Endovascular clipping of intracranial aneurysms is a technique that has been available for more than 10 years in certain centers. The technique has been FDA approved in the United States since the mid-1990s. A number of publications have demonstrated that endovascular treatment may be effective in reducing rebleeding after subarachnoid hemorrhage due to aneurysmal rupture. Coils have also been used in unruptured aneurysms. This has typically occurred where direct surgical clipping is thought to be of higher risk. As coil technology has evolved, a steadily increasing number of patients have had aneurysms treated with coils. The question as to whether to clip or coil a specific aneurysm has been the topic of many debates and symposia. In order to shed some light on the use of endovascular coils specifically in patients with subarachnoid hemorrhage, a randomized multicenter trial was designed and the results of this trial, the International Subarachnoid Aneurysm Trial (ISAT), were published in The Lancet. While this study was highly referenced in the lay press, there are many features of the study that merit careful consideration as conclusions are drawn.

The Lancet study provides us with a comparison of neurosurgical clipping versus endovascular clipping in 2143 patients. The study was designed as a prospective randomized trial, and treating centers were required to have between 60 and 200 cases of patients with subarachnoid hemorrhage annually. A total of 43 centers entered patients. Sixteen centers returned complete ascertainment logs (37% of all centers), 16 centers returned incomplete logs (649 patients randomized), and 11 centers did not return logs (64 patients randomized). To be a participating center, endovascular operators had to have done a minimum of 30 aneurysm treatment procedures before they were permitted to treat patients in the trial. There was no minimum number of criteria for surgeons to enter the study in terms of the number of patients. This is an important feature of the study. It has been demonstrated that for both surgical and endovascular treatment of aneurysms, the volume of patients treated by the operating physician influences outcome. The more patients treated, the lower the risk of the overall management of the patient for both ruptured and unruptured aneurysms. One issue that has been raised by the ISAT trial is how generalizable the results are to all patients with aneurysms or even all patients with subarachnoid hemorrhage. In this study there were 9559 patients with subarachnoid hemorrhage who were assessed for eligibility. Of these patients, 7416 were excluded (77.6%); 671 patients refused the study and 6745 patients were excluded for “other reasons” that are not fully explained. This left 2143 patients for randomization (22.4% of total). Of these, 1073 patients were allocated to endovascular treatment and 1070 were allocated to neurosurgical treatment.

The majority of patients randomized were in good clinical condition prior to treatment. Eighty-eight percent of the endovascular group and 88% of the surgical group were World Federation of Neurological Surgery (WFNS) grade 1 or 2. The majority of patients entered in the study had anterior circulation aneurysms (97.3%). Thus the group studied represents only a small fraction of all subarachnoid hemorrhage patients. After accrual of patient data, the main outcome for the study used was the modified Rankin scale. The incidence of further subarachnoid hemorrhage after treatment was also recorded in the study.

The major finding of the study that has been highly publicized both in medical literature and lay press was that after 1 year of follow-up there was a statistically significant difference in the Rankin outcome scales. The authors report that at 1 year, 190 patients (23.7%) of 801 patients endovascularly had modified Rankin outcome scales of 3 to 6 (pooled results) compared with 243 of 793 patients treated with surgical clipping (30.6%). This yields an absolute difference of 6.9% with a confidence interval of 2.5 to 11.3%. In further analysis of this data, the grouping of modified Rankin scales 3 to 6 must be done in order to...
achieve statistical significance. In fact, if one compares the difference in outcome between endovascular and neurosurgical treatment for each outcome scale, there is no statistical difference. This applies to those patients identified as modified Rankin scale 3 (significant restriction in lifestyle), scale 4 (partly dependent), scale 5 (fully dependent), and scale 6 (dead). The fact that the difference in isolated outcomes is not statistically significant, yet the pooled data show statistical significance, raises the issue of whether we are really observing a significant event. By grouping Rankin outcome scores, the results are diluted significantly. The whole concept of using Rankin disability scores is to stratify outcomes in more detail than other scales that simply group clinical outcome as “excellent, good, fair, poor, or dead” such as the Glasgow Outcome Scale. By pooling the Rankin scales, the authors have reduced the analysis to a binary outcome measure: good versus poor/dead. The results at 1 year may look quite different than the results at 3 or 5 years if there is a hemorrhage rate that persists in incompletely treated aneurysms (for which we are given no data in the endovascular group). For instance, in the ISAT study the rate of hemorrhage in the clipped patients from time of treatment to 1 year was reported as 26/801 = 3.2% and 10/793 in the clipped patients = 1.3%. If one assumes that when a hemorrhage occurs, 70% of patients will have a resulting outcome of Rankin scale 3 or higher, then at 3 years’ follow-up, the absolute risk reduction in clipped patients is 4.19% (95% CI, −0.32% to 8.68%), and is not statistically significant. At 6 years, the absolute risk reduction is 0.02% in favor of surgery and is not significant. By year 10, the absolute risk reduction is −5.6% in favor of surgery and is highly significant (P = 0.02).

The concept of completeness of aneurysm treatment, which has come to be known as “effectiveness” of treatment, is a concept that has evolved as endovascular strategies have become available to treat aneurysms. In the past, surgical treatment involved complete clipping of the aneurysm with high likelihood of obliteration and a definite incidence of recurrence or rehemorrhage if the aneurysm were incompletely clipped. It is well known that when coiling an aneurysm, much of the risk of thromboembolic complications or parent vessel occlusion occurs while treating the last 8% to 10% of the aneurysm volume. Therefore, if one is less aggressive in treating the whole volume of the aneurysm with coils, the overall risks can be kept lower. What that does to the overall effectiveness of treatment in terms of long-term aneurysmal regrowth and subsequent rupture is unknown. Two recent studies have documented longer-term follow-up after coil embolization of aneurysms. While the ISAT did not address the percent of obliteration, this has been addressed in a number of other studies and is almost always reported in papers describing the results of coil endovascular treatment of aneurysms. In a recent study by Raymond et al, long-term (>1 year) follow-up was obtained in 55% of 501 aneurysms treated over a 10-year interval from 1992 to 2002. Recurrence was identified in 33.6% of the total number of aneurysms followed. Major recurrences were identified in 20.7% of patients and appeared at a mean interval of 16.49±15.93 months. In fact, in their total number of 501 patients, only 35.9% were treated with what was defined as complete occlusion. In 46.3% there was residual neck, in 13.8% there was residual aneurysm, and in 4% there was failure to place coils. What is unknown at present is what long-term effects these recurrences may have in terms of clinical outcome for patients. Raymond et al defined a 0.8% bleed rate in a clinical follow-up interval of 31.32 months. In what is probably one of the largest experiences with Guglielmi detachable coil embolization of aneurysms, Murayama et al report the results of an 11-year experience with follow-up on 818 patients with 916 aneurysms. Although angiographic follow-up was available in only 53.4% of patients, recanalization was identified in 20.9% of the total number of patients treated. While the ISAT does not provide any information regarding completeness of aneurysm treatment, there are data presented on rehemorrhage rates. In the ISAT, there were a total of 40 patients who rehemorrhaged before treatment or between 30 days or up to 1 year after endovascular treatment. There were 22 deaths in these 40 patients (55%). Of the endovascular group, there were 26 patients who bled after the procedure and up to 1-year follow-up; 15 of these died (68%). This overall rate of 26/801 patients who bled after treatment and up to 1 year after follow-up yields a 3.2% rehemorrhage rate. In the surgical group there were a total of 33 patients who bled after embolization and up to 1-year follow-up. There were only 10 of 793 who bled after treatment and up to 1-year follow-up (1.26%). Of these patients, 5 (50%) died. It is of interest that the biological observation here is that coils prevent the majority of acute rehemorrhages from aneurysms; however, if one simply looks statistically, it could be concluded that surgery reduces rebleeding by more than 50% compared with endovascular coiling. In addition, 2 patients in the endovascular group and no patients in the surgical group hemorhaged after 1 year of follow-up. This small category of patients who have rebled may prove crucial in further follow-up of the ISAT data. In summary, the ISAT has provided us with an excellent first attempt to compare endovascular coiling with surgical clipping in a randomized fashion; however, a “prospective randomized trial” does not imply no flaws in the trial design. There may well exist a “crossover point” where the rupture rate from coiled aneurysms and associated morbidity and mortality will be greater than the surgical risk. While the ISAT was designed to evaluate clipping and coiling in patients with subarachnoid hemorrhage, it actually addresses only a small fraction of those good-grade patients where each individual technique is thought to be of equal benefit. As stated earlier, this becomes a small fraction of the aneurysm patients with subarachnoid hemorrhage. In addition, these results cannot and should not be generalized to unruptured aneurysms. The unruptured aneurysm represents a totally different entity. One of the interesting facets of the ISAT was the great attention it received in the lay press. This is most certainly generated in large part with intense pressure to prove significance from the commercial sector. While commercial forces are known to influence different areas of scientific research, the zealousness to produce a marketable
commercial product should not cloud the overall analysis of the available data. We will watch and wait with great interest to observe the longer-term follow-up of the ISAT. In addition, other randomized trials, which may include both ruptured and unruptured aneurysms for comparison for clipping and coiling, are in the planning stages. While endovascular strategies to treat intracranial aneurysms may hold the key to future success, each technique must be evaluated in careful, well-designed studies prior to generalized usage.

References

Key Words: endovascular coiling ■ intracranial aneurysm ■ subarachnoid hemorrhage
Neurosurgical Clipping Versus Endovascular Coiling of Patients With Ruptured Intracranial Aneurysms
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Stroke. 2003;34:2540-2542; originally published online September 18, 2003;
doi: 10.1161/01.STR.0000092894.71909.FF

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