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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

Colin P. Derdeyn, John D. Barr, Alejandro Berenstein, John. J. Connors, Jacques E. Dion, Gary R. Duckwiler, Randall T. Higashida, Charles M. Strother, Thomas A. Tomsick and Patrick Turski

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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

The recent publication of the initial data from the International Subarachnoid Aneurysm Trial (ISAT) represents a landmark in the evolution of the treatment of cerebral aneurysms (1). Endovascular treatment of ruptured cerebral aneurysms with detachable coils was proven superior to surgical clipping as defined by the proportion of patients dead or disabled at 1 year in a carefully selected group of patients deemed suitable for either therapy. The purpose of this position statement is to review the ISAT data, to discuss questions this study has answered and those that remain, and to evaluate the implications this study has for patients with ruptured cerebral aneurysms in North America and worldwide.

ISAT Study Design

ISAT was a randomized, prospective, international controlled trial of endovascular coiling versus surgical clipping for a selected group of patients with ruptured intracranial saccular aneurysms deemed suitable for either therapy. The study began with an initial pilot phase from 1994 through 1996 and continued enrollment through 2002. Most patients were treated at high-volume centers in the United Kingdom (77%), with the rest from other European countries, Australia, Canada, and the United States.

All centers were required to have treated more than 60 patients with aneurysmal subarachnoid hemorrhage per year and to offer both surgical clipping and endovascular coiling. The key inclusion criterion was that both the study surgeon and the interventional neuroradiologist considered the patient to be a good candidate for either treatment. In other words, a state of clinical equipoise existed as to the best treatment for each randomized patient. If the surgeon or the interventional neuroradiologist thought that clinical factors or vascular anatomy was not ideal for their mode of therapy, the patient was not randomized. The full details of the study protocol are available on the ISAT Web site (http://users.ox.ac.uk/~isat/).

The primary end point was patient outcome, defined as a modified Rankin scale of 3–6 (dependent or dead) at 1 year. This outcome was assessed by a questionnaire mailed to patients or their caregivers. The primary hypothesis was that endovascular treatment would reduce by 25% the proportion of patients dependent or dead at 1 year. Outcome analysis was conducted on an intention-to-treat basis. Planned secondary end points included neuropsychological and angiographic outcomes, with continued follow-up out to 5 years.

Enrollment and Randomization

A total of 9559 patients with aneurysmal subarachnoid hemorrhage were screened, and 2143 (22.4%) were randomly assigned to surgical or endovascular groups. Most screened patients were not considered to be equally suited for surgery or endovascular therapy. Those patients who were screened but not randomly selected were treated surgically (n = 3615 [39%]), endovascularly (n = 2737 [29%]), or by an unrecorded therapy (n = 1064 [11%]). Thus, for most screened patients between 1994 and 2002, the surgeon and the interventional neuroradiologist thought that the best treatment for a patient was clear and that randomization would not be ethical or appropriate. This almost certainly accounts for the underrepresentation of posterior circulation and middle cerebral artery aneurysms in the trial. In Europe, as well as North America, endovascular therapy is generally accepted as the preferred treatment for most posterior circulation aneurysms (2), whereas clipping is presently preferred for most middle cerebral artery aneurysms. Most randomly assigned patients had aneurysms located at the anterior communicating artery location (50.5%) or the distal internal carotid artery (32.5%). There were no significant differences in clinical characteristics between the surgical and endovascular groups.

ISAT Results

A total of 1070 patients were randomly selected for surgical clipping, and 1073 for endovascular therapy with detachable platinum coils. There were very few

Members of the Writing Group: Colin P. Derdeyn, John D. Barr, Alejandro Berenstein, John. J. Connors, Jacques E. Dion, Gary R. Duckwiler, Randall T. Higashida, Charles M. Strother, Thomas A. Tomsick, and Patrick Turski.

Address correspondence to Randall T. Higashida, MD, University of California, San Francisco, Medical Center, 505 Parnassus Avenue, Room L-352, San Francisco, CA 94143-0628.

crossover cases (those assigned to one treatment group, but having another treatment)—38 from surgery to coils and 10 from coiling to surgery. Randomly assigned patients were nearly all in good neurologic condition: 94% were categorized on presentation as World Federation of Neurosurgical Societies (WFNS) grades I–III (3).

Enrollment was prematurely halted by the study steering committee after the results of a planned interim analysis by the data monitoring committee (DMC). One-year follow-up data were available for 1594 (74%) of the 2143 patients. The interim results were as follows: at 1 year, 23.7% (190/801) of the patients allocated to endovascular treatment were dependent or dead, as compared with 30.6% (243/793) of patients in the surgically allocated group of patients. Although 1-year follow-up data regarding all randomly assigned patients were not yet available, this difference was highly significant ($P < .001$). The absolute risk reduction for dependency or death—the difference in the risk of dependency or death between the two groups (derived by subtracting 23.7% from 30.6%)—was 6.9% (95% CI 2.5%–11.3%), and the relative risk reduction—derived by dividing the absolute risk reduction (6.9%) by the risk in the surgical group (30.6%)—was 22.6% (95% CI 8.9%–34.2%). The data monitoring committee voted unanimously to advise the steering committee of these results. On the basis of these results, the steering committee closed recruitment and randomization of patients and agreed to continue the follow-up of enrolled patients for an additional 5 years.

Since publication of this initial data in the *Lancet,* on October 26, 2002, additional 1-year follow-up data from enrolled patients have been analyzed and were reported by the ISAT investigators at the Sixth Annual Joint Meeting of the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Section on Cerebrovascular Surgery and the American Society of Interventional and Therapeutic Neuroradiology (R. Kerr and A. Molyneux, Results from the ISAT Study, February 16–19, 2003, Phoenix, AZ). These revised outcome results are better than those initially published and demonstrate an even greater absolute risk reduction for dependency or death of 8.7% and a relative risk reduction of 26.8% for aneurysm coiling over clipping. The study continues for the enrolled patients with planned follow-up out to 5–10 years. The ongoing data collection will include clinical, neuropsychological, and angiographic outcomes and will specifically address long-term rebleeding rates.

There were more patients who rebled before treatment in the group allocated to surgery than in the group allocated to endovascular therapy. Fourteen allocated endovascular patients rebled before treatment, compared with 23 allocated surgical patients. This may be due to a significantly longer interval between randomization and surgery (mean, 1.7 days) than for endovascular surgery (1.1 days; $P < .0001$). This difference may reflect differences in the availability of the neurointerventional suite and the operating room.

One carefully analyzed and important issue in this study was the risk of rebleeding after coiling. It is critical to note that the morbidity of these patients was incorporated in the 1-year clinical outcome reported in ISAT. Rebleeding occurred in 2.6% (26/1048) of patients who underwent coiling or attempted coiling and in 1.0% (10/994) of those who underwent surgery or attempted surgery. Twenty of the 26 patients in the coiling group who rebled did so within 30 days of their allocated treatment. Six patients treated with coils rebled between 30 days and 1 year, and four patients treated with surgical clips rebled between 30 days and 1 year. Despite slightly more rebleeding, the overall outcome at 1 year remained better in the endovascular group.

ISAT Issues and Responses

Durability

Question: Is it likely that aneurysm recurrence or rebleeding over the long-term will affect the results of the study? *Response*: No. *Reason*: The end point in ISAT was assessed at 1 year. The long-term durability of endovascular therapy, however, remains to be determined. The planned 5- and 10-year follow-up of enrolled patients in ISAT will provide this information. In light of the present data, however, it is unlikely that late aneurysm recurrence and rebleeding will occur at a rate that would significantly affect the difference in outcome between surgery and endovascular therapy. More than 6% of the endovascular patients surviving in good condition at 1 year would have to rebleed or suffer a fatal or disabling complication due to retreatment to negate the benefit observed at 1 year. The initial ISAT data indicated a risk of bleeding after 1 year of 2 per 1276 (0.16%) patient-years of follow-up. Assuming that this estimate is accurate, that this rate remains constant, and that all hemorrhage results in death or dependency, it would take more than 40 years to overcome the benefit seen at 1 year with endovascular treatment.

Surgical Expertise

Question: Would North American neurosurgeons have achieved a better outcome? *Response*: No. *Reason*: Most patients enrolled in ISAT were treated at centers in the United Kingdom. These sites were major referral centers for cerebrovascular disease, with 60–200 annual cases of aneurysmal subarachnoid hemorrhage patients. All neurosurgeons were accredited and experienced in the care of patients with aneurysmal subarachnoid hemorrhage. There was no requirement for outcome data from individual neurosurgical or endovascular operators. No single center treated a disproportionate number of patients. It cannot be said that the ISAT neurosurgeons had little experience. In fact, the ISAT neurosurgeons clipped three aneurysms in the nonrandomized group for every one surgically clipped aneurysm in the ran-

domized group. In fact, relative to endovascular operators, the opposite may have been true. Interventional neuroradiologists were required to have performed only 30 aneurysm procedures to participate in ISAT, and the study began in 1994, very soon after the introduction of coils in Europe in 1992.

Furthermore, the outcomes of surgically treated patients in ISAT were similar to those reported in the tirilazad study, a prospective, multicenter, North American trial involving surgically treated patients with aneurysmal subarachnoid hemorrhage published in the *Journal of Neurosurgery* in 1997 (4). Although the data from ISAT and the tirilazad study are not directly comparable because of differences in outcomes assessment, distribution of clinical grades of enrolled patients, and reporting of data, this study does provide some estimate of surgical outcome in good-grade (WFNS grades I–III) patients in North American centers. In this study, conducted between 1991 and 1993 at 54 North American centers, 897 patients with aneurysmal subarachnoid hemorrhage were randomly assigned to placebo or one of two treatment arms. Ninety-three percent of the patients in the tirilazad study underwent surgical clipping as compared with 96% of the surgically allocated patients in ISAT. The study was designed to determine whether tirilazad, a 21-aminosteroid with proven brain-protective effects in animal models of ischemia (5, 6), improved outcome in surgically treated patients with aneurysmal subarachnoid hemorrhage. No difference in outcome was observed between study groups. At the 3-month follow-up, 9.2% of the grades I–III patients had died. By contrast, in ISAT 8.3% of patients randomly selected for surgery were dead at 2 months, increasing to 10.1% at 1 year. Similar data were reported from the European/Australasian tirilazad study, in which 12.2% of grades I–III patients receiving drug infusion had died by the 3-month follow-up (7). These data do not support the argument that the quality of neurosurgical care for ruptured cerebral aneurysms is better in North America than in the United Kingdom.

Relevance of the Outcome Measurement

Question: Was the observed difference in outcome between the surgical and the endovascular groups meaningful? *Response*: Yes. *Reason*: First, the primary end point—dependency or death (modified Rankin score of 3–6 inclusive)—was not set in a post hoc data analysis, but was predetermined. The difference in the primary outcome between the two groups in ISAT was highly statistically significant ($P < .001$). A trend toward better outcome with endovascular therapy was seen across all subgroups, but the study was not powered to address these differences, particularly when enrollment was prematurely halted. Second, the preset end point of dependency or death is meaningful: the difference between an existence with a significant lifestyle restriction (modified Rankin score of 2) compared with partial dependency (modified Rankin score of 3) would be important to most people. Furthermore, this end point reflects the goal of stroke therapy: to prevent disability and death from stroke.

The end point, equivalent to functional independence with the ability to carry on the activities of daily living, became a standard for interventional therapy in the PROACT II trial (8). The end point is relevant for subarachnoid hemorrhage as well, in which "treatment" does not lead to early recovery, and fewer than 50% of affected patients return to their prehemorrhage status.

Third, the degree of relative (22.6%) and absolute (6.9%) risk reduction observed in ISAT is comparable to other important clinical trials that have been embraced by the North American cerebrovascular surgical, interventional, and medical communities, including the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (9). In the NASCET trial, there was an absolute risk reduction of 10.6% for a major or fatal ipsilateral stroke. In the National Institute of Neurological Disorders and Stroke tissue plasminogen activator (rt-PA) for acute ischemic stroke study, there was an 11–13% absolute, and relative increase in the number of patients with minimal or no disability of more than 30% in the rt-PA group compared with that in the placebo group, as measured by the National Institutes of Health Stroke scale and Rankin, Barthel, and Glascow outcome scales (10). In the American Carotid Atherosclerosis Study (ACAS), a trial of surgical endarterectomy versus medical therapy for patients with asymptomatic carotid stenosis, the absolute risk reduction was 1% (11).

Randomization Rate

Question: Does the low (22.4%) randomization rate limit the validity of the study data? *Response*: No. *Reason*: This randomization rate reflects the reality of modern clinical trials as well as current clinical practice regarding intracranial aneurysm clipping and coiling. Most screened patients in ISAT were best treated by one technique or the other, not by both, in the opinion of the study neurosurgeons and interventional neuroradiologists. To randomly assign patients in whom clinical equipoise did not exist would not be ethical or practical, and the data generated from such a study would not be useful. Finally, this rate of randomization is not dramatically different from other major clinical trials.

Randomization rates were less than 40% in NASCET and less than 4% in ACAS (>42,000 patients screened and 1662 randomly assigned [9, 11]).

Implications of ISAT

Treatment of Unruptured Aneurysms

Question: What are the implications for the treatment of patients with unruptured aneurysms? *Response*: Significant. *Reason*: The primary issues regarding treatment decisions for patients with unruptured cerebral aneurysms relate to their natural history risk: what is the risk of hemorrhage over time

relative to the risks of treatment? Much of the surgical morbidity and mortality observed in the present study may be exacerbated by subarachnoid hemorrhage. These complications should be less frequent in asymptomatic patients. Nevertheless, the present data provide firm evidence that coiling is nearly as effective as surgery in preventing rebleeding in the first year and is significantly safer, in terms of overall morbidity and mortality, in a similar cohort of patients.

Ruptured Aneurysms

Question: Should all ruptured aneurysms be treated by endovascular methods? *Response*: No. *Reason*: Patients who have aneurysms unsuitable for endovascular treatment should be treated surgically if that option is considered viable by a vascular neurosurgeon. This still accounts for a substantial proportion of patients with ruptured aneurysms; however, the further development of bioactive coils, dedicated intracranial stents, and newer and better aneurysm coil devices may have some impact in the future. These developments will expand our definition of aneurysms considered suitable for endovascular therapy.

Repeating ISAT

Question: Do we need another similar trial of surgery versus endovascular therapy for ruptured aneurysms in North America? *Response*: No. *Reason*: As reviewed above, ISAT was a well-designed and well-executed clinical trial. The major question that remains to be answered is the long-term protection from rebleeding after detachable coil therapy. Further follow-up of the patients enrolled in ISAT will provide these data.

Another clinical trial would be expensive, require enormous resources, take an additional 5–7 years to complete, and would still require long term follow-up of an additional 5–10 years. Furthermore, endovascular techniques for the treatment of cerebral aneurysms continue to evolve and improve. Data from a second trial lasting until 2012–2021 may not be relevant to the field because of these changes. Finally, as previously stated, there is an increasing trend toward more favorable results with endovascular coiling versus surgery as more data are analyzed from ISAT. It is doubtful that significant differences in overall outcomes could be obtained that would justify another trial.

Furthermore, it is difficult to conceive of a trial design for patients with ruptured cerebral aneurysms that would not simply repeat ISAT. The most ethical and practical design for a trial of surgical clipping versus endovascular coiling was the same basic design of ISAT: only patients considered to be good candidates for either treatment at clinical equipoise could be randomly assigned for surgery or endovascular treatment.

Informed Consent

Question: Should all patients and their families receive a consultation from a neuroendovascular or interventional neuroradiology specialist? *Response*: Yes. *Reason*: Endovascular neurosurgical therapy must be considered as a treatment option for every patient with a ruptured cerebral aneurysm. Consultation with a neuroendovascular specialist with advanced training in interventional neuroradiological techniques and procedures is optimal. Standards of training for these specialists have been published and accepted by a special writing group of the American Society of Interventional and Therapeutic Neuroradiology, the Joint Section for Cerebrovascular Neurosurgery, the American Association of Neurological Surgeons, the Congress of Neurosurgery, and the American Society of Neuroradiology (12, 13). These training standards are recognized by the Accreditation Council of Graduate Medical Education (ACGME Program Requirements for Residency Education in Endovascular Surgical Neuroradiology [http://www.acgme.org]).

If one treatment method is recommended over another, the reasons for this decision should be documented as in accordance with the usual standards for informed consent. There will, of course, be emergency situations in which a formal consultation may not be practical, although patients and their families should still be informed about their treatment options and risks of therapy based on these results.

Cerebrovascular Centers of Excellence

Question: Should the care of patients with aneurysmal subarachnoid hemorrhage be consolidated in neurovascular centers? *Response*: Yes. *Reason*: There is considerable evidence that outcomes for patients with subarachnoid hemorrhage are better in high-volume centers and that patients with acute subarachnoid hemorrhages have better outcomes at hospitals offering neuroendovascular services (14–19). It follows logically from these data and from ISAT that patients with ruptured aneurysms should be evaluated and treated in centers that offer both neurosurgery and neuroendovascular treatment. This allows a team of experienced vascular neurosurgeons and interventional neuroradiologists the best opportunity to directly weigh the advantages and disadvantages for clipping or coiling for every individual patient.

Conclusion

The ISAT study was a well-designed and well-executed, randomized, controlled trial on a large number of patients. These data provide the highest level of evidence supporting the use of detachable coils for patients with ruptured cerebral aneurysms suitable for endovascular therapy (level 1 evidence [20, 21]). The study data allow us to conclude that patients with subarachnoid hemorrhage and aneurysm anatomy indicating a high likelihood of success with endovascular therapy should be offered that option.

This conclusion must be tempered by limited data for long-term durability beyond 1 year. The ISAT data add further support for the treatment of patients with aneurysmal subarachnoid hemorrhage in high-volume centers that offer both surgery and endovascular therapy. Finally, repeating a similar trial in North America for patients with ruptured cerebral aneurysms is not justified.

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