Safety and efficacy of the eCLIPs bifurcation remodelling system for the treatment of wide necked bifurcation aneurysms

Original research

Safety and efficacy of the eCLIPs bifurcation remodelling system for the treatment of wide necked bifurcation aneurysms: 1 year results from the European eCLIPs Safety, Feasibility, and Efficacy Study (EESIS)

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ABSTRACT

Background The eCLIPs bifurcation remodelling system is a non-circumferential implant that bridges the neck from outside of a bifurcation aneurysm. The goal of the multicenter, post-marketing European eCLIPs Safety, FeasIbility, and Efficacy Study (EESIS), was to present the efficacy and safety results of the eCLIPs device after 365 days of follow-up.

Methods All patients were to receive an eCLIPs in conjunction with coils. The study was conducted according to good clinical practices and included independent adjudication of safety and efficacy outcomes.

Results Twenty patients were enrolled at four European centers. Mean age was 60 years (range 41–74) and aneurysms were located at the basilar tip (n=19) and carotid tip (n=1). Average aneurysm dome height was 6.0 mm (range 2.0–15.0). Mean neck length was 5.1 mm (range 2.6–8.5). The technical success rate was 90% (18 of 20). No major territorial strokes or deaths occurred between the index procedure and after 365 days of follow-up. Complete occlusion was achieved in 60% of patients (12 of 20 patients) and 67% of patients with an eCLIPs device (12 of 18) after 365 days of follow-up. Adequate occlusion (complete occlusion and neck remnant) was achieved in 80% of patients (16 of 20 patients) and 89% of patients with an eCLIPs device (16 of 18 patients) after 365 days of follow-up.

Conclusion In this small series, treatment with eCLIPs was feasible, safe, and efficacious, considering the challenging nature of the aneurysms.

Trial registration number ClinicalTrials.gov NCT02607501.

INTRODUCTION

Wide necked bifurcations aneurysms (WNBAs) are difficult to treat with endovascular techniques. A recent meta-analysis showed a complete occlusion rate of 39.8% after endovascular treatment of WNBAs.[1] High post-treatment recurrence rates are also documented; specifically, the recurrence rates of basilar tip WNBAs are higher than those at other locations.[2–4] The reason for these recurrences might be the difficulty in adequately disrupting the inertia driven flow at the aneurysm neck. Reasons for this inadequate flow disruption could be incomplete neck packing or coverage of the aneurysm in the case of bare coiling, or the use of a high porosity intravascular device (eg, a stent).[1] Even for more recently developed intrasaccular devices, high post-treatment recurrence rates have been reported.[5 6]

The eCLIPs bifurcation remodeling system is a non-circumferential implant that bridges the neck from outside of a WNBA allowing for coil retention, flow diversion, and remodeling. Initial studies have demonstrated a favorable safety and efficacy profile.[7–9] As the eCLIPs is not routinely used by neurointerventionalists and needs a different implantation strategy compared with other more widely used devices, the European ECLIPs Safety, Feasibility, and Efficacy Study (EESIS) was initiated. EESIS is a multicenter post-marketing study evaluating the safety, technical feasibility, and efficacy of the eCLIPs in conjunction with coiling for the treatment of WNBAs or aneurysms with a dome:neck ratio <2 at the basilar tip (BT) and carotid tip (CT). The goal of this study is to present the efficacy and safety results of EESIS after 365 days of follow-up.

METHODS

Study design

The EESIS study is a multicenter, prospective, non-randomized, single arm interventional trial of the eCLIPs device (Evasc Medical Systems Corp, Vancouver, BC, Canada) conducted at eight European centers. The study called for enrollment of 60 patients with 60 target aneurysms in the cohort; this number was for pragmatic reasons. The cohort was defined as all enrolled patients (ie, patients that had signed the informed consent form with an intention to treat these patients with the eCLIPs device). All participants gave informed consent before taking part in the study. Ethics approval was obtained, and local institutional review boards approved the study protocol at each participating center. The study was conducted according to good clinical practices. An independent core laboratory adjudicated effectiveness outcomes. Clinical assessments were performed by independent qualified personnel. Patient charts were externally reviewed with

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50% source document verification. A clinical event committee conducted study safety reviews. Furthermore, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used as a guideline to write this paper.

A full description of the study enrollment criteria can be found in the study protocol (ClinicalTrials.gov NCT02607501, and online supplemental file 2). Patients with an unruptured (treated or untreated) or previously ruptured aneurysm could be enrolled. When the aneurysm was previously ruptured, enrollment was at least 1 month from the date of rupture, the aneurysm dome had to be partially occluded, and the patient had to be in a stable neurological condition (World Federation of Neurological Surgeons subarachnoid hemorrhage grade I and II with good recovery, as assessed by a modified Rankin Scale (mRS) score of at least 2).

Target aneurysm characteristics were: saccular, intracranial aneurysm, arising at a bifurcation of BT or CT, maximal diameter <25 mm, neck length of >4 mm or dome:neck ratio <2, and branch artery diameters in the range 1.5–3.25 mm. As only limited data on long term aneurysm occlusion rates after eCLIPs implantation were available when the study protocol was designed, the protocol, for ethical reasons, required the aneurysm to be coiled after eCLIPs implantation. The study design included presentation of patient demographics, procedural characteristics, procedural technical success, safety data (at 30 and 365 days), and efficacy data (at 180 and 365 days).

Device characteristics

The eCLIPs device requires a minimum 0.034 inch microcatheter internal diameter for delivery. The implant is connected mechanically to a hypotube delivery mechanism and bridges the neck from the outside of the aneurysm to act as both a coil retention and a flow diverting device (figure 1). The non-tubular eCLIPs implant has two distinct sections: an anchor section with a set of anchoring ribs to secure the device in one of the post-bifurcation vessels, and a second leaf section with higher density ribs to cover the aneurysm neck. The porosity of the eCLIPs, approximately 65% (range 58–77%), is similar to that of a conventional flow diverter. In contrast with a braided flow diverter, the ribs of the eCLIPs are parallel and the device can thus be crossed with a microcatheter by gently pushing the ribs aside. A more detailed description of the device can be found in previously published reports.[7 9]

Procedural preparations

Procedural preparation included reporting of demographics, medical history, and medications, examination of physical and neurological condition (including National Institutes of Health Stroke Scale (NIHSS) score and mRS score), blood testing, and preprocedural DSA and/or MR angiography (MRA). Dual antiplatelet agents were required both before and after the eCLIPs implantation as follows:

1. Administration of aspirin (81–325 mg daily) was required for at least 2 days before the investigational procedure. Aspirin resistance testing was not mandatory and it was not documented whether these tests were performed.
2. P2Y12 receptor blockers, such as clopidogrel, ticagrelor, prasugrel, or ticlopidine, were allowed in a standard daily dose for at least 2 days before the procedure. The choice was based on the institution's preference. P2Y12 resistance testing was not mandatory and it was not documented whether these tests were performed.
3. Following device implantation, aspirin (81–325 mg daily) was required to be continued for a minimum of 6 months and P2Y12 receptor blocker for at least 3 months.

Endovascular procedure

All patients underwent a procedure with a quadriaxial technique (figure 1). The aneurysm neck was passed with a 4.2 F Fargo mini-catheter (Balt, Montmorency, France) and a Prowler Select Plus microcatheter (Johnson & Johnson, New Brunswick,

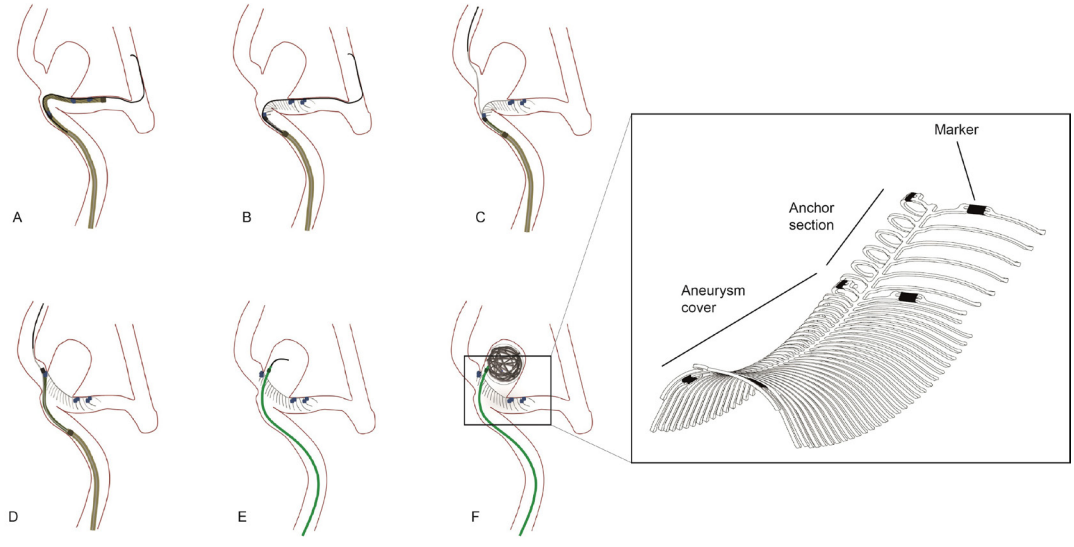

Figure 1 Deployment steps of eCLIPs: advancing the eCLIPs through the Fargo mini or eCLIPs microcatheter over a 0.014 inch microwire into the side branch (A). Stabilizing the delivery wire and withdrawing the microcatheter to commence eCLIPs delivery (B). Advancing the microwire into the contralateral side branch (C). Advancing the eCLIPs over the wire until complete neck coverage is achieved (D). Crossing the eCLIPs with a 0.017 inch microcatheter (E). Coiling the aneurysm (F). The insert shows the eCLIPs device in more detail and displays the two distinct sections: an anchor section with a set of anchoring ribs to secure the device in a daughter vessel lumen, and a section with higher density ribs to cover the aneurysm neck. The porosity of the eCLIPs is approximately 65% (range 58–77%).

New Jersey, USA) or a 3.3 F eCLIPs microcatheter (Evasc Medical Systems Corp) and 1.9 F eCLIPs micro-introducer (Evasc Medical Systems Corp), over a 0.014 inch microwire. After removal of the Prowler microcatheter or eCLIPs micro-introducer and the wire, the eCLIPs implant was advanced through the Fargo mini or eCLIPs microcatheter over a 0.014 inch microwire into the P1 segment or the A1 segment. The eCLIPs implant was deployed by stabilizing the delivery wire and withdrawing the Fargo mini or eCLIPs microcatheter. After unsheathing of the implant, the microwire was advanced into the contralateral P1 or M1 segment and the implant was advanced over this wire until complete neck coverage was achieved. Once the eCLIPs was adequately positioned, the implant was mechanically detached from its delivery system. After detachment, the device was crossed with a 0.017 inch microcatheter and the aneurysm coiled. The degree of coiling was left to the discretion of the operator.

Study endpoints

Primary endpoints

1. Safety endpoint: the rate of a major territorial stroke or death within 30 days (procedural) adjudicated by independent qualified personnel and reviewed by the clinical event committee. Major territorial stroke was defined as an ischemic or hemorrhagic stroke resulting in an increase of ≥4 points on the NIHSS and that persisted for >24 hours.
2. Safety endpoint: the rate of a major territorial stroke or death between 31 and 365 days adjudicated by independent qualified personnel and reviewed by the clinical event committee. Major territorial stroke was defined as an ischemic or hemorrhagic stroke resulting in an increase of ≥4 points on the NIHSS and that persisted for >24 hours.
3. Efficacy endpoint: complete aneurysm occlusion (modified Raymond–Roy classification (mRRc) I) at 180 days, adjudicated by an independent core laboratory.
4. Efficacy endpoint: complete aneurysm occlusion (mRRc I) at 365 days, Adjudicated by an independent core lab.

Secondary endpoints

1. eCLIPs procedural technical success: the proportion of successfully implanted eCLIPs devices at the target aneurysm, adjudicated by an independent core laboratory. All device observations, defined as difficulties with device navigation or orientation, were documented by the operator. Time to implant the eCLIPs device was also documented by the operator.
2. Degree of flow diversion (reduction of blood flow into aneurysm according to the O'Kelly–Marotta (OKM) grading scale) immediately after successful eCLIPs implantation, adjudicated by an independent core laboratory.[10]
3. Success of adjunctive coiling into aneurysm after successful eCLIPs implantation, assessed by the operator.
4. Efficacy endpoint: complete or near complete (mRRc I and II) after 180 and 365 days of follow-up, adjudicated by an independent core laboratory.
5. Change in mRS from baseline to 30, 180, and 365 days of follow-up, adjudicated by independent qualified personnel.
6. Occurrence of unplanned aneurysm retreatment within 365 days (endovascular or surgical repair), assessed by the operator.
7. Assessment of device migration at 365 days, adjudicated by an independent core laboratory.
8. Assessment of artery stenosis at the device location at 180 and 365 days, adjudicated by an independent core laboratory.
9. Assessment of artery patency at the target aneurysm at 180 and 365 days, adjudicated by an independent core laboratory.

Although not a secondary endpoint, the end of procedure mRRc was also assessed (adjudicated by an independent core laboratory). The reason for this assessment was to document whether there was progressive aneurysm occlusion over time.

Serious adverse events (SAEs), adverse events, unanticipated adverse device events (UADEs) were documented by independent qualified personnel. Reports of all SAEs were submitted to, and reviewed by, the clinical event committee. In this analysis, subjects that had no eCLIPs implanted (for whatever reason) were called primary treatment failures and were counted as failures for the study's primary efficacy endpoints (intent to treat analysis). If a patient was unavailable at a scheduled follow-up time, a new appointment was planned at a later time. If a patient was lost to follow-up, that patient was considered a failure. If data were missing, we also considered those as failures.

RESULTS

Patient enrollment

Patients were enrolled between February 2016 and January 2020. In total, 20 patients were enrolled at four participating centers. The other four investigational sites did not enroll patients (online supplemental table 1). Due to a recruitment rate of only five patients per year, the enrollment was halted in March 2020.

Baseline patient and aneurysm characteristics

Mean age at treatment was 60±9.2 years (range 41–74 years) and 80% of patients were women. There was one protocol violation according to the exclusion criteria because a patient with active anticoagulation treatment was included. Baseline patient characteristics are shown in table 1.

Ten patients (50%) presented with recurrent aneurysms. In seven of these the index aneurysm had been treated previously because of rupture. Baseline aneurysm characteristics are shown in table 2.

Follow-up and protocol violations

All included patients underwent follow-up at 30 days. We registered five protocol violations, which concerned a neurological investigation later than the predefined 30 days (±7 days) post-operative time window in five patients (table 3).

Five patients did not undergo MRA after 180 days of follow-up. One patient had a contraindication to MRA, two patients refused, in one patient a logistic mistake was made, and in the last patient MRI was performed without adequate MRA sequences. In three patients no neurological assessment was performed. We registered eight protocol violations, which concerned neurological assessment and/or MRA outside the predefined 180±20 day window or no assessment (table 3).

One patient (patient No 12) could not attend the hospital after 365 days of follow-up due to SARS-CoV-2 restrictions and underlying lung cancer, with a 10×11 mm metastatic tumor at the pineal gland. Neurological assessment was done by telephone and no DSA was performed. This patient died 14 months post-procedure from cancer. We registered four protocol violations, which concerned neurological assessment and/or DSA later than the predefined 365±20 day window (table 3).

Table 1 Baseline patient characteristics

Patient characteristics			
Age at procedure (years)			
Mean±SD	60.4±9.2		
Range	41–74		
Sex (n (%))			
Women	16 (80)		
Men	4 (20)		
Smoking status (n (%))			
Current smoker	6 (30)	Pack years (mean±SD)	18±10.6
Former smoker	7 (35)	Pack years (mean±SD)	26.8±19.1
Non-smoker	7 (35)		
Alcohol use (n (%))			
Current user	13 (65)	Drinks per week (mean±SD)	6±2.9
Former user	0 (0)	Drinks per week (mean±SD)	n/a
Non-user	7 (35)		
Body mass index (kg/m^2)			
Mean±SD	27.4±5.2		
Blood pressure (mm Hg)			
Systolic (mean±SD)	126.4±17.5		
Diastolic (mean±SD)	72.7±11.9		

n/a, not applicable.

Primary endpoint: safety

None of the 20 patients experienced a major territorial stroke or died within the first 365 days after eCLIPs implantation.

Primary endpoint: efficacy

A total of 15 patients underwent MRA after 180 days of follow-up. mRRc was I in six patients, II in six patients, and III in three patients. Two of the three patients with mRRc III had no eCLIPs implanted. The primary efficacy endpoint at 180 days was reached in 30% of patients (6 of 20).

A total of 19 patients underwent DSA after 365 days of follow-up. mRRc was I in 12 patients, II in four patients, and III in three patients. Two of three patients with mRRc III had no eCLIPs implanted. Images of the remaining patient with mRRc III after 365 days of follow-up are shown in figure 2. The primary efficacy endpoint at 365 days was reached in 12 of 20 patients (60%). All registered mRRc scores are provided in detail in online supplemental figure 1.

All registered mRRc scores can provided in detail in online supplemental figure 1).

Table 2 Baseline aneurysm characteristics

Aneurysm characteristics			
Aneurysm location (n (%))			
Basilar tip	19 (95)		
Carotid tip	1 (5)		
Dome height (mm)			
Mean±SD	6.01±3.25		
Dome width (mm)			
Mean±SD	6.78±2.31		
Dome depth (mm)			
Mean±SD	6.84±2.48		
Neck length (mm)			
Mean±SD	5.08±1.42		
Dome:neck ratio			
Width/neck (mean±SD)	1.36±0.36	Depth/neck (mean±SD)	1.36±0.33
Width/neck (range)	0.87–2.12	Depth/neck (range)	0.78–2.07
Aspect ratio (height/neck)			
Mean±SD	1.19±0.52		
Range	0.43–2.14		

Secondary endpoints

Core laboratory adjudication confirmed technical success in 18 of 20 patients (ie, all detached implants). In one patient who did not receive an implant (patient No 15, table 3), all available eCLIPs devices had expired and a balloon assisted coiling was performed. In the other patient (patient No 17, table 3), proper alignment of the implant across the aneurysm neck could not be achieved, despite several attempts. This patient was treated with stent assisted coiling (SAC). All 18 patients received a single eCLIPs implant. Of these 18 patients, the first device was removed in two patients (patient Nos 1 and 13, table 3) due to a device observation and replaced with a second, new device, without incident. In total, five device observations were documented (table 3). The median time from the start of the procedure (first incision/groin puncture) to insertion of the final eCLIPs was 1 hour 22 min (range 36 min to 2 hours 46 min).

Differences in the OKM grading scale immediately after eCLIPs implantation and before coil insertion showed that there was a reduction in blood flow inside the aneurysm in 14 of 18 (78%) patients (table 3). In all 18 cases, the eCLIPs was successfully crossed with a microcatheter to perform adjunctive coiling. No migration or disruption of the implant occurred during post-implantation coiling.

After 180 days of follow-up, 60% (12 of 20) of patients had complete or near complete (mRRc I and II) aneurysm occlusion. After 365 days of follow-up, 80% (16 of 20) had complete or near complete (mRRc I and II) aneurysm occlusion. The mRS score of 11 patients (55%) remained stable during the entire 365 days of follow-up. Four patients (20%), who all started at mRS 0, worsened during follow-up, resulting in a final mRS of 1 (n=2), 2 (n=1), and 3 (n=1). The patient with an mRS score of 3 was the aforementioned lung cancer patient with cerebral metastasis, which likely influenced the clinical deterioration. Three patients (15%) had transient worsening of their mRS score to 1, but all three patients recovered to mRS 0 after 365 days of follow-up. Two patients (10%) clinically improved over time and ended with a final mRS score of 0 after 365 days of follow-up. All registered mRS scores can be viewed in detail in the online supplemental figure 2.

None of the 20 patients underwent unplanned aneurysm retreatment (endovascular or surgical) within 365 days. None of the 18 implanted eCLIPs devices showed signs of device migration after 365 days of follow-up. All 18 arteries in which an eCLIPs device was implanted were patent and none showed signs of stenosis.

Additional parameters

The end of procedure mRRc was I in three patients, II in nine patients, and III in seven patients. Images for one patient were not suitable for mRRc classification. This patient did

Table 3 Detailed overview of outcomes for each included patient

Patient No	Device observation*	Remarks	Solution	Procedural technical success†	OKM grade pre-eCLIPs†	OKM grade post-eCLIPs (before coiling)†	Flow reduction	mRRc end of procedure†	Follow-up time	Serious adverse event¶¶¶¶	Status
1	Yes	First attempt: eCLIPs damaged during navigation. Attempt was aborted and first device was not used	Second eCLIPs device was implanted	Yes	C1	C2	Y	1	<24 hours	None	N/A
									30 days	None	N/A
									180 days‡	None	N/A
									365 days§	None	N/A
2	No	N/A	N/A	Yes	B1	B1	N	3	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
3	Yes	Incomplete neck coverage: part of neck covered by anchor section instead of aneurysm section	None. Device was left in place	Yes	A1	A3	Y	2	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
4	No	N/A	N/A	Yes	A1	A2	Y	3	<24 hours	None	N/A
									30 days¶	None	N/A
									180 days**	None	N/A
									365 days	None	N/A
5	No	N/A	N/A	Yes	B1	B3	Y	2	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
6	No	N/A	N/A	Yes	A1	A2	Y	2	<24 hours	None	N/A
									30 days††	None	N/A
									180 days‡‡	None	N/A
									365 days§§	None	N/A
7	No	N/A	N/A	Yes	A1	A1	N	2	<24 hours	None	N/A
									30 days¶¶	None	N/A
									180 days***	Missing	Missing
									365 days†††	None	N/A
8	No	N/A	N/A	Yes	A1	A2	Y	2	<24 hours	None	N/A
									30 days	None	N/A
									180 days‡‡‡	Missing	Missing
									365 days§§§	None	N/A
9	No	N/A	N/A	Yes	A1	A1	N	3	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
10	No	N/A	N/A	Yes	A1	A3	Y	3	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
11	No	N/A	N/A	Yes	A1	A2	Y	2	<24 hours	Loss of consciousness +confusion	Both SAEs were resolved, without sequelae
									30 days¶¶¶	None	N/A
									180 days****	Missing	Missing
									365 days	None	N/A
12	No	N/A	N/A	Yes	A1	A2	Y	2	<24 hours	Dizziness	Ongoing
									30 days††††	Ataxia	Ongoing
									180 days‡‡‡‡	Missing	Missing
									365 days	Dizziness and tiredness	Ongoing

Continued

Table 3 Continued

Patient No	Device observation*	Remarks	Solution	Procedural technical success†	OKM grade pre-eCLIPs†	OKM grade post-eCLIPs (before coiling)†	Flow reduction	mRRc end of procedure†	Follow-up time	Serious adverse event¶¶¶¶	Status
13	Yes	First attempt: eCLIPs positioned too proximal. Attempt was aborted and first device was not used	Second eCLIPs device was implanted	Yes	A1	A3	Y	3	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
14	No	N/A	N/A	Yes	A1	A2	Y	1	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
15	Yes	All eCLIPs devices were expired	No eCLIPs implanted. Balloon assisted coiling was performed	No–no eCLIPs device implanted	N/A	N/A	N/A	N/A (images not suitable)	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
16	No	N/A	N/A	Yes	A1	A2	Y	2	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
17	Yes	First attempt: eCLIPs device malorientation. Attempt was aborted and first device was not used. Second attempt: eCLIPs device malorientation. Attempt was aborted and second device was not used	No eCLIPs implanted. Stent assisted coiling was performed	No–no eCLIPs device was implanted	N/A	N/A	N/A	3	<24 hours	Dizziness	Resolved, without sequelae
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
18	No	N/A	N/A	Yes	A1	A1	N	1	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
19	No	N/A	N/A	Yes	A1	A2	Y	2	<24 hours	None	N/A
									30 days	None	N/A
									180 days	None	N/A
									365 days	None	N/A
20	No	N/A	N/A	Yes	A1	A2	Y	3	<24 hours	Minor stroke resulting in vision impairment	Resolved, without sequelae
									30 days	Blood loss requiring transfusion	Resolved without sequelae
									180 days	None§§§§	N/A
									365 days	None	N/A

*Documented by the operator.
†Core laboratory adjudicated.
‡Protocol violation: follow-up 252 days after operation.
§Protocol violation: follow-up 486 days after operation.
¶Protocol violation: follow-up 121 days after operation.
**Protocol violation: follow-up 218 days after operation.
††Protocol violation: follow-up 76 days after operation.
‡‡Protocol violation: follow-up 146 days after operation.
§§Protocol violation: follow-up 392 days after operation.
¶¶Protocol violation: follow-up 146 days after operation.
***Protocol violaton: follow-up missing.
†††Protocol violation: follow-up 397 days after operation.
‡‡‡Protocol violaton: follow-up missing.
§§§Protocol violation: follow-up 394 days after operation.
¶¶¶Protocol violation: follow-up 61 days after operation.
****Protocol violation: follow-up 68 days after operation.
††††Protocol violation: follow-up 128 days after operation.
‡‡‡‡Protocol violaton: follow-up missing.
§§§§Protocol violation: follow-up 211 days after operation.
¶¶¶¶Documented by independent qualified personnel and reviewed by clinical event committee.
mRRc, modified Raymond–Roy classification; N/A, not applicable; OKM, O'Kelly–Marotta scale; SAEs, serious adverse events.

not receive an eCLIPs but was treated with SAC (patient No 15, table 3). The number of complete aneurysm occlusions (mRRc I) increased over time: mRRc I was obtained in 15% (3 of 20) at the end of the procedure. After 180 days of follow-up, this had increased to 30% (6 of 20) and by 12 months this was 60% (12 of 20).

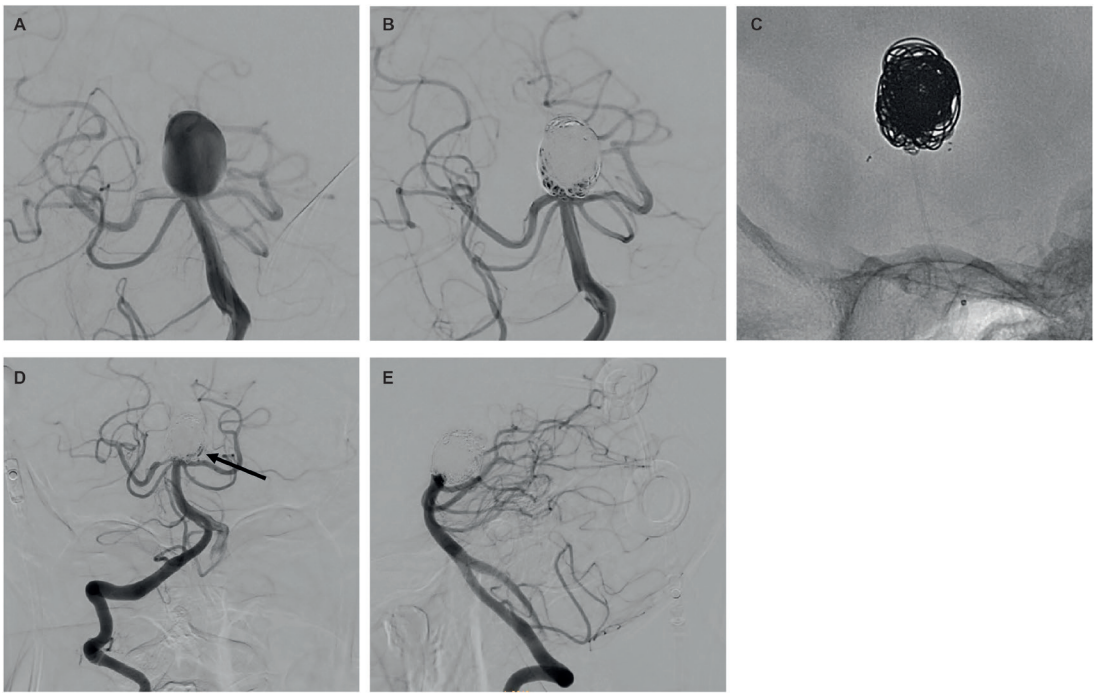

Figure 2 The only case (patient No 20) with an eCLIPs implanted and modified Raymond–Roy classification of III at the 1 year follow-up. DSA snapshot at the start of the procedure of the large basilar tip aneurysm (A). End of procedure (B). Single shot end of procedure with eCLIPs in situ and coiled aneurysm (C). One year follow-up anteroposterior (D) and lateral images, with a small amount of contrast in between the coils (arrow).

Adverse events (≤30 days)

Seven postprocedural SAEs in four patients were registered. Six SAEs were procedure related. A detailed description of all SAEs can be found in table 3. In total, 39 postprocedural adverse events were registered in 13 patients. Of these, three were categorized as 'severe' and six were ongoing at 30 days postprocedure. No UADEs were registered.

Adverse events (31 days up to 365 days)

No additional SAEs were documented between 31 and 365 days of follow-up. The SAE in patient No 12, who had a metastatic tumor at the pineal gland, was still ongoing. Another 10 new adverse events in eight patients were reported. One adverse event was classified as moderate and nine as mild. Three were ongoing from the last follow-up.No UADEs were registered.

DISCUSSION

This study showed that treatment of selected WNBAs with eCLIPs was technically feasible and had a 365 day safety profile comparable with other devices. Efficacy seemed to be favorable, especially when taken into consideration the fact that nearly all WNBAs in this study were located at the BT.

Safety

No primary safety endpoints were met in the first 365 days after implantation in any of the patients. Our results are comparable with other recent publications on the treatment of WNBAs. The Atlas trial reported no permanent postprocedural neurological deficits in 30 patients within 12 months.[11] The LVIS trial reported at least one primary safety event within 12 months, in eight of 153 patients (5.2%).[12] In a previously published WEB device trial, one primary safety event occurred in 150 patients in the first 12 months after implantation (0.7%),[13] while aggregate data from three French prospective WEB studies showed a 1 year all cause mortality of five of 153 patients (3.3%).[14] In a recent trial on the Contour Neurovascular System, major disabling stroke or death occurred in two of 34 cases (6%) within 12 months.[15] A meta-analysis on pCONUS bifurcation aneurysm implants found perioperative mortality rates of 0% (95% CI 0.00 to 0.01).[16]

Seven SAEs were registered in the first 30 days of follow-up and six of those were probably procedure related. No additional SAEs were registered between 31 and 365 days. Anemia in patient No 20 (table 3) was most likely caused by gastrointestinal bleeding, which was probably provoked by dual antiplatelet therapy. Patient No 11 (table 3) had confusion, which was probably related to postprocedural pneumonia. There was no explanation for the transient loss of consciousness in patient No 11 (table 3). In patient No 17 (table 3), dizziness was most likely related to the contrast burden associated with a long procedure (two attempts at eCLIPs placement and subsequent SAC). Postprocedural CT/CT perfusion showed no signs of ischemia or hemorrhage. All of these SAEs were transient and all patients recovered completely. The second patient who experienced dizziness (patient No 12, table 3) underwent a CT, which revealed a subarachnoid hemorrhage. The subarachnoid hemorrhage might have been caused by an unnoticed periprocedural guidewire perforation. This patient developed also ataxia. The SAEs in this patient were still ongoing after 365 days of follow-up, although we expect that this was partially caused by a 10×11 mm contrast enhancing metastatic tumor at the pineal gland. The patient died of cancer 14 months after eCLIPs implantation.

The thromboembolic complication rate was low (one of 20 patients, 5%). This patient suffered a minor stroke probably caused by a thromboembolism, with full recovery after 30 days of follow-up (patient No 20, table 3). No transient ischemic attacks, no parent artery occlusions, and no branch occlusions were reported. These safety results compare favorably with most other recent studies of endovascular devices. The authors of a recent meta-analysis found that complications (strokes and

thromboembolic events) occurred in 5.6–50% of SAC cases and in 8.6–16% of balloon assisted coiling cases.[17] In the WEB-IT study, 2.7% transient ischemic attacks were documented within 30 days of follow-up.[18] Composite data of the three recent French WEB studies showed 14.4% thromboembolic events at 1 month[14], while a recent meta-analysis of 36 WEB studies documented 9% thromboembolic events.[19]

Technical success

The technical success rate was 90% (18 of 20 patients, according to the intent to treat analysis). The technical success rate was even higher when excluding the patient with no attempt at eCLIPs implantation due to expired product (18 of 19 patients, 94.7%), which is comparable with the success rate of the WEB device.[18]

Mean time from groin puncture to deployment of the eCLIPs was 1 hour 22 min. The eCLIPs system navigation times were relatively long. Lack of experience with the large and complex quadriaxial microcatheter system made navigation difficult. Unlike operators in the WEB-IT trial, EESIS operators did not have the advantage of an anatomy replicated model to practice on, before the procedure.[18] Early experience with eCLIPs provided a learning curve and limited the recommendation to implant the eCLIPs in BT and CT aneurysms only.[7 20] Procedural time, as well as procedural complexity, has demonstrated a strong association with the occurrence of procedure related complications.[21 22] In this small series, it did not result in more safety events compared with other recent studies[14 17–19]; nevertheless, shortening total procedure times is an important objective. Therefore, new generations of eCLIPs devices can be navigated through 0.021 and 0.027 inch inner diameter microcatheters through a triaxial delivery system, which will likely decrease implantation time.

The literature on procedure time is sparse. Total procedure time, from groin puncture to occlusion of the puncture site for coiling of unruptured aneurysms in a retrospective clinical study of 51 patients, was 2 hours 44 min.[23] In a recent study, a third of patients undergoing coiling had a total procedure time >2 hours.[21] A longer procedure time was seen in patients who underwent SAC and in cases where multiple catheters were needed.

Efficacy

After 365 days of follow-up, 12 of 20 patients (60%) had complete aneurysm occlusion (mRRc I) and 16 of 20 patients (80%) had complete aneurysm occlusion or a neck remnant (mRRc I or II). Looking at the occlusion numbers of patients who received the eCLIPs device, 12 of 18 (67%) had complete aneurysm occlusion (mRRc I) and 16 of 18 patients (89%) had complete aneurysm occlusion or a neck remnant (mRRc I or II).

Efficacy studies after treatment of BT WNBAs are limited. Henkes reported a single center retrospective series of coil treated BT aneurysms with a mean size of 9.9 mm and a mean neck width of 4.9 mm.[3] After 19 months, complete or near complete occlusion was obtained in 70% of patients but coil compaction was evident on 24% of angiograms. Another single center series of 235 coiled or SAC BT aneurysms showed recanalization rates of 38.9% after coiling and 17.2% after SAC. A stable occlusion was reached in about 50% of aneurysms with either technique.[24] A systematic review emphasized the difficulty of treating WNBAs in the BT, with recanalization rates of up to 60%.[2] In a large multicenter review of 1675 patients, aneurysm location at the BT was an independent predictor for late recanalization after treatment.[4] When looking at SAC, complete occlusion can be obtained in 30.6–92% of aneurysms, depending on the size, location, and type of aneurysms, and study quality factors, such as retrospective or prospective analysis and core laboratory adjudication.[25–28]

In the Answer trial, the PulseRider device achieved mRRc I or II in 87.9% of WNBAs, similar to those in the EESIS after 6 months of follow-up.[29] In the LVIS trial, 70.6% of aneurysms met the complete occlusion criteria.[12] Cumulative data of three French WEB studies showed 52.9% complete occlusion at the 1 year follow-up[14] and aneurysm occlusion in the WEB-IT trial was similar, with 53.8% at the 12 month follow-up.[13] Complete aneurysm occlusion at the 12 month follow-up after placement of the Contour Neurovascular System was obtained in 69% of patients.[15] A meta-analysis of the results reported on the pCONUS demonstrated a complete occlusion rate of 60% (95% CI 0.52 to 0.69) at a mean follow-up time of 9.9 months.[16] Dmytriv *et al* found a complete and near complete occlusion rate of 68.8% at a mean of 6 months of follow-up when using flow diverters.[30]

The abovementioned studies show the efficacy of several recently developed devices but the populations studied in most of these publications differed substantially from the population in the EESIS, as BT aneurysms formed only a small subset in nearly all of these studies. An exception is the Branch study, where 60% of the studied aneurysms were located at the BT, with mRRc I 34% and mRRC I and II 70%.[26] The EESIS thus included only the most difficult subset of aneurysms to reach complete aneurysm occlusion.

An explanation for the relatively high aneurysm occlusion rates could be that the low porosity of the device results in a flow diverting effect at the aneurysm neck. The intraprocedural differences in OKM scale before and after eCLIPs implantation as well as progressive aneurysm occlusion rates over time suggest a flow diverting effect of the eCLIPs, as this last feature has also been documented after tubular flow diverter implantation.[31]

Limitations

This was a small series of 20 patients. The study had called for enrollment of 60 patients but the enrollment rate was unexpectedly low, accounted for by the strict inclusion criteria and the fact that the eCLIPs, with its requirement for a large microcatheter and double branch access, is not navigable in all anatomical situations at the BT and CT.

With unfavorable anatomy, such as side branches<2 mm or with a very steep angle, the eCLIPs cannot be implanted. Furthermore, as the necessary navigation technique was different compared with other implants, and a quadriaxial system had to be used, there appeared to be some reluctance to use the device in some centers. This triggered the expedited development of the newer generation of eCLIPs which has an improved delivery technique and can be navigated through a 0.021–0.027 inch microcatheter.

CONCLUSION

In this small series of very challenging WNBAs at the BT and CT, treatment with eCLIPs, although technically challenging, was feasible, safe, and efficacious. Technical success was obtained in 18 of 19 (95%) attempts. No major territorial strokes or deaths occurred between the index procedure and the 365 day follow-up. Complete occlusion was achieved in 60% of patients (12 of 20 patients) and 67% of all patients with an eCLIPs device (12 of 18) after 365 days of follow-up. Adequate occlusion (complete occlusion and neck remnant) was achieved in 80% of patients (16 of 20 patients) and 89% of patients with an eCLIPs device (16 of 18 patients) after 365 days of follow-up.

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