The ARUBA trial

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The ARUBA trial: Current Status, Future Hopes

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A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA – U01 NS051483) was funded by the National Institute of Neurological Disorders (NINDS) with a pragmatic, simple plan: to determine for those brain arteriovenous malformations (BAVMs) discovered without having bled, whether prophylactic intervention (endovascular, surgical, radiotherapy, alone or in combination) or deferral of intervention unless hemorrhage occurred would prove superior as tested by the outcomes of death, stroke, or functional outcomes status (measured by the modified Rankin Scale) at a minimum of 5 years from randomization.[1] Both groups are treated medically for the common symptoms of headaches, seizures, or co-existing other medical conditions. Eligibility is limited to patients with a brain arteriovenous malformation that has not bled and is deemed suitable for attempted eradication based on the judgment and expertise of the local clinical site investigators. Those randomized to the deferred-intervention arm who experience hemorrhage during follow-up are then eligible for intervention at the discretion of the treating team.

Begun in April 2007, as of Mid-March 2010, ARUBA has randomized 112 patients in a steadily upward slope. Over 900 cases have been screened by a growing multi-continental list of centers (64 approved for randomization and another 23 at various stages of approval and initiation.) With increasing web access, patients are even referring themselves to the trial. The active centers continue to recruit at the expectedrate, indicating the accuracy of the pre-trial estimates of availability of cases by center size,[2, 3] population base,[4] and bled-unbled frequencies.[5, 6]

Initially planned for 800 patients to be recruited in a 30-month period, ARUBA experienced the slow accumulation of centers and randomizations common among clinical trials. As a result, the recruitment period was lengthened to 60 months, and the follow-up period will be between 5 and 10 years for all enrolled subjects; this lengthening, plus the continuous addition of new centers, allowed the opportunity for more events during the course of the trial. Based on a sensitivity analysis, these changes permitted a decrease of the trial's sample size from 800 to 400. The changes affected power and the detectable treatment effect: 800 patients provided 87.5% power to detect a 40% reduction in the hazard of stroke or death (the trial's primary endpoint) while 400 patients provides 80% power to detect a 46% reduction. To meet these goals of 400 patients within the 60-month period, even faster recruitment is being sought. (These changes in the study design, which have been endorsed by the DSMB and approved by NINDS, have been made in the web sites describing the trial.)

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Given that BAVMs are embedded in brain, where functionally important tissue may be displaced by or pass through the lesion, intervention for any BAVMs, especially those unbled, is among the most challenging tasks in the clinical neurosciences. It is not a wonder that complications can occur, but that many pass through without major adverse events.[7] How to achieve the goals with acceptable outcomes? It is possible that treatment-related hemorrhage or ischemic stroke could even be occurring at rates and degrees of clinical severity that exceed what is seen in those whose intervention is deferred.[8, 9, 10] Interventional outcomes are not notably worsened for those having bled.[11] BAVM hemorrhage severity appears less than that from parenchymal hemorrhage of other cause.[12, 13, 14] The true natural history for BAVMs may have lower risk of hemorrhage than for intervention.[9] Hence the question, "which is worse, the disease or the cure?"[15] Although its rationale is still unchallenged by the latest literature, ARUBA appears to need some reiteration to address criticisms from those who may not be fully familiar with the study protocol.[16, 17] First, the trial is limited to those whose lesions have not yet bled. Bleeding being the dominant concern for BAVMs, the strongest predictor for hemorrhage is the occurrence of prior hemorrhage.[18] Once hemorrhage had occurred, there is ample justification for intervention. ARUBA tests the outcomes for those not yet having bled. For them, intranidal pressure (not easily measured),[19] deep lesion location and deep venous drainage are the major angioarchitectural risk factors;[20] headaches and seizures are not.[5, 15]

Second, length of follow-up has been criticized as possibly too short for the natural history hemorrhage rate to exceed the complication rate of procedures. In the application for NIH funding, the trialists several possible scenarios: the most favorable for intervention was based on earlier widely-quoted pre-trial neurosurgical literature estimates of rates of hemorrhage[21] and complications for interventions.[22, 23, 24, 25] Applying these values showed a 5-year follow-up would have sufficed to allow demonstration of the superiority of intervention. However, it is now well understood that the earlier literature included the outcomes for the full range of BAVMs, including many having bled and/or many not considered suitable for intervention, using current techniques.[26] Hemorrhage risks and event rates for those having bled are of great clinical interest but, as noted, are not the subject of ARUBA. Where published, the natural history hemorrhage rate for ARUBA- eligible BAVM subtypes seems far lower than that for the overall BAVM cohort.[27] Given the possibility the this inferred lower rate may take longer than 5 years for the natural history event rates to cross those of intervention, the ARUBA investigators happily reviewed with the DSMB and laid plans for follow-up to at least 10 years, assuming continued NIH funding via competitive renewal.

Third, fears of an imbalance in randomization of BAVM subtypes have not materialized. Many interventionalists were concerned the trial would be confined to those cases that posed major challenges for eradication, thereby biasing the outcomes towards those with higher complication rates, and misrepresenting success for the presumably more easily managed cases of the lower Spetzler-Martin grades.[28] To date, participating centers have not refused to randomize Spetzler-Martin I-II grade BAVMs and the trial has a satisfactory balance: There are no grade Vs, and few grade IVs, this despite success by some publications.[29] At present, those randomized have a median age 43; 52% are female; and the Spetzler-Martin Grades are 21% S-M I, 26% S-M II, 40% S-M III, 13% S-M IV, 0% S-M Vs.

Finally, the study has been criticized for its lack of a standard plan for therapy. Such lack has been inferred by some to allow too wide a variation in approach for useful analysis. The ARUBA investigators agree that a single treatment comparator might have simplified interpretation of the results. However, there is no single plan for eradication of BAVMs overall or for any individual subtype. Proponents exist for each of the various approaches, including one-stage neurosurgical resection;[30] embolization alone;[31] embolization to reduce

lesion size followed by surgery or radiosurgery; radiosurgery before or after endovascular or surgical efforts. or radiosurgery alone.[32] Some case series demonstrate spontaneous occlusion of the lesion,[33] recurrence despite successful surgical resection[34] or stereotaxic radiosurgery.[35] Much of the literature includes case series where several of the approaches are used in the same institutional cohort. Thus far no widely-accepted plan endorsed by the interventional societies has appeared in the published literature for any Spetzler-Martin grade, size, or even for the prominent hemorrhage risk factors such as deep location, deep venous drainage, or for aneurysms (intranidal, on feeding arteries, or both).[36 37] This situation exists to varying degrees in other interventional trials, such as stenting or carotid endarterectomy,[38] extracranial-intracranial bypass,[39] clipping or coiling of aneurysms,[40] all of which contain variations in the fine details of techniques subject to post-hoc debate, depending on the results of the studies.

The choice of treatment modality for eradication of brain AVMS remains a complex therapeutic decision, which depends heavily on local expertise. Variation in treatment approach will undoubtedly continue for some time to come. Thus, the standard for comparing alternative treatments is the range of available treatment approaches. This is the rationale for the large simple trial design selected for ARUBA, where on a case-by-case basis local experts determine the optimal approach to AVM eradication.

Despite the variations in treatment options, outcome rates for the range of interventions appears relatively stable over the last 2 decades.[24, 41, 42] However, assessing the functional details of the outcomes for interventions has proved difficult. The descriptive terms used to characterize adverse events leave many readers unclear what is meant by “permanent”, “major”, or other terms describing the deficits. Few reports cite more quantitative assessments like the modified Rankin Scale (mRS, the usual break point for “minor” versus “major” being 0–1 vs. ≥2)or Barthel Index (BI). Almost none cite quality of life

In the submission and protocol, the ARUBA investigators cited the range of complication rates (and, where reported, by severity) by intervention(s). These values were used in calculating sample size and post-randomization time course for the trial to allow comparison against hemorrhage rate and severity for the medical management arm. The trial is based on the good faith assumption that clinical teams would use their best judgment for the selection of procedure(s) for the cases randomized to intervention and for those in the medical management arm who experience hemorrhage during follow-up. The modified Rankin Scale status at the end of the trial will also provide a means of assessing the late outcome for all patients in the trial. The protocol calls for subset analyses wherever feasible. The larger the cohort randomized in ARUBA the better such opportunities.

Results from a randomized clinical trial have long been shown preferable to relying on the wide range of outcomes based on case series. The current concern is that failure to complete the trial as planned could leave referring clinicians and insurers unclear whether intervention in any form should be delayed pending hemorrhage, when or whether it occurs in the useful lifetime of the patient, or undertaken in hopes of its prevention.[43] Considerable resources are used in BAVM management.[44] The matter could be left to outcomes research or effectiveness research, which, if applied to pre-trial data in the past, might well have ended carotid endarterectomy,[45, 46] or continued the enthusiasm for anticoagulation for non-embolic stroke.[47, 48]

There is also a rising interest in the basic biology of BAVMs.[49] Although the outcomes for those already bled and those too daunting for intervention have no relevance to the ARUBA trial, they pose a need for innovations in therapy. The large number of cases being screened for the ARUBA trial provides a database for studies of biomarkers of hemorrhage risk,[50]

assessment of the utility of tensor diffusion tractography on management options.[51] They may even permit the eventual posing of a minocycline medical trial to delay vascular changes and hemorrhage risk.[52] Recent studies of functional reorganization following non-iatrogenic focal infarct raise hopes that similar outcomes might apply for BAVMs after hemorrhage or intervention,[53, 54] The periodic assessments of functional status during long-term follow-up planned for ARUBA participants will allow such insights, but await the data. The tide is running strongly for evidence-based treatment plans. We encourage intrepid interventionists to join the effort for ARUBA.

References

1. www.arubastudy.org
2. Brown RD Jr, Wiebers DO, Torner JC, O'Fallon WM. Incidence and prevalence of intracranial vascular malformations in Olmsted County, Minnesota, 1965 to 1992. Neurology 1996;46:949–952. [PubMed: 8780070]
3. Hofmeister C, Stapf C, Hartmann A, Sciacca RR, Mansmann U, terBrugge K, Lasjaunias P, Mohr JP, Mast H, Meisel J. Demographic, morphological, and clinical characteristics of 1289 patients with brain arteriovenous malformation. Stroke 2000;31:1307–10. [PubMed: 10835449]
4. Stapf C, Labovitz DL, Sciacca RR, et al. Incidence of adult brain arteriovenous malformation hemorrhage in a prospective population-based stroke survey. Cerebrovasc Dis 2002;13:43–46. [PubMed: 11810010]
5. Stapf C, Mast H, Sciacca RR, et al. The New York Islands AVM Study: Design, study progress, and initial results. Stroke 2003;34:e29–e33. [PubMed: 12690217]
6. Al-Shahi R, Bhattacharya JJ, Currie DC, Papanastassiou V, Ritchie VR, Roberts RC, Sellar RJ, Warlow CP. SIVMS collaborators. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). Stroke 2003;34:1163–69. [PubMed: 12702837]
7. Morgan MK, Sekhon LH, Finfer S, Grinnell V. Delayed neurological deterioration following resection of arteriovenous malformations of the brain. J Neurosurg 1999;90:695–701. [PubMed: 10193615]
8. Wedderburn CJ, van Beijnum J, Bhattacharya JJ, Counsell CE, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP, Al-Shahi Salman R. SIVMS Collaborators. Outcome after interventional or conservative management of unruptured brain arteriovenous malformations: a prospective, population-based cohort study. Lancet Neurol 2008;7:223–30. [PubMed: 18243054]
9. Stapf C. The Rationale Behind "A Randomized Trial of Unruptured Brain AVMs" (ARUBA). Acta Neurochir Suppl 2010;107:83–5. [PubMed: 19953376]
10. van Beijnum J, Lovelock CE, Cordonnier C, Rothwell PM, Klijn CJ, Salman RA. Outcome after spontaneous and arteriovenous malformation-related intracerebral haemorrhage: population-based studies. Brain 2009;132:537–543. [PubMed: 19042932]
11. Hartmann A, Mast H, Mohr JP, Pile-Spellman J, Connolly ES, Sciacca RR, Khaw A, Stapf C. Determinants of staged endovascular and surgical treatment outcome of brain arteriovenous malformations. Stroke 2005;36:2431–5. Epub 2005 Oct 13. [PubMed: 16224095]
12. Hartmann A, Mast H, Mohr JP, Koennecke HC, Osipov A, Pile-Spellman J, Duong DH, Young WL. Morbidity of intracranial hemorrhage in patients with cerebral arteriovenous malformation. Stroke 1998;29:931–934. [PubMed: 9596237]
13. Choi JH, Mast H, Hartmann A, Marshall RS, Pile-Spellman J, Mohr JP, Stapf C. Clinical and morphological determinants of focal neurological deficits in patients with unruptured brain arteriovenous malformation. J Neurol Sci 2009;287:126–30. Epub 2009 Sep 3. [PubMed: 19729171]
14. Choi JH, Mast H, Sciacca RR, Hartmann A, Khaw AV, Mohr JP, Sacco RL, Stapf C. Clinical outcome after first and recurrent hemorrhage in patients with untreated brain arteriovenous malformation. Stroke 2006;37:1243–7. [PubMed: 16614321]
15. Delorme S. Arteriovenöse Malformationen des Gehinrs: Was ist schlimmer – die Krankheit oder die Kur? Der Radiologie 2007;8:661.

16. Cockroft KM. Unruptured brain arteriovenous malformations should be treated conservatively: no. Stroke 2007;38:3310–1. [PubMed: 17962584]
17. Stapf C, Mohr JP. Unruptured brain arteriovenous malformations should be treated conservatively: yes. Stroke 2007;38:3308–9. [PubMed: 17962585]
18. Mast H, Young WL, Koennecke HC, Sciacca RR, Osipov A, Pile-Spellman J, Hacein-Bey L, Duong H, Stein BM, Mohr JP, et al. Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. Lancet 1997;350:1065–1068. [PubMed: 10213548]
19. Duong DH, Young WL, Vang MC, Sciacca RR, Mast H, Koennecke HC, Hartmann A, Joshi S, Mohr JP, Pile-Spellman J. Feeding artery pressure and venous drainage pattern are primary determinants of hemorrhage from cerebral arteriovenous malformations. Stroke 1998;29:1167–76. [PubMed: 9626290]
20. da Costa L, Wallace MC, Ter Brugge KG, O'Kelly C, Willinsky RA, Tymianski M. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. Stroke 2009;40:100–5. Epub 2008 Nov 13. [PubMed: 19008469]
21. Ondra SL, Troupp H, George ED, Schwab K. The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. J Neurosurg 1990;73:387–91. [PubMed: 2384776]
22. Castel JP, Kantor G. Postoperative morbidity and mortality after microsurgical exclusion of cerebral arteriovenous malformations. Current data and analysis of recent literature. Neurochirurgie 2001;47:369–83. [PubMed: 11404718]
23. Morgan MK, Rochford AM, Tsahtsarlis A, Little N, Faulder KC. Surgical risks associated with the management of Grade I and II brain arteriovenous malformations. Neurosurgery 2004;54:832–7. [PubMed: 15046648]
24. Taylor CL, Dutton K, Rappard G, Pride GL, Replogle R, Purdy PD, White J, Giller C, Kopitnik TA Jr, Samson DS. Complications of preoperative embolization of cerebral arteriovenous malformations. J Neurosurg 2004;100:810–2. [PubMed: 15137598]
25. Hillman J. Population-based analysis of arteriovenous malformation treatment. Neurosurg 2001;95:633–7.
26. Hernesniemi JA, Dashti R, Juvela S, Väärt K, Niemelä M, Laakso A. Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. Neurosurgery 2008;63:823–9. [PubMed: 19005371]
27. Stapf C, Mast H, Sciacca RR, Choi JH, Khaw AV, Connolly ES, Pile-Spellman J, Mohr JP. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. Neurology 2006;66:1350–5. [PubMed: 16682666]
28. Spears J, Terbrugge KG, Moosavian M, Montanera W, Willinsky RA, Wallace MC, Tymianski M. A discriminative prediction model of neurological outcome for patients undergoing surgery of brain arteriovenous malformations. Stroke 2006;37:1457–64. [PubMed: 16690897]
29. Chang SD, Marcellus ML, Marks MP, Levy RP, Do HM, Steinberg GK. Multimodality treatment of giant intracranial arteriovenous malformations. Neurosurgery 2003;53:1–11. [PubMed: 12823868]
30. Davidson AS, Morgan MK. How safe is arteriovenous malformation surgery? A prospective, observational study of surgery as first-line treatment for brain arteriovenous malformations. Neurosurgery 2010;66:498–504. [PubMed: 20173544]
31. Meisel HJ, Mansmann U, Alvarez H, Rodesch G, Brock M, Lasjaunias P. Effect of partial targeted N-butyl-cyano-acrylate embolization in brain AVM. Acta Neurochir (Wien) 2002;144:879–87. [PubMed: 12376769]
32. Maruyama K, Kawahara N, Shin M, Tago M, Kishimoto J, Kurita H, Kawamoto S, Morita A, Kirino T. The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. N Engl J Med 2005;352:146–53. [PubMed: 15647577]
33. Abdulrauf SI, Malik GM, Awad IA. Spontaneous angiographic obliteration of cerebral arteriovenous malformations. Neurosurgery 1999;44:280–287. [PubMed: 9932881]
34. Kader A, Goodrich JT, Sonstein WJ, et al. Recurrent cerebral arteriovenous malformations after negative postoperative angiograms. J Neurosurg 1996;85:14–18. [PubMed: 8683264]

35. Shin M, Kawahara N, Maruyama K, Tago M, Ueki K, Kirino T. Risk of hemorrhage from an arteriovenous malformation confirmed to have been obliterated on angiography after stereotactic radiosurgery. J Neurosurg 2005;102:842–6. [PubMed: 15926707]
36. Stapf C, Mohr JP, Choi JH, Hartmann A, Mast H. Invasive treatment of unruptured brain arteriovenous malformations is experimental therapy. Curr Opin Neurol 2006;19:63–8. [PubMed: 16415679]
37. van Beijnum J, Bhattacharya JJ, Counsell CE, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow C, Al-Shahi Salman R. Scottish Intracranial Vascular Malformation Study Collaborators. Patterns of brain arteriovenous malformation treatment: prospective, population-based study. Stroke 2008;39:3216–21. [PubMed: 18787195]
38. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ. Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003 Jan 11;361(9352):107–16. [PubMed: 12531577]
39. Barnett HJ, Sackett D, Taylor DW, Haynes B, Peerless SJ, Meissner I, Hachinski V, Fox A. Are the results of the extracranial-intracranial bypass trial generalizable? N Engl J Med 1987 Mar 26;316:820–4. [PubMed: 3821825]
40. Ryttlefors M, Enblad P, Kerr RS, Molyneux AJ. International subarachnoid aneurysm trial of neurosurgical clipping versus endovascular coiling: subgroup analysis of 278 elderly patients. Stroke 2008;39:2720–6. [PubMed: 18669898]
41. Ledezma CJ, Hoh BL, Carter BS, Pryor JC, Putman CM, Ogilvy CS. Complications of cerebral arteriovenous malformation embolization: multivariate analysis of predictive factors. Neurosurgery 2006;58:602–11. [PubMed: 16575323]
42. Lawton MT, Du R, Tran M, Achrol AS, McCulloch CE, Johnston SC, Quinnine NJ, Young WL. Effect of presenting hemorrhage on outcome after microsurgical resection of brain arteriovenous malformations. Neurosurgery 2005;56:485–493. [PubMed: 15730573]
43. Fiehler J, Stapf C. ARUBA--beating natural history in unruptured brain AVMs by intervention. Neuroradiology 2008 Jun;50(6):465–7. Epub 2008 Apr 22. [PubMed: 18427796]
44. Berman MF, Hartmann A, Mast H, Sciacca RR, Mohr JP, Pile-Spellman J, Young WL. Determinants of resource utilization in the treatment of brain arteriovenous malformations. Am J Neuroradiol 1999;20:2004–8. [PubMed: 10588135]
45. Dyken ML, Pokras R. The performance of endarterectomy for disease of the extracranial arteries of the head. Stroke 1984;15:948–50. [PubMed: 6506121]
46. Pokras R, Dyken ML. Dramatic changes in the performance of endarterectomy for diseases of the extracranial arteries of the head. Stroke 1988;19:1289–90. [PubMed: 3176089]
47. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP Jr, Jackson CM, Pullicino P. Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirinfor the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444–51. [PubMed: 11794192]
48. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Kasner SE, Benesch CG, Sila CA, Jovin TG, Romano JG. Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005;352:1305–16. [PubMed: 15800226]
49. Leblanc GG, Golanov E, Awad IA, Young WL. Biology of Vascular Malformations of the Brain NINDS Workshop Collaborators. Biology of Vascular Malformations of the Brain. Stroke. 2009 Oct 15;
50. Zhuge Q, Zhong M, Zheng W, Yang GY, Mao X, Xie L, Chen G, Chen Y, Lawton MT, Young WL, Greenberg DA, Jin K. Notch-1 signalling is activated in brain arteriovenous malformations in humans. Brain. 2009 Oct 7;
51. Berntsen EM, Gulati S, Solheim O, Kvistad KA, Lindseth F, Unsgaard G. Integrated pre-and intraoperative imaging in a patient with an arteriovenous malformation located in eloquent cortex. Minim Invasive Neurosurg 2009;52:83–5. [PubMed: 19452415]
52. Frenzel T, Lee CZ, Kim H, Quinnine NJ, Hashimoto T, Lawton MT, Guglielmo BJ, McCulloch CE, Young WL. Feasibility of minocycline and doxycycline use as potential vasculostatic therapy

for brain vascular malformations: pilot study of adverse events and tolerance. Cerebrovasc Dis 2008;25:157–63. [PubMed: 18212521]

53. Lazar RM, Marshall RS, Pile-Spellman J, et al. Interhemispheric transfer of language in patients with left frontal cerebral arteriovenous malformation 1. Neuropsychologia 2000;38:1325–1332. [PubMed: 10869575]
54. Marshall RS, Zarahn E, Alon L, Minzer B, Lazar RM, Krakauer JW. Early imaging correlates of subsequent motor recovery after stroke. Ann Neurol 2009;65:596–602. [PubMed: 19479972]