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Impact of Treatment Delay on Outcome in the International Subarachnoid Aneurysm Trial

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Background and Purpose—ISAT (International Subarachnoid Aneurysm Trial) demonstrated that 1 year after aneurysmal subarachnoid hemorrhage, coiling resulted in a significantly better clinical outcome than clipping. After 5 years, this difference did not reach statistical significance, but mortality was still higher in the clipping group. Here, we present additional analyses, reporting outcome after excluding pretreatment deaths.

Methods—Outcome measures were death with or without dependency at 1 and 5 years after treatment, after exclusion of all pretreatment deaths. Treatment differences were assessed using relative risks (RRs). With sensitivity and exploratory analyses, the relation between treatment delay and outcome was analyzed.

Results—After exclusion of pretreatment deaths, at 1-year follow-up coiling was favorable over clipping for death or dependency (RR, 0.77 [95% CI, 0.67–0.89]) but not for death alone (RR, 0.88 [95% CI, 0.66–1.19]). After 5 years, no significant differences were observed, neither for death or dependency (RR, 0.88 [95% CI, 0.77–1.02]) nor for death alone (RR, 0.82 [95% CI, 0.64–1.05]). Sensitivity analyses showed a similar picture. In good-grade patients, coiling remained favorable over clipping in the long-term. Time between randomization and treatment was significantly longer in the clipping arm (mean 1.7 versus 1.1 days; $P<0.0001$), during which 17 patients died because of rebleeding versus 6 pretreatment deaths in the endovascular arm (RR, 2.81 [95% CI, 1.11–7.11]).

Conclusions—These additional analyses support the conclusion of ISAT that at 1-year follow-up after aneurysmal subarachnoid hemorrhage coiling has a better outcome than clipping. After 5 years, with pretreatment mortality excluded, the difference between coiling and clipping is not significant. The high number of pretreatment deaths in the clipping group highlights the importance of urgent aneurysm treatment to prevent early rebleeding. **(*Stroke*. 2020;51:1600-1603. DOI: 10.1161/STROKEAHA.120.028993.)**

Key Words: aneurysm ■ death ■ mortality ■ risk ■ subarachnoid hemorrhage

The treatment of aneurysmal subarachnoid hemorrhage (aSAH) has significantly changed following publication of the results of the ISAT (International Subarachnoid Aneurysm Trial). ISAT demonstrated that in patients considered eligible for both treatments, clinical outcome at 1 year after aSAH was significantly better with endovascular coiling than with neurosurgical clipping.[1,2] Also after longer follow-up, the benefit in terms of death alone was significantly better with coiling.[3] As a result, most neurovascular centers in Europe now preferentially use coiling.

Pretreatment rebleeding is the most serious risk to patients after aSAH and typically occurs in the early days after the ictus. Therefore, guidelines recommend to treat all patients with aSAH as soon as feasible.[4] In the 1990s, some centers preferred to delay neurosurgical clipping to avoid the vasospasm period, to allow for better operative conditions. As a result, in ISAT a significant difference in the interval between randomization and treatment between the 2 arms was observed (clipping mean 1.7 days versus coiling 1.1 days; $P<0.0001$).[1] More patients with neurosurgical allocation suffered pretreatment rebleeding compared with coiling allocation.[3]

The standard analysis in a prospective randomized controlled trial is intention-to-treat (ITT) analysis. The ITT method is appropriate for a trial when all events after randomization are considered an intrinsic part of the allocated treatment. However, delaying neurosurgical clipping is nowadays no longer considered appropriate. As such, a significant interest, particularly in the neurosurgical community, has been noted for an additional analysis considering time-to-treatment.[5–7]

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Current CONSORT-guidelines (Consolidated Standards of Reporting Trials) recommend that in addition to ITT analysis additional analyses that not have been prespecified should be accurately described to allow readers to interpret the effect of an intervention.[8] In this article, we present such additional analyses, investigating the impact of death and rebleeding after randomization but before treatment on outcomes in ISAT.

Methods

Patients

Data are available on request from the authors. ISAT included 2143 patients with aSAH considered equally eligible for both coiling and clipping. Inclusion criteria and treatment protocol are detailed in the primary article.[1] ISAT included 1644 patients (77%) from 22 UK centers and 499 patients (23%) from 22 non-UK centers. Ethics approval was obtained from the local institutional review board, due to the retrospective nature of these additional analysis of ISAT, the board waived the need for informed consent.

Outcome Measures

The primary outcome was death or dependency. The secondary outcome was death alone, also measured at 1 and 5 years following aSAH. The modified Rankin Scale was used to classify the clinical outcome, with dependency defined as modified Rankin Scale 3–5. Allocation was to a policy of coiling or clipping. Rebleeding was in the original protocol defined as the occurrence of symptoms of clinical deterioration, confirmed by the increase of blood on a subsequent computed tomography scan.

Study Design

In this study, additional analyses were made on ISAT data. We analyzed the outcome of coiling and clipping after exclusion of postrandomization pretreatment deaths. Thus, we aimed to adjust for events that occurred before treatment initiation. Our hypothesis is that after exclusion of pretreatment deaths, there will be no significant difference between coiling and clipping in long-term.[6,8]

We performed 3 additional sensitivity analyses. First, we excluded all pretreatment rebleedings, whether fatal or not. Second, we performed an as-treated analysis, in which patients were analyzed as actual treatment received, omitting untreated patients. Last, as treatment delay is more common in poor-grade patients, we performed an as-treated analysis in all patients with a good clinical condition at randomization (World Federation of Neurosurgical Societies grade I–II).

Statistical Analysis

All patients' vital status was known, modified Rankin Scale scores were missing for 25 (1%) and 364 (17%) patients at 1 and 5 years not significantly different between groups. Missing values were imputed with modified Rankin Scale scores at other time points. Categorical data were analyzed with the Pearson χ^2 tests. Mann-Whitney *U* tests were used to compare nonparametric data. Relative risk (RR) was used to describe treatment effect. A 2-tailed $P<0.05$ was considered statistically significant. All statistical analyses were performed using STATA 15.0 (StataCorp, College Station, TX).

Results

Exclusion of Pretreatment Deaths

The Figure shows that 1073 patients were allocated to coiling and 1070 to clipping. After randomization, 27 patients died before treatment; 19 in the neurosurgical arm and 8 in the endovascular arm. Baseline patient characteristics after exclusion of pretreatment deaths show no significant differences (Table I in the Data Supplement). Outcome of these patients is shown in Table II in the Data Supplement. After excluding pretreatment deaths, RR for death or dependency at 1 year was significantly in favor of coiling (0.77 [95% CI, 0.67–0.89]; Table); RR for death was 0.88 (95% CI, 0.66–1.19). At 5 years, the difference did not reach statistical significance, for either death or dependency (RR, 0.88 [95% CI, 0.77–1.02]) or for death alone (RR, 0.82 [95% CI, 0.64–1.05]).

Sensitivity Analyses

Baseline characteristics and outcome of the different populations can be found in Table II–VI in the Data Supplement. Fifty patients suffered a rebleeding before treatment was initiated; 31 in the neurosurgical arm and 19 in the endovascular arm. At 1 year, rebleeding resulted in 5 additional deaths; 15 patients were functionally dependent.

The Figure shows the population of the as-treated analysis, excluding pretreatment deaths and analyzing cross-overs with actual treatment received. The majority of included patients (1861/2143, 87%) were in a good clinical condition at randomization. Of these, 964 (52%) actually had coiling and 897 (48%) had clipping.

Using these populations as sensitivity analyses, similar results are found (Table). However, in good-grade patients, the long-term benefit of coiling remained (RR death or dependency 0.82 [95% CI, 0.71–0.96]; death alone 0.72 [95% CI, 0.54–0.97]).

Treatment Delay

Median interval between randomization and fatal rebleeding (n=23) was 2 days (interquartile range, 1–4 days), with for coiling a mean of 0.8 days (range 0–2) and for clipping a mean of 3.7 days (range 0–17). Overall, a significantly longer interval between randomization and treatment was noted with clipping (mean 1.7 versus 1.1 days; $P<0.0001$), in which respectively 17 patients died following a rebleed versus 6 in the endovascular arm (RR, 2.81 [95% CI, 1.11–7.11]). Additional analysis of this treatment delay showed a significant difference between UK and non-UK centers (mean 1.4 versus 0.4 days; $P<0.0001$). In non-UK centers, 3/499 rebleeds were observed, versus 47/1644 in the UK. All pretreatment deaths occurred in UK centers. Median time from SAH to admission was 0 days (interquartile range 0–1), balanced between 2 arms. Median time from admission to randomization was 1 day (interquartile range, 1–3).

Discussion

This study aims to investigate the effect of treatment delay on the ISAT outcomes. These analyses support the conclusion of ISAT that at 1 year after aSAH, coiling had a better outcome. After 5 years, with pretreatment deaths excluded, the difference between coiling and clipping did not reach significance. The most dreaded complication of aSAH is early rebleeding, which is often lethal. In ISAT, 50 patients suffered from a rebleeding before treatment. It is likely that the interval between randomization and treatment played a significant role. This is further supported by the absence of pretreatment deaths in the non-UK cohort, as treatment was initiated faster than in UK centers.

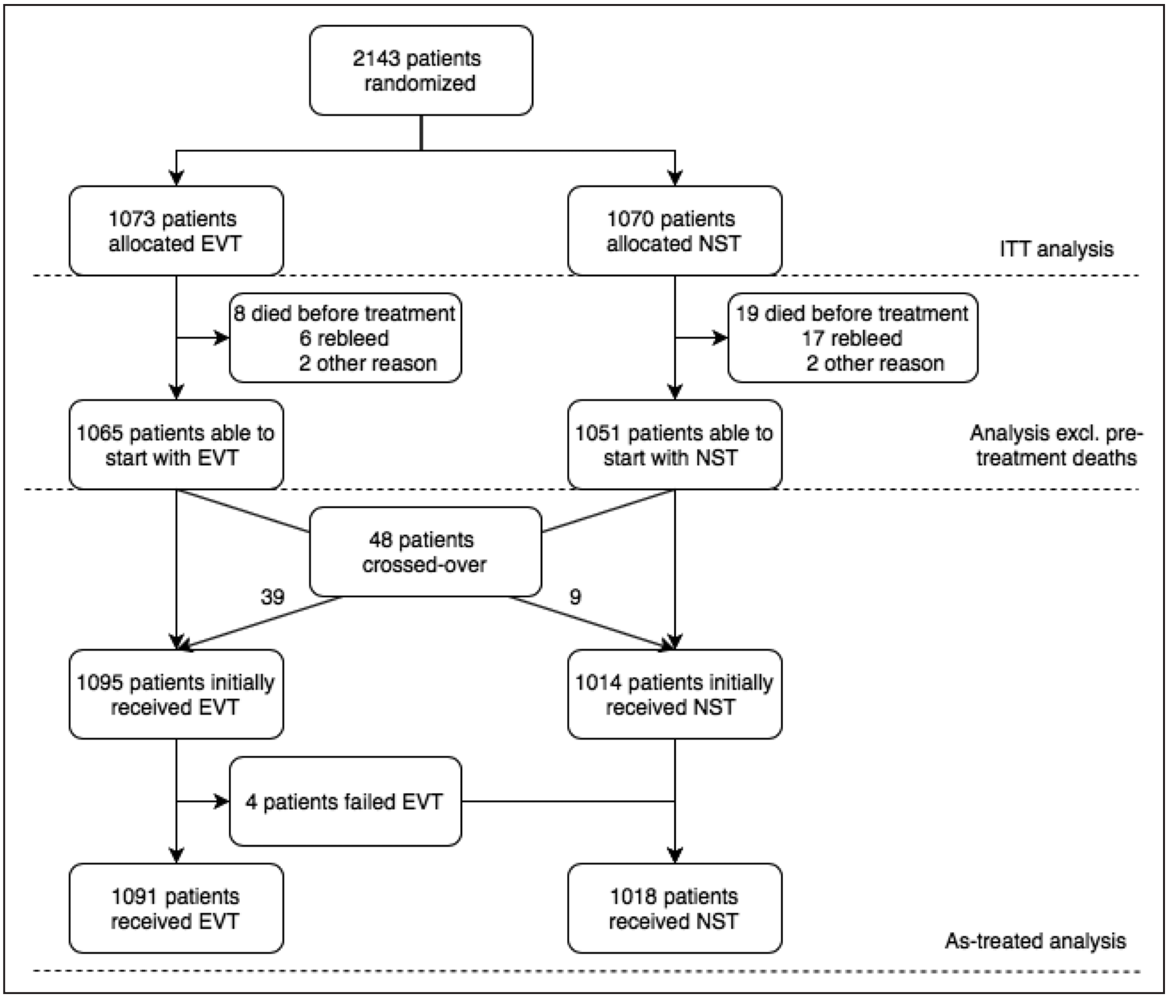

Figure. Flowchart of randomization to actual treatment. EVT indicates endovascular treatment; ITT, intention-to-treat; and NST, neurosurgical treatment.

Poor-grade patients more often receive delayed treatment and have a worse clinical outcome due to the primary hemorrhage. In line with this, a Cochrane review on coiling versus clipping emphasized that the original ISAT results applied primarily for good-grade patients and that for poor-grade patients, the favorability of coiling is not well established.[9] Currently, ISAT II is ongoing, including patients not originally recruited in ISAT, mainly focusing on poor-grade patients or patients in whom clipping was considered a better alternative. The interim results show that at 1 year 16/42 (38%) and 10/34 (29%) patients were dead or dependent in the surgical and endovascular allocations respectively but with wide confidence intervals.[10]

It is important to recognize that the originally applied ITT analysis is considered the gold standard when comparing 2 types of treatment. However, current CONSORT-guidelines recommend that also other relevant analyses should be reported if underestimation of treatment effect is expected. The additional analyses allow for a wider understanding of ISAT, which is important as the main evidence on supremacy of coiling is originating from ISAT.[9]

Table. Relative Risk (95% CI) of Death or Dependency and Death Alone, for Endovascular Coiling Compared With Neurosurgical Clipping, at 1 and 5 Years, for the Original ITT Analyses and the 4 Additional Analyses

	1 Y		5 Y	
Type of analysis	Death or Dependency	Death	Death or Dependency	Death
Original ITT analysis	0.76 (0.66–0.88)*	0.81 (0.61–1.06)	0.85 (0.76–0.99)	0.78 (0.62–0.98)*
After exclusion of all pretreatment deaths	0.77 (0.67–0.89)*	0.88 (0.66–1.19)	0.88 (0.77–1.02)	0.82 (0.64–1.05)
After exclusion of all pretreatment rebleedings	0.77 (0.67–0.90)*	0.89 (0.66–1.20)	0.88 (0.77–1.02)	0.82 (0.64–1.05)
As-treated analysis	0.80 (0.69–0.92)*	0.87 (0.64–1.16)	0.90 (0.78–1.03)	0.85 (0.66–1.08)
Good-grade patients, as-treated analysis	0.73 (0.62–0.87)*	0.74 (0.52–1.06)	0.82 (0.71–0.96)*	0.72 (0.54–0.97)*

ITT indicates intention-to-treat.
*Significance.

Some limitations need to be addressed. Given the retrospective design, the reasons of treatment delay in individual patients were not identified. Furthermore, it is likely that results of endovascular treatment have substantially improved over the last decades, due to better techniques, better quality of angiographic imaging and increased experience of physicians.[11] Also, other changes in treatment of patients with SAH occurred, for example, blood pressure management. Because of these changes over time, the results from ISAT do likely not reflect current clinical outcomes. Three recent prospective RCTs compared different coil types, providing reliable prospective data on contemporary clinical outcome of coiling in good-grade patients.[12–14] Nevertheless, the current additional ISAT analyses do show that outcome of clipping in the original ITT analysis was negatively impacted by the higher number of early rebleeds in the neurosurgical arm because of treatment delay. This implies that in patients with aneurysms suitable for both treatment modalities, delaying treatment because of nonavailability of one treatment option may not be justified because of the cumulative risk of rebleeding. The high number of pretreatment deaths clearly warrants urgent aneurysm treatment to prevent early rebleeding.

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Dr van Donkelaar analyzed data and drafted the article. Dr Bakker co-analyzed data and drafted the article. J. Birks co-analyzed data, facilitated the study, and revised the article. A. Clarke and M. Sneade interpreted data and revised the article. R.S.C. Kerr and Dr Veeger interpreted data and revised the article. Dr. van Dijk supervised the study and revised the article. A.J. Molyneux supervised and facilitated the study and revised the article.

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Disclosures

None.

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