Original research

National reduction in cerebral arteriovenous malformation treatment correlated with increased rupture incidence

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnis-2022-019110).

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Received 28 April 2022
Accepted 12 July 2022
Published Online First 28 July 2022

To cite: Luther E, McCarthy DJ, Burks J, *et al*. *J NeuroIntervent Surg* 2023;**15**:735–740.

ABSTRACT

Background Recently, there has been a shift in management of unruptured cerebral arteriovenous malformations (AVMs) following studies suggesting that medical management alone was superior to interventional therapy.

Objective To evaluate the influence of contemporary AVM management on AVM rupture patterns in the United States.

Methods 154 297 AVM admissions were identified between 2003 and 2017 in the National Inpatient Sample. Annual AVM intervention and rupture rates were computed and multivariable logistic regression assessed the likelihood of AVM intervention pre- and post-2014. Segmented regression identified significant change points and fitted segmented linear models for annual intervention and rupture rates. Correlation coefficients assessed the relationship between annual AVM intervention and rupture rates.

Results For unruptured AVMs, intervention likelihood and proportion decreased after 2014 (28.1% to 22.3%, p<0.0001; adjusted OR=0.857, 95% CI 0.751 to 0.977, p=0.02). Ruptured AVM admissions increased from 14.7% to 18.6% after 2014 (p<0.0001). Between 2003 and 2017, segmented linear regression identified one significant change point in intervention rate between 2014 and 2015. Average annual percent change for rupture incidence and intervention rate increased by 0.49% (p=0.0001) and decreased by 1.17% (p=0.0001), respectively. Annual AVM intervention rates were inversely correlated with annual AVM rupture incidence (Pearson coefficient=−0.82, p=0.0002). In 2017, the annual AVM rupture rate (20.6%) surpassed the annual AVM intervention rate (19.7%).

Conclusions After 2014, the likelihood of intervention for unruptured AVMs decreased while the incidence of ruptured AVMs increased. These findings suggest that fewer unruptured AVM treatments may lead to increases in AVM rupture incidence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The ARUBA trial (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) was the first prospective, randomized trial evaluating treatment for unruptured brain arteriovenous malformations (AVMs) and concluded that medical management alone was superior to intervention.
⇒ Subsequent studies on ARUBA-eligible patients have demonstrated results in direct conflict with the findings of ARUBA.

WHAT THIS STUDY ADDS

⇒ Limited data exist evaluating the effect of ARUBA on AVM treatment patterns.
⇒ This study demonstrates that unruptured AVM treatments are increasingly declining post-ARUBA while AVM rupture incidence is correspondingly increasing.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ These results suggest that further research must be done before we conclude that no unruptured AVMs should receive treatment.

INTRODUCTION

A Randomised trial of Unruptured Brain Arteriovenous malformations (ARUBA) found that medical management alone was superior to intervention for unruptured cerebral arteriovenous malformations (AVMs).[1 2] These findings challenged prior AVM treatment paradigms and demonstrated that AVM treatment risk was higher than previously perceived. Subsequent studies reported more favorable outcomes than ARUBA but were mostly retrospective and from single centers.[3–10] Thus, there remains no clear consensus on AVM management guidelines.[11–13] Using the National Inpatient Sample (NIS), our study aimed to provide a descriptive analysis of contemporary AVM treatment trends. Furthermore, we perform the first longitudinal epidemiology study detailing the relationship between unruptured AVM treatment rate and AVM rupture incidence.[14 15]

METHODS

National Inpatient Sample associated indices

The Elixhauser Comorbidity Index identifies specific comorbidities in the NIS that are extrapolated to assess overall patient health, mortality risk, and 30-day readmission risk.[16 17] The NIS-subarachnoid hemorrhage outcome measure (NIS-SOM) is a scoring system for aneurysmal subarachnoid hemorrhage that acts as a surrogate for the modified Rankin Score, with a poor neurologic outcome correlating to a modified Rankin Score at discharge of >2–3.[18] Given the de-identified nature of the

data, institutional review board approval and patient consent were not required.

Definition of cases and covariates

All the International Classification of Diseases (ICD)−9/10 codes and their associated diagnoses/procedures are listed in the online supplemental table S1. All patients with a brain AVM identified between 2003 and 2017 were included. AVMs with intracranial or subarachnoid hemorrhage were labeled as ruptured AVMs.[19] Treatment modalities were stratified into surgical excision, endovascular treatment (EVT), and stereotactic radiosurgery. Owing to the impact of the ARUBA study, we analyzed and compared treatment patterns before and after its publication in 2014.

Statistical analyses

Aggregate national estimates of annual discharge frequencies were calculated using weighted observations. Two time periods were analyzed: 2010–2017 and 2003–2017. Alterations in AVM intervention and rupture rates were compared between 2010–2013 and 2014–2017. Changes in annual AVM rupture incidence and interventions between 2003 and 2017 were quantified via segmented regression models.

Normality of continuous variables was assessed graphically and statistically with a Shapiro-Wilks test. Continuous variables with non-parametric and parametric distributions were represented as annual weighted median and mean estimates, respectively, with their associated IQR or SD. Comparisons of means/distributions of normally continuous variables were performed using least squared means analysis; while, non-parametric distributions were compared with a modern extension of the Wilcoxon rank sum test, adjusting for survey clustering, stratification, and weights.[20] Categorical variables were presented as an estimated weighted frequency and percent. Statistical analyses of categorical variables were carried out using X^2 and Fisher's exact t-tests, as appropriate.

Annual interventions were calculated using the following formula:

$$Annual\ Interventions_Y = \frac{(\#Treated\ AVM\ discharges)_Y}{(\#Total\ AVM\ discharges)_Y}$$

where Y=year of interest.

Change in the intervention proportion from pre-ARUBA (P1) to post-ARUBA (P2) is represented as:

$$\%\Delta_{Tx} = \frac{\sum_{P2} Annual\ Intervention\ Rate}{4} - \frac{\sum_{P1} Annual\ Intervention\ Rate}{4}$$

Each year's rupture incidence was calculated as:

$$Annual\ Rupture\ Incidence_Y = \frac{(\#Ruptured\ AVMs)_Y}{(\#Total\ AVMs)_Y}$$

To describe and quantify temporal trends in annual intervention and rupture rates, segmented regression identified significant change points and fitted segmented linear models.[21 22] For the estimation of average annual percent change, regression coefficients and the weighted sum of slopes was used for linear and segmented models, respectively.[23 24] Segmented average annual percent change was defined as the change in annual AVM rupture incidence or intervention rate over time before and after 2014. Pearson and Spearman correlation examined the relationship between annual interventions, annual ruptures, and time.

Univariate logarithmic regression was used to identify significant covariates associated with likelihood of AVM intervention. A multivariable model, adjusted for significant covariates and potential confounders (p<0.20), was used to assess the independent relationship between pre/post-2014 temporality and likelihood of any AVM intervention. P values of ≤0.05 were considered statistically significant. Statistical analysis was performed with SAS 9.4 (Cary, North Carolina, USA) and RStudio using procedures that account for NIS stratified-cluster sampling methodology.[25] Owing to the low rate of missing data, imputation was foregone for statistical analyses. Rates of missing covariates are listed in the online supplemental table S2.

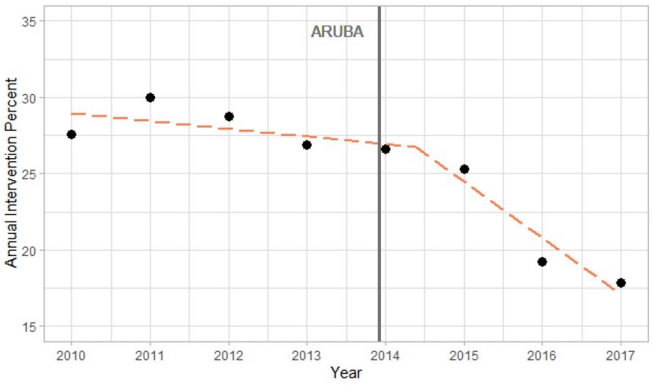

Figure 1 Pre- and post-2014 annual arteriovenous malformation intervention rates with segmented linear regression. ARUBA, A Randomized Trial of Unruptured Brain Arteriovenous Malformations.

RESULTS

Pre- and post-2014 demographics and outcomes

A total of 90 296 AVM admissions were identified between 2010 and 2017. Demographics and outcomes for unruptured and ruptured AVMs, stratified by pre- and post-2014 status, are depicted in the online supplemental table S3. Higher average annual AVM rupture incidence was observed in the post-2014 period (14.7 vs 18.6%, p<0.0001). Patients with ruptured AVMs post-2014 were older (p=0.0139), less commonly admitted at an academic institution (p=0.0002), and received more cerebrospinal fluid (CSF) diversion (p=0.0002). Unruptured AVMs post-2014 had longer length of stay (p<0.0001) and had more associated aneurysms (p=0.0045). Additionally, regardless of rupture status, post-2014 AVMs were from smaller hospitals, had Medicare or Medicaid, more medical comorbidities, higher NIS-SOM rates, and were discharged home less frequently.

Pre- and post-2014 treatment comparison 2010–2017

Segmented regression modeling identified a significant change in unruptured AVM interventions between 2014 and 2015 (figure 1). Overall adjusted average annual percent change for interventions was −1.70% (95% CI −2.2% to −1.2%, p=0.0006). The segmented average annual percent change before 2014 was −0.50% (95% CI −1.8% to 0.8%, p=0.35) and −3.71% (95% CI −6.7% to −0.8%, p=0.025) after 2014.

A significant decrease in unruptured AVM interventions was observed post-2014 (28.1% to 22.3%, p<0.0001). There was no change in ruptured AVM interventions. figure 2 and table 1 display the differences in treatment patterns for ruptured and unruptured AVMs pre- and post-2014. For unruptured AVMs, surgical excision and EVT experienced the largest decreases (10.7% to 8% and 15.2% to 12.8%, respectively). While there was no change in overall ruptured AVM interventions, type of intervention changed (p=0.0039), with a decrease seen in surgical excision and an increase in EVT (15.7% to 12.2% and 9.3% to 11.9%, respectively).

Figure 3 displays AVM interventions stratified by CSF diversions, concurrent aneurysms, and age. Ruptured AVMs that

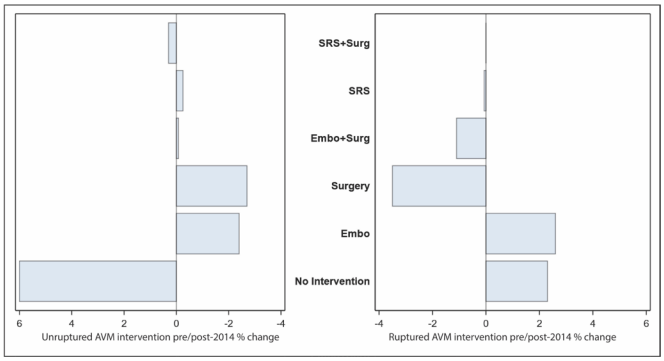

Figure 2 Ruptured and unruptured AVM percent treatment changes pre- and post-2014. AVM, arteriovenous malformation; Embo, embolization; SRS, stereotactic radiosurgery.

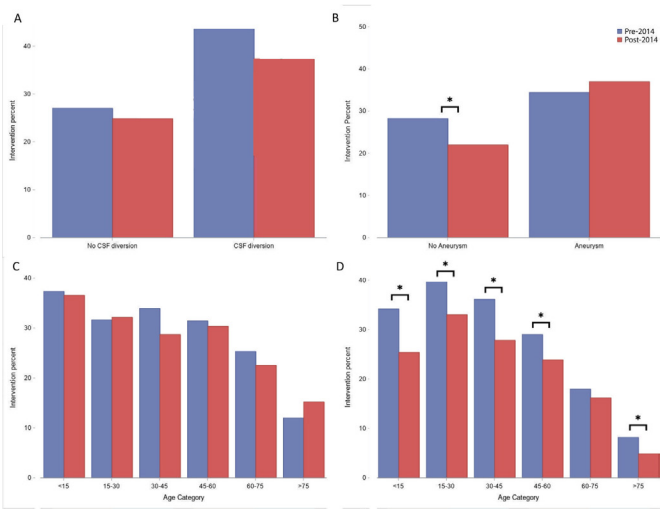

Figure 3 Arteriovenous malformation (AVM) intervention rates stratified by (A) CSF diversion in ruptured AVMs; (B) aneurysms associated with unruptured AVMs; and age for (C) ruptured AVMs and (D) unruptured AVMs; *Indicates statistical significance. CSF, cerebrospinal fluid.

underwent CSF diversion had higher intervention rates (24.7% vs 14.7%, p<0.0001) regardless of pre- or post-2014 status (p=0.13). Interventions for unruptured AVMs with associated aneurysms did not decrease following 2014. There was a significant decrease in unruptured AVM interventions across all age groups except ages 60–75. No significant change was seen in interventions for any ruptured AVM age group. Online supplemental figure S1 displays AVM rupture rates stratified by age. Rupture rates increased in every group except ages 46–60 post-2014.

In adjusted logistic regression analysis, unruptured AVMs post-2014 had a significantly lower likelihood of undergoing intervention than pre-2014 (table 2, OR=0.857, 95% CI 0.75 to 0.98, p=0.02). Similar modeling demonstrated no significant difference in interventions before and after 2014 for ruptured AVMs (table 2, OR=0.94, 95% CI 0.78 to 1.13, p=0.511).

AVM intervention and rupture incidence from 2003 to 2017

Since a higher ruptured AVM incidence was observed in more recent years, the analysis was expanded to 2003 to evaluate trends in rupture incidence and interventions over the last 15 years. The online supplemental table S4 displays the overall annual AVM discharges, annual per capita adjusted AVM discharges, median age over time, overall/treatment-specific annual interventions, and the annual rupture incidence over the 15-year period. A total of 46% of patients had an unruptured AVM as a primary diagnosis. In those with non-AVM primary diagnoses, the most common primary diagnoses were stroke, seizure, or syncope. Since 2003, the per capita number of unruptured and ruptured AVMs has increased by 0.038 (p=0.039) and 0.025 (p=0.0005) per 100 000 people per year, respectively. Similarly, the median age of unruptured and ruptured AVMs has increased by 0.51 (p<0.0001) and 0.52 (p=0.0004) per year, respectively, over the past 15 years.

Segmented regression modeling identified a significant change in annual rupture rates in 2011 and intervention rates in 2014 (figure 4A). The overall adjusted average annual percent change from 2003 to 2017 was −1.17% (95% CI −1.5% to −0.81%, p=0.0001) for annual interventions and +0.49% (95% CI 0.33% to 0.63%, p=0.0001) for annual rupture incidence. Additionally, increasing year was strongly correlated with higher annual rupture incidence (Pearson coefficient 0.75, p=0.001)

Table 1 Intervention rates for ruptured and unruptured arteriovenous malformations in the 4-year periods pre- and post-ARUBA

	Ruptured					Unruptured				
	2010–2013		2014–2017		P value	2010–2013		2014–2017		P value
	Freq	%	Freq	%		Freq	%	Freq	%	
Discharges	6613	14.7	8415	18.6	<0.0001	38 488	85.3	36 780	81.4	<0.0001
No Intervention	4658	70.4	6115	72.7	0.2229	27 581	71.7	28 595	77.7	<0.0001
Intervention performed	1955	29.6	2300	27.3	0.2229	12 155	28.1	8755	22.3	<0.0001
Intervention type					0.0039					<0.0001
EVT	617	9.3	1000	11.9		5844	15.2	4720	12.8	
EVT+SRS	5	0.07	0	0		14	0.03	5	0.01	
EVT+SRS+surgery	5	0.07	0	0		5	0.01	0	0	
EVT+Surgery	270	4.1	250	3		784	2	440	1.2	
SRS	20	0.3	20	0.23		157	0.4	55	0.15	
SRS+surgery	0	0	0	0		0	0	10	0.3	
Surgery	1038	15.7	1030	12.2		4103	10.7	2955	8	

ARUBA, A Randomized Trial of Unruptured Brain Arteriovenous Malformations; EVT, endovascular treatment; SRS, stereotactic radiosurgery.

Table 2 Adjusted likelihood of undergoing intervention pre- vs post-ARUBA

	OR	95% Confidence limits	P value
Unruptured	0.857	0.751 to 0.977	0.0207
Ruptured	0.940	0.782 to 1.130	0.5110

*Listed values are adjusted by all confounders, including age, presence of aneurysms, insurance status, hospital size, teaching status, comorbidities, sex, etc with p<0.2.
ARUBA, A Randomized Trial of Unruptured Brain Arteriovenous Malformations.

and lower annual intervention rate (Pearson coefficient −0.84, p<0.001).

The segmented average annual percent change for annual interventions was −0.63% (95% CI −1.1% to −0.2%, p=0.0048) before 2014 and −3.71% (95% CI −7.5% to 0.06%, p=0.0596) after 2014. The segmented average annual percent change for annual rupture incidence was −0.07% (95% CI −0.45% to 0.30%, p=0.67) before 2011 and +1.24% (95% CI 0.8% to 1.7%, p=0.0006) after 2011. In 2017, the annual rupture incidence (20.6%) appeared higher than the annual intervention rate (19.7%) for the first time since 2003.

Annual intervention and rupture rates had a strong inverse correlation (Pearson coefficient −0.82, p=0.0002; Spearman coefficient −0.77, p=0.0008). figure 4B displays the correlation as a linear model that estimates a 0.44% decrease in annual rupture incidence and a 1% increase in annual intervention (p=0.0001).

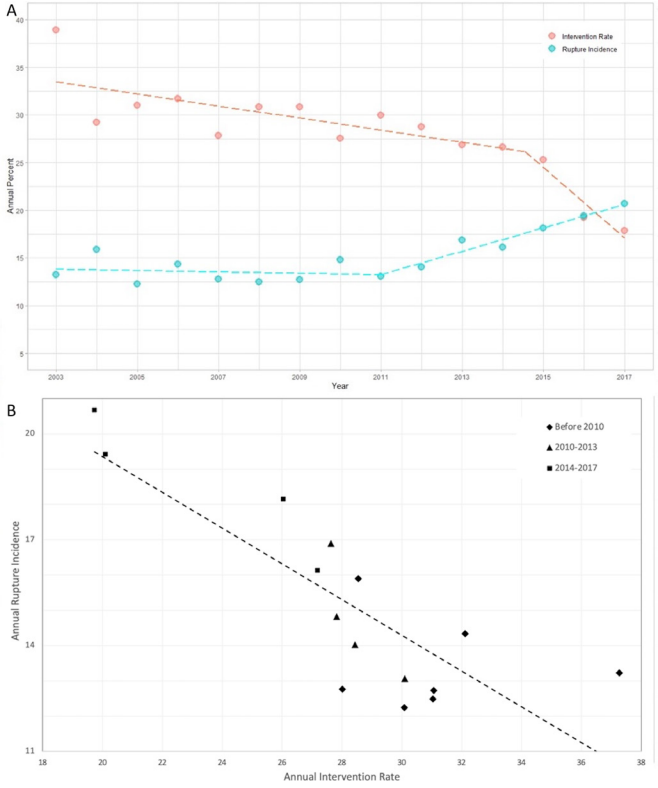

Figure 4 Analyses of annual arteriovenous malformation intervention rate and rupture incidence from 2003 to 2017. (A) Segmented linear regression of annual intervention rate and rupture incidence. (B) Correlation analysis of annual intervention rate, annual rupture incidence, and time.

DISCUSSION

Although prior studies suggested that unruptured AVM treatments were declining post-ARUBA, their analyses do not appear comprehensive as they did not account for NIS hospital weighting or changes in population over time. Thus, they were unable to fully capture the cumulative risk of declining intervention on AVM rupture and inaccurately represented changes in intervention type.[14] Herein, we present the first analysis fully detailing contemporary AVM treatment patterns post-ARUBA. Although our results also suggest that unruptured AVM interventions have significantly decreased post-2014, our longitudinal epidemiological analysis was able to demonstrate that annual AVM interventions are inversely correlated with annual AVM rupture incidence. This suggests that the treatment threshold for unruptured AVMs has increased in recent years.[3–10]

National AVM epidemiology trends

We observed that annual AVM rupture incidence was inversely correlated with annual AVM interventions, with rupture incidence increasing as interventions decreased. Theoretically, if every AVM was discovered and cured at birth then annual rupture incidence would be 0%. Conversely, if all patients with AVMs received medical management alone, then annual rupture incidence would plateau at an unknown value below 100%, as not all AVMs rupture. Therefore, there should be a mathematical correlation between AVM treatment and rupture incidence. Our data suggest that this relationship may be profound, as we observed that rupture incidence surpassed interventions for the first time in 2017 (figure 4A).

Unruptured AVMs are believed to have an annual rupture risk of 2–4%.[2 10 26–29] This risk compounds over time until a rupture occurs or the person dies from other causes. Owing to this cumulative risk, the effect that decreasing annual interventions has on rupture incidence must be shared between several subsequent years. An AVM–rupture correlation analysis that ignores temporality fails to address the cumulative nature of AVM rupture. Both annual interventions and annual rupture incidence were correlated with time, forming a three-way correlation (later time to both increasing ruptures and decreasing intervention) that one would expect in a cumulative risk model (best illustrated in figure 4B).

Between 2003 and 2017, the significant change-points for annual rupture incidence and annual intervention were 2011–2012 and 2014–2015, respectively. Segmented regression revealed a significant annual intervention percent change of −0.6% from 2003 to 2014; whereas there was no significant average annual percent change for annual rupture incidence before 2011. This suggests that the cumulative risk, incurred from a repeated decrease in annual interventions from 2003 to 2011, might have resulted in a lagged-linear annual rupture incidence increase starting in 2012. If this latency is in fact causal, it suggests that the full effect of the observed annual intervention decreases following 2014 may not be adequately reflected in the annual rupture incidence of the same time period. In fact, a further increase in rupture incidence may not be identifiable until 2021 given that a lag period of 8 years was previously identified.

A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)

In 2013, ARUBA was prematurely halted after interim analyses found that medical therapy alone resulted in less death and/or symptomatic stroke than interventional therapy for adults

harboring unruptured AVMs.[2] These findings challenged the clinical practice of many cerebrovascular specialists and resulted in various critiques which served as the impetus for several subsequent investigations.[2 30–33] In general, these studies demonstrated better long-term outcomes than the interventional arm of ARUBA using identical endpoints.[3 5–10] Multiple authors suggested that the outcome discrepancy between their cohorts and ARUBA was primarily due to careful patient selection and their increased use of surgery as the primary therapy.

Our data may help to explain the discrepancies between the results of the numerous retrospective articles and the ARUBA trial. Although the trial was initially designed with an upper limit follow-up of 12 years, its early cessation resulted in an average follow-up of less than 3 years at initial evaluation and 4.2 years at final analysis. Many clinicians question ARUBA's ability to compare upfront treatment risk with the lifetime rupture risk of AVMs.[1 2 34 35] In our epidemiology study, we observed a lag time of 8 years between AVM treatment reduction and the resultant increase in AVM rupture incidence. An 8-year correlation lag could help to explain the different results of ARUBA and -the various retrospective studies, most of which had extended follow-up periods.

AVM treatment patterns post-2014

We observed a decrease in unruptured AVM interventions and an independent lower likelihood of intervention in the post-2014 period. Furthermore, segmented regression from 2010 to 2017 identified a shift in interventions between 2014 and 2015 with the latter segment exhibiting a significantly decreasing annual percent change (−3.7%). Surgical excision and EVT demonstrated the largest treatment-specific decreases for unruptured AVMs, suggesting that treating specialists have become less inclined to pursue aggressive therapies that incur a high upfront risk. Unruptured AVM interventions remained stable when we stratified by the presence of an unruptured intracranial aneurysm, confirming that high risk angioarchitectural characteristics remain of paramount importance in AVM treatment decisions.[26 29 36–42] While no change in the overall ruptured AVM interventions was observed post-2014, there were higher rates of EVT and lower rates of surgical excision for these lesions in the post-2014 period. We hypothesize that these changes are due to increased use of preoperative embolization, with surgery occurring during a separate hospital admission, rather than direct alterations in ruptured AVM management.[43] Our results have also demonstrated a decrease in AVM ruptures treated at academic centers, whereas treatment rates of unruptured AVMs did not significantly change. This unique finding may be explained by the decrease in overall intervention rates for unruptured AVMs. In this setting, patients with AVM rupture might have been sent to the nearest hospital for emergent treatment, which might not have necessarily been at an academic center.

Limitations

Although this study draws strength through the power of a national database, the NIS does not specifically sample hospitals containing every subspecialty. As a result, it can potentially underrepresent certain interventions if a high-volume AVM center that uses a specific intervention did not participate in the NIS. Each NIS discharge is also considered a separate entity, so patients admitted for re-treatment of a recurrent or partially obliterated AVM would be analyzed as a new patient. This prevents evaluation of multiple treatments on separate admissions or unruptured AVMs with multiple admissions due to seizures, skewing the observed rates in either direction. Our reported annual rupture incidence cannot discriminate index rupture admissions from re-ruptured AVMs.

As annual rupture incidence increases, re-ruptures probably increase as well, potentially inflating the correlation between annual rupture incidence and annual intervention. Owing to the short post-2014 period, the observed decrease in AVM interventions following 2014 precludes correlation of ARUBA with AVM rupture incidence. The NIS also provides no post-discharge course or readmission information, limiting evaluation of long-term outcomes. NIS provides no AVM characteristics such as grade, morphology or location, which are known to significantly effect clinical decision-making. Moreover, the NIS provides no information on the specifics of EVT or medical therapies administered, limiting analysis of the effects of improved technologies and neurocritical care. No ICD-9/10 codes exist for partial AVM treatments, so the effects of incompletely obliterated lesions cannot be assessed.

Furthermore, as the NIS accounts only for hospitalizations, outpatient management of unruptured AVMs is excluded. This is reflected in the relatively small number of stereotactic radiosurgery treatments identified for unruptured AVMs as these do not frequently warrant a hospital admission. Increasing average life expectancy and better access to imaging modalities are additional considerations that can introduce bias into these results as they both can increase the likelihood of AVM diagnosis. Lastly, all NIS analyses are dependent on the accuracy of the ICD coding of each participating institution, which can be prone to error and result in overestimating rupture incidence if a hypertensive intraparenchymal hemorrhage is incorrectly associated with an unruptured AVM. Furthermore, aggressive ICD coding to capture more revenue may ultimately overstate the severity of a rupture.

These limitations preclude this study from being used as a means to condemn the results of ARUBA and we are not suggesting that cerebrovascular specialists should instead be universally treating all unruptured AVMs. Rather, it is our hope that these results will further prompt the discussion that some of these lesions would probably benefit from thoughtful evaluation and potential intervention prior to rupture.

CONCLUSIONS

A significant national decrease in unruptured AVM interventions was observed in the years following 2014. From 2003 to 2017, decreases in unruptured AVM interventions have been followed by a correlated lagged increase in the incidence of ruptured AVMs. Although further studies are necessary to formally establish causality between ARUBA and the decline in AVM interventions, this study suggests that treatment patterns for unruptured AVMs were altered in response to the trial. However, the corresponding increase in rupture incidence suggests that cumulative AVM rupture risk must be appropriately balanced with potential periprocedural complications to achieve optimal outcomes. Further research must be done before we conclude that no unruptured AVMs should receive treatment.

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Funding RMS's research is supported by the NREF, Joe Niekro Foundation, Brain Aneurysm Foundation, Bee Foundation, and by National Institute of Health (R01NS111119-01A1) and (UL1TR002736, KL2TR002737) through the Miami Clinical and Translational Science Institute, from the National Center for Advancing Translational Sciences and the National Institute on Minority Health and Health Disparities.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but given the de-identified nature of the NIS database, IRB approval and patient consent were not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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