Feasibility, complications, morbidity, and mortality results at 6 months for aneurysm treatment with the Flow Re-Direction Endoluminal Device: report of SAFE study

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ABSTRACT

Background and purpose Flow diverters are increasingly used for the treatment of intracranial aneurysms. Evaluation of the first devices available for clinical use showed high efficacy of this treatment although safety results were worse compared with coiling or balloon-assisted coiling. The Safety and Efficacy Analysis of FRED Embolic Device in Aneurysm Treatment (SAFE) trial is a single-arm, multicenter, prospective study conducted to precisely analyze the safety and efficacy of the FRED and FRED Jr devices.

Methods Unruptured and recanalized aneurysms located in the anterior circulation treated with FRED and FRED Jr were prospectively included. Adverse events were independently evaluated by a Clinical Event Committee with a vascular neurosurgeon and an interventional neuroradiologist. Primary safety outcome measures were morbidity and mortality rates at 6 months after treatment.

Results A total of 103 patients/aneurysms were included in 13 interventional neuroradiology (INR) centers. Aneurysm locations were suprachinoid internal carotid artery (ICA) in 71 (68.9%), cavernous ICA in 15 (14.6%), anterior cerebral artery or anterior communicating artery in nine (8.7%), and middle cerebral artery in eight (7.8%). Aneurysms were small (<10 mm) in 71 patients (68.9%). Treatment was successfully performed in 98/103 patients (95.1%). Thromboembolic (TE) complications occurred in 5/103 patients (4.9%), intraoperative rupture in 2/103 patients (1.9%), delayed aneurysm rupture in 1/103 patient (1.0%), and delayed hematoma occurred in 1/103 patient (1.0%). Six-months’ morbidity and mortality rates were 1/102 (1.0%) and 2/102 (2.0%), respectively.

Conclusions Aneurysm treatment with the FRED device is safe with low mortality (1.0%) and morbidity (2.0%).

Clinical trial registration NCT02921698.

INTRODUCTION

Flow diversion (FD) is increasingly used in the endovascular management of intracranial aneurysms.1,2 After the initial results of the Pipeline of Uncoilable or Failed Aneurysms (PUFS) study showing their good safety and high efficacy, flow diverters were recommended for the treatment of large and giant aneurysms, principally located at the internal carotid artery, and recanalized aneurysms.3,4 Subsequent studies showed, the treatment of posterior circulation aneurysms was associated with a higher risk of mortality, ischemic stroke, and perforator infarction, making this indication controversial.6

It quickly became obvious that placement of the flow diverter altogether in front of the aneurysm neck and of collateral branches or perforators carried the risk of modifying the flow in these branches.7,8 Several studies have shown that, depending on the collateral status, the covered vessel may occlude. In a recent large FD series, the rate of collateral branch occlusion was quite variable: 5.3% of ophthalmic arteries, 42.6% of posterior communicating arteries, 14.3% of anterior communicating arteries, but 0.0% of anterior choroidal arteries were occluded.9 Most occlusions were not associated with any clinical change.

Complications relatively specific to flow diversion were encountered with the increasing use of these devices: in-stent thrombosis or stenosis, delayed aneurysm rupture, or delayed remote hematomas.10,11

The Flow Re-Direction Endoluminal Device (FRED TM) is a double-layer flow diverter with a stent-like outer layer and a flow diverter part inside the stent. This design has the theoretical advantage of improving the navigability of the device especially in tortuous anatomy and closely apposing the device against the arterial wall, a key point in achieving aneurysm occlusion. According to the specific indications, complications, and issues encountered with flow diversion, every flow diverter has to be carefully evaluated in terms of safety and efficacy. Several series have already evaluated the performance of the FRED device, but these were small, retrospective, and mostly single-center studies.12–20

The Safety and Efficacy Analysis of FRED Embolic Device in Aneurysm Treatment (SAFE) trial is a single-arm, multicenter, prospective study conducted in France to precisely analyze the safety
and efficacy of this device. Here we present safety results at 6 months after the procedure.

MATERIALS AND METHODS
SAFE is a single-arm, prospective, multicenter, observational study focused on the evaluation of aneurysm treatment with the FRED device in 13 interventional neuroradiology centers in France.

SAFE received national regulatory authorization, including approvals in France from the Consultative Committee of Information Processing in Healthcare Research program (CCTIRS), the Reims Institutional Review Board, and the National Commission for Data Processing and Freedom (CNIL). All included patients were fully informed of the study objectives by the investigators and with a patient information sheet. Patients agreed with anonymized data collection in the study frame. According to French law, no written informed consent was necessary.

FRED and FRED Jr
The Flow Re-Direction Endoluminal Device (FRED and FRED Jr) systems (Microvention, Aliso Viejo, CA) have a self-expanding nickel titanium, single wire braid, closed cell pair-stent design allowing the flow diverter to closely appose the vessel wall (Figure 1). The FRED and FRED Jr can be simultaneously deployed and retrieved by a single operator. The external stent permits the accurate positioning of the device, while the internal lower porosity stent enables the diversion of blood flow. The FRED and FRED Jr systems feature integrated dual layer coverage designed to focus mainly at the neck of an aneurysm. The FRED and FRED Jr systems have distal and proximal markers on their ends as well as interwoven helical strands delineating the inner working length of the stent to provide fluoroscopic visibility.

FRED and FRED Jr are expected to be associated with the following advantages:
► Improvement of the accuracy of the positioning due to the spontaneous opening of the device.
► Improvement of the visualization and the control of deployment due to the multiple radio-opaque markers.
► Securing of placement due to the possibility to recapture the device until 80% of its deployment.

FRED and 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 primary objectives of SAFE were:
► Safety: to evaluate the morbidity-mortality rate within 6 months after treatment. Morbidity was defined as a modified Rankin scale (mRS) score >2.
► Efficacy: to evaluate the rate of complete aneurysmal occlusion without parent artery stenosis (<50%) at 6 months.

Several secondary objectives were also defined by evaluation of treatment feasibility, description of per- and post-operative complications, and clinical and anatomical outcome at 12 months.

Patients were included if:
► They were older than 18 years.
► They had a mRS between 0 and 2.
► They had an intracranial aneurysm (unruptured or recanalized)
  – for which endovascular treatment was indicated,
  – which was not treatable with a standard method (coiling with or without remodeling),
  – and for which use of FRED or FRED Jr was deemed appropriate.

Patients were not included if:
► They had an intracranial hemorrhage within 30 days prior to the procedure.
► They had an aneurysm associated with an arteriovenous malformation or a dissecting aneurysm (including blister-like).
► They had already had an aneurysm treated, located on the same vessel.
► They were already treated with a stent or a flow diverter.
► The aneurysm was located in the posterior circulation.
► The aneurysm had to be treated with another flow diverter.
SAFE was conducted according to Good Clinical Practice (GCP) rules:
► All data were controlled by independent clinical research associates (CRA).
► All adverse events were independently evaluated by the Clinical Event Committee (CEC) that included a vascular surgeon and an interventional neuroradiologist.
► Anatomical results were independently evaluated by a core laboratory that included two interventional neuroradiologists.

A minimal experience of five flow-diversion procedures, whatever the medical device, and two procedures with FRED, was requested for each investigational site.

Procedural modalities
Pre-, intra-, and post-operative antiplatelet therapy was managed in each center. Antiplatelet activity testing was not required in the study protocol. Appropriate device sizing was determined based on 2D and 3D digital subtraction angiography (DSA). Depending on the type of device used (FRED or FRED Jr), two microcatheters were used to deploy the flow diverter (respectively, Headway 27 and Headway 21, Microvention, Aliso Viejo, CA). Treatment with additional devices (balloons, coils, and stents) could be performed, if deemed necessary by the treating physician.

Data collection
Each center completed a patient file with the following data:
► Demographic: patient’s age and gender.
► Aneurysm: rupture status, location, size, and neck size.
Procedure: date, type, and size of device used (FRED or FRED Jr), perioperative antiplatelet medications, occurrence of complications during or after the procedure, and use of additional devices during the procedure (coils, balloons, stents).

Clinical evaluation including modified Rankin Scale score (mRS) was performed before treatment, at hospital discharge, at 30 days (±7 days), 6 months (±3 months), and 12 months (−3 months/+6 months). Six months (±3 months) and 12 months (−3 months/+6 months) vascular imaging were collected. Vascular imaging was performed as per usual practice (digital subtraction angiography, magnetic resonance angiography, computed tomographic angiography). Data from retreatment procedures were also collected.

Data analysis
All complications were independently evaluated by the CEC. Thromboembolic events were diagnosed intraoperatively by angiography regardless of type (clothing near the neck of the aneurysm, clotting in the distal branches, and parent vessel occlusion). Postoperative thromboembolic events were diagnosed by MRI and/or digital subtraction angiogram performed in cases of sudden neurological compromise. Intraoperative rupture was diagnosed by the exit of the tip of the coil or the microcatheter outside the limit of the aneurysmal sac and/or extravasation of contrast media and/or by post-operative CT or MRI showing subarachnoid or parenchymal bleeding. Morbidity was defined as mRS >2.

Anatomical results are currently under evaluation by an independent core laboratory, post-operatively, at 6 months (±3 months), and at 12 months using a 3-grade scale: complete occlusion, neck remnant, or aneurysm remnant. A direct comparison was also performed between post-operative to 6 months and 6 to 12 months’ vascular imaging to determine if aneurysm occlusion was better, stable, or worse. The core laboratory did not evaluate the quality of device deployment nor its vessel wall apposition.

Statistical analysis
At the time of preparation of the SAFE study, only one prospective, multicenter study was published (PUFS). The SAFE study was designed by using the results of PUFS (number of patients, endpoints, ...).

The safety analysis was performed on the full analysis set (FAS). The FAS consisted of all participants who met all inclusion and non-inclusion criteria and had undergone at least one treatment with the intention of implanting the FRED or FRED Jr device.

Continuous variables were described as mean ±SD deviation (SD). Categorical variables were described by their frequency distribution and by the bilateral 95% confidence intervals (CI) of the range(s). The mortality rate at 6 months was calculated with its 95%CI determined as per the Wald modified method. The morbidity rate, where morbidity was defined as mRS >2, was calculated with its 95%CI determined as per the Wald modified method. The primary endpoint results were compared with the PUFS study, using a comparative percentage test (Chi square or Fisher’s Exact Test for small samples). Statistical tests were performed with a type I error risk of 5%.

Analyses were performed by using statistical analysis software (SAS version 9.2, SAS Institute, Cary, NC).

### RESULTS

#### Patient and aneurysm population

From July 2014 to June 2016, 113 patients were enrolled in 13 French INR centers. Nine patients did not meet inclusion and non-inclusion criteria. One patient was included before initiation of the center. The final population was 103 patients (including 16 males: 15.5% and 87 females: 84.5%). Age ranged from 25 to 80 years (mean: 52.4±11.0 years). Smoking and elevated blood pressure were encountered in 44 patients (42.7%) and 33 patients (32.0%), respectively. Twenty-eight patients (27.2%) had a hemorrhagic stroke more than 30 days before inclusion. Pre-operative mRS was 0 in 73 patients (70.9%), 1 in 25 (24.3%), and 2 in 5 (4.9%).

Among the 103 aneurysms, 76 (73.8%) were unruptured and 27 (26.2%) recanalized. For recanalized aneurysms, initial treatment was coiling in 26/27 patients (96.3%) and clipping in one (3.7%). Aneurysm locations per core laboratory analysis were supraclinoid internal carotid artery (ICA) in 71 (68.9%), cavernous ICA in 15 (14.6%), anterior cerebral artery (ACA), anterior communicating artery (Acom) in nine (8.7%), and middle cerebral artery (MCA) in eight (7.8%).

Aneurysms were small (<10 mm) in 71 patients (68.9%), large (10/24 mm) in 29 (28.2%), and giant in three (2.9%). Aneurysm necks were narrow (<4 mm) in 34 aneurysms (33.0%) and wide in 69 cases (67.0%).

Antiplatelet treatment before, during, and after the procedure is reported in table 1 and was typically based on clopidogrel, ticagrelor, prasugrel, and/or aspirin. Antiplatelet activity testing was performed in 52 patients (50.5%) and was not analyzed.

#### Treatment feasibility and adjunctive treatments

Treatment was successfully performed in 98/103 patients (95.1%) (figure 2). Causes for failure (five patients; 4.9%) were misdeployment of the proximal part of the device in three patients, slow flow in the parent artery after deployment of the device in one patient, and slow flow in the parent artery and migration of the device in one patient. In all cases the device was successfully retrieved. In these patients, another flow diverter was implanted in two patients, stent-assisted coiling was performed in one, and no further treatment was done in two patients.

Among the 98 patients effectively treated with a FRED or FRED Jr, 97 (99.0%) were treated with 1 FRED (86) or FRED Jr (11) and one (1.0%) was treated with 2 FRED Jr devices. Coils were placed in addition to FRED/FRED Jr in 22 patients (22.4%) and WEB intrasaccular device in two cases (2.0%).

#### Complications with clinical impact

Thromboembolic (TE) complications occurred in 5/103 patients (4.9%), three during the procedure and two after the procedure (1 and 4 days’ after). One patient treated for a right ICA aneurysm had a loss of vision of the right eye immediately after the procedure. There was no abnormality on diffusion-MRI, but

<table>
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<tr>
<th>Table 1</th>
<th>Number of antiplatelet medications before, during, and after FRED procedure</th>
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<tr>
<td>Antiplatelet</td>
<td>Before (n=103)(%)</td>
</tr>
<tr>
<td>0</td>
<td>1 (1.0)</td>
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<tr>
<td>1</td>
<td>34 (33.0)</td>
</tr>
<tr>
<td>2</td>
<td>66 (64.1)</td>
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<td>3</td>
<td>2 (1.9)</td>
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</table>
Hemorrhagic stroke

ophthalmic examination showed the presence of retinal emboli. There was a slow improvement and the patient recovered to mRS 1 at 6 months (similar to its mRS before the procedure). In one patient treated for a large cavernous ICA aneurysm, the device was not fully deployed after its placement, despite balloon angioplasty. Due to slow flow in the ICA, occlusion of the parent artery was performed but was associated with brain ischemia. The patient was hemiplegic and aphasic immediately after the procedure and had mRS score of 4 at 6 months. In another patient treated for a recanalized MCA aneurysm initially treated with coils, there was a migration of the flow diverter associated with a decrease of blood flow. The flow diverter was removed and no further treatment was performed. Postoperatively the patient was hemiplegic, aphasic, and had a hemianopia, and MRI showed an ischemic lesion. Clinical evolution was partially favorable and the patient had mRS score of 2 at 6 months.

Intraoperative rupture occurred in two patients (1.9%). One was not detected during the procedure (MCA aneurysm) but on the CT performed immediately after the procedure showing limited subarachnoid hemorrhage and no clinical symptoms (mRS at 3 months was unchanged). In the other case (ACA/Acom aneurysm), the parent artery was perforated with the microguidewire, leading to intraparenchymal bleeding and death 2 days after the procedure.

Delayed aneurysm rupture was reported in one patient (1.0%) treated for a large (20 mm) supraclinoid aneurysm with FRED but no coils. Bleeding occurred 21 days after the procedure, associated with morbidity at 6 months (mRS=5, coma). Delayed remote hematoma occurred in one patient (1.0%) treated for a large supraclinoid ICA aneurysm (figure 3). It was associated with strong initial clinical worsening and was surgically evacuated. At 6 months, clinical evolution was favorable with mRS=2 (slight hemiparesis and mild aphasia).

Mortality/morbidity at 6 months

Six-months’ follow-up was obtained in 102/103 patients (99.0%). Mortality rate was 1/102 (1.0%). This patient had a perforation of the parent artery during intracranial catheterization, resulting in intracranial bleeding. The patient died 2 days after the procedure. Morbidity rate was 2/102 (2.0%). One patient had a TE complication (see above) and was mRS 4 at 6 months. One patient had a delayed hemorrhage 21 days after the procedure and was mRS 5 at 6 months.

DISCUSSION

SAFE is the first prospective, multicenter study evaluating the safety and efficacy of the FRED device for aneurysm treatment. The preliminary results show the high feasibility (95.1%) and good safety of the FRED device with 6 months’ morbidity 2.0% and mortality 1.0% with a global rate of bad clinical outcome at 3.0%. In the PUFS trial that was a prospective, multicenter trial evaluating the Pipeline device (Medtronic, Minneapolis, MN) in large and giant aneurysms, major ipsilateral stroke or neurological death was observed in 5.6% of cases.4

Figure 2 Unruptured supraclinoid ICA aneurysm. A: 2D-DSA and B: 3D DSA of the aneurysm measuring 7.2 mm in height, 8.0 mm in transverse diameter with a 6.1 mm neck. C: flat panel CT showing good deployment and vessel wall application of the FRED. 2D-DSA. D: lateral view, unsubtracted, non-injected. E: lateral view, subtracted, injected, showing good deployment of the FRED and residual flow in the aneurysm. F: 6 months’ follow-up DSA (lateral view, subtracted, injected) with complete occlusion of the aneurysm and no stenosis of the ICA.
Although coiling is now the first-line treatment for both ruptured and unruptured intracranial aneurysms, it still has some limitations. Wide-neck aneurysms are difficult to treat, as it is difficult to stabilize coils inside the aneurysm using the balloon-remodeling technique. Aneurysm coiling is also associated with a risk of aneurysm recanalization of roughly 20% and this risk is more significant in large and giant aneurysms. To overcome these limitations, several technical approaches have been proposed that includes stents, flow diverters, and flow disrupters. The initial indication for flow diversion was limited to large and giant, unruptured intracranial aneurysms located at the ICA, but usage progressively expanded to smaller aneurysms and more distal aneurysms. For this reason and in order to have a more contemporary evaluation of the device, SAFE was not restricted to already approved indications, but extended to current indications that included small aneurysms and distal aneurysms. For this reason and in order to have a more contemporary evaluation of the device, SAFE was not restricted to already approved indications, but extended to current indications that included small aneurysms and distal aneurysms. However, as there were still several uncertainties regarding the use of flow diverters in posterior circulation and ruptured aneurysms, they were excluded from the present series.

As reported in previous FRED series (table 2), treatment with the device had a high feasibility (95.1%). Most failures were related to technical problems (misdeployment or migration of the device), in which the decision of the physician was to retrieve the device and to use, for safety reasons, another endovascular approach or another device. As in the case of other flow diverters, FRED deployment was dependent on several factors, including vascular tortuosity and device length and diameter. Unsuccessful deployment was encountered in only 2.9% of patients. In PUFS, feasibility with the Pipeline Embolization Device (PED) was similar to what was observed with FRED in SAFE with a success

<table>
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<th>Table 2 Summary of the FRED series/studies</th>
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<td>Patients/aneurysms</td>
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<tr>
<td>Kocer<strong>12</strong></td>
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<tr>
<td>Diaz<strong>13</strong></td>
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<tr>
<td>Möhlenbruch<strong>14</strong></td>
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<td>Briganti<strong>15</strong></td>
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<td>Luecking<strong>17</strong></td>
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<tr>
<td>Mohboobani<strong>18</strong></td>
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<td>Möhlenbruch<strong>19</strong></td>
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<td>Present series</td>
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rate of 99.1%.4 Similarly, in a large series of 165 patients/190 aneurysms treated with the Surpass flow diverter, FD placement was successfully placed in 98% of patients.26 Failures were mostly related to the stiffness of the device.

SAFE confirms the high degree of safety of the FRED device already observed in previous small series (table 2). The rate of thromboembolic complications was 4.9%, with only one event (1.0%) associated with morbidity at 6 months. In the analysis of three large series of patients treated with PED (PUFS, IntrePED, ASPIRE), the rate of major ipsilateral ischemic stroke was 3.7%.27 Also the rate of delayed intracranial hemorrhage (1.0%) is similar to what is observed in PUFS (1.9%) and in the pooled population of three studies (2.0%). In SAFE, mortality (1.0%) was lower compared with what was reported in PUFS (3.7%), in the pooled PED population (4.0%), and in the Surpass series (2.7%). Similarly, SAFE morbidity (2.0%) was lower compared with PUFS (4.7%), the pooled population (7.1%), and the Surpass series (2.7%).

As previously reported, there are several types of hemorrhagic complications in the setting of flow diversion treatment. Besides intraoperative hemorrhagic complications, delayed hemorrhagic complications were also encountered, including delayed aneurysm rupture and delayed remote hematomas. These delayed complications were reported with different flow diverters and their mechanisms are still not completely known.28 29

Comparing the safety of different flow diverters is a difficult task as most series dealing with flow diverters were uncontrollable, retrospective, often single-center series. Also patient and aneurysm populations often differ from one series to another as do the precise modalities of treatment and perioperative medications.

LIMITATIONS
A limitation of the data collected is the non-randomized nature of the study and lack of a control arm. However, none of the currently available flow diverters was evaluated in a randomized trial. A second important limitation is that most aneurysms were small, which is not the typical indication for flow diversion. It was logical to evaluate the FRED device in real-life practice and, as previously mentioned, the trend is actually to expand flow diverter indications to smaller aneurysms, especially with the new small diameter FRED Jr devices.

CONCLUSION
The analysis of 6 months’ clinical data in the SAFE study shows a high degree of safety of the FRED device compared with other flow diverters, specifically the Pipeline Embolization Device and Surpass Flow Diverter. Morbidity and mortality rates at 6 months are 2.0% and 1.0%, respectively.

REFERENCES

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Hemorrhagic stroke


