SHOULD PATIENTS WITH UNRUPTURED AVM BE REFERRED FORM INTERVENTION: NO

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A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA), funded by the National Institute of Neurological Diseases and Stroke (NINDS) of the US National Institutes of Health, had its randomization phase ended in April 2013. At that time 226 patients had been randomized from 39 centers in 4 continents. The cohort had a mean follow-up of 3.3 years. This action by the NIH-appointed Data and Safety Monitoring Board was due to a disparity in outcomes (death or stroke documented by MR imaging) favoring the medical arm (HR=3.41 95%CI: 1.72-6.76).

The trial was limited to those brain arteriovenous malformations (bAVMs) discovered not having bled, and only those considered by the treating centers to have a bAVM suitable for attempted eradication. The cases were randomized 1:1 to medical management alone versus medical management plus intervention to eradicate brain arteriovenous malformations. Eight hundred cases were originally planned for randomization. Based on the slow enrollment rates typical of many clinical trials, and the resulting need for a lengthened time of follow-up (allowing more events to occur in the medical-only group) prompted the DSMB to authorize a reduced sample size of 400. In the end, the great disparity between events, worse in the interventional group, brought the randomization phase to a close at the recommendation of the DSMB before these numbers were reached. The DSMB strongly recommended continued follow-up for those in the trial.

For those treated with medical management alone, only 8 of the 110 suffered outcome events, and for 6 of them the effects were clinically mild (modified Rankin Score 0-1). By contrast, 38 outcome events occurred in the interventional arm, clinically serious for 28 (modified Rankin Score 2-5).

Longer follow-up is needed to determine if the disparity in outcome events will persist. However, based on current event rates, some 12-30 years may be needed for the medical arm to suffer outcome events to reach the number already documented from intervention. Should the stroke events be counted only if they are clinically serious, many more years might be needed.

The group characterized as Spetzler-Martin Grade I had the closest to comparable outcomes for the medical vs interventional group. This group had a bAVM <3 cm in size and superficial location, no deep venous drainage, and located in an area no expected to produce major clinical syndrome from lesion eradication. They remain a subject of further study. Those larger, or with deep venous drainage, and/or located in clinically-important areas seem by current techniques too prone to adverse events from intervention. They have yet to prove such lesions are at great enough risk for major hemorrhage to justify intervention.

The participants were disappointed that an NINDS Study Section and Council decided against funding the follow-up plan submitted by the investigators. Among the reasons cited was the unlikelihood that the disparities would change enough over the proposed additional 5 years of follow-up to justify the support with federal funds.

Undeterred, the investigators continue their effort at their own expense. They seek insights into what factors promote hemorrhage; whether the 2 occurrences of clinically serious outcomes in the medical group portend more such events in this setting of low-grade bAVM; whether and what form of intervention may be justified in small bAVMs, and the degree to which those suffering adverse events from intervention may undergo enough improvement and in timely enough fashion to take the risks of intervention prior to hemorrhage. These concerns justify continued efforts.