaches have yet to be established. We undertook a randomised, multicentre trial to compare the safety and efficacy of endovascular coiling with standard neurosurgical clipping for such aneurysms judged to be suitable for both treatments.

Methods We enrolled 2143 patients with ruptured intracranial aneurysms and randomly assigned them to neurosurgical clipping (n=1070) or endovascular treatment by detachable platinum coils (n=1073). Clinical outcomes were assessed at 2 months and at 1 year with interim ascertainment of rebleeds and death. The primary outcome was the proportion of patients with a modified Rankin scale score of 3–6 (dependency or death) at 1 year. Trial recruitment was stopped by the steering committee after a planned interim analysis. Analysis was per protocol.

Findings 190 of 801 (23·7%) patients allocated endovascular treatment were dependent or dead at 1 year compared with 243 of 793 (30·6%) allocated neurosurgical treatment (p=0·0019). The relative and absolute risk reductions in dependency or death after allocation to an endovascular versus neurosurgical treatment were 22·6% (95% CI 8·9–34·2) and 6·9% (2·5–11·3), respectively. The risk of rebleeding from the ruptured aneurysm after 1 year was two per 1276 and zero per 1081 patient-years for patients allocated endovascular and neurosurgical treatment, respectively.

Interpretation In patients with a ruptured intracranial aneurysm, for which endovascular coiling and neurosurgical clipping are therapeutic options, the outcome in terms of survival free of disability at 1 year is significantly better with endovascular coiling. The data available to date suggest that the long-term risks of further bleeding from the treated aneurysm are low with either therapy, although somewhat more frequent with endovascular coiling.

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*Members listed at end of paper

Correspondence to: Dr Andrew Molyneux, ISAT, Neurovascular Research Unit, Radcliffe Infirmary, Oxford OX2 6HE, UK (e-mail: isat@radiology.ox.ac.uk)

Introduction

Rupture of an intracranial aneurysm causing subarachnoid haemorrhage (SAH) occurs with a frequency of between six and eight per 100 000 in most western populations.[1] Neurosurgical intervention to clip the aneurysm and prevent further bleeding carries both risks and benefits. In the 1960s, McKissock and colleagues published a series of prospective randomised trials,[2–4] which showed that the benefits of surgery outweighed the risks in some circumstances (depending on the location of the aneurysm).

Since then, there have been incremental reductions in the risk of surgery for ruptured intracranial aneurysms. These risk reductions have been achieved by advances in many aspects of management, including the introduction of the operating microscope, the development of better microsurgical techniques and instruments, advances in anaesthetic and intensive-care management, improved diagnostic facilities, and the development of vascular neurosurgery as a subspecialty. Nonetheless, even with these advances, relatively few patients return to a normal lifestyle after SAH, and many have persistent disabling neurological or cognitive defects.[5] In 1990, a detachable platinum coil device, the Guglielmi detachable coil (GDC; Boston Scientific/Target Therapeutics, Freemont, CA, USA)[6] was introduced into clinical use. It was first used as an investigational device in the USA, and then introduced in Europe in 1992 and was approved by the US Food and Drugs Administration in 1995. This device allowed the development of endovascular techniques for the occlusion of intracranial aneurysms, which offered the prospect of reducing the risk of further rupture without the need for craniotomy. Since 1995, endovascular coiling has become widely used in patients with ruptured and unruptured intracranial aneurysms.[7–9]

The introduction of an alternative to neurosurgical clipping raised the questions of how, when, and in whom endovascular treatment should be used. The frequency of use of this technique varies widely around the world and there is an urgent need for high quality evidence to establish the safety and efficacy of endovascular treatment compared with neurosurgical treatment, and to determine which treatment provides the best outcomes for patients. Only one small randomised trial of 109 patients with a ruptured intracranial aneurysm comparing the detachable coil technique with neurosurgical clipping has been published to date.[10,11]

This paper describes the protocol, methods, and primary outcome results of the International Subarachnoid Aneurysm Trial (ISAT). ISAT is a multicentre, randomised clinical trial, which compares a policy of neurosurgical clipping with a policy of endovascular treatment with detachable platinum coils in

patients with ruptured intracranial aneurysms considered suitable for either treatment.

Methods

Aims and objectives

The aim of ISAT was to compare the safety and efficacy of a policy of endovascular treatment of ruptured intracranial aneurysms versus a policy of conventional neurosurgical treatment in patients who were suitable for either treatment. The primary objective was to determine whether a policy of endovascular treatment compared with a policy of neurosurgical treatment reduced the proportion of patients dependent or dead, as defined by modified Rankin scale 3–6 (panel), at one year by 25%.[12–15] In addition, ISAT set out to assess the differences between endovascular treatment and neurosurgery in prevention of rebleeding from the treated aneurysm, quality of life at 1 year (using a Euroqol measure), the frequency of epilepsy, cost-effectiveness, and neuropsychological outcomes (a substudy conducted in seven UK centres). ISAT will also examine the long-term outcome of treatment (over at least 5 years) with a particular assessment of the frequency of further haemorrhage, and it will examine the long-term significance of angiographic results.

Randomisation commenced in 1994 with a pilot phase, and the full study started in 1997. The trial protocol was published in 1999,[16] and is also available via the ISAT website.[17]

Patients

Patients were eligible for the trial if: (1) they had a definite subarachnoid haemorrhage, proven by computed tomography (CT) or lumbar puncture, within the preceding 28 days; (2) they had an intracranial aneurysm, demonstrated by intra-arterial or by CT angiography, which was considered to be responsible for the recent subarachnoid haemorrhage; (3) they were in a clinical state that justified treatment, at some time, by either neurosurgical or endovascular means; (4) they had an intracranial aneurysm that was judged by both the neurosurgeon and the interventional neuroradiologist to be suitable for either technique on the basis of its angiographic anatomy; (5) there was uncertainty as to whether the ruptured aneurysm should be treated by neurosurgical or endovascular means; and (6) they gave appropriate informed consent, according to the criteria laid down by the local ethics committee. If a patient was not competent to give consent (because of his or her cognitive state), assent from relatives was obtained if the ethics committee regarded it as an acceptable alternative.

Questionnaire used to assess modified Rankin scale after Lindley and colleagues[14]

Scale	Functional outcome	Questionnaire response
0	No symptoms	I have no symptoms and I cope well with life
1	Minor symptoms	I have a few symptoms but these do not interfere with my everyday life
2	Some restriction in lifestyle	I have symptoms which have changed my life but I am still able to look after myself
3	Significant restriction in lifestyle	I have symptoms which have significantly changed my life and prevent me from coping fully, and I need some help looking after myself
4	Partly dependent	I have quite severe symptoms which mean I need to have help from other people but I am not so bad as to need attention day and night
5	Fully dependent	I have major symptoms which severely handicap me and I need constant attention day and night
6	Dead	. .

Patients were not eligible if any of the following criteria were met: (1) SAH occurred more than 28 days before randomisation; (2) the patient was regarded as unsuitable for one or both treatments; (3) consent was refused; or (4) the patient was participating in another randomised clinical trial of a treatment for subarachnoid haemorrhage.

If the patient had more than one aneurysm, the responsible clinician had to judge which aneurysm had bled. This became the "target aneurysm". If the treating clinician intended to treat additional aneurysms during the first procedure, and additional aneurysms were suitable for both neurosurgical and endovascular treatments, the patient could be entered into ISAT. Further aneurysms could be treated subsequently by whichever technique was judged appropriate for that aneurysm.

All participating centres included in ISAT were major neurosurgical centres, treating large numbers of patients after aneurysmal SAH, each centre treating between 60 and 200 cases annually. ISAT was a pragmatic trial of the care available to the population served by the participating centres. Centres had to have expertise in both neurosurgical and endovascular management of ruptured aneurysms.

Only accredited neurosurgeons with experience of aneurysm surgery were permitted to manage patients in the trial. Endovascular operators had to have done a minimum of 30 aneurysm treatment procedures, before they were permitted to treat patients in the trial. Because of the heterogeneity in SAH management and wide outcome variation depending on the patient's clinical grade, age, aneurysm location, and the relatively small numbers of procedures each year for individual surgeons or endovascular operators, it was deemed inappropriate to demand, as a prerequisite to being a participating centre, outcome figures from individual operators for managing patients in ISAT.

Patients with SAH present as acute medical emergencies and they are frequently admitted to a general hospital before transfer to the nearest available neurosurgical unit. In Europe, these units are invariably based in large regional centres, serving defined populations. The population served by each ISAT centre ranged between 1 and 3 million and the total population served by all participating centres in ISAT was about 80 million. Unlike elective surgery, such as carotid endarterectomy, patients did not generally have the option of choosing to which hospital they were admitted or which clinician would treat them. Services are regionally planned, and this arrangement explains the higher annual case volumes seen in the participating ISAT centres than are reported by many North American centres.[18–20]

Procedures

All random assignments were done through a 24-h telephone randomisation service, provided by the Clinical Trial Service Unit at the University of Oxford. Key

baseline data were recorded before the treatment allocation was issued. A minimisation algorithm was used to ensure balance between the two groups. This algorithm was based on age, sex, clinical grade on the World Federation of Neurological Surgeons (WFNS) grading scale,[21] size and location of the target aneurysm, and extent of blood on the CT scan.

The main outcome measure was the modified Rankin scale.[12–15] This measure was assessed at 2 months, 1 year, and annually thereafter. Data were collected by a validated method by use of a postal questionnaire[14] mailed to the patient with a Euroqol Health state questionnaire[22] and a questionnaire concerning employment status, further hospital admissions, or any episodes of rebleeding. The full text of the questionnaires and the protocol are available on the ISAT website.[17] If the patient was unable to complete the questionnaire, their carer could help them complete it. The use of such proxies for the completion of these instruments has also been validated.[15]

We specifically collected data on the resource-use implications of both the endovascular and neurosurgical procedures. These data include the number of admissions, the number of inpatient and intensive-care unit (ICU) days per admission, procedure time, details of adverse events and additional procedures, use of thrombolytic agents, number of coils used, number and details of readmissions, and whether the patient was discharged to rehabilitation. This questionnaire was administered to all patients 2 months and 1 year after randomisation.

Some patients underwent further procedures either on the target aneurysm or for treatment of other aneurysms after their first procedure. These additional procedures were all recorded and any sequelae were included in the outcome results. Information on additional procedures will form part of the health economic evaluations to be reported in a later paper.

Particular care was taken to identify ISAT patients who had a further SAH. When a rebleed occurred, a separate case record form was completed. Such rebleeds were classified into one of three broad categories: (1) preprocedural if it occurred after randomisation but before the first trial procedure; (2) procedural if it occurred during the first (or subsequent) procedures; and (3) postprocedural. Patients who had a postprocedural rebleed were further divided into those who had a rebleed in the first 30 days, those who had a rebleed after 30 days but before 1 year, and those who rebled more than 1 year after randomisation. All the reported postprocedural rebleeds were individually adjudicated by trial research staff, a neurosurgeon, and an endovascular therapist after review of the case record forms, CT scans, and any relevant angiograms. This analysis allowed separate consideration of those in whom the rebleed was due to delayed rupture of the target aneurysm, from another aneurysm, or where the further bleeding occurred into an ischaemic area or after thrombolytic treatment. Further bleeds that occurred during another procedure on the target or other aneurysm have been identified separately.

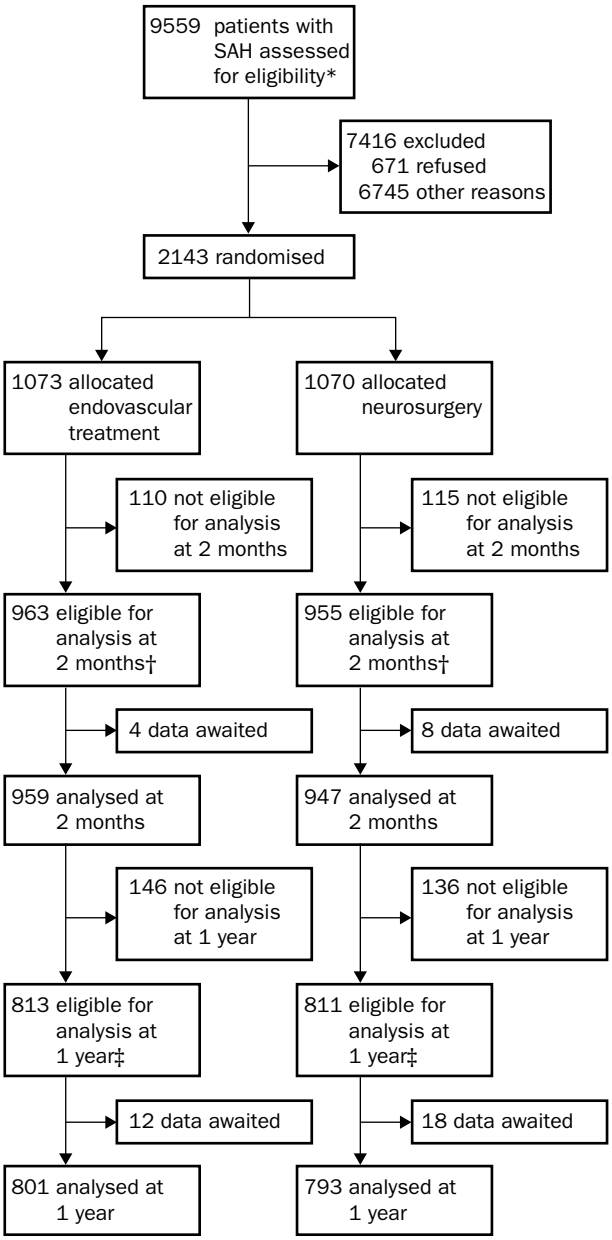
All hospital admissions that occurred at any time after randomisation were recorded and data collected on length of stay, any further procedures, and adverse events.

The findings from the diagnostic angiograms were recorded, as were the angiographic findings after endovascular treatment, including an estimate of aneurysm occlusion. Any subsequent angiographic findings were recorded on follow-up forms. Follow-up angiography was required in all endovascular patients, except where clinically contraindicated. Angiography was also requested in neurosurgical patients, but this procedure was not mandatory, since it would have meant a change in practice for many centres. The angiographic images from all patients are stored in a centrally held database and will be the subject of a detailed analysis in the future.

Statistical analysis

Power calculations were based on the assumption that the trial should be able to detect a reduction in the proportion of patients dependent or dead at 1 year from 24% after surgical treatment to 19% after endovascular treatment. The trial aimed to recruit 2500 patients to achieve a 90% power at a 0·01% level of significance to detect a 25% relative improvement in outcome at 1 year.

The data are stored in the Clinical Trials Management System (CTMS) of the Diabetes Trials Unit at the



Trial profile

SAH=subarachnoid haemorrhage. *Based on those centres that returned ascertainment logs. †Based on patients randomised before Dec 1, 2001. ‡Based on patients randomised before Feb 1, 2001.

University of Oxford. All variables used in the analysis have been subjected to checking for distribution, range, and missing values within the CTMS. The data for this report were extracted from the CTMS on Sept 8, 2002, and include some data on all 2143 randomised patients. Data are shown as counts (with proportion as a percentage) or median with IQR. Tables for outcomes subsequent to discharge include data from only patients who might have been expected to have data at that visit. For example, the assessment of outcome at 1 year includes data from those patients who had been randomised before Feb 1, 2001.

All analyses were done with SAS software. Ordered categorical data were examined by Mantel-Haenszel χ^2 statistics. Mann-Whitney *U* tests were used to compare the non-parametric data, and *t* tests were used to compare normally distributed data. Life table methods and Cox's proportional hazard models were used to examine time-to-event data.

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 sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The Data Monitoring Committee met on April 29, 2002, to consider the results of a planned interim analysis. They unanimously agreed that the trial steering committee be advised of the interim results. The steering committee met on May 2, 2002, and decided that recruitment should stop, but that follow-up must continue. Recruitment ceased immediately.

The proportion of all aneurysmal SAH patients entered in the trial varied widely, between 1% and 44%, among the centres. 16 centres were able to return complete ascertainment logs. The 16 centres that returned incomplete logs randomised 649 patients. The 11 centres that did not return logs at all randomised only a further 54 patients. During the period of randomisation, 9559 patients were admitted with proven aneurysmal SAH to the centres that made adequate returns and were recorded in the ascertainment database at the time of manuscript preparation. Of these 9559 patients, 7416 were excluded and 2143 were randomised (figure).

Baseline data, collected at the time of randomisation, were available for all 2143 patients from the 43 centres. Age, sex, and WFNS grade are shown in table 1. There were no significant imbalances between the two treatment groups. Table 2 gives the details of the aneurysm location in all 2143 patients. Almost all (97·3%) were in the anterior circulation, with the most common sites being anterior cerebral, internal carotid, and middle cerebral.

Most patients (2042 [95·3%]) received their allocated treatment as the first procedure. However, nine patients allocated endovascular treatment received neurosurgery, and 38 allocated neurosurgery received endovascular treatment ($p<0·0001$ for difference between groups). Patients who crossed over were analysed in the group to which they were originally allocated. There was no significant heterogeneity in crossover rates between the 18 centres in which there were crossovers ($\chi_1^2=16·9$ on 17 df, $p=0·461$). Reasons for crossovers varied. For crossovers from neurosurgery to endovascular treatment, 15 were for clinical reasons, 18 were because of the patient's preference, and the reasons were unknown for the other five. For those changing from endovascular to neurosurgical treatment, the reason was a clinical decision in one, the patient's decision in four, and due to equipment malfunctions in four.

There was a small but significant difference in the time between randomisation and the first procedure in the two groups ($p<0·0001$, Mann-Whitney *U* test). For those allocated to endovascular treatment, the mean interval was 1·1 days (IQR 0–1, range 0–30), and for those allocated to neurosurgery, the mean interval was 1·7 days (0–2, 0–41). Table 3 shows the technical outcome of the first procedure, based on the actual procedure performed, and includes the patients who crossed over.

	Endovascular treatment (n=1073)	Neurosurgery (n=1070)
Male sex	400 (37%)	399 (37%)
Age (years)*	52 (44–60, 18–87)	52 (43–60, 18–84)
WFNS grade		
1	674 (63%)	661 (62%)
2	269 (25%)	280 (26%)
3	66 (6%)	68 (6%)
4	38 (4%)	36 (3%)
5	11 (1%)	9 (1%)
6 (not assessable)†	15 (1%)	16 (1%)
Maximum target aneurysm lumen size (mm)		
⩽5	552 (51%)	572 (53%)
6–10	438 (41%)	426 (40%)
⩾11	83 (8%)	72 (7%)
Number of aneurysms detected		
1	836 (78%)	850 (79%)
2	173 (16%)	170 (16%)
3	44 (4%)	35 (3%)
⩾4	20 (2%)	15 (1%)
Time between SAH and randomisation (days)*	2 (1–4, 0–26)	2 (1–5, 0–28)

WFNS=World Federation of Neurological Surgeons clinical grading scale.[18] *Median (IQR, range). †Patient ventilated and clinical state could not be assessed.

Table 1: **Baseline characteristics**

	Right	Midline	Left	Total
Anterior cerebral artery				
Anterior communicating	219	549	205	973
Proximal to anterior communicating	9	..	7	..
Pericallosal	46	..	49	..
Subtotal	..	..	..	1084 (50·5%)
Internal carotid artery				
Proximal or ophthalmic region	12	..	18	30
Posterior communicating region	313	..	223	536
Bifurcation	34	..	45	79
Other internal carotid	27	..	26	53
Subtotal	286	..	304	698 (32·5%)
Middle cerebral artery				
Proximal to bifurcation	14	..	14	..
Bifurcation	163	..	94	..
Distal to main bifurcation	7	..	11	..
Subtotal	184	..	119	303 (14·1%)
Posterior circulation				
Basilar bifurcation	..	17	..	..
Basilar trunk	..	1	..	..
Superior cerebellar	..	5	..	..
Posterior cerebral	1	..	3	..
Posterior inferior cerebellar	9	..	22	..
Subtotal	..	..	..	58 (2·7%)
Total	..	..	..	2143 (100%)

Table 2: **Aneurysm locations**

Outcome	Number of patients
Endovascular procedure	
Completed	1005 (92·5%)
Failed to catheterise target aneurysm	29 (2·7%)
Aneurysm catheterised but anatomy unsuitable	36 (3·3%)
Not attempted*	16 (1·5%)
Total	1086 (100%)
Neurosurgical procedure	
Clipped	968 (96·4%)
Wrapped	14 (1·4%)
Not completed (partial clipping or wrapping)	14 (1·4%)
Not attempted*	8 (0·8%)
Total	1004 (100%)

*Anaesthesia started but procedure not completed—eg, because of change in patient's condition or presence of severe vasospasm preventing immediate endovascular treatment.

Table 3: **Technical outcome of first procedure**

170 patients had a further procedure on the same aneurysm, 154 during the first year and 16 more than 1 year after randomisation. Of the patients allocated to endovascular treatment, 121 underwent a further procedure during the first year compared with 33 who were allocated neurosurgery. The numbers and timing of the further procedure are shown in table 4. Two patients allocated to neurosurgery who crossed over to endovascular treatment required a second endovascular procedure during the first year and one further patient required this after the first year. The clinical outcome of further procedures during the first year is included in the 1-year primary outcome data. The median time between the randomisation and the second procedure did not differ between the two randomised groups (p=0·51, Mann-Whitney *U* test).

Of the 1918 patients for whom data should have been available on outcome at 2 months (ie, those randomised before Dec 1, 2001), data were available for analyses on 1906 (99·4%) patients (figure; table 5). 244 of 959 (25·4%) patients allocated to endovascular treatment were dependent or dead at 2 months, compared with 345 of 947 (36·4%) allocated to neurosurgery (relative risk 0·698 [95% CI 0·609–0·801], p<0·0001).

Of the 1624 patients for whom data should have been available on outcome at 1 year (ie, those who were randomised before Feb 1, 2001) data were available for analysis on 1594 patients (98·2%). 1-year data are awaited or missing for 12 patients allocated to endovascular treatment and 18 patients allocated to neurosurgery (figure). 433 (27·2%) of the 1594 patients with data analysed at 1 year were dependent or dead. This rate is similar to the 20–25% 1-year rate assumed for the sample size calculations (table 6). 190 of 801 patients (23·7%) allocated to endovascular treatment were dependent or dead or at 1 year, compared with 243 of 793 (30·6%) allocated to neurosurgery (relative risk 0·774 [0·658–0·911], p=0·0019). The relative risk reduction was 22·6% (8·9–34·2), with an absolute risk reduction of 6·9% (2·5–11·3). 1-year case fatality rates did not differ significantly between the two treatment groups (8·1% [6·3–10·2] and 10·1% [8·1–12·4] for endovascular treatment and neurosurgery, respectively).

	<30 days	30 days –1 year	>1 year	Total
Allocated endovascular				
Second procedure endovascular	14	30	9	53
Second procedure neurosurgery	67	10	6	83
Allocated neurosurgery				
Second procedure endovascular	24	5	1	30
Second procedure neurosurgery	4	0	0	4

Table 4: **Time to second procedure on same aneurysm**

	Endovascular treatment (n=959)	Neurosurgery (n=947)
Modified Rankin scale		
0 No symptoms	192 (20·0%)	138 (14·6%)
1 Minor symptoms	275 (28·7%)	245 (25·9%)
2 Some restriction in lifestyle	248 (25·9%)	219 (23·1%)
(0–2 inclusive)	*715 (74·6%)*	*602 (63·6%)*
3 Significant restriction in lifestyle	95 (9·9%)	172 (18·2%)
4 Partly dependent	29 (3·0%)	39 (4·1%)
5 Fully dependent	48 (5·0%)	55 (5·8%)
6 Dead	72 (7·5%)	79 (8·3%)
(3–6 inclusive)	*244 (25·4%)*	*345 (36·4%)*

Data in Italics are primary outcome.

Table 5: **Outcome at 2 months in 1906 patients**

The following subgroups were prespecified and will be reported when the full ISAT dataset is complete: WFNS grade at randomisation, age-groups by decade (<40, 40–49, 50–59, 60–69, ⩾70 years), amount of blood on CT scan (Fischer grade), and lumen size of aneurysm and its site. There is currently no strong evidence from any of these prespecified subgroup analyses to suppose that 1-year outcomes are better for any subgroup of patients allocated to neurosurgery versus endovascular treatment. To assess the role of a centre's contribution, we compared the effect of treatment in the six largest recruiting centres and the sum of all the smaller centres, and found no evidence of heterogeneity of treatment effect.

The frequency of non-procedural rebleeding is shown in table 7, together with the associated case fatality. Of the 20 patients allocated endovascular treatment who rebled after the first procedure and before 30 days, in five the procedure had failed to occlude the aneurysm (no coils were placed) and the patients rebled before neurosurgery, in seven there was incomplete coil occlusion of the aneurysm, and in three the aneurysm was judged to be completely occluded. Five patients who had received thrombolytic therapy to treat a thromboembolic complication after endovascular treatment rebled and all of these patients died. Of the six patients allocated neurosurgery who rebled before discharge, three had incomplete aneurysm occlusion (two had been wrapped and one clipped), and three patients had complete neurosurgical clipping.

Of the six patients allocated endovascular treatment who rebled after 30 days and before 1 year, one had failed coil treatment but had not undergone neurosurgery, two had incomplete coil occlusion, and three were judged to have complete aneurysm occlusion. Of the four patients allocated neurosurgery, two had complete occlusion after treatment and two had incomplete occlusion. Rebleeding

	Endovascular treatment (n=801)	Neurosurgery (n=793)
Modified Rankin scale		
0 No symptoms	207 (25·8%)	152 (19·2%)
1 Minor symptoms	217 (27·1%)	220 (27·7%)
2 Some restriction in lifestyle	187 (23.4%)	178 (22·4%)
(0–2 inclusive)	*611 (76·3%)*	*550 (69·4%)*
3 Significant restriction in lifestyle	80 (10·0%)	106 (13·4%)
4 Partly dependent	24 (3·0%)	32 (4·0%)
5 Fully dependent	21 (2·6%)	25 (3·2%)
6 Dead	65 (8·1%)	80 (10·1%)
(3–6 inclusive)	*190 (23·7%)*	*243 (30·6%)*

Data in Italics are primary outcome.

Table 6: **Outcome at 1 year in 1594 patients (primary outcome)**

	Endovascular treatment	Neurosurgery
Before first procedure	14 (7)	23 (16)
After procedure up to 30 days	20 (10)	6 (3)
30 days to 1 year	6 (5)	4 (2)
Total up to 1 year	40 (22)	33 (21)
After 1 year	2 (0)	0

Numbers in parentheses indicate deaths. All deaths from rebleeding occurred within first week except for one at 20 days. Rebleeding was confirmed on CT scanning in all cases.

Table 7: **Non-procedural bleeding from target aneurysm**

after 1 year has been reported so far in five patients of the 1594 who have passed the 1-year primary outcome assessment. Two of these patients bled from another aneurysm. Two patients had undergone endovascular treatment: one had incomplete occlusion on follow-up angiography, and the other had complete occlusion but developed a recurrence of the aneurysm that bled at 3 years. Both patients were treated by neurosurgery and are alive and independent. A further patient who had undergone neurosurgery (allocated endovascular) had a second aneurysm and rebled at 3 years and died; we could not determined which aneurysm had bled. The risk of rebleeding from the ruptured aneurysm after 1 year was two per 1276 and zero per 1081 patient-years for patients allocated endovascular and neurosurgical treatment, respectively (table 7). Late rebleeding will continue to be monitored carefully and will be the subject of later reports.

Discussion

The results show that endovascular intervention with detachable platinum coils in patients with ruptured intracranial aneurysms can improve the chances of independent survival compared with neurosurgical intervention to clip the neck of the aneurysm. At 1 year, the relative risk of dependence or death was reduced by 22·6%, with an absolute risk reduction of 6·9%. This result, achieving the primary ISAT objective, led to trial recruitment being stopped early by the steering committee.

The results of this trial can be generalised to patients similar to those enrolled. These were patients with ruptured aneurysms that were judged to be suitable for either treatment by the clinicians caring for them. The baseline characteristics of those randomised, showed that they were overwhelmingly of good clinical grade with small anterior circulation aneurysms. Patients with ruptured posterior circulation aneurysms, and, to a lesser extent, middle cerebral aneurysms and those in poor clinical grade, are under-represented in the ISAT cohort. Most participating centres considered endovascular treatment the favoured option for posterior circulation aneurysms,[23] particularly aneurysms arising from the basilar artery because of the high surgical risk, and hence regarded it as unethical to include such patients in ISAT. Patients with middle cerebral aneurysms, in whom the anatomy of the aneurysm neck is more often unfavourable for endovascular treatment, are under-represented.[24] For poor-grade patients and elderly patients, early surgical treatment was frequently felt inappropriate, but early endovascular treatment was sometimes feasible.

The analysis of the primary outcome at 1 year has allowed not only direct treatment effects to be compared, but also the likehood and effects of any subsequent procedures and the occurrence of early rebleeding, which was more common after endovascular treatment. Most published reports of the results of neurosurgical or endovascular treatment of ruptured aneurysms are based on case series with their inherent bias in selection of patients and wide variation and poor definition of the outcome assessment method used. This bias makes accurate comparison of neurosurgical treatment with endovascular treatment of aneurysms difficult outside the context of randomised trials, when the outcome differences between two techniques are modest. Several studies have tried to achieve this by using large observational databases of aneurysm treatment, and then trying to make independent assessments of relative outcomes. Results of these studies have all suggested that the risk of dependency or death is higher after neurosurgical treatment than after endovascular treatment for both ruptured and unruptured aneurysms.[19,20] Randomised studies of sufficient size are essential if accurate and objective information and advice is to be provided to patients and their relatives to decide which treatment course to pursue.

The patients included in ISAT are not a random sample of all patients in the community with SAH due to rupture of an aneurysm, but were selected in accordance with the eligibility criteria. Once a patient was included in the trial, treatment allocation was centrally randomised, follow-up was rigorous, and, with respect to the primary outcome, unbiased between the two treatment groups. The results from this trial should not be interpreted as indicating that neurosurgery for aneurysms should cease; there will be a proportion of patients who, for clinical or anatomical reasons, are unsuitable for coil treatment.

The case fatality rates in ISAT did not differ significantly between the two groups: the overall rate was 9·03% at 1 year (95% CI 7·79–10·27). This is similar to those published from European and North American neurosurgical centres after the trials of the drug tirilazad.[25–27] In North America, case fatality in 676 patients with WFNS grades 1–3 was 10·1% (7·9–12·5).[25] Another North American study[26] of 823 female patients reported case fatality rates in patients with WFNS grades 1–3 of 7·8% and 10·5% in the tirilazad and placebo groups, respectively. Although a case fatality rate of 18% was reported from European centres undertaking a similar trial, this rate included all WFNS grades,[27] and good-grade patients were not separately identified. Comparison of morbidity data across series will be unreliable because of wide variations in the method of outcome collection.

There were no significant differences in the frequency of preprocedural rebleeding between the groups. The risk of rebleeding in the month after the randomised procedure and before discharge was higher after allocation to an endovascular treatment than a neurosurgical treatment policy for various reasons. Several patients rebled after failure of coil treatment while awaiting neurosurgery, suggesting that, where possible, such further procedures should be done promptly unless there are clinical contraindications. Also notable was the increased case fatality that occurred due to rebleeding after the use of thrombolytic therapy to treat procedural thromboembolic complications or parent-vessel occlusion. This phenomenon has been widely recognised by interventionists in recent years, and thrombolytic agents have largely been abandoned in favour of the new powerful antiplatelet agents such as abciximab.[28]

The crucial results are the relative and absolute effects on the frequency of delayed rebleeding from the treated aneurysm and the effect this has on clinical outcome. A major reason for choosing a 1-year primary outcome at the design stage of the trial was to ensure that any difference in early rebleeding between the two treatment strategies would be taken into account. The risk of late rebleeding exists after all aneurysm treatments, as does the risk of new aneurysm formation. These risks are low,

as is the risk of recurrent haemorrhage from aneurysm remnants after surgery.[29] Rebleeding risks after endovascular treatment have been reported, but usually in association with defined aneurysm recurrence.[30] The risk of rebleeding more than 1 year after endovascular treatment in ISAT is so far low. This risk will be monitored carefully in the longer term, with planned annual follow up of all patients for at least 5 years to provide reliable prospective data on the risk of late rebleeding and its correlation with angiographic findings.

ISAT compared a policy of an endovascular treatment strategy with detachable platinum coils with a strategy of craniotomy and microneurosurgical clipping. Various technical evolutions of endovascular treatment have occurred since ISAT started. A wider range of coil shapes and sizes, and much softer coils have been introduced to improve the range and effectiveness of the device. Improvements in technique also included the use of balloon remodelling[31] to retain the coils during placement. This modification has enabled the treatment of broader-necked aneurysms and increased the anatomical range of aneurysms that are suitable for endovascular coil occlusion. Technological change has also occurred with improved angiographic radiography equipment, the more widespread use of biplane equipment, very high quality fluoroscopy, and three-dimensional rotational angiography. Newer endovascular devices are likely to become available in the future, and could improve durability, but are unlikely to have any significant effect on procedural morbidity.

Neuroanaesthesia and intensive-care management techniques have also evolved, but apply equally to both groups. Surgical techniques have also developed in terms of approaches and access. However, an observational study of unruptured aneurysm treatment in California[19] showed no change in surgical outcomes from 1990 to 1998. The experience of the endovascular operators over the duration of the trial has also increased and the same study reported a significant improvement over that time in the outcomes after endovascular treatment.

Although the trial has achieved its primary objective, continued follow-up will produce valuable additional information. Many aspects of the existing data also remain to be analysed when the full dataset is available. These aspects will include the outcomes in predefined subgroups, the incidence of epilepsy, assessments of delayed ischaemic neurological deficit from vasospasm, any change in relative outcomes of the duration of the trial, and examination of detailed angiographic data to determine its relation to the early or late rebleeding risk. The precise neuropsychological assessment being undertaken will allow comparisons of any subtle differences in the effects of the neurosurgical and endovascular interventions. Health economic assessment will produce cost utility data to help inform health care providers and society, and will provide information concerning the proportion of patients returning to work or those requiring continued care.

The results presented here indicate that, for the types of patients in ISAT, with ruptured intracranial aneurysms suitable for both treatments, endovascular coil treatment is significantly more likely to result in survival free of disability 1 year after the subarachnoid haemorrhage than neurosurgical treatment. Longer-term follow up, however, is vital to answer the question of durability of benefit.

International Subarachnoid Aneurysm Trial Collaborative Group
Writing Committee—Andrew Molyneux, Richard Kerr, Irene Stratton, Peter Sandercock, Mike Clarke, Julia Shrimpton, Rury Holman.

Principal investigators—Andrew Molyneux, Richard Kerr (Oxford Radcliffe Hospitals NHS Trust, Oxford, UK).
Central Coordinating Team—Julia Shrimpton (Trial Manager), Mary Sneade (Assistant Trial Manager), Caroline Cowsill, Joan Rischmiller (research nurses), Fiona Bacon (UK Coordinator and Co-trial Manager 1994–Sept 2000), Irene Stratton (statistician).
MRC Trial Steering Committee—John Pickard (Chairman), Barbara Sahakian (University of Cambridge, UK); Peter Sandercock, Gordon Murray (University of Edinburgh, UK); Evelyn Teasdale (Southern General Hospital, Glasgow, UK); Mark Sculpher (Brunel University (UK).
Data Monitoring Committee—Charles Warlow (Chairman; University of Edinburgh); Richard Greenhall (Radcliffe Infirmary, Oxford); Richard Gray (University of Birmingham); Donald Shaw (Walton Centre for Neurology and Neurosurgery, Liverpool, UK); Allan Fox (University of Toronto, Canada).
ISAT Executive Group—Andrew Molyneux, Richard Kerr, Julia Shrimpton, Katherine Carpenter (Radcliffe Infirmary, Oxford); Irene Stratton, Rury Holman (Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford); Jane Wolstenholme, Alastair Gray (University of Oxford); Mike Clarke (UK Cochrane Centre and Clinical Trial Services Unit, Oxford).
Coordinating team for France—Didier Dormont (principal investigator for French centres); Cecile Jourdain; Jean-Marc Lacombe.

Participating Centres and Investigators
Nottingham, UK, Queens Medical Centre (272)—Tim Jaspan, Norman McConachie, Robert Lenthall, Barrie White, Nick Phillips, Sharon Stephenson.
Oxford, UK, Radcliffe Infirmary (249)—Andrew Molyneux, Richard Kerr, James Byrne, Peter Teddy, Mary Sneade.
Salford, UK, Hope Hospital and Manchester Royal Infirmary (222)—David Hughes, Roger Laitt, Jeremy Holland, Debi Horsfall.
Newcastle, UK, General Hospital (217)—A David Mendelow, Anil Gholkar, Sharon Bradley.
London, UK, Kings College Hospital (131)—Martin Jeffree, Neil Deasy, Michael Sharr, Peter Bullock, Liz Hall, Liane Cook.
Gothenburg, Sweden, Sahlgrenska University Hospital (100)—Gunnar Wikholm, Miriam Rodriguez, Luigi Pellettieri, Gudrun Barrows, Pål Svendsen.
Glasgow, UK, Southern General Hospital (70)—J J Bhattacharya, K W Lindsay, Irene Scott.
Haywards Heath, UK, Hurstwood Park Neuro Centre (69)—Jonathan Olney, John Norris, Giles Critchley, Valerie Botting.
Edinburgh, UK, Royal Infirmary (63)—Robin Sellar, John Steers, Lynn Horribine.
Turku, Finland, University Central Hospital (63)—Arto Haapanen, Simo Valtonen, Ville Vuorinen, Irma Vlasoff.
Toronto, Canada, Western General Hospital (62)—Robert A Willinsky, M C Wallace, Luc Harvey.
Birmingham, UK, Queen Elizabeth Hospital (60)—David Yates, Richard West, Beverley Hudson, Jonathan Wasserberg.
Bristol, UK, Frenchay Hospital (59)—Richard J Nelson, Shelley A Renowden, Elizabeth A W Varian, Yvonne P Clarke.
Cardiff, UK, University Hospital of Wales (57)—Shawn Halpin, Richard Hatfield.
Liverpool, UK, Walton Centre for Neurology and Neurosurgery (54)—Thomas Nixon, Patrick Foy, Hans Nahser, Donald Shaw, Sam Saminaden.
Freiburg, Germany, Universitatsklinikum (52)—Martin Schumacher, Uwe Spetzger, Vera van Veltoven, Albrecht Hochmuth.
London, UK, Atkinson Morley Hospital (37)—Andrew Clifton, Anthony Bell.
Paris, France, Pitié Salpêtrière (31)—Alessandra Biondi, Jean-Pierre Sichez, Stéphane Clemenceau, Jean-Noël Vallée.
Perth, Australia, Royal Perth and Charles Gardiner Hospitals (27)—Makhan Khangure, Neville Knuckey, Jennie Linto.
Montréal, Canada, Hôpital Notre Dame (27)—Daniel Roy, Jean Raymond, Michel W Bojanowski, Jean-Louis Caron, Valérie Côté.
Plymouth, UK, Derriford Hospital (25)—William Adams, Louis Pobereskin, Edna Piper.
Odense, Denmark, Universitetshospital (25)—Frank Gaarskjaer, Joergen Nepper-Rasmussen, Ann Bali Mains.
Mainz, Germany, Johannes Gutenburg Universitats Hospital (24)—Kurt Ringel, Hans Boecher-Schwarz.
Uppsala, Sweden, Akademiska Sjukhuset (23)—Per Enblad, Gyula Gál, Elisabeth Ronne, Lennart Persson, Thomas Youngman.
Belfast, UK, Royal Hospitals (22)—Peter Flynn, R Stephen Cooke, Steven Mckinstry, Teresa Weir.
Sheffield, UK, Royal Hallamshire Hospital (19)—Stuart C Coley, Tim J Hodgson, David Jellinek, Bridget Billingham.
Dresden, Germany, Universitätsklinikum Carl Gustav Carus Hospital (15)—Angela Müller, Dietmar Krex, Rüdiger von Kummer, Gabriele Schackert.
Augsburg, Germany, Krankenhauszweckverband Zentralklinikum (12)—Andreas Roesler, Markus Bittl, Kourad Kretzschmar, Hendryk Kalbarczyk, Guenter Lewentat.

Wurzburg, Germany, Bayerische Julius-Maximilians-Universtitat Hospital (11)—Laslo Solymosi, Klaus Roosen, Monika Warmuth-Metz.
Lausanne, Switzerland, Centre Hospitalier Universitaire Vaudois (8)—Luca Regli, Antoine Uske, Javier Minguez.
Hull, UK, Royal Infirmary (7)—Christopher Rowland Hill, Bruce Mathew, Richard Bartlett, Joy Jackson.
Rennes, France, Hôspital Pontchaillou (5)—Emmanuel Chabert, Xavier Morandi, Abderrhamane Hamlat.
Cambridge, UK, Addenbrookes Hospital (4)—Nicholas Higgins, Peter Kirkpatrick, Chrissie Richardson.
Hamburg, Germany, University Hospital Eppendorf (4)—Ulrich Gryszka, Jan Regelsberger.
London, UK, National Hospital for Neurological Diseases (3)—Neil Kitchen, Tim Cox.
London, UK, Royal London Hospital (3)—Paul Butler, Fari Afshar, Ian Leigh.
Baltimore, MD, USA, Johns Hopkins University Hospital (2)—Kieran Murphy, Daniel Rigamonti.
Amiens, France, Hôpital Nord (2)—Claude Depriester, Hervé Deramond, Christine Desenclos.
Montpellier, France, Hôspital Gui de Chauliac (2)—Alain Bonafe, Beatrix Jean, Luc Bauchet.
Paris, France, Centre Hospitalier Sainte-Anne (2)—Denis Trystam, Philippe Page.
Romford, UK, Oldchurch Hospital (1)—Sanjiv Chawda, Robert Aspoas, Andrew Wing.
Lille, France, Centre Hospital Universitaire (1)—Jean-Yves Gauvrit.
Prague, Czech Republic, Central Military Hospital (1)—Vladimir Benes, Frantisek Charvat.

Conflict of interest statement

Andrew Molyneux has consulting and advisory agreements with Microtherapeutics Inc and Micrus Inc, which are manufacturers of microcatheters and other neurointerventional devices including detachable platinum coils, with stock interest in the companies.

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