Editorial

Barrow Ruptured Aneurysm Trial

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We are grateful to the editor for this opportunity to comment on the report of the 3-year outcomes of the Barrow Ruptured Aneurysm Trial (BRAT).15

Before making specific comments on the trial it may be helpful to readers to set out the widely accepted standards and procedures for the conduct design and reporting of randomized clinical trials. These are set down in the Consolidated Standards of Reporting Trials (CONSORT).1,14 These criteria have been adopted by more than 300 international medical journal editors including all the major medical journals.

The purpose of the CONSORT criteria is to ensure that studies published in these journals fulfill methodological rigor to ensure the quality and scientific reliability of the published data.

Three key requirements of CONSORT are:

1) Publication of the full protocol, and any later modifications, before and during the trial. Most importantly this must include any proposed subgroups (preplanned subgroup analysis).

2) Registration and protocol submission to a central database of randomized clinical trials such as Clinical Trials.gov.

3) Full accounting for all enrolled patients including those lost to follow-up and reporting of all deaths. Reporting the extent of missing patient data is essential.

Methodological Issues

There are a number of design and reporting features of BRAT that do not fulfill CONSORT criteria, which have exposed the design and methodological weaknesses of the trial.

The authors of the current paper state that the protocol was described in their original report.5 This is not correct, as the full BRAT protocol to our knowledge has not been published, and it would be very helpful if the protocol was in the public domain and accessible. BRAT was not registered with any of the clinical trial databases until April 2012, sometime after its completion of recruitment and the first publication (Clinicaltrials.gov 30 April 2012 NCT01593267). The importance of both of these, as CONSORT requirements, is to specify any planned sub-

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In this report and in the first BRAT paper, the extent of the missing outcomes is not explicitly stated. Of the total of 471 patients enrolled, 403 had outcome data reported (Table 3)—about 13% missing. In the present paper the authors are able to report 349 of 408 outcomes for treated patients at 3 years (Table 1)—about 15% missing.

It would be usual when reporting a clinical trial to state the distribution of these missing outcomes between the groups and to know how many deaths there are in each allocation. There may be significant imbalances between the groups in the extent of the missing data that could seriously affect the results.

Without these data, any conclusions drawn may be unreliable. It would be very helpful to have tables of the individual outcomes and deaths listed and the exact distribution of this missing data, and whether this included all enrolled patients or just treated patients.

Misleading Statements Regarding ISAT

The authors make a number of statements in the current paper that are misleading and factually inaccurate regarding ISAT.9,10

Throughout the paper, the authors cite as fact that 80% of eligible patients were not enrolled in ISAT. Whilst it is correct that about 80% of all patients who were admitted to ISAT centers during the recruitment period of the trial with a confirmed aneurysmal SAH (aSAH) were not enrolled, many potentially eligible patients were not enrolled for operational reasons, such as no interventionist available to treat the patient, no angiography room available, unsuitable aneurysm anatomy, or lack of consent. The trial protocol, published by The Lancet in 1997,7 stated clearly that the patient had to have an aneurysm suitable for both treatments and clinical equipoise existed for these patients. The proportion of aSAH patients enrolled in individual centers varied widely between 1% and 44%, reflecting individual clinical views and belief at the time that a particular treatment was better (that is, lack of clinical equipoise). We have addressed this widespread fallacy in a recent letter published in the Journal of Neurosurgery.6

The statement suggesting that there was selection bias in ISAT. We have always stated in all the ISAT-related publications that it is a study of a selected population of aSAH patients. It is not correct to call this bias. The selected population is fully described; within that population the allocation was concealed, and reporting was by intention to treat. Once patients were enrolled there was no bias in the trial. The population of patients in ISAT was balanced for known prognostic factors by the minimization process, with the allocation group revealed after the patient’s baseline data had been collected. In practice, 97% of the patients had anterior circulation aneurysms, 88% were in good grade (World Federation of Neurosurgical Societies [WFNS] Grade I or II), and 90% had aneurysms less than 10 mm in diameter. In the United Kingdom (UK) national audit data this represented about 80% of more than 2000 patients treated between 2001 and 2002 in the UK.4,13 The ISAT patient population inevitably shows some differences from BRAT.

They state that the outcomes in ISAT are similar in the 2 groups at 5 years. In ISAT this was the case if the patients were alive. It ignores the fact that there was a significant excess mortality in the clip-treated group at 5 years after treatment. The similarity of outcome with respect to dependence in the report was conditional on patient survival. This was clearly stated in the 2009 Lancet Neurology paper.8 Therefore, the bald statement they make in this respect that the late outcomes are similar is not valid as stated.

In the Discussion, the authors reference the paper of Gnanalingham and colleagues3 as being from a major ISAT participating institution. This is incorrect, the data used for this paper were not from an ISAT recruiting center.

The authors stated in their response to the letter by Drs. Darsaut and Raymond2 that although the ISAT’s ratio of screened to enrolled patients was a common criticism, they “did not suggest that it invalidated the findings with respect to the population studied or even that it was a valid criticism.” This current paper appears to contradict that statement.

Comments Regarding the Discussion

The Discussion cites O’Kelly and colleagues11 study of cases in the Ontario Stroke database involving patients treated between 1995 and 2004 as evidence that there were worse outcomes in the coil-treated patients. This presupposes that the characteristics of the population in the clip-treated and coil-treated groups have similar baseline clinical characteristics, which of course they could not have because they were not randomized. Whilst the authors attempted to stratify for initial condition in that paper and adjust statistically for the inevitable differences between the groups, there were insufficient clinical data available from an administrative database such as this to stratify for major prognostic features—notably, even clinical grade on admission. For example, a significantly higher proportion of patients treated with coil embolization were ventilated on admission, and O’Kelly et al. recognized these shortcomings. Thus, attempting to draw scientifically valid conclusions from such data may be misleading.

A larger administrative database study was published by Qureshi and colleagues,12 who used the US National Inpatient Sample database. Their paper compared the in-hospital mortality in the years 2000–2002 and 2004–2006 on the basis of a total sample size of 147,000 patients. It showed a 3% fall in in-hospital mortality and an increase in the rate of treatment with coil embolization from 3% to 17% of patients with SAH.

We appreciate that the BRAT investigators have made a significant effort to address what was widely perceived to be a weakness of ISAT. BRAT was originally designed as a pilot study to test the feasibility of a larger trial, and in the report of the 1-year results, the authors stated that the study was not expected to be powered sufficiently to demonstrate differences in outcome between the groups.5 However in that report, despite the extent of the missing outcomes, the primary outcome, based on intention to treat, showed a larger absolute benefit of coiling—10%