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Original Article

Clinical and Angiographic Outcome Predictors of Cerebral Aneurysms Treated with Endovascular Coil Embolization

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BACKGROUND: Endovascular coiling of cerebral aneurysms (CA) has been showing exponential growth over the last decades. Currently, aneurysmal coiling, either assisted or alone, constitutes the vast majority of all endovascular treatment (EVT) modalities for CA treatment.

OBJECTIVE: The authors aimed to assess the clinical and angiographic outcomes and their predictors as well as aneurysm characteristics for patients with CA after endovascular coil embolization.

PATIENTS AND METHODS: Patients with CA who have been treated with endovascular coiling were recruited from two centers and had their medical records retrospectively reviewed and analyzed. Clinical outcome was assessed using the modified Rankin Scale (mRS) 6 months and 1 year after coiling, while Raymond scale was used for angiographic outcome assessment.

RESULTS: A total of 38 patients (harboring 38 CA) were included in this study. Ruptured aneurysms constituted 60.53 % of all aneurysms. Seventy-four percent of ruptured CA were having a size of < 7 mm, while 83.3% of aneurysms < 5 mm were found ruptured with a trend of smaller-sized aneurysms to rupture. Simple coiling was utilized in 39.47 % of cases. Aspect ratio >1.6 was associated with ruptured status (p-value = 0.006). Among ruptured aneurysms, 11 out of 23 ended up requiring retreatment (p-value = 0.028). Favorable clinical outcome was observed in 65.8 % and 68.4 % of the patients at 6 months and 1-year post coiling, respectively.

CONCLUSION: Initial incomplete aneurysm occlusion and ruptured status were predictors of recurrence and retreatment. Aneurysm size and aspect ratio have a significant association with aneurysm rupture. The majority of ruptured CA were small ones.

KEYWORDS: Aneurysm rupture, Aneurysm size, Endovascular coil embolization, Outcome.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a significant cause of death and continuing disability with an annual incidence of 6-12 cases per 100,000 population in most western countries.[1,2] Ruptured cerebral aneurysms (CA) have been found to account for approximately 85% of all subarachnoid hemorrhage (SAH) events.[3]

While some aneurysms are thought to stay quiescent for years,[4] most CA are clinically silent until they start to evolve either with further growth or rupture.[5] Over the last decades, aneurysm size has been reported as a well-known risk factor to predict rupture.[6-9] Albeit, more recent studies contradict such results and reported a higher risk of rupture in small-sized (5-7 mm) aneurysms.[10-13]

The natural history of ruptured CA is such that about 30% of patients will die within 24 hours after the initial bleeding and a further 25 - 30% will succumb within the following four weeks if no intervention took place.[14] Such sinister outcome is almost always attributed to re-rupture of the aneurysm and/or the delayed neurologic deficit related to spasm of the intracranial vasculature.[15,16]

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Endovascular treatment (EVT) of CA has been showing exponential growth since the Food and Drug Administration (FDA) approval of Guglielmi detachable coils (GDC), for the endovascular treatment of high-risk CA.[17,18] Moreover, ongoing outstanding advances in imaging modalities and endovascular tools led to a significant improvement in catheters and guide wire technology as well as digital angiography technology.[16,19] Therefore, endovascular coiling has progressed from just an alternative option to microsurgical clipping for inaccessible aneurysms, to be a frontline treatment choice for a wide variety of CA.[20]

Aneurysm remnant and/or recurrence after treatment as well as the need for re-treatment are not uncommon after endovascular coiling.[21] Aneurysm recanalization has been estimated to occur in one aneurysm for every four unruptured aneurysms being treated with endovascular coiling, with even higher rates for ruptured ones.[21-23] Despite the results of the International Subarachnoid Aneurysm Trial (ISAT) that showed the superiority of endovascular coiling over microsurgical clipping for ruptured CA as regard to the functional outcome,[20] such results faced a storm of criticism owing to many critical flaws in the study design as well as its data analysis.[24,25]

The authors sought to assess the clinical and angiographic outcomes of patients with CA who underwent endovascular coiling as the initial treatment modality, aiming to characterize aneurysm-related and patient-related factors and to identify possible outcome predictors.

PATIENTS AND METHODS

Study design and patient selection

In this study, we retrospectively reviewed the medical records (from the hospital-based registry system) of patients diagnosed with cerebral aneurysms who have been evaluated and treated with coil embolization at the University of Miami Hospital (UMH) and Suez Canal University Hospitals (SCUH) during the period from January 2016 to January 2017 and met our inclusion criteria. Data from charts of 38 patients (harboring 38 CA) who underwent endovascular coiling and met the inclusion criteria, were retrospectively analyzed. Data collected included; demographic and clinical data, diagnoses, imaging reports, aneurysm characteristics, treatment received, perioperative data, outcome and follow-up data. These data were statistically analyzed.

Inclusion and exclusion criteria

Patients aged 16 years old or more, who were diagnosed with CA (either ruptured or unruptured), treated with endovascular coiling, and have their clinical/ angiographic initial and follow-up data for at least one year available were included. Patients who have been treated initially with microsurgical clipping or other endovascular tools (e.g. flow diverters) were excluded.

Embolization procedure

All endovascular procedures were performed in the neuroangiography suite with the patients under general anesthesia, using a biplane C-arm angiographic system with 3-dimensional reconstruction and following the standard coiling procedures. A simple technique of using a single microcatheter was usually utilized when a satisfactory aneurysm occlusion was expected. Balloon-assisted coiling (BAC), double catheter, or stent-assisted coiling (SAC]) as well as using Onyx were frequently used for aneurysms when needed. The appropriate sizes, types and shapes of the coils were selected according to the geometric and morphological features of each aneurysm. A final angiographic image was taken immediately after the last coil has been placed.

Angiographic results

Angiographic findings mainly of the magnetic resonance angiography (MRA) have been recorded for most patients 6 and 12 months after the procedure. Digital subtraction angiography (DSA) with multiple projections that served to define any residual/recurrent lesions has been utilized for selected patients. Angiographic results have been assigned to 1 of 3 categories according to the Raymond-Roy Grading Scale,[26] [Class I = complete occlusion, Class II = neck remnant, and Class III = aneurysm sac remnant]. Class I and II were considered "satisfactory occlusion" as long as the neck remnant is minimal and stable over time. Class III and any progressive recanalization, as per operator discretion, were regarded as "unsatisfactory occlusion" and considered for re- treatment.

Clinical results

Patients presented with aSAH were graded according to the Hunt and Hess (H&H) grading scale **(Table 1)**.[27] The clinical outcome has been recorded using the modified Rankin Scale (mRS) **(Table 2)**,[28] at 6 and 12 months thereafter during the follow-up visits. Periprocedural complications were also recorded.

Ethical approval and informed consent

Approval for this study was granted by the ethics committee in the institutions where the study was conducted. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

The influence of age, gender, aneurysm dimensions (size, neck diameter and aspect ratio), location, initial angiographic results, aneurysmal recanalization/ recurrence, need to retreat, rebleeding, periprocedural complications and functional outcome have been analyzed with use of the t-test for continuous variables, and the Pearson's chi-square test or Fisher's exact test for categorical variables, as appropriate (significance defined as p value < 0.05). All statistical analyses were performed using the statistical packages for the social sciences (SPSS) software. The results are presented as mean ± standard deviation (SD) unless noted otherwise.

RESULTS

Baseline demographic and clinical characteristics

In total, thirty-eight CA (from 38 patients) were included in this analysis. Ages of our study population range between 17- 83 years old with women constituting 68.42% of our patients and the majority of patients (81.58%) were symptomatic **(Table 3)**. Patients presented with ruptured aneurysms constituted 60.53 % of all aneurysms **(Table 3)** and they were slightly older than those presented with unruptured CA, with a mean age of 56.6 ± 14.2 versus 54.5 ± 18.6 years, respectively **(Table 4).**

Aneurysm characteristics

The mean aneurysms sizes were 5.99±2.51 mm, while aneurysms' neck diameters were 3.43±2.32 mm **(Table 3)**. The internal carotid artery (ICA) was the most frequent location (39.5%) for CA followed by the anterior communicating artery (AcommA) location (34.2%) **(Table 3)**. A higher aspect ratio with a cut-off of

1.6 was found to be associated with ruptured aneurysms (p-value = 0.006) **(Table 4)**. A significant correlation was found between the ruptured status of the aneurysm and the need for retreatment (due to recurrence) after initial coiling during the follow-up period (p-value = 0.028) **(Table 4)**. Moreover, 74% of ruptured CA were having a size of < 7 mm, and 83.3% of aneurysms less than 5 mm were presented with aSAH **(Fig. 1)** with a trend of smaller-sized aneurysms to rupture with a mean size of 5.47±2.8 mm versus 7.56±4 mm for unruptured ones **(Table 5)**.

Treatment characteristics

Simple coiling (stand-alone coiling) was the most frequent coiling modality (n = 15), while BAC and SAC were utilized in 26.32 % and 23.68%, respectively, and only 4 patients were treated with coiling + Onyx **(Fig. 2)**. No significant correlation was found between the initial coiling modality and the aneurysm recurrence and/or retreatment.

Clinical and angiographic characteristics

An initial complete aneurysm occlusion was achieved in 60.52% of cases, while 3 patients only (7.89%) showed unsatisfactory occlusion **(Table 6)**. At the end-point time (one-year post coiling), 65.79% of coiled aneurysms showed satisfactory angiographic occlusion [Class I and II occlusion], while 34.21% showed aneurysm significant recurrence that required retreatment **(Table 6)**. While 65.8% and 68.4% of patients showed favorable outcomes (mRS ≤ 2) at 6 months and 1 year respectively, the unfavorable outcome at 1 year was encountered in only 31.6% **(Table 7)**.

The symptomatic peripheral thromboembolic events (TEE) as well as, residual motor weakness were the most frequent periprocedural adverse events (7.89% each), while 2 patients (5.26%) developed added neurological deficit, and only one patient had intraoperative rupture during coiling with no adverse consequences **(Table 8)**.

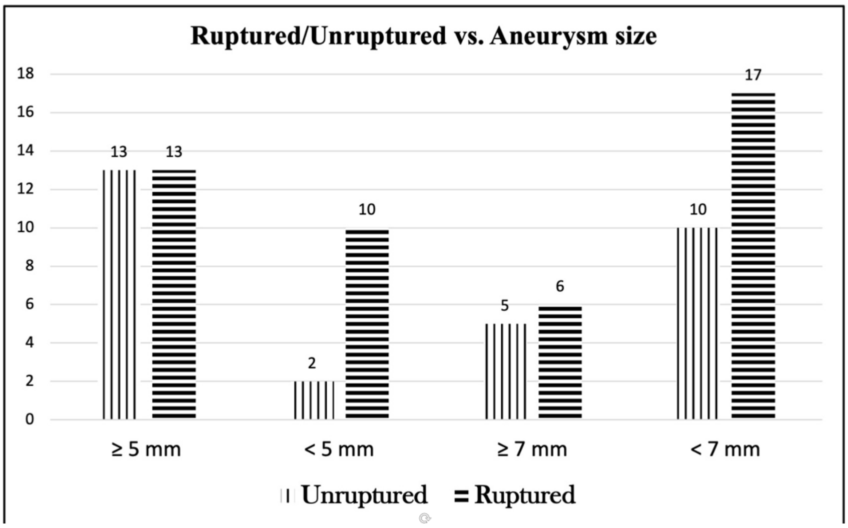

Fig 1: Ruptured/unruptured versus aneurysm size.

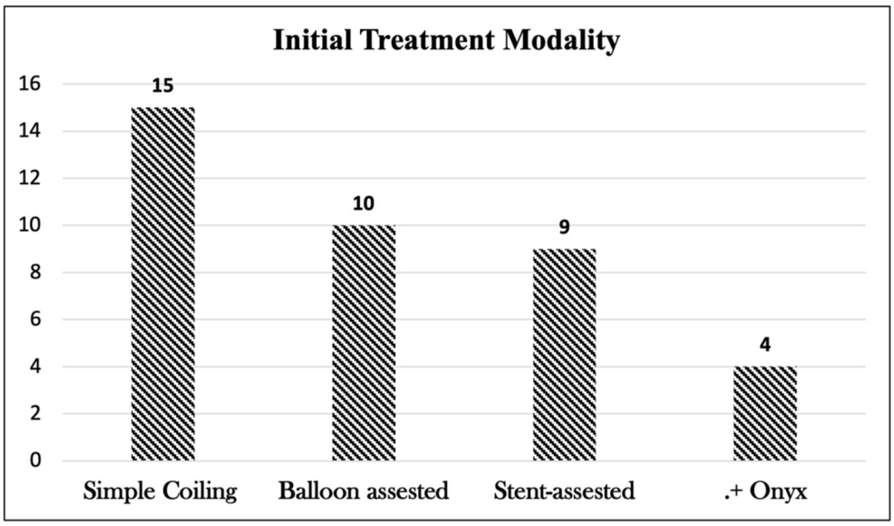

Fig 2: Modalities of initial coiling.

Table 1: Hunt and Hess grading System[77]

Grade*	Criteria [27]
I	Asymptomatic, or minimal headache and slight nuchal rigidity.
II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy.
III	Drowsiness, confusion, or mild focal deficit.
IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances.
V	Deep coma, decerebrate rigidity, moribund appearance.

* Serious systemic disease such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on arteriography, result in placement of the patient in the next less favorable category.

Table 2: Modified rankin scale[28]

Grade*	Modified rankin scale (mRS)
0	No symptoms at all.
1	No significant disability: despite symptoms, able to carry out all usual duties and activities.
2	Slight disability: unable to perform all previous activities, but able to look after own affairs without assistance.
3	Moderate disability: requiring some help but able to walk without assistance.
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability: bedridden, incontinent and requires constant nursing care and attention.
6	Death.

Table 3: Summary of demographic & aneurysm data

Characteristic	Number of cases (%)
Mean patient age (in years)*	55.76 ± 16.13
	Range [17 – 83 years]
Gender	
Male	12 (31.85)
Female	26 (68.42)
Aneurysm status	
Ruptured	23 (60.53)
Unruptured	15 (39.47)
Patient status	
Symptomatic	31 (81.58)
Asymptomatic	7 (18.42)
Mean aneurysm size (in mm)*	5.99 ± 2.51 Range [1.9 – 11 mm]
Neck diameter (mm)*	3.43 ± 2.32
Aspect ratio*	2.18 ± 1
Aneurysm location	
ICA (including posterior communicating artery)	15 (39.47)
AcommA	13 (34.21)
Posterior circulation	8 (21.05)
Middle cerebral artery (MCA)	1 (2.63)
Pericallosal artery	1 (2.63)

* Value as the mean ± Standard deviation.

Table 4: Aneurysm status (ruptured/unruptured versus other variables

Rupture		**No**	**Yes**	**p-value**
Variable		**mm ± SD**	**mm ± SD**	
Aneurysm Size (mm)		7.56 ± 4.0	5.47 ± 2.8	0.119
Age (years)		54.53 ± 18.97	56.57 ± 14.38	0.834
Variable	**Attribute**	**N (%)**	**N (%)**	**p-value**
Retreatment	No	13 (86.67)	12 (52.17)	0.028*
	Yes	2 (13.33)	11 (47.83)	
	Total	15 (100)	23 (100)	
Aspect ratio	More than 1.6	5 (33.33)	18 (78.26)	0.006*
	Less than 1.6	10 (66.67)	5 (21.74)	
	Total	15 (100)	23 (100)	

* Statistically significant.

Table 5: Aneurysm status (ruptured/unruptured) versus aneurysm size

Rupture		**No**	**Yes**	**Total (%)**	**p-value**
Variable	**Attribute**	**N (%)**	**N (%)**		
Aneurysm size	≥ 5 mm	13 (50)	13 (50)	26 (100)	0.21
	< 5 mm	2 (16.66)	10 (83.33)	12 (100)	< 0.001*
	Total	15	23	Total (%)	
Aneurysm size	≥ 7 mm	5 (45.45)	6 (54.54)	11 (100)	0.16
	< 7 mm	10 (37.03)	17 (62.96)	27 (100)	0.015*
	Total	15 (100)	23 (100)		

* Statistically significant.

Table 6: Initial versus final angiographic occlusion

Initial results N (%)	**Final result**	**N (%)**
Complete occlusion 23 (60.53)	Complete occlusion	14 (60.9)
	Minimal recurrence	6 (26.1)
	Recurrence + Retreatment	3 (13.0)
Residual neck 12 (31.58)	Recurrence + Retreatment	7 (58.3)
	Stable minimal residual	5 (41.7)
Residual dome 3 (7.90)	Recurrence + Retreatment	3 (100)
	Complete occlusion	0 (0)

Table 7: Functional outcome at 6 months and 1 year

Variable		**6 months**	**1 year**
Favorable outcome (mRS 0 - 2)	Frequency	25	26
	Percentage	65.8 %	68.4 %
Unfavorable outcome (mRS 3 - 5)	Frequency	13	12
	Percentage	34.2 %	31.6 %

Table 8: Types of periprocedural complications/adverse events

Peri-procedural complications	N (%)
Thrombo-embolic event (peripheral)	3 (7.89)
Residual motor weakness	3 (7.89)
Added neurological deficit	2 (5.26)
Others	
Cerebral Hemorrhage (frontal)	1 (2.63)
Cerebral Vasospasm	1 (2.63)
Intraoperative rupture (cavernous ICA)	1 (2.63)
Obstructed ventriculoperitoneal shunt	1 (2.63)

DISCUSSION

Despite the results of some large studies, e.g. International Study on Unruptured Intracranial Aneurysms (ISUIA) 1 and 2 that reported a negligible - or even no - risk of rupture (in a certain subgroup) for small-sized CA,[6,9,29] a recently published meta-analysis showed that the mean size of ruptured CA reported by most studies was < 7.0 mm, which considerably varies with the aneurysm location.[30] Interestingly, such small size of CA fairly represents the majority of diagnosed aneurysms, and surprisingly, the vast number of ruptured ones.[11-13] Moreover, while larger aneurysms seem to harbor a higher risk for rupture,[8,9,31] (owing to physical dimensions), they express their existence earlier via space-occupying nature (compressive effect on nearby structures), on the other hand small-sized aneurysms frequently lack such early mass effect and thus be expressed only when ruptured. Joo et al.,[12] reported that 71.8% of ruptured aneurysms in their series (889 patients) were < 7 mm, while 59% of ruptured aneurysms in Beck et al. cases were less than 7 mm.[13]

Interestingly, CA formation, growth, and rupture have been extensively studied and were known to occur via multifactorial pathobiological processes, with complex contributions from inflammatory processes, hemodynamic stress, possible genetic role, and environmental factors.[32,33]

It would be understandable that larger aneurysms carry a higher risk of poor outcome when ruptured (owing to more extensive SAH) than smaller ones, nonetheless, Dolati et al. reported a high Hunt and Hess grade for ruptured CA with size < 5mm as well.[34] Aneurysms of the anterior circulation were found to rupture at smaller sizes when compared to other anatomical sites.[35] Our results show a trend of smaller-sized aneurysms to rupture (p-value=0.05), with 74% of ruptured CA having aneurysm size < 7 mm, and 83.3% of aneurysms less than 5 mm were presented with aSAH. It is worth noting that, the mere aneurysm size should not be considered as an independent risk factor for aneurysm rupture in isolation of other aneurysm- and patient-related factors.[11]

In terms of morphology, a study concluded that only the aspect ratio was found to be a significant independent parameter for CA rupture.[36] Ujiie et al. proposed a cut- off ratio of 1.6 to predict CA rupture.[37,38] Our study showed a statistically significant association between high aspect ratio and risk of rupture, with 78% of ruptured CA having an aspect ratio of > 1.6, while 67% of unruptured CA were < 1.6.

The posterior location of CA has been suggested to be a risk factor for aneurysm rupture.[9,29] However, Rinkel et al. found the ICA location was the most common site for ruptured CA in their systemic review.[39] Our data showed that ICA was the most frequent location (39.5%) for CA followed by the AcommA location (34.2%). In their follow-up of 181 unruptured CA, Juvela et al. showed that patient age was an independent statistically significant predictor of aneurysm rupture.[8] Our study shows that patients presenting with aSAH were slightly older than those presenting with unruptured CA (p-value = 0.834).

Roy et al. reported (in their study of 125 unruptured aneurysms) immediate angiographic results of Class I and II obliteration in 47.2% and 42.4%, respectively, while follow-up angiogram after 12-30 months showed 47.2 % and 43.4 % for Class I and II, respectively.[26] Our results for the immediate angiographic images, showed Class I occlusion in 60% of patients, while Class II was encountered in 32% and Class III in only 8%.

During the follow-up, among the 23 aneurysms with initial complete occlusion, 40% continue to do so, while 6 aneurysms showed minimal recurrence that was stable with no need for further intervention. While Raymond et al. showed in their study a recurrence in 33.6 % of all coiled aneurysms, only 20.7 % were significant enough to require retreatment during the follow-up period.[21] Nearly two-thirds of aneurysms (n=25) in our study showed a satisfactory angiographic occlusion by 1 year, while only 34.2% showed recurrence during the follow-up period that warranted retreatment. Initial incomplete aneurysm occlusion (class II and III occlusion) as well as treatment during the acute phase of rupture, have been suggested to be a major predictor for recurrence.[26,40] Therefore, since 40 % of CA in our study showed initial Class II and III occlusion and 61% of aneurysms were ruptured, our study showed such a higher retreatment rate.

Thromboembolic events (TEE) after endovascular coiling is a known major periprocedural complication and their incidence rate in the literature considerably varies, being higher when more than simple coiling is being commenced.[26,41,42] A range between 2% and 7% has been reported in many studies but may reach up to 13% in ruptured aneurysms.[43,44] Our results showed that two patients (2.6%) developed added neurological deficit, while another 3 patients (7.9%) had lower limb deep venous thrombosis (DVT) and one patient had intraoperative aneurysm rupture. Lindgren et al. in their 852 coiled aneurysms showed that the overall proportion of poor outcome at 90-day was 30.2%.[45] Our results showed that good functional outcome (mRS $\leq$ 2) has been achieved in 65.8% and 68.4% in six months and one year, respectively..

CONCLUSION

Cerebral aneurysms have been known and dealt with for decades, owing to their sinister outcome that has been well known to be particularly devastating especially when they rupture. Small-sized aneurysms (size < 5 mm) seem to have a higher tendency, when compared with larger ones, to present with aSAH. Cerebral aneurysms at the anterior circulation seem to harbor a higher chance to present with aSAH at relatively smaller sizes. Moreover, aneurysm aspect ratio with a cutoff point of 1.6 has been shown to strongly predict aneurysmal rupture, which could be utilized to help with the decision of intervention over observation for such aneurysms.

Ruptured status and the initial incomplete occlusion of the aneurysm were found to be strongly associated with a higher incidence of recurrence/retreatment. The majority of CA treated with coil embolization continued to show satisfactory occlusion by the end of the follow-up period. Thromboembolic events following aneurysm coiling, while still being frequently reported, their rates are low and frequently resolve without significant adverse consequences. Lastly, a favorable functional outcome at 6 and 12 months after aneurysm coiling was reported in more than two-thirds of all patients and thought to be related to the initial clinical status.

In the light of our overall study results, we argue against that small-sized aneurysms carry a low risk of rupture, as previously perceived, nonetheless, size alone should not be utilized as a solo criterion to predict rupture risk. Poor clinical status at presentation, aneurysm rupture, and inadequate initial embolization are predictors of unfavorable outcome.

List of abbreviations

AcommA: Anterior communicating artery.
aSAH: Aneurysmal subarachnoid hemorrhage.
BAC: Balloon-assisted coiling.
CA: Cerebral aneurysms.
DSA: Digital subtraction angiography.
DVT: Deep vein thrombosis.
EVT: Endovascular treatment.
FDA: Food and Drug Administration.
GDC: Guglielmi detachable coils.
H&H: Hunt and Hess grading scale.
ICA: The internal carotid artery.
ISAT: International Subarachnoid Aneurysm Trial.
ISUIA: International Study on Unruptured Intracranial Aneurysms.
MCA: Middle cerebral artery.
MRA: Magnetic resonance angiography.
mRS: Modified Rankin Scale.
SAC: Stent-assisted coiling.
SAH: Subarachnoid hemorrhage.
SCUH: Suez Canal University Hospitals.
SD: Standard deviation.
SPSS: Statistical packages for the social sciences.
TEE: Thromboembolic events.
UMH: University of Miami Hospital.

Disclosure

The authors report no conflict of interest in the materials or methods used in this study or the findings specified in this manuscript.

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