The purpose of this paper was to define the sensitivity of the superiority of coil embolization observed in the International Subarachnoid Aneurysm Trial (ISAT) according to the rate of late rebleeding over a reasonable range, and to find the range of rebleeding rates for which it may be overturned. Treatment of aneurysmal subarachnoid hemorrhage (SAH) involves protecting the aneurysm responsible from further hemorrhage. Currently there are 2 methods available to do this: intravascular coil embolization and surgical clip ligation. The relative merits of these treatments depend on 2 factors: how safe they are and how they perform at preventing rebleeding. This leaves open the question of which is better in the longer term.

Methods. The authors calculate the life expectancy of patients following a subarachnoid hemorrhage (SAH) and compare the life expectancy of those who underwent coil embolization with those who underwent clip ligation in the ISAT cohort.

Results. The 1-year poor outcome rate following treatment climbs rapidly with advancing age. A consequence is that the absolute difference between the poor outcome rates after coil embolization and clip occlusion is lower in those < 50 years of age (3.3%) than it is for those > 50 years of age (10.1%). This difference may be enough to give clip application the advantage in the < 40-year-old group despite the small size of the difference in 1-year rebleeding rates thus far observed (0.152%).

Conclusions. When treating ruptured cerebral aneurysms, the advantage of coil embolization over clip ligation cannot be assumed for patients < 40 years old. In this age range the difference in the safety of the 2 procedures is small, and the better long-term protection from SAH afforded by clip placement may give this treatment an advantage in life expectancy for patients < 40 years of age. (DOI: 10.3171/JNS/2008/108/3/0437)

Key Words • clip occlusion • coil embolization • International Subarachnoid Aneurysm Trial • intracranial aneurysm • long-term result

Abbreviations used in this paper: ISAT = International Subarachnoid Aneurysm Trial; SAH = subarachnoid hemorrhage; UK = United Kingdom.
These observations have prompted careful follow-up, and consequently the durability of coil embolization is better defined than that of clip occlusion. The rates of persistent aneurysm filling at first angiographic follow-up observed in the ISAT were 34% after coil embolization and 18% after clip ligation, but the denominators were very different. Of patients treated with coil embolization, 89% underwent postoperative angiography, but this test was performed in only 47% of those with clip occlusion.

Concerns about the long-term durability of coil embolization have prompted measurement of posttreatment rebleeding rates for clip ligation as well as coil embolization. Case reports and angiographic series have shown that aneurysms can recur and rebleed following satisfactory clip placement. Estimates of the recurrence rate of SAH after clip placement in these series are complicated because patients who had late angiography formed a selected group.

The ISAT provides prospective comparative data it divides rebleeding episodes into 3 groups—those occurring within 30 days of treatment, between 30 days and 1 year, and after 1 year. Following coil embolization, 1.9% of cases rebled within 30 days (23% per patient year); between 30 days and 1 year the rate was 0.6% per patient year. The corresponding figures after clip ligation were 0.7% of cases within the first 30 days (9% per patient year) and 0.3% per patient year from 30 days to 1 year. The decline within the 1st year has credibility because it accords with the natural history of ruptured aneurysms. Beyond 1 year, natural history data suggest a constant rebleeding rate.

Rebleeding > 1 year after treatment (referred to as “late rebleeds”) observed in the ISAT were rare, so the confidence limits that can be placed on rebleeding rates are quite wide. The rebleeding rate so far in those randomized to coil embolization is 0.21% per patient year, based on 7 hemorrhages, and in those randomized to clip ligation it is 0.063% per patient year based on 2 rebleeding episodes, although 1 of these patients received coil embolization rather than clip placement, and in the other the aneurysm was treated with clips. The “intention to treat” rates given earlier thus differ from “treatment received” rates, which were 0.24 and 0.032% per patient year for coil embolization and clip placement, respectively. For this analysis we adhere to the intention to treat values.

The primary ISAT outcome result includes the effect of rebleeding within the 1st year, so forward extrapolation involves the rebleeding rate after 1 year only. Some series have shown higher rebleeding rates following coil embolization (0.5%, 1.4%, and 1.65% per year), and a recent systematic review of bleeding following coil embolization put the hemorrhage rate at 0.9% (95% confidence interval 0.41–1.4%) per year, but these results do not distinguish between rebleeding rates before and after 1 year. Results similar to those in the ISAT have recently been found in a smaller nonrandomized series.

### Clinical Material and Methods

**Patient Population**

Calculations were based on the ISAT results. In that trial, 2143 patients were randomized to receive either neurosurgical clip ligation or endovascular coil embolization of their aneurysm following SAH. Of these patients, 1073 were randomized to coil embolization and 1070 to clip occlusion. Thirty seven percent were male and 63% were female. The median age was 52 years, with an interquartile range of 44–60 years and a total range of 18–87 years. At the time of this study, the mean follow-up period was 4 years; further details are given in the 2 ISAT papers.

The life expectancy of patients following an SAH but prior to repair of the aneurysm was calculated for coil embolization and clip occlusion, and the outcomes for the 2 treatments were compared. Calculations were done using the computer program Matlab version 6.5. The ISAT good outcome rates were taken as the first posttreatment survival rates. Beyond that, the age-specific annual risk of death or severe disability was calculated by adding the force of mortality of the background population, a fixed annual excess risk of death not related to the index aneurysm as observed in SAH survivors (see Appendix), and a fixed risk from rehemorrhage.

The 1-year poor outcome rates measured in the ISAT are age dependent (see Table 1). In the coil embolization group the 1-year outcome rates are stable at younger ages but rise significantly in older patients. In the surgical group there is a steady rise in the poor outcome rates with advancing age. The values in Table 1 were used as a step function of age to calculate survival rates.

The age-specific annual risk of death was taken for the population as a whole from the 2001 census mortality statistics of the total population of the UK. Persons who have made a good recovery after treatment of a ruptured cerebral aneurysm maintain a higher annual mortality risk than the background population. This is partly due to a risk of further SAH from recurrent or de novo aneurysms. An excess risk of cerebrovascular deaths that are not of aneurysmal origin and of cardiovascular deaths in general has also been observed. Overall, the excess risk of death not directly attributable to the treated aneurysm has been observed to be 0.3% per year.

Ranges of rebleeding rates after clip ligation and coil embolization were studied. If these are considered as independent variables, the large number of possible combinations leads to graphs that are intractably complex and results that are correspondingly inaccessible. Instead we present a range of differences between rebleeding rates after clip occlusion and coil embolization. The rebleeding rate after clip ligation is assumed to be constant at 0.063% per year as observed in the ISAT cohort, and a series of rebleeding rates was picked to cover the range of excess rebleeding rates after coil embolization. The range of rebleeding rates used is 0–0.3% per year, which covers reported rates and is the symmetrical 99% confidence interval on the ISAT late rebleeding rates (Poisson distribution) after coil embolization.

The annual risk of a poor outcome (death or severe disability) posed by an aneurysm was estimated by multiplying the hemorrhage rates by the poor outcome rate following SAH. Death was the result of 65% of hemorrhages observed prospectively in the 2003 International Study of Unruptured Intracranial Aneurysms report. The morbidity rate was not given, but other studies of outcome following SAH suggest that 30% of the survivors are left with serious disability. Combining these figures leads to an overall poor outcome rate of 75% following rupture of an
Late aneurysm rebleeding and coil versus clip treatment

aneurysm. The hemorrhage risk is scaled by this factor before adding it to the population’s force of mortality to obtain the overall risk. The hemorrhage risk was assumed to remain constant over time, as has been observed of the late behavior of aneurysms.5,34

Life expectancy at a specific age was calculated by integrating the survival plot (Fig. 1) from that age to the age of 110 years. This was done for all ages in the range 20–85 years, allowing life expectancy to be expressed as a function of age at the time of treatment of an SAH. The function for clip ligation was then subtracted from that for coil embolization to give the plots in Fig. 2. In this figure, the excess rebleeding rates after coil embolization are printed on the graph, and the rebleeding rate after clip occlusion is assumed to be 0.063% per year as observed in the ISAT clip-treated cohort.13,14

The 95% confidence limits were calculated using compound distributions. The observed rebleeding and poor outcome rates following surgery were modeled as discrete random variables with Poisson and binomial distributions, respectively. These distributions were truncated at the extremes where probability fell below 10.10 Life years gained or lost at the age of 20 years were calculated for each combination of rebleeding, and outcome values and the probability of that combination were noted. The results were ranked according to life years saved, and a cumulative compound probability distribution was calculated accordingly. From this distribution the 0.025 and 0.975 values were taken.

Results

Age-specific outcomes for surgical clip ligation and endovascular coil occlusion are available from the ISAT data. The findings are in accord with other results, which show that the poor outcome rate climbs rapidly with advancing age.12,27,31 A consequence of this trend is that the absolute difference between the poor outcome rates of coil embolization and clip occlusion is much lower in the <50-year age range (3.3%) than it is for patients > 50 years of age (10.1%). The significance of this difference is marginal (p = 0.037, compound binomial), especially because it was a post hoc analysis, but the same effect has been observed in other data sets.25,31

Survival plots are shown in Fig. 1 for patients 30 years of age. This graph reflects what the result of a reexamination of a trial cohort after different time intervals would find. As an example, if the rebleeding rate after coil embolization were 0.3% per year, reexamination after 10 years of a cohort of patients who were 30 years of age at the time of treatment would find no difference between the outcomes from clip ligation and coil embolization. From this analysis it appears that clip occlusion could regain the advantage in young patients with excess rebleeding rates as low as 0.05% per year after coil embolization. We believe this to be misleading because the survival type of analysis gives no credit to a treatment that delays rather than prevents a poor outcome as measured at some time point. A life expectancy analysis, which has the additional feature that 1 graph covers all ages at the time of treatment, yields a fairer assessment.

This analysis shows that the impact of the ongoing hemorrhage risk is highest in young patients, and that at the age of 20 years, clip occlusion may have an advantage for excess hemorrhage rates of ≥ 0.1% per year after coil embolization. The observed excess rate thus far is 0.152% per year, and this may give clip ligation the advantage up to the age of 40 years. Beyond this, the escalating morbidity from all treatments is likely to widen the gap between coil embolization and clip occlusion at the time of treatment, implying that it would take a considerably higher rebleeding rate after coil embolization before clip occlusion would gain the advantage.

Discussion

With the substantial advantage of coil embolization over clip ligation and low rebleeding rates after either procedure, it seems intuitively unlikely that episodes of rebleeding would ever overturn the initial ISAT result. That they could do so in younger persons is partly because of the higher rebleeding rate after coil embolization, and partly because the difference between the poor outcome rates of coil embolization and clip ligation is much smaller for young people than for the whole population.

The possible advantage for clip occlusion over coil embolization at younger ages is based on several observations with wide margins of error. The poor outcome rates in the relatively small < 40-year age groups are based on 34 and 35 poor outcomes for coil embolization and clip occlusion, respectively. The rebleeding rates are based on 7 observed hemorrhages for coil embolization and 2 for clip occlusion (based on treatment received, 8 hemorrhages for aneurysms treated with embolization and 1 for a lesion treated with clip placement were observed, which gives results on the 0.2% line of Fig. 2). The possible advantage of clip ligation in a younger age group is also sensitive to the method by which the dependence of operative outcomes on age is modeled. If no age dependency is assumed and the overall average outcomes are used at all ages, then any advantage of clip occlusion is abolished, but other data support a strong age dependence.25,31 If the relationship is modeled as being linear with age, the advantage of clip occlusion at a young age is retained but diminished.

The curves in Fig. 2 cross over the zero line and come to favor clip occlusion at advanced age. This is against the general trend of the data. The risks of coil embolization and clip ligation are both high in this age group and dominate.
life expectancy, ongoing rebleeding rates being of little importance. They are based on small numbers and the confidence limits are correspondingly wide. The key question in this age range is whether to treat at all, which cannot be addressed based on the ISAT data.

The risks on which these calculations are based were observed during follow-up periods that extended to 4 years on average. It is necessary to extrapolate these observations to periods of up to 60 years. There is some evidence to suggest that hemorrhage rates from unruptured aneurysms are reasonably constant over time, but this has been contested with the assertion that hemorrhage rates decline with time. Extrapolating these observations to ruptured aneurysms is speculative. A similar decline in the rebleeding rate has been observed over the 1st year in the ISAT data, and further decline remains credible. Any such decline would strengthen the superiority of coil embolization. There has been no serious suggestion of an acceleration in hemorrhage rates from specific aneurysms over time.

A concern is that recanalization of coil-treated aneurysms may reduce their protection over the longer term and that rebleeding rates may climb, and at worst revert to the natural history. The rebleeding rate in untreated aneurysms > 1 year after an SAH cannot be reliably stated because of the difficulty in confirming causes of death. The Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage measured the rebleeding rate as 1.4% per year. Any trend toward a rate this high strengthens the case for clipping in young patients.

We have assumed that the nonaneurysmal excess risk of death after 12 months is the same for both clip- and coil-treated cases, but this may not be so. In the ISAT, 45 deaths after 12 months have been reported from all causes in the group treated with clip placement compared with 33 deaths in the coil-treated group. This difference is not significant, but were it sustained, any advantage of clip placement would be abolished. This question will only be resolved by continued follow-up.

An assumption concerning the force of mortality is that current values are appropriate for calculating the life expectancy of persons alive now. This is not totally justified, because for the past 100 years the life expectancy of inhabitants of the developed world has increased steadily, with no signs of plateauing. Statistics for the UK give a rate of increase in life expectancy at the age of 20 years of 11.2 minutes for every hour over the period from 1981 to 2003. The effect of including this statistic is marginally to strengthen the advantage of clip ligation over coil embolization, particularly in the patient group < 45 years of age. The ISAT was conducted in an international population that may have a different background force of mortality from the UK population statistics that were used, although the UK was the largest contributing country, with > 50% of recruitment.

Improvements have been made in coil embolization techniques. Murayama et al., reporting their experience over the 11 years beginning in 1990, found an overall rebleeding rate of 1.65% per patient year but only 0.5% in the last 5 years. The distinction between historical periods cannot be made for some series, and it may not be appropriate to assume that rates observed in the early 1990s are applicable today.

These results were primarily derived from the ISAT, and suffer from the same problems of extrapolation and applicability that have been raised in regard to the trial’s conclusions.

Conclusions

The merits of clip occlusion and coil embolization as treatments for ruptured aneurysms depend on both the safe-
ty and the as yet poorly defined long-term rebleeding rates of treatments. Rebleeding rates between 0.1 and 0.3% higher per year after coil embolization than after clip occlusion could overturn the superiority of coil embolization in young persons that was observed in the ISAT. Currently available data give rebleeding rates that are in this range for the ISAT cohort.

Appendix

Force-of-mortality data from Census 2001 is available with a time resolution of 10 years. This had to be fitted with a function that allowed higher time resolution. The choice of function to do this was somewhat arbitrary, but we required that it be a simple polynomial, exponential, or trigonometric function that was the best least-squares fit and fulfilled the criteria of increasing at all points between the ages of 20 and 80 years. The function used is the following polynomial:

$$y = 0.000004664932 \ a^3 - 0.000505389666 \ a^2 + 0.018858815331 \ a - 0.027733043720$$

where $y = \text{force of mortality}$ and $a = \text{age in years}$.

To this was added a correction factor for the observed excess risk of death from all causes in a population that has made a good recovery after an SAH from an aneurysm that has been successfully treated. Sparse data from this highly selected group makes it impossible to give accurate long-term time-dependent predictions, but there appears to be a reasonably age-independent annual excess risk of death of 0.003.

Disclosure

A. Molyneux has a consulting and advisory agreement with Micros, 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. R. Kerr and A. Molyneux have received support for travel to meetings from Boston Scientific. There are no other conflicts of interest.

References

1. CARAT Investigators: Rates of delayed rebleeding from intracranial aneurysms are low after surgical and endovascular treatment. Stroke 37:1437–1442, 2006
8. Lin T, Fox AJ, Drake CG: Regrowth of aneurysm sacs from resid-

Acknowledgments

Primary authorship was the responsibility of P. Mitchell, whereas A. Molyneux, R. Kerr, and A. D. Mendelow provided direct input into the writing, editing, and decisions on content, and advice on analysis interpretation.


The UK Medical Research Council funded the ISAT and continues to fund ongoing follow-up. This funding was received by A. M. and R. K., but not by P. M. or A. D. M.

Address correspondence to: Patrick Mitchell, F.R.C.S., Department of Neurosurgery, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, United Kingdom. email: patrick.mitchell@ncl.ac.uk.