Treatment Outcomes of A Randomized Trial of Unruptured Brain Arteriovenous Malformation-Eligible Unruptured Brain Arteriovenous Malformation Patients

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Received, May 16, 2017.
Accepted, September 18, 2017.
Published Online, October 10, 2017.

BACKGROUND: The guideline for treating unruptured brain arteriovenous malformations (ubAVMs) remains controversial. A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) reported lower risk of stroke or death with conservative management compared to interventional treatment. There were numerous limitations to the study, including short follow-up period and disproportionate number of patients treated with surgery and embolization.

OBJECTIVE: To evaluate whether treatment of ARUBA-eligible patients have acceptable outcomes at our institution.

METHODS: Retrospective analysis was performed on 673 patients with brain AVMs treated at our institution between 2001 and 2014. One hundred five patients were ARUBA eligible and included in the study. Patients were divided into the microsurgery or Gamma Knife Radiosurgery (GKS; Elekta, Stockholm, Sweden) arm depending on their final treatment. Mean follow-up period was 43 mo (range 4-136 mo). Primary outcome was stroke or death.

RESULTS: A total of 8 (7.6%) patients had a stroke or died. The overall risk of stroke or death was 11.4% (5 of 44 patients) for the microsurgery arm and 4.9% (3 of 61 patients) for the GKS arm. The annual rates of stroke or death were 2.1%, 4.0%, and 1.2% for the entire patient cohort, microsurgery arm, and GKS arm, respectively. AVM obliteration rates at the end of the follow-up period were 95.5% and 47.5% for the microsurgery and GKS arms, respectively.

CONCLUSION: We report a lower overall risk of stroke or death in our ARUBA-eligible patients following treatment than ARUBA. Our results suggest that microsurgery and GKS may be appropriate treatments for patients with ubAVM.

KEY WORDS: Microsurgery, Radiosurgery, Gamma Knife, Embolization, Stroke, AVM, ARUBA

Neurosurgery 83:548–555, 2018 DOI:10.1093/neuros/nyx506 www.neurosurgery-online.com

Management of unruptured brain arteriovenous malformations (ubAVMs) is controversial. The morbidity and mortality associated with treatment must be weighed against the 2% to 4% annual risk of hemorrhage.[1-8] Treatments include endovascular embolization, microsurgical resection, or stereotactic radiosurgery alone or in combination with the final goal of total nidal obliteration.

A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) compared conservative medical management to invasive treatment in patients with ubAVMs.[1] Their results suggested that conservative medical management is superior to interventional therapy for prevention of stroke and death.[1] However, there are numerous limitations to the study, such as a disproportionate number of patients from contributing institutes, relatively short follow-up period, and a disproportionate number of patients treated with embolization alone and those treated by surgery.

ABBREVIATIONS: ARUBA, A Randomized Trial of Unruptured Brain Arteriovenous Malformations; **GKS,** Gamma Knife Radiosurgery; **SIVMS,** Scottish Intracranial Vascular Malformation Study; **SM,** Spetzler-Martin; **ubAVM,** unruptured brain arteriovenous malformation

Following the ARUBA trial, several groups published their results of ARUBA-eligible cohorts treated with embolization, microsurgery, and radiosurgery, in combination or alone. Rutledge et al,[9] Ding et al,[10] Wong et al,[16] and Javadpour et al[11] all reported lower overall risk of stroke or death in their treatment arm than the 30.7% reported in ARUBA.[9] Furthermore, patients with low Spetzler-Martin (SM) grades (I or II) appear to benefit from interventional treatment over conservative medical management.[9-12] Here, we report the outcomes of the 105 ARUBA-eligible patients treated at our institution between 2001 and 2014.

METHODS

Patients

An institutional review board approved retrospective analysis was performed on 673 patients with brain AVMs who were treated at our institution between 2001 and 2014. Patient consent was not required as this study was retrospective in nature, has minimal risk, and had no impact on patient care. The same inclusion and exclusion criteria from the ARUBA trial were used for patient selection.[1] All included patients were 18 years or older with an ubAVM diagnosed by neurovascular imaging (MRI, MR angiography, CT angiography, or catheter angiography). Patients with previous hemorrhage, prior treatment, a brain AVM that was deemed unsuitable for treatment, or had other diagnosis including cavernous malformation, moyamoya changes, or dural arteriovenous fistulas, were excluded from the study.

Of the 673 patients with AVMs, 105 were considered ARUBA eligible and were included in the current study. Baseline characteristics including age, sex, risk factors, and clinical presentation were extracted from the electronic medical record. AVM characteristics including location, size, eloquence, venous drainage, and SM grade were determined from neurovascular imaging.

All patients were treated with microsurgical resection or Gamma Knife radiosurgery (GKS; Elekta, Stockholm, Sweden; alone or in combination), with or without endovascular embolization. The primary outcome of this study is stroke or death from any cause. Secondary complications recorded include infection, cerebrospinal fluid leakage, hydrocephalus, cerebral edema, meningocele, and seizure. Follow-up information was obtained from subsequent clinic visits or telephone interviews as an alternative. Mean follow-up period was 43 mo (range 4-136 mo).

Statistics

Continuous variables were presented as mean and standard deviation and compared using unpaired *t*-test. Categorical variables were compared by the Pearson's chi-squared test. Statistical significance is set at $P < .05$. Statistical analysis was performed using RStudio (Boston, Massachusetts) and GraphPad Prism software (La Jolla, California).

RESULTS

Compared to the interventional arm of ARUBA, our treatment cohort had significantly more female patients (59% vs 42%, $P = .018$), lower percentage of patients that were right handed (81% vs 96%, $P = .001$), more AVMs in eloquent location (70% vs 47%, $P = .001$), greater percentage of AVMs with size greater than 3 cm (48% vs 32%, $P = .022$), more patients with SM grade III, IV, and V AVMs (56% vs 32%, $P = .002$), and more AVMs in the posterior fossa (15% vs 6%, $P = .048$; Table 1).[1]

Patients were divided into either GKS or microsurgery arm depending on their final treatment modality. Sixty-one patients received GKS as their final treatment and 44 patients received microsurgery as their final treatment (Table 1). The microsurgery group was significantly younger than the GKS group on average (39 ± 6 yr vs 45 ± 6 yr, respectively; $P = .03$) and had significantly smaller proportion of patients with hypertension (7% vs 34%, respectively; $P = .002$; Table 1). The characteristics of AVMs were significantly different between the 2 treatment arms: a higher proportion of GKS-treated patients had AVMs with deep and brainstem localization, and AVMs with deep venous drainage, whereas a higher proportion of microsurgery-treated patients had cerebellar AVMs (Table 1).

Of the 105 ARUBA-eligible patients, no patients were treated with embolization alone. Fourteen (13%) patients were treated by microsurgery alone, 28 (27%) by microsurgery with embolization, 51 (49%) by GKS alone, 7 (7%) by GKS with embolization, and 5 (5%) by a combination of GKS and microsurgery with or without embolization (Table 2). Of the 51 patients who underwent GKS treatment alone, 14 patients were treated with GKS twice; of the 7 patients who underwent GKS with embolization, 1 patient was treated with GKS twice, and 1 was treated with GKS 3 times. The mean length of time between the GKS treatments was 32.3 mo.

A total of 8 (7.6%) patients had a stroke or died during a mean follow-up period of 43 mo (range 4-136 mo; Table 2). The cumulative follow-up period was 377 person-years. The annual postoperative stroke or death rate was 2.1%. The Kaplan-Meier survival curves of the microsurgery arm and GKS arm as well as that of the entire patient cohort are presented in Figure 1.

Of the 44 patients that had microsurgery as the final treatment, 2 patients died. One patient (SM grade III) died from a heart attack within 1 mo after surgery and 1 patient (SM grade II) died from urosepsis. Two patients (both SM grade IV) suffered from hemorrhagic strokes and 1 patient (SM grade IV) suffered from an ischemic stroke. Postoperatively, 3 (6.8%) patients developed an infection, 2 (4.5%) had cerebrospinal fluid leakage, 2 (4.5%) developed hydrocephalus, 1 (2.3%) develop cerebral edema, 2 (4.5%) developed meningocele, 5 of the 15 patients with a history of seizures continued to have seizures, and 4 (9.1%) developed new seizure (Table 3). Forty-two of 44 patients (95.5%) had complete AVM obliteration as confirmed by postoperative angiography. The cumulative follow-up period for the microsurgery arm was 124.4 person-years, with a mean follow-up period of 34 mo. The annual postoperative stroke or death rate was 4.0%.

Of the 61 patients that had GKS as the final intervention, 2 (1 SM grade III and 1 SM grade IV) patients had a hemorrhagic stroke and died (Table 3). Both of these patients did not have complete AVM obliteration at the time of hemorrhage, which

TABLE 1. Summary of Baseline Clinical and AVM Characteristics of the 105 ARUBA-Eligible Patients

Characteristic	Total (n = 105)	Microsurgery ± embo (n = 44)	GKS ± embo (n = 61)	*P* Value
Female	62 (59)	23 (52)	39 (64)	.32[a]
Mean age (yr)	43 ± 1.3	39 ± 5.9	45 ± 5.8	**.03**[b]
Right handed	85 (81)	33 (75)	52 (85)	.29[a]
Risk factors				
Hypertension	24 (23)	3 (7)	21 (34)	**.002**[a]
Smoker	46 (44)	23 (52)	23 (38)	.71[a]
Ex-smoker	14 (13)	7 (16)	7 (12)	
Clinical presentation				
Seizure	35 (33)	15 (34)	20 (33)	1.00[a]
Headache	57 (54)	23 (52)	34 (56)	.88[a]
Focal neurological deficits	45 (43)	20 (45.5)	25 (41)	.80[a]
Location				**.001**[a]
Cortical	71 (68)	31 (70)	41 (67)	
Deep	17 (16)	2 (5)	15 (25)	
Cerebellar	14 (13)	11 (25)	3 (5)	
Brainstem	2 (2)	0	2 (3)	
Eloquence				.28[a]
No	31 (30)	16 (36)	15 (25)	
Yes	74 (70)	28 (64)	46 (75)	
Deep venous drainage				**.03**[a]
No	65 (62)	33 (75)	32 (52)	
Yes	40 (38)	11 (25)	29 (48)	
Size				.66[a]
<3 cm	55 (52)	21 (48)	34 (56)	
3-6 cm	48 (46)	22 (50)	26 (43)	
>6 cm	2 (2)	1 (2)	1 (2)	
Mean size (cm)	3.0 ± 0.1	3.2 ± 0.3	2.9 ± 0.2	.23[b]
Spetzler-Martin grade				.51[a]
1	15 (14)	9 (20)	6 (10)	
2	31 (30)	13 (30)	18 (30)	
3	35 (33)	14 (32)	21 (34)	
4	23 (22)	8 (18)	15 (25)	
5	1 (1)	0	1 (2)	

AVM, arteriovenous malformation; ARUBA, A Randomized Trial of Unruptured Brain Arteriovenous Malformations; GKS, Gamma Knife Radiosurgery; embo, embolization.
[a]Pearson's Chi-square test, [b]unpaired 2 tailed *t*-test.
Microsurgery arm include patients that received microsurgical resection as their final treatment. GKS arm includes patients that received GKS as their final treatment modality.

TABLE 2. Treatment Modalities of the 105 ARUBA-Eligible Patients

Treatment	No. of patients (%)
Resection alone	14 (13)
Resection w/embolization	28 (27)
Radiosurgery alone	51 (49)
Radiosurgery w/embolization	7 (7)
Embolization alone	0 (0)
Combination	5 (5)

occurred at 10 mo and 72 mo following treatment (Figure 1A). A third patient (SM grade II) had a hemorrhagic stroke at 17 mo following GKS treatment complicated with residual hemiplegia (Figure 1A). Postoperatively, 3 (4.9%) patients developed hydrocephalus, 6 (9.8%) patients developed cerebral edema, 8 of the 20 patients with a history of seizure continued to have seizures, and 3 (4.9%) developed new seizure (Table 3). Of the 61 patients treated by GKS, 29 (47.5%) had complete AVM obliteration confirmed by follow-up angiography, with a mean AVM nidus obliteration time of 45 mo post-GKS. The cumulative follow-up period for the GKS arm was 252.6 person-years, with a mean follow-up period of 50 mo. The annual postoperative stroke or death rate was 1.2%.

DISCUSSION

The ARUBA was a prospective, multicenter, randomized, controlled trial designed to compare outcomes of conservative medical management to interventional treatment in ubAVM

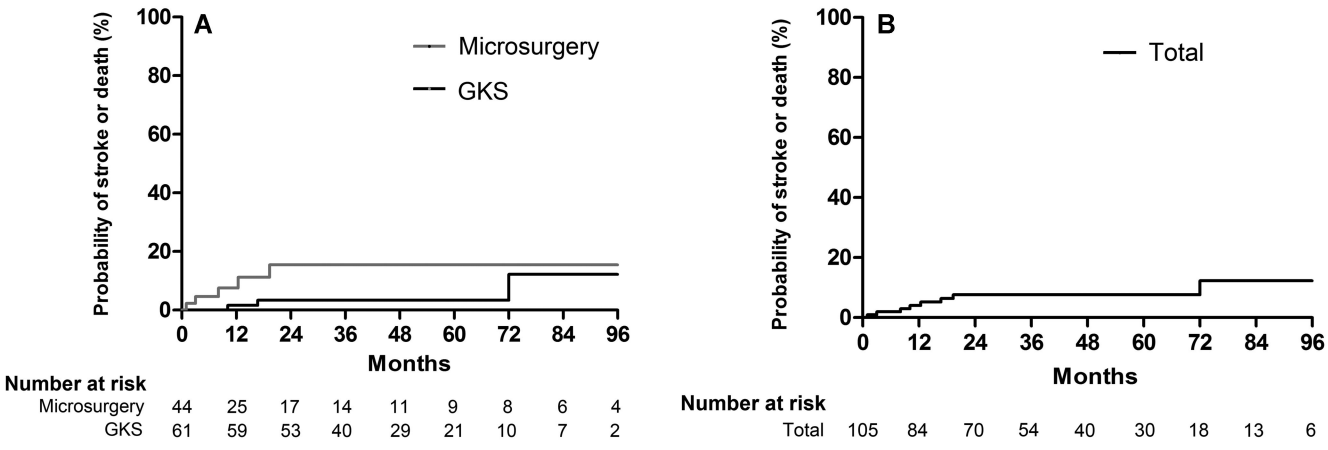

FIGURE 1. **A**, *Kaplan-Meier survival plot of ARUBA-eligible patients in the microsurgery arm (gray line) and Gamma-Knife (Elekta) radiosurgery arm (black line).* **B**, *Kaplan-Meier survival plot of all 105 ARUBA-eligible patients. Number of patients at risk at each follow-up time point is presented below each graph.*

TABLE 3. AVM Obliteration Rates, Complications, and Outcomes of the 105 ARUBA-Eligible Patients

	All treatment (n = 105)	Microsurgery ± embo (n = 44)	GKS ± embo (n = 61)
Obliteration rate	67.6%	95.5%	47.5%
Outcomes			
Stroke or death	8 (7.6%)	5 (11.4%)	3 (4.9%)
Death	4 (3.8%)	2 (4.5%)	2 (3.3%)
Stroke	6 (5.7%)	3 (6.8%)	3 (4.9%)
Hemorrhagic	5 (4.8%)	2 (4.5%)	3 (4.9%)
Ischemic	1 (1.0%)	1 (2.3%)	0 (0%)
Infection	3 (2.9%)	3 (6.8%)	0 (0%)
CSF leak	2 (1.9%)	2 (4.5%)	0 (0%)
Hydrocephalus	5 (4.8%)	2 (4.5%)	3 (4.9%)
Cerebral edema	7 (6.7%)	1 (2.3%)	6 (9.8%)
Meningocele	2 (1.9%)	2 (4.5%)	0 (0%)
New onset seizure	7 (6.7%)	4 (9.1%)	3 (4.9%)

embo – embolization.

patients.[1] Despite the study being planned for 5 yr, the trial was stopped early in April of 2013 because medical management was found to be superior to interventional treatments. However, many raised concerns regarding the limitations of the trial including the relatively small sample size, short follow-up period, and underrepresentation of surgical treatment.[13-15]

In recent years, several groups have reported the outcomes of their ARUBA-eligible patient studies (Figure 2; Table 4). Many reported lower risk of stroke or death in their study cohort than ARUBA.[9-12,16] In contrast, the Scottish Intracranial Vascular Malformation Study (SIVMS) showed conservative medical management to be superior to treatment. However, the difference was small at 4-yr follow-up and disappeared at 12-yr follow-up.[17] Whether medical management was superior to treatment remained unclear.

The primary treatment goal for brain AVMs is always complete nidal obliteration. A large meta-analysis reported obliteration rates of 96%, 38%, and 13% for surgical resection, stereotactic radiosurgery, and embolization, respectively.[18] We found similar rates of AVM obliteration post-treatment (95.5% for microsurgery and 47.5% for GKS). ARUBA, however, did not report their cure rates. With a high risk of death or stroke (30.7%) in ARUBA's treatment arm, the patients who underwent intervention in the trial were unlikely to have good curative rates, thereby subjecting them to the morbidity of the natural history of incompletely treated AVMs[1,9,19] Furthermore, embolization

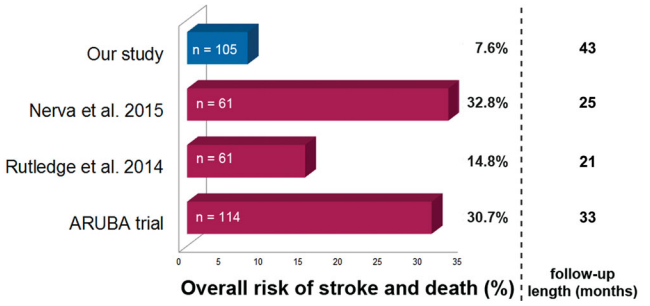

FIGURE 2. *A comparison between ARUBA and subsequent ARUBA-eligible patient studies that include microsurgery, radiosurgery, and embolization treatment modalities. The overall risk of stroke or death in percentage was 7.6%, 32.8%, 14.8%, and 30.7% in the current study, Nerva et al,[12] Rutledge et al,[9] and ARUBA,[1] respectively. The average follow-up period is listed on the right of the dashed line.*

alone is unlikely to yield complete AVM obliteration, and yet, 26% of patients from ARUBA were treated with embolization alone.[1] The overrepresentation of endovascularly treated patients in ARUBA may partly explain the high risk of stroke or death compared to subsequent ARUBA-eligible cohort studies (Table 4).

With the development of new embolization technologies, including embolysates such as n-butyl cyanoacrylate and Onyx, as well as new microcatheters, the goals of embolization to treat brain AVMs are shifting.[20] Preoperative embolization used to be the prevailing indication for brain AVMs. However, there is now evidence to suggest pre- and post-radiosurgery embolization to reduce AVM nidus size and obliteration of residual AVMs, respectively.[21-24] Furthermore, AVM cure rates using Onyx is superior to embolysates used in the past, with reported obliteration rates of 28% to 94%.[21,25-32] Embolization alone may be an appropriate treatment for specific patient populations, such as those with small AVMs that have limited arterial feeders and are located in areas difficult to access surgically.[20] While embolization is still used predominately in an adjuvant manner, further technological advancement may make it a stand-alone treatment for select patient populations in the future.

Surgical resection is relatively safe for SM grades I/II AVMs. A meta-analysis of 12 publications from 1986 to 2014 found an overall 0.3% mortality rate, 2.2% morbidity rate, and 0.3% postoperative hemorrhage rate in surgically treated ubAVM patients.[19] Three ARUBA-eligible patient studies also found surgical resection to be safe with good prognosis.[11,12,16] In our study, out of 22 SM grade I/II patients treated with microsurgical resection, only 1 patient died from a cause unrelated to the AVM (urosepsis). This adds to the growing evidence that surgery is a relatively safe option for low risk ubAVMS.[11,12,16] Whether surgery is superior to conservative medical management for these low-risk patients, however, will require further investigation. On the other hand, risk of surgery is higher for SM grade III and IV patients. In our microsurgery arm, 1 SM grade III patient died from an unrelated cardiac complication, and 3 SM grade IV patients experienced postoperative stroke.

The annual rate of stroke or death was 4.0% in our microsurgery arm. The high annual rate observed may be affected by the poor follow-up of the patients (Figure 1). Theoretically, total nidal obliteration should completely eliminate the risk of future AVM rupture. The annual rate of stroke or death may have been lower if those patients with complete nidal obliteration were not lost to follow-up. Interestingly, the risk of stroke or death is highest during the first 2 yr post-surgery, with the annual risk appearing to decrease thereafter (Figure 1A). A similar pattern can be observed in the Kaplan-Meier plots of ARUBA,[1] SIVMS,[17] and Rutledge et al's study.[9] With decreasing annual risk after the initial 2 yr, a long follow-up period may be required to see the full benefit of surgical resection.

TABLE 4. Risk of Stroke or Death of ARUBA and All Subsequent ARUBA-Eligible Cohort Studies

Author and year	Treatment modality	No. of patients in study	No. of patients that had a stroke or died (%)
Mohr et al 2014 (ARUBA)[1]	Grouped intervention	114	35 (30.7%)
	Medical management	109	11 (10.1%)
Rutledge et al 2014[9]	Grouped intervention	61	9 (14.8%)
	Medical management	13	1 (7.7%)
Nerva et al 2015[12]	Microsurgery ± embo	31	14 (45.2%)
	Radiosurgery ± embo	30	6 (20.0%)
Ding et al 2016[10]	Radiosurgery	509	49 (9.6%)
Javadpour et al 2016[11]	Microsurgery ± embo	34	0 (0%)
Wong et al 2016[16]	Microsurgery ± embo	155	6 (3.9%)
Our study	Grouped intervention	105	8 (7.6%)

embo – embolization.
Grouped intervention includes patients treated with microsurgery ± embo and GKS ± embo.

Stereotactic radiosurgery is an alternative to surgical resection. The technique is favorable for small-to-moderate size brain AMVs, especially those located in deep or eloquent regions, making surgery a challenge.[33] This was consistent with selecting treatment modalities for our patient cohort as deep AVMs and AVMs located in eloquent centers were more prevalent in the GKS arm than the microsurgery arm (Table 1).

Similar to our findings, the mean AVM nidal obliteration time after stereotactic radiosurgery was reported to be approximately 37 mo, with only 70% to 90% of brain AVMs being obliterated after a latency period of 3 yr.[34,35] The risk of hemorrhage still exists during this latency period. This emphasizes the importance of a long follow-up time, as the benefit of treatment may not be fully realized until well after the latency period is over. The annual rate of stroke was 1.2% in our GKS arm, similar to the 0.9% annual rate reported previously.[10] With the annual hemorrhage rate of ubAVMs being reported at 2.2%, radiosurgery may offer greater benefit than conservative management.[36]

Finally, we found a significantly lower risk of stroke or death in our ARUBA-eligible patients than ARUBA's interventional arm (7.6% vs 30.7%; $P < .0001$).[1] We think this may be due to several reasons. First, we had a greater percentage of patients treated with microsurgery. Second, embolization was used only as an adjunct to microsurgery and radiosurgery. Third, we had more patients receiving multidisciplinary treatment, whereas most patients in ARUBA underwent single modality treatment. Lastly, we had a longer average follow-up period of 43 mo compared to the 33 mo in ARUBA.[1]

Limitations

There were several limitations to our study. First, the study was retrospective in nature and may include possible selection and referral bias. Second, we did not have an observational cohort, preventing any comparison to be made between interventional treatments and conservative management. Third, there was limited functional follow-up data from our patients. For this reason, we were unable to report Modified Rankin Scores for the patient cohort.

CONCLUSION

The results of this study suggest that interventions (microsurgery and radiosurgery, with or without embolization) may be appropriate for ubAVMs, especially for select patients such as those with low SM grades. Furthermore, findings from our study and other ARUBA-eligible studies suggest that a long follow-up period is necessary to realize the risk reduction by microsurgery and radiosurgery. More detailed investigations are needed to determine if there are AVMs or patient characteristics that would make patients better suited for specific treatment modality or conservative medical management.

Disclosures

Funding was received from the American Heart Association - Student Scholarship in Cerebrovascular Disease and Stroke. Dr Bain is a consultant for Stryker Neurovascular. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

The conclusions derived from the randomized trial of Unruptured Brain AVMs (ARUBA) have been a widely discussed and controversial topic since the study's publication in 2014.[1] Lack of subgroup analyses (including endpoints and cure rates pertaining to various treatment modalities), enrollment rates, under-representation of surgical treatment, duration of follow-up, as well as selection bias have all been cited as points of contention with regard to ARUBA's conclusion regarding the superiority of medical management alone when compared to interventional therapy for patients with ubAVMS.[2] A number of retrospective analyses in ARUBA-eligible patients have found significantly lower morbidity and mortality in patients treated with interventional therapies using the primary endpoints of death or symptomatic stroke employed in ARUBA.[3-6] The current study adds to this body of evidence with a 7.6% risk of stroke or death in the 105 patients treated with either GKS, microsurgery, or both, which is the lowest reported cumulative risk with regard to interventional therapy in ARUBA-eligible patients to date. Of note, embolization was used as an adjunctive therapy in this study, which differs from ARUBA in which embolization was the sole intervention in 26% of patients in the treatment arm.[1] We would like to congratulate the authors on their clinical outcomes in this analysis. The current study, although retrospective, adds to the growing body of evidence that uAVMs may be optimally managed with interventional approaches when sub-stratified by Spetzler-Martin/Lawton-Young grading, employment of multimodal treatment modalities (eg embolization with microsurgery and/or GKS) and referral to high volume AVM centers.

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A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) was a randomized trial of intervention versus conservative management for unruptured brain AVMs.[1] The trial demonstrated a lower risk of stroke and death in the conservative arm. The trial has been heavily criticized for lack of standardization of the treatment arm, disproportionate number of patients treated with embolization alone, choice of outcome measures, low enrollment rates, selection bias, disproportionate number of patients from contributing institutes, premature interruption of enrollment, short follow-up period, the lack of subgroup analyses, the lack of details on the results of the various treatments, and a contentious interpretation of results.[2] The short follow-up period is probably the most important limitation of ARUBA, given that the true risk of stroke and death in the conservative cohort is experienced over a lifetime, not 3 years.

In turn, a number of studies have been published demonstrating alternative experiences with "ARUBA-eligible" patients in an effort to demonstrate better outcomes with intervention in comparison to the ARUBA results.[3-6] The present article contributes to that literature, demonstrating an overall risk of stroke or death of 7.6% for treated patients (microsurgery 11.4% and radiosurgery 4.9%), a far better outcome than the reported outcome in the ARUBA treatment arm (30.7%) and slightly better than that in the ARUBA conservative arm (10.1%). The authors should be congratulated on their contribution to the growing body of literature that demonstrates real-life outcomes following unruptured AVM treatment. Not only are we seeing that unruptured AVMs

are a disease worth treating, but that these lesions are treated best in regional centers of excellence with dedicated specialists and high-volume practices. This manuscript demonstrates the need for well designed, pragmatic studies to evaluate rare and complex neurological diseases such as brain AVMs.

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1. 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*. Feb 15 2014; 383(9917):614-621.
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