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The evaluation of the flow re-direction endoluminal device (FRED) for the treatment of selected intracranial aneurysms: a Polish multicenter study

Maciej Jaworski[1], Remigiusz Krysiak[1]✉, Jarosław Żyłkowski[1], Mariusz Banach[2], Miłosz Zbroszczyk[3], Kamila Smulska[3], Sławomir Bereza[4], Katarzyna Lubkowska[4], Ewa Horoch-Łyszczarek[5], Paweł Brzegowy[6], Tadeusz Popiela[6], Wojciech Poncyljusz[7], Michał Zawadzki[8], Błażej Nowak[8], Mateusz Pinkiewicz[8], Jarosław Wrzyszcz[9], Katarzyna Mokrzycka[9], Maciej Szajner[10], Christophe Cognard[11], Edoardo Boccardi[12], Raphael Blanc[13] & Michel Piotin[13]

This Polish multicenter study aims to evaluate the effectiveness and safety of the Flow Direction Endoluminal Device (FRED) in treating selected unruptured intracranial aneurysms. The FRED Poland Study was an observational, multicenter, prospective study conducted in 8 Polish investigational sites. Imaging results were independently assessed by a Corelab and adverse events were adjudicated by a Clinical Events Committee (CEC). Clinical results up to 24 months and anatomical results at 6-, 12- and 24-months post-treatment were reported. A total of 86 patients with 89 target aneurysms were enrolled between January 2016 and September 2017. Most aneurysms were located on the anterior circulation (93.2%, 83/89 aneurysms) with the majority (64.0%, 57/89) being small (<10 mm) in size. Treatment was successfully performed in 86 out of 89 cases (96.6%). The permanent neurological morbidity rate was 3.6%, and the neurological mortality rate was 2.4%. Imaging follow-up at 6 months showed complete occlusion of the aneurysm in 64.9% of cases, increasing to 79.5% at 12 months and 85.5% at 24 months. This study offers a comprehensive overview of the flow diversion treatment approach, demonstrating that the FRED device is effective and safe for use in intracranial aneurysm treatment. These results align with existing literature, reaffirming the device reliability and suitability for clinical use.

Abbreviations

FRED	Flow Re-Direction Endoluminal Device
CEC	Clinical Events Committee
ASA	acetylsalicylic acid

[1]II Department of Clinical Radiology Warszawa, Medical University of Warsaw, Warszawa, PL, Poland. [2]Department of Neurosurgery Kraków, Saint Raphael Hospital, Kraków, PL, Poland. [3]Department of Radiodiagnostic and Interventional Radiology Katowice, Medical University of Silesia, Katowice, PL, Poland. [4]Departement of Interventional Neuroradiology Wrocław, Lower Silesian Specialistic Marciniak Memorial Hospital, Wrocław, PL, Poland. [5]Departement of Neurology Wrocław, Lower Silesian Specialistic Marciniak Memorial Hospital, Wrocław, PL, Poland. [6]Radiology Department Kraków, Medical College Jagiellonian University, Kraków, PL, Poland. [7]Department of Diagnostic Imaging and Interventional Radiology Szczecin, Pomeranian Medical University in Szczecin, Szczecin, PL, Poland. [8]Department of Radiology Warszawa, Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw, Division of Interventional Neuroradiology, Warszawa, PL, Poland. [9]Department of Neurosurgery Grudziądz, Regional Specialist Hospital named after Dr. WI. Bieganski, Grudziądz, PL, Poland. [10]Department of Interventional Neuroradiology Lublin, Medical University of Lublin, Lublin, PL, Poland. [11]Diagnostic and Therapeutic Neuroradiology Place du Dr Baylac Toulouse , Hôpital Purpan , Toulouse, FR, France. [12]Neuroradiology Milano, Ospedale Niguarda Ca'Granda, Milano, IT, Italy. [13]Departement of Interventional Neuroradiology Paris Fondation de Rothschild , Paris, FR, France. ✉email: remik.krysiak@gmail.com

PICA Posterior Inferior Cerebellar Artery

Unruptured intracranial aneurysms (UIAs) are common cerebrovascular abnormalities occurring in approximatively 3% of the population[1]. Currently approved endovascular approaches include the use of detachable coils, with or without the assistance of balloons and stents, intraluminal flow diverters, and intrasaccular flow disruptors[2]. Flow diverters have emerged as a suitable option for treating wide-neck and giant aneurysms, as well as, more recently, small and medium-sized aneurysms[3]. These devices are designed with low porosity and high flexibility, enabling them to preserve intraluminal blood flow in the parent artery and adjacent perforating vessels while redirecting blood flow away from the aneurysm. This mechanism facilitates thrombosis in the aneurysm, ultimately promoting its occlusion[4].

Published rates of complete aneurysm occlusion with flow diverters are variable, ranging from 55 to 95% at 12 months[5]. Current long-term follow-up data from the Pipeline trial (Medtronic Neurovascular, Irvine, California, USA) for Uncoilable or Failed Aneurysms (PUFS) suggests that these angiographic results are stable and should not be viewed as failures of therapy[6]. Moreover, incidence of aneurysm remnants is still lower comparing to coiling[7], and remnants after flow diversion are associated with minimal clinical impact[8].

The Flow Re-Direction Endoluminal Device (FRED; MicroVention, Aliso Viejo, California, USA) stent system is a self-expanding nickel titanium, single wire braid, compliant closed cell paired-stent. The device design consists of a 16-wire outer stent and a denser 48-wire inner stent. The outer stent allows a smooth and precise delivery and the inner stent combined with the outer stent allows flow diversion.

This article reports the results of a Polish multicenter clinical study, which evaluated the safety of the FRED stent system throughout the complete follow-up period of 24 months and its effectiveness at 6, 12, and 24-month follow-up in the treatment of unruptured intracranial aneurysms in selected locations.

Methods

Study Design

This study was a prospective, multicenter, observational clinical study.

The FRED stent devices obtained CE Mark certification in June 2013 and are routinely used at each institution. The study was conducted in compliance with ethical principles based on the Declaration of Helsinki concerning medical research in humans, the relevant requirements outlined in ISO 14,155, and national regulations. Patient data were collected according to the guidelines of the International Conference on Harmonization Guideline for Good Clinical Practice (GCP). All patients provided a written consent for the processing of their personal data. They were informed that treatment decisions would remain unchanged and that they could withdraw their consent at any time. At the time of study setup, observational studies in Poland did not require approval from an Ethics Committee. Inclusion criteria at baseline were patients aged 18 to 80 years with unruptured intracranial saccular or fusiform aneurysms located on the anterior circulation (C2-C6 segments of the internal carotid artery according to the Bouthillier classification[9]). Aneurysms in C6 segments with a maximal sac size of 5 mm, and aneurysms in C2-C4 segments were considered only in cases of skull base destruction, neurological deficits of cranial nerves, epistaxis or transient ischemic deficits related to the aneurysm. Additionally, aneurysms located on the posterior circulation above PICA branch could be included. Patients with previously ruptured aneurysms were eligible if the hemorrhage occurred at least 4 weeks before the procedure. Previously unsuccessfully treated aneurysms could be included unless they had been treated with another flow diverter. Patients were mainly excluded if they had contraindications to the use of dual antiplatelet therapy with Aspirin and Plavix, contraindications to general anesthesia, or hypersensitivity to nickel-titanium.

Procedural and follow-up modalities

Endovascular deployment of the FRED stent and subsequent follow-up evaluations were conducted per the standard of care. During the index procedure, additional coiling was performed if deemed necessary by the treating physician.

The study protocol recommended the following standard pharmacological treatments before, during and after the FRED stent deployment: Plavix 75 mg/d orally and ASA 150 mg/d orally starting five days before the procedure, with Plavix 75 mg/d orally to be continued for at least 3 months and ASA 150 mg/d orally for at least 6 months post-procedure. The decision to discontinue antiplatelet therapy was at the discretion of the treating physician. Antiplatelet treatment could be continued until the last follow-up visit at 24 months. Platelet aggregation inhibition testing was recommended on the day of the procedure. In cases of resistance to Plavix, the investigators could modify the treatment regimen based on their medical experience or the standard regimen used at their institution. Following vessel puncture, an intravenous heparin bolus adjusted to body weight was administered, with an additional 5000 IU of heparin after stent deployment.

DSA was the primary imaging modality for follow- up at 6 and 12 months. At the 24-month follow-up, an MRI exam could be performed according to each site standard practice.

Data collection and analysis

All data were collected using an electronic Case Report Form (eCRF) and independently monitored by a Contract Research Organization (CRO). To minimize bias, a Corelab composed of two independent and experienced neuroradiologists assessed all images collected during the procedure and follow-up to assess aneurysm occlusion, stent placement, and patency of the parent artery. All adverse events were adjudicated by a Clinical Events Committee (CEC) consisting of two other independent and experienced neuroradiologists.

The analysis was conducted on the per-protocol population, which included all patients meeting the inclusion/exclusion criteria and implanted with at least one FRED device. Patients who did not meet inclusion/

exclusion criteria and who were not implanted with a FRED stent were not followed in the study as per protocol. Therefore, the population description included all patients meeting the inclusion/exclusion criteria. The safety analysis comprised all patients meeting the inclusion/exclusion criteria and implanted with a FRED stent. The effectiveness analysis included all patients meeting the inclusion/exclusion criteria, implanted with a FRED stent and whose imaging was assessable by the Corelab.

Primary endpoints

The primary safety endpoint was defined as the rate of clinical complications, including early thromboembolic complications (within the first 3 months), late thromboembolic complications (between 3 and 24 months) and/or hemorrhage from the treated aneurysm, as adjudicated by the CEC.

The primary effectiveness endpoint was defined as the percentage of aneurysms successfully isolated from the rest of the circulation (Grade 4) and patency of the flow-diverter lumen (> 50%: Grade C and D) at 6-, 12- and 24-months of follow-up. Aneurysm isolation was classified into five levels by the imaging Corelab (Grade 0 - total filling of the aneurysmal sac; Grade 1 - filling more than 75% and less than 100%; Grade 2 - filling more than 25% and less or equal to 75%; Grade 3 - filling more than 1% and less or equal to 25%; Grade 4 - total isolation). The patency through the flow-diverter was classified in four levels by the imaging Corelab (Grade A - total occlusion; Grade B - partial thrombosis 50–99%; Grade C - partial thrombosis 1–49%; Grade D - full patency).

Statistical analysis

The study used a standard frequentist approach for statistical analyses. Descriptive statistics including mean, standard deviation, number evaluated, median, minimum and maximum were presented for continuous baseline characteristics. For categorical variables, the number evaluated and percentage were presented for each characteristic as appropriate. Missing data was not replaced and was considered as such. All data analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY, US).

Results

Between January 2016 and September 2017, 86 consecutive patients with 89 intracranial aneurysms were enrolled and treated at 8 interventional neuroradiology centers in Poland and were analyzed in the per-protocol population.

Patient and aneurysm characteristics

The mean age of patients recruited in this study was 56.8 ± 11.0 years, ranging from 30 to 78 years. Among the 86 patients, 74 (86.0%) were women. At baseline, all the patients (86/86, 100%) had a Glasgow Coma Scale of 15. Previous subarachnoid hemorrhage was reported in 8 patients (9.3%, 8/86). In 76 patients (88.4%) the aneurysm was associated with neurological symptoms, including headache (66.3%) and dizziness (44.2%), while in the remaining patients (11.6%, 10/86), the aneurysm was incidentally diagnosed. Patient characteristics are summarized in Table 1.

The 86 patients included in the analysis were eligible for treatment with a FRED for 89 aneurysms. Three patients had two target aneurysms. Six aneurysms (6.7%) had been previously treated. Of the 89 target aneurysms, 87 (97.8%) were saccular and only two were fusiform. Large and Giant aneurysms (≥ 10 mm in greatest dimension) represented 35.9% (32/89) of the aneurysms. Neck width measurement was unavailable for one of the fusiform aneurysms. Most aneurysms (73.9%, 65/88) had a maximum neck width ≥ 4 mm (mean neck width: 5.6 mm) and most aneurysms (69/88, 78.4%) had a dome-to-neck ratio (DNR) less than 2 (mean DNR: 1.7). Eighty-four aneurysms (94.4%) were located on the Internal Carotid Artery, and the remaining aneurysms were located on the basilar artery (2/89, 2.2%) and the vertebral artery (3/89, 3.4%). Aneurysm characteristics are summarized in Table 2.

Procedural results

The FRED procedure was completed for most aneurysms (86/89, 96.6%). The three aneurysms without a FRED implanted were finally treated with another flow-diverter. In all cases, one device was sufficient to treat one or two target aneurysms. Vascular access was femoral in all the patients (86/86, 100.0%).]. Adjunctive coiling was used in 31/89 cases (34.8%).

Safety results

Primary safety endpoint

The primary safety endpoint is the rate of clinical complications classified by the CEC as early thromboembolic complications, late thromboembolic complications and/or hemorrhage from the treated aneurysm. The safety population was the patients who met all inclusion/exclusion criteria and were implanted with at least one FRED (i.e. 83 patients). Ten complications on 9 out of 83 patients (10.8%) met the primary safety endpoint within 24-month follow-up. Safety results are presented in Table 3.

Permanent neurological morbidity and neurological mortality

Of the complications meeting the primary endpoint, some had a permanent clinical impact on patients, defining a permanent neurological morbidity rate of 3.6% (3/83). Three patients had an early thromboembolic complication resulting in permanent deficits: blindness of the right eye for one patient, periodic blurred vision of the left eye for the second patient and slight psychomotor retardation and paresis of the right extremities for the third one.

	Mean ± SD or Value (*n*) *N* = 86	Percentage	Min	Max
Age (years)	56.8 ± 11.0		30	78
Women	74	86.0%		
Neoplasm	11	12.8%		
Heart Failure	3	3.5%		
Heart rhythm disturbances	4	4.7%		
Diabetes	8	9.3%		
Hypertension	43	50.0%		
Hypercholesterolemia	17	19.8%		
Autosomal Polycystic Kidney Disease	1	1.2%		
Smoking				
Current	20	23.3%		
Past	11	12.8%		
Excessive alcohol intake	0	0.0%		
Frequent caffeine consumption	11	12.8%		
High level and/or frequent stress	15	17.4%		
Family history of SAH	3	3.5%		
Reasons for aneurysm diagnosis				
Headache	57	66.3%		
Dizziness	38	44.2%		
Sight disturbances	13	15.1%		
Acuity disturbances	11	12.8%		
Eye movement disturbances	3	3.5%		
Diplopia	5	5.8%		
Field of view disturbances	5	5.8%		
Sensation disturbances	2	2.3%		
Tinnitus	3	3.5%		
Swallowing disturbances	0	0.0%		
Other	22	25.6%		

Table 1. Patient baseline characteristics.

Two neurological complications led to the patient deaths, resulting in a neurological mortality rate of 2.4% (2/83). One patient had a late thromboembolic complication 14 months after treatment of the target aneurysm. He underwent a second FRED procedure to treat another fusiform ICA aneurysm 6 months after the first one and discontinued antiplatelet therapy for liver tumor surgery. He died from cerebral ischemic stroke 12 days after surgery. The other patient was treated for a large aneurysm of the vertebral artery (17*20 mm) with a flow-diverter without coiling. Fifteen days after stopping Plavix, he had a thrombosis of the aneurysm responsible for brainstem mass effect (which spontaneously resolved in a few days). One month later, he had a hemorrhage from the treated aneurysm and died 5 months after the procedure.

All-cause mortality

The all-cause mortality rate at 24 months post-treatment was 3.6% (3/83 patients). The first two deaths were described above. The third death was neither related to the device nor the procedure. The patient died of gastrointestinal hemorrhage and hypovolemic shock 22 months post-procedure.

Effectiveness results

Follow-up imaging data were available for 78 aneurysms at 6 months (90.7%), 73 aneurysms at 12 months (84.9%) and 62 aneurysms (72.1%) at 24 months. Image artefacts made it impossible to assess aneurysm isolation in 1 patient at 6 month and to assess flow diverter patency in 2 patients at 12 months and 3 patients at 24 months. The primary effectiveness endpoint defined as the percentage of aneurysms with successful isolation from the rest of the circulation and patency of flow-diverter lumen was achieved in 61.8% of aneurysms at 6 months, 76.1% at 12 months, and 82.5% at 24 months. All the effectiveness results are described in the Table 4.

Most aneurysms had complete occlusion at 6 months (50/77, 64.9%), at 12 months (58/73, 79.5%) and at 24 months (53/62, 85.5%). Adequate occlusion (Grade 3 and 4) was observed in 79.2%, 86.3% and 90.3% of aneurysms at 6, 12 and 24 months, respectively. Among the aneurysms with residual contrast flow (Grade 0 to 2), 4 out of 10 (40%) at 12 months and 3 out of 6 (50%) at 24 months had an ophthalmic artery arising from the aneurysm sac (Corelab assessment), thereby maintaining aneurysm patency and residual contrast flow in the sac.

	Mean ± SD or Value (*n*) *N* = 89	Percentage	Min	Max
Aneurysm type				
Saccular	87	97.8%		
Fusiform	2	2.2%		
Aneurysm previously treated	6	6.7%		
Aneurysm Height (mm)	10.5 ± 6.3		2.4	36.0
Aneurysm Width 1, (mm)	9.3 ± 5.4		3.0	25.0
Aneurysm Width 2 (mm)	9.0 ± 5.5		2.8	28.0
Giant aneurysm (≥ 25 mm)	1	1.1%		
Large aneurysm ([10; 24 mm])	31	34.8%		
Small aneurysm (< 10 mm)	57	64.0%		
Neck Width (mm)	5.6 ± 2.7		1.9	15.0
Dome-to-Neck Ratio	1.7 ± 0.8		0.6	4.4
Aneurysm Location				
ICA – C3 segment*	1	1.1%		
ICA – C4 segment*	8	9.0%		
ICA – C5 segment*	14	15.7%		
ICA – C6 segment*	61	68.5%		
Vertebral Artery	3	3.4%		
Basilar Artery – PCA/SCA segment	1	1.1%		
Basilar trunk	1	1.1%		

Table 2. Aneurysm baseline characteristics. * Bouthillier classification of the ICA (Internal Carotid Artery). Aneurysm measurement Width 2 is vertical to Width 1.

	Value (*n*) *N* = 83	Percentage
Primary safety endpoint (Neurological morbidity and mortality):	9*	10.8%
Early thromboembolic complications (before 3 months)	5	6.0%
Late thromboembolic complications (between 3 and 24 months)	4	4.8%
Hemorrhage from the treated aneurysm	1	1.2%
Neurological Permanent Morbidity	3	3.6%
Neurological death	2	2.4%
Non neurological death	1	1.2%

Table 3. Safety results based on the CEC adjudicated complications until 24 months. *One patient had two complications (a late thromboembolic complication and a hemorrhage from the treated aneurysm).

Retreatment rate

Two aneurysms (2.3%) required retreatment within 24-months post procedure. The first patient, with an aneurysm located on the C6 segment of the right ICA, measuring 6 × 4 × 3.5 mm (height x width x neck), was treated with a FRED device alone. Within the first 6 months after the index procedure, a distal stent migration occurred, and the aneurysm was retreated with an additional flow-diverter 6 months after the initial treatment. The second patient, with an aneurysm located on the C6 segment of the left ICA, measuring 15 × 16 × 6.4 mm (height x width x neck) was treated with a FRED device and adjunctive coiling. During the procedure, the FRED stent was badly positioned, failing to cover the neck, requiring retreatment with another flow-diverter 6 months after the initial procedure.

Discussion

Flow diversion has become a well-accepted option for the treatment of the cerebral aneurysms[10]. The device used for parent vessel reconstruction produces both hemodynamic and biological effects: Flow redirection induces stasis and thrombosis within the aneurysm sac. Tissue overgrowth provides scaffolding for the development of endothelial and neointimal tissue across the aneurysm neck[11].

The Flow Direction Endoluminal Device (FRED) was evaluated in this observational, prospective, multicenter conducted in 8 polish investigational sites. Study objectives were to provide safety and effectiveness data on the FRED stent system in the treatment of selected types of intracranial aneurysms in selected locations, including clinical results within 24 months and anatomical results at 6, 12 and 24 months.

The results demonstrated both a high technical success rate (96.6%) and the safety of the FRED stent system as demonstrated from the low neurological permanent morbidity rate (3.6%) and the low neurological mortality

	6 months Aneurysm No (%)	12 months Aneurysm No (%)	24 months Aneurysm No (%)
Aneurysm isolation rate:			
Grade 0 (total filling)	11/77 (14.3%)	7/73 (9.6%)	4/62 (6.5%)
Grade 1 (filling 75 – 100%)	1/77 (1.3%)	0/73 (0.0%)	1/62 (1.6%)
Grade 3 (filling 25 – 75%)	4/77 (5.2%)	3/73 (4.1%)	1/62 (1.6%)
Grade 3 (filling 1 – 25%)	11/77 (14.3%)	5/73 (6.8%)	3/62 (4.8%)
Grade 4 (total isolation)	50/77 (64.9%)	58/73 (79.5%)	53/62 (85.5%)
Missing Data[*]	*9*	*11*	*11*
Patency of flow-diverter lumen:			
Grade A (total occlusion)	2/78 (2.6%)	2/71 (2.8%)	2/59 (3.4%)
Grade B (partial thrombosis 50–99%)	0/78 (0.0%)	2/71 (2.8%)[**]	2/59 (3.4%)[**]
Grade C (partial thrombosis 1–49%)	6/78 (7.7%)	5/71 (7.0%)	0/59 (0.0%)
Grade D (full patency)	70/78 (89.7%)	62/71 (87.3%)	55/59 (93.2%)
*Missing Data**	*8*	*13*	*14*
Primary effectiveness endpoint	**47/76 (61.8%)**	**54/71 (76.1%)**	**47/57 (82.5%)**

Table 4. Effectiveness results based on the Corelab imaging assessment at 6, 12 and 24 months. [*] Missing data are missing imaging, images not evaluable by Corelab or retreatment. [**] Concerns only one patient who had 2 aneurysms treated with the same flow-diverter.

rate (2.4%) within 24 months following the index procedure. These results are consistent with previously published data on the FRED device and other flow-diverters. In the SAFE study, Pierot et al. showed cumulative 1-year mortality and morbidity rates of 1.9% and 2.9%, respectively[12]. In the Eu-FRED study, Killer-Oberpfalzer et al. reported an overall mortality rate of 1.5%, and transient and permanent morbidity in 3.2% and 0.8% of procedures respectively, from the time of treatment to last follow-up (>1 year)[13]. Similarly, the FRED Italian Registry reported overall mortality and morbidity rates of 4.3% and 7.3%, respectively[14]. The US FRED pivotal trial reported that 6.2% of patient met the primary safety endpoint of major stroke/death within 30 days and major ipsilateral stroke/neurological death after 30 days and within 1 year[15], and the BRED study reported mortality and morbidity rates within 12 months of 0.9% and 1.8% respectively[16]. In the North American experience published in 2022, the morbidity and mortality rates were 8.6% and 0.9% respectively[17]. In a meta-analysis on flow-diverters by Briganti et al., results from 18 studies showed a mortality rate ranged from 0.5 to 8% (mean 3.4%) and permanent morbidity related to the procedure was from 1 to 15% (mean 3.5%)[18]. In a pooled analysis of 3 studies (IntrePED, PUFS, ASPIRe), Kallmes et al. reported a major neurological morbidity rate of 5.7% and a neurological mortality rate of 3.3% for the Pipeline Embolization Device (Medtronic, Inc, Minneapolis, MN, USA)[19]. In the SCENT study (Surpass, Stryker, Neurovascular, Fremont, CA, USA), the 12-month major ipsilateral stroke or neurological death rate was 8.3%[20]. In a meta-analysis of multiple flow diverters, Brinjikji et al. reported procedure-related morbidity and mortality of 5% and 4% respectively, a rate of post-operative SAH, intraparenchymal hemorrhage, and ischemic stroke rates of 4.0%, 3.0%, and 6.0%, respectively[21]. In a recent comparative study, Vivanco-Suarez et al. showed similar ischemic and hemorrhagic event rates for the different flow-diverters of 5% and 3% respectively[22].

Regarding effectiveness outcomes, progressive improvement in occlusion status has been demonstrated in the complete occlusion rate of 64.9%, 79.5% and 85.5% at 6, 12, and 24 months, respectively. The primary efficacy endpoint (successful aneurysm isolation with parent artery patency) was met in 47/76 aneurysms (61.8%) at 6 months, 54/71 aneurysms (76.1%) at 12 months and 47/57 (82.5%) at 24 months. The complete occlusion rate for aneurysms treated with flow-diverters reported in the literature has a wide range because of the difference of the target aneurysm characteristics, the number of devices used to treat one aneurysm and the patient follow-up period. In the meta-analysis by Briganti et al., results from 18 studies showed that flow-diverter stenting of intracranial aneurysms achieves a good percentage of occlusion (81.5%, range 69–100%)[18]. Different studies or registries evaluated the use of the FRED stent system. In the SAFE study, complete occlusion rate was obtained in 73.3% of aneurysms at 12 months[12]. In a European retrospective multicenter study, which compiled the experience of 15 high-volume neurovascular centers, Killer-Oberpfalzer et al. reported a complete occlusion rate of 91.3% at 12 months[13]. The Italian FRED Registry in 30 Italian centers, reported a complete occlusion rate of 77% at 12–24 months[14], and the Spanish FRED Registry in one therapeutic neuroangiography department in Barcelona reported a complete and near complete occlusion rate (OKM C and D) of 84.6% at the end of follow-up[23]. More recently, the BRED study reported high rates of complete occlusion: 91% at 6 months and 95% at 12 months[16]. In the US pivotal trial, the complete occlusion rate at 12 months was 62.9%[15]. However, complete occlusion rate of 55.4%, reported by the North American experience, is lower compared to the previously published studies[17]. Low rate of adjunctive coiling (3.3%), could be an explanation of this low occlusion rate. In our series adjunctive coiling was used in 31/89 cases (34.8%), which may have led to high occlusion rate.

In the PUFS trial on Pipeline Embolization Device (PED), the rate of completely occluded aneurysms at 1 year was 86.6% with a median of 3 PEDs used per target aneurysm[24]. In a prospective observational registry on the same device (ASPIRe), the complete occlusion rate at the last follow-up (median and mean time: 7.8 and 9.7 months respectively) was 74.8% with multiple PEDs used in 18.8% of aneurysms[25]. In the more recent

PREMIER study, which evaluated the use of PED in small to medium unruptured aneurysms, a complete occlusion rate of 81.9% was reported at 1 year. The primary endpoint, defined as complete occlusion without significant stenosis of the parent artery or retreatment, was met in 76.8% of patients, with multiple PEDs used in 6.4% of aneurysms[26]. In the SCENT trial evaluating the Surpass Flow Diverter, 62.8% of patients met the 12-month primary effectiveness endpoint of aneurysm complete occlusion without clinically significant stenosis or retreatment, and the rate of complete occlusion was 66.1% at 12 months[20]. In SCENT, the average number of devices was 1.1 per patient: 11.7% patients received 2 devices to treat the target aneurysm. In the FRED Poland Study, only one device was sufficient to treat one or two target aneurysms in all cases.

A progression of complete aneurysm occlusion (from 64.9 to 85.5%) and near complete occlusion (from 79.2 to 90.3%) was observed between 6 and 24 months, thereby demonstrating that the development of aneurysm occlusion is improving with time. This was consistent with other studies. In the long-term results of the PUFS study, aneurysm occlusion for patients with angiographic follow-up progressively increased over time to 86.8%, 93.4% and 95.2% at 1, 3, and 5 years, respectively[6]. Two retrospective monocentric studies of the FRED device reported similar results, with an increase in complete occlusion rates over time up to 3 or 5 years[27,28].

It was also noticed during Corelab assessment that among the aneurysms with residual contrast flow (Grade 0 to 2), 4/10 (40%) at 12 months and 3/6 (50%) at 24 months had an ophthalmic artery arising from the aneurysm sac thereby maintaining aneurysm patency and residual contrast flow in the sac. These findings are consistent with the results of a retrospective study including 116 patients[29]. Indeed, Trivelato et al. showed that aneurysms treated with PEDs are less likely to be totally occluded if they have a branch arising from the sac than aneurysms without these branches (84% vs. 40% at 6 months). Manzato et al. also demonstrated that branch involvement was positively associated with lower odds of occlusion at 12 months[16].

Two aneurysms required retreatment during the follow up period. In both cases they were retreated with another flow-diverter. Retreatment was necessitated by bad positioning or stent migration, not by treatment failure following adequately placed stent. Goertz et al. have demonstrated the safety and efficacy of placing additional flow-diverter as a retreatment strategy[30].

Limitation

The major limitation of this study was the lack of a control group. Although the results were compared with studies of similar design, differences in patient and aneurysm characteristics may exist, along with variations in study practices depending on hospital location and time of patient inclusion. Furthermore, variations in the definition of primary endpoints among studies could also impact comparability. Another significant limitation concerning the effectiveness endpoint was the high number of non-evaluable images at follow-up. Despite a high clinical follow-up rate (83.7% of patients returned for clinical follow-up at 24 months), some images could not be evaluated by Corelab. However, the assessment bias for primary endpoints was minimized by the independent assessment performed by the CEC and Corelab.

Conclusion

In summary, the results indicate that the FRED stent system is safe and effective in treating unruptured intracranial aneurysms. The rate of total aneurysm isolation with patency of flow-diverter lumen (>50%) was favorable and improved from 64.9% at 6 months to 85.5% at 24 months, with only one flow diverter used per case. The overall safety profile of the FRED device within 24 months is satisfactory with a low neurological permanent morbidity rate of 3.6% and neurological mortality rate of 2.4%. These results were consistent with other FRED studies published to date.

Contributors All authors have provided a substantial contribution to the conception and design of the studies and/or the acquisition and/or the analysis of the data and/or the interpretation of the data; drafted the work or revised it for significant intellectual content; approved the final version of the manuscript; agree to be accountable for all aspects of the work, including its accuracy and integrity.

Data availability

The data that support the findings of this study are available from MicroVention Europe but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of MicroVention Europe.

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Author contributions

M.J. designed the work, collected and analysed data, substantively revised the work R.K. collected, analysed data and drafted the work J.Ż. collected and analysed data M.B. collected and analysed data M.Z. collected and analysed data K.S. collected and analysed data S.B. collected and analysed data K.L collected and analysed data E.H-Ł collected and analysed data P.B. collected and analysed data T.P. collected and analysed data W.P. collected and analysed data M.Z collected and analysed data B.N. collected and analysed data M.P collected and analysed data J.W collected and analysed data K.M collected and analysed data M.S collected and analysed data C.C supervised the work and analysed data E.B supervised the work and analysed data R.B supervised the work and analysed data M.P supervised the work and analysed data.

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Declarations

Competing interests

It was a Mcrovention Europe funded study. MP has got shares in Basecamp Vascular, Synchron, Sim &Size, EB is a consultant for Microvention, Stryker, Cerenovus, Balt, Medtronic, CC is a consultant for Medtronic, Microvention, MIVI, Cerenovus, JŻ has been paid for lectures for PENUMBRA.

Additional information

Correspondence and requests for materials should be addressed to R.K.

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