JNS

CLINICAL ARTICLE

J Neurosurg 138:891–899, 2023

Surgical treatment of brain arteriovenous malformations: clinical outcomes of patients included in the registry of a pragmatic randomized trial

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ABBREVIATIONS ARUBA = A Randomized trial of Unruptured Brain Arteriovenous malformations; AVM = arteriovenous malformation; bAVM = brain AVM; DSMC = data safety and monitoring committee; mRS = modified Rankin Scale; RCT = randomized controlled trial; SAE = serious adverse event; SM = Spetzler-Martin; SRS = stereotactic radiosurgery; TOBAS = Treatment of Brain Arteriovenous Malformations Study.

SUBMITTED April 7, 2022. **ACCEPTED** July 15, 2022.

INCLUDE WHEN CITING Published online September 9, 2022; DOI: 10.3171/2022.7.JNS22813.

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OBJECTIVE The Treatment of Brain Arteriovenous Malformations Study (TOBAS) is a pragmatic study that includes 2 randomized trials and registries of treated or conservatively managed patients. The authors report the results of the surgical registry.

METHODS TOBAS patients are managed according to an algorithm that combines clinical judgment and randomized allocation. For patients considered for curative treatment, clinicians selected from surgery, endovascular therapy, or radiation therapy as the primary curative method, and whether observation was a reasonable alternative. When surgery was selected and observation was deemed unreasonable, the patient was not included in the randomized controlled trial but placed in the surgical registry. The primary outcome of the trial was mRS score > 2 at 10 years (at last follow-up for the current report). Secondary outcomes include angiographic results, perioperative serious adverse events, and permanent treatment-related complications leading to mRS score > 2.

RESULTS From June 2014 to May 2021, 1010 patients were recruited at 30 TOBAS centers. Surgery was selected for 229/512 patients (44%) considered for curative treatment; 77 (34%) were included in the surgery versus observation randomized trial and 152 (66%) were placed in the surgical registry. Surgical registry patients had 124/152 (82%) ruptured and 28/152 (18%) unruptured arteriovenous malformations (AVMs), with the majority categorized as low-grade Spetzler-Martin grade I–II AVM (118/152 [78%]). Thirteen patients were excluded, leaving 139 patients for analysis. Embolization was performed prior to surgery in 78/139 (56%) patients. Surgical angiographic cure was obtained in 123/139 all-grade (89%, 95% CI 82%–93%) and 105/110 low-grade (95%, 95% CI 90%–98%) AVM patients. At the mean follow-up of 18.1 months, 16 patients (12%, 95% CI 7%–18%) had reached the primary safety outcome of mRS score > 2, including 11/16 who had a baseline mRS score ≥ 3 due to previous AVM rupture. Serious adverse events occurred in 29 patients (21%, 95% CI 15%–28%). Permanent treatment-related complications leading to mRS score > 2 occurred in 6/139 patients (4%, 95% CI 2%–9%), 5 (83%) of whom had complications due to preoperative embolization.

CONCLUSIONS The surgical treatment of brain AVMs in the TOBAS registry was curative in 88% of patients. The participation of more patients, surgeons, and centers in randomized trials is needed to definitively establish the role of surgery in the treatment of unruptured brain AVMs.

Clinical trial registration no.: NCT02098252 (ClinicalTrials.gov)

https://thejns.org/doi/abs/10.3171/2022.7.JNS22813

KEYWORDS brain arteriovenous malformation; randomized trial; care trial; ruptured AVM; unruptured AVM; surgical treatment registry; vascular disorders

The best management of patients with brain arteriovenous malformations (bAVMs) remains uncertain. This is particularly true for unruptured bAVMs. A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA) reported better clinical outcomes at 5 years for unruptured bAVM patients managed medically as compared with those who received any interventional treatment,[1,2] but the trial conclusions cannot be applied to surgery, which was used in only 21/223 patients (9%) in ARUBA. Multiple case series and meta-analyses have been published to support the safety and efficacy of surgery,[3–7] but nonetheless many clinicians have been more hesitant to offer curative surgical treatment to unruptured bAVM patients since the publication of the ARUBA results.[8] The benefit of the preventive surgical treatment of bAVM patients remains to be shown in a randomized controlled trial (RCT). The surgical treatment of ruptured, low-grade bAVM is rarely questioned, but the role of nonsurgical treatment modalities such as embolization or radiotherapy, either as adjuncts or to replace surgery, remains uncertain.

The international, multicenter Treatment of Brain Arteriovenous Malformations Study (TOBAS) was launched in 2014. Initially conceived to address some of the shortcomings of ARUBA, its scope was widened to provide clinicians with a transparent research context in which to offer treatment to all patients with bAVMs, ruptured or unruptured.[9,10] TOBAS offers randomized allocation of 2 care options, curative treatment versus observation (stratified for treatment type and minimized for arteriovenous malformation [AVM] grade and rupture status); it also offers randomized allocation of pre-embolization to eligible patients in a second RCT. Unlike the design of a classic RCT, TOBAS is fully integrated into practice and is all-inclusive; non-RCT patients are offered participation in observation and treatment registries.

The TOBAS registries serve several purposes.[11] First, registries are essential because of the all-inclusive nature of the study. Second, the registries permit the identification of patients treated outside of RCTs; this can help interpret and assess the generalizability of the RCT results, which is a common concern with previous trials in the neurovascular field.[12] Third, registry data can provide insight into the clinical outcomes of various treatment modalities and prespecified subgroups monitored by the data safety and monitoring committee (DSMC) to ensure that emerging concerns are addressed in a timely manner to prevent additional patient morbidity. Finally, registry data may also indicate that a change of practice is in order and identify which treatment modality or modalities should be limited to randomized allocation as the trial progresses.

Here, we present the clinical and angiographic out-

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comes of patients with bAVM, both ruptured and unruptured, who were treated within the TOBAS surgical registry.

Methods

This study follows the transparent reporting policy of the Consolidated Standards of Reporting Trials (CONSORT) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[13,14] The surgical treatment results of the patients included in the TOBAS registry are reported as an observational study, as detailed in the TOBAS protocol.[11]

TOBAS is an investigator-led, pragmatic, multicenter care trial, which includes 2 randomized (1:1) parallel-group trials and 4 registries (observation, surgical, endovascular, and stereotactic radiosurgery [SRS]). The study is being conducted in 3 American, 3 Canadian, 2 Brazilian, 1 Chilean, and 21 French centers (the participating investigators and sites are listed in the *Appendix*). TOBAS centers were not selected, but all offer multidisciplinary care for patients with AVMs.

The trial protocol was published in 2015.[11] The pilot phase with 107 patients recruited at 1 center was published in 2018.[15] The protocol is approved by the local institutional review boards of participating centers prior to patient enrollment, and all patients or delegates have provided written informed consent. Data capture and management are done through secure servers (MedSciNet) in compliance with Good Clinical Practice (GCP) requirements. The trial is monitored in Montreal, Canada, and Brest, France. The electronic case report forms are simple, with data collection kept to a minimum.

The published protocol specified that patients entered in the registry will be included in secondary analyses designed to estimate treatment morbidity for each modality and natural history of untreated patients, just as an observational study for unruptured and ruptured AVMs and for high-grade and low-grade lesions. Four groups and multiple predetermined subgroups will be examined: 1) according to treatment modality; 2) according to presentation (hemorrhagic vs all other presentations); and 3) according to Spetzler-Martin (SM) grade (I–II vs III–V).

All patients included in TOBAS from trial initiation on June 1, 2014, until May 20, 2021, were included in this report. The sole inclusion criterion for TOBAS is that the patient has a bAVM of any size and in any location, with any clinical presentation. Baseline patient characteristics collected at enrollment include the modified Rankin Scale (mRS) score at time of inclusion, the presence of any neurological deficit or epilepsy, and whether the patient had received any AVM treatment prior to inclusion. AVM characteristics are recorded to calculate SM grade, including size, eloquence, and presence of deep venous drainage, as well as side (left or right) and supratentorial or infratentorial location. The rupture status of the AVM is recorded; if ruptured, the date of the most recent AVM rupture was noted. Technical details of AVM treatment were left to the discretion of the treating physicians. The primary outcome measure of TOBAS is mRS score > 2 at 10 years. Other recorded outcomes include mortality (all cause), serious adverse events (SAEs), intracranial hemorrhages after enrollment, permanent disabling treatment-related complications, and angiographic outcomes. In this pragmatic trial, blinding of outcome assessors was not performed.

The TOBAS Algorithm

For each patient, usually at the time of a multidisciplinary meeting, a management plan is chosen according to an algorithm that combines clinical judgment and randomized allocation (Fig. 1). The final management plan is validated by the participating clinicians. Informed consent is sought after registration and randomization, whenever pre-randomization has been approved by the local IRB, as previously explained.[16]

The TOBAS algorithm poses 5 questions in the following order to determine "intent-to-treat" patient management (Fig. 1). The first question, "Is the patient being considered for curative treatment?" has yes/no possible answers. When the answer is "no," the patient is automatically placed in the observation registry. When the answer is "yes," the second question appears regarding the intended curative treatment, with the possible answers—surgery, radiosurgery, or embolization—determined by clinical judgment. The third question opens the way to the first TOBAS randomized trial, "Given the lack of randomized evidence treatment is beneficial: Is observation a reasonable alternative option to curative treatment?" When the answer is "yes," observation or the previously selected treatment (i.e., surgery) is randomly allocated. When the answer is "no," the patient is included in the surgical treatment registry, as reported here.

The fourth question of the algorithm pertains to only those patients who, if they are to be treated, have had surgery or SRS selected/allocated, and states: "Is pre-embolization being considered?" If the answer is "yes," the fifth and final question appears: "Can surgery or radiation therapy be offered without pre-embolization?" If the answer is "no" and the patient is to be treated, pre-embolization is scheduled as it was judged necessary for safe treatment. If the answer is "yes" and the patient is to be treated, pre-embolization or no pre-embolization is randomly allocated. This is the second TOBAS randomized trial. The final management plan is then approved by the clinicians in attendance, and informed consent is obtained.

Outcomes

The primary outcome of the trial was mRS score > 2—a functional outcome measure administered by unblinded care providers using a standardized questionnaire—at 10 years. In the spirit of pragmatic care trials, this outcome was selected because it is hard, easily ascertainable for all patients, relatively resistant to bias, and meaningful for patients and clinicians.[11] Outcomes are measured and presented in multiple ways in order to offer, in as transparent a manner as possible, a clinically clear and meaningful result that can be used for both ruptured and unruptured AVMs of all grades.

For the purpose of this report, the primary outcome was mRS score > 2 at last follow-up. Secondary TOBAS out-

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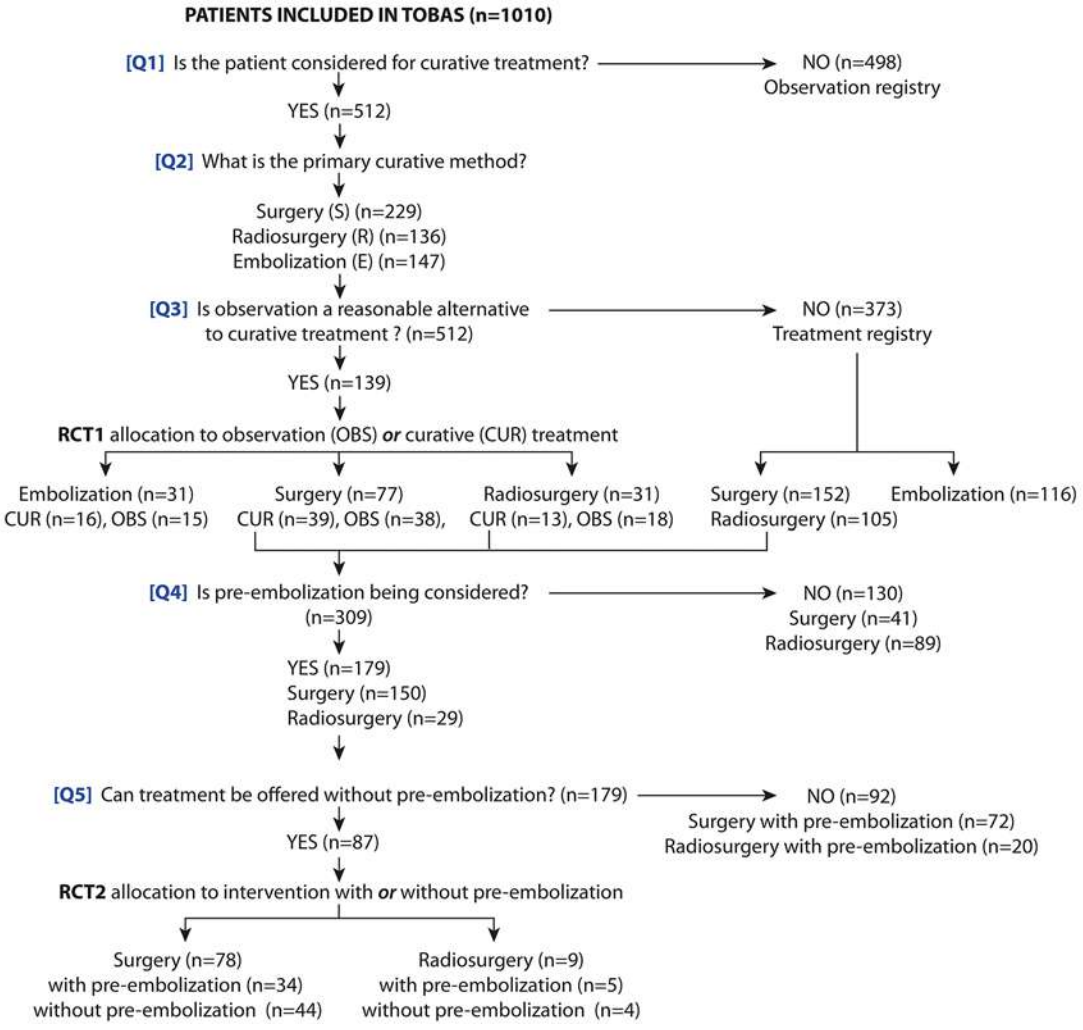

FIG. 1. TOBAS flowchart. Figure is available in color online only.

comes (detailed in the published protocol[11]) include overall mortality (all cause) and overall morbidity (mRS score > 2, all cause) at 1, 5, and 10 years, as well as "disabling treatment-related complications" defined as a permanent (lasting more than 3 months), periprocedural (within 31 days) complication leading to mRS score > 2 (or if the baseline mRS score was > 2, an increase in mRS score of 1 or more); peritreatment hospitalization lasting more than 15 days; discharge to a location other than home; and failure to eradicate the AVM (as determined with angiography) with the intended treatment modality.

Trial Monitoring

Monitoring of trial data quality is web-based and performed in Montreal and Brest. Blinded data are prepared for periodic safety reviews at prespecified intervals by an independent DSMC, which is composed of volunteer physicians not involved in the conduct of the trial and a statistician. SAEs are recorded 1) per management group (observation or active treatment), 2) per treatment group (observation, surgery, embolization, or SRS), and 3) according to clinical criteria (ruptured or unruptured AVM; SM grade I–II or III–V). More specifically, the DSMC ensures that the incidence rates of treatment-related complications are within the confidence intervals compatible with the study hypotheses. A DSMC charter predefined all trial monitoring procedures, including specific stopping rules.

On June 29, 2021, after examination of the blinded results, the DSMC informed the steering committee that TOBAS could continue recruitment. On September 20, 2021, the steering committee, after consultation with the DSMC, decided to make public the results of the available treatment registries to promote participation in the RCTs.

Funding

The coordinating center in Montreal received a seed grant from Medtronic to initiate the web-based platform in 2014. The coordinating center in Brest received unrestricted research grants from Balt (2017), MicroVention (2018), and Medtronic (2019) and provided financial compensation to French participating centers.

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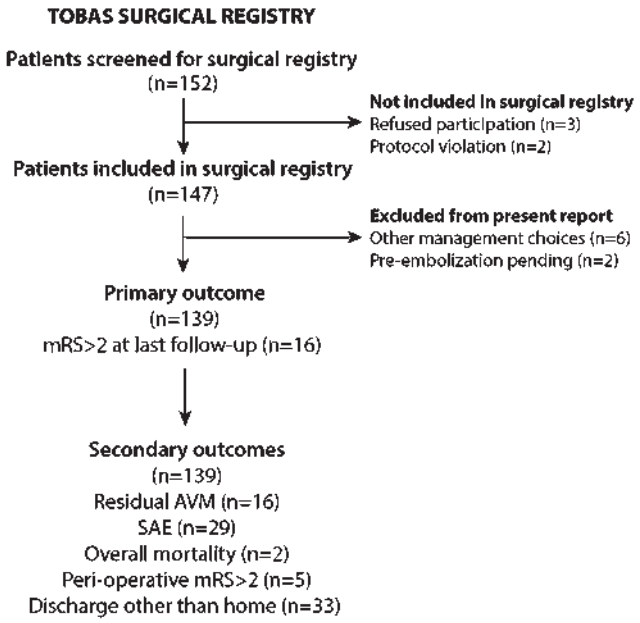

FIG. 2. Flowchart of patients included in the TOBAS surgical registry.

Statistical Analysis

As specified in the protocol, continuous variables are summarized with means, standard deviations, medians, and ranges. Categorical variables are presented as frequencies and percentages (with 95% CIs). No statistical hypothesis testing was undertaken for this report.

Results

The flowchart of the overall TOBAS structure, including how the 152 patients in the surgical treatment registry were identified for this report, is available in Fig. 1.

As detailed in the flowchart of surgical patients (Fig. 2), 13 patients were excluded from analyses because of patient refusal (n = 3), protocol violations (n = 2), change to nonsurgical management (n = 6), or any treatment was still pending (n = 2). The demographic characteristics of the remaining 139 treated patients (with all SM grades) are presented in Table 1.

The overall results of surgery are presented in Table 2. Complete resection was obtained in 123/139 patients (89%, 95% CI 82%–93%), with 109/123 (89%) confirmed with catheter angiography. Complete resection rates decreased with increasing SM grade, from 105/110 grade I+II AVMs (95%, 95% CI 90%–98%) to 13/20 grade III (65%, 95% CI 43%–82%) and 5/9 grade IV+V (56%, 95% CI 27%–81%) AVMs (Online Tables 1–3).

Embolization was performed prior to surgery for 78/139 patients (56%); 21 patients had more than 1 embolization session (mean [range] 1.5 [1–6] sessions). Sixteen of 139 patients (12%) did not undergo surgery: 9 were cured with preoperative embolization, 3 halted AVM treatment after preoperative embolization complications, and 4 underwent embolization but surgical treatment is pending.

After the initial operation, 24/139 patients (17%, 95% CI 12%–24%) had a residual AVM. Five patients were cured with repeat surgery and 3 with subsequent embolization, leaving 16 patients (12%, 95% CI 7%–18%) with a residual AVM (1 was treated with SRS). The 3 patients who halted AVM treatments after embolization complications and 4 with surgical treatment pending are included in the 16/139 patients with residual AVM.

TABLE 1. Characteristics of treated patients and AVMs included in the TOBAS surgical registry

Characteristic	Unruptured	Ruptured	Total
No. of patients	25	114*	139
Age, yrs	41.5 ± 13.7	41.1 ± 16.2	41.2 ± 15.8
Female	11 (44)	53 (46)	64 (46)
AVM location			
Supratentorial	21 (84)	97 (85)	118 (85)
Infratentorial	4 (16)	17 (15)	21 (15)
Preop mRS score			
0	12 (48)	30 (26)	42 (30)
1	12 (48)	34 (30)	46 (33)
2	1 (4)	20 (18)	21 (15)
3	0	13 (11)	13 (9)
4	0	13 (11)	13 (9)
5	0	4 (4)	4 (3)
SM grade			
I	14 (56)	32 (28)	46 (33)
II	7 (28)	57 (50)	64 (46)
III	1 (4)	19 (17)	20 (14)
IV	2 (8)	6 (5)	8 (6)
V	1 (4)	0	1 (1)
Eloquence	6 (24)	52 (46)	58 (42)
Deep venous drainage	6 (24)	42 (37)	48 (35)
AVM size	19 (76)	95 (83)	114 (82)
0–3 cm			
3–6 cm	5 (20)	19 (17)	24 (17)
>6 cm	1 (4)	0	1 (1)
History of any previous AVM treatment	7 (28)	7 (6)	14 (10)

Values are shown as number, number (%), or mean ± SD.
* Four patients had AVMs that ruptured more than 6 months prior to study inclusion.

SAEs occurred in 29/139 patients (21%, 95% CI 15%–28%), including 1 death. SAEs occurred in 15/110 patients (14%, 95% CI 8%–21%) with low-grade AVM and 14/29 patients (48%, 95% CI 31%–66%) with high-grade AVM. Fourteen of the 29 SAEs (48%, 95% CI 31%–66%) were postembolization complications (Table 3). Permanent (lasting at least 3 months) treatment-related (within 31 days) complications leading to mRS score > 2 (or if the baseline mRS score was > 2, then an increase ≥ 1 on the mRS) occurred in 6/139 patients (4%, 95% CI 2%–9%), 3/110 patients (3%, 95% CI 1%–8%) with low-grade AVM and 3/29 patients (10%, 95% CI 4%–26%) with high-grade AVM. Five of the 6 such complications were due to preoperative embolization.

The primary safety outcome (mRS score > 2) at last

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TABLE 2. Outcomes of treated patients in the surgical registry (all grades)

Characteristic	Unruptured	Ruptured	Total
No. of treated patients	25 (18)	114 (82)	139
Preop embolization	18 (72)	60 (53)	78 (56)
Angiographic outcome*			
Complete occlusion	23 (92)	100 (88)	123 (89)
Residual AVM	2 (8)	14 (12)	16 (12)
Missing data	0	0	0
Mean follow-up, mos	10.6	19.8	18.1
mRS score at final follow-up			
0	12 (48)	36 (32)	48 (35)
1	9 (36)	43 (38)	52 (37)
2	1 (4)	22 (19)	23 (17)
3	2 (8)	9 (8)	11 (8)
4	0	3 (3)	3 (2)
5	0	0	0
6	1 (4)	1 (1)	2 (1)
mRS score >2	3 (12)	13 (11)	16 (12)
Improvement/no change in mRS score	20 (80)	95 (83)	115 (83)
Increase in mRS score by ≥1	5 (20)	19 (17)	24 (17)
Increase in mRS score by ≥2	3 (12)	4 (4)	7 (5)
Permanent periop complication†	2 (8)	1 (1)	3 (2)
Hospitalized >15 days	1 (4)	41 (36)	42 (30)
Discharged to a location other than home	4 (16)	29 (25)	33 (24)

Values are shown as number (%) or mean.
* Angiography was not exclusively catheter angiography.
† Defined as a permanent (lasting at least 3 months), perioperative (within 31 days) complication leading to mRS score > 2 (or if mRS score was > 2 at baseline, then an increase ≥ 1 on mRS).

follow-up was reached in 16/139 patients (12%, 95% CI 7%–18%), with increasing frequency with greater SM grade: grade I+II (10/110 patients, 9%, 95% CI 5%–16%), grade III (3/20, 15%, 95% CI 3%–26%), and grade IV+V (3/9, 33%, 95% CI 12%–65%). Clinical details of all patients with final mRS score > 2, including those with baseline mRS score 3 or more, are available in Online Table 4.

At last clinical follow-up (mean 18.1 ± 16.3 months), 3/25 patients (12%, 95% CI 4%–30%) with unruptured AVM had an mRS score > 2. Two patients had hemorrhagic complications from preoperative embolization, and 1 patient was found deceased 3 years after angiographically confirmed complete resection (unknown cause of death). For ruptured AVM patients, 13/114 (11%, 95% CI 7%–18%) had a final mRS score > 2, including 11 patients with a baseline mRS score of 3 or more; the 2 other patients had complications from preoperative embolization (1 of whom died).

Discussion

The TOBAS study was designed to address 2 fundamental clinical dilemmas (whether preventive treatments are beneficial, and whether pre-embolization is beneficial to patients) by using RCTs integrated into practice. The all-inclusive design also comprises various registries that allow monitoring of the use and results of various treatment modalities (outside RCTs) at multiple centers that provide care for all patients with AVM, ruptured and unruptured. In this report, we focus on surgical treatment.

Overall, the surgical management of all grades of ruptured and unruptured AVMs included in the TOBAS registry was curative in 88% of patients. Surgery (with or without embolization) was associated with a 4% risk of disabling complications. The TOBAS surgical registry included a majority of AVMs that had previously ruptured (82%). Even though safety remains a relative judgment, the overall surgical results of the prospective TOBAS registry are in line with previous publications on the surgical treatment of AVMs.[6,17] However, the overall results should be interpreted with caution because of the mixture of low- and high-grade, ruptured and unruptured lesions. The prospective TOBAS registry results are nevertheless original and instructive, as they differ in important ways from case series and meta-analytical retrospective studies published in response to ARUBA, which are at risk for publication bias.[3] Because the study was registered and the protocol publicly available, the analysis and publication of the TOBAS results are not conditioned on the results being good enough to be reported. Patients were registered prior to treatment initiation, and the outcomes of all patients were accounted for in the analyses, including those of patients who did not actually undergo surgery (because they had a pre-embolization complication, for example). Because treatments were performed by multiple surgeons in multiple centers that were not selected according to their surgical results, the TOBAS findings better reflect real-world conditions and practice, and the conclusions may be more generalizable to future AVM patients encountered in any center.

The findings of the unruptured AVM registry patients will be discussed in light of the findings of the first TOBAS RCT, from which they were excluded. When unruptured bAVM patients were considered for treatment (n = 224), surgery was the most frequently selected treatment alternative (100/224 patients [45%]). It is encouraging that most low-grade unruptured AVM patients considered for surgery were included in the first RCT that compared treatment with conservative management (49/70 patients [70%]). However, in the absence of randomized evidence that preventive treatments should be recommended, too many unruptured low-grade bAVM patients were placed in the surgical treatment registry (21/70 [30%]) rather than included in the observation versus active treatment trial.

The current results do not mean that unruptured bAVM patients should undergo surgery rather than observation. However, they do confirm that surgical treatment is a promising preventive treatment. Thus, low-grade unruptured AVM patients should be informed of these results and encouraged to participate in the first RCT, in order to have a 50% chance of being protected from future rupture and a 50% chance of being spared potential surgical complications, until the best management strategy is identified. Thus, participation in the RCT remains in the best interest

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TABLE 3. Treatment-related complications and SAEs in surgical registry patients

Characteristic	Unruptured	Ruptured	Surgery Alone	Pre-embolization & Surgery	Total
No. of treated patients	25	114	62	77	139
Total SAEs	6 (24)	23 (20)	8 (13)	21 (27)	29 (21)
Treatment-related death	0	1 (1)	0	1 (1)	1 (1)
Total permanent complications* leading to final mRS score >2†	2 (8)	4 (4)	1 (2)	5 (6)	6 (4)
Pre-embolization	2 (100)	3 (75)	0	5 (100)	5 (83)
Hemorrhagic	2	3	1	4	5
Ischemic	0	1	0	1	1
Other	0	0	0	0	0
Total complications not leading to final mRS score >2†	4 (16)	19 (17)	7 (11)	16 (21)	23 (17)
Pre-embolization	1 (25)	8 (42)	0	9 (56)	9 (39)
Hemorrhagic	1	6	1	6	7
Ischemic	2	6	1	7	8
Wound/puncture complications	0	6	4	2	6
Epilepsy	0	1	0	1	1
Other	1	0	1	0	1
Non-SAEs	1 (4)	13 (11)	5 (8)	9 (12)	14 (10)

Values are shown as number or number (%).
* Defined as occurring within 31 days of treatment and lasting at least 3 months.
† Or if mRS score was > 2 at baseline, then an increase ≥ 1 on mRS.

of patients. It should be noted that the TOBAS RCT comparing surgery with conservative management has so far included more than 3 times as many surgical patients (n = 77) than the ARUBA trial (n = 21).

As expected, most acutely ruptured (within 6 months) bAVM patients enrolled in TOBAS were treated (206/237 patients [87%]) and most frequently by surgical means (110/206 [53%]). Yet, given the good results presented here, surgery may still be underused for acutely ruptured bAVMs at many TOBAS centers.

The number of residual AVMs identified after surgical treatment should be interpreted in light of the pragmatic and all-inclusive study design. An acute operation for a ruptured AVM may not reveal the entire malformation at the time of preoperative angiography. Patients may have refused further treatments (or clinicians judged further treatment unwise), even though residual AVM had been identified.

While the majority of surgeons did not question whether ruptured AVM patients should be treated, the use of preoperative embolization remains controversial. None of the patients included in this surgical registry underwent endovascular treatment as the intended curative treatment. In TOBAS, 150/191 patients (79%) (with ruptured and unruptured AVMs) for whom surgery was chosen as the curative treatment modality underwent preoperative embolization that was considered potentially beneficial. For 78/150 patients (52%), surgeons were willing to perform surgery without preoperative embolization. These patients were appropriately included in the second TOBAS RCT. However, preoperative embolization was thought to be necessary for 72 cases (48%).

Of concern, almost half of the SAEs in the surgical registry and most of the disabling treatment-related complications were due to preoperative embolization. This was not the case in other reports on the surgical treatment of bAVMs.[6,18] The necessity of preoperative embolization was previously questioned.[19,20] The TOBAS results presented here suggest that, when possible, preoperative embolization should be limited to the randomized context of the second TOBAS RCT.

There were limitations to this pragmatic study. Clinical outcomes were not assessed by independent blinded research personnel, and angiographic outcomes were not verified by an independent core laboratory. The mean follow-up period of this report (18.1 months) is much shorter than the 10-year outcome of the overall trial. The total number of patients, especially unruptured AVM patients, remains small. Other pragmatic aspects of this study should be considered strengths, even if they contribute to increased study heterogeneity, including the all-inclusive nature of the study and its integration into normal practice, and the lack of selection of surgical centers, which promotes the generalizability of study results.

The TOBAS registries were necessary because of the all-inclusive nature of the enterprise. The registries were also meant to encourage the recruitment of as many centers as possible, including those that are reluctant to question their practice, so that all can collaborate to define and offer optimal care for this challenging medical condition. Registries also serve to remind clinicians, each time they contemplate surgery for unruptured AVMs, of the current lack of evidence and existence of an RCT. The registries can also identify emerging concerns, such as an alarming incidence of adverse events.

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Care trials were conceived as a platform to guide care in the presence of uncertainty, to change practice immediately before generalizable knowledge becomes available, and to optimize patient outcomes in real time.[10,21] The current report suggests that more patients with low-grade unruptured AVMs should be offered participation in the RCT comparing conservative management versus surgical treatment, instead of being managed in the context of the observation or surgical registries.

Conclusions

The surgical treatment of bAVMs in the TOBAS registry was curative for 88% of patients. The participation of more patients, surgeons, and centers in RCTs is needed to determine the potential benefits of preoperative embolization and to definitively establish the role of surgery in the treatment of unruptured bAVMs.

Acknowledgments

We recognize the following members of the DSMC: Georges Rodesch (DSMC Chair, Hôpital Foch, Suresnes), Miguel Chagnon (University of Montreal), Maurice Giroud (CHU-Dijon), Bernard Irthum (CHU–Clermont-Ferrand), and David Mathieu (University of Sherbrooke).

Appendix

List of participating TOBAS centers and physicians

Canada

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University of Alberta: Tim E. Darsaut, Jeremy L. Rempel, Cian J. O'Kelly, Michael M. C. Chow, J. Max Findlay

University of Ottawa: Robert Fahed, Howard Lesiuk, Brian Drake, Marlene dos Santos

France

CHU-Brest: Jean-Christophe Gentric, Elsa Magro, Romuald Seizeur, Michel Nonent, Serge Timsit, Olivier Pradier, Julien Ognard, Mourad Cheddad El-Aouni

CHU-Nantes: Hubert Desal, Romain Boursier, François Thillays, Vincent Roualdes

Fondation Ophtalmologique Rothschild: Michel Piotin, Sorin Aldea, Raphael Blanc

CHU-Toulouse: Christophe Cognard, Anne-Christine Januel, Jean-François Sabatier, Lionel Calviere

CHU-Rennes: Jean Yves Gauvrit, Isabelle Lecouillard, Xavier Morandi, Elodie Nouhaud, Hélène Raoult, François Eugene, Anthony Le Bras, Jean-Christophe Ferre, Christophe Paya, Thomas Ronziere

CHU–Ste.-Anne: Denis Trystram, Olivier Naggara, Christine Rodriguez-Regent, Basile Kerleroux

CHU-Caen: Thomas Gaberel, Charlotte Barbier, Evelyne Emery, Emmanuel Touze

CHU-Rouen: Chrysanthi Papagiannaki, Stephane Derrey

CHU-Lyon: Isabelle Pellisou-Guyotat, Omer Eker, Jacques Guyotat, Monsef Berhouma, Roberto Riva, Chloé Dumot

CHRU-Besançon: Alessandra Biondi, Laurent Thines, Guillaume Charbonnier, Nassim Bougaci

CHRU-Nancy: Serge Bracard, René Anxionnat, Valérie Bernier-Chastagner, Thierry Civit, Benjamin Gory

CHU-Bordeaux: Xavier Barreau, Vincent Jecko, Guillaume Penchet, Edouard Gimbert, Gaulthier Marnat, Aymeri Huchet

CHRU-Tours: Denis Herbreteau, Grégoire Boulouis, Stéphane Velut, Richard Bibi, Héloïse Ifergan, Kévin Janot

Assistance Publique-Hôpitaux de Marseille: Pierre-Hugues Roche, Thomas Graillon, Hervé Brunel, Hadrien Peyriere, Jean-Marc Kaya, Adamou Touta, Lucas Troude, Sébastien Boissonneau

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CHU-Montpellier: Vincent Costalat, Marine Le Corre, Alain Bonafe, Cyril Dargazanli, Gregory Gascou, Pierre-Henri Lefevre, Carlos Riquelme

CHRU-Strasbourg: Francois Proust, Rémy Beaujeux, Hélène Cebula, Irène Ollivier, Raoul Pop, Giorgio Spatola

Hôpital Bicêtre: Laurent Spelle, Vanessa Chalumeau, Sophie Gallas, Léon Ikka, Cristian Mihalea, Augustin Ozanne, Jildaz Caroff

CHU–Clermont-Ferrand: Emmanuel Chabert

CHU-Limoges: Charbel Mounayer, Aymeric Rouchaud, Francois Caire

CHU-Dijon: Frédéric Ricolfi, Catherine Cao, Klaus-Luc Mourier, Pierre Thouant, Walid Farah

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Disclosures

Dr. Barbier is a consultant for Balt Extrusion. Dr. Nguyen receives non–study-related research support from Medtronic and the Society of Vascular and Interventional Neurology. Dr. Tawk owns stock in Medtronic. Dr. Iancu is a consultant for MicroVention and Stryker. Dr. Gentric is a consultant for Balt, Stryker, Medtronic, and MicroVention. Medtronic provided a seed grant (Montreal coordinating center) to initiate the web-based platform in 2014. The French coordinating center (Brest) received unrestricted research grants from Balt (2017), MicroVention (2018), and Medtronic (2019) to provide financial compensation to the French centers.

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Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Online Tables 1–4. https://thejns.org/doi/suppl/10.3171/2022.7.JNS22813.

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