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Original Article

FRED-EPI study: Safety and efficacy of FRED/FRED Jr aneurysm treatment in current clinical practice

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ABSTRACT

Objective: Flow diversion is increasingly used as an endovascular treatment for intracranial aneurysms. FRED-EPI is a prospective, multicenter, French study, conducted to analyze the safety and efficacy of aneurysm treatment with FRED/FRED Jr (Microvention, AlisoViejo, CA, USA) in current clinical practice.
Patients and methods: Patients with intracranial aneurysms treated with FRED and FRED Jr who agreed to participate were prospectively and consecutively included in all French centers using these devices.
Results: From June 2020 to January 2022, 135 patients (110 females, 81.5%, and 25 males, 18.5%) with 154 aneurysms were included in 13 French interventional neuroradiology centers. The mean age was 53.9 ± 12.2 years (range: 20 – 77 years). Aneurysm was unruptured in 123 cases (79.9%), ruptured in 4 cases (2.6%), and recanalized in 27 cases (17.5%). Most aneurysms were small (135/154, 87.7%). Aneurysm locations were supraclinoid ICA in 83 (53.9%), cavernous and petrous ICA in 25 (16.2%), anterior cerebral artery or anterior communicating artery in 19 (12.3%), MCA in 7 (4.5%), and posterior circulation in 20 (13.0%). Three patients (2.2%) had hemorrhagic complications (1 delayed aneurysm rupture and 2 delayed remote hematoma) and 3 (2.2%) ischemic complications (2 intrastent thrombosis and 1 stroke related to atherosclerosis) leading to 1-year morbimortality of 4.4%. Complete aneurysm occlusion was reported in 105/139 aneurysms (75.5%).
Conclusions: FRED-EPI confirms good safety of aneurysm treatment with FRED/FRED Jr in current clinical practice with 4.4% 1-year morbimortality.
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Introduction

Flow diversion was introduced more than 10 years ago to treat large and giant intracranial aneurysms (IA) located at the ICA. Flow diverters (FDs) are dense mesh stents placed in front of the aneurysm neck to decrease the flow into the aneurysm inducing intraaneurysmal thrombosis. The initial evaluation of FDs conducted with the Pipeline Embolization Device (Medtronic, Dublin, Ireland) showed great efficacy with complete aneurysm occlusion at 6 months in 86.8% of aneurysms with moderate safety (5.6% of major ipsilateral stroke or neurologic death at day 180).[1] Analysis of the large, combined population of three series (1092 patients with 1221 aneurysms treated with Pipeline) showed a relatively high rate (7.1%) of morbimortality including 3.3% neurologic death.[2] However, the development of new FD generations and the improving skills of physicians in device use has led to a progressive decrease of morbimortality associated with this treatment. In the large series (420 patients) dedicated to the evaluation of p64 FD (phenox, Bochum, Germany) the composite morbimortality at the first follow-up was 2.4% with a mortality of 1.0%, whereas in PREMIER study (141 patients treated with Pipeline)

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2.1% experienced major stroke leading to death in 0.7% of patients.[3-4] In a European, multicenter study including 119 patients treated with the Derivo FD (Acandis, Pforzheim, Germany), mortality was 0.0% and morbidity 3.1%.[5] Similar results were reported in BRAIDED study (146 patients treated with the Derivo FD), but with a slightly higher mortality (1.4%).[6]

The Flow Re-Direction Endoluminal Device FRED/FRED Jr (Microvention, AlisoViejo, CA, USA) was evaluated in several prospective and retrospective series. In the SAFE study, the 6-month morbidity and mortality was 2.0% and 1.0%, respectively.[7] At 1 year, anatomical results were as follows: complete occlusion in 73.3%, neck remnant in 7.8%, and aneurysm remnant in 18.9%.[8] In a large, retrospective, multicenter series (531 patients with 579 aneurysms), the morality rate was 1.5%, whereas transient and permanent morbidity occurred in 3.2% and 0.8%, respectively.[9] At 1 year, the rate of complete aneurysm occlusion was 91.3% and the overall retreatment rate was 1.2%.[9]

Given the great efficacy of flow diversion, a widening of its indications has been observed with the treatment of small aneurysms located on the ICA, but also of distal aneurysms.[8] Use of flow diversion for the treatment of bifurcation aneurysms remains a matter of debate.[10]

FRED-EPI is a prospective, multicenter, French study to evaluate the safety and efficacy of the FRED and FRED Jr devices in the treatment of IAs.

Materials and methods

FRED-EPI is a single-arm, prospective, multicenter, observational study conducted in France to evaluate the safety of bare FRED and FRED Jr devices in treating IAs in real world conditions. The study was sponsored and completely funded by Microvention and registered on www.clinicaltrials.gov (NCT02862756). FRED-EPI received national regulatory approval from the South-West III Ethics Committee. The investigators fully informed all included patients of the study objectives and provided a patient information sheet. Patients agreed with anonymized data collection in the study frame. According to French law and study design, written informed consent was not required.

FRED and FRED Jr

The FRED/FRED Jr systems (Microvention, AlisoViejo, CA, USA) have a self-expanding nickel titanium, single wire braid, closed cell paired-stent design. The external stent permits accurate positioning and arterial wall apposition of the device while the internal lower porosity stent enables flow diversion. FRED/FRED Jr systems have several radiopaque markers. FRED is delivered through a 0.027" microcatheter (Headway 27, Microvention, AlisoViejo, CA, USA) and FRED Jr through a 0.021" microcatheter (Headway 21, Microvention, AlisoViejo, CA, USA). FRED/FRED Jr can be recaptured until 80% deployed. FRED/FRED Jr exist in various diameters (FRED between 3.5 and 5.5 mm; FRED Jr between 2.5 and 3.00 mm) and lengths.

Study design

The goal was to include all patients treated in France for an IA using a FRED or FRED Jr device.

The FRED-EPI primary objective was to evaluate the morbidity-mortality rate (neurologic death or major ipsilateral stroke defined by an increase of NIHSS score ≥ 4 and a duration ≥ 7 days) within 1 year of treatment. Morbidity was defined as a mRS score >2.

Several secondary objectives were also evaluated:

- Rate of patients with a mRS >2 at 1 year (if mRS was ≤ 2 before treatment) or with a mRS increase of 1 point or more if mRS was >2 before the treatment;
- Rate of patients having a complete aneurysm occlusion, 1 year post-procedure; and
- Rate and type of aneurysm retreatment in the year following the initial treatment.

As the goal was to evaluate treatment with FRED/FRED Jr in real world conditions, no inclusion/exclusion criteria were defined. All French interventional neuroradiology (INR) centers using FRED/FRED Jr were contacted and those patients who agreed to participate were included. Reasons for non-participation were not collected.

FRED-EPI was conducted according to Good Clinical Practice (GCP) rules:

- All data were verified by independent Clinical Research Associates (CRA).
- All adverse events were independently evaluated by an interventional neuroradiologist who did not participate in the study.
- Anatomical results were not independently evaluated because they were not part of the primary objective.

Procedural modalities

Pre-, intra-, and post-operative antiplatelet therapy (APT) was managed in each center according to current practice. The study protocol did not require antiplatelet activity testing. If deemed necessary by the treating physician, treatment with additional devices (balloons, coils, and stents) could be performed.

Data collection

Each center completed a patient file with demographic (patient, age and gender), aneurysm (rupture status, location, size, and neck size), and procedural data including APT pre-, during, and post-procedure.

Clinical evaluation including mRS was performed pre-treatment, at hospital discharge, between 3 and 6 months, and between 12 and 18 months. Vascular imaging was performed as per usual practice (DSA, MRA, and CTA). Data from retreatment procedures were also collected.

Data analysis

The complications outcome was independently evaluated by an independent neuroradiologist.

Anatomical results were self-evaluated by the participating centers post-operatively and between 12 and 18 months using a 3-grade scale: complete occlusion, neck remnant, or aneurysm remnant. The parent artery status was also evaluated with a 4-grade scale: no stenosis, stenosis < 50%, stenosis ≥ 50%, or complete occlusion.

Statistical analysis

This article reports the study design, patient demographics, procedural results, and 1-year safety and efficacy outcomes. Statistical analysis was performed on the intention-to-treat (ITT) population, which included all patients who had a FRED/FRED JR device inserted at the puncture site with the intention of treating the target aneurysm. A standard frequentist approach was used for the statistical analyses. Descriptive statistics were presented for continuous baseline characteristics including the mean, standard deviation, number evaluated, minimum, and maximum values. For categorical variables, the number evaluated and percentage for each characteristic were provided as appropriate. Missing data were not imputed and were analyzed as missing. All data analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY, USA).

Results

Participating centers

Among the 37 French INR centers, 20 were using FRED/FRED Jr at the time of FRED-EPI set up. Of these, 4 did not agree to participate: 3 due to a limited use of FRED/FRED Jr and 1 due to the absence of a CRA during the study period. Among the 16 centers using FRED/FRED Jr and agreeing to participate, 3 did not include patients during the study period.

Patient and aneurysm population

From June 2020 to January 2022, 135 patients were included in the 13 French INR centers (Fig. 1) and were treated for 154 aneurysms (Table 1) during 138 procedures (2 patients were treated for 2 aneurysms during 2 different procedures; 1 patient had a cardiac problem during a first procedure that was discontinued before aneurysm treatment but subsequently treated during a second procedure). Among 135 patients, 110 were female (81.5%) and 25 male (18.5%). The mean age was 53.9 ± 12.2 years (range: 20 – 77 years). Pre-operative mRS was 0 in 108 patients (80.0%), 1 in 19 (14.1%), 2 in 6 (4.4%), 3 in 1 (0.7%), and 4 in 1 (0.7%). Smoking was encountered in 41/135 patients (30.4%) and elevated blood pressure in 42/135 (31.1%). Among 135 patients, 121 (89.6%) had 1 treated aneurysm, 9 (6.7%) had 2, and 5 (3.7%) had 3.

Aneurysm was unruptured in 123 cases (79.9%), acutely ruptured in 4 cases (2.6%), and recanalized in 27 cases (17.5%). Among the recanalized aneurysms, 18 were ruptured at the time of initial treatment. In recanalized aneurysms, previous treatment was coiling in 19, intrasaccular flow disrupter in 5, and other in 3. Indications for flow diversion in ruptured aneurysms were fusiform aneurysms in 2 patients and giant aneurysms in 2 patients.

Aneurysm shape was saccular in 138 (89.6%), fusiform or dissecting in 15 (9.7%), and blister-like in 1 (0.6%). Dome-to-neck ratio (1 missing data) was <2 in 134/153 aneurysms (87.6%) and ≥2 in 19/153 (12.4%). Aneurysm was small in 135/154 cases (87.7%), large (>10 and <25 mm) in 17/154 (11.0%), and giant in 2/154 (1.3%).

Aneurysm locations were supraclinoid ICA in 83 (53.9%), cavernous and petrous ICA in 25 (16.2%), anterior cerebral artery (ACA) or anterior communicating artery (Acom) in 19 (12.3%), MCA in 7 (4.5%), and posterior circulation in 20 (13.0%).

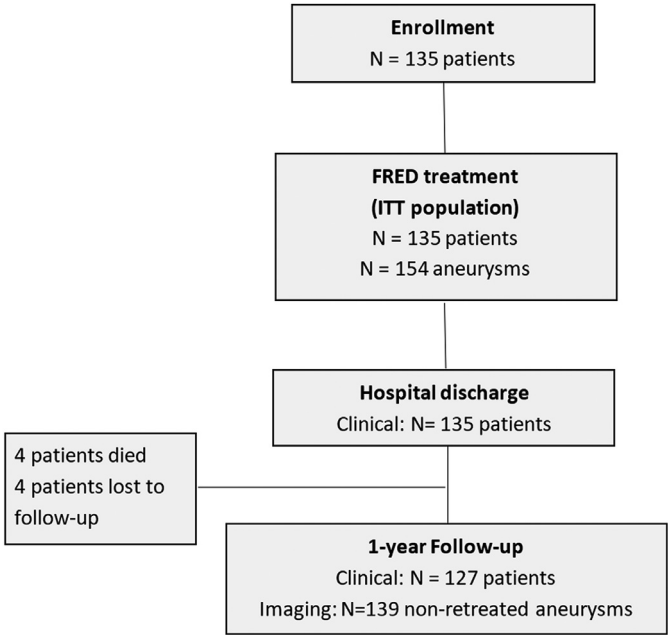

Fig. 1. Study flowchart.

Table 1
Demographics and aneurysms characteristics.

Patient characteristics	*N* = 135
Age, years, mean±SD	53.9 ± 12.2
Male sex, n (%)	25 (18.5%)
Medical history, n (%)	
Smoking	41 (30.4%)
Hypertension	42 (31.1%)
Family history of aneurysm	14 (10.4%)
Score mRS, n (%)	
0	108 (80.0%)
1	19 (14.1%)
2	6 (4.4%)
3	1 (0.7%)
4	1 (0.7%)
Aneurysm Characteristics	***N* = 154**
Aneurysm status, n (%)	
Unruptured	123 (79.9%)
Recanalized	27 (17.5%)
Acutely ruptured	4 (2.6%)
Aneurysm location, n (%)	
Supraclinoid ICA	83 (53.9%)
Cavernous and petrous ICA	25 (16.2%)
ACA or Acom	19 (12.3%)
MCA	7 (4.5%)
Posterior circulation	20 (13.0%)
Aneurysm size, n (%)	
Small (≤ 10 mm)	135 (87.7%)
Large (>10 and <25 mm)	17 (11.0%)
Giant (≥ 25 mm)	2 (1.3%)
Dome-to-neck ratio, n (%)	
<2	134 (87.6%)
≥ 2	19 (12.4%)

*ICA = internal carotid artery; ACA = anterior cerebral artery; Acom = anterior communicating artery; MCA = middle cerebral artery.

Treatment feasibility and adjunctive treatments

Treatment was successfully performed in all aneurysms (100.0%) (Table 2). One hundred thirty-nine FDs were implanted to treat 154 aneurysms including 105 FRED (75.5%) and 34 FRED Jr (24.5%). One FD was used to treat 1 aneurysm in 124 patients, 2 aneurysms in 10 patients, and 3 aneurysms in 3 patients. One patient with a single

Table 2
Clinical and angiographic outcomes.

	N = 154
Treatment success	154 (100%)
Morbimortality rate	6 (4.4%)
Complications	
Hemorrhagic complications	3 (2.2%)
Ischemic complications	3 (2.2%)
mRS score at long-term follow-up, n (%)	
0 – 2	124 (94.7%)
> 2	7 (5.3%)
Angiographic results at final follow-up, n (%)	
Complete occlusion (Raymond I)	105/139 (75.5%)
Neck remnant (Raymond II)	17/139 (12.2%)
Aneurysm remnant (Raymon III)	17/139 (12.2%)
Missing data	15
Parent artery status at final follow-up, n (%)	
No stenosis	139/142 (97.9%)
Stenosis < 50%	1/142 (0,7%)
Stenosis ≥ 50%	1/142 (0,7%)
Complete occlusion	1/142 (0,7%)
Missing data	12
Retreatment rate, n (%)	3 (1.9%)

aneurysm was treated with 2 FDs due to insufficient neck coverage after placement of the first FD.

No APT was given in the days before the treatment in 34/138 procedures (24.6%). In these patients, antiplatelet treatment was initiated on the day of the procedure. Single APT was given before 36/138 procedures (26.1%) including aspirin in 4 (2.9%), clopidogrel in 13 (9.4%), ticagrelor in 18 (13.0%), and prasugrel in 1 (0.7%). Dual APT was given pre-operatively in 68/138 procedures (49.3%) including aspirin + clopidogrel in 21/138 (15.2%), aspirin + ticagrelor in 27/138 (19.6%), and aspirin + prasugrel in 20/138 cases (14.5%). During most procedures, patients received heparin (120/138, 87.0%) and at least 1 antiplatelet medication (123/138, 89.1%) that was typically aspirin (102/138, 73.9%). At hospital discharge (137 procedures [1 patient died during hospital stay, see below]), the number of antiplatelet medications was 0 (2/137, 1.5%), 1 (2/137, 1.5%), 2 (132/137, 96.4%), and 3 (1/137, 0.7%). Of 2 patients who did not receive antiplatelet medication at hospital discharge, 1 patient had a cardiac problem during anesthesia leading to procedure termination before FD placement and 1 was discharged with no antiplatelet medication and DAPT began after hospital discharge (3 days post-procedure). Of 2 patients receiving 1 antiplatelet medication at hospital discharge, 1 had a hemorrhagic complication (remote hematoma occurring 1 day post-procedure) and only received ticagrelor thereafter, and 1 only received clopidogrel (no complication).

Additional devices were used to treat 39/154 aneurysms (25.3%), including coils in 38 and stent in 1.

Morbimortality rate at 1 year (Primary objective)

Complications as defined in the primary objective occurred in 6/135 patients (4.4%). Three patients had hemorrhagic complications (2.2%). In 1 patient treated exclusively with a FD (no coils) for an unruptured giant MCA aneurysm (width: 27 mm), a delayed aneurysm rupture occurred after hospital discharge 4 days post-procedure, inducing a huge temporal hematoma leading to coma and death. In 1 patient treated for a large, unruptured carotid-ophthalmic aneurysm, a delayed remote hematoma occurred 1-day post-procedure leading to left hemiparesis and confusion. This patient received Ticagrelor the day of the procedure (before it) and aspirin was introduced the day after the procedure. Both medications were interrupted after the intracranial bleeding and Ticagrelor was introduced again 1.4 month after the bleeding for 3 months. The patient was subsequently mRS 4 at hospital discharge and at 12 months. In 1 patient treated for an unruptured carotid-ophthalmic aneurysm, retreatment was performed 9 months after the initial procedure by placing another FD (Silk Vista Baby, Balt, Montmorency, France). This 2nd endovascular procedure was performed after premedication with clopidogrel. A remote, parietal hematoma occurred 1 day later leading to right hemiplegia and aphasia with mRS 4 leading to discontinuation of clopidogrel replaced with aspirin.

Three patients had ischemic complications (2.2%) of which 2 were treated for ruptured aneurysms. In 1 patient, a FD was placed to treat a dissecting aneurysm of the posterior cerebral artery. Cangrelor infusion was used during the procedure followed by DAPT (ticagrelor and aspirin). Two days post-procedure, the patient had an in-stent thrombosis leading to right hemiplegia and aphasia and was successfully treated by intravenous tissue plasminogen activator (IV tPA). At hospital discharge, the patient was mRS 3 and at 13 months mRS 2. Another patient treated for a large (16 mm in height) ruptured Acom aneurysm with a FRED Jr under IV Cangrelor had an ischemia in the anterior cerebral territory due to an in-stent thrombosis which occurred 2 days post-procedure after discontinuing Cangrelor to place a ventricular shunt (hydrocephalus). The patient presented a progressive clinical worsening (vasospasm) leading to death 3 days post-initial aneurysm treatment. Finally, a third patient who had a right MCA stroke several months earlier was treated for 3 aneurysms in the same procedure including 1 postero-inferior cerebellar artery (PICA) aneurysm treated with a FRED Jr and the 2 others with coiling. Thirty-seven days post-procedure, the patient presented with an ischemic stroke in the left MCA territory and was treated with IV thrombolysis with a subsequent left temporal hematoma leading to death.

Global mortality / morbidity up to 1 year

One-year follow-up (mean 16.0 ± 4.0 months) was obtained in 131/135 patients (97.0%).

The cumulated morbimortality rate at 1 year was 7/131 (5.3%) including 4 deaths (3.1%) and 3 clinical worsening (2.3%) with mRS >2 (1 patient with mRS 3 and 2 patients with mRS 4).

Three deaths were related to hemorrhagic or ischemic stroke (see above). An additional patient died during the 1-year follow-up period from cancer. Clinical worsening in 2 cases was related to ischemic stroke (see above) and 1 to strong intercostal pain unrelated to the aneurysm (mRS 3 at 1 year).

Anatomical results at 12 months

Anatomical results at 12 months (mean: 16.0 ± 4.0 months) were evaluated in 139/154 aneurysms (90.3%). Fifteen aneurysms had no 12-month follow-up (4 deaths, 3 retreatments, 4 patients with 5 aneurysms lost to follow-up, and 3 with no 12-month imaging).

Vascular imaging technique was DSA in 49/139 (35.3%) patients, MRA in 83/139 patients (59.7%), and CTA in 7/139 patients (5.0%).

Complete occlusion was observed in 105/139 aneurysms (75.5%), neck remnant in 17/139 aneurysms (12.2%), and aneurysm remnant in 17/139 aneurysms (12.2%). Adequate occlusion (complete occlusion or neck remnant) was observed in 122/139 aneurysms (87.8%). Of the 105 aneurysms with complete aneurysm occlusion, 30 (28.6%) were treated with coiling.

The parent artery status was evaluated in 142/154 aneurysms with results of no stenosis in 139 (97.9%), stenosis < 50% in 1 (0.7%), stenosis ≥ 50% in 1 (0.7%), and complete occlusion in 1 (0.7%).

Retreatment

At 1 year, 3/154 aneurysms (1.9%) were retreated one each with coils, FD, and FD and coils.

Discussion

FRED-EPI is a prospective, multicenter, consecutive study evaluating the safety and efficacy of the FRED/FRED Jr device for aneurysm treatment. The goal was to collect all patients with an IA treated with these devices to evaluate their safety when used in current clinical practice. The study confirms the high feasibility (100.0%) and excellent safety of the FRED/FRED Jr device with cumulated morbimortality at 12 months at 4.4% (morbidity and mortality at 2.2%, respectively). Self-evaluated anatomical results also show good efficacy of both devices with complete occlusion at 12 months in 75.5% of aneurysms with a very low rate of intrastent stenosis or parent artery occlusion (2.1%) and of retreatment (1.9%).

These results are similar to what was reported in SAFE study with the difference that SAFE selected patients and aneurysms according to specific inclusion/exclusion criteria. In FRED-EPI, patients were not selected, but consecutively included in the participating centers according to current clinical practice.[7-8] Therefore, the two studies include different populations with fewer unruptured aneurysms included in FRED-EPI (exclusion criteria in SAFE); fewer ICA and MCA aneurysms included in FRED-EPI; more Acom/ACA and posterior circulation aneurysms included in FRED-EPI (posterior circulation was an exclusion criteria in SAFE); and more small aneurysms in

FRED-EPI (87.7% versus 68.9% in SAFE). Despite these study population differences, the rate of morbidity and mortality at 12 months were similar in SAFE (2.9% and 1.9%, respectively) and FRED-EPI (2.2% and 2.2%, respectively). Additionally, complete aneurysm at 12 months was obtained in a similar rate in both SAFE (73.3%) and FRED-EPI (75.5%) as well as retreatment rate at 12 months (SAFE: 2.2%; FRED-EPI: 1.9%).

When compared to other FDs, safety results often differ from one device to another. Cumulative morbimortality at 12 months with Pipeline (Medtronic; PUFS study), Surpass FD (Stryker Neurovascular, Fremont, CA, USA; SCENT study), Derivo (Acandis, Pforzheim, Germany) is slightly higher (5.6%, 8.3%, and 7.3%, respectively) compared to FRED/FRED Jr (4.4%).[1, 5, 11] In the large population of three series (PUFS, Intreped, and ASPIRe) treated with Pipeline, Kallmes et al. reported a neurological mortality of 3.3% and morbidity of 5.7%.[2] In contrast, in the large p64 FD series (phenox, Bochum, Germany), the composite morbidity/mortality rate was slightly lower (2.7%).[3] These differences must be analyzed cautiously as they are likely related to different factors including device design, period of recruitment (and the fact that operator skills have improved since flow diversion was introduced), as well as peri-operative management.

Four patients with ruptured aneurysms were included in FRED-EPI. The reason for treating ruptured aneurysms with FRED/FRED Jr were anatomical (fusiform aneurysm shape, large aneurysm size, and wide neck). Two of these patients had an intrastent thrombosis leading to death in 1 case and neurological worsening in the other (mRS 2 at 12 months). Even if in the first case the death was likely multifactorial (also related to hydrocephalus and vasospasm), these complications suggest that treatment of ruptured aneurysms at the acute phase of bleeding with bare FDs is a questionable option and should be avoided as much as possible. When necessary, it is probably better to use a staged procedure, which means coiling of the aneurysm (singularly the dome) immediately after aneurysm rupture, followed several days or weeks later by placing a FD in front of the aneurysm neck (and, if necessary, additional coils).[12] In future, another potential option will be to use surface-modified FD if appropriate trials demonstrate that they can be used with single (or no) APT with limited risk of thromboembolic complications.[13]

Using the FRED-EPI study to compare the efficacy of FRED/FRED Jr to other FDs is more difficult since anatomical results were not evaluated by an independent core lab. However, as shown with other FDs, the rate of complete occlusion after aneurysm treatment with FRED/FRED Jr is quite high (75.5%) with a rate of adequate occlusion (complete occlusion and neck remnant) of 87.7%. Long-term analysis was not foreseen in FRED-EPI study. However recent series have shown quite good results in long-term follow-up with complete aneurysm occlusion in 77.4% at 2-year and 88.4% at 4-year.[14]

A new generation of FRED device is now available with an antithrombotic coating (FRED X) and a first retrospective, multicenter study showed a good safety of the device: 1.9% morbidity and 1.2% mortality with 66.0% complete aneurysm occlusion at 7-month.[15]

Limitations

This study has several limitations. One limitation is that FRED-EPI is not a randomized trial and safety and efficacy cannot be directly compared to a control group. A second important limitation is that anatomical results were not independently evaluated given that this study was conducted to evaluate the 1-year safety of patients with aneurysms treated with FRED/FRED Jr. Since status of 1-year aneurysm occlusion was precisely evaluated in the SAFE study, it was deemed unnecessary to collect images or include an independent evaluation. A third limitation is that 1-year anatomical results were analyzed in the majority of cases (59.7%) with MRA that is not clearly analyzing the intra-stent stenosis. It probably explains the relatively low rate of intra-stent stenosis compared to other series.[16-17]

Conclusions

The 1-year clinical data analysis in the FRED-EPI study confirms the FRED/FRED Jr device high degree of safety. The results are quite similar to the SAFE study showing a cumulated morbimortality at 1 year of 4.4% with 2.2% mortality (4.8% and 1.9% in SAFE, respectively). Self-evaluated anatomical results also show a rate of complete aneurysm occlusion at 1 year (75.5%) similar to what was reported in the SAFE study (73.3%).

Clinical trial registration

URL: http://www.clinicaltrials.gov.
Unique identifier: NCT04315168

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship. All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship. Individual author contributions are as follows:

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers. The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article and that this report does not contain any personal information that could lead to their identification. The authors declare that the work described does not involve patients or volunteers.

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Declaration of competing interest

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper. The authors declare the following financial or personal relationships that could be viewed as influencing the work reported in this paper:

References

1. Beckse T, Kallmes DF, Saatci I, et al. Pipeline for Uncoilable or failed aneurysms: results from a multicenter, clinical trial. *Radiology*. 2013;267:858–868. https://doi.org/10.1148/radiol.13120099.
2. Kallmes DF, Brinjikji W, Cekirge S, et al. Safety and efficacy of the Pipeline embolization device for treatment of intracranial aneurysms: a pooled analysis of 3 large studies. *J. Neurosurg.* 2017;127:775–780. https://doi.org/10.3171/2016.8.JNS16467.
3. Bonafé A, Aguilar Perez M, Henkes H, et al. Diversion-p64: results from an international, prospective, multicenter, single-arm post-market study to assess safety and effectiveness of the p64 Flow Modulation device. *J Neurointerv Surg*. 2022;14:898–903. https://doi.org/10.1136/neurintsurg-2021-017809.
4. Hanel RA, Kallmes DF, Lopes DK, et al. Prospective study on embolization of intracranial aneurysms with the Pipeline device: the PREMIER study one-year results. *J Neurointerv Surg*. 2020;12:62–66. https://doi.org/10.1136/neurintsurg-2019-015091.
5. Taschner CA, Stracke CP, Dorn F, et al. Derivo Embolization Device in the treatment of unruptured intracranial aneurysms: a prospective multicenter study. *J Neurointerv Surg*. 2021;13:541–546. https://doi.org/10.1136/neurintsurg-2020-016303.
6. Padovani Trivelato F, Abud DG, Ulhôa AC, et al. Derivo embolization device for the treatment of intracranial aneurysms: a multicenter study of 183 aneurysms. *Stroke*. 2019;50:2351–2358. https://doi.org/10.11161/STROKEAHA.119.025407.
7. Pierot L, Spelle L, Berge J, et al. Feasibility, complications, morbidity, and mortality at 6 months for aneurysm treatment with the Flow *Re*-Direction Embolization

Device: report of SAFE study. *J Neurointerv Surg*. 2018;10:765–770. https://doi.org/10.1136/neurintsurg-2017-013559.
8. Pierot L, Spelle L, Berge J, et al. SAFE study (Safety and Efficacy Analysis of FRED embolic device in aneurysm treatment): 1-year clinical and anatomical results. *J Neurointerv Surg*. 2019;11:184–189. https://doi.org/10.1136/neurintsurg-2018-014261.
9. Killer-Oberpfalzer M, Kocer N, Griessenhauer H, et al. European Multicenter Study for the evaluation of dual-layer Flow-Diverting Stents for treatment of wide-neck intracranial aneurysms: the European Flow-Redirection Intraluminal Device Study. *AJNR Am J Neuroradiol*. 2018;39:841–847. https://doi.org/10.3174/ajnr.A5592.
10. Kashkoush A., El-Abtah M.E., Petitt J.C., et al. Flow Diversion for the treatment of intracranial bifurcation aneurysms: a systematic review and meta-analysis. J Neurointerv Surg doi: 10.1136/jnis-2023-020582.
11. Meyers PM, Coon AL, Kan PT, et al. SCENT trial. *Stroke*. 2019;50:1473–1479. https://doi.org/10.1161/STROKEAHA.118.024135.
12. Wei Y, Zhang X, Zhang R, et al. Staged stenting strategy of acutely wide-neck ruptured intracranial aneurysms: a metaanalysis and systematic review. *Font Neurol*. 2023;14:1070847. https://doi.org/10.3389/fneur.2023.1070847.
13. Pierot L, Lamin S, Barreau X, et al. COATING (Coating to Optimize Aneurysm Treatment in the New FD Generation) study. The first randomized controlled trial evaluating a coated FD (p64 MW HPC): study design. *J Neurointerv Surg*. 2023;15:684–688. https://doi.org/10.1136/neurintsurg-2022-018969.
14. Vollherbst DF, Lücking H, DuPlessis J, et al. The FRESH study: treatment of intracranial aneurysms with the new FRED X flow diverter with antithrombotic surface treatment technology – First experience in 161 patients. *AJNR Am J Neuroradiol*. 2023;44:474–480. https://doi.org/10.3174/ajnr.A7834.
15. Hohenstatt S, Ulfert C, Herweh C, et al. Long-Term follow-up after aneurysm treatment with the Flow Redirection Endoluminal Device (FRED) Flow Diverter. *Clin Neuroradiol*. 2024;34:184–188. https://doi.org/10.1007/s00062-023-01346-3.
16. McDougall CG, Diaz O, Boulos A, et al. Safety and efficacy results of the Flow Redirection Endoluminal Device (FRED) stent system in the treatment of intracranial aneurysms: US pivotal trial. *J Neurointerv Surg*. 2022;14:577–584. https://doi.org/10.1136/neurintsurg-2021-017469.
17. Dinc H, Saatci I, Oguz S, et al. Long-term clinical and angiographic follow-up results of the dual-layer flow diverter device (FRED) for the treatment of intracranial aneurysms in a multicenter study. *Neuroradiology*. 2021;63:943–952. https://doi.org/10.1007/s00234-020-02627-1.