Ischemic and Hemorrhagic Update: Current Practices and Future Directions

Vascular Malformations: AVM, Cavernoma, DAVF

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Disclosures

No relevant disclosures

Arteriovenous Malformations

AVM

- **High flow, high pressure** vascular malformations with arteriovenous shunting
- Histology shows intervening brain tissue (gliotic, generally not functional), in comparison to cavernous malformations
- Clinical presentation
  - Hemorrhage
  - Seizures
  - Headache, other symptoms
  - Incidental

AVM

- Prevalence- 0.005-0.6%
- Hemorrhage rate/yr- 2-4%
- Lifetime bleeding risk (%)- 105 - age
- Morbidity with hemorrhage- 20-30%
- Mortality with hemorrhage- 5-30%

Management

- Observation
- Surgery
- Embolization
- Radiosurgery
- Multi-modality management (embolization + surgery, embolization + radiosurgery, radiosurgery -> surgery)

Surgery

- Generally curative
- Surgical risk predicted by Spetzler-Martin grade
  - Larger size
  - Eloquent surrounding brain
  - Deep venous drainage

TABLE 1

*Determination of arteriovenous malformation (AVM) grade**

Graded Feature	Points Assigned
size of AVM	
small (< 3 cm)	1
medium (3–6 cm)	2
large (> 6 cm)	3
eloquence of adjacent brain	
non-eloquent	0
eloquent	1
pattern of venous drainage	
superficial only	0
deep	1

* Grade = [size] + [eloquence] + [venous drainage]; that is (1, 2, or 3) + (0 or 1) + (0 or 1).

Embolization

- Injection of liquid embolic agents to occlude flow through the AVM
- Can be curative in select cases (small AVMs < 1 cm with simple architecture)
- Probably best used as an adjunct to surgery
- "Partial" embolization does not improve the natural history

Radiosurgery

- Least invasive treatment option
- Can achieve high cure rates (80-90%) for small to medium size AVMs, especially with compact nidus
- Lag time of 2-3 years where the AVM may still be at risk for hemorrhage (and hemorrhage risk may be slightly higher)
- Radiation induced changes in surrounding brain – more significant at higher treatment doses and more symptomatic in eloquent locations

Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial

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See Comment page 581

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Summary

Background The clinical benefit of preventive eradication of unruptured brain arteriovenous malformations remains uncertain. A Randomised trial of Unruptured Brain Arteriovenous malformations (ARUBA) aims to compare the risk of death and symptomatic stroke in patients with an unruptured brain arteriovenous malformation who are allocated to either medical management alone or medical management with interventional therapy.

Methods Adult patients (≥18 years) with an unruptured brain arteriovenous malformation were enrolled into this trial at 39 clinical sites in nine countries. Patients were randomised (by web-based system, in a 1:1 ratio, with random permuted block design [block size 2, 4, or 6], stratified by clinical site) to medical management with interventional therapy (ie, neurosurgery, embolisation, or stereotactic radiotherapy, alone or in combination) or medical management alone (ie, pharmacological therapy for neurological symptoms as needed). Patients, clinicians, and investigators are aware of treatment assignment. The primary outcome is time to the composite endpoint of death or symptomatic stroke; the primary analysis is by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00389181.

Findings Randomisation was started on April 4, 2007, and was stopped on April 15, 2013, when a data and safety monitoring board appointed by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health recommended halting randomisation because of superiority of the medical management group (log-rank Z statistic of 4·10, exceeding the prespecified stopping boundary value of 2·87). At this point, outcome data were available for 223 patients (mean follow-up 33·3 months [SD 19·7]), 114 assigned to interventional therapy and 109 to medical management. The primary endpoint had been reached by 11 (10·1%) patients in the medical management group compared with 35 (30·7%) in the interventional therapy group. The risk of death or stroke was significantly lower in the medical management group than in the interventional therapy group (hazard ratio 0·27, 95% CI 0·14–0·54). No harms were identified, other than a higher number of strokes (45 *vs* 12, p<0·0001) and neurological deficits unrelated to stroke (14 *vs* 1, p=0·0008) in patients allocated to interventional therapy compared with medical management.

Interpretation The ARUBA trial showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured brain arteriovenous malformations followed up for 33 months. The trial is continuing its observational phase to establish whether the disparities will persist over an additional 5 years of follow-up.

ARUBA

- Prospective, randomized, multicenter, parallel design, nonblinded
- 39 centers in 9 countries
- Medical management alone vs. medical management with any interventional therapy
- Primary outcome: risk of death or symptomatic stroke between the two treatment groups

ARUBA

- 223 patients randomized from April 4, 2007, to April 15, 2013
- 114 patients in interventional group, 109 patients in medical management group.
  - microsurgery alone (n=5), embolization alone (n=30), or radiotherapy alone (n=31), or using a multimodal approach combining embolization with either neurosurgery (n=12), radiotherapy (n=15), or both (n=1)
  - 7 patients in the medical management crossed over to interventional therapy.
  - 20 patients in the interventional therapy group did not receive interventional therapy and are deemed crossovers to medical management.
  - 3 patients randomized to interventional therapy had a stroke before the initiation of interventional therapy and were placed in the medical management group for the as-treated analysis
- Trial stopped early due to superiority of medical management

ARUBA

	Interventional therapy (n=114)	Medical management (n=109)	Risk ratio (95% CI)
Death or stroke	35 (30·7%)	11 (10·1%)	0·33 (0·18–0·61)
Death			
All cause	3 (2·6%)	2 (1·8%)	0·70 (0·12–4·09)
AVM-related	2 (1·8%)	0	..
First stroke			
All	34 (29·8%)	9 (8·3%)	0·28 (0·14–0·55)
Haemorrhagic	25 (21·9%)	6 (5·5%)	0·25 (0·11–0·59)
Ischaemic	9 (7·9%)	3 (2·8%)	0·35 (0·10–1·25)

Data are number of patients (%). AVM=arteriovenous malformation. *Primary outcome events only.

Table 2: Stroke and mortality by randomisation assignment*

	Interventional therapy (n=98)	Medical management (n=125)	Risk ratio (95% CI)
Death or stroke	36 (36·7%)	10 (8·0%)	0·22 (0·11–0·42)
Death			
All cause	3 (3·1%)	2 (1·6%)	0·52 (0·09–3·07)
AVM-related	2 (2·0%)	0	..
First stroke			
All	35 (35·7%)	8 (6·4%)	0·18 (0·09–0·37)
Haemorrhagic	24 (24·5%)	7 (5·6%)	0·23 (0·10–0·51)
Ischaemic	11 (11·2%)	1 (0·8%)	0·07 (0·10–0·54)

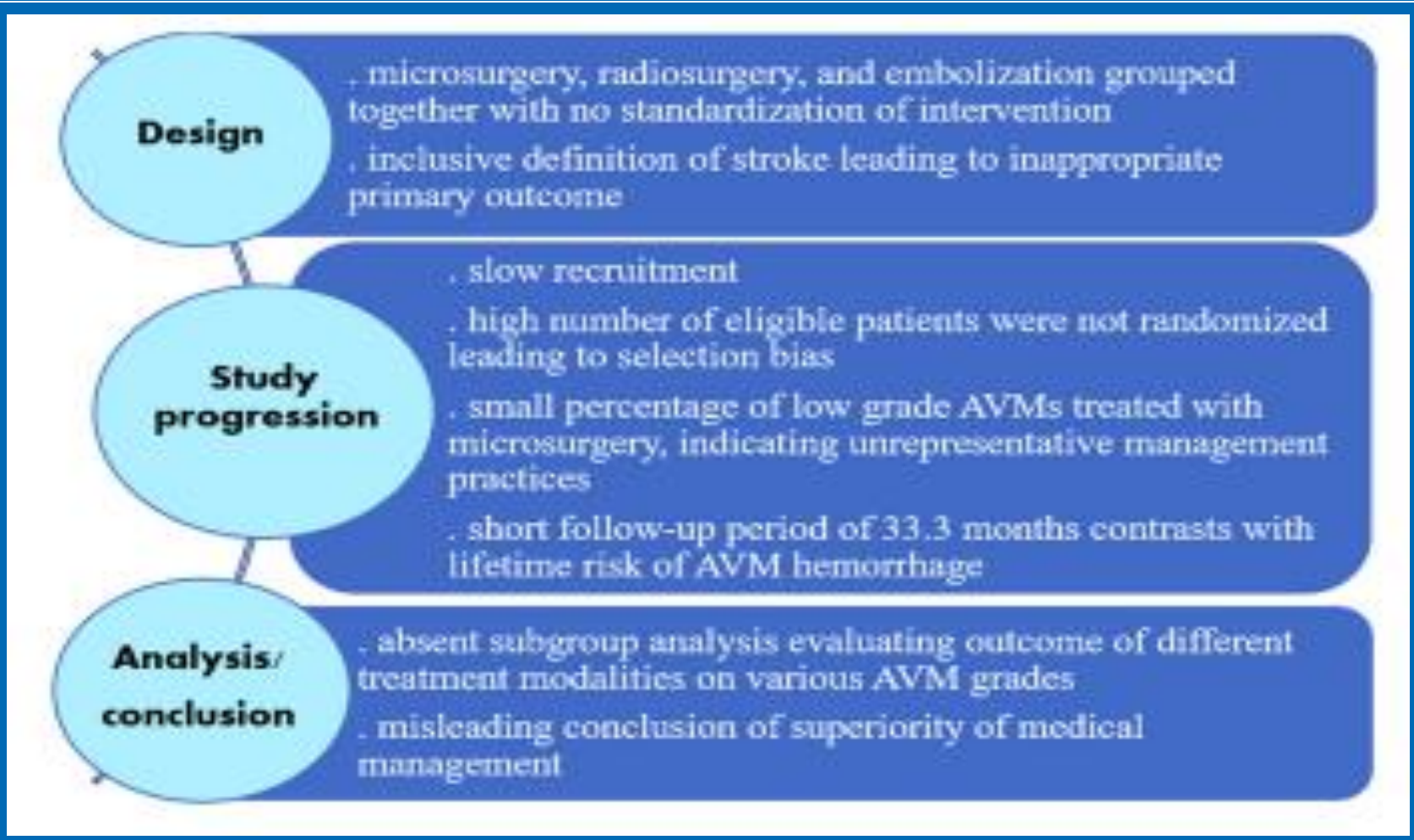
Data are number of patients (%). AVM=arteriovenous malformation. *Primary outcome events only.

Table 3: Stroke and mortality as treated*

ARUBA

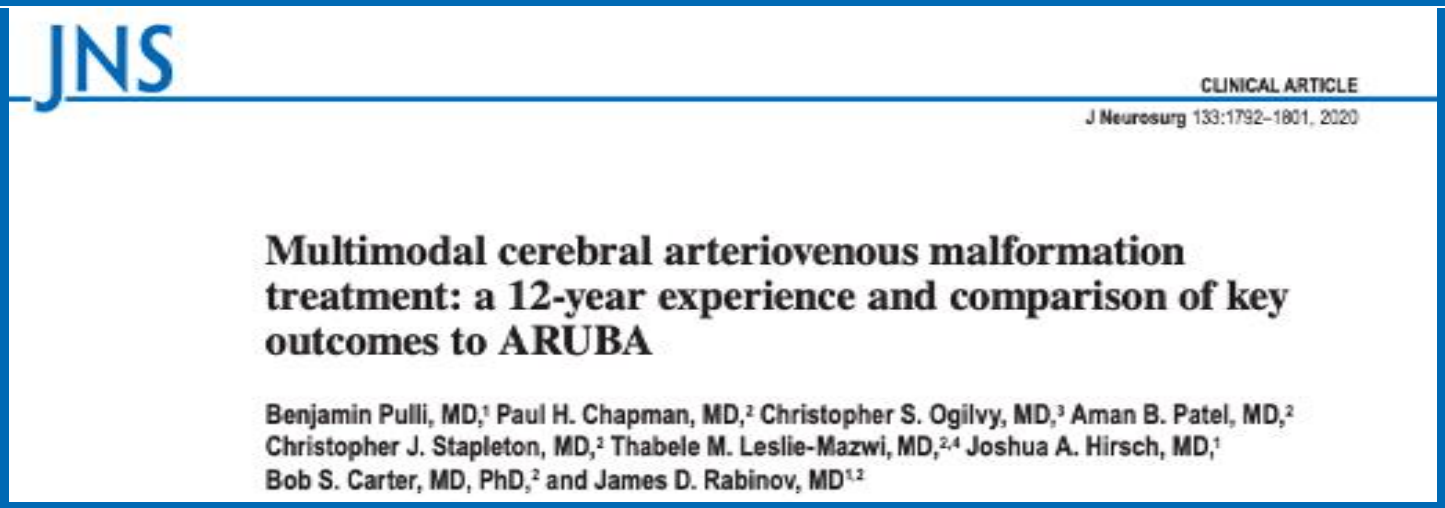
- After 33 months of follow-up, the ARUBA data provide evidence that medical management alone is superior to preventive interventional management for the prevention of death or stroke in patients diagnosed with an unruptured brain arteriovenous malformation.
- Over the same follow-up period, the secondary endpoint analysis showed the risk of death and neurological disability is significantly lower for patients managed without intervention.
- The risk associated with preventive interventional therapy has proven to be higher than previously anticipated.

ARUBA - Criticisms



Feghali J, Huang J. Updates in arteriovenous malformation management: the post-ARUBA era. Stroke & Vascular Neurology 2019;0. doi:10.1136/svn-2019-000248

ARUBA – Comparative Data



JNS

CLINICAL ARTICLE

J Neurosurg 133:1792–1801, 2020

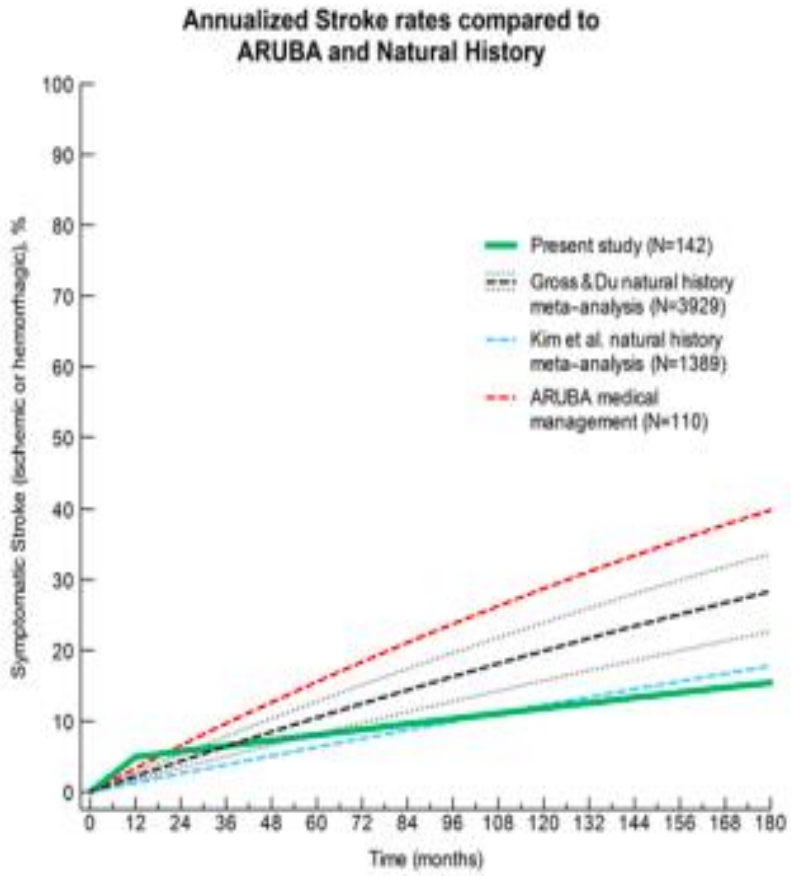
Multimodal cerebral arteriovenous malformation treatment: a 12-year experience and comparison of key outcomes to ARUBA

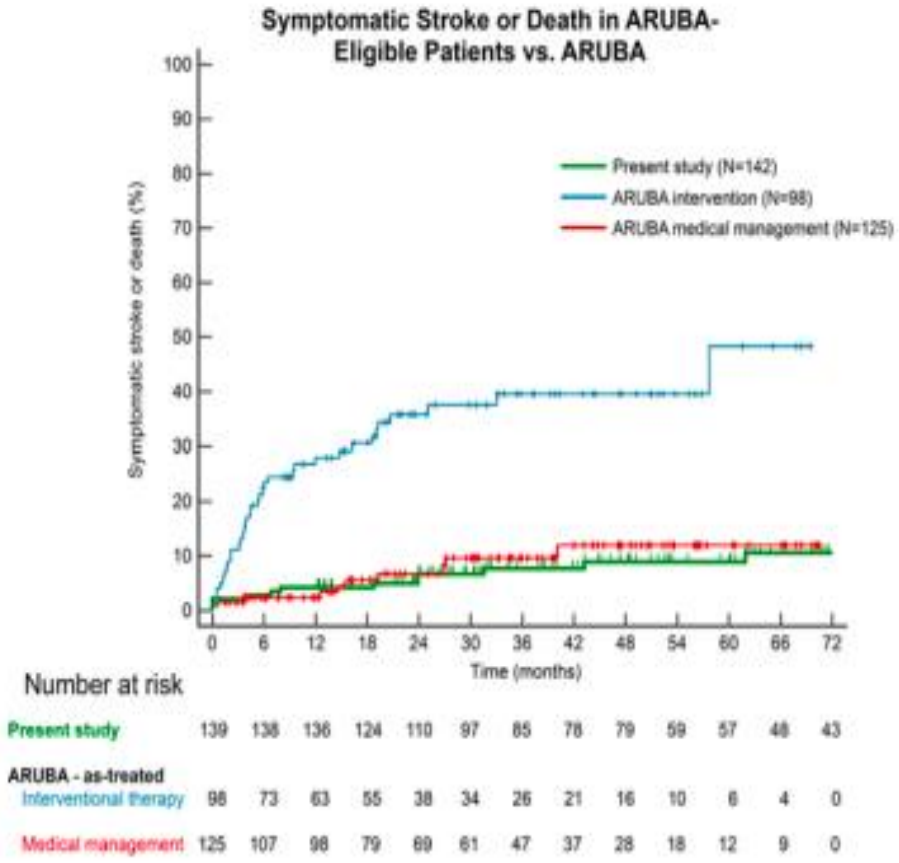
Benjamin Pulli, MD,[1] Paul H. Chapman, MD,[2] Christopher S. Ogilvy, MD,[3] Aman B. Patel, MD,[2] Christopher J. Stapleton, MD,[2] Thabele M. Leslie-Mazwi, MD,[2,4] Joshua A. Hirsch, MD,[1] Bob S. Carter, MD, PhD,[2] and James D. Rabinov, MD[1,2]

- Retrospective review of 142 ARUBA - eligible patients treated at a single institution
- Annual stroke, hemorrhagic or ischemic rate, was 1.8%, lower than in natural history studies and the ARUBA medical management arm.
- The primary ARUBA endpoint of symptomatic stroke was reached in 9.2% of patients, compared to the ARUBA intervention arm, 39.6%, and equal to the ARUBA medical management arm.
- The secondary ARUBA endpoint, mRS score ≥ 2 at 5 years of follow-up, was seen in only 14.3% of patients, compared to 40.5% in the ARUBA intervention arm and 16.7% in the ARUBA medical management

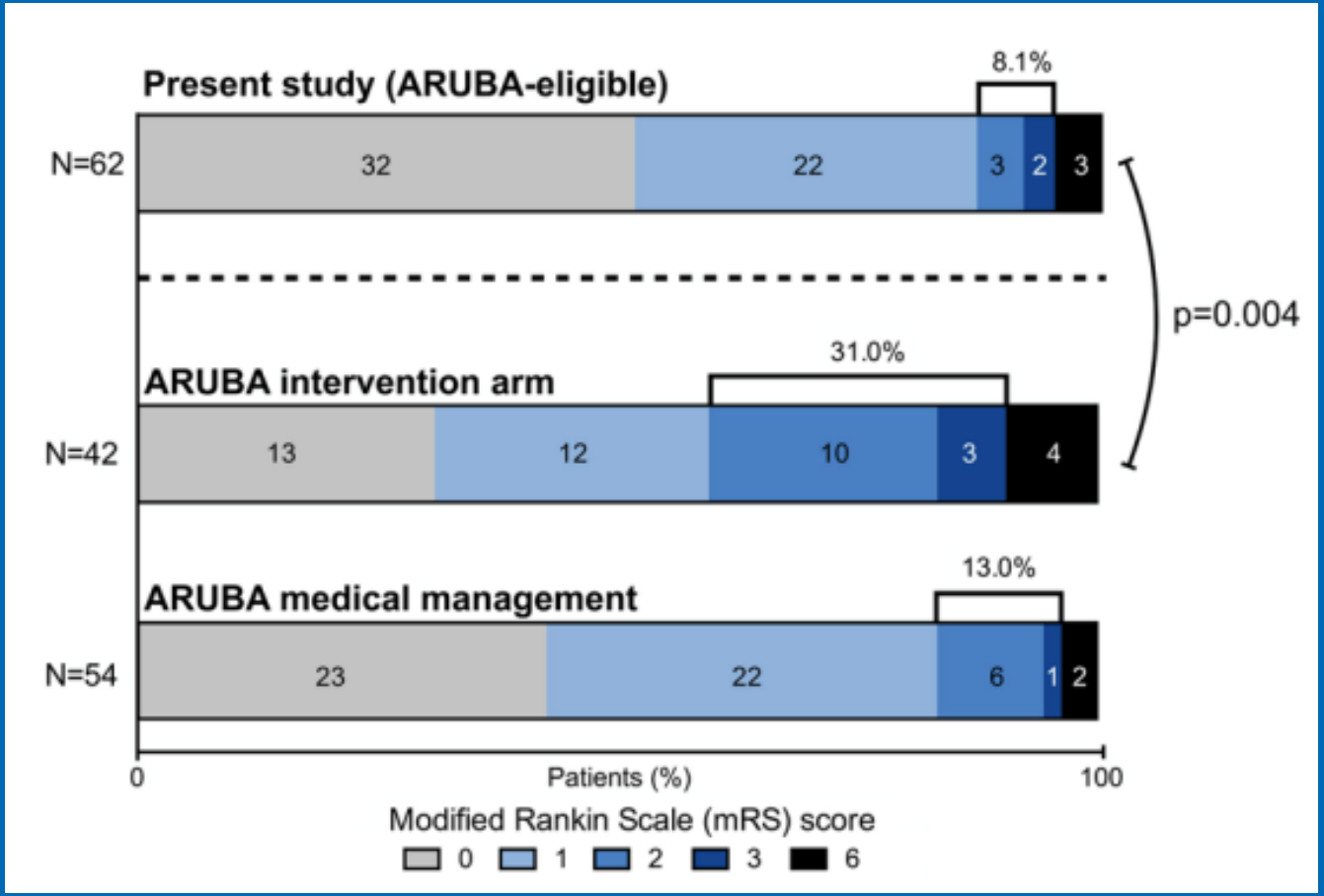
ARUBA – Comparative Data

Pulli et al.





ARUBA – Comparative Data



ARUBA – Comparative Data

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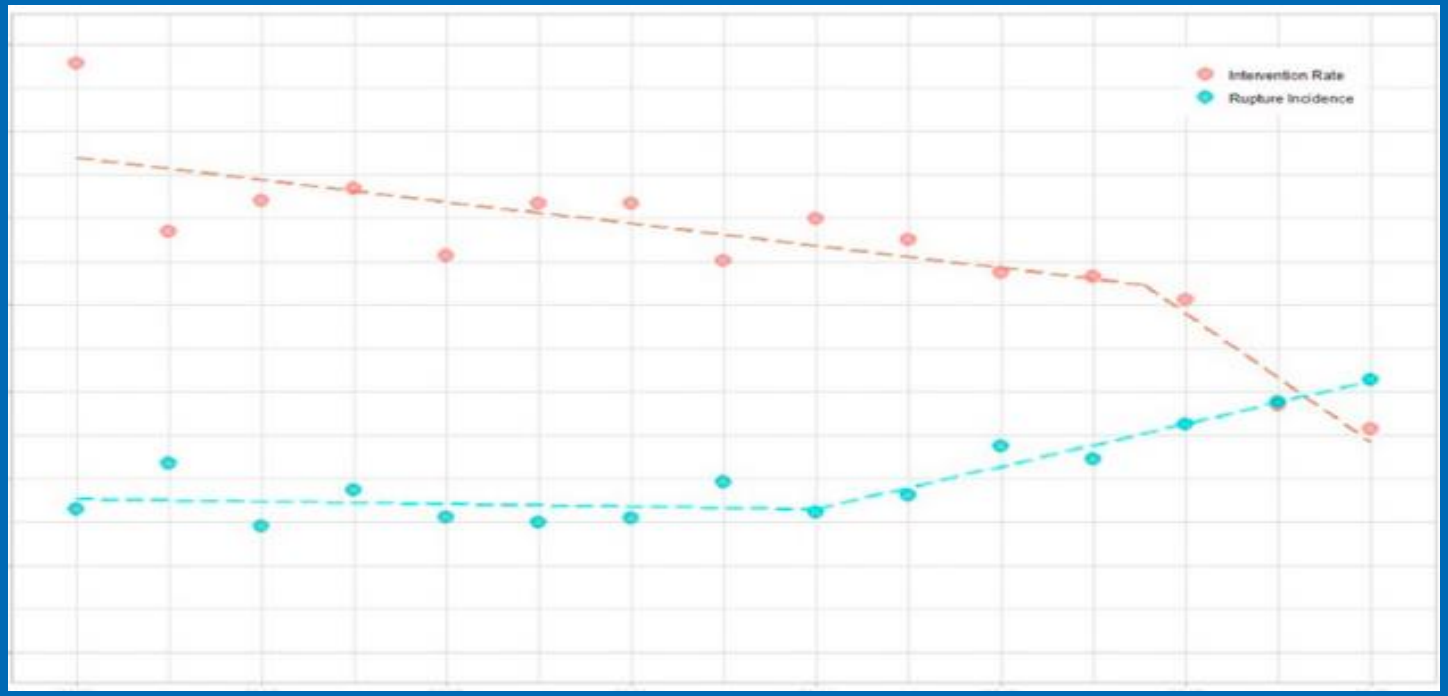
Hemorrhagic stroke

Original research

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

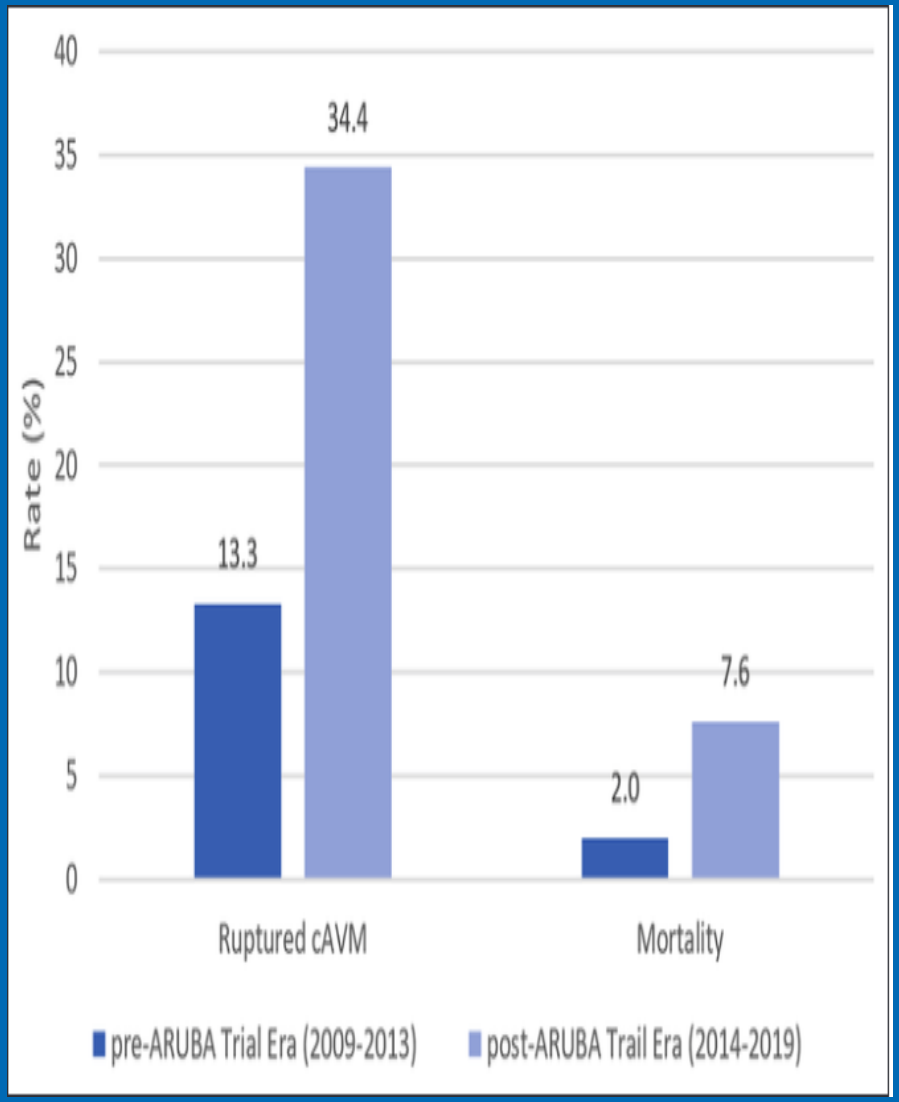
Evan Luther ,[1] David J McCarthy,[1] Joshua Burks,[1] Vaidya Govindarajan,[1] Victor M Lu ,[2] Michael Silva,[1] Michael Lang,[3] Bradley A Gross,[3] Robert M Starke[1]



ARUBA Comparative Data

Increase in Ruptured Cerebral Arteriovenous Malformations and Mortality in the United States: Unintended Consequences of the ARUBA Trial?

Alis J. Dicpinigaitis, BA; Jonathan V. Ogulnick, BS; Stephan A. Mayer, MD; Chirag D. Gandhi, MD; Fawaz Al-Mufti, MD



Dural Arteriovenous Fistulae

DAVFs

- DAVFs are rare vascular abnormalities; fistulas connecting the branches of dural arteries to dural veins or a venous sinus.
- Most commonly found at **the transverse and cavernous sinus**.
- Reported incidence is **approx. 10-15%** of all intracranial vascular abnormalities.
- **DSA remains the gold standard for diagnosis**.

DAVFs

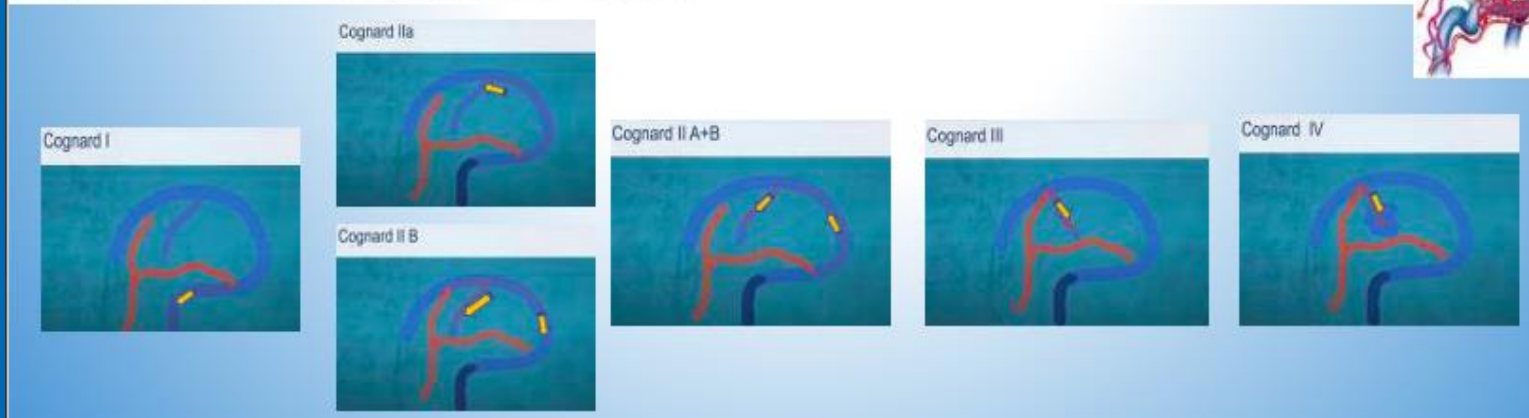
- DAVFs are **distinguished from parenchymal or pial AVM** by the presence of a dural arterial supply and the absence of a parenchymal nidus.
- Pathophysiology**:** predominantly idiopathic
- Trauma, or dural sinus thrombosis
- Heritable risk factors for venous thrombosis, such as antithrombin, protein C and protein S deficiencies.

Presentation

- Present in the **fifth and sixth decades** with symptoms related to lesion **location and pattern of venous drainage**.
- Pulsatile tinnitus is a common symptom
- Hemorrhage, seizures, failure to thrive, cranial neuropathies
- Hemorrhagic presentations are more frequent in high-grade (Borden types II and III, Cognard types IIb to IV) DAVFs

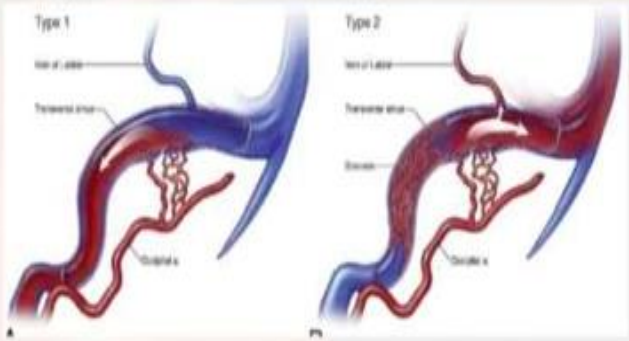
	Borden classification			Cognard classification			
Natural course	Type	Venous drainage site	CVR	Type	Venous drainage site	Flow pattern in sinus	CVR
Benign	I	Dural sinus	No	I	Dural sinus	Antegrade	No
Benign				IIa	Dural sinus	Retrograde	No
Aggressive	II	Dural sinus	Yes	IIb	Dural sinus	Antegrade	Yes
Aggressive				IIa+b	Dural sinus	Retrograde	Yes
Aggressive	III	Cortical vein	Yes	III	Cortical vein		Yes without venous ectasia
Aggressive				IV	Cortical vein		Yes with venous ectasia
Aggressive				V	Cortical vein with spinal medullary drainage		Yes

CVR, cortical venous reflux; dAVF, dural arteriovenous fistula.



Natural History

- Venous Drainage
- Presentation
- Venous Ectasia



	Type I	Type II	Type III	Type III w/ VE	Type II-III
Mean Age	51	60	59	57	59
M : F	0.7	0.7	1.9	2.0	1.5
Location	51% TS 38% Cav	61% TS 10% Cav	28% Tentorial 13% Petrosal 8% Ant Fossa	42% Tentorial 17% Ant Fossa 17% Petrosal	31% TS 17% Tent 9% Petrosal
Annual Bleed Rate	0%	6%	10%	21%	Asymptomatic 2% Prior NHND 10% Prior Hemorrhage 46%

Gross BA, Du R: The natural history of cerebral dural arteriovenous fistulae. Neurosurgery 71: 594-603, 2012.

Treatment

- Endovascular approaches have become the **mainstay of DAVF therapy**
- High-grade lesions should be treated early to avoid the risks of hemorrhage and neurologic deficits.
- Conservative treatment is generally indicated in patients with low-grade fistulas (Borden I; Cognard I, IIa) with close follow-up.
- Low-grade lesions with severe debilitating symptoms (severe tinnitus or visual symptoms resulting in poor quality of life) may be candidates for treatment

RESEARCH—HUMAN—CLINICAL STUDIES

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(Continued on next page)

An oral presentation of this paper was presented at the International Stroke Conference in Los Angeles, California, on February 20, 2020.

Observation Versus Intervention for Low-Grade Intracranial Dural Arteriovenous Fistulas

BACKGROUND: Low-grade intracranial dural arteriovenous fistulas (dAVF) have a benign natural history in the majority of cases. The benefit from treatment of these lesions is controversial.

OBJECTIVE: To compare the outcomes of observation versus intervention for low-grade dAVFs.

METHODS: We retrospectively reviewed dAVF patients from institutions participating in the CONsortium for Dural arteriovenous fistula Outcomes Research (CONDOR). Patients with low-grade (Borden type I) dAVFs were included and categorized into intervention or observation cohorts. The intervention and observation cohorts were matched in a 1:1 ratio using propensity scores. Primary outcome was modified Rankin Scale (mRS) at final follow-up. Secondary outcomes were excellent (mRS 0-1) and good (mRS 0-2) outcomes, symptomatic improvement, mortality, and obliteration at final follow-up.

RESULTS: The intervention and observation cohorts comprised 230 and 125 patients, respectively. We found no differences in primary or secondary outcomes between the 2 unmatched cohorts at last follow-up (mean duration 36 mo), except obliteration rate was higher in the intervention cohort (78.5% vs 24.1%, $P < .001$). The matched intervention and observation cohorts each comprised 78 patients. We also found no differences in primary or secondary outcomes between the matched cohorts except obliteration was also more likely in the matched intervention cohort ($P < .001$). Procedural complication rates in the unmatched and matched intervention cohorts were 15.4% and 19.2%, respectively.

CONCLUSION: Intervention for low-grade intracranial dAVFs achieves superior obliteration rates compared to conservative management, but it fails to improve neurological or functional outcomes. Our findings do not support the routine treatment of low-grade dAVFs.

KEY WORDS: Dural arteriovenous fistula, Radiosurgery, Surgery, Endovascular, Embolization, Cortical venous reflux, Intracranial

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Endovascular therapy

- Transarterial, transvenous, or combined approaches
- Treatment is aimed at complete elimination of the arteriovenous shunt; incomplete treatment allows recruitment of collateral vessels and persistent risk of hemorrhage.
- TAE involves **super selective distal catheterization of arterial feeders**. Ideally, the microcatheter tip should be "wedged" in the feeding artery and the embolic agent should penetrate the fistulous connection and proximal aspect of the vein.
- TVE is more safely used when the diseased sinus segment has minimal contributions to normal venous outflow and can be completely occluded.

Surgery

- Surgery may be an option in which endovascular approaches have failed or are not feasible.
- Disconnection of the draining vein
- Certain anatomic locations of DAVFs are more amenable for surgery

Cavernomas

- Low flow, low pressure vascular malformation of the brain, brainstem, or spinal cord
- Thin walled vascular channels without intervening brain tissue
- Abnormal tight junctions
- Other names: cavernoma, cavernous angioma, cavernous hemangioma
- “Angiographically occult” vascular lesions
- Present with seizures, hemorrhage, or incidentally

Epidemiology

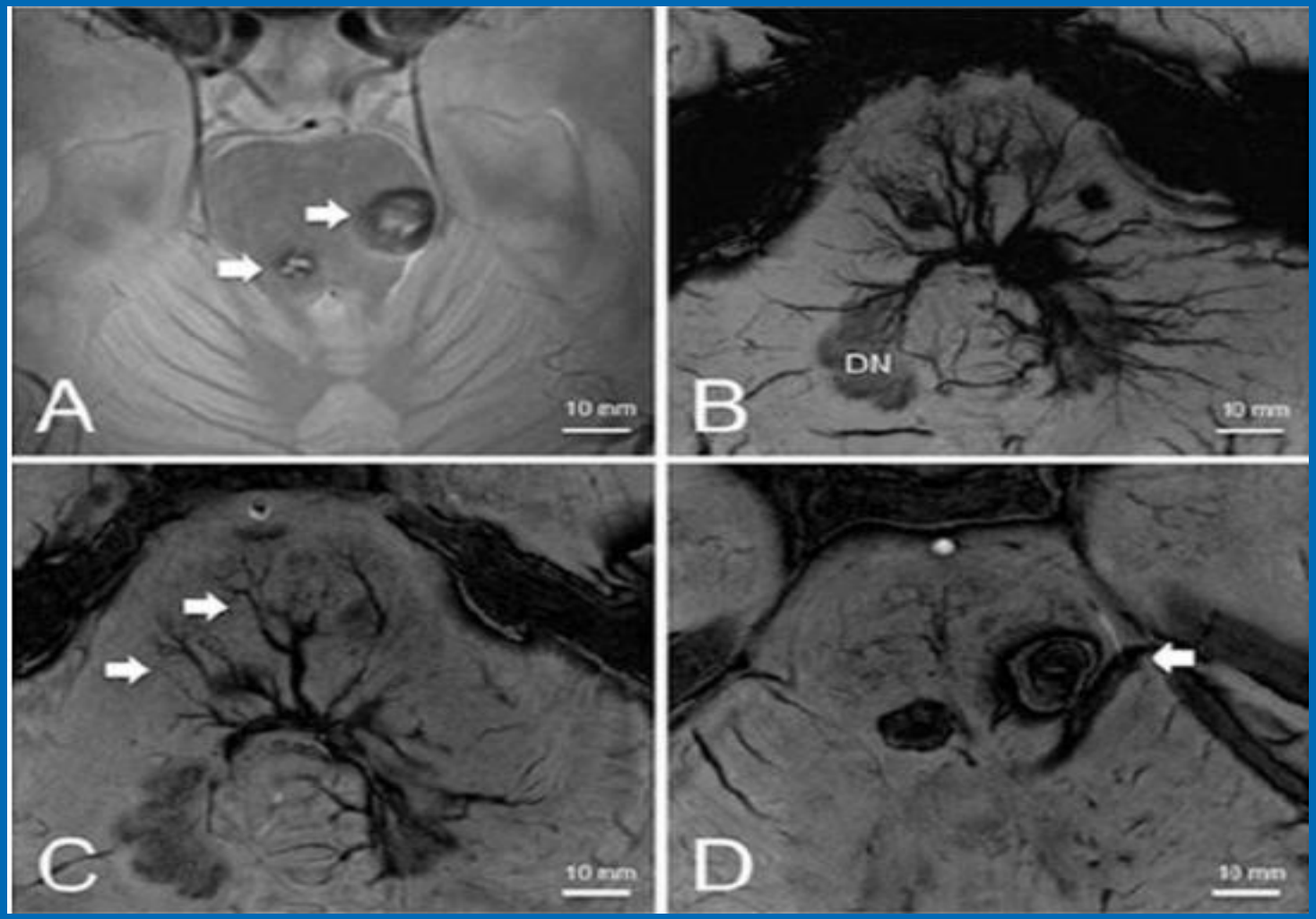
- Sporadic vs. familial
- Estimated prevalence 0.4% (imaging and autopsy studies)
- Up to 20% asymptomatic
- Supratentorial location most common

Familial cavernous malformations

- 3 gene mutations identified
- Autosomal dominant with variable penetrance
- CCM 1 (Krit1)
- CCM2 (malcavernin)
- CCM3 (PDCD10)

Radiology

- "Popcorn" lesions on MRI
- Hemosiderin deposition in surrounding brain
- Most cases have associated DVA (developmental venous anomaly)
  - May not be present in familial cases
- Non-specific hyperdensity on CT, may be associated with calcifications
- Angiography: "occult," may see faint blush or DVA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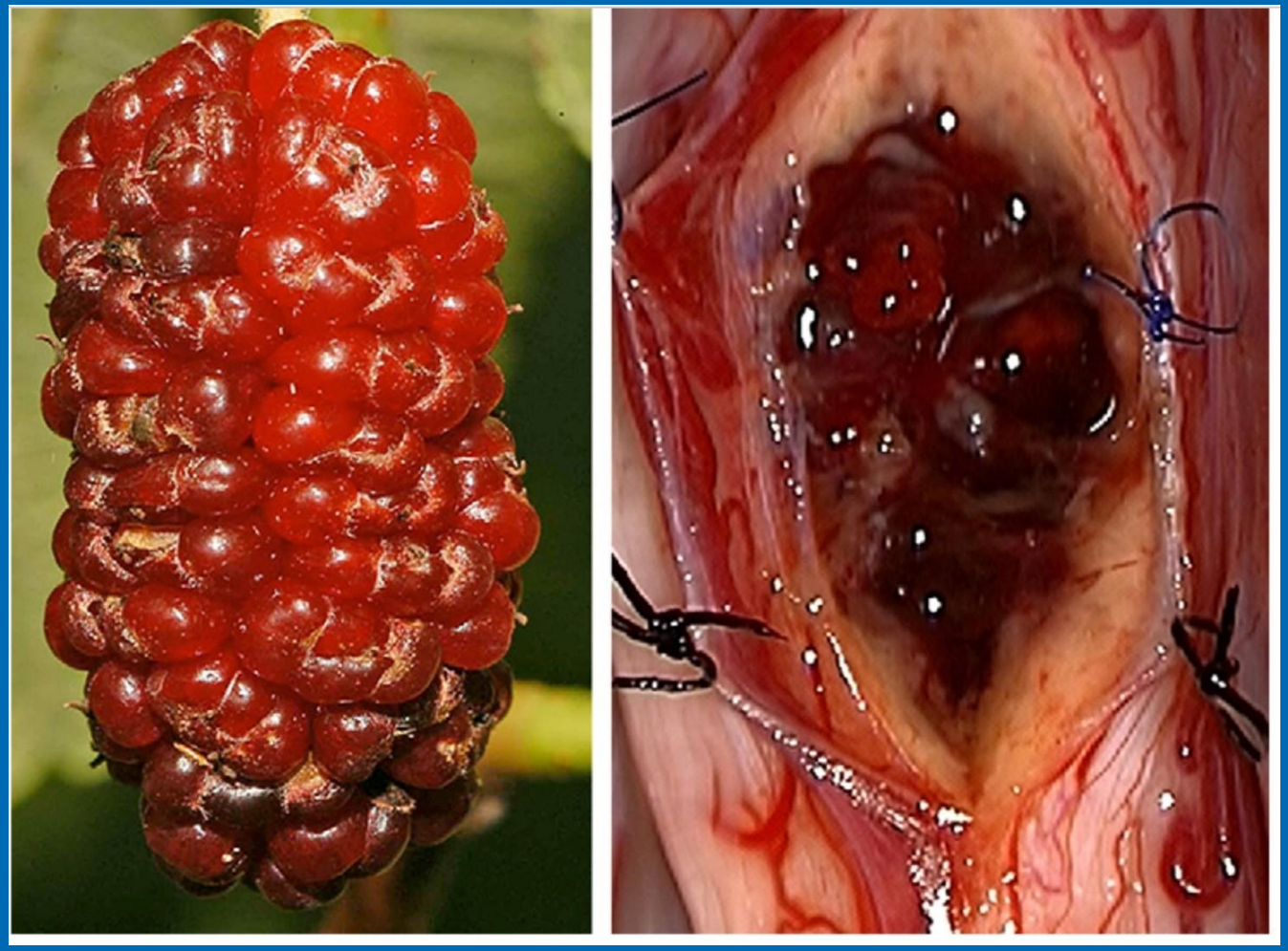
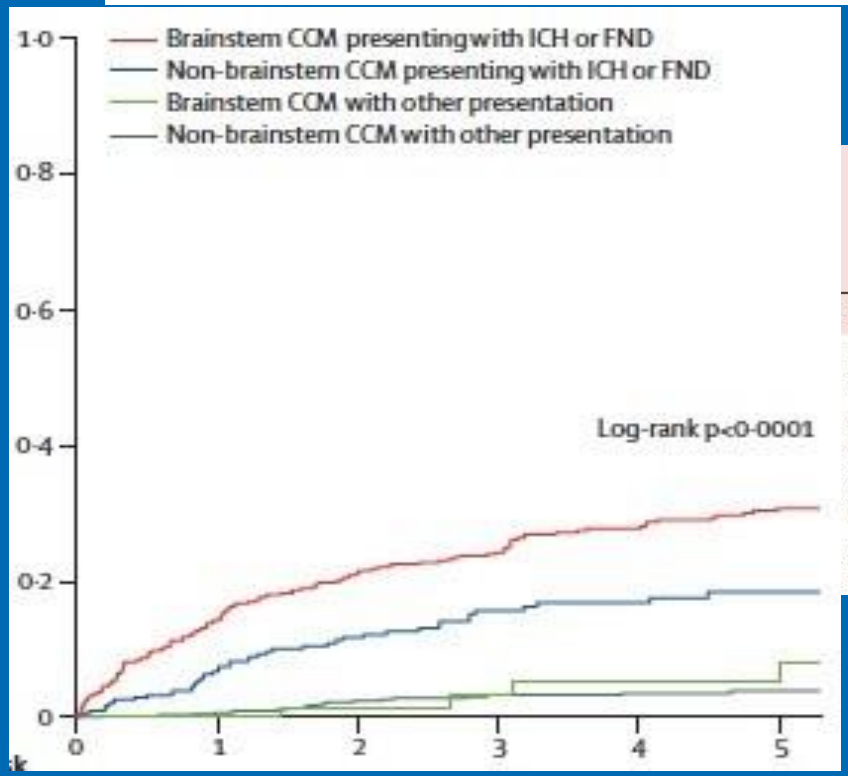


Management

- Conservative management for most asymptomatic/incidental lesions
- Surgery for lesions causing hemorrhage/neurological deficit if surgical risks acceptable
- Surgery for lesions causing seizures if surgical risks acceptable
- Radiosurgery?
- Medical therapies to reduce bleeding risk?
    - ASA, Statins

Clinical course of untreated cerebral cavernous malformations: a meta-analysis of individual patient data

*Margaret A Horne, Kelly D Flemming, I-Chang Su, Christian Stapf, Jin Pyeong Jeon, Da Li, Susanne S Maxwell, Philip White, Teresa J Christianson, Ronit Agid, Won-Sang Cho, Chang Wan Oh, Zhen Wu, Jun-Ting Zhang, Jeong Eun Kim, Karel ter Brugge, Robert Willinsky, Robert D Brown Jr, Gordon D Murray, Rustam Al-Shahi Salman, and the Cerebral Cavernous Malformations Individual Patient Data Meta-analysis Collaborators**



	Number of people (%)	Number of outcome events during 5-year follow-up	Hazard ratio (95% CI)*	Estimated 5-year risk (95% CI)
Primary outcome: ICH (n=1620)				
ICH or FND presentation, brainstem CCM location	495 (31%)	135	10·2 (5·0–23·9)	30·8% (26·3–35·2)
ICH or FND presentation, other CCM location	327 (20%)	45	5·6 (3·7–9·4)	18·4% (13·3–23·5)
Other presentation, brainstem CCM location	80 (5%)	4	1·8 (1·3–2·6)	8·0% (0·1–15·9)
Other presentation, other CCM location	718 (44%)	20	Reference	3·8% (2·1–5·5)

Bleeding Risk of Cerebral Cavernous Malformations in Patients on Statin and Antiplatelet Medication: A Cohort Study

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TABLE 3. Risk for Hemorrhage at Diagnosis in 933 CCMs/688 Patients

	Univariable model		Multivariable model	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Statin only	0.52 (0.18-1.52)	.23	0.63 (0.23-1.69)	.355
Antiplatelet only	0.2 (0.05-0.77)	.019	0.26 (0.08-0.86)	.028
Statin and antiplatelet	0.12 (0.03-0.51)	.004	0.19 (0.05-0.66)	.009
Deep location	3.08 (1.78-5.34)	<.001	3.21 (1.91-5.41)	<.001
Multiple CCMs	0.45 (0.27-0.75)	.002	0.33 (0.19-0.58)	<.001
Older age	0.98 (0.96-0.99)	.008	0.99 (0.98-1)	.079
Female sex	0.97 (0.6-1.56)	.89	0.82 (0.52-1.29)	.401
Associated DVA	1.1 (0.64-1.87)	.74	0.88 (0.53-1.47)	.637

TABLE 4. Risk for Hemorrhage During Follow-up in 840 CCMs/605 Patients

	No. of CCMs	Lesion years	No. of follow-up hemorrhages	5-y Incidence rate
Entire cohort	840	3566.5	69	9.7%
None	703	3228.1	67	10.4%
Statin only	48	100.6	0	—
Antiplatelet only	43	137.1	2	7.3%
Statin and antiplatelet	46	100.7	0	—

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Stereotactic radiosurgery for cavernous malformations

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Object. The use of stereotactic radiosurgery to treat cerebral cavernous malformations (CMs) is controversial. To evaluate the efficacy and safety of CM radiosurgery, the authors reviewed the experience at the Mayo Clinic during the past 10 years.

Methods. Seventeen patients underwent radiosurgery for high-surgical-risk CMs in the following sites: thalamus/basal ganglia (four patients), brainstem (12 patients), and corpus callosum (one patient). All patients had experienced at least two documented hemorrhages before undergoing radiosurgery. Stereotactic magnetic resonance (MR) imaging was used for target localization in all cases. The median margin radiation dose was 18 Gy and the median maximum dose was 32 Gy. The median length of follow-up review following radiosurgery was 51 months.

The annual hemorrhage rate during the 51 months preceding radiosurgery was 40.1%, compared with 8.8% in the first 2 years following radiosurgery and 2.9% thereafter. In 10 patients (59%) new neurological deficits developed that were associated with regions of increased signal on long–repetition time MR imaging performed a median of 8 months (range 5–16 months) after radiosurgery. Three patients recovered, giving the group a permanent radiation-related morbidity rate of 41%. Compared with 31 patients harboring arteriovenous malformations (AVMs) of sizes and in locations similar to those of the aforementioned CMs, who underwent radiosurgery during the same time period, the patients with CMs were more likely to experience radiation-related complications (any complication, 59% compared with 10%; $p < 0.001$; permanent complication, 41% compared with 10%; $p = 0.02$).

Conclusions. It is impossible to conclude that radiosurgery protects patients with CMs against future hemorrhage risk based on the available data, although it appears that some reduction in the bleeding rate occurs after a latency interval of several years. The risk of radiation-related complications after radiosurgery to treat CMs is greater than that found after radiosurgery in AVMs, even when adjusting for lesion size and location and for radiation dose.

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CLINICAL ARTICLE

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Stereotactic radiosurgery for cerebral cavernous malformation: comparison of hemorrhage rates before and after stereotactic radiosurgery

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OBJECTIVE Cerebral cavernous malformation (CM) is an angiographically occult vascular pathology. Although microsurgery is the gold standard treatment to control the symptoms of CM, resection carries high risk in some situations, especially eloquent areas. The objective was to evaluate annual hemorrhage rates (AHRs) before and after stereotactic radiosurgery (SRS) treatment of cerebral CM in different locations.

METHODS A total of 195 patients (119 women and 76 men) with CM treated at the Gazi University Gamma Knife Center between April 2005 and June 2017 were analyzed. The mean ± SD follow-up period was 67.4 ± 31.1 months (range 12 days to 170 months). AHR before SRS, AHR after SRS, morbidity associated with radiation, seizure control rate after SRS, lesion volume, coexistence with developmental venous anomaly, and SRS treatment parameters were analyzed, with evaluation of radiological data and clinical charts performed retrospectively. The seizure control rate was assessed using the Engel outcome scale.

RESULTS The AHR before SRS was 15.3%. Application of SRS to these patients significantly reduced the AHR rates to 2.6% during the first 2 years after treatment and to 1.4% thereafter. Favorable seizure control (Engel class I and II) after radiosurgery was achieved in 23 patients (88.5%) with epilepsy. Radiation-related temporary complications occurred in 15.4% of patients, and permanent morbidity occurred in 4.6%.

CONCLUSIONS SRS is a safe and effective treatment modality for reducing the hemorrhage risk of CM. The authors suggest that SRS should be considered for the treatment of patients with CM, high surgical risks, and hemorrhage history, instead of a using a wait-and-see policy.

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KEYWORDS cavernous malformation; stereotactic radiosurgery; Gamma Knife; annual hemorrhage rate; vascular disorders

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