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Original article

A randomized trial of endovascular versus surgical management of ruptured intracranial aneurysms: Interim results from ISAT2☆

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ABSTRACT

Background and purpose. – Appropriate management of ruptured intracranial aneurysm (RIA) in patients eligible for surgical clipping but under-represented in or excluded from previous randomized trials remains undetermined.
Methods. – The International Subarachnoid Aneurysm Trial-2 (ISAT-2) is a randomized care trial comparing surgical versus endovascular treatment (EVT) of RIA. All patients considered for surgical clipping but eligible for endovascular treatment can be included. The primary endpoint is death or dependency on modified Rankin score (mRS > 2) at 1 year. Secondary endpoints are 1 year angiographic results and length of hospital stay.
Results. – An interim analysis was performed after 103 patients were treated from November 2012 to July 2017 in 4 active centers. Fifty-two of the 55 patients allocated to surgery were treated by clipping, and 45 of the 48 allocated to EVT were treated by coiling, with 3 crossovers in each arm. The main endpoint (1 year mRS > 2), available for 76 patients, was reached in 16/42 patients allocated to clipping (38%; 95%CI: 25%–53%), and 10/34 patients allocated to coiling (29%; 17%–46%). One year imaging results were available in 54 patients: complete aneurysm occlusion was found in 23/27 patients allocated to clipping (85%; 67%–94%), and 18/27 patients allocated to coiling (67%; 47%–81%). Hospital stay exceeding 20 days was more frequent in surgery (26/55 [47%; 34%–60%]) than EVT (9/48 [19%; 10%–31%]).
Conclusion. – Ruptured aneurysm patients for whom surgical clipping may still be best can be managed in a randomized care trial, which is feasible in some centers. More participating centers are needed.

☆ Clinical Trial Registration-URL: http://www.clinicaltrials.gov. Unique identifier: NCT01668563.

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1. Introduction

The International Subarachnoid Aneurysm Trial (ISAT), published in 2002, radically changed the management of many ruptured intracranial aneurysms (RIAs) [1]. ISAT showed an absolute increase in good clinical outcomes (mRS <3) of 7% at 1 year when patients were treated with endovascular coiling compared to surgical clipping. Endovascular treatment (EVT) had one drawback: a relatively high angiographic recurrence rate, with a higher although still small risk of recurrent subarachnoid hemorrhage (SAH) from the target aneurysm: 13/1073 (1.2%) rebleeds in coiling vs. 4/1070 (0.4%) in clipping at 18.5 years' follow-up [2].

ISAT was a pragmatic trial with broad inclusion criteria, a design that in principle should ensure that results apply in real world clinical practice [3]. We must, however, remember that centers could only include patients eligible for both interventions at a time when simple coiling was the rule. Endovascular coiling had just recently been introduced, and patients considered for the study were likely selected to be favorable for the new treatment: 2143 of the 9559 (22.4%) of SAH patients screened between 1994 and 2002 were included in the trial. Most patients recruited in ISAT had good-grade (WFNS grade 1 or 2; 88%), small (< 10 mm; 90%) anterior circulation aneurysm, with few middle cerebral artery (MCA) aneurysms, which at that time was often a surgical' indication [4]. But what about the other patients? The Barrow Randomized Aneurysm Trial (BRAT), a subsequent all-inclusive, pre-randomized trial [5], provided some indications of the applicability of coiling: between 2003 and 2007, 38% of RIA patients (75/199) assigned to coiling crossed over to surgical clipping [6,7], although the reasons for crossover were unclear. A recent meta-analysis of randomized trials of coiling and clipping, while confirming better one 1-year outcomes for coiling, recommended that more inclusive randomized trials be carried out [8]. For many patients, whether to clip or to coil is an open question, as shown in a recent survey showing little agreement between clinicians on the management of a wide range of RIA patients [9].

The use of surgical clipping is declining and neurovascular surgeons are increasingly trained in endovascular techniques and decreasingly experienced in open surgery [10], to the point that some authors have already announced the demise of clipping [11]. This may be premature, as clipping may still be best for aneurysms that were not included or under-represented in ISAT, or that require the use of more complex endovascular devices or techniques that were not available at the time. A pragmatic trial may be the most prudent way to offer clipping in spite of Level 1 evidence in favor of coiling [12]. The International Subarachnoid Aneurysm Trial-2 was designed not only to address and seek answers to remaining uncertainties in the post-ISAT and post-BRAT era, but also to provide a care trial context, offering clipping to patients for whom surgery may still be best.

2. Materials and methods

ISAT-2 is an investigator-led pragmatic randomized (1:1) parallel-group trial conducted in 2 Canadian and 2 European centers. The hypothesis, based on the best evidence available, is that "endovascular management of patients with ruptured intradural intracranial aneurysms suitable for both endovascular and surgical management, for whom the treating physician is unsure whether the results of ISAT apply, will lead to a decrease in the number of poor outcomes (defined as mRS > 2) from 30 to 23% at 1 year." With target alpha of 0.05, power of 90%, and 10% expected loss to follow-up, the number of patients required was estimated at 1896. The study protocol was published in 2013 [13].

To ensure that patients are not subjected to needless risks as convincing evidence accrues, blinded data for a number of previously published pre-specified subgroups [3] are to be examined by the Data and Safety Monitoring Committee (DSMC) at pre-planned intervals, but there are no explicit pre-specified statistical stopping rules.

Data input and management use secure servers in compliance with Good Clinical Practice (GCP) requirements. The protocol was approved by local Institutional Review Boards, and all patients (or representatives) provided written informed consent prior to participation. Case report forms are simple, and the data collected are parsimonious, to facilitate completion by normal care personnel. Screening logs are not required by the protocol.

2.1. Patients

Inclusion criteria comprise: age ≥ 18 years; at least one intradural aneurysm, ruptured within the previous 30 days, and considered appropriate for both surgical and endovascular management. Exclusion criteria comprise: Grade 5 SAH patients, for whom death or morbidity is considered likely; absolute contraindications to administration of contrast medium; associated arteriovenous malformation; or aneurysm located at the basilar apex, for which surgical treatment is considered risky [14] The trial involves 4 tertiary neurosurgical centers: University of Alberta Hospital, Edmonton, Alberta; CHUM Notre-Dame Hospital, Montreal, Quebec; Rio Hortega Hospital, Valladolid, Spain; and Vall d'Hebron Hospital, Barcelona, Spain.

2.2. Interventions

Patients are treated by surgical clipping or endovascular coiling as per local practice, with technical details regarding treatment left to the individual operators. The use of stents or other adjunctive techniques is recorded.

2.3. Outcome measures

The primary endpoint is measured at 1 year on modified Rankin score (mRS), assessed by physicians not blinded to treatment assignment. Secondary endpoints include: aneurysm re-rupture following randomization but before treatment, new peri-operative (30 days) neurological deficits (defined as any new weakness, sensory abnormality, decreased level of consciousness, or cranial nerve deficit), intracranial hemorrhage after treatment, peri-treatment hospital admission lasting > 20 days, discharge from hospital to a location other than home, angiographic results at 1 year, and overall all-cause mortality at 1 and 5 years.

Follow-up tests and consultations are standard as per local practice, including neurological examinations, brain imaging and functional assessment on mRS at discharge and 1 year. Vascular imaging at 12 ± 2 months to check aneurysm occlusion is expected as standard care, with results centrally adjudicated by an independent diagnostic neuroradiologist. The core lab classified angiographic results at one year according to a previously published 3-tier system (complete occlusion, residual neck, residual aneurysm) [15].

2.4. Randomization

Parallel-group randomization (1:1) is concealed, generated through a web-based platform (MedSciNet). A minimization algorithm uses the following criteria: age ≥ 70 years, aneurysm size ≥ 10 mm, WFNS grade < 4, and aneurysm location in the posterior circulation. Posterior communicating artery aneurysms are considered to be in the anterior circulation. Randomization/minimization functions were tested to ensure the processes

were robust. In May 2016, the protocol was modified in one center (CHUM) to enable pre-randomization, for reasons outlined in [7].

2.5. Blinding

In this pragmatic trial, blinding to treatment assignment of patients, physicians, and outcome assessors was not possible.

2.6. Statistical analyses

Analyses were performed by a statistician according to a protocol using R.3.2.2 (R Foundation for Statistical Computing). No formal hypothesis testing was performed at the time of this interim analysis. Primary and secondary endpoints were assessed using binomial proportions and 95% confidence intervals, using the Wilson score method to allow for small numbers.

3. Results

From November 2012 to July 2017, 103 patients with 152 intracranial aneurysms (103 index aneurysms and 49 additional aneurysms) were recruited. Given the relatively slow study accrual, the Steering Committee (SC) decided to examine the trial results made available to the DSMC after recruitment of the first 100 patients.

Results for all registered and randomized patients are presented in the trial profile (Fig. 1). The number of patients with RIA managed outside the trial cannot be provided because eligibility logs were not required per protocol. Baseline patient and aneurysm characteristics (Table 1) were similar between treatment arms. Many of the patients included in ISAT2 had aneurysms with atypical or difficult characteristics, as seen in Fig. 2. In all, 52/55 patients (95%) randomized to clipping finally underwent clipping; 3 crossed over to EVT (2 MCA and 1 previously coiled recurrent anterior communicating artery aneurysm). 45/48 patients (94%) randomized to coiling finally underwent coiling; 3 crossed over to the clipping arm (2 MCA and 1 posterior communicating artery aneurysm). During the initial hospitalization for SAH, 2 EVT patients required an additional procedure to re-treat the aneurysm (1 surgically, and 1 with flow diverter 2 weeks after simple partial coiling of a giant aneurysm), and 2 surgical patients underwent re-clipping of residual aneurysm found on postoperative angiography.

Primary intent-to-treat outcome data is available for 76 patients: 16/42 patients (38%; 95% CI 25%–53%) allocated to surgical

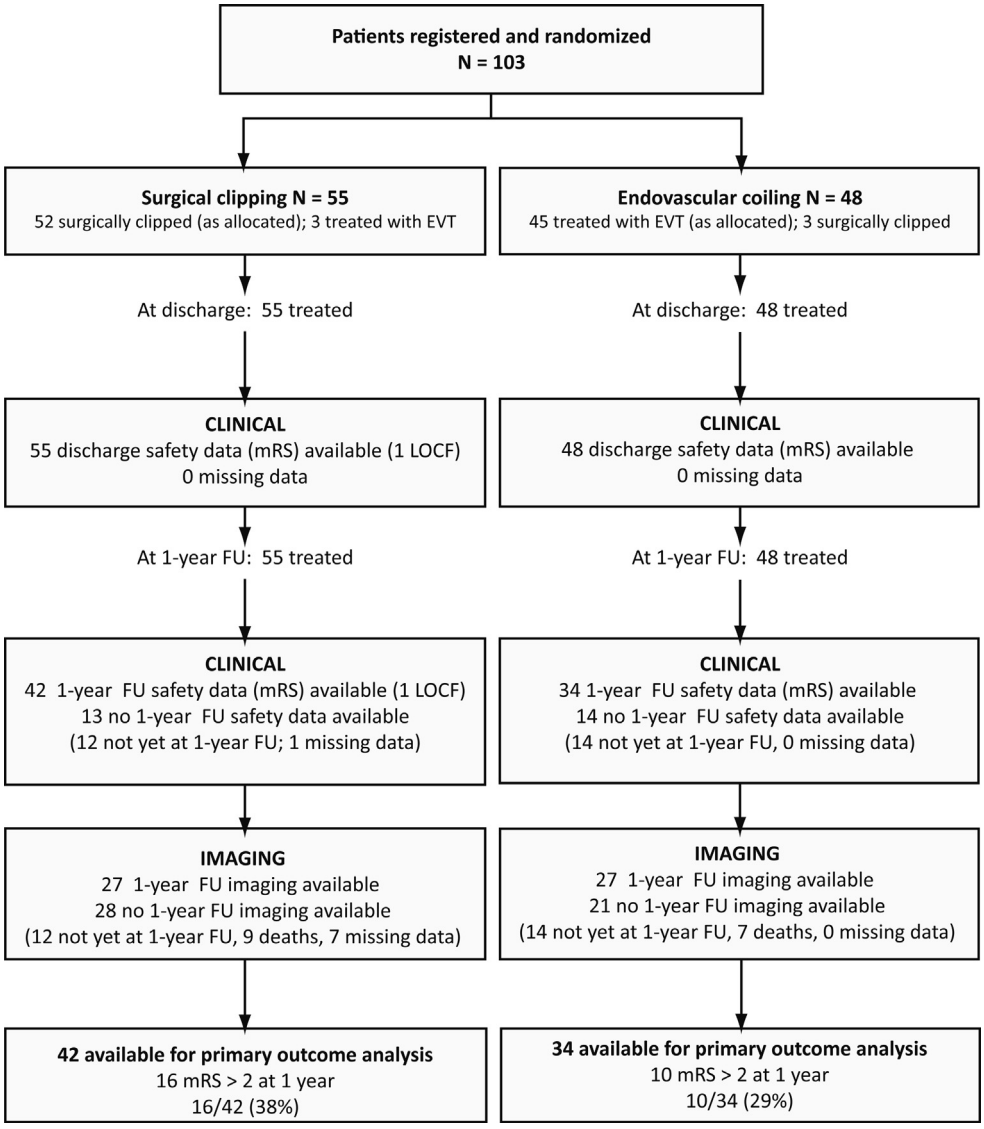

Fig. 1. Study flowchart.

Table 1
Patient and aneurysm characteristics.

Characteristic	Surgical	Endovascular
	n = 55	*n* = 48
Patient		
Mean age at treatment – years	58.5	56.5
Age		
Number of pts < 50 years old	11	1
≥ 70 years old	9	5
Female gender – *n* (%)	37 (67%)	31 (65%)
Pre-rupture modified Rankin score		
= 0 – *n* (%)	48(87%)	44 (92%)
= 1 – *n* (%)	7 (13%)	3 (6%)
= 2 – *n* (%)	0	1 (2%)
WFNS		
1	26 (47%)	20 (42%)
2	12 (22%)	15 (31%)
3	5 (9%)	4 (8%)
4	12 (22%)	6 (13%)
Index aneurysm		
Location		
Anterior circulation	52 (95%)	46 (96%)
Ophthalmic/Paraophthalmic	3	1
Posterior Communicating	7	8
Carotid Terminus	1	1
MCA	25	19
Anterior Communicating	13	15
Pericallosal	3	2
Posterior circulation	3 (6%)	2 (4%)
Size (mm) – mean, median, (range)	7.8, 6, (2–48)	6.8, 6, (2–25)
Aneurysm		
Size ≤ 3 mm	13 (24%)	9 (19%)
Size 4–9 mm	29 (53%)	30 (63%)
Size ≥ 10 mm	13 (24%)	9 (19%)
Wide-necked (≥ 4 mm)	17 (31%)	13 (27%)
Recurrent, previously treated index aneurysm	2	0
Patients with multiple aneurysms	10	15
Intraparenchymal hematoma > 2 cm	11	8
Pre-treatment infarction	3	3
Fisher		
Grade 0–2	18 (33%)	16 (33%)
3–4	37 (67%)	32 (67%)
Treatment		
Time from SAH to treatment (days) – mean, median	4.8, 1	2.3, 1
Adherence to allocated treatment – *n* (%)	50/53 (94%)	45/48 (94%)
Aneurysm re-rupture after randomization, prior to treatment	3	3

Table 2
Primary endpoint (available in 76 patients).

Intent-to-treat analysis	Surgical (*n* = 42)	Endovascular (*n* = 34)
1 year clinical outcome		
mRS > 2	16 (38%) (95%CI 25–53%)	10 (29%) (95%CI 17–46%)
mRS 6	9	7
As-treated analysis	Surgical (*n* = 40)	Endovascular (*n* = 36)
1 year clinical outcome		
mRS > 2	15 (38%) (95%CI24–53%)	11 (31%) (95%CI19–49%)
mRS 6	9	7

clipping had died or were dependent at 1 year, compared to 10/34 patients (29%; 95% CI 0.17–0.46) allocated to coiling (Table 2). Nine of the 55 patients (16.4%; 8.2%–29.3%) in the surgical group and 7 of the 48 patients (14.6%; 6.5%–28.3%) in the EVT group died within a year of randomization.

As-treated analysis gave similar results. Secondary outcome data, including discharge mRS (available in all patients) and 1 year angiographic results (available in 54 patients) are presented in Table 3. A saccular residual index aneurysm at 1 year, as assessed by core lab, was found in 1 patient who was allocated to and received EVT (none in the surgical group). Complete aneurysm occlusion was found in 23/27 patients (85%; 95%CI 68%–94%) allocated to clipping, and 18/27 patients (67%; 95%CI 48%–81%) allocated to coiling. The number of patients with > 20 days' hospital stay was greater in the surgical clipping group: 26/55 (47%; 95%CI 37%–60%) vs. 9/48 (19%; 95%CI 10%–32%) for EVT.

After discharge, no patients were retreated for the index aneurysm during follow-up. Additional details of treatments and complications are provided in Supplementary Table 1.

4. Discussion

The first interim analysis of an ongoing care trial on RIA patients showed outcomes that are within the confidence intervals of the study hypothesis. The only significant difference between the 2 treatments shown to date was that a greater number of clipped patients had hospital stay exceeding 20 days, an expected finding not associated with higher incidence of morbidity at discharge. The most important result of the current study is the demonstration that it is feasible for RIA patients for whom the appropriate treatment modality is uncertain to be managed in the context of a care trial.

The pragmatic design of ISAT-2 allows the inclusion of any patient considered for clipping and eligible for endovascular treatment, but the patients in this study are not the same as those in the original ISAT, as shown by the relatively high proportion of very small (< 3 mm) and MCA aneurysms. ISAT-2 patients cannot

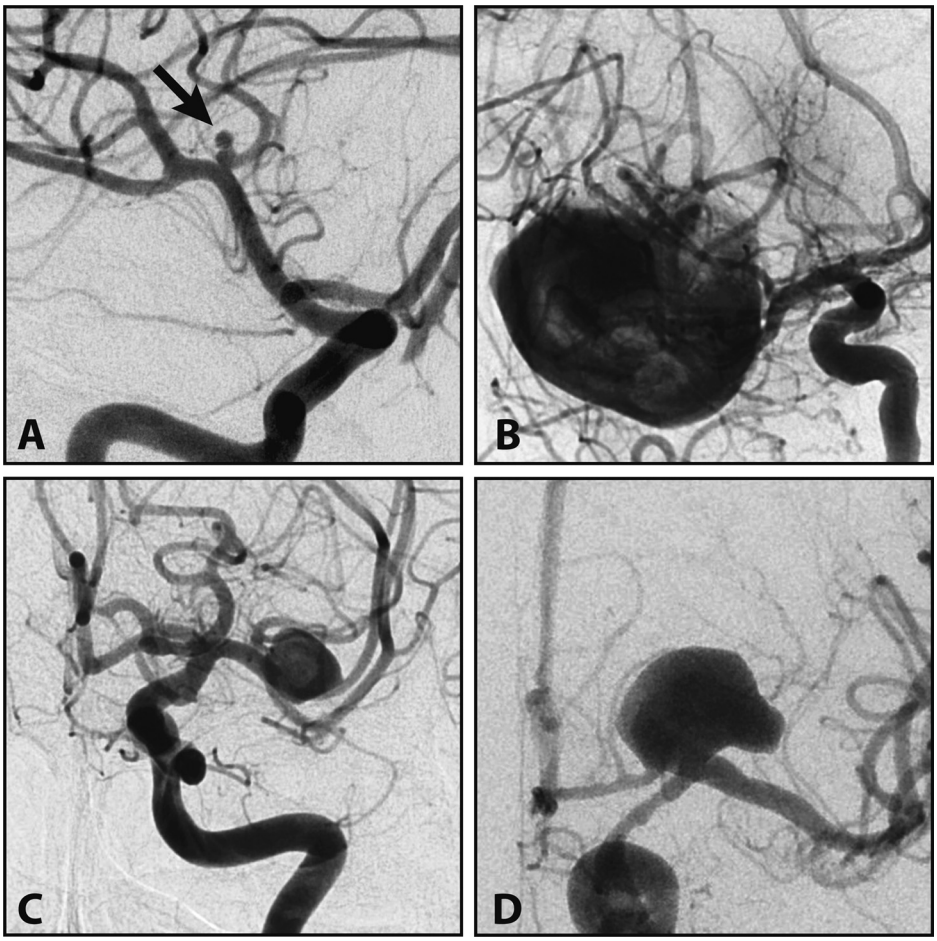

Fig. 2. Selection of ruptured aneurysm cases from ISAT-2 to demonstrate the variety of types of lesions for which treatment was randomly allocated. Panels A–C show very small, giant, and more routine MCA bifurcation aneurysms; panel D shows a very large carotid terminus aneurysm (partially thrombosed).

be grouped into a single well-defined 'natural kind' of RIA patient, a problem that occurs when RCTs are stopped as soon as the trial hypothesis is supported by the overall data, even when clinicians suspect that trial results may not apply to various specific subgroups [16–18]. In the spirit of care trials, the study is open to any patient for whom surgical clipping is considered in spite of Level 1 evidence in favor of coiling, but various kinds of RIA patient are pre-specified for eventual subgroup analysis. Candidates for ISAT-2 may include patients/aneurysms that were excluded from ISAT or BRAT, or for whom the results were not definitive (such as MCA aneurysm), or candidates for stents or flow diverters, requiring dual anti-platelet therapy with its attendant risks [3,19–21]. For some surgeons, clipping may still be indicated in young patients (who might benefit from a more durable treatment as compared to older patients), and in case of very small (< 3 mm) aneurysm (at higher risk of hemorrhagic complications with coiling) [22] or large aneurysm (prone to recurrence after EVT) [3,15,23,24]. These potential indications for clipping have not been validated, as they were identified in terms of different outcomes for the same treatment in different patients. Such comparison cannot inform clinical decisions, because the optimal treatment for a group of patients can only be found by comparing the results of 2 different treatments in the same patients in a randomized trial. The BRAT and ISAT studies recruited patients 12–24 years ago (ISAT recruited from 1994 to 2002; BRAT, from 2003 to 2007) and, although endovascular treatment was shown to be superior, results may not apply to the aforementioned subgroups, or in circumstances where new endovascular devices are needed.

The pragmatic trial methodology of ISAT-2 is frequently misunderstood. Many clinicians claim they would have preferred an explanatory trial design, with narrower patient selection, expert centers, and more rigid treatment protocols, to increase the chance that the trial could identify one treatment as superior. An explanatory trial design would, for example, exclude the use of innovative devices (such as stents, or flow diverters) and the difficulties they introduce. As devices, treatment indications and practices change with time, the concern is the 'moving target' problem: that the verdict of the trial may concern treatments that changed or were modified during the course of the study, and that at the end of the trial the results no longer apply to the devices or techniques under consideration. However, a narrowly defined explanatory trial is only appropriate when one is interested in a theoretical answer to the question: Does the treatment work in optimal conditions? Of course, a negative answer to such a question would mean that the treatment cannot possibly work. Although explanatory trial methodologies are often inappropriately used, such as when a manufacturer is trying to introduce a new device, that is not what the ISAT-2 trial is working towards. We know that clipping can work in selected circumstances, and it remains available in most centers treating aneurysms. The question of interest is: Which treatment is actually better in real life? That kind of question requires a pragmatic trial methodology, including a wide diversity of patients: i.e., all patients eligible for surgical clipping. It also needs a diversity of centers. Of course, to do this assessment properly, we would need many more centers. As for inclusion of new devices, if endovascular treatment of a patient required the

Table 3
Secondary outcomes (intent to treat).

	Surgical ($n = 55$)	Endovascular ($n = 48$)
Clinical outcome		
Peri-treatment hospital stay (days): mean (median) (range)	30 (17.5) (4–206)	17.1 (12) (2–101)
Number of patients hospitalized for > 20 days	26 (47%)	9 (19%)
Patients with new neurological deficits following treatment	4	2
Additional procedures during initial hospitalization for SAH		
Directed against ruptured index aneurysm	2	3
Decompressive hemicraniectomy	6	2
VP shunt or other permanent CSF diverting procedure	8	4
Tracheostomy and/or PEG	11	7
Symptomatic vasospasm	17	8
Vasospasm leading to balloon angioplasty	2	4
Discharge location		
Home	30	25
Other hospital/rehabilitation center	20	19
Death	5	4
mRS at discharge		
0	11	16
1	11	10
2	10	7
3	9	4
4	4	5
5	5	2
6	5	4
mRS > 2 at discharge	23/55 (42%)	15/48 (31%)
	Surgical ($n = 27$)	Endovascular ($n = 27$)
Angiographic imaging outcome – one year, intent to treat		
Complete aneurysm occlusion	23	18
Residual Saccular aneurysm	0	1
Residual Aneurysm Neck	3	7
Artifact (images not interpretable)	1	1
Angiographic imaging outcome – one year, as treated		
Complete aneurysm occlusion	24	17
Residual Saccular aneurysm	0	1
Residual aneurysm neck	2	8
Artifact (images not interpretable)	1	1

use of a device not available at the time of original ISAT study, then that patient had a 'difficult aneurysm', and that clinical context has never been properly compared with surgery, which could still be best for those patients. Such patients certainly belong in ISAT-2.

A previous study showed that, for a substantial number of patients for whom reliable evidence is still lacking, treatment decisions are eminently variable and non-reproducible, putting patients at risk of unnecessary morbidity [9]. When confronted with such a dilemma, the alternative to opinion-based care is to transparently address the uncertainty and practice in the context of a care trial [12].

If the pragmatic trial methodology is not well understood, the more advanced care trial philosophy is even less so [12]. The basic idea is that care trial methodology serves not only to address research questions. Long before answers can be obtained, the trial is designed to guide practice and optimize care under conditions of uncertainty. This philosophy requires that all items in the trial protocol are selected in the best medical interest of the participating patient [12].

The integration of clinical research methods with routine care offers a means to guide the use of treatments that have yet to show their comparative merit. In a care trial, scientific methods such as randomized allocation are used, not only to provide answers to research questions, but to impact and guide clinical care during the entire course of the trial, balancing risks by giving each patients a 50% chance (no more) of getting a treatment hypothesized (but not proven) to be better, and an equal 50% chance of getting the alternative treatment, because for the time being no one knows which one is best. This is how the uncertainty can best be addressed in the interest of each patient. According to this view, ISAT-2 can be seen as a prudent way to offer clipping to some RIA patients.

An incidental benefit of ISAT-2 is to document surgical outcomes in a randomized trial, thereby giving clipping (as well as society and future patients that could benefit from clipping) a chance to demonstrate its potential value. Clipping is still recommended on a case-by-case basis, but outside the context of care research, making it essentially unverifiable. Without evidence that clipping may be superior to endovascular treatment in some patients, the surgical skills, training and experience may eventually disappear. The superiority of endovascular treatment would then become a self-fulfilling prophecy. In this sense, ISAT-2 is at least a way to preserve a surgical option that may still be best for some patients.

Whether interim results should be reported and held to the same reporting standards as completed trials is an open question. We have followed the CONSORT guidelines, even though our primary aim was not to communicate outcome results but to demonstrate how the use of the care trial methodology can guide surgical practice in the best interest of current patients long before definitive trial results become available, and to recruit more centers and patients. We chose to present the raw data with confidence intervals rather than perform formal hypothesis testing, which we consider inappropriate and would have unnecessarily increased alpha error.

We have shown the feasibility of the approach to care for current patients, but whether it can provide definitive conclusions will depend on the participation of more centers. The received view that early publication could endanger further recruitment and completion of the trial only makes sense when the trial as currently conducted will likely reach definite conclusions. On the

contrary, the steering committee decided to publish interim results to encourage the recruitment of additional participating centers without which the long-term goal of level 1 evidence cannot be reached.

The use of surgical clipping is declining, and so is microsurgical expertise in aneurysm repair [16]. It would be unfortunate to prematurely abandon a treatment that could provide better clinical outcomes in some patients. In the meantime, it is increasingly difficult for centers that offer surgical clipping to justify such an invasive intervention if real-life benefit cannot be demonstrated. RCTs are difficult [25,26] but remain necessary: we believe outcome-based neurovascular care should use interventions supported by the results of pragmatic trials when available, and perform such interventions with the guidance of the trial when they are not.

There are many limitations to this study, including the small number of centers and patients and the unblinded assessment of the clinical and angiographic results. Patient heterogeneity is considered a strength when a pragmatic trial is designed to offer a care research context in which to practice a treatment that has yet to prove benefit.

5. Conclusion

ISAT-2 provides a means for clinicians to prudently manage patients with ruptured aneurysms to whom the results of previous RCTs may not apply. The results of this interim analysis are within the confidence intervals of the study hypothesis. The participation of more centers is required before meaningful conclusions can be drawn.

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Ethical approval

All procedures performed in the study involving human participants were in accordance with the ethical standards of the participating institutions and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Disclosure of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neuchi.2019.05.008.

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