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Conservative management of brain arteriovenous malformations: results of the prospective observation registry of a pragmatic trial

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ABBREVIATIONS ARUBA = A Randomized Trial of Unruptured Brain Arteriovenous Malformations; AVM = arteriovenous malformation; bAVM = brain AVM; mRS = modified Rankin Scale; RCT = randomized controlled trial; SAE = serious adverse event; SM = Spetzler-Martin; TOBAS = Treatment of Brain Arteriovenous Malformations Study. **SUBMITTED** March 26, 2024. **ACCEPTED** May 31, 2024.

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OBJECTIVE Many patients recruited in the Treatment of Brain Arteriovenous Malformations Study (TOBAS) are managed conservatively. The aim of this study was to monitor what happened to those patients.

METHODS TOBAS comprises two randomized controlled trials and multiple prospective registries. All patients with brain arteriovenous malformations (AVMs) can participate. This report concerns patients selected for conservative management. The primary trial outcome measure is related death or dependency (modified Rankin Scale [mRS] score > 2) at 10 years. Secondary outcomes include intracranial hemorrhages, nonhemorrhagic neurological events, and serious adverse events (SAEs). For this report, outcome results are presented using patient-years, Kaplan-Meier survival curves, and Cox log-rank tests. There was no blinding.

RESULTS From June 2014 to May 2021, 1010 patients were recruited, of whom 498 (49%) were proposed the prospective observation registry. After exclusions, 434 (87%) patients remained for analysis. The majority of patients had unruptured AVMs (378/434 [87%]), of which 195 (52%) were low grade (Spetzler-Martin grade I or II). During a mean follow-up period of 3.2 years (total 1368 patient-years), the primary outcome occurred in 23 of 434 (5%) patients, corresponding to an incidence of 1.7 (95% CI 1.1–2.5) per 100 patient-years. For unruptured AVMs the incidence was 1.1 (95% CI 0.7–1.9) per 100 patient-years, and for low-grade unruptured AVMs it was 0.6 (95% CI 0.2–1.7) per 100 patient-years. Poor outcomes were more frequent in patients with a history of rupture (HR 5.6 [95% CI 2.4–13.0], $p < 0.001$), infratentorial AVMs (HR 2.9 [95% CI 1.1–7.3], $p = 0.027$), and age ≥ 55 years (HR 3.2 [95% CI 1.4–7.6], $p = 0.007$). Major intracranial hemorrhage occurred in 35 of 434 (8%) patients (incidence of 2.6 [95% CI 1.9–3.6] per 100 patient-years; 2.0 [95% CI 1.3–2.9] per 100 patient-years for unruptured AVMs and 1.3 [95% CI 0.6–2.6] per 100 patient-years for low-grade unruptured AVMs). Major AVM hemorrhages were more frequent in ruptured (HR 4.4 [95% CI 2.1–8.9], $p < 0.001$), large (HR 2.6 [95% CI 1.1–6.6], $p = 0.039$), and high-grade (HR 2.5 [95% CI 1.2–5.3], $p = 0.013$) AVMs and those with deep venous drainage (HR 2.1 [95% CI 1.1–4.2], $p = 0.032$). SAEs occurred in 48 of 434 (11%) patients (incidence of 3.6 [95% CI 2.7–4.8] per 100 patient-years). For unruptured AVMs the incidence was 2.8 (95% CI 2.0–4.0) per 100 patient-years, and for low-grade unruptured AVMs it was 1.8 (95% CI 1.0–3.2) per 100 patient-years.

CONCLUSIONS Nearly half of TOBAS participants were observed. Rates of untoward neurological events were within expected boundaries.

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

<https://thejns.org/doi/abs/10.3171/2024.5.JNS24623>

KEYWORDS brain arteriovenous malformation; randomized trial; care trial; observation registry; conservative management; unruptured AVM; ruptured AVM; vascular disorders

THE most appropriate management of brain arteriovenous malformations (bAVMs) is controversial. This is particularly true for unruptured bAVMs, especially after the publication of the results of A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA), which showed better clinical outcomes with observation rather than active interventional treatment.^{1,2} In 2014, the international, multicenter Treatment of Brain Arteriovenous Malformations Study (TOBAS) was launched (identifier no. NCT02098252 [ClinicalTrials.gov]). Initially designed to address some of the shortcomings of the ARUBA trial,³ the scope of the study was widened to provide clinicians with a transparent research context to offer treatment to all patients with bAVMs, ruptured or unruptured.⁴ The all-inclusive TOBAS study includes two randomized controlled trials (RCTs), but patients excluded from the RCTs are offered participation in parallel treatment or observation registries. We here report the progress of the TOBAS observation registry.

By May 2021, 1010 patients were recruited in TOBAS; 498 patients (49%) of these patients had been placed in the observation registry. The progress of the TOBAS RCTs and the results from the surgical and endovascular treatment registries were examined at that time and published in 2023,^{5–7} but the steering committee decided to delay analysis of the patients in the observation registry until at least 2 years of additional follow-up time had accrued for all observed patients. The goal of this study was to examine the patient and arteriovenous malformation (AVM) characteristics of the TOBAS observation registry and to report AVM ruptures, neurological events, and unplanned treatments that occurred during follow-up. Our main goal was to verify whether observed patients had an unacceptable rate of serious adverse events (SAEs) such as intracranial hemorrhage.

Methods

This article follows the transparent reporting policy

of the Consolidated Standards of Reporting Trials.⁸ The results of patients included in the TOBAS observation registry are reported, as detailed in the protocol,⁴ using STROBE guidelines.⁹

TOBAS is an investigator-led, pragmatic, multicenter care trial. TOBAS includes two randomized (1:1) parallel-group trials and multiple prospective registries (observation, surgical, endovascular, stereotactic radiosurgery, and combined treatments). At the time the data were collected for the patients included in this report, the study was being conducted in 3 American, 3 Canadian, and 21 French centers (current participating investigators and sites are listed in the *Appendix*). The trial protocol,⁴ published in 2015, was approved by the local institutional review boards of the participating centers prior to enrollment, and all patients or delegates provided written informed consent. Data capture and management are done through secure servers (Omda, Sweden) in compliance with Good Clinical Practice requirements. Electronic case report forms are simple, with only essential data collected.

The TOBAS trial is all-inclusive; the sole inclusion criterion is that the patient has a bAVM of any size and in any location, with any clinical presentation. Baseline patient characteristics collected include the modified Rankin Scale (mRS) score at time of inclusion, the presence of neurological deficits and seizures, and whether the AVM had previously been treated (historically) prior to inclusion. The following AVM characteristics are recorded to calculate the Spetzler-Martin (SM) grade: size, eloquence, and presence of deep venous drainage, as well as involved side (left or right), and supra- or infratentorial location. The rupture status of the AVM is recorded; if ruptured, the date of the most recent AVM rupture is recorded.

The TOBAS protocol specified that patients entered in the observation registry would be included in secondary analyses designed to estimate morbidity for 4 subgroups: unruptured, ruptured, SM grade I or II (low grade), and SM grade III–V (high grade) AVMs.⁴ Prespecified risk factors included age (< 55 or ≥ 55 years), sex, AVM location, size, SM grade, eloquence, presence of deep venous drainage, and presenting rupture status.

The TOBAS Algorithm

For each patient presented at the multidisciplinary meeting, a management plan is chosen according to an algorithm that combines clinical judgment and randomized allocation. The final plan is validated by the participating clinicians. Informed consent is sought after registration and randomization when the prerandomization scheme is approved by local IRBs.¹⁰

The TOBAS algorithm poses 5 questions to determine the intent-to-treat patient management (Supplemental 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 was proposed participation in the observation registry. The present report includes only those patients for whom observation was selected.

Outcomes

The primary outcome measure of TOBAS is death or

stroke due to any cause leading to an mRS score > 2 at 10 years, but for this interim report, the primary outcome is an mRS score > 2 at any time related to the AVM or to treatment, measured using a simplified standardized questionnaire administered by unblinded care personnel.¹¹ For patients entering the study with an enrollment mRS score > 2, the primary outcome was an increase in the mRS score of 1 or more point during follow-up.

Secondary outcomes include mortality (all cause), major and minor intracranial hemorrhage after enrollment, and major or minor nonhemorrhagic neurological events. These secondary outcomes did not include hemorrhagic or nonhemorrhagic perioperative complications of patients treated during follow-up. Major events were defined as any event requiring hospitalization for ≥ 2 days. Only one event was counted per patient. When patients had more than one event, only the most severe was retained for analyses. Other secondary outcomes include the incidence of any SAEs (life-threatening, requiring hospitalization or prolongation of hospitalization) related to the AVM, and the incidence of active AVM treatment during follow-up (along with the reason for the change in management). Treatment-related death, disability, and SAEs were recorded.

Statistical Analysis

Descriptive tables on demographic variables and potential risk factors at baseline are provided using the number of patients per group. Continuous variables are summarized in tables using means and standard deviations, while categorical variables are presented as frequencies and percentages.

For primary and secondary outcomes, incidence rates and 95% confidence intervals are provided overall and for prespecified subgroups using patient-years. Survival analysis results for prespecified subgroups and risk factors are visually presented as Kaplan-Meier curves, with log-rank tests and 95% confidence intervals determined by the Hall-Wellner method. Univariate analyses of the primary and secondary outcomes were done using Cox models and hazard ratios with 95% confidence intervals. Analyses were done with a 5% significance level using IBM SPSS version 28 (IBM Corp.) and Stata version 16 (StataCorp) software.

Trial Monitoring

Monitoring of trial data quality was web-based and performed in Montreal, Canada (for all centers except in France), and Brest, France (for French centers), by periodic database review. Blinded data were prepared for periodic safety reviews by an independent Data and Safety Monitoring Committee, composed of volunteer physicians not involved in the conduct of the trial as well as a statistician to ensure patient safety. SAEs were recorded, separate or aggregated, according to stratified criteria (ruptured or unruptured; SM grade I or II vs III–V).

Roles of the Sponsor and Funding Source

The trial was sponsored by the Centre Hospitalier de l'Université de Montréal. Neither the sponsor nor the companies granting financial support to French centers had any part in study design, data collection, analysis, or reporting,

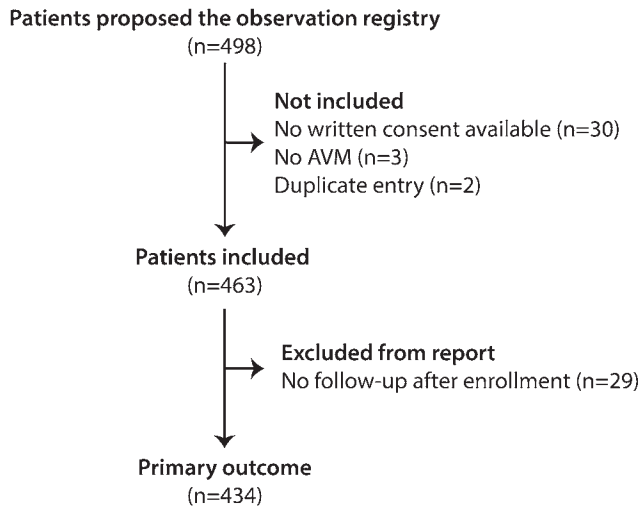


FIG. 1. Flowchart of patient inclusion.

and no access to the data or source documents. The corresponding author had full access to all the data and takes final responsibility for the decision to submit for publication.

Results

Between June 2014 and May 20, 2021, 1010 patients were recruited in TOBAS, of whom 498 (49%) were proposed participation in the observation registry (Supplemental Fig. 1). Of these, 35 patients (7%) were excluded for the following reasons: no written consent available (n = 30), no AVM found at angiography (n = 3), and duplicate entry (n = 2). Twenty-nine (6%) other patients were excluded because they had no follow-up data after the date of enrollment, leaving 434 patients (87%) for analysis. The flowchart of patients included in this report is shown in Fig. 1.

For this report, the follow-up data were locked on July 4, 2023. AVM and patient characteristics are presented in Table 1. The majority of patients had unruptured AVMs (378/434; 87%), of which 195/378 (52%) were low grade.

TABLE 1. Patient and AVM characteristics at enrollment in the TOBAS observation registry

	SM Grade I or II, n = 215		SM Grades III–V, n = 219		All Grades, n = 434		All AVMs
	Unruptured	Ruptured*	Unruptured	Ruptured*	Unruptured	Ruptured	
No. of patients	195 (91)	20 (9)	183 (84)	36 (16)	378 (87)	56 (13)	434
Mean age ± SD, yrs	49.8 ± 15.5	56.7 ± 21.8	44.6 ± 15.9	48.8 ± 17.8	47.3 ± 15.9	51.6 ± 19.5	47.8 ± 16.4
Age ≥55 yrs	80 (41)	12 (60)	56 (31)	13 (36)	136 (36)	25 (45)	161 (37)
Female sex	104 (53)	8 (40)	95 (52)	14 (39)	199 (53)	22 (39)	221 (51)
AVM location							
Supratentorial	174 (89)	15 (75)	161 (88)	32 (89)	335 (89)	47 (84)	382 (88)
Infratentorial	21 (11)	5 (25)	22 (12)	4 (11)	43 (11)	9 (16)	52 (12)
mRS score at enrollment							
0	147 (75)	10 (50)	114 (62)	10 (28)	261 (69)	20 (36)	281 (65)
1	38 (19)	4 (20)	51 (28)	13 (36)	89 (24)	17 (30)	106 (24)
2	8 (4)	2 (10)	15 (8)	3 (8)	23 (6)	5 (9)	28 (6)
3	2 (1)	2 (10)	3 (2)	7 (19)	5 (1)	9 (16)	14 (3)
4	0	1 (5)	0	2 (6)	0	3 (5)	3 (1)
5	0	1 (5)	0	1 (3)	0	2 (4)	2 (0.5)
SM grade							
I	69 (35)	6 (30)	NA	NA	69 (18)	6 (11)	75 (17)
II	126 (65)	14 (70)	NA	NA	126 (33)	14 (25)	140 (32)
III	NA	NA	97 (53)	14 (39)	97 (26)	14 (25)	111 (26)
IV	NA	NA	61 (33)	13 (36)	61 (16)	13 (23)	74 (17)
V	NA	NA	25 (14)	9 (25)	25 (7)	9 (16)	34 (8)
Eloquence	82 (42)	11 (55)	163 (89)	34 (94)	243 (64)	45 (80)	288 (66)
Deep venous drainage	25 (13)	17 (85)	134 (73)	29 (81)	145 (38)	46 (82)	191 (44)
AVM size, cm							
0–3	176 (90)	19 (95)	37 (20)	7 (19)	213 (56)	26 (46)	239 (55)
3–6	19 (10)	1 (5)	112 (61)	18 (50)	131 (35)	19 (34)	150 (35)
>6	0	0	34 (19)	11 (31)	34 (9)	11 (20)	45 (10)
History of any previous AVM Tx	9 (5)	6 (30)	19 (10)	22 (61)	28 (7)	28 (50)	56 (13)

NA = not applicable; Tx = treatment.

Values are presented as the number of patients (%) unless stated otherwise.

* Ten grade I or II and 23 grade III–V AVMs had ruptured more than 6 months prior to enrollment.

TABLE 2. Primary and secondary outcomes reached during follow-up according to AVM grade (per patient)

Outcome	SM Grade I or II, n = 215		SM Grades III–V, n = 219		All Grades, n = 434		All AVMs
	Unruptured, n = 195	Ruptured, n = 20*	Unruptured, n = 183	Ruptured, n = 36*	Unruptured, n = 378	Ruptured, n = 56	
Primary outcome: death or dependency (mRS score >2)†	4 (2)	3 (15)	10 (5)	6 (17)	14 (4)	9 (16)	23 (5)
Secondary outcomes‡							
All-cause mortality	5 (3)	5 (25)	9 (5)	5 (14)	14 (4)	10 (18)	24 (6)
All (major & minor) new ICH	8 (4)	2 (10)	18 (10)	10 (28)	26 (7)	12 (21)	38 (9)
Major new ICH	8 (4)	2 (10)	16 (9)	9 (25)	24 (6)	11 (20)	35 (8)
All (major & minor) new nonhemorrhagic neuro event	4 (2)	1 (5)	9 (5)	1 (3)	13 (3)	2 (4)	15 (3)
Major new nonhemorrhagic neuro event	2 (1)	1 (5)	4 (2)	1 (3)	6 (2)	2 (4)	8 (2)
Related SAE§	11 (6)	4 (20)	23 (13)	10 (28)	34 (9)	14 (25)	48 (11)
AVM treated during follow-up	11 (6)	2 (10)	10 (5)	3 (8)	21 (6)	5 (9)	26 (6)
Tx triggered by new major event	6 (55)	1 (50)	6 (60)	1 (33)	12 (57)	2 (40)	14 (54)

ICH = intracranial hemorrhage; neuro = neurological.

Values are presented as the number of patients (%) unless stated otherwise.

* Ten grade I or II and 23 grade III–V AVMs had ruptured more than 6 months prior to enrollment.

† If the mRS score was > 2 at enrollment, an increase of 1 point was considered.

‡ Major: requiring hospitalization for ≥ 2 days.

§ Includes the hemorrhagic and nonhemorrhagic events above.

Overall, 88% of AVMs were supratentorial, 66% were in eloquent territory, and 44% had deep venous drainage.

The numbers of patients that reached the primary and secondary outcomes, stratified according to the SM grade (I or II vs III–V) and rupture status at presentation are summarized in Table 2. Survival curves for the same groups are shown in Fig. 2 and the incidence of events per 100 patient-years are summarized in Table 3. The univariate risk factor analyses of the primary and secondary outcomes and hazard ratios are provided in Supplemental Table 1.

After a mean of 3.2 ± 1.7 years of follow-up (total 1368.4 person-years), 23 (5.3%) patients had reached the primary outcome (16 of 219 [7%] SM grade III–V AVMs and 7/215 [3%] grade I or II AVMs). The patients who reached the primary outcome are detailed in Supplemental Table 2.

The total incidence of death or new or worsened dependency was 1.7 (95% CI 1.1–2.5) per 100 patient-years. For unruptured AVMs, the incidence was 1.1 (95% CI 0.7–1.9) per 100 patient-years, and for low-grade unruptured AVMs it was 0.6 (95% CI 0.2–1.7) per 100 patient-years (Table 3). Poor outcomes were more frequent in ruptured AVMs (HR 5.6 [95% CI 2.4–13.0], $p < 0.001$), infratentorial AVMs (HR 2.9 [95% CI 1.1–7.3], $p = 0.027$), and in patients 55 years of age or older (HR 3.2 [95% CI 1.4–7.6], $p = 0.007$) (Supplemental Table 1).

Overall, 38 (9%) patients experienced a new intracranial hemorrhage, 35 (92%) of which were major, with 8 deaths and 8 patients whose mRS score became 3–5) (Table 2). Major AVM rupture occurred in 24 of 378 (6%) patients with unruptured AVMs, including 8 of 195 (4%) patients with low-grade unruptured AVMs, one of which proved fatal (0.5%). The patients who experienced a new major hemorrhage during follow-up are detailed in Supplemental Table 3.

The overall incidence of any new hemorrhage was 2.8

(95% CI 2.1–3.9) per 100 patient-years while the incidence of new major hemorrhage was 2.6 (95% CI 1.9–3.6) per 100 patient-years. In patients with unruptured AVMs the incidence of new major hemorrhage was 2.0 (95% CI 1.3–2.9) per 100 patient-years; in low-grade unruptured AVMs the incidence of new major hemorrhage was 1.3 (95% CI 0.6–2.6) per 100 patient-years (Table 3). New major hemorrhages were more frequent in AVMs that had a history of previous rupture (HR 4.4 [95% CI 2.1–8.9], $p < 0.001$), those with a large size (HR 2.6 [95% CI 1.1–6.6], $p = 0.039$), those that were high grade (HR 2.5 [95% CI 1.2–5.3], $p = 0.013$), and those that had deep venous drainage (HR 2.1 [95% CI 1.1–4.2], $p = 0.032$) (Supplemental Table 1).

The incidence of related SAEs for the entire cohort was 3.6 (95% CI 2.7–4.8) per 100 patient-years. For unruptured AVMs the incidence was 2.8 (95% CI 2.0–4.0) per 100 patient-years and for low-grade unruptured AVMs the incidence was 1.8 (95% CI 1.0–3.2) per 100 patient-years (Table 3). SAEs were more common in ruptured AVMs (HR 3.7 [95% CI 2.0–6.9], $p < 0.001$), high-grade AVMs (HR 2.3 [95% CI 1.2–4.2], $p = 0.008$), and infratentorial AVMs (HR 2.2 [95% CI 1.1–4.3], $p = 0.032$) (Supplemental Table 1).

Major nonhemorrhagic neurological events were infrequent, with an incidence of 0.6 (95% CI 0.3–1.2) per 100 patient-years for the entire cohort (Table 3). All major adverse events and all SAEs are detailed in Supplemental Table 3 and all-cause mortality is available in Supplemental Table 4.

Twenty-six of 434 patients (6%) were treated during the follow-up period; 21 of 378 (6%) were patients with unruptured AVMs, and 11 of 295 (6%) were patients with low-grade unruptured AVMs. In 14 of 26 cases (6/11 unruptured low-grade AVMs) treatment was triggered by a major neurological event. Rationale for treatment and case details are summarized in Supplemental Table 5.

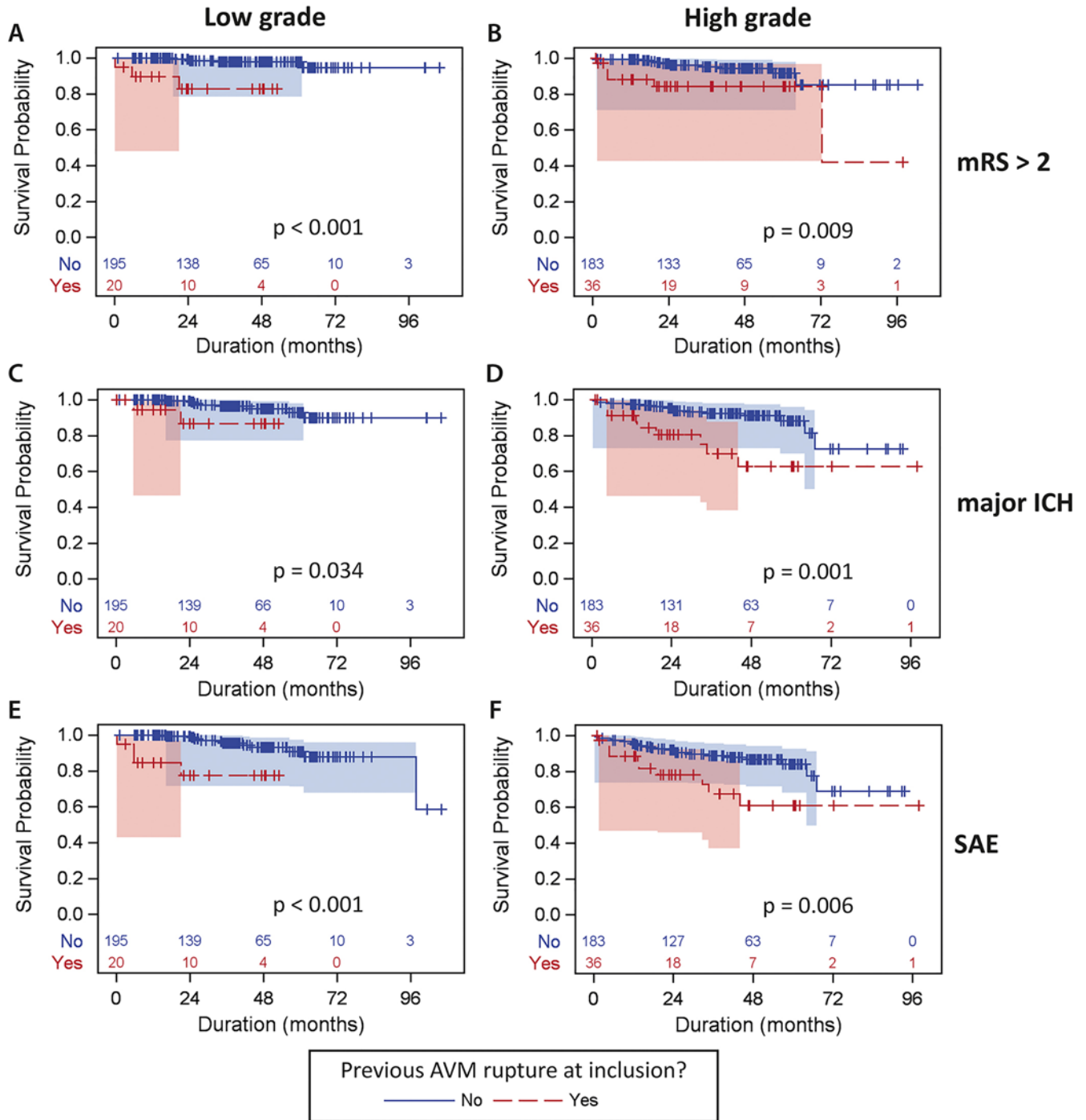


FIG. 2. Kaplan-Meier survival according to rupture status and grade. Kaplan-Meier survival curves regarding the primary outcome (mRS score > 2; **A and B**), major hemorrhages (**C and D**), and SAEs (**E and F**) of patients with low-grade (**A, C, and E**) or high-grade (**B, D, and F**) AVMs. Survival according to rupture status at presentation (yes, red; no, blue) and 95% confidence intervals according to Hall-Wellner (corresponding red or blue areas) are compared with log-rank tests. ICH = intracranial hemorrhage. Figure is available in color online only.

Discussion

In this pragmatic study, nearly half of the participants were proposed observation, as opposed to curative treatment or participation in one of the RCTs. This registry is mainly composed of patients with unruptured AVMs

(87%), with low- and high-grade AVMs in equal proportions. Over a short follow-up period of 3 years, observed patients have experienced reassuringly low risks of new or worsened disability or death (1.7% per year), mainly driven by new major intracranial hemorrhages (2.6% per

TABLE 3. Event incidence per 100 patient-years

	No. of Patients	Patient-yr Follow-Up*	Incidence per 100 Patient-yr (95% CI)				
			mRS Score >2†	All ICH	Major ICH‡	Major non-ICH Neuro Event‡	Related SAE§
Unruptured AVMs							
SM grade I or II	195	625.2	0.6 (0.2–1.7)	1.3 (0.7–2.6)	1.3 (0.6–2.6)	0.3 (0.1–1.3)	1.8 (1.0–3.2)
SM grades III–V	183	604.2	1.7 (0.9–3.1)	3.1 (1.9–4.9)	2.7 (1.7–4.4)	0.7 (0.2–1.8)	4.0 (2.6–6.0)
Total all grades unruptured	378	1229.4	1.1 (0.7–1.9)	2.2 (1.5–3.2)	2.0 (1.3–2.9)	0.5 (0.2–1.1)	2.8 (2.0–4.0)
Ruptured AVMs							
SM grade I or II	20	43.0	7.0 (2.2–21.6)	5.0 (1.3–20.1)	4.7 (1.2–18.9)	2.3 (0.3–16.5)	9.6 (3.6–25.6)
SM grades III–V	36	96.0	6.2 (2.8–13.9)	10.3 (5.5–19.1)	10.0 (5.2–19.0)	1.0 (0.1–7.2)	11.1 (5.9–20.5)
Total all grades ruptured	56	139.0	6.5 (3.4–12.4)	8.8 (5.0–15.4)	8.3 (4.6–14.9)	1.4 (0.4–5.6)	10.6 (6.3–17.9)
All AVMs (ruptured & unruptured)	434	1368.4	1.7 (1.1–2.5)	2.8 (2.1–3.9)	2.6 (1.9–3.6)	0.6 (0.3–1.2)	3.6 (2.7–4.8)

* Patient-years are presented only for the primary outcome and were censored at the time of the first event.

† If the mRS score was > 2 at enrollment, an increase of 1 point was considered.

‡ Major: requiring hospitalization for ≥ 2 days.

§ Related to AVM or AVM treatment.

year). This was particularly true for treatable low-grade unruptured AVM patients, with a yearly incidence of major hemorrhages of 1.3%, resulting in death or disability in 0.6% per year.

The inclusion of various sorts of patients in the TOBAS observation registry allows comparisons between various kinds of patients for whom observation was selected (always to be interpreted with caution), as well as comparisons with previous publications on the so-called natural history of bAVMs (which typically include periods of observation of patients who, although selected to be treated, were at risk prior to complete eradication of the AVM). In other words, we are reporting the clinical events that occurred during the follow-up of patients who clinicians did not want to treat. The main goal of this study was to verify that such clinical decisions did not result in poor outcomes that could have been prevented by active treatment.

We selected death or disability as the study primary endpoint of the TOBAS RCT comparing conservative and active treatment, as well as for this report, because we needed an outcome measure that can apply to and provide valid comparisons between all management options. It would be inappropriate, for example, to compare the risks of hemorrhage from an untreated AVM to the risks of AVM treatment; the mRS score can measure the clinical impact of all management strategies.

Previous studies on the natural history of bAVMs have mainly focused on risk factors for future hemorrhage, but some patients can experience repeat hemorrhages with little overall impact on their neurological condition. While preventing future rupture or rerupture is the most frequent reason bAVM patients are treated, other reasons (such as uncontrollable seizures, progressive neurological deficits, nonhemorrhagic strokes, or new imaging findings) can also justify the initiation of active treatment (Supplemental Table 5). We therefore included both secondary outcome measures of intracranial hemorrhage as well as nonhemorrhagic neurological events, and we also distinguished between major and minor events.

The current trial differs from previous studies on the

natural history of bAVMs.¹² The New York Islands AVM study¹³ and the Scottish Vascular Malformation study¹⁴ were populational studies, the Kaiser Permanente of Northern California AVM study¹⁵ was a review of administrative electronic case records, and the Multicenter AVM Research Study (MARS)¹⁶ collaboration used individual patient data from various sources. Other studies were retrospective reviews of prospectively maintained unregistered monocentric databases of treated and untreated patients over 10–20 years.^{17,18} None of these studies were clinical trials of individual patients prospectively recruited to be managed conservatively.

The relative risks observed in the TOBAS registry are in line with previous studies that have almost universally identified rupture status, deep venous drainage, and infratentorial location as risk factors for future hemorrhages and poor clinical outcomes.^{13,16,17,19–28} In addition, the absolute risks of major intracranial hemorrhage are very similar (2%–3% per year for unruptured and 4%–8% for ruptured bAVMs). We must emphasize that these numbers concern patients who were selected for observation; they are not necessarily applicable to patients who are offered active treatment or participation in the TOBAS RCT. This is particularly true for patients with low-grade unruptured AVMs, which have been the object of controversy since the publication of ARUBA.³ In TOBAS, 43% of patients with low-grade AVMs were offered some form of curative treatment and 15% participation in RCT-1, leaving only 42% to be included in the current study⁷ (Supplemental Fig. 1).

Comparisons between various patients managed the same way, as done here, are informative, but they are not able to guide clinical decisions; evidence-based decisions require valid comparisons of the outcomes of the same patients managed in different, competing ways (in other words, a randomized trial).²⁹ Nonetheless, the TOBAS observational study does serve other important purposes.

The TOBAS registries allow for the identification of patients managed outside of RCTs; this can eventually help assess the generalizability of the RCT results, which has

been a common concern with previous trials in the neurovascular field.³⁰ More importantly, the observation registry can also serve to verify that untreated patients (by clinicians' decisions) do not experience an inordinately high rate of neurological events. Monitoring of these events by the Data and Safety Monitoring Committee could provide a reason to alert TOBAS centers that some of these patients may be better managed within the context of the RCTs. The current study shows that, at least until now, patients who have been selected for observation have not experienced an unacceptable rate of AVM-related SAEs. For patients with high-grade AVMs, the question is almost theoretical, because the currently available treatments are frequently either ineffective or carry prohibitive risk. For patients with low-grade unruptured AVMs, the question is of importance, for surgical treatment (as opposed to curative embolization) has been shown in TOBAS centers to be effective and relatively safe.^{5,6} Yet, in the absence of randomized evidence of therapeutic benefits, the burden of proof remains on treatment.³¹ Thus, we believe that treatment should be offered for low-grade unruptured AVMs in some cases, but within the context of TOBAS RCT-1.

The limitations of this study include the relatively small number of patients ($n = 434$) prospectively followed for a short follow-up period (mean 38 months). Given the primary safety objective of the study, we could not wait too long to verify whether observed patients had an unacceptable rate of adverse events. The protocol provisions a 10-year follow-up period, which should allow more conclusive evidence. All patients were selected for observation. Patients considered for treatments or for RCT participation were excluded. Therefore, these results are not representative of a natural history of all bAVMs. In particular, these results do not readily apply to patients for whom best management remains uncertain, who should rather be enrolled, in our opinion, in TOBAS RCT-1. The decision to observe patients was made by a multidisciplinary team on a case-by-case basis, limiting the generalization of results to future patients. The collection of patients remains heterogeneous, with a mixture of low-grade unruptured and high-grade ruptured AVMs with different rates of rupture, necessitating stratified analyses that further decreased the number of patients in each subgroup. Angiographic data were not reviewed. Thus, angioarchitectural features (such as arterial or nidal aneurysms or venous stenoses) that could be risk factors for hemorrhage were not studied. Finally, clinical outcomes were not assessed by blinded observers.

Conclusions

Patients with bAVMs observed over a mean of 3.2 years had a relatively low rate of untoward neurological events. This was particularly true for patients with low-grade unruptured AVMs.

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Author Contributions

Conception and design: Darsaut, Gentric, Jabre, Roy, Weill, Chaalala, Beaujeux, Magro, Raymond. Acquisition of data: Darsaut, Gentric, Lopez, Iancu, Roy, Weill, Bojanowski, Chaalala, Comby, Roberge, Cognard, Januel, Sabatier, Desal, Roualdes, Ferre, Alias, Papagiannaki, Smajda, Aldea, Gaberel, Barbier, Barreau, Marnat, Jecko, Anxionnat, Merlot, Nguyen, Abdalkader, Riva, Graillon, Troude, Kerleroux, Ollivier, Beaujeux, Boulouis, Planty-Bonjour, Spelle, Chalumeau, Naggara, Lefevre, Le Corre, Shotar, Carlson, Biondi, Thines, Tawk, Chabert, Klink, Magro, Raymond. Analysis and interpretation of data: Darsaut, Gentric, Heppner, Weill, Chaalala, Roberge, Riva, Thines, Fahed, Klink, Magro, Raymond. Drafting the article: Darsaut, Gentric, Heppner, Smajda, Planty-Bonjour, Thines, Tawk, Huynh, Fahed, Raymond. Critically revising the article: Darsaut, Gentric, Heppner, Jabre, Iancu, Roy, Weill, Bojanowski, Chaalala, Roberge, Cognard, Januel, Desal, Roualdes, Papagiannaki, Derrey, Smajda, Marnat, Jecko, Dumot, Riva, Graillon, Troude, Boulouis, Spelle, Naggara, Shotar, Biondi, Thines, Huynh, Fahed, Magro, Raymond. Reviewed submitted version of manuscript: Darsaut, Heppner, Jabre, Iancu, Roy, Weill, Bojanowski, Chaalala, Roberge, Cognard, Cognard, Ferre, Papagiannaki, Smajda, Gaberel, Barbier, Marnat, Anxionnat, Nguyen, Abdalkader, Kerleroux, Ollivier, Beaujeux, Boulouis, Spelle, Naggara, Lefevre, Shotar, Carlson, Biondi, Tawk, Huynh, Fahed, Findlay, Chabert, Zehr, Gevry, Klink, Magro, Raymond. Approved the final version of the manuscript on behalf of all authors: Darsaut. Statistical analysis: Zehr. Administrative/technical/material support: Gentric, Jabre, Barbier, Findlay, Gevry. Study supervision: Darsaut, Gentric, Jabre, Gevry, Klink, Magro, Raymond. Study coordinator: Viard.

Supplemental Information

Online-Only Content

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

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