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organic) and fiber, a diet akin to what we now call Mediterranean eating. No, they were not malnourished characters from a Dickens novel. They were actually healthy, and their physical activity is said to have been 3–4 times as much as ours.[15] Recent evidence suggests that back then, life expectancy was not much different from now, the incidence of degenerative disease was 10% of ours, and cancer was basically nonexistent (of course, infections were rampant and childbirth fatalities and accidents were common). By the mid-Victorian times, diet and health had deteriorated significantly (cheap sugar, salted meats, and vegetable oils are just 3 popular products from the Agricultural Revolution responsible for obesity). The year 1900 was probably the last time we were a lean human race. Coming back to where I started, obesity was basically unknown in pre-Columbian Mesoamerica where the diet was gluten-free, low-carb, nutrient attenuated, and high in protein and fiber. Unfortunately, it is now in Mesoamerica where obesity is more prominent.

NB: For those who are interested in this topic, this is a very nice article: Caballero B. **The global epidemic of obesity: an overview.** *Epidemiol Rev* 2007;29:1–5

REFERENCES

1. Food and Agriculture Organization of the United Nations. The nutrition transition and obesity. http://www.fao.org/focus/e/obesity/obes2.htm. Accessed January 22, 2014
2. LATINOVOICES. Mexico obesity rate surpasses the United States', making it fattest country in the Americas. http://www.huffingtonpost.com/2013/07/09/mexico-obesity_n_3567772.html. Accessed January 22, 2014
3. Flegal KM, Carroll MD, Kit BK, et al. **Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010.** *JAMA* 2012;307:491–97
4. Centers for Disease Control and Prevention. Adult obesity facts. http://www.cdc.gov/obesity/data/adult.html. Accessed January 22, 2014
5. Passel JS, Cohn D. **US population projections: 2005–50.** *Pew Research Hispanic Trends Project*. February 11, 2008. http://www.pewhispanic.org/2008/02/11/us-population-projections-2005-2050. Accessed January 28, 2014
6. Grill HJ, Skibicka KP, Hayes MR. **Imaging obesity: fMRI, food reward, and feeding.** *Cell Metabolism* 2007;6:423–25
7. Moleres A, Martinez JA, Marti A. **Genetics of obesity.** *Curr Obes Rep* 2013;2:23–31
8. Rajia S, Chen H, Morris MJ. **Maternal overnutrition impacts offspring adiposity and brain appetite markers: modulation by postweaning diet.** *J Neuroendocrinol* 2010;22:905–14
9. Juonala M, Viikari JSA, Kanonen M, et al. **Life-time risk factors and progression of carotid atherosclerosis in young adults: the cardiovascular risk in young Finns study.** *Eur Heart J* 2010;31:1745–51
10. Kelly A, Barlow SE, Rao G, et al. **Severe obesity in children and adolescents: identification of health risks, and treatment approaches—a scientific statement from the American Heart Association.** *Circulation* 2013;128:1698–712
11. Heuch I, Heuch I, Hagen K, et al. **Body mass index as a risk factor for developing chronic low back pain: a follow-up in the Nord-Trondelag health study.** *Spine* 2013;38:133–39
12. Park YW, Palaniappan L Heshka S, et al. **The metabolic syndrome: prevalence and associated risk factor findings in the US population from the third national health and nutrition examination survey, 1988–1994.** *Arch Intern Med* 2003;163:427–36
13. Ha JY. **Evaluation of metabolic syndrome in patients with chronic low back pain: using the fourth Korea national health and nutrition examination survey data.** *Chonnam Med J* 2011;47:160–64
14. Westcott P. Healthy eating Victorian style. Saga. http://www.saga.co.uk/health/healthy-Eating/healthy-eating-victorian-style.aspx. Accessed January 30, 2014
15. Clayton P, Rowbotham J. **How the mid-Victorians worked, ate and died.** *Int J Environ Res Public Health* 2009;6:1235–53

EDITORIAL

Viewpoints on the ARUBA Trial

J.P. Mohr, A. Hartmann, H. Kim, J. Pile-Spellman, and C. Stapf

A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA), the first randomized clinical trial for brain arteriovenous malformations (bAVMs), was planned as a straightforward simple attempt to learn whether deferring intervention for a bAVM that had not bled would prove superior to incurring the risks of intervention needed to eradicate the lesion. The trial was justified by longitudinal data on true natural history (ie, for those receiving no intervention to eradicate the bAVM), reports of mild syndromes from many who had bled, and literature with treatment outcomes that were a mix of those who had bled before treatment versus those who had not. Having no wish to disturb current established interventional practice, the investigators offered randomization only to those whose bAVMs were considered suitable for eradication; none whose bAVMs were deemed too daunting for intervention would be eligible. Medical management for headaches and seizures is well-established, but no standards have yet appeared dictating interventional management. Widely misquoted literature citing annual hemorrhage rates approximating 4% and estimates of low risks for intervention allowed the assumption that the trial might well end within 5 years with a win for intervention.[1] Moreover, more insight would be gained for the true natural history.

The National Institute of Neurological Disorders and Stroke (NINDS) application followed well-established guidelines: an aim, a primary null hypothesis, clear and simple primary outcomes, and a host of secondary aims should enough data be available for useful analysis, with all information posted on the Web.[2] Participating centers sought, were offered, and were assumed to use their experience-based choices of interventions to achieve the goals of lesion eradication. The 39 active centers randomized fully 61% of those eligible. They also showed their qualifications by publishing fully 630 PubMed references for bAVMs during 2000–2010. Outcomes were reported at fixed intervals and after each intervention (many interventions not yielding single-stage eradication) and were adjudicated by a distinguished 4-member panel. An NINDS-appointed equally distinguished Data and Safety Monitoring Board (DSMB) provided independent oversight of study conduct and participant safety. National Institutes of Health (NIH) trials are typically funded in cycles of 5 years or less. Continuation depends on successful review and priority scores

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for the reapplication when the research questions remain unsettled.

In April 2013, with 226 subjects randomized (3 within the previous month) and outcome data available for 223 subjects with a mean follow-up for the cohort of 3.3 years, the DSMB recommended halting the randomization phase after a planned interim analysis found superiority for the medical arm. They also recommended continued follow-up to determine whether the disparity would persist. The results were presented at the 22nd European Stroke Conference in May, and published in *The Lancet* as an Epub in November 2013 and in print in February 2014.[3]

Although pleased that ARUBA has generated so much interest, we remain bemused at the nature of the commentaries. During the trial, some critical publications suggested that those offering the criticisms were either unaware of the design or were also unaware the investigators were blinded to outcomes.[4] After the first public presentation of the data but before our formal publication, the first of the outcome-based critical reviews appeared.[5] Despite our responses in the publication and to letters to the editor and published debates at national and international meetings along with favorable reviews, similar criticisms continue to accumulate.

ARUBA is indeed a biased sample. Compared with population-based studies and many case series, there is overrepresentation of the smaller bAVMs with lower Spetzler-Martin grades. It is no surprise that the centers chose for randomization those expected to show more favorable results from intervention. ARUBA did not have numerous contentious cases considered at higher risk for intervention, despite published speculations.[6] For transparency, we reported those screened, eligible, having refused participation, and treated outside the trial, a plan lacking in most of the major stroke trials. We offered to organize a registry option to meet the objections directed at earlier trials. No centers replied.

Objections against randomized clinical trials as a process led to our publishing not only the classic "as-randomized" but also "as-treated" analyses. (The latter assigned to the medical arm those outcomes that occurred for those randomized to intervention before intervention could begin; it also assigned to the interventional arm those randomized to the medical arm who elected intervention and then had an interventional outcome event.) The disparity favoring medical management for the "as randomized" analysis was even greater for the "as-treated" analysis: The latter showed a more than 5-fold increased risk of the primary outcomes for those undergoing invasive therapy (hazard ratio, 5.26; 95% CI, 2.63–11.11) and a significantly increased risk of major neurologic deficits (relative risk, 2.77; 95% CI, 1.20–6.25). The distribution of modified Rankin score by Spetzler-Martin Grade refutes speculations that the clinical severity of outcome events in the interventional arm was overestimated, a concern raised by Gary Steinberg, MD, from the audience after presentation of the results at the Treatment of Unruptured Brain Arteriovenous Malformations debate on February 11 at the 2014 International Stroke Conference in San Diego, California.[7]

The outcomes for the medical arm were the new data. As expected, the randomization process yielded essentially the same clinical characteristics in the 2 arms. All patients in the medical arm continued their normal activities of daily living, though their personal quality of life reports showed a higher degree of anxiety for their future.

It has been inferred by comments in the literature that hemorrhage rates are expected to be stable, steadily accumulating with time, making the risk for hemorrhage likely in the lifetime of the individual. However, recent publications suggest a decline in hemorrhage events with time.[8] Yet even if one assumes stable event rates, the disparity between the medical and interventional arms in ARUBA is great enough that 12–30 years may be needed before outcomes in the medical arm will cross those of the interventional arm.[9] (These calculations are based on the assumption that no further outcomes will occur in the interventional arm, in which a number of participants were still in the incomplete treatment phase when randomization was halted.)

Considerable literature exists on the anatomic features of those who presented with hemorrhage, many sharing the well-known Spetzler-Martin grading system predicting risks for surgical intervention. Except for deep venous drainage, these factors did not predict the frequency or severity of the first hemorrhage in our earlier reports or in ARUBA. Perhaps the anatomic features for those considered suitable for attempted eradication are less likely to predict hemorrhage.

Most reports—including meta-analyses—typically describe a demographic table that includes those who bled or did not bleed before intervention, after which the outcomes are described as if all the patients share the same risk for adverse events and their severity.[10] Only a few publications provide direct comparison with ARUBA and show that results are in the same range. The lack of registry data prevents comments on the outcomes for those eligible but not randomized to ARUBA.

Concerns that primary surgical intervention was not well-represented cannot be answered from ARUBA, in which intervention choice was made by the local centers. However, the latest meta-analyses do not emphasize the superiority of outcomes for surgery.[10] Single-technique surgery was not a recommended option in the 1 published management algorithm we found for bAVMs that did not bleed,[11] despite objections about too few surgical cases in ARUBA lodged by the senior author in letters to *The Lancet*.[12]

The Future

To our disappointment and despite insistence from us, the ARUBA participants, the DSMB, and many critics, the NINDS Study Section and Council recommended against NIH funding for continuation of the follow-up. The review cited the assumption of no likely changes in the outcomes disparity. Our goals of assessing long-term hemorrhage risk and the degree of clinical improvement after adverse events during intervention remain unsatisfied. Although we could cite the decisions of reviewers as acceptance of the trial as definitive, we hope ARUBA will prove a starting point for further studies.

Preventive eradication of bAVMs remains costly: $75,000–

$100,000 per patient when last estimated 15 years ago, plus additional costs for potential treatment complications.[13]

Although intervention after hemorrhage often shows little worsening and sometimes improvement, ARUBA documents the difficulties in achieving lesion eradication without some disturbance in perilesional brain function for those previously asymptomatic. While we await new studies, the need for interventional management for those who have bled should justify studying elements of bAVMs that predict hemorrhage. The ARUBA data can be read as a challenge to the justification of interventions in those who have not bled.

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REFERENCES

1. Ondra SL, Troupp H, George ED, et al. **The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment.** *J Neurosurg* 1990;73:387–91
2. A Randomized Trial of Unruptured Brain AVMs (ARUBA). http://clinicaltrials.gov/ct/show/NCT00389181. Accessed March 23, 2006
3. Mohr JP, Parides MK, Stapf C, et al. **Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial.** *Lancet* 2014;383:614–21
4. Cockroft KM, Jayaraman MV, Amin-Hanjani S, et al. **A perfect storm: how a randomized trial of unruptured brain arteriovenous malformations' (ARUBA's) trial design challenges notions of external validity.** *Stroke* 2012;43:1979–81
5. Bambakidis NC, Cockroft K, Connolly ES, et al. **Preliminary results of the ARUBA study.** *Neurosurgery* 2013;73:E379–81
6. Mocco J, O'Kelly C, Arthur A, et al. **Randomized clinical trials: the double edged sword.** *J Neurointerv Surg* 2013;5:387–90
7. Mohr JP, Parides M, Moquete E, et al. **Spetzler-Martin Grade and outcomes by randomization assignment in the ARUBA trial (abstract).** *Stroke* 2014;45:A160
8. Kim H, Al-Shahi Salman R, McCulloch CE, et al. **Untreated brain arteriovenous malformation: patient-level meta-analysis of hemorrhage predictors.** *Neurology* 2014;83:590–97
9. Parides MK, Overbey JR, Stapf C, et al. **Projecting longer term results in the ARUBA trial.** In: *Proceedings of the 23rd European Stroke Meeting*, Nice, France. May 6–9, 2014:97
10. van Beijnum J, van der Worp HB, Buis DR, et al. **Treatment of brain arteriovenous malformations: a systematic review and meta-analysis.** *JAMA* 2011;306:2011–19
11. Stieg PE, Janardhan V, Riina HA. **Multimodality therapy: treatment algorithms.** In: Stieg PE, Batjer HH, Samson D, eds. *Intracranial Arteriovenous Malformations*. New York: Informa Healthcare; 2006: 135–43
12. Knopman J, Stieg PE. **Management of unruptured brain arteriovenous malformations.** *Lancet* 2014;383:581–83
13. Berman MF, Hartmann A, Mast H, et al. **Determinants of resource utilization in the treatment of brain arteriovenous malformations.** *AJNR Am J Neuroradiol* 1999;20:2004–08

EDITORIAL

The Role of AVM Microsurgery in the Aftermath of A Randomized Trial of Unruptured Brain Arteriovenous Malformations

M.T. Lawton

Microsurgical resection is the first-line therapy or criterion standard for many brain arteriovenous malformations because of its high cure rate, low complication rate, and immediacy. Surgical results have improved with time with the following: 1) the creation of grading systems to select patients likely to experience optimal outcomes; 2) the development of instruments like bipolar forceps and AVM microclips that coagulate or occlude feeding arteries effectively; 3) the recognition of AVM subtypes that help decipher AVM anatomy; and 4) the refinement of surgical approaches, strategies, and dissection techniques that facilitate safe AVM resection.[1-3] This impressive evolution of AVM surgery is at odds with the finding of A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) that medical management alone was superior to interventional therapy for the prevention of death or stroke in patients with unruptured AVMs followed for 33 months.[4]

An important explanation for the ARUBA finding is the surprisingly nonsurgical management of patients in the interventional group in the trial. Overall, 81% of patients were treated with embolization alone (32%), radiosurgery alone (33%), or combined embolization and radiosurgery (16%), and only 17 patients (18%) were treated surgically, with or without embolization. Therefore, the 3-fold increase in death or stroke in the interventional arm reflects current nonsurgical therapies and should not be interpreted as an indictment of AVM surgery. In the aftermath of ARUBA, it is important to clarify the safety, efficacy, and outcomes associated with AVM resection.

Our experience in managing 232 Spetzler-Martin grade I and II AVMs, the most favorable AVMs for surgery and the ones most likely to have been selected for treatment outside the randomization process of ARUBA, exemplifies a surgical posture toward low-grade AVMs that regards curative resection as the first-line or criterion standard therapy for most lesions.[5] We used embolization as a preoperative adjunct and reserved radiosurgery for risky AVMs in deep, inaccessible locations; in eloquent areas that might be associated with postoperative neurologic deficits; and/or with diffuse nidus morphology that might complicate microdissection. Patients were carefully selected to optimize outcomes, with a mean age of 38 years, Lawton-Young grades of ≤III in 69% of

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