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Original research

# Endovascular treatment of unruptured intracranial aneurysms: Rate of thromboembolic events depicted by diffusion-weighted imaging in relation to different techniques

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## ABSTRACT

**Background** The rate of thromboembolic events (TEEs) associated with endovascular treatment (EVT) of intracranial aneurysms is not reported uniformly in the literature due to the various ways that are used to evaluate them. Analysis of Thromboembolic Complications after Endovascular Treatment of Unruptured Intracranial Aneurysms study (ACET) is a prospective, multicenter study, which analyzes the rate of TEEs using diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) in patients treated for unruptured aneurysms with different endovascular techniques.

**Methods** Patients were prospectively included in six French centers. Postoperative DWI-MRI was performed within 72 hours post-procedure and independently evaluated. Univariate and multivariate analyses were conducted to determine factors associated with the occurrence of DWI lesions.

**Results** Of the 233 included patients (54.5±11.2 years, 162 women, (69.5%)), 226 were effectively treated by EVT (coiling: 90 patients, 39.8%; balloon-assisted coiling (BAC): 62, 27.4%; stent-assisted coiling (SAC): 10, 4.4%; flow diversion (FD): 21, 9.3%; intrasaccular flow disruption (ISFD): 43, 19.0%) and had a postoperative MRI showing DWI lesions in 133 patients (58.8%). Univariate and multivariate analyses show the rate of patients with DWI lesions to be significantly higher with BAC (75.8%,  $P=0.001$ ), SAC (90.0%,  $P=0.02$ ), and FD (95.2%,  $P=0.001$ ) compared with coiling alone (41.1%).

**Conclusions** The rate of DWI lesions after EVT of unruptured aneurysms is primarily influenced by the EVT technique used. Techniques using transient (BAC) or permanent (SAC and FD) device placement in the parent artery are associated with a higher rate of DWI lesions.

**Trials registration number** ACET: Unique identifier: [NCT02862756](https://clinicaltrials.gov/ct2/show/study/NCT02862756).

## INTRODUCTION

The main complication associated with endovascular treatment (EVT) of intracranial aneurysms (IA) is thromboembolic events (TEE), which were reported to occur after coiling in 10.4% of patients in the Analysis of Recanalization after Endovascular Treatment (ARETA) study.<sup>1</sup> Typically, this

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) has been used for several years to evaluate thromboembolic complications occurring during coiling and more general endovascular treatment (EVT) of intracranial aneurysms. A detailed analysis of factors affecting the occurrence of DWI lesions has not been performed in a prospective, multicenter patient series.

## WHAT THIS STUDY ADDS

⇒ The Analysis of Thromboembolic Complications after Endovascular Treatment of Unruptured Intracranial Aneurysms (ACET) study shows that the primary factor affecting the occurrence of DWI lesions is the EVT used. A higher rate of DWI lesions is observed when a device is transiently (balloon) or permanently (stent, flow diverter) placed in the parent artery.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that the transient or permanent placement of a device in the parent artery in front of the neck during the treatment of intracranial aneurysms is associated with a higher risk of thromboembolic events.

complication occurs during the procedure, but it can be delayed in rare instances.<sup>2</sup> TEEs are not uniformly reported from one series to another, making comparison of different series or different techniques challenging. Some series exclusively report symptomatic events, while others report all TEEs including those that were successfully treated during aneurysm treatment and those that were not associated with symptoms.

After a first article outlining the value of the MRI sequence diffusion-weighted imaging (DWI) to depict TEEs after aneurysm coiling, a large series of 382 patients reported an incidence of DWI lesions of 54.5%.<sup>3,4</sup> In this study, the number of DWI lesions was significantly higher in the patient group with symptomatic ischemic complications.



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Due to the technical difficulties encountered when treating some aneurysms (eg, large, giant, or wide-necked) with coiling, alternative EVT techniques have been progressively developed including balloon-assisted coiling (BAC), stent-assisted coiling (SAC), flow diversion (FD), and intrasaccular flow disruption (ISFD).<sup>5</sup> A limited number of studies have used DWI to compare the rate of TEEs occurring with these different EVT techniques. Takigawa *et al.*, demonstrated a higher rate of hyperintense lesions on DWI after SAC (58%) and double BAC (58%) compared with single BAC (25%).<sup>6</sup> In a series dedicated to FD, the percentage of patients with at least one new hyperintense DWI lesion was 92.1%.<sup>7</sup> In a meta-analysis, Bond *et al.*, reported a higher incidence of DWI lesions after FD (67%) compared with coiling alone (45%), BAC (44%), and SAC (43%).<sup>8</sup> In an updated meta-analysis, Habtezghi *et al.*, also showed a higher incidence of DWI ischemic lesions after FD (62.4%) than after coiling (47.1%), BAC (37.0%), and SAC (47.5%).<sup>9</sup>

The Analysis of Thromboembolic Complications after Endovascular Treatment of Unruptured Intracranial Aneurysms study (ACET) is a prospective, multicenter, French study, which analyzes the rate of TEEs depicted by DWI-MRI imaging in patients with unruptured aneurysms treated with various EVT techniques.

## MATERIALS AND METHODS

### The ACET study

ACET was designed to analyze TEEs detected by DWI-MRI occurring during EVT of unruptured IAs and to evaluate factors affecting their frequency. The study was sponsored and completely funded by the French Ministry of Health in a Programme Hospitalier de Recherche Clinique (PHRC) no. 2015-A02018-41, and registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT02862756). ACET received national regulatory authorization approval from the Est III Ethic Committee (no. 16.02.04). The full study protocol and data generated or analyzed during the study are available from the corresponding author on request.

The following inclusion criteria were used: age  $\geq 18$  years and treatment by EVT technique of one unruptured aneurysm during the index procedure. Exclusion criteria were patients with ruptured aneurysms, a contraindication for MRI, clinical status incompatible with MRI, aneurysms associated with a brain arteriovenous malformation (AVM), previously treated aneurysm (regardless of technique used), and patients protected by the law, namely those lacking independent decision-making capacity due to psychiatric or somatic reasons. Treatment of several aneurysms within the same procedure was not authorized.

The sample size was calculated to evaluate precision of the prevalence on diffusion MRI of thromboembolic complication following EVT for an intracranial aneurysm. Assuming a prevalence of 30%, a sample size of 250 patients was required to estimate frequency of this complication with 6% accuracy. This precision was calculated using the formula for the 95% CI.

Patients were prospectively enrolled by convenience sampling in six French centers between November 2016 and January 2020. The following baseline patient characteristics were reported by participating study sites: age, sex, current cigarette use, and elevated blood pressure (defined as blood pressure  $> 140/90$  mmHg uncorrected by medical treatment). Preoperative clinical status was evaluated 72 hours before a procedure using the modified Rankin Scale (mRS).

Recorded aneurysm characteristics were aneurysm sac diameter (dichotomized into  $< 7$  mm and  $\geq 7$  mm); neck size (wide-necked being defined as  $\geq 4$  mm); and aneurysm location (internal carotid artery (ICA) including the posterior communicating artery, middle

cerebral artery (MCA), anterior communicating/anterior cerebral artery (ACA/Acom), or vertebrobasilar (VB)). Aneurysm location was dichotomized into anterior and posterior circulation.

Treatment modalities were at the discretion of the treating interventional neuroradiologist and categorized into coiling only, BAC, SAC, FD, and ISFD. All stents and flow diverters used in this study were bare devices. There was no standardized antiplatelet and anticoagulation regimen. For anticoagulant treatment, the therapeutic target was aPTT 2–3 x baseline. Data on preoperative, intraoperative, and postoperative antiplatelet treatment (APT) were also collected. No biological test of the antiplatelet efficacy before the procedure was required in the protocol. Information as to whether or not antiplatelet testing was performed was not collected.

TEEs were recorded according to their time of occurrence, during, and post-procedure (before the postoperative MRI). TEEs were diagnosed intraoperatively by angiography regardless of type (clotting near the aneurysm neck in distal branches or parent vessel occlusion). Postoperative TEEs (before postoperative MRI) were completed in cases of neurological deterioration. Clinical outcome was evaluated by mRS at the time of postoperative MRI, at hospital discharge, and 1 month. Poor clinical outcome was defined by a mRS 3–6. TEEs management modalities were collected.

DWI-MRI was used to precisely analyze TEEs. Two MRI examinations were performed with a 3T system: one in the 72 hours pre-procedure and one in the 72 hours post-procedure. Two MRI sequences were mandatory: DWI and fluid-attenuated inversion recovery (FLAIR). DWI comprised a multisection, single-shot, spin-echo echo-planar imaging sequence. Diffusion gradients were applied in each of the x, y, and z directions with 2b values (0 and 1000 SE/mm<sup>2</sup>). Imaging parameters included a field of view of 23 cm, 112/89 matrix, TE of 55 msec, section thickness of 4 mm, and an intersection gap of 0.

The following patients within the overall ACET cohort were excluded from our analysis: Patients with a previously treated aneurysm that was treated again, patients who had no procedure, or who withdrew their consent.

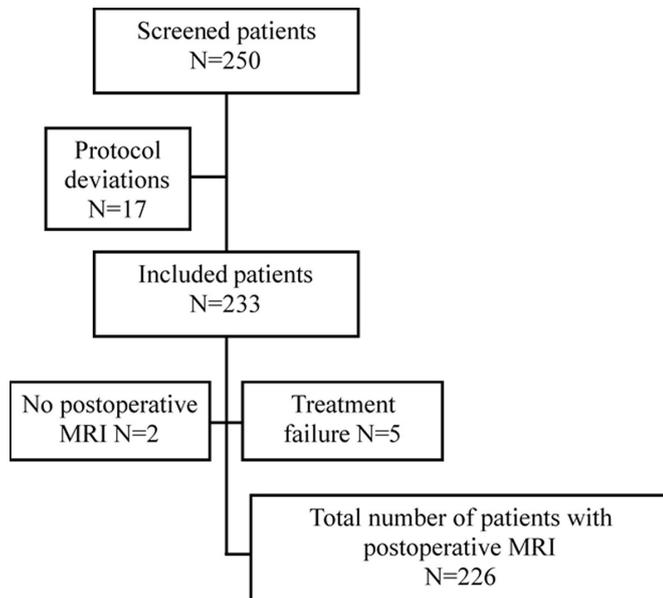
### Data management

Patient, aneurysm, and procedure data were collected in an electronic case report form.

The centers also collected preoperative digital subtraction angiography (DSA), immediate postoperative DSA, and postoperative MRI, and transferred results in an anonymized form to Reims University Hospital. Aneurysm characteristics, treatment modalities, and all patient complications were reviewed, checked for accuracy and, if necessary, revised by a core lab of two independent neuroradiologists (with 10 year's experience in neuroradiology).

Postoperative MRIs were independently evaluated by the core lab. Two members of the core lab independently evaluated MRIs and, in case of discrepancy, obtained a consensus. The core lab evaluated location in seven groups: right and left MCA, right and left ACA, and right and left PCA territories for the supratentorial lesions, and posterior fossa for the infratentorial lesions. MRIs were categorized in two groups according to the absence or presence of DWI abnormalities in postoperative MRI. Another analysis was conducted using the 4-grade scale proposed by Kang *et al*: grade 0: no DWI lesion; grade 1:  $< 6$  lesions; grade 2:  $\geq 6$  lesions; grade 3: territorial infarct by cumulating grades 0 and 1 and grades 2 and 3.<sup>4</sup>

The territories to evaluate DWI lesions were selected according to the treated aneurysm location. For MCA aneurysms, the ipsilateral MCA territory was observed; for Acom aneurysms, both ACA territories; for ICA aneurysms, ipsilateral MCA and ACA



**Figure 1** Flow chart of the study population.

territories; and for posterior circulation aneurysms, posterior fossa and both PCA territories.

### Statistical analysis

Statistical analysis was conducted by the Department of Research and Public Health of Reims Hospital. Descriptive statistics were used: data are presented with mean  $\pm$  standard deviation (SD) for quantitative variables and number and percentage for qualitative variables. Factors associated with TEE were compared using a Student's *t*-test, Chi-squared test, or Fisher's exact test, as appropriate.

Associations between potential prognostic factors and the outcome of interest were explored first using univariate analysis where a *P* value  $<0.20$  was used to define statistical significance. Multivariate analysis employed logistic regression using stepwise procedure with an entry criterion of 0.20 and a stay criterion of 0.10. Statistical significance was declared if the two-sided *P* value was  $<0.05$ . All statistical analyses were performed using the SPSS System.

## RESULTS

### Study population, patient, and aneurysm characteristics

After applying inclusion criteria to the overall cohort of 250 patients, the study population for this analysis consisted of 233 patients ( $54.5 \pm 11.2$  years, 162 women, (69.5%)) (figure 1).

Sixty-two (26.6%) patients had multiple aneurysms (2 in 44 patients, 3 in 12, 4 in 3, 5 in 2, and 6 in 1). In all patients, only one aneurysm was treated during the index procedure.

Table 1 describes additional patient and aneurysm characteristics.

### Treatment failure, preoperative MRI, postoperative MRI, and treatment modalities

All patients had a normal preoperative MRI while two patients (0.9%) had no postoperative MRI. The mean delay between the procedure and the postoperative MRI was  $28 \pm 7$  hours.

Treatment failed in 5 of 233 patients (2.1%). The causes of failure were dissection of a vertebral artery (two patients, one died); lack of reliable working projection (one patient);

**Table 1** Patient and aneurysm characteristics

Patient characteristics	N=233
Sex	
Women – n (%)	162 (69.5)
Men – n (%)	71 (30.5)
Age (years) – Mean $\pm$ SD	
Overall	54.5 $\pm$ 11.2
Women	54.6 $\pm$ 10.6
Men	54.3 $\pm$ 12.5
Elevated blood pressure* – n (%)	100 (42.9)
Current smoking – n (%)	171 (73.4)
Preoperative mRS	
0	200 (85.8%)
1	31 (13.3%)
2	2 (0.9%)
Patient characteristics	
Aneurysm size† (mm)	
Mean $\pm$ SD	7.1 $\pm$ 4.1
<7 mm – n (%)	133 (57.1)
$\geq$ 7 mm – n (%)	100 (42.9)
Neck size	
<4 mm – n (%)	173 (74.6)
$\geq$ 4 mm – n (%)	59 (25.4)
Aneurysm location	
Anterior	220 (94.4)
ACA/Acom – n (%)	76 (32.6)
MCA – n (%)	60 (25.8)
ICA – n (%)	84 (36.1)
Posterior (VB) – n (%)	13 (5.6)

\*Defined as blood pressure  $>140/90$  mmHg uncorrected by medical treatment.  
 †Maximum diameter.  
 ACA, anterior cerebral/communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; SD, standard deviation; VB, vertebrobasilar.

catheterization failure (one patient), and lack of adequate device for aneurysm treatment (one patient).

Of 226 patients who were effectively treated by EVT, treatment modality was coiling alone in 90 (39.8%), BAC in 62 (27.4%), SAC in 10 (4.4%), FD in 21 (9.3%), and ISFD in 43 (19.0%). EVT modalities differed according to aneurysm location (online supplemental table 1).

Preoperative APT treatment was no APT medication in 130 out of 226 (57.5%) patients, one APT medication in 38 (16.8%), and two APT medications in 58 out of 226 (25.7%) patients. The percentage of patients receiving 0, one, or two APT medications differed according to EVT technique (table 2). In patients treated with FDs and receiving preoperatively only one APT medication, IV aspirin was administered during the procedure.

All but one patient (225 out of 226; 99.6%) received intraoperative heparin (mean dose:  $5327 \text{ UI} \pm 218 \text{ UI}$ ). Intraoperative APT (IV aspirin) was given during the procedure in 109 out of 226 patients (48.2%) with some variation based on the EVT techniques: coiling alone in 33 out of 90 (36.7%), BAC in 50 out of 62 (80.6%); SAC in 4 out of 10 (40.0%), FD in 8 out of 21 (38.1%), and ISFD in 14 out of 43 (32.6%) patients.

**Table 2** Preoperative and postoperative antiplatelet treatment by endovascular technique

APT* medications (number)	Coiling (n=90) n (%)	BAC (n=62) n (%)	SAC (n=10) n (%)	FD (n=21) n (%)	ISFD (n=43) n (%)	Total (n=226) n (%)
Preoperative treatment						
0	71 (78.9)	49 (79.0)	0 (0.0)	1 (4.8)	9 (20.9)	130 (57.5)
1†	15 (16.7)	7 (11.3)	5 (50.0)	5 (23.8)	6 (14.0)	38 (16.8)
2‡	4 (4.4%)	6 (9.7)	5 (50.0)	15 (71.4)	28 (65.1)	58 (25.7)
Postoperative treatment						
0	62 (68.9%)	9 (14.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	71 (31.4%)
1§	28 (31.1%)	39 (62.9%)	0 (0.0%)	0 (0.0%)	30 (69.8%)	97 (42.9%)
2¶	0 (0.0%)	14 (22.6%)	10 (100.0%)	21 (100.0%)	13 (30.2%)	58 (25.7%)

\* Antiplatelet treatment.  
† Preoperative Single Antiplatelet Treatment was: in coiling: Aspirin in 10 patients, clopidogrel in 3 patients, and ticagrelor in 2 patients; in BAC: clopidogrel in 1 patient and ticagrelor in 6 patients; SAC: ticagrelor in 5 patients; FD: Ticagrelor in 5 patients; ISFD: Aspirin in 4 patients and Ticagrelor in 2 patients.  
‡ Preoperative DAPT was: in coiling: aspirin+clopidogrel in 1 patient, aspirin+ticagrelor in 3 patients; in BAC, aspirin+ticagrelor in 6 patients; in SAC, aspirin+clopidogrel in 1 patient and aspirin+ticagrelor in 4 patients; in FD, aspirin+ticagrelor in 15 patients; in ISFD: aspirin+ticagrelor in 28 patients. Doses were 75 mg/day for aspirin, 75 mg/day for clopidogrel, and 90mg x2/day for ticagrelor.  
§ Postoperative Single Antiplatelet Treatment was aspirin in 28 patients treated by coiling and 39 patients treated with BAC.  
¶ Dual Antiplatelet Treatment was aspirin and ticagrelor in all patients treated by SAC and FD, but one treated with aspirin and clopidogrel. Doses are similar to those reported in ‡.  
BAC, balloon-assisted coiling; FD, flow diversion; ISFD, intrasaccular flow disruption; SAC, stent-assisted coiling.

Postoperatively heparin was discontinued in all patients 8 to 24 hours after the procedure. Postoperative APT is shown in [table 2](#).

### Rate, management, and clinical outcome of thromboembolic events

Intraoperative TEEs were reported in 31 out of 226 patients (13.7%). The rate did not differ significantly ( $P=0.269$ ) depending on EVT technique: coiling alone in 15 out of 90 (16.7%) patients, BAC in 10 out of 62 (16.1%), SAC in 2 out of 10 (20.0%), FD in 2 out of 21 (9.5%), and ISFD in 2 out of 43 (4.7%). Treatment was medical in 25 out of 31 patients (80.6%) and endovascular in 19 out of 31 (61.3%) patients; some patients received both. Intraoperative TEEs had no clinical consequence (mRS 0 at the time of postoperative MRI) in 28 out of 31 patients (90.3%), was associated with transient neurological worsening (mRS 1 at the time of postoperative MRI) in one patient (3.2%), and permanent neurological worsening (mRS 4 and 5 at the time of postoperative MRI) in two patients (6.5%). In the patient group having intraoperative TEEs, 9 out of 31 patients (29.0%) had no abnormalities on DWI-MRI and 22 patients (71.0%) had DWI abnormalities including two (6.5%) with a territorial infarct.

Postoperative TEEs occurring were reported in 7 out of 226 patients (3.1%) before postoperative MRI, and 4 out of 226 (1.8%) after postoperative (before 1 month). Clinical outcome was good (mRS 0–2) in 6 out of 7 patients with TEEs occurring before postoperative MRI and in all patients with TEEs occurring after postoperative MRI. One patient with TEE occurring before postoperative MRI was mRS 4 at the time of MRI.

### Rate and factors associated with DWI-MRI lesions

The global rate of patients with DWI lesions after aneurysm EVT was 133 out of 226 (58.8%). In the univariate analysis ([table 3](#)), two aneurysm factors were associated with a higher rate of DWI+ patients: aneurysm size  $\geq 7$  mm (68.0% vs 51.9% for aneurysm  $< 7$  mm;  $P=0.02$ ) and neck size  $\geq 4$  mm (71.9% vs 54.4% for neck  $< 4$  mm;  $P=0.03$ ). Compared with coiling alone (41.1%), the rate of patients with DWI lesions was higher

with all other EVT techniques, and significantly higher with BAC 75.8% ( $P=0.001$ ), SAC 90.0% ( $P=0.02$ ), and FD 95.2% ( $P=0.001$ ). The rate was not significantly higher with ISFD (58.8%;  $P=0.56$ ).

In the multivariate analysis ([table 4](#)), aneurysm factors (aneurysm and neck sizes) were no longer significant. Three EVT techniques were associated with a significantly higher rate of DWI lesions compared with coiling: BAC (odds ratio (OR)=4.6 (2.1–9.8),  $P=0.001$ ), SAC (OR=10.8 (1.2–94.9),  $P=0.03$ ), and FD (OR=29.6 (3.6–244.0),  $P=0.001$ ).

Another analysis was conducted using the Kang *et al.*, scale to analyze the DWI lesions burden according to the EVT technique used (online supplemental table 2). The rate of grade 2 and 3 was higher in patients treated with BAC (43.5%), SAC (50.0%) and FD (38.1%) compared with coiling (12.2%) ( $P=0.0001$ , 0.009, and 0.009, respectively). In ISFD the rate of grade 2/3 was not significantly different compared with coiling (18.6% vs 12.2%,  $P=0.427$ ).

### DISCUSSION

The ACET study shows that DWI abnormalities on MRI occur in 58.8% of patients after EVT of unruptured aneurysms. As demonstrated by univariate and multivariate analysis, the rate of patients with DWI lesions primarily depends on the EVT technique used. When an intravascular device is temporarily used

**Table 3** DWI lesions by EVT technique

	0	$\geq 1$
Coiling alone: n (%)	53 (58.9)	37 (41.1)
BAC <sup>1</sup> : n (%)	15 (24.2)	47 (75.8)
SAC <sup>1</sup> : n (%)	1 (10.0)	9 (90.0)
FD <sup>1</sup> : n (%)	1 (4.8)	20 (95.2)
ISFD <sup>1</sup> : n (%)	23 (53.5)	20 (46.5)
Total	93 (41.2)	133 (58.8)

BAC, balloon-assisted coiling; FD, flow diverter; ISFD, intrasaccular flow diverter; SAC, stent-assisted coiling.

**Table 4** Factors associated with occurrence of thromboembolic events

Patient and aneurysm characteristics	DWI-MRI lesions (one or more)	Univariate analysis (p value)	Multivariate analysis*	
			OR(95% CI)	P value
<b>Age</b>				
<60	88/146 (60.3%)	0.574		
≥60	45/80 (56.3%)			
<b>Sex</b>				
Women	35/69 (50.7%)	0.108		–
Men	98/157 (62.4%)			
<b>Elevated blood pressure†</b>				
Yes	56/99 (56.6%)	0.587	–	–
No	77/127 (60.6%)			
<b>Current smoking</b>				
Yes	95/166 (57.2%)	0.447	–	–
No	38/60 (63.3%)			
<b>Aneurysm location</b>				
Anterior	128/215 (59.5%)	0.366		
Posterior	5/11 (45.5%)			
<b>Aneurysm size‡</b>				
<7 mm	67/129 (51.9%)	0.020		
≥7 mm	66/97 (68.0%)			
<b>Neck size</b>				
<4 mm	92/169 (54.4%)	0.029	–	–
≥4 mm	41/57 (71.9%)			
<b>EVT technique</b>				
Coiling	37/90 (41.4%)			
BAC	47/62 (75.8%)	0.001	4.6 (2.1 to 9.8)	0.001
SAC	9/10 (90.0%)	0.02	10.8 (1.2 to 94.9)	0.03
FD	20/21 (95.2%)	0.001	29.6 (3.6 to 244.0)	0.001
ISFD	20/43 (58.8%)	0.56	0.903 (0.4 to 2.0)	0.81

\*Factors included in the multivariable analysis: sex, aneurysm size (< 7 mm; ≥ 7 mm), neck size (< 4 mm; ≥ 4 mm), and EVT technique.  
†Defined as blood pressure >140/90 mmHg uncorrected by medical treatment.  
‡Maximum diameter.  
BAC, balloon-assisted coiling; FD, flow diversion; ISFD, intrasaccular flow disruption; SAC, stent-assisted coiling.

for coil placement (balloon) or permanently implanted (stent or flow diverter), the rate of DWI abnormalities (75.8%, 90.0%, and 95.2%, respectively) is higher compared with techniques involving device placement in the aneurysm sac (coils or intrasaccular devices like WEB: 41.1% and 46.5%, respectively). Patient and aneurysm factors have little or no impact on DWI lesion occurrence.

TEE is the most frequent intraoperative complication with intracranial aneurysm EVT. In ARETA, this complication was reported to occur in 10.4% of participants.<sup>1</sup> Delayed TEEs occurring after endovascular procedures also occur in a relatively low percentage of patients with aneurysms treated by EVT (2.4%).<sup>2</sup> Evaluation of TEE is quite diverse from one series to another. Some series report all TEEs occurring during the EVT, even when they are completely treated during the procedure by medications or EVT, or when they are completely asymptomatic. Other series focus on TEEs associated with clinical worsening. For several years, DWI-MRI has been recommended to

precisely evaluate TEEs occurring during EVT of intracranial aneurysms. By using such imaging, the proportion of patients with DWI lesions will be higher than the proportion of patients with TEEs. As shown in our series, the percentage of patients who experienced TEE during the procedure or after, but before the postoperative MRI, was 16.5%, while the rate of patients with DWI lesions was 58.8%. This data suggests that what DWI-MRI detects is not only related to TEE occurring during or after the procedure, but also the occurrence of very small clots or even air bubbles that were invisible during treatment and which could occur at all treatment steps (catheterization in the aortic arch in case of atheroma at this level; long introducer sheath and the intermediate catheter placement in the parent artery; microcatheter placement in the aneurysm sac or the parent artery; or treating device placement).

The relationship between DWI lesions and clinical symptoms was not direct. Looking at patients who underwent an intraoperative TEE, some had no DWI lesions (29.0%), while 71.0% had DWI lesions including territorial infarct in 6.5% of cases. As clots occurring during aneurysm treatment can be rapidly (spontaneously or by EVT techniques) dissolved, it is not surprising that some TEEs were associated with normal DWI. On the other hand, it is clear that most patients having DWI lesions have no symptoms. Several factors probably play a role in the clinical expression of DWI lesions including their size, number, and location. In an analysis of DWI lesions after aneurysm coiling, Kang *et al.*, suggested that the number of DWI lesions was higher in patients with symptomatic ischemic complications.<sup>4</sup> A very precise clinical evaluation including sequential National Institutes of Health Stroke Scale (NIHSS) and cognitive evaluation is certainly helpful to better understand the clinical consequences of the DWI lesions occurring after EVT.

The global percentage of patients with DWI abnormalities was 58.8% and slightly higher than what was reported by Bond *et al.* in their meta-analysis.<sup>8</sup> Indeed, Bond *et al.*, reported that in 2148 patients with 2268 aneurysms treated by various EVTs, the overall incidence of DWI+ was 49%.<sup>8</sup> This result can be explained by two points: (1) Articles included in the meta-analysis were published between 2000 and 2016, meaning that at least some of the MRI machines and sequences used in the different series were likely less efficient, while in ACET, all patients were examined with a more advanced 3T MRI scanner; (2) Most series included in the Bond *et al.*, meta-analysis were self-analyzed in contrast to ACET, where a core lab of two neuroradiologists analyzed all postoperative MRIs.

In ACET, the rate of patients with DWI ischemic lesions differed by EVT technique. As in our series, the highest rate in the Bond *et al.*, meta-analysis was observed after FD (62.4% compared with 95.2% in our series), followed by complex procedures (a category which does not exist in our series), SAC (47.5% compared with 90% in our series), and simple coiling (47.3% compared with 41.1% in our series). Results regarding intrasaccular devices (such as WEB) are not reported in the meta-analysis. Surprisingly, results are very different with BAC given that the rate of DWI lesions was 37.5% in the meta-analysis and 75.8% in our series. Interestingly when analyzing the DWI lesions burden in the different EVT techniques using the Kang scale, we observe that it is higher in BAC (43.5%), SAC (50.0%), and FD (38.1%), compared with coiling (12.2%), whereas ISFD is not significantly different (18.6%).

Unsurprisingly, permanent device placement (stent or flow diverter) in the parent artery in front of the aneurysm neck created flow disturbances in the parent artery and blood stagnation in the stent mesh, which likely explains the higher rate

of patients with DWI lesions. Similar results were reported in the series of Kang *et al.*, which showed a higher risk of six or more DWI lesions in patients treated with a stent (44.2% vs 28.2% in patients treated without stent,  $P=0.007$ ).<sup>4</sup> The risk of symptomatic ischemic complication was also higher (but not significantly) with stent use (6.5% vs 3.0 in the absence of stent use,  $P=0.139$ ). Similarly, in the large meta-analysis conducted by Zhang *et al.*, for ruptured aneurysms, the rate of ischemic complications was higher with stent use (12.3% vs 8.4% in the absence of stent).<sup>10</sup> In the Bond *et al.*, meta-analysis, the rate of DWI lesions was only higher in patients treated with FD (67% vs 44% in patients treated with coiling and 43% in patients treated with stent,  $P=0.07$ ).

The most unexpected result of our study is the high rate of DWI lesions in patients treated with BAC (75.8%). In analyses comparing patients treated with coiling and BAC, the rate of TEEs was similar in both groups in ruptured (12.7% and 11.3%, respectively) and unruptured aneurysms (6.2% and 5.4%, respectively).<sup>11,12</sup> Looking at TEEs that occurred during the procedure in the ACET study, the percentage was very similar after coiling (16.7%) and BAC (16.1%). This result reaffirms the fact that DWI lesions were not directly connected to TEE and likely the consequence of micro emboli (clot or microbubble) in distal vessels.

Our study has several limitations when interpreting the data. First, the number of patients in some EVT subgroups (eg, SAC) was small. Second, patients with multiple aneurysms that were treated in the same session were excluded in order to conduct an analysis on both patient and aneurysm factors. Third, consecutive inclusion of patients did not occur at the participating centers, which may limit generalizability. Fourth, due to the low number of patients with a posterior circulation aneurysm, it is difficult to generalize the results of ACET to this aneurysmal location. Fifth, as APT regimens differed by technique, it is difficult to evaluate their influence on the rate of DWI lesions; in future studies, APT will be standardized or collected with great detail and APT testing systematically performed. Sixth, the results are not presenting the total number of lesions per patient and per technique. Seventh, the core lab was not completely blinded regarding the EVT technique used that can be identified on MRI.

## CONCLUSION

In conclusion, the rate of DWI lesions after intracranial aneurysm EVT is primarily influenced by the EVT technique used and not by patient or aneurysm factors. Techniques that use transient (BAC) or permanent (SAC and FD) device placement in the parent artery in front of the aneurysm neck are associated with a higher rate of DWI lesions (BAC: 75.8%; SAC: 90.0%; and FD: 95.2%). Techniques with exclusive device placement in the aneurysm sac (coiling and ISFD) are associated with a lower rate of DWI lesions (41.1% and 46.5%, respectively). These findings suggest that DWI lesions are probably multifactorial and not exclusively related to TEEs and are also linked to microthrombi that can occur at the surface of intra-arterial devices (balloons, stents, and flow diverters) or microbubbles. Moreover the link between TEE and DWI lesions is not straightforward given that 29.0% of patients with intraoperative TEEs have no DWI lesions, and most patients with DWI lesions have no symptoms.

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