Improved Cognitive Outcomes With Endovascular Coiling of Ruptured Intracranial Aneurysms

Neuropsychological Outcomes From the International Subarachnoid Aneurysm Trial (ISAT)

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Background and Purpose—The International Subarachnoid Aneurysm Trial (ISAT) reported lower rates of death and disability with endovascular versus neurosurgical treatment of ruptured intracranial aneurysms. However, assessment of functional outcome was limited to the modified Rankin Scale, which is known to be insensitive to cognitive function. A neuropsychological substudy (N-ISAT) was therefore done in all recruits from 8 ISAT centers in the United Kingdom.

Methods—Detailed neuropsychological assessment was performed at a 12-month follow-up visit. Impairment was defined as performance below the 5th percentile of the study population on at least 2 tests in ≥2 major cognitive domains. Analysis was restricted to patients who were not known to be otherwise disabled according to the modified Rankin Scale (ie, modified Rankin Scale 0 to 2).

Results—Of 836 patients randomized in ISAT in the 8 UK centers (411 allocated endovascular treatment versus 425 neurosurgery), 224 were dead or disabled before 12-month follow-up (78 allocated endovascular treatment versus 135 neurosurgery). Of the remaining 612 patients eligible for neuropsychological assessment, 137 (65 allocated endovascular treatment versus 72 neurosurgery) did not attend. Of the 474 nondisabled patients who were assessed, 152 (32.1%) had cognitive impairment. Patients with cognitive impairment had reduced self-reported health-related quality of life ($P<0.001$) in both treatment groups, but cognitive impairment was less common in those allocated endovascular treatment (70 of 262 versus 82 of 212 allocated neurosurgery, OR=0.58, 95% CI 0.38 to 0.87, $P=0.0055$). The incidence of epilepsy was also lower in the N-ISAT endovascular group (7 versus 18, OR=0.30, 0.11 to 0.77, $P=0.005$) but was independent of the effect on cognitive function.

Conclusions—Cognitive impairment occurred in approximately one third of patients who were not otherwise disabled according to the modified Rankin Scale in N-ISAT and was more frequent in the neurosurgery group. These results have implications for management of ruptured intracranial aneurysms and more generally for interpretation of the outcomes of clinical trials that use the modified Rankin Scale. **(*Stroke*. 2010;41:1743-1747.)**

Key Words: aneurysm ■ endovascular treatment ■ neuropsychology outcomes ■ neurosurgery

The International Subarachnoid Aneurysm Trial (ISAT) initially reported the primary clinical outcomes on the modified Rankin Scale (mRS) at 2 months and 1 year after neurosurgical clipping or endovascular coiling as a treatment for ruptured intracranial aneurysms.[1,2] Unfavorable outcomes at 12 months (ie, mRS Grade 3 to 6) were reported in 30.9% of cases randomized to neurosurgery and 23.5% to embolization with a difference in mortality still evident at 5-year follow-up.[3] However, clinical disability and handicap scales such as the mRS are insensitive to poor neuropsychological outcomes,[4,5] and the effect of endovascular versus neurosurgical treatment on cognitive outcomes in patients without physical disability is uncertain. Previous small studies have identified clinically significant neuropsychological impairments with an impact on overall quality of life in patients with an apparently "good" neurological outcome (ie, Glasgow Outcome Scale Grade 1) after subarachnoid hemorrhage (SAH).[5–7]

The ISAT protocol therefore included a substudy (N-ISAT) in which detailed neuropsychological assessments at 12-month follow-up were performed in all patients randomized from 8 UK centers. We report the rates of cognitive impairment in patients who had no major physical disability (mRS 0 to 2) to

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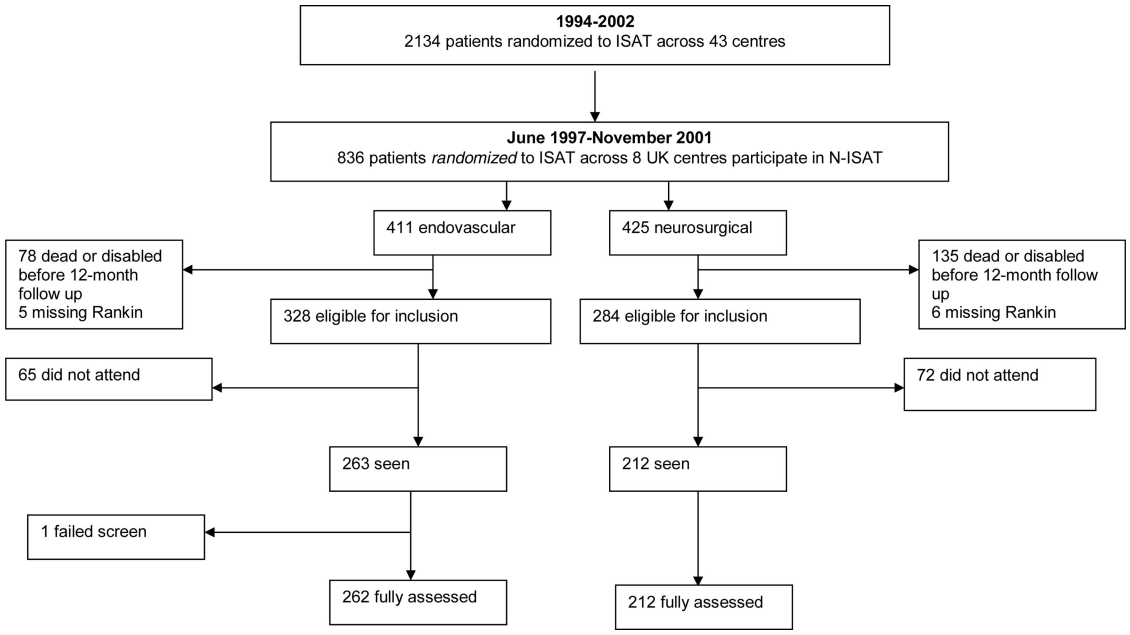

Figure. N-ISAT analysis cascade for 12-month face-to-face neuropsychological assessments.

more fully determine the overall clinical outcome in the 2 treatment groups in ISAT. These results also allow a better understanding of the distribution of neuropsychological outcomes across clinical handicap scales in patients who have had acute neurological events.

Methods

The eligibility, recruitment, and characteristics of ISAT, from which the N-ISAT subsample was drawn, have been reported together with the main trial design and methods.[1] The detailed methods of N-ISAT in terms of organization, training, recruitment, and assessment protocols have also been reported together with an analysis of data quality.[8,9] The study was approved by the Oxford Research Ethics Committee.

All patients who had been enrolled in the 8 UK centers participating in N-ISAT and who had survived to 12 months were followed-up as per the main ISAT protocol[1] and were also eligible for face-to-face neuropsychological assessment as part of N-ISAT. Patients were contacted by letter followed by a telephone call initially. Multiple attempts were made to contact nonresponders.[9] Given the uncertainty about the number of cases that would be randomized in the United Kingdom, the pragmatic aim was to study all randomized cases.

Given the likely multiplicity of lesion distribution and severity, the N-ISAT assessment battery was designed to sample cognitive function comprehensively. Evaluation of general verbal and nonverbal intellectual skills and memory, language and spatial skills, attention, psychomotor/processing speed, and executive function was included in the test battery, which has been described and referenced in detail elsewhere.[8,9] Health-related quality of life (HRQol) was assessed with the EuroQol.[10] mRS and HRQol were assessed independently of the cognitive assessment as part of the main trial protocol.

Cognitive assessments were carried out by trained assistant psychologists in each center under the supervision of consultant clinical psychologists. The assessors were blind to the treatment allocation and patients were requested not to reveal any information about the treatment that they had received. The effectiveness of blinding was tested after the assessment by asking the assessor to record whether they became aware of the allocation.

To accommodate a range of cognitive impairment, the cognitive battery was organized into "screening," "core," and "full" protocols of increasing length and sensitivity.[8] A preassessment "screening" test battery was administered if a patient was thought likely to have significant cognitive impairment. If this was found to be the case on these tests, testing was discontinued. The "core" test protocol comprised 22 measures drawn from 15 "pencil and paper" tests. The "full" battery comprised the "core" protocol and an additional 7 measures from 6 computerized tests. All tests were administered in the same sequence, beginning with prescreening, followed by the "core" battery through to complete the "full" battery.

A detailed methodology for classifying individual patients' neuropsychological profiles as cognitively "impaired" versus "unimpaired" has been reported elsewhere.[8] Briefly, all individual test scores were transformed into a common metric (z-score) and scores below the fifth percentile "cutoff" taken as indicating impairment. A principal components analysis identified 6 uncorrelated principal components or cognitive "domains" (ie, verbal memory, general verbal skills, processing speed, nonverbal skills, spatial working memory, and executive skills). Cognitive impairment was defined as presence of at least 2 impaired test scores on $\geq$2 of these 6 cognitive domains. In a few patients with some missing data, cognitive impairment was defined if they were below the fifth centile on at least 5 tests.

N-ISAT was planned before the start of recruitment into ISAT and was included in the ISAT protocol, but sample size was not predefined. Rather, the study sample size was determined on pragmatic grounds based on the availability for funding for 8 UK centers. These centers were selected on the basis of high predicted recruitment rates.

Comparisons of the baseline characteristics and outcomes in the trial arms were undertaken using χ^2 and t tests, as appropriate.

Results

Of the 836 patients enrolled in the 8 UK centers participating in N-ISAT, 65 died before the 12-month follow-up (24 allocated to endovascular treatment and 41 allocated to neurosurgery). Of the 771 12-month survivors (387 allocated to endovascular treatment and 384 allocated to neurosurgery), 148 were disabled (mRS $>$2) at the 12-month follow-up (54 allocated to endovascular treatment and 94 allocated to neurosurgery) and mRS grades were unavailable for 11 patients (5 allocated to endovascular, 6 allocated to neurosurgery) leaving 612 patients (328

Table 1. Baseline Characteristics of the N-ISAT Sample

	N-ISAT Subsample (mRS 0 to 2)	
Treatment Groups	Endovascular (n=262)	Neurosurgery (n=212)
Male sex	103 (39%)	82 (39%)
Age, years*	51.5 (41–58; 23–77)	50 (41–57; 19–77)
WFNS grade		
1	205 (78%)	162 (77%)
2	44 (17%)	40 (19%)
3	9 (3%)	10 (5%)
4	4 (2%)	0
5	0	0
6	0	0
Maximum target aneurysm lumen size, mm		
≤5	146 (56%)	123 (58%)
6–10	104 (40%)	76 (36%)
≥11	12 (4.6%)	13 (6%)
No. of aneurysms detected		
1	198 (76%)	173 (82%)
2	42 (16%)	31 (15%)
3	16 (6%)	5 (2%)
≥4	6 (2%)	3 (1%)
No. of crossover procedures	2 (0.8%)	6 (2.8%)
Time between SAH and randomization, days*	2 (1–5; 0–25)	2 (1.25–5; 0–23)

*Median (interquartile range; range).
WFNS indicates World Federation of Neurological Surgeons clinical grading scale.

allocated endovascular treatment and 284 neurosurgery) eligible for the current analysis.

Of the 612 eligible patients, 474 (262 allocated endovascular treatment and 212 neurosurgery) were assessed (Figure). Multiple attempts were made to contact nonresponders,[9] but 137 patients could not be contacted or declined to attend (65 allocated endovascular treatment and 72 neurosurgery). As a proportion of eligible patients, the rate of assessment tended to be higher in the endovascular treatment group (262 of 328 [79.9%] versus 212 of 284 [74.6%], $P=0.12$). Reasons for nonassessment were similar in the 2 randomized treatment groups. Effective blinding of assessors to original randomized treatment allocation was similarly effective: 210 cases (79.8%) in the endovascular group versus 168 (79.2%) in the neurosurgery group.

There were no significant differences in baseline clinical characteristics between the N-ISAT and main ISAT cohorts, including World Federation of Neurological Surgeons grade, aneurysm size and number, crossover procedures, and time from SAH to randomization, and no significant imbalances between the randomized treatment groups in N-ISAT overall or for those who were assessed (Table 1).

Of the 474 nondisabled patients who were fully assessed (262 allocated endovascular treatment and 212 neurosurgery), cognitive impairment was less common in those allocated endovascular treatment (70 of 262 versus 82 of 212 allocated neurosurgery, OR=0.58, 95%CI 0.38 to 0.87, $P=0.0055$). In the 395 (82.6%) patients for whom complete data were available for at least 10 tests, there was also a statistically significant trend ($P=0.0057$) toward impairment in a greater number of cognitive domains in the neurosurgery group than in the endovascular group (Table 2).

Table 2. No. of Patients With Deficits in 0 to 6 Domains

No. of Domains With Deficits	Endovascular	Neurosurgery
0	95 (44.0%)	61 (34.1%)
1	63 (29.2%)	48 (26.8%)
2	34 (15.7%)	37 (20.7%)
3	13 (6.0%)	15 (8.4%)
4	5 (2.3%)	9 (5.0%)
5	5 (2.3%)	6 (3.4%)
6	1 (0.5%)	3 (1.7%)
Total	216	179

Data available on 395 patients who had data in all domains.

There was no interaction between incidence of epilepsy on follow-up and the presence of cognitive impairment at 1 year. The incidence of epilepsy was lower in the N-ISAT endovascular group (7 versus 18, OR=0.28, 0.10 to 0.73, $P=0.003$). Among patients with no cognitive impairment, 12 had at least 1 seizure during follow-up in the neurosurgery group versus 3 in the endovascular group. Among patients with cognitive impairment, 6 had at least 1 seizure in the neurosurgery group versus 4 in the endovascular group.

Self-reported HRQol based on the mean (SD) EuroQol "thermometer" score was available in 456 (95.0%) patients. Mean (SD) HRQol was lower in patients with cognitive impairment than in those without in both randomized treatment groups ($P<0.001$ overall): 78.4 (17.3) versus 85.2 (12.3) in the endovascular group (n=257); and 77.1 (15.4) versus 83.8 (12.0) in the neurosurgery group (n=199). The frequency of cognitive impairment also increased with mRS score (P trend=0.007; Table 3) but was more frequent in the neurosurgery group at each grade.

Among patients who were in full-time employment before their SAH, those who had returned to work by the 1-year follow-up visit were nonsignificantly less likely to have cognitive impairment than those who did not return to work (42 of 177 versus 21 of 63, OR=0.63, 0.32 to 1.22, $P=0.14$).

Discussion

Until the development of endovascular techniques in the early 1990s, neurosurgical repair was the only available treatment option following aneurysmal SAH. Developments in clinical

Table 3. The Proportions of Patients With Cognitive Impairment Stratified According to mRS Score and Randomized Treatment Allocation

	No. (%) With Cognitive Deficit		
mRS Score	Endovascular	Neurosurgery	Overall
0	17/86 (20%)	15/48 (31%)	32/134 (24%)
1	17/91 (19%)	32/97 (33%)	49/188 (26%)
2	31/85 (36%)	27/67 (40%)	58/152 (38%)

management and surgical technique were associated with reductions in the risk of death or major morbidity,[11,12] but there has been an increasing awareness that cognitive dysfunction is a significant neurological impairment after SAH.[7] Some studies have suggested relatively benign cognitive outcomes in uncomplicated cases,[13,14] but predictors of poor cognitive outcome have included the timing, management, or complications of surgery[6,15]; the severity of or complications associated with the SAH[16]; World Federation of Neurosurgical Societies grade/score at admission or discharge[7,17]; CT/MRI/single photon emission CT/angiographic abnormalities[12]; clinical and radiographic risk factors[18]; lesion distribution[17–20]; and demography.[21,22] Only 1 small randomized trial of endovascular coiling versus neurosurgical treatment has studied cognitive outcome, reporting consistent but nonsignificant trends toward better outcome with endovascular treatment.[23] However, the analysis was underpowered with 75 of 111 randomized patients assessed at 12-month follow-up. Other small nonrandomized studies have also found less cognitive impairment with endovascular treatment.[24] However, both studies had limitations; the former was conducted on a relatively small sample and the latter on a nonrandomized group.

We have shown in N-ISAT that cognitive impairment was common in patients who were not otherwise disabled according to the mRS and that cognitive impairment was more frequent in the neurosurgery group. The trial cohort comprised predominantly anterior circulation aneurysms, and especially anterior communicating region lesions, that would require frontal lobe retraction and possible gyrus rectus dissection to enable surgical clipping. This may account for the cognitive domains that were most adversely affected in the neurosurgery group (verbal memory, processing speed, and executive skills; Table 4). These results have important implications for management of ruptured intracranial aneurysms and more generally for interpretation of the outcomes of clinical trials that use the mRS. We found that patients with cognitive impairment reported significantly lower HRQoL and were more likely to report mRS score >0, consistent with the impact that cognitive impairment can have on patient-centered outcomes such as quality of relationships and performance at work.

In terms of more general implications for interpretation of the outcomes of clinical trials in neurology that use the mRS without cognitive assessment, our data suggest that clinically important impairments may be missed, leading to a likely underestimation of the overall effect of the intervention on patients. For example, the mRS is the standard primary outcome for trials of treatment for acute stroke[25–27] and few such trials make any additional assessment of cognitive function. Yet, cognitive impairment is a common consequence of stroke.[28]

Table 4. Percentage of Patients With Deficits in Each Domain

	Percent With Domain Deficit (≥2 tests)		
	Endovascular	Neurosurgery	*P*
Domain 1 (verbal memory)	27% (59/216)	38% (68/179)	0.03
Domain 2 (general verbal skills)	5% (11/216)	7% (13/179)	0.40
Domain 3 (processing speed)	18% (38/216)	29% (52/179)	0.008
Domain 4 (nonverbal skills/memory)	25% (54/216)	25% (44/179)	1.000
Domain 5 (spatial working memory)	10% (22/216)	16% (29/179)	0.097
Domain 6 (executive skills)	17% (37/216)	25% (45/179)	0.06

Data available on 395 patients who had data in all domains.

Although we believe that our findings are reliable, our analysis does have a number of shortcomings. First, we were unable to perform detailed cognitive testing in all ISAT centers. However, at least in terms of baseline clinical characteristics, there was no evidence that the patients recruited in the N-ISAT centers differed systematically from those recruited in the trial as a whole. Moreover, our sample size was justifiable a priori and N-ISAT was 1 of the largest ever studies with full cognitive assessment as opposed to a short screening test such as the Mini Mental State Examination in a randomized trial. Second, we were unable to persuade all eligible ISAT patients to take part in the study. However, there was little difference between the treatment groups in the rate of participation (79.9% for the endovascular groups versus 74.6% for the neurosurgery group) and participation was similar to that achieved previously in similarly detailed studies (ie, a 3-hour battery of neuropsychological tests).[23] Third, although the N-ISAT substudy was part of the original ISAT protocol, the N-ISAT outcome (cognitive impairment was defined as presence of at least 2 impaired test scores on 2 of the 6 major cognitive domains) was not prespecified. However, the neuropsychological tests used were, of course, prespecified and the assessments were detailed and systematic. Moreover, a principal components analysis was used to select the core neuropsychological tests for analysis, which is an objective method and was independent of any knowledge of randomized treatment. Furthermore, those patients who were defined as being cognitively impaired had a worse self-reported HRQoL and tended to be less likely to return to full-time paid employment, indicating that the cognitive outcome had some validity. Fourth, it is possible that there might be delayed improvement in cognitive function in the neurosurgery group beyond our 1-year assessment.

In conclusion, cognitive impairment occurred in approximately one third of patients who were not otherwise disabled according to the mRS in N-ISAT and was more frequent in the neurosurgery group. These results have implications for management of ruptured intracranial aneurysms and more generally for interpretation of the outcomes of clinical trials that use the mRS.

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Disclosures

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