# Intervention for unruptured high-grade intracranial dural arteriovenous fistulas

Consortium Dural Arteriovenous Fis; van Dijk, J. Marc C.; Potgieser, Arnoud

*Published in:*
Journal of Neurosurgery

*DOI:*
10.3171/2021.1.JNS202799
10.3171/2021.1.JNS202799



*Publication date:*
2022

JNS

CLINICAL ARTICLE

# Intervention for unruptured high-grade intracranial dural arteriovenous fistulas: a multicenter study

**Ching-Jen Chen, MD,[1] Thomas J. Buell, MD,[1] Dale Ding, MD,[18] Ridhima Guniganti, MD,[2] Akash P. Kansagra, MD, MS,[2,15,16] Giuseppe Lanzino, MD,[3] Enrico Giordan, MD,[3] Louis J. Kim, MD, MBA,[4] Michael R. Levitt, MD,[4] Isaac Josh Abecassis, MD,[4] Diederik Bulters, FRCS(SN),[5] Andrew Durnford, MA, MSc,[5] W. Christopher Fox, MD,[6] Adam J. Polifka, MD,[6] Bradley A. Gross, MD,[7] Minako Hayakawa, MD, PhD,[8] Colin P. Derdeyn, MD,[8] Edgar A. Samaniego, MD,[8] Sepideh Amin-Hanjani, MD,[9] Ali Alaraj, MD,[9] Amanda Kwasnicki, MD,[9] J. Marc C. van Dijk, MD, PhD,[10] Adriaan R. E. Potgieser, MD, PhD,[10] Robert M. Starke, MD, MSc,[11,17] Samir Sur, MD,[11] Junichiro Satomi, MD, PhD,[12] Yoshiteru Tada, MD, PhD,[12] Adib A. Abla, MD,[13] Ethan A. Winkler, MD, PhD,[13] Rose Du, MD, PhD,[14] Pui Man Rosalind Lai, MD,[14] Gregory J. Zipfel, MD,[2] and Jason P. Sheehan, MD, PhD,[1] on behalf of the Consortium for Dural Arteriovenous Fistula Outcomes Research**

[1]Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia; [2]Department of Neurological Surgery, Washington University School of Medicine, St. Louis, Missouri; [3]Department of Neurosurgery, Mayo Clinic, Rochester, Minnesota; [4]Department of Neurosurgery, University of Washington, Seattle, Washington; [5]Department of Neurosurgery, University of Southampton, United Kingdom; [6]Department of Neurosurgery, University of Florida, Gainesville, Florida; [7]Department of Neurological Surgery, University of Pittsburgh, Pennsylvania; [8]Department of Radiology, University of Iowa, Iowa City, Iowa; [9]Department of Neurosurgery, University of Illinois at Chicago, Illinois; [10]Department of Neurosurgery, University of Groningen, University Medical Center Groningen, The Netherlands; [11]Department of Neurosurgery, University of Miami, Florida; [12]Department of Neurosurgery, Tokushima University, Tokushima, Japan; [13]Department of Neurosurgery, University of California, San Francisco, California; [14]Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts; [15]Mallinckrodt Institute of Radiology and [16]Department of Neurology, Washington University School of Medicine, St. Louis, Missouri; [17]Department of Radiology, University of Miami, Florida; and [18]Department of Neurosurgery, University of Louisville, Kentucky

**OBJECTIVE** The risk-to-benefit profile of treating an unruptured high-grade dural arteriovenous fistula (dAVF) is not clearly defined. The aim of this multicenter retrospective cohort study was to compare the outcomes of different interventions with observation for unruptured high-grade dAVFs.

**METHODS** The authors retrospectively reviewed dAVF patients from 12 institutions participating in the Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR). Patients with unruptured high-grade (Borden type II or III) dAVFs were included and categorized into four groups (observation, embolization, surgery, and stereotactic radiosurgery [SRS]) based on the initial management. The primary outcome was defined as the modified Rankin Scale (mRS) score at final follow-up. Secondary outcomes were good outcome (mRS scores 0–2) at final follow-up, symptomatic improvement, all-cause mortality, and dAVF obliteration. The outcomes of each intervention group were compared against those of the observation group as a reference, with adjustment for differences in baseline characteristics.

**RESULTS** The study included 415 dAVF patients, accounting for 29, 324, 43, and 19 in the observation, embolization, surgery, and SRS groups, respectively. The mean radiological and clinical follow-up durations were 21 and 25 months, respectively. Functional outcomes were similar for embolization, surgery, and SRS compared with observation. With observation as a reference, obliteration rates were higher after embolization (adjusted OR [aOR] 7.147, $p = 0.010$) and surgery (aOR 33.803, $p < 0.001$) and all-cause mortality was lower after embolization (imputed, aOR 0.171, $p = 0.040$). Hemorrhage rates per 1000 patient-years were 101 for observation versus 9, 22, and 0 for embolization ($p = 0.022$), surgery ($p = 0.245$), and SRS ($p = 0.077$), respectively. Nonhemorrhagic neurological deficit rates were similar between each intervention group versus observation.

**ABBREVIATIONS** aOR = adjusted OR; CONDOR = Consortium for Dural Arteriovenous Fistula Outcomes Research; CVD = cortical venous drainage; dAVF = dural arteriovenous fistula; DSA = digital subtraction angiography; mRS = modified Rankin Scale; NHND = nonhemorrhagic neurological deficit; SRS = stereotactic radiosurgery.

**SUBMITTED** July 19, 2020. **ACCEPTED** January 20, 2021.
**INCLUDE WHEN CITING** Published online September 10, 2021; DOI: 10.3171/2021.1.JNS202799.

**CONCLUSIONS** Embolization and surgery for unruptured high-grade dAVFs afforded a greater likelihood of obliteration than did observation. Embolization also reduced the risk of death and dAVF-associated hemorrhage compared with conservative management over a modest follow-up period. These findings support embolization as the first-line treatment of choice for appropriately selected unruptured Borden type II and III dAVFs.

https://thejns.org/doi/abs/10.3171/2021.1.JNS202799

**KEYWORDS** dural arteriovenous fistula; radiosurgery; surgery; endovascular; embolization; unruptured; high grade; intracranial; vascular disorders

Intracranial dural arteriovenous fistulas (dAVFs) are abnormal connections between meningeal arteries and dural venous sinuses or cortical veins, and they account for approximately 10%–15% of all intracranial vascular malformations.[1] Intracranial dAVFs are classified based on the presence of cortical venous drainage (CVD) or lack thereof.[2,3] Hemorrhage and neurological deficits are rarely associated with low-grade dAVFs (CVD absent), and they have been reported to have annual neurological event and mortality incidences of 0%–0.6% and 0%, respectively.[4–6]

In contrast, high-grade dAVFs (CVD present) are associated with a considerably more aggressive natural history, with annual neurological event and mortality incidences of 15% and 10.4%, respectively.[7] Furthermore, rebleeding rates for those presenting with hemorrhage can be as high as 35% within 20 days of the initial hemorrhage.[6,8–10] Hence, treatment of high-grade dAVFs with embolization, surgery, or stereotactic radiosurgery (SRS), alone or in combination, is advocated in most patients.[1] Since the hemorrhage risk of unruptured high-grade dAVFs is lower than that of ruptured lesions, the risk-to-benefit profile of unruptured high-grade dAVF treatment is incompletely defined.[6,9,10] The aim of this multicenter retrospective cohort study was to compare the outcomes of different interventions with those of observation for unruptured high-grade dAVFs.

## Methods

### Patient Selection

Patients with intracranial dAVFs who presented to the 12 institutions participating in the Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR) were identified, and their data were retrospectively collected. This study was approved by the IRB of each individual center. Data from each institution were de-identified and pooled by an independent third party. Each contributing center was responsible for its own verification and attestation of data accuracy. The pooled data were transmitted to the institution of the first and senior authors for analysis.

The following inclusion criteria were devised for this study: 1) no history of dAVF-related intracranial hemorrhage, 2) high-grade (Borden type II or III) intracranial dAVF diagnosed or confirmed on digital subtraction angiography (DSA), and 3) availability of treatment data (yes or no).[2] Patients included in the study were categorized, based on initial management, into four groups (observation, embolization, surgery, or SRS).

### Baseline Data and Variables

Baseline data included patient and dAVF variables. Patient variables included age, sex, medical history (myocardial infarction, coronary artery disease, atrial fibrillation, ischemic stroke, diabetes mellitus, and hypertension), alcohol use, smoking history, antiplatelet use, anticoagulant use, dAVF-related symptomatic presentation, and baseline modified Rankin Scale (mRS) score. The dAVF variables included Borden and Cognard classifications, perilesional MRI hyperintensities (on FLAIR or T2-weighted sequences), venous ectasia, and location.[2,3]

### Follow-Up

Radiological and clinical follow-up protocols and intervals were implemented at the discretion of the individual institutions. Primary outcome was defined as the mRS score at final clinical follow-up. Secondary outcomes were good outcome (defined as mRS scores 0–2 at final clinical follow-up), all-cause mortality, symptom improvement, and dAVF obliteration confirmed by DSA. Treatment failure was considered when patients required any additional treatment for residual or recurrent dAVFs (i.e., nonobliteration of the dAVF) after the initial intervention. Procedure-related complications were categorized into technical (no neurological sequelae, including arterial dissection and asymptomatic perforation), temporary with neurological sequelae, and permanent with neurological sequelae. Dural AVF–related hemorrhages and nonhemorrhagic neurological deficits (NHNDs) during the follow-up period were recorded. Durations of radiological and clinical follow-up were also recorded.

### Statistical Analysis

All statistical analyses were performed using Stata (version 14.2, StataCorp). Baseline patient and dAVF characteristics were compared among the observation, embolization, surgery, and SRS groups. Continuous variables were compared using ANOVA or Kruskal-Wallis test, and categorical variables were compared using Pearson's chi-square or Fisher's exact tests as appropriate. Univariable ordered logistic and binary logistic analyses were performed to assess the associations between each intervention (embolization, surgery, and SRS) and the primary and secondary outcomes. The findings from the logistic and linear regression analyses were adjusted for covariates with $p < 0.10$. To avoid listwise deletions due to missing data in multivariable regression models, multiple imputation by chained equations with $m = 50$ was performed. Imputed values for baseline mRS score (1%), dAVF location (1%), history of ischemic stroke (1.2%), smoking history (16.6%), coronary artery disease (1.4%), symptomatic presentation (0.2%), follow-up mRS score (5%), dAVF obliteration (4.3%), hemorrhage during follow-up (5.1%),

NHND during follow-up (5.5%), symptomatic improvement (5.8%), radiological follow-up duration (0.7%), and clinical follow-up duration (1.2%) were generated using conditional regression models with the following auxiliary variables: age, sex, and Borden classification. Parameter estimates from analyzing the imputed data sets were pooled according to Rubin's rules.[11] The observation group was the reference in these analyses. Incidence rates of dAVF-related hemorrhage and NHND during follow-up were generated for each intervention group and compared with those of the observation group using Fisher's exact test. Statistical significance was defined as $p < 0.05$, and all tests were two-tailed.

## Results

### Patient Cohort

Of the 1077 dAVF patients in the CONDOR database, 415 were eligible for inclusion in the study cohort. The observation, embolization, surgery, and SRS groups comprised 29, 324, 43, and 19 patients, respectively (Fig. 1). Prior ischemic stroke ($p = 0.005$), symptomatic presentation ($p < 0.001$), Borden grade distribution ($p = 0.010$), dAVF location ($p < 0.001$), and radiological ($p < 0.001$) and clinical ($p < 0.001$) follow-up durations were different among the four groups (Table 1). The majority of patients were symptomatic, with a presentation of NHND in 39%. Only 4% of unruptured high-grade dAVFs were diagnosed incidentally. The mean radiological follow-ups were 8, 22, 13, and 41 months, and the mean clinical follow-ups were 13, 25, 25, and 51 months in the observation, embolization, surgery, and SRS groups, respectively.

### Primary Outcome

In the unadjusted model with the observation group as a reference, the mRS score at final follow-up was lower in the embolization group (median 0 vs 1; OR 0.373 [95% CI 0.177–0.784], $p = 0.009$) but similar in the surgery ($p = 0.172$) and SRS ($p = 0.420$) groups (Table 2). After adjustments for differences in baseline characteristics with the observation group as the reference, the mRS score at final follow-up was similar in the embolization, surgery, and SRS groups in both the nonimputed and imputed models (Table 3).

### Secondary Outcomes

In the unadjusted model with the observation group as a reference, good outcome rates were higher in the embolization group (90% vs 71%; OR 3.707 [95% CI 1.504–9.138], $p = 0.004$) but similar in the surgery ($p = 0.329$) and SRS ($p = 0.123$) groups (Table 2). After adjustments for differences in baseline characteristics with the observation group as a reference, good outcome rates were similar in each intervention group in both the nonimputed and imputed models (Table 3). Symptomatic improvement rates were similar between each intervention compared with observation in all models.

In the unadjusted model with the observation group as a reference, all-cause mortality rates were lower in the embolization (3% vs 21%; OR 0.110 [95% CI 0.036–0.338], $p < 0.001$) and surgery (2% vs 21%; OR 0.087 [95% CI 0.010–0.771], $p = 0.028$) groups but similar in the SRS group ($p = 0.237$; Table 2). After adjustments for differences in baseline characteristics with the observation group as a reference, all-cause mortality rates remained lower in the embolization group in the imputed model (adjusted OR [aOR] 0.171 [95% CI 0.032–0.921], $p = 0.040$) but were similar in the nonimputed model ($p = 0.082$); rates were also similar in the surgery and SRS groups in both the nonimputed and imputed models (Table 3). Dural AVF–related mortality occurred in 3.7% (n = 1/27) and 1.6% (n = 5/308) of the observation and embolization groups, respectively. No dAVF-related mortality was encountered in either the surgery or SRS group.

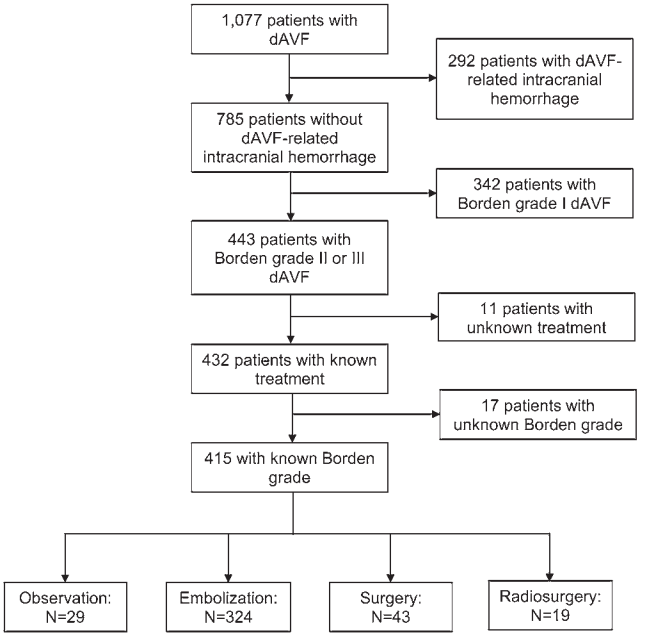


**FIG. 1.** Flow diagram demonstrating patient selection process. dAVF = dural arteriovenous fistula; N = number.

In the unadjusted model with the observation group as the reference, obliteration rates were higher in the embolization (43% vs 17%; OR 3.825 [95% CI 1.086–13.471], $p = 0.037$) and surgery (86% vs 17%; OR 30.833 [95% CI 6.810–139.600], $p < 0.001$) groups (Table 2). After adjustments for differences in baseline characteristics with the observation group as the reference, the embolization group had higher obliteration rates only in the nonimputed model (aOR 7.147 [95% CI 1.603–31.872], $p = 0.010$), whereas the surgery group had higher obliteration rates in both the nonimputed (aOR 33.803 [95% CI 5.112–223.507], $p < 0.001$) and imputed (aOR 20.215 [95% CI 4.296–95.113], $p < 0.001$) models (Table 3). Obliteration rates were similar between the observation and SRS groups in the unadjusted, nonimputed adjusted, and imputed adjusted models.

### Subsequent Treatments and Complications

Of the 324 patients in the embolization group, 223 (68.8%), 67 (20.7%), and 34 (10.5%) underwent 1, 2, or ≥ 3 embolizations, respectively. In the embolization group, 41 (12.7%) and 26 (8%) patients underwent subsequent sur-

**TABLE 1. Comparison of baseline characteristics among patients with unruptured high-grade DAVFs who underwent surgery, SRS, embolization, or observation**

| | Overall Cohort (n = 415) | Observation (n = 29) | Embolization (n = 324) | Surgery (n = 43) | SRS (n = 19) | p Value |
|---|---|---|---|---|---|---|
| Mean age, yrs (SD) | 59.1 (14.4) | 61.3 (16.6) | 58.9 (14.2) | 61.2 (13) | 53.9 (17.9) | 0.249 |
| Female, n (%) | 169/415 (40.7) | 13/29 (44.8) | 135/324 (41.7) | 15/43 (34.9) | 6/19 (31.6) | 0.662 |
| Myocardial infarction, n (%) | 20/409 (4.9) | 3/29 (10.3) | 13/318 (4.1) | 2/43 (4.7) | 2/19 (10.5) | 0.178 |
| Coronary artery disease, n (%) | 38/409 (9.3) | 5/28 (17.9) | 26/319 (8.2) | 3/43 (7) | 4/19 (21.1) | 0.090 |
| Atrial fibrillation, n (%) | 30/409 (7.3) | 4/29 (13.8) | 23/318 (7.2) | 2/43 (4.7) | 1/19 (5.3) | 0.518 |
| Ischemic stroke, n (%) | 36/410 (8.8) | 8/29 (27.6) | 26/319 (8.2) | 1/43 (2.3) | 1/19 (5.3) | **0.005** |
| Diabetes mellitus, n (%) | 71/410 (17.3) | 7/29 (24.1) | 55/319 (17.2) | 8/43 (18.6) | 1/19 (5.3) | 0.405 |
| Hypertension, n (%) | 183/410 (44.6) | 17/29 (58.6) | 137/319 (43) | 20/43 (46.5) | 9/19 (47.4) | 0.426 |
| Smoking, n (%) | 142/346 (41) | 15/26 (57.7) | 102/272 (37.5) | 17/31 (54.8) | 8/17 (47.1) | 0.069 |
| Alcohol use, n (%) | 35/387 (9) | 2/25 (8) | 30/302 (9.9) | 1/42 (2.4) | 2/18 (11.1) | 0.403 |
| Antiplatelet use, n (%) | 106/408 (26) | 9/29 (31) | 80/317 (25.2) | 12/43 (27.9) | 5/19 (26.3) | 0.868 |
| Anticoagulant use, n (%) | 32/409 (7.8) | 3/29 (10.3) | 27/318 (8.5) | 2/43 (4.7) | 0/19 (0) | 0.546 |
| Symptomatic, n (%) | 297/414 (71.7) | 8/29 (27.6) | 248/323 (76.8) | 30/43 (69.8) | 30/43 (69.8) | **<0.001** |
| Baseline mRS score, n (%) | | | | | | 0.057 |
| 0 | 162/411 (39.4) | 14/29 (48.3) | 122/320 (38.1) | 19/43 (44.2) | 7/19 (36.8) | |
| 1 | 152/411 (37) | 8/29 (27.6) | 120/320 (37.5) | 16/43 (37.2) | 8/19 (42.1) | |
| 2 | 51/411 (12.4) | 2/29 (6.9) | 44/320 (13.8) | 2/43 (4.7) | 3/19 (15.8) | |
| 3 | 29/411 (7.1) | 0/29 (0) | 23/320 (7.2) | 5/43 (11.6) | 1/19 (5.3) | |
| 4 | 12/411 (2.9) | 4/29 (13.8) | 8/320 (2.5) | 0/43 (0) | 0/19 (0) | |
| 5 | 5/411 (1.2) | 1/29 (3.4) | 3/320 (0.9) | 1/43 (2.3) | 0/19 (0) | |
| Borden classification, n (%) | | | | | | **0.010** |
| II | 136/415 (32.8) | 7/29 (24.1) | 119/324 (36.7) | 6/43 (14) | 4/19 (21.1) | |
| III | 279/415 (67.2) | 22/29 (75.9) | 205/324 (63.3) | 37/43 (86) | 15/19 (79) | |
| Cognard classification, n (%) | | | | | | 0.058 |
| IIb | 49/412 (11.9) | 4/28 (14.3) | 40/322 (12.4) | 4/43 (9.3) | 1/19 (5.3) | |
| IIa+b | 85/412 (20.6) | 3/28 (10.7) | 77/322 (23.9) | 2/43 (4.7) | 3/19 (15.8) | |
| III | 134/412 (32.5) | 13/28 (46.4) | 97/322 (30.1) | 17/43 (39.5) | 7/19 (36.8) | |
| IV | 113/412 (27.4) | 7/28 (25) | 87/322 (27) | 15/43 (34.9) | 4/19 (21.1) | |
| V | 31/412 (7.5) | 1/28 (3.6) | 21/322 (6.5) | 5/43 (11.6) | 4/19 (21.1) | |
| MRI T2/FLAIR hyperintensity, n (%) | 110/364 (30.2) | 9/25 (36) | 79/282 (28) | 17/41 (41.5) | 5/16 (31.2) | 0.299 |
| Venous ectasia, n (%) | 155/397 (39) | 10/26 (38.5) | 122/311 (39.2) | 17/42 (40.5) | 6/18 (33.3) | 0.962 |
| Location, n (%) | | | | | | **<0.001** |
| Anterior cranial fossa | 31/411 (7.5) | 3/27 (11.1) | 10/323 (3.1) | 17/43 (39.5) | 1/18 (5.6) | |
| Middle cranial fossa | 10/411 (2.4) | 0/27 (0) | 10/323 (3.1) | 0/43 (0) | 0/18 (0) | |
| Transverse-sigmoid sinus | 130/411 (31.6) | 3/27 (11.1) | 117/323 (36.2) | 6/43 (14) | 4/18 (22.2) | |
| Tentorial | 65/411 (15.8) | 6/27 (22.2) | 50/323 (15.5) | 4/43 (9.3) | 5/18 (27.8) | |
| Convexity/SSS | 44/411 (10.7) | 1/27 (3.7) | 40/323 (12.4) | 3/43 (7) | 0/18 (0) | |
| Other | 131/411 (31.9) | 14/27 (51.9) | 96/323 (29.7) | 13/43 (30.2) | 8/18 (44.4) | |
| Mean radiological follow-up, mos (SD) | 21.3 (27.9) | 8.3 (17.6) | 22.4 (28.8) | 13 (16) | 40.5 (34) | **<0.001** |
| Mean clinical follow-up, mos (SD) | 25.1 (29) | 12.7 (18.9) | 24.9 (27.4) | 24.7 (33.8) | 51 (43.7) | **<0.001** |

SSS = superior sagittal sinus.
Boldface type indicates statistical significance.

gery or SRS, respectively. Of the 43 patients in the surgery group, 4 (9.3%) underwent subsequent embolization, and none underwent subsequent SRS. Among the 19 patients in the SRS group, 3 (15.8%) and 1 (5.3%) underwent subsequent embolization and surgery, respectively. At final follow-up, dAVF obliteration was achieved in 21.1% (n = 4/19), 82.5% (255/309), 92.5% (n = 37/40), and 73.3% (n = 11/15) of patients in the observation, embolization, surgery, and SRS groups, respectively.

Compared with the likelihood of dAVF-related hemorrhage during follow-up in the observation group (6.9%, n = 2/29; 100.9 hemorrhages per 1000 patient-years), hem-

**TABLE 2. Comparison of primary and secondary outcomes among patients with unruptured high-grade dAVFs who underwent surgery, SRS, or embolization versus observation as reference**

| | Observation (n = 29) | Embolization (n = 324) | Surgery (n = 43) | SRS (n = 19) | OR (95% CI), p Value* | | |
|---|---|---|---|---|---|---|---|
| | | | | | Embolization | Surgery | SRS |
| Primary outcome | | | | | | | |
| Median mRS score (IQR) | 1 (0–4) | 0 (0–1) | 1 (0–2) | 1 (0–2) | 0.373 (0.177–0.784), **0.009** | 0.532 (0.215–1.316), 0.172 | 0.627 (0.202–1.951), 0.420 |
| Secondary outcomes | | | | | | | |
| mRS score 0–2, n (%) | 20/28 (71.4) | 278/308 (90.3) | 35/43 (81.4) | 14/15 (93.3) | 3.707 (1.504–9.138), **0.004** | 1.750 (0.569–5.382), 0.329 | 5.600 (0.628–49.946), 0.123 |
| Symptomatic improvement, n (%) | 9/29 (31) | 134/304 (44.1) | 15/43 (34.9) | 4/15 (26.7) | 1.752 (0.773–3.972), 0.180 | 1.190 (0.435–3.256), 0.734 | 0.808 (0.202–3.240), 0.764 |
| All-cause mortality, n (%) | 6/28 (21.4) | 9/308 (2.9) | 1/43 (2.3) | 1/15 (6.7) | 0.110 (0.036–0.338), **<0.001** | 0.087 (0.010–0.771), **0.028** | 0.262 (0.028–2.413), 0.237 |
| dAVF obliteration, n (%) | 3/18 (16.7) | 140/323 (43.3) | 37/43 (86) | 4/13 (30.8) | 3.825 1.086–13.471), **0.037** | 30.833 (6.810–139.600), **<0.001** | 2.222 (0.402–12.285), 0.360 |

Boldface type indicates statistical significance.
* In reference to the observation cohort.

orrhage rates were lower in the embolization group (1.6%, n = 5/306; 8.6 hemorrhages per 1000 patient-years, p = 0.022) but similar in the surgery (2.3%, n = 1/43; 21.7 hemorrhages per 1000 patient-years, p = 0.245) and SRS (0%, n = 0/16; 0 hemorrhages per 1000 patient-years, observation p = 0.077) groups. Procedure-related complication rates were 19.3% in the embolization group (n = 62/322; technical = 8.4% [n = 27/322], complication with temporary neurological sequelae = 6.8% [n = 22/322], and complication with permanent neurological sequelae = 4.0% [n = 13/322]) and 0% in both the surgery (n = 0/43) and SRS (n = 0/19) groups. Compared with the likelihood of dAVF-related NHND during follow-up in the observation group (6.9%, n = 2/29; 66.3 NHNDs per 1000 patient-years), NHND rates were similar in the embolization (4.0%, n = 12/303; 18.3 NHNDs per 1000 patient-years, p = 0.146), surgery (2.3%, n = 1/43; 11.5 NHNDs per 1000 patient-years, p = 0.181), and SRS (5.9%, n = 1/17; 14.0 NHNDs per 1000 patient-years, p = 0.239) groups.

## Discussion

In contrast to the typically benign natural history of low-grade dAVFs, the presence of CVD in high-grade dAVFs poses a significant hemorrhagic risk and confers an aggressive clinical course.[2–6,12–15] The mechanism of dAVF-related hemorrhage is posited to be rupture of fragile arterialized veins that have been progressively weakened by persistent cortical venous reflux and venous hypertension.[1,13,16] The hemorrhagic risk of high-grade dAVFs is variable, and the mode of presentation likely has the greatest impact on the likelihood of rupture. Duffau et al. observed a high rebleeding rate of 35% among 20 high-grade dAVFs at a mean interval of 20 days.[8] In a retrospective natural history study comprising 81 high-grade dAVFs with a cumulative follow-up of 49.6 patient-years, Söderman et al. observed annual hemorrhage rates of 7.4% and 1.5% in patients presenting with and those presenting without hemorrhage, respectively.[9] Similarly, Strom et al. reported significantly higher rates of hemorrhage among dAVF patients presenting with hemorrhage or NHND.[10] Hence, further characterization of hemorrhage risk among subgroups of high-grade dAVFs may help to guide the timing and selection of their treatment.

Modification of traditional dAVF angiographic classification systems (i.e., Borden and Cognard) by Zipfel et al. incorporated the presence of aggressive symptoms (hemorrhage or NHND) in high-grade dAVFs to further differentiate subgroups of these lesions.[14] In the proposed modification, symptomatic high-grade dAVFs harbored annual hemorrhage and mortality risks of 7.4%–7.6% and 3.8%, respectively. In contrast, the annual hemorrhage and mortality risks observed in asymptomatic high-grade dAVFs were 1.4%–1.5% and 0%, respectively.[9,10,14] As such, early intervention for symptomatic high-grade dAVFs was recommended to prevent recurrent hemorrhage or progressive NHND, whereas treatment of asymptomatic high-grade dAVFs was deemed elective.[1,14] Given the lower hemorrhage risk and potentially tamer clinical course of unruptured high-grade dAVFs, the optimal management strategy for these patients is unclear. Therefore, we retrospectively compared functional and radiological outcomes of different treatment modalities with observation in a large, multicenter cohort of unruptured high-grade dAVFs.

Endovascular embolization is often regarded as the first-line treatment for dAVFs, affording complete obliteration in most cases.[17] In a recent study comprising 52 pa-

**TABLE 3. Comparison of primary and secondary outcomes among patients with unruptured high-grade dAVFs who underwent surgery, SRS, or embolization versus observation as reference, after adjustments for baseline differences**

| | aOR (95% CI), p Value* | | | aOR (95% CI), p Value*† | | |
|---|---|---|---|---|---|---|
| | Embolization | Surgery | SRS | Embolization | Surgery | SRS |
| Primary outcome | | | | | | |
| mRS score | 0.540 (0.200–1.458), 0.224 | 1.595 (0.455–5.585), 0.465 | 0.512 (0.120–2.180), 0.365 | 0.462 (0.187–1.141), 0.094 | 1.029 (0.348–3.040), 0.959 | 0.525 (0.134–2.051), 0.354 |
| Secondary outcomes | | | | | | |
| mRS scores 0–2 | 4.420 (0.750–26.066), 0.101 | 1.887 (0.222–16.079), 0.561 | 6.893 (0.332–143.284), 0.212 | 0.339 (0.097–1.186), 0.091 | 0.818 (0.161–4.144), 0.809 | 1.714 (0.310–9.464), 0.537 |
| Symptomatic improvement | 1.011 (0.358–2.860), 0.983 | 0.485 (0.125–1.886), 0.297 | 0.735 (0.140–3.869), 0.716 | 1.286 (0.494–3.342), 0.606 | 0.807 (0.245–2.654), 0.724 | 0.936 (0.203–4.314), 0.932 |
| All-cause mortality | 0.174 (0.024–1.245), 0.082 | 0.468 (0.025–8.830), 0.612 | 0.299 (0.010–9.370), 0.492 | 0.171 (0.032–0.921), **0.040** | 0.300 (0.020–4.529), 0.385 | 0.221 (0.013–3.879), 0.302 |
| dAVF obliteration | 7.147 (1.603–31.872), **0.010** | 33.803 (5.112–223.507), **<0.001** | 6.410 (0.828–49.643), 0.075 | 3.066 (0.903–10.401), 0.072 | 20.215 (4.296–95.113), **<0.001** | 2.719 (0.485–15.242), 0.255 |

Boldface type indicates statistical significance.
* In reference to observation cohort. Adjusted for coronary artery disease, history of ischemic stroke, smoking, symptomatic presentation, baseline mRS score, Borden grade, Cognard classification, location, radiological follow-up, and clinical follow-up.
† Values are based on pooled parameter estimates from multiply imputed data using chained equations with m = 50.

tients with high-grade dAVFs (ruptured and unruptured) who underwent transarterial Onyx embolization, Mantilla et al. reported an initial angiographic obliteration rate of 55.7% with an overall complication rate of 15%.[18] In the same study, 80.5% of patients were functionally independent after a mean follow-up of 34 months. In a meta-analysis of 19 studies comprising 463 dAVFs transarterially embolized with Onyx, Sadeh-Gonike et al. reported initial angiographic occlusion and recurrence rates of 82% and 2%, respectively.[19] Pooled rates of postprocedural neurological deficit, procedure-related morbidity, and mortality in the same study were 4%, 3%, and 0%, respectively. In the present study of unruptured high-grade dAVFs with observation as the reference, the embolization group had a higher obliteration rate (43% vs 17%, p = 0.037) and lower dAVF-related hemorrhage rate (9 vs 101 hemorrhages per 1000 patient-years, p = 0.022). Although functional outcomes after embolization were better in the unadjusted analysis, the mRS score was similar between the two groups after adjustment for baseline differences. The lack of difference in functional outcome between embolization versus observation may be a result of symptomatic procedural complications in the embolization group, the small sample size of the observation group, and/or the method of patient selection for both groups. All-cause mortality was lower after embolization (21% vs 3%, p < 0.001), and it remained lower after adjusting for baseline differences in the imputed model (p = 0.040).

Surgical ligation is an alternative, more invasive, treatment for dAVFs that also provides immediate symptomatic relief when obliteration is achieved. In a study of 15 surgically treated unruptured Borden type III dAVFs, Gross and Du reported obliteration, functional independence at last follow-up, and combined morbidity and mortality rates of 93.3%, 80%, and 33.3%, respectively.[20] Other recent dAVF surgical series have demonstrated similarly high obliteration rates.[21–23] We found no difference in functional outcomes between surgery and observation. All-cause mortality was less likely after surgery in the unadjusted analysis, but its rates were similar between the two groups after adjustments for baseline differences. The crude obliteration rate was higher in the surgery versus observation group (86% vs 17%, p < 0.001), and it remained higher in both adjusted analyses. As such, surgical treatment of unruptured high-grade dAVFs yields substantially higher obliteration rates than does conservative management without incurring worse short-term clinical outcomes. Additional postoperative follow-up may be necessary in these patients to realize a benefit from surgery with regard to hemorrhage and neurological symptoms.

Due to the high recurrent hemorrhage risk of ruptured dAVFs, SRS is a suboptimal therapy in many cases due to the relatively prolonged latency period between treatment and obliteration.[1,24] However, SRS could be a viable treatment option for appropriately selected unruptured high-grade dAVFs. In a recent study of 41 high-grade dAVFs treated with SRS, 62% achieved obliteration (based on MRI or DSA) without a new permanent neurological deficit.[25] In a meta-analysis of 6 studies comprising 197 high-grade dAVFs, Tonetti et al. reported lower rates of post-SRS hemorrhage (6.9% vs 0%, p = 0.003) and adverse

radiation effects (8.2% vs 0%, p = 0.001) in nonaggressive (no history of hemorrhage or NHND) versus aggressive high-grade dAVFs.[26] In our analyses, we found no difference in primary or secondary outcome measures between SRS and observation. The lack of significant findings in our SRS versus observation comparisons may be attributed to the small number of cases in both cohorts and insufficiently long-term follow-up. However, the absence of procedure-related complications in the SRS group may be a testament to both the operators and small treatment volumes of these lesions.

We recognize the present study's limitations. Our results depend on the accuracy and reliability of data provided by each participating institution and could be subject to reporting bias. The decision-making process regarding intervention, including the specific modality, or observation was at the discretion of the treating physician. In addition, unruptured high-grade dAVFs treated with embolization accounted for the majority of the study cohort. Conversely, the small sample size of the observation group hinders its generalizability, and it reflects a bias toward intervention for these lesions. One can infer that the majority of contributing centers or treating physicians adopted an embolization-first strategy for the management of unruptured high-grade dAVFs. However, we were unable to extrapolate whether other interventions were considered prior to embolization based on the available data. Therefore, the outcomes are susceptible to the inherent selection, treatment, and referral biases of each contributing center and its physicians, despite our attempts to adjust for baseline differences using multivariable models.

Variations and inadequacies of follow-up durations among the groups likely impacted our ability to address the longitudinal risks associated with the different dAVF management strategies. Despite our attempts to account for confounders in our multivariable analyses, unmeasured variables, such as the decision-making process in dAVF treatment, were not fully adjusted for. One can assume that dAVFs believed to harbor a higher risk of hemorrhage and those causing progressive or intolerable symptoms were selected for intervention, thus biasing the intervention groups toward less favorable outcomes. Inferences derived from the secondary outcome analyses should be interpreted with caution, since multiple tests could elevate the false discovery rate. Due to constraints of multiple access routes, fluoroscopy time, and contrast load, planned staged embolization may be required for some dAVF treatments. However, our retrospective data do not allow us to differentiate between staged versus single-session embolizations, which could confound our designation of treatment failure (i.e., nonobliteration) as a secondary outcome.

## Conclusions

In a comparison of intervention versus conservative management for unruptured high-grade dAVFs, we failed to identify a benefit from any treatment modality, with respect to functional outcomes, at interim follow-up. With observation as a reference, embolization and surgery afforded a greater likelihood of obliteration, and embolization also reduced the risk of hemorrhage and death. As such, embolization appears to be the first-line therapy of choice for appropriately selected unruptured Borden type II and III dAVFs. The modest follow-up period of the study may have precluded our analysis from realizing some merits of high-grade dAVF treatment, particularly with regard to SRS.

## Appendix

### CONDOR Collaborators

Washington University School of Medicine: Gregory J. Zipfel, MD; Akash P. Kansagra, MD, MS; Ridhima Guniganti, MD; Jay F. Piccirillo, MD; Hari Raman, MD; and Kim Lipsey.

Mayo Clinic: Giuseppe Lanzino, MD; Enrico Giordan, MD; Waleed Brinjikji, MD; Roanna Vine, RN; Harry J. Cloft, MD; David F. Kallmes, MD; Bruce E. Pollock, MD; and Michael J. Link, MD.

University of Virginia Health System: Jason Sheehan, MD, PhD; Ching-Jen Chen, MD; Mohana Rao Patibandla, MCh; Dale Ding, MD; Thomas Buell, MD; and Gabriella Paisan, MD.

University of Washington: Louis J. Kim, MD, MBA; Michael R. Levitt, MD; Isaac Josh Abecassis, MD; R. Michael Meyer IV, MD; and Cory Kelly.

University of Southampton: Diederik Bulters, FRCS(SN); Andrew Durnford, MA, MSc, FRCS; Jonathan Duffill, MBChB; Adam Ditchfield, MBBS; John Millar, MBBS; and Jason Macdonald, MBBS.

University of Florida: W. Christopher Fox, MD; Adam J. Polifka, MD; Dimitri Laurent, MD; Brian Hoh, MD; Jessica Smith, MSN, RN; and Ashley Lockerman, RN.

University of Pittsburgh: Bradley A. Gross, MD; L. Dade Lunsford, MD; and Brian T. Jankowitz, MD.

University of Iowa Hospitals and Clinics: Minako Hayakawa, MD, PhD; Colin P. Derdeyn, MD; Edgar A. Samaniego, MD; Santiago Ortega Gutierrez, MD, MS; David Hasan, MD; Jorge A. Roa, MD; James Rossen, MD; Waldo Guerrero, MD; and Allen McGruder.

University of Illinois at Chicago: Sepideh Amin-Hanjani, MD; Ali Alaraj, MD; Amanda Kwasnicki, MD; Fady T. Charbel, MD; Victor A. Aletich, MS, MD (posthumous); and Linda Rose-Finnell.

University of Groningen, University Medical Center Groningen: J. Marc C. van Dijk, MD, PhD; and Adriaan R. E. Potgieser, MD, PhD.

University of Miami: Robert M. Starke, MD, MSc; Eric C. Peterson, MD; Dileep R. Yavagal, MD; Samir Sur, MD; and Stephanie H. Chen, MD.

Tokushima University: Junichiro Satomi, MD, PhD; Yoshiteru Tada, MD, PhD; Yasuhisa Kanematsu, MD, PhD; Nobuaki Yamamoto, MD, PhD; Tomoya Kinouchi, MD, PhD; Masaaki Korai, MD, PhD; Izumi Yamaguchi, MD, PhD; and Yuki Yamamoto, MD.

University of California, San Francisco: Adib Abla, MD; Ethan Winkler, MD, PhD; Ryan R. L. Phelps, BA; Michael Lawton, MD; and Martin Rutkowski, MD.

Brigham and Women's Hospital: Rose Du, MD, PhD; Pui Man Rosalind Lai, MD; M. Ali Aziz-Sultan, MD; Nirav Patel, MD; and Kai U. Frerichs, MD.

## References

1. Reynolds MR, Lanzino G, Zipfel GJ. Intracranial dural arteriovenous fistulae. *Stroke*. 2017;48(5):1424–1431.
2. Borden JA, Wu JK, Shucart WA. A proposed classification for spinal and cranial dural arteriovenous fistulous malformations and implications for treatment. *J Neurosurg*. 1995;82(2):166–179.
3. Cognard C, Gobin YP, Pierot L, et al. Cerebral dural arterio-

venous fistulas: clinical and angiographic correlation with a revised classification of venous drainage. *Radiology*. 1995; 194(3):671–680.
4. Satomi J, van Dijk JM, Terbrugge KG, et al. Benign cranial dural arteriovenous fistulas: outcome of conservative management based on the natural history of the lesion. *J Neurosurg*. 2002;97(4):767–770.
5. Shah MN, Botros JA, Pilgram TK, et al. Borden-Shucart Type I dural arteriovenous fistulas: clinical course including risk of conversion to higher-grade fistulas. *J Neurosurg*. 2012; 117(3):539–545.
6. Gross BA, Du R. The natural history of cerebral dural arteriovenous fistulae. *Neurosurgery*. 2012;71(3):594–603.
7. van Dijk JM, terBrugge KG, Willinsky RA, Wallace MC. Clinical course of cranial dural arteriovenous fistulas with long-term persistent cortical venous reflux. *Stroke*. 2002; 33(5):1233–1236.
8. Duffau H, Lopes M, Janosevic V, et al. Early rebleeding from intracranial dural arteriovenous fistulas: report of 20 cases and review of the literature. *J Neurosurg*. 1999;90(1):78–84.
9. Söderman M, Pavic L, Edner G, et al. Natural history of dural arteriovenous shunts. *Stroke*. 2008;39(6):1735–1739.
10. Strom RG, Botros JA, Refai D, et al. Cranial dural arteriovenous fistulae: asymptomatic cortical venous drainage portends less aggressive clinical course. *Neurosurgery*. 2009; 64(2):241–248.
11. Rubin DB. Multiple imputation for nonresponse in surveys. In: *Wiley Series in Probability and Statistics*. John Wiley & Sons, Inc; 1987.
12. Davies MA, Saleh J, Ter Brugge K, et al. The natural history and management of intracranial dural arteriovenous fistulae. Part 1: benign lesions. *Interv Neuroradiol*. 1997;3(4): 295–302.
13. Brown RD Jr, Wiebers DO, Nichols DA. Intracranial dural arteriovenous fistulae: angiographic predictors of intracranial hemorrhage and clinical outcome in nonsurgical patients. *J Neurosurg*. 1994;81(4):531–538.
14. Zipfel GJ, Shah MN, Refai D, et al. Cranial dural arteriovenous fistulas: modification of angiographic classification scales based on new natural history data. *Neurosurg Focus*. 2009;26(5):E14.
15. Awad IA, Little JR, Akarawi WP, Ahl J. Intracranial dural arteriovenous malformations: factors predisposing to an aggressive neurological course. *J Neurosurg*. 1990;72(6): 839–850.
16. Lasjaunias P, Chiu M, ter Brugge K, et al. Neurological manifestations of intracranial dural arteriovenous malformations. *J Neurosurg*. 1986;64(5):724–730.
17. Gross BA, Albuquerque FC, Moon K, McDougall CG. Evolution of treatment and a detailed analysis of occlusion, recurrence, and clinical outcomes in an endovascular library of 260 dural arteriovenous fistulas. *J Neurosurg*. 2017;126(6): 1884–1893.
18. Mantilla D, Le Corre M, Cagnazzo F, et al. Outcome of transarterial treatment of dural arteriovenous fistulas with direct or indirect cortical venous drainage. *J Neurointerv Surg*. 2018;10(10):958–963.
19. Sadeh-Gonike U, Magand N, Armoiry X, et al. Transarterial Onyx embolization of intracranial dural fistulas: a prospective cohort, systematic review, and meta-analysis. *Neurosurgery*. 2018;82(6):854–863.
20. Gross BA, Du R. Surgical treatment of high grade dural arteriovenous fistulae. *J Clin Neurosci*. 2013;20(11):1527–1532.
21. Piippo A, Niemelä M, van Popta J, et al. Characteristics and long-term outcome of 251 patients with dural arteriovenous fistulas in a defined population. *J Neurosurg*. 2013;118(5): 923–934.
22. Meneghelli P, Pasqualin A, Lanterna LA, et al. Surgical treatment of anterior cranial fossa dural arterio-venous fistulas (DAVFs): a two-centre experience. *Acta Neurochir (Wien)*. 2017;159(5):823–830.
23. Bertuccio A, Robba C, Spena G, Versari PP. Intracranial and spinal dural arterio-venous fistula (DAVF): a surgical series of 107 patients. *Acta Neurochir Suppl*. 2016;123:177–183.
24. Chen CJ, Lee CC, Ding D, et al. Stereotactic radiosurgery for intracranial dural arteriovenous fistulas: a systematic review. *J Neurosurg*. 2015;122(2):353–362.
25. Chen CJ, Buell TJ, Diamond J, et al. Stereotactic radiosurgery for high-grade intracranial dural arteriovenous fistulas. *World Neurosurg*. 2018;116:e640–e648.
26. Tonetti DA, Gross BA, Jankowitz BT, et al. Reconsidering an important subclass of high-risk dural arteriovenous fistulas for stereotactic radiosurgery. *J Neurosurg*. 2018;130(3): 972–976.

## Disclosures

Dr. Kansagra reports consultant fees from Medtronic and Penumbra and non–study-related clinical or research effort from MicroVention and Medtronic. Dr. Lanzino is a consultant for Superior Medical Editing and Nested Knowledge. Dr. Kim reports funding support from the NINDS, consultant fees from MicroVention, and stock ownership in SPI Surgical. Dr. Levitt reports funding support from the NINDS, AHA, Stryker, and Medtronic, and consultant fees from Medtronic, Minnetronix, and Metis Innovative; and ownership in Synchron, Cerebrotech, and Proprio. Dr. Polifka is a consultant for DePuy Synthes. Dr. Gross reports consultant fees from MicroVention and Medtronic. Dr. Derdeyn reports ownership in Pulse Therapeutics; is a consultant for Penumbra, Rapid Medical, and NoNo; and received clinical or research support for this study from Siemens Healthineers. Dr. Alaraj reports funding support from the NIH, and consultant fees from Cerenovus and Siemens. Dr. Starke reports funding support from NREF, Joe Niekro Foundation, Brain Aneurysm Foundation, Bee Foundation, and the NIH, and consultant fees from Penumbra, Abbott, Medtronic, and Cerenovus.

## Author Contributions

Conception and design: Sheehan, Chen, Zipfel. Acquisition of data: Chen, Buell, Guniganti, Kansagra, Lanzino, Giordan, Kim, Levitt, Abecassis, Bulters, Durnford, Fox, Polifka, Gross, Hayakawa, Derdeyn, Samaniego, Amin-Hanjani, Alaraj, Kwasnicki, Van Dijk, Potgieser, Starke, Sur, Satomi, Tada, Abla, Winkler, Du, Lai, Zipfel. Analysis and interpretation of data: Chen, Buell, Ding, Guniganti, Kansagra, Lanzino, Giordan, Kim, Levitt, Abecassis, Bulters, Durnford, Fox, Polifka, Gross, Hayakawa, Derdeyn, Samaniego, Amin-Hanjani, Alaraj, Kwasnicki, Van Dijk, Potgieser, Starke, Sur, Satomi, Tada, Abla, Winkler, Du, Lai, Zipfel. Drafting the article: Chen. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sheehan. Statistical analysis: Chen. Administrative/technical/material support: Sheehan, Guniganti, Zipfel. Study supervision: Sheehan, Zipfel.

## Supplemental Information

### Companion Papers

Zipfel GJ: Introduction. The Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR). DOI: 10.3171/2021.1.JNS2174.

Cockcroft KM: Editorial. The challenges of managing "benign" disease. DOI: 10.3171/2020.10.JNS203420.

Samaniego EA, Roa JA, Hayakawa M, Chen CJ, Sheehan JP, Kim LJ, et al: Dural arteriovenous fistulas without cortical venous drainage: presentation, treatment, and outcomes. DOI: 10.3171/2021.1.JNS202825.

Guniganti R, Giordan E, Chen CJ, Abecassis IJ, Levitt

MR, Durnford A, et al: Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR): rationale, design, and initial characterization of patient cohort. DOI: 10.3171/2021.1.JNS202790.

Abecassis IJ, Meyer RM, Levitt MR, Sheehan JP, Chen CJ, Gross BA, et al: Assessing the rate, natural history, and treatment trends of intracranial aneurysms in patients with intracranial dural arteriovenous fistulas: a Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR) investigation. DOI: 10.3171/2021.1.JNS202861.

Abecassis IJ, Meyer RM, Levitt MR, Sheehan JP, Chen CJ, Gross BA, et al: Recurrence after cure in cranial dural arteriovenous fistulas: a collaborative effort by the Consortium for Dural Arteriovenous Fistula Outcomes Research (CONDOR). DOI: 10.3171/2021.1.JNS202033.

## Correspondence

Jason P. Sheehan: University of Virginia Health System, Charlottesville, VA. jsheehan@virginia.edu.