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EVIDENCE Trial: design of a phase 2, randomized, controlled, multicenter study comparing flow diversion and traditional endovascular strategy in unruptured saccular wide-necked intracranial aneurysms

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Abstract
Introduction Endovascular treatment of large, wide-necked intracranial aneurysms with coils is associated with low rates of initial angiographic occlusion and high rates of recurrence. The Pipeline™ Embolization Device has shown high rates of complete occlusion in uncontrolled clinical series.

Methods The study is a prospective, controlled, randomized, multicenter, phase 2 open-label trial. Intention-to-treat population includes age ≥18, unruptured saccular aneurysm located in the intra-dural area, neck diameter ≥4 and ≤10 mm, sac diameter ≥7 mm and ≤20 mm, "dome/neck" ratio is ≥1, diameter of the parent artery ≥2 mm and ≤5 mm, and no prior

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treatment of the aneurysm. Site can only participate if five patients have been previously treated with the Pipeline device. The primary end point of the study is complete occlusion of the aneurysm on angiogram performed 12 months after the endovascular procedure. Complete aneurysm occlusion is defined as the absence of visible blood flow, grade 1 according to the Raymond scale for the standard procedure group and grade 4 according to the grading scale of Kamran for the flow diverter group.

Results The trial is currently enrolling and results of the data are pending the completion of enrollment and follow-up.

Conclusion This paper details the trial design of the French EVIDENCE phase 2 trial, a blinded, controlled randomized trial of wide-neck intra-dural aneurysms amenable to either traditional endovascular strategy or flow diversion with Pipeline device.

Keywords Intracranial aneurysms · Endovascular treatment · Coiling · Flow diversion · Randomized trial

The prevalence of intracranial aneurysms in the adult population is estimated to be around 2 % [1]. Most remain asymptomatic, but there is a risk of rupture of 1.2 % per year, and this risk increases in line with the diameter of the aneurysm [1, 2]. If rupture occurs, subarachnoid hemorrhage and its associated acute complications are responsible for high mortality (between 30 and 67 %) and morbidity (between 15 and 30 %) [3].

Given this risk, preventative treatment is generally suggested to patients with an unruptured saccular aneurysm with a diameter greater than 7 mm [4]. In 80 % of cases, treatment is endovascular and consists of implanting embolization coils in the aneurysm sac in order to occlude it and prevent the flow of blood to enter the aneurysm [1, 5]. If the neck is wide, an adjunctive technique may be used to assist the implantation of the coils, either by using a temporary balloon [6–8], or by inserting an intracranial stent at the neck of the aneurysm [8–12] to prevent coil herniation and aid in aneurysm occlusion.

This strategy is, however, associated with high rates of incomplete occlusion in the mid-term (12 months), possibly making it necessary to perform a secondary procedure with additioned implantation of coils while taking into consideration the risk of secondary rupture (benefit/risk ratio). The rate of aneurysm recanalization is 20.8 % and the rate of retreatment 10.3 % [13]. Furthermore, in particularly large aneurysms, the large number of coils implanted during the procedure (sometimes more than 20) could perpetuate the mass effect initially present and be responsible for neurological complications.

Flow diverters are new implantable medical devices that make possible to embolize wide-necked aneurysms without the use of coils [14]; the efficacy results published to date are encouraging in terms of complete occlusion in the medium-term, thereby confirming the innovative nature of the flow diversion technique that we aim to evaluate without the use of coils [15–19]. Recently, a study comparing flow diversion with traditional embolization strategies in terms of safety, efficacy, and clinical outcomes in patients with unruptured, large saccular aneurysms (≥10 mm) was published. Forty patients treated with the Pipeline™ Embolization Device (ev3/Codman, Irvine, CA, USA) were matched in a 1:3 fashion with 120 patients treated with coiling. A significantly higher proportion of aneurysms treated with the Pipeline (86 %) achieved complete obliteration compared with coiled aneurysms (41 %; $p<0.001$), with no additional morbidity and similar clinical outcomes [17]. The Pipeline device will be the only flow diverter used in our study. At the beginning of EVIDENCE trial, the two available devices were Pipeline and Silk™ system (Balt, Montmorency, France), and the current instructions of the Silk state that it must be used in addition to coils. In this context, the Pipeline device will be the only flow diverter used in EVIDENCE trial.

Spreading of these innovative devices is hampered by the relatively high cost of the devices around 12,000 euros. In France, embolization with coils and stents is reimbursed by the government to the hospital in addition to the hospital budget. Pipeline is reimbursed for aneurysms superior or equal to 15 mm [20]. Consequently, health economic assessment with a high level of proof is necessary to confirm the interest of flow diverters.

The aim of EVIDENCE trial is to demonstrate that the treatment of unruptured, saccular, wide-neck aneurysms using flow diverters results in a higher rate of complete occlusion of the aneurysm at 12 months in comparison to a conventional embolization technique and perform a health economic assessment comparing the two techniques in terms of the two aspects of efficacy and cost at 12 months.

Material and methods

Design

EVIDENCE is a French prospective controlled randomized multicenter (20 centers) phase 2 trial (NCT01811134) to

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compare the safety and efficacy of flow diversion with current version of the Pipeline versus the endovascular coiling in the endovascular treatment of wide-necked unruptured intracranial aneurysms. Subjects will be randomized to either flow diversion or endovascular coiling (with or without adjunctive devices [stents, balloons]) cohorts in a 1:1 fashion and will be assessed for the primary outcome at 12 months with subsequent outcomes until 2 years from aneurysm repair. The primary end point is complete occlusion of the aneurysm on angiogram performed 12 months after the endovascular procedure.

Intention-to-treat population

Intention-to-treat population includes patients aged 18 years and over, with an unruptured saccular aneurysm diagnosed by angiography or CT angiogram or MR angiogram and with the following characteristics: aneurysm located in the intra-dural area, with a neck diameter between 4 and 10 mm, with a sac diameter between 7 and 20 mm, with aneurysm dimensions such that the "dome/neck" ratio is ≥1, and diameter of the parent artery between 2 and 5 mm. Patients with prior treatment of the aneurysm are not eligible. Detailed study inclusion and exclusion criteria are shown in Table 1. The subject is enrolled in the study after he/she has signed the subject informed consent, and it has been determined that he/she meets all of the inclusion criteria and none of the exclusion criteria. The point of enrolment is defined as when the patient has been randomized.

Table 1 Study inclusion and exclusion criteria

Inclusion criteria	General exclusion criteria
1. Agreement with the patient for participation in the study and informed consent signed by the patient, and patient affiliated with a social security scheme or similar.	1. Minor patient or adult patient under law protection
2. Age 18 years and over	2. Contraindication to endovascular therapy
3. Unruptured saccular aneurysm located in the intra-dural area, with a neck diameter between 4 and 10 mm, with a sac diameter between 7 and 20 mm, with aneurysm dimensions such that the "dome/neck" ratio is ≥1	3. Contraindication to anti-platelet therapy or anti-coagulant
4. Diameter of the parent artery between 2 and 5 mm	4. Patient with a cerebral arteriovenous malformations
5. No prior treatment of the aneurysm	5. Aneurysm located in the extra-dural territory, or fusiform aneurysm
6. Patient is willing to conduct follow-up visits	6. Active bacterial infection (clinical signs)
	7. History of aneurysm bleeding within 30 days prior to treatment date
	8. Pregnancy or lactating

Randomization

Randomization will occur in a 1:1 ratio to either flow diversion or endovascular coiling. Once the patient is determined to meet all study eligibility criteria and signed the consent form, randomization takes place centrally via the EVIDENCE Study Web site (www.etude-evidence.com). The patient will not be blinded to procedures as the patient will be verbally informed by the investigator to what treatment group he/she has been assigned. The first patient was included on 20 November 2012.

Treatment

Subjects assigned to coil embolization will undergo treatment of the target intracranial aneurysm with endovascular coiling with CE-approved technologies. Procedures will be performed according to the technology instructions for use. Other devices (balloons, intravascular stents) may be used adjunctively.

Subjects assigned to flow diversion will undergo placement of flow diverter(s) across the target aneurysm. One or more flow diverters may be placed as deemed necessary by the investigator.

Aspirin and clopidrogel are used according to the operator's protocol.

Primary outcome

The primary efficacy end point of the study is complete occlusion of the aneurysm on angiogram performed 12 months after the endovascular procedure. Complete aneurysm occlusion is defined as the absence of visible blood flow, a grade 1 according to the Raymond scale for the standard procedure group [21] and a grade 4 according to the grading scale of Kamran for the flow diverter group [22].

Secondary outcomes

Ancillary secondary efficacy end points are percentage of patients within each class of occlusion at the 12-month post-procedural angiogram, as measured according to the Raymond scale for the standard procedure group and according to the grading scale of Kamran et al. for the flow diverter group.

The primary safety end point is the incidence of morbidity/mortality events over 12 and 24 months:

- Mortality—(1) occurrence of a death during the endovascular procedure and during hospitalization; (2) occurrence of a death (from whatever the cause) during the 12 and 24 months of follow-up; and (3) occurrence of

a death due to rupture of the aneurysm over the 12 and 24 months of follow-up.

– Morbidity—(1) occurrence of a hemorrhagic cerebrovascular accident due to the rupture of the treated aneurysm during the 12 and 24 months of follow-up; (2) occurrence of an ischemic cerebrovascular accident due to thrombosis over the 12 and 24 months of follow-up; (3) occurrence of non-cerebral bleeding over the 12 and 24 months of follow-up; (4) percentage of patients with neurological deficit associated with a mass effect during hospitalization and at 3, 6, and 12 months post-intervention; and (5) retreatment of the aneurysm scheduled in the 12 and 24 months after the intervention.

Additional safety end points are (1) rate of technical complications during the endovascular procedure; (2) rate of thromboembolic complications, intraoperative ruptures, complications at the puncture site, or other; (3) rate of correct placement of the flow diverter stents, according to the investigator; (4) degree of occlusion at the end of the procedure, according to the Raymond scale for the standard procedure group and according to the grading scale of Kamran et al. for the flow diverter group; (5) dose of irradiation related to angiographic monitoring during the endovascular procedure; (6) neurological condition including modified Rankin score (mRS) measured at inclusion and at 3 and 12 months after the endovascular procedure, National Institutes of Health Stroke Scale (NIHSS) measured at inclusion and at 3 and 12 months, and Barthel index at 3 and 12 months after the endovascular procedure.

Health economic assessment is analyzed by calculation of the incremental cost-effectiveness ratio between the two techniques at 12 months. Table 2 shows the schedule of study visits.

Data safety monitoring board

The data safety monitoring board (DSMB) will be comprised of three individuals not involved in study conduct who have expertise in multiple disciplines, including a neuroradiologist, neurologist, and biostatistician. The DSMB will also be responsible for ensuring that the data are analyzed completely and correctly.

Table 2 Study visits

	Inclusion visit	Procedure and hospitalization	Follow-up visit at 3 months	Follow-up visit at 6 months	Follow-up visit at 12 months	Follow-up visit at 24 months
Visit	V1	V2	V3	V4	V5	V6
Time in relation to the intervention	Day 7/day 60	Day 0	Month 3 +/− 7 days	Month 6 +/− 7 days	Month 12 +/− 14 days	Month 24 +/− 30 days
Inclusion/exclusion criteria	X					
Signed consent form	X					
Randomization	X					
Physical examination	X	X	X	X	X	X
Angiogram[a]		X	(X)		X	
MRI[a]	(X)	X	X	(X)	X	
Endovascular procedure[b]		X				
Assessment of neurological function[c]	X		X		X	
Recording of mortality		X	X	X	X	X
Recording of morbidity		X	X	X	X	X
Hospital costs		X	X	X	X	
GP costs		X	X	X	X	
Adverse events		X	X	X	X	X

X examination obligatory, *(X)* examination not obligatory; to be conducted at the discretion of the investigator

[a] The angiogram and MRI images obtained before the procedure and at 12 months must be anonymized and recorded on CD for centralized blinded review

[b] The following will be recorded: duration of irradiation, technical complications, success of the procedure (good position of the flow diverter stent without complications), initial degree of occlusion

[c] A consultation with an independent neurologist working at the site will be held between inclusion and the procedure, and at 3 and 12 months, with measurement of the modified Rankin score, the NIHSS score, and the Barthel index

Sample size

The primary end point is the percentage of patients with complete occlusion of their aneurysm at 12 months after the endovascular procedure. Based on data available in the literature, we formulate the following hypotheses: 90 % of patients will have complete occlusion at 12 months for the group treated using the "flow diverter" technique; 70 % of patients will have complete occlusion at 12 months for the group treated using the conventional technique.

Taking into account a type I error of 0.05 and a power of 80 % (two-sided test), the number of subjects required to demonstrate a significant difference of 20 % between the two groups is 59 patients per group. Taking into account a patient drop-out or loss-to-follow-up rate of 10 %, the total number of patients to be included in the study is 130 patients (65 patients per group).

Statistical analyses

The statistical analysis will be conducted independently of the investigators in order to guarantee the objectivity of the results. All of the analyses will be conducted with a significance level of 5 %. No interim analysis of the primary end point is planned.

The characteristics of the two groups will be compared using Student's *t* tests for the quantitative variables and chi-squared tests for the qualitative variables, in order to guarantee comparability.

The percentage of patients with complete occlusion of the aneurysm at 12 months post-intervention will be calculated in each of the two groups studied, matched to a confidence interval of 95 %. The percentages in the two groups will be compared using a chi-squared test.

Study organization and funding

The EVIDENCE trial was funded in November 2010 by the French government (STIC program). The STIC program is a medico-economic study, supporting expansive innovations. The sponsor is Hospices Civils de Lyon (HCL). The independent CRO is Pôle Information Médicale Evaluation Recherche (François Chapuis, Laure Huot) from the HCL.

A public contract has been signed between HCL and Covidien company to buy the Pipeline at a determined price. Any flow diverter used over is provided free by the Covidien company.

Discussion

EVIDENCE is designed to provide definitive information on the efficacy and safety of flow diversion with Pipeline device in comparison to an established endovascular coiling.

EVIDENCE is the first phase 2 trial to conduct a direct, randomized comparison of the Pipeline device versus standard coiling. Prior studies leading to clearance of flow diverters for endovascular treatment of intracranial aneurysms have been single-arm studies with only historical controls [15–19]. Recently, 40 patients treated with the Pipeline Embolization Device were matched in a 1:3 fashion with 120 patients treated with coiling. In this study, the Pipeline provided higher aneurysm occlusion rates than coiling, with no additional morbidity and similar clinical outcomes [17]. The randomized design of the EVIDENCE trial ensures minimization of bias in the selection of patients for the treatment and comparator groups, enables the primary outcome to be assessed in a blinded and uniform manner, and assures that any observed differences in group outcomes are not due to evolution of general internationalist technique.

No published health economic data about the flow diverter embolization technique is available to date. The objective of the health economic assessment will be to compare both the efficacy results and costs (at 12 months) between the two endovascular techniques in the treatment of unruptured intracranial aneurysms. The cost-effectiveness analysis, characterized by the consideration of both costs and efficacy results, will be used as part of this study. The costs and efficacy results will be combined in the calculation of the incremental cost-effectiveness ratio, which makes it possible to determine a cost differential and an efficacy differential between the two techniques studied.

Conclusion

This paper details the trial design of the French EVIDENCE phase 2 trial, a blinded, controlled randomized trial of wide-neck intra-dural aneurysms amenable to either traditional endovascular strategy or flow diversion with Pipeline device.

Ethical standards and patient consent We declare that all human and animal studies have been approved by the Comité de Protection des Personnes SUD-EST IV (12/060) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest FT consults for Balt, Covidien and Codman. AB consults for Covidien, Stryker Neurovascular and Codman.

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