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Functional impairments for outcomes in a randomized trial of unruptured brain AVMs

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ABSTRACT

Objective: To investigate the effects of medical vs interventional management on functional outcome in A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA).

Methods: We used the initial results of a nonblinded, randomized, controlled, parallel-group trial involving adults ≥18 years of age with an unruptured brain arteriovenous malformation (AVM) to compare the effects of medical management (MM) with or without interventional therapy (IT) on functional impairment, defined by a primary outcome of death or symptomatic stroke causing modified Rankin Scale (mRS) score ≥2. ARUBA closed recruitment on April 15, 2013.

Results: After a median of 33.3 months of follow-up (interquartile range 16.3–49.8 months), of the 223 enrolled in the trial, those in the MM arm were less likely to experience primary outcomes with an mRS score ≥2 than those who underwent IT. The results applied for both those as randomized (MM n = 109 vs IT n = 114) (hazard ratio [HR] 0.25, 95% confidence interval [CI] 0.11–0.57, $p = 0.001$) and as treated (MM n = 125 vs IT n = 98) (HR 0.10, 95% CI 0.04–0.28, $p < 0.001$). Functional impairment for the outcomes showed no significant difference by Spetzler-Martin grade for MM but was more frequent with increasing grades for IT ($p < 0.001$).

Conclusion: Death or stroke with functional impairment in ARUBA after a median follow-up of 33 months was significantly lower for those in the MM arm both as randomized and as treated compared with those with IT. Functional severity of outcomes was lower in the MM arm, regardless of Spetzler-Martin grades.

ClinicalTrials.gov identifier: NCT00389181.

Classification of evidence: This study provides Class II evidence that for adults with unruptured brain AVMs, interventional management compared to MM increases the risk of disability and death over ≈3 years. *Neurology*® 2017;89:1499–1506

GLOSSARY

ARUBA = A Randomized Trial of Unruptured Brain Arteriovenous Malformations; **AVM** = arteriovenous malformation; **CI** = confidence interval; **DSMB** = Data and Safety Monitoring Board; **HR** = hazard ratio; **IQR** = interquartile range; **IT** = interventional therapy; **MM** = medical management; **mRS** = modified Rankin Scale; **NINDS** = National Institute of Neurological Disorders and Stroke; **S-MG** = Spetzler-Martin grade.

A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) was the first clinical trial evaluating treatment strategies for brain arteriovenous malformations (AVMs).[1] Sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) (http://clinicaltrials.gov/ct/show/NCT00389181), it was a phase 3 multinational

Supplemental data at Neurology.org

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Coinvestigators are listed at Neurology.org.

The data presented here were a platform presentation at the 68th annual meeting of the American Academy of Neurology, April 16, 2016, Vancouver, Canada, in Session S7, Stroke Clinical Trials, "Clinical Impairment in Patients Followed With or Without Interventional Therapy in a Randomized Trial of Unruptured Brain AVMs (ARUBA)."

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

study assessing the outcomes for medical management (MM) alone or MM with interventional therapy (IT) for lesion eradication. Randomization was offered only to those whose brain AVM was unruptured as shown by imaging and who were deemed suitable for attempted eradication by participating experienced multidisciplinary treatment centers.

The initial publication documented the baseline demographics and outcomes by randomization assignment and as treated for event rates, death, stroke, stroke cause, and adverse events. The clinical functional impairment of the primary endpoint events (stroke severity) and the association with Spetzler-Martin grade (S-MG) were not analyzed in detail at that time.

METHODS As previously reported,[1] the trial was undertaken to determine whether MM improves long-term outcomes of patients with unruptured brain AVMs compared to IT (with endovascular procedures, neurosurgery, or radiotherapy, alone or in combination). The trial was designed to test whether MM or IT will reduce the risk of death or stroke (due to hemorrhage or infarction) by at least 46% (an absolute magnitude of ≈9.5% over 5 years). The details below document the basis for the trial classification as Class II, lacking only concealed allocation (Item a. Class I) based on the American Academy of Neurology classification.[2]

Adult patients (age ≥18 years) with an unruptured brain AVM were enrolled in this trial at 39 clinical sites in 9 countries. Patients were randomized (by a web-based system, in a 1:1 ratio, with random permuted block design [block size 2, 4, or 6], stratified by clinical site) to MM with IT (i.e., neurosurgery, embolization, or stereotactic radiotherapy, alone or in combination) or MM alone (i.e., pharmacologic therapy for neurologic symptoms as needed). Patients, clinicians, and investigators were aware of treatment assignment.

The primary outcome was time to the composite endpoint of death or stroke; the primary analysis is by intention to treat. Stroke was defined as an event presenting with a new focal neurologic deficit, seizure, or new-onset headache and associated with brain imaging indicating recent hemorrhage or infarction.

The primary null hypothesis was that no difference existed in the risk of symptomatic stroke or death between patients randomized to MM compared with patients randomized to IT.

Assignments were not masked to participants, clinicians, or investigators. A senior study neurologist who was not involved in the provision of the interventional procedures performed the clinical outcome assessment.

All primary and secondary outcome events and imaging studies were assessed by an independent multidisciplinary committee of international adjudicators representing the neurovascular specialties of neurology, neurologic surgery, interventional neuroradiology, and radiosurgery.

Data at the time of the Data and Safety Monitoring Board (DSMB) meeting April 15, 2013, which ended the randomization phase, were the basis for the initial[1] and current report. The results of the analyses were reviewed at semiannual meetings of the DSMB, all participants having been blinded to overall trial outcomes during the course of the trial.

The functional severity of primary outcome events in each arm was graded with the modified Rankin Scale (mRS). A score ≥2 was considered a clinically important event according to the protocol and most stroke clinical trials.[3] The proportion of participants with a primary outcome event that yielded an mRS score ≥2 was compared between the MM and IT groups with χ^2 tests.[4] The median postevent mRS score was compared between randomization groups with a Wilcoxon test.

A secondary outcome of time to a primary outcome event that resulted in an mRS score ≥2 was evaluated with a Cox proportional hazards model.[5] Time to a primary outcome event with mRS ≥2 was modeled with randomization assignment as the only covariate. Patients who had a primary outcome event with an mRS score <2 were censored at the time of their event. The association between the incidence of primary outcome events and the S-MG[6] was assessed within each arm with either the χ^2 or Fisher exact test as appropriate. In addition, the proportion of patients experiencing a primary outcome event was stratified by S-MG and compared between groups with either the χ^2 or Fisher exact test as appropriate. The significance level for this stratified analysis was adjusted with a Bonferroni correction to account for multiple testing. Values of p were considered significant if $p < 0.0125$.

Because of the small number of events in the MM arm, the analysis of the differential effect of treatment on event functional severity (mRS score) by S-MG is descriptive and presented as counts in each group.

All analyses were first conducted by intention to treat (as randomized). As in the original publication,[1] we also present the results of as-treated analyses, with patients who crossed over analyzed according to the type of management they received. Patients allocated to MM who subsequently received IT were deemed to have crossed over to the IT arm if the reason for intervention was other than stroke related to their brain AVM. Patients who were assigned to MM but received IT after reaching a primary endpoint were not counted as crossovers. All patients allocated to the IT arm who either switched to MM after randomization or did not receive IT before a primary outcome event by the date of database closure were defined as having crossed over to the MM arm.

All analyses were conducted with SAS version 9.4 (SAS Institute Inc, Cary, NC).

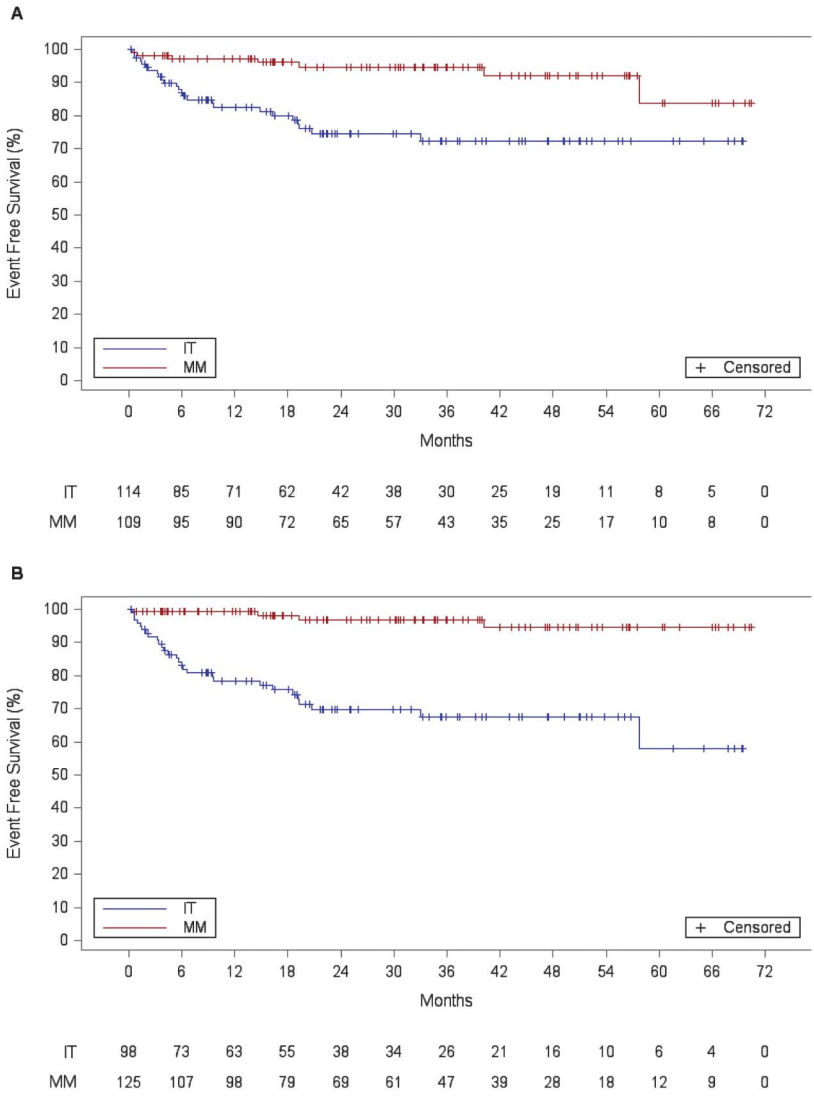
Standard protocol approvals, registrations, and patient consents. Approval for the study was received from an ethics standards committee of human experimentation in each of the participating centers. Written informed consent was obtained from all participants.

RESULTS The study started in April 2007. Recruitment was halted in April 2013 by recommendation of the NINDS-appointed DSMB. This action occurred after a planned interim analysis showed that the risk of death or stroke was significantly lower in the MM group than in the IT group (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.14–0.54).[1] The analysis was based on 223 enrolled patients with a median follow-up time of 33.3 months (IQR 16.3–49.8). An additional 3 patients were enrolled between analysis cohort lock and the halting of the trial. The original and current publications are based on the interim analysis dataset, which contains 109 patients randomized to MM and 114 randomized to IT plus MM (figure e-1 at Neurology.org).

The baseline demographics and brain AVM profiles were comparable between the 2 groups. (table e-1) In addition, as-treated analyses were performed. In this analysis, the MM arm contained 125 patients, and the IT arm contained 98 participants.

After a median of 33.3 months of follow-up (interquartile range [IQR] 16.3–49.8 months), of the 223 enrolled in the trial, those in the MM arm were less likely to experience primary outcomes with an mRS score ≥2 than those who underwent IT. The results applied for both those as randomized (MM n = 109 vs IT n = 114 [2 without angiogram]) (HR 0.25, 95% CI 0.11–0.57, $p = 0.001$) and those as treated (MM n = 125 [2 without angiogram] vs IT n = 98) (HR 0.10, 95% CI 0.04–0.28, $p < 0.001$). Functional impairment for the outcomes showed no significant difference by S-MG for MM but was more frequent with increasing grades for IT ($p < 0.001$).

Figure 1 Kaplan-Meier curves for time to a primary outcome with initial mRS score ≥2



(A) As-randomized outcomes for medical only (MM; red) vs medical plus intervention (IT; blue). (B) As-treated outcomes for MM only (red) vs IT (blue). mRS = modified Rankin Scale. Reprinted from Mohr JP, Parides MK, Stapf C, et al., for the International ARUBA Investigators. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. Lancet 2014;383:614–621. Copyright © 2013, reprinted with permission from Elsevier.[1]

Time to first event with an mRS score ≥2. In the analysis of the risk of a primary outcome event with functional impairment (mRS score ≥2), the results favored MM for those as randomized (HR 0.25, 95% CI 0.11, 0.57, $p = 0.001$) and showed greater disparity for those as treated (HR 0.10, 95% CI 0.04–0.28, $p < 0.001$). Figure 1 shows the Kaplan-Meier curves for those with functional impairment. Table 1 shows the HRs for the cohort without consideration of the mRS and for those with an mRS score ≥2.

mRS score for outcome events by randomization group. Table 2 shows each patient's mRS score at the time of the primary outcome event. In the as-randomized analysis including all participants, the median MM group mRS score was 2 (IQR 1–5) vs 4 (IQR 1–5) in the IT group ($p = 0.67$). Functional impairment after a primary outcome event was seen in 7 of 109 (6.4%) in the MM arm vs 25 of 114 (21.9%) in the IT arm ($p = 0.001$). In the as-treated analysis including all participants, the median postevent mRS score was 1 (IQR 1–5) in the MM group vs 4 (IQR 2–5) in the IT group ($p = 0.30$). The number of patients with functional impairment was 4 of 125 (3.2%) in the MM arm vs 28 of 98 (28.6%) in the IT arm ($p < 0.0001$).

Primary outcomes by S-MG. The S-MG was estimated at baseline for all patients imaged by magnetic resonance and/or formal angiogram. Two patients did not undergo diagnostic angiography at baseline and are excluded from S-MG analyses. As shown in the original publication, the cohorts were well matched, with more than half of each assigned group graded as SMG 1 or 2. In the as-treated analyses, the distributions of lesion size, venous drainage, eloquent location, and S-MG were also not significantly different.[1]

In the MM arm, no association was found between S-MG and the occurrence of a primary outcome event in both the as-randomized ($p = 0.87$) and the as-treated ($p = 0.14$) analyses. However, in the IT arm, the occurrence of primary outcome events was significantly associated with S-MG in both the as-randomized ($p < 0.001$) and as-treated ($p = 0.001$) analyses, with the incidence of events in the IT arm increasing with increasing grade.

For those classified as S-MG 1, the primary outcome events showed no significant difference between the IT and MM arms in both the as-randomized and as-treated analyses. However, the number of primary outcome events was significantly higher in the IT arm

Table 1 HRs comparing medical management to interventional therapy for as-randomized and as-treated analyses of primary outcome and secondary outcome of events with mRS score >2

	HR (95% CI)
Primary outcome (symptomatic stroke or death)	
As randomized	0.27 (0.14–0.54)
As treated	0.19 (0.09–0.38)
Primary outcome event with mRS score ≥2	
As randomized	0.25 (0.11–0.57)
As treated	0.10 (0.04–0.28)

Abbreviations: CI = confidence interval; HR = hazard ratio; mRS = modified Rankin Scale.

than in the as-randomized analysis for those scored as S-MG 2 (IT 34.1% vs MM 7.4%, $p = 0.01$) and S-MG 3 (IT 57.1% vs MM 8.8%, $p < 0.0001$). Similarly, in the as-treated analysis, the number of primary outcome events was also significantly higher in the IT group for those scored as S-MG 2 (IT 43.2% vs MM 2.9%, $p < 0.0001$) and S-MG 3 (IT 57.1% vs MM 8.8%, $p < 0.0001$). A p value is shown for participants with S-MG 4, but the small number makes the value underpowered. The incidence of all primary outcome events and those with mRS score ≥2 by S-MG for those as randomized and as treated is shown in table 3 and in figure 2).

DISCUSSION The primary outcomes for participants in ARUBA after a median of 33.3 months of follow-up showed significant differences favoring MM vs IT both as randomized and as treated. Greater disparity was found for those with functional impairment (mRS score ≥2). Disability was not associated with S-MG in the MM group but was in the IT group.

To the best of our knowledge, ARUBA was the first randomized clinical trial comparing treatment strategies for unbled brain AVM. Its primary justification was the management dilemma for the substantial number of patients being discovered by noninvasive imaging not to have bled.[7,8] The trial generated frequent criticisms, prompting replies, before,[9] during,[10,11] and after the initial publication.[12–17] The majority of ARUBA participants differ from those of most prior publications, with smaller lesion size, fewer located in areas sensitive for clinical abnormalities, and fewer with deep venous drainage. This bias toward the lower SMGs indicates that participating centers tended to select those deemed more likely to have successful, low-morbidity lesion eradication.

Functional effects of brain hemorrhage, both spontaneous and treatment related, are the main subjects of this report. It was long assumed that the clinical syndrome from AVM rupture was as clinically relevant as that from primary brain hemorrhage or ruptured aneurysm.[18] This concern was not confirmed by the results of ARUBA and has been blunted by recent reports showing that the clinical severity from brain AVM hemorrhage is far lower than that of either brain hemorrhage or ruptured aneurysm .[19,20]

The relatively low mRS values for the medical arm in ARUBA are in agreement with earlier observations. Studies before modern noninvasive imaging show a wide range of syndrome severity, a substantial proportion with no or only mild deficits. As far back as in 1964, Svien and McRae[21] reported 95 patients with ruptured brain AVM whose late outcome at 20 years was found to be as follows: 66% good, 22% fair, and 10% invalid. More modern quantitative observations have been made in subsequent decades. The 1966 Cooperative Study of Subarachnoid Hemorrhage reported outcomes from 545 patients, with 58% experiencing handicap from brain AVM hemorrhage and, by inference, 42% without handicap.[22] In 1986, Crawford et al.[23] noted no handicap among 62% of 136 with brain AVM hemorrhage, 25% with minor handicap, and only 6% with major handicap. The 1988 Mayo Clinic report by Brown et al.[24] described

Table 2 Outcome event frequencies by as-randomized and as-treated status vs mRS score at primary outcome

	Primary outcome events by mRS score, n							
	0	1	2	3	4	5	6	Total
As randomized								
MM (n = 109)	2	2	2	0	2	1	2	11
IT (n = 114)	1	9	5	2	7	10	1	35
As treated								
MM (n = 125)	2	4	0	0	1	1	2	10
IT (n = 98)	1	7	7	2	8	10	1	36

Abbreviations: IT = interventional therapy; MM = medical management; mRS = modified Rankin Scale.

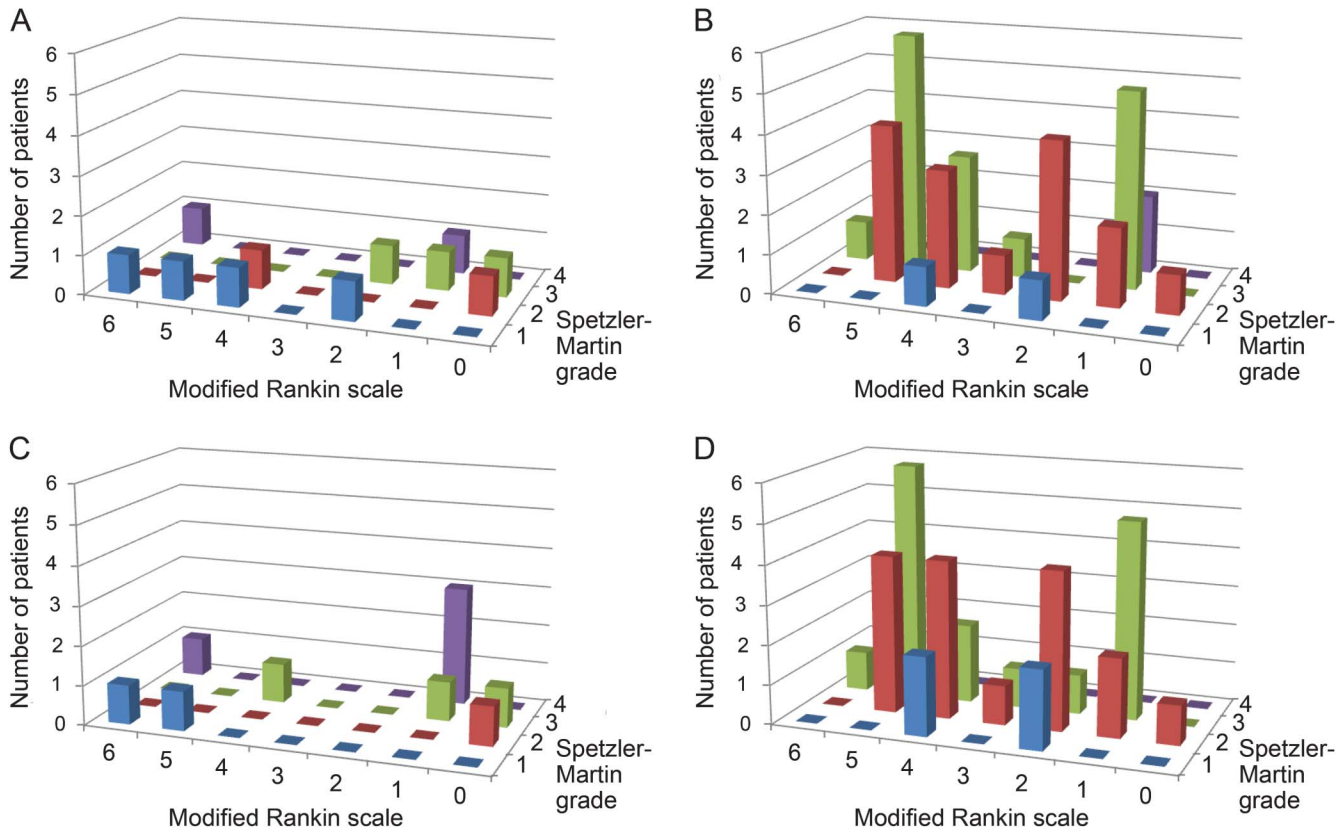
Table 3 First event outcomes without regard to mRS score and for those with mRS score ≥2 by S-MG for IT and MM

S-MG	IT (n = 112)[a] Patients, n	Patients with primary outcome events, n (%)	Patients with primary outcome event and mRS score ≥2, n (%)	MM (n = 109) Patients, n	Patients with primary outcome events, n (%)	Patients with primary outcome events and mRS score ≥2, n (%)	p Value[b]
As randomized							
I	32	2 (6.3)	2 (6.3)	33	4 (12.1)	4 (12.1)	0.67
II	44	15 (34.1)	12 (27.3)	27	2 (7.4)	1 (3.7)	0.0105
III	28	16 (57.1)	11 (39.3)	34	3 (8.8)	1 (2.9)	<0.0001
IV	8	2 (25.0)	0 (0)	15	2 (13.3)	1 (6.7)	0.59
	IT (n = 98)			MM (n = 123)[a]			p Value[b]
As treated							
I	28	4 (14.3)	4 (14.3)	37	2 (5.4)	2 (5.4)	0.39
II	37	16 (43.2)	13 (35.1)	34	1 (2.9)	0 (0)	<0.0001
III	28	16 (57.1)	11 (39.3)	34	3 (8.8)	1 (2.9)	<0.0001
IV	5	0 (0)	0 (0)	18	4 (22.2)	1 (5.6)	0.54

Abbreviations: IT = interventional therapy; MM = medical management; mRS = modified Rankin Scale; S-MG = Spetzler-Martin grade.
[a] Baseline S-MG not available for 2 patients because they did not have diagnostic angiography.
[b] IT vs MM comparison of proportion of patients who experienced a primary outcome event. The p value is considered significant if $p < 0.0125$. Outcome events for mRS score ≥2 were deemed too few for useful analysis.

168 AVMs, and for the 22 with nonfatal bleeding, "the risk of significant disability was 23%." The 1998 Columbia AVM Study series of 119 first hemorrhage events in untreated brain AVMs reported by Hartmann et al.[25] noted 54 (47%) with no neurologic deficit, 43 (37%) with an mRS score of 1, 15 (13%) with

Figure 2 Three-dimensional plot of modified Rankin Scale scores and counts of patients by Spetzler-Martin grade



(A) Medical management (MM) as randomized, (B) interventional therapy (IT) as randomized, (C) MM as treated, and (D) IT as treated.

an mRS score of 2 to 3, and none with an mRS score of 4. In ARUBA, 2 fatalities were noted: 1 participant died of lymphoma without AVM hemorrhage during lifetime, and the other failed to awaken one morning, with unspecified cause of death and no prior sign of hemorrhage.

Concerns for the incidence of hemorrhage were greatly increased by the widely quoted 1990 report by Ondra et al.[26] On the basis of referral center case material dating from the 1950s, the reported annual hemorrhage rates were 4% with fatalities of 1%. Although the report was characterized as natural history, the authors clearly pointed out that the majority (67%) of those had bled and were considered unsuitable for attempted intervention. A recent publication from the same source now cites an annual hemorrhage rate of 2.4% overall, with half this value for those who had not previously bled.[27] A 1.3% annual rate of hemorrhage was reported for those presenting without prior hemorrhage among the 2,525 patients from the Multicenter Arteriovenous Research Study.[28] The noninterventional arm in ARUBA also shows a similar low annual incidence of hemorrhage. Overall, the ARUBA data suggest that those spared intervention may have both lower hemorrhage rates and lower deficit severity from the events.

The outcomes from intervention in ARUBA are supported by a recent meta-analysis of 137 observational nonrandomized studies totaling 13,698 patients.[29] Studies before ARUBA (including those in the meta-analysis) focused on outcomes from intervention (those left untreated rarely cited); the outcomes usually were not segregated by pretreatment hemorrhage or no hemorrhage and rarely reported with formal assessment of clinical syndromes or severity, e.g., mRS score. Such features apply to 22 major publications dating from the first report of 10 patients in 1948 by Olivecrona and Riives[30] to the 2000 report of 305 patients by Meisel et al.[31] A major impact on the literature resulted from the grading system generated by Spetzler and Martin.[6] Their system assigned 1 to 3 points for lesion size, 0 to 1 point for eloquent location, and 0 to 1 point for deep venous drainage. The consecutive 100 surgical patients (preoperative hemorrhage status not reported) experienced 11% major and 32% minor deficits. The frequency of the deficits was strongly related to the S-MG: for grade I, virtually zero; grade II, 5% minor; grade III, 4% major and 12% minor; grade IV, 7% major and 20% minor; and grade V, 12% major and 19% minor. No deaths were reported. The system has been widely used and is usually cited as the basis for surgical intervention in the smaller (grade I–II) lesions, assuming others achieve similar outcomes. The grading system has had further revisions for surgery[32,33] but only limited efforts at validation for other modes of intervention. Reports for outcomes based on surgery or endovascular procedures from the Columbia AVM Study supplement this literature.[34–36]

Modern randomized clinical trials are expected to feature as-randomized outcome data using currently accepted clinical markers. The as-treated ARUBA analysis was undertaken by protocol plan to address expected criticisms that randomized trials are unsuitable for disorders such as AVM.[13] The concern was that as-randomized analyses published alone might exaggerate outcome rates in the treatment arm from the inclusion of participants who had events before intervention could begin. The data show otherwise. Widespread use of mRS score in stroke trials[3] also counters criticisms that brain AVMs are not suited for mRS outcome assessments[13] Despite claims that a registry is a more suitable instrument for brain AVMs,[14] no centers volunteered to participate in the registry offered by the organizers, so the outcomes for those eligible but not randomized remain unreported. Nonetheless, interventional case series are already appearing and will likely continue the controversy of such benefits. However, at least there is a cohort from a randomized trial for a medical arm with pretreatment lesion classification and standardized assessments to provide a useful comparison.

This study provides Class II evidence that for adults with unruptured brain AVMs, interventional management compared to MM increases the risk of disability and death over ≈3 years. The current ARUBA data and supporting literature suggest that a useful management plan may be deferral of intervention awaiting a hemorrhage, which may never occur or may be mild if it does.

AUTHOR CONTRIBUTIONS

J.P. Mohr: principal investigator and director of the Clinical Coordinating Center, Columbia University; study concept and design; principal author of the manuscript; corresponding author. J.R. Overbey: associate of principal statistician Michael Parides, analysis and interpretation, critical revisions of the manuscript for intellectual content. R. von Kummer, M.A. Stefani, and R. Libman,: acquisition of data, critical revision of the manuscript for important intellectual content. C. Stapf: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, obtaining funding. M.K. Parides: study concept and design, analysis and interpretation, statistical analysis, and critical revision of the manuscript for important intellectual content. J. Pile-Spellman: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content. E. Moquete: study concept and design, study coordinator, management of submitted data, critical revision of the manuscript for important intellectual content. C.S. Moy: study concept and design; study oversight, critical revision of the manuscript for important intellectual content. E. Vicaut: study concept and design, coinvestigator for the Aruba European Coordinating Center, analysis and interpretation, critical revision of the manuscript for important intellectual content. A. J. Moskowitz: study concept and design, coauthor of the manuscript, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. K. Harkness, C. Cordonnier, A. Biondi, and E. Houdart: acquisition of data, critical revision of

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DISCLOSURE

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