

# Brazilian FRED Registry: A Prospective Multicenter Study for Brain Aneurysm Treatment—The BRED Study

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## ABSTRACT

**BACKGROUND AND PURPOSE:** The development of flow diverters has changed the endovascular approach to intracranial aneurysms. On the basis of good results, the indications for flow diverters have expanded to include aneurysms of different shapes, locations, and sizes. The objective of the study was to report on the performance of the Flow Re-Direction Endoluminal Device (FRED) in intracranial aneurysm treatment at early and medium-term follow-up.

**MATERIALS AND METHODS:** This single-arm, multicentric, prospective, observational study assessed aneurysm treatment with the FRED. The primary outcome was complete aneurysm occlusion at 6 and 12 months, and the secondary outcome was to evaluate the safety of the FRED with respect to stroke and death rates.

**RESULTS:** Between June 2016 and August 2018, a total of 100 consecutive patients with 131 aneurysms were treated in 107 procedures. Total occlusion rates were 91% and 95% at 6 and 12 months. There was 1 death, and the total final morbidity rate was 1.8%. The complication rate was 4.6%.

**CONCLUSIONS:** As reported previously, the FRED has proved to be a safe and effective tool, with high occlusion rates. The design of the stent makes it more difficult to perform balloon angioplasty compared with similar devices. A branch arising from the aneurysm sac was found to be a predictor of nonocclusion at 12 months, though larger series are needed to estimate the magnitude of the association.

**ABBREVIATIONS:** FD = flow diverter; FRED = Flow Re-Direction Endoluminal Device

Endovascular coiling is currently the treatment of choice for intracranial aneurysms.<sup>1,2</sup> The use of flow diverters has changed the concept of intracranial aneurysm treatment by shifting the focus from the sac to the parent vessel, where the aneurysm is actually located.<sup>3,4</sup> Large studies have demonstrated the efficacy and safety of flow-diverter stents,<sup>5,6</sup> and the range of indications has grown considerably, including aneurysms at the level of the circle of Willis and beyond.<sup>7,8</sup> Several stent-design enhancements have been incorporated in recent years, such as the development of low-profile devices compatible with small-lumen microcatheters, improvement of fluoroscopic visibility, surface modifications to reduce thrombus formation, and implementation of resheathing mechanisms to allow accurate deployment and repositioning of the stent.<sup>9,10</sup> The Flow Re-Direction Endoluminal Device (FRED;

MicroVention) is a braided stent-in-stent device composed of an inner closed-cell stent with low porosity and an outer mesh with high porosity. It has been assessed in only prospective multicenter studies, mainly with medium- and long-term follow-up.<sup>11-15</sup> In this registry, we report the performance of FRED as used in the treatment of intracranial aneurysms at early and medium-term follow-up. In this multicenter series, we prospectively evaluated the safety and efficacy of FRED and identified predictors of occlusion and complications.

## MATERIALS AND METHODS

### Study Design

We conducted a single-arm, prospective, observational study to assess intracranial aneurysms treated with the FRED at 3 interventional neuroradiology centers in Brazil (Interventional Neuroradiology Department, Dr. Astrogildo Hospital, Santa Maria, Rio Grande do Sul, Brazil). The study was approved by the research ethics committees of the participating centers, and written informed consent was obtained from each study participant.

All surgeons were certified by the Brazilian Society of Neuroradiology. Centers were eligible for participation in this

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study if they had treated >100 aneurysms in each of the preceding 3 years with a minimum of 50 cases treated with flow-diverter stents and had a neurosurgical team participating in all treatment decisions.

The inclusion criteria were patients of all ages with intracranial aneurysms, regardless of size, topography, location, and ruptured or unruptured status, and untreated or recurrent aneurysms after previous surgical or endovascular treatment. Coils were allowed during treatment. Patients were excluded if they had a history of a coagulation disorder, evidence of active infection, or unfavorable arterial anatomy for stent deployment (an acute angle formed by the side branch and parent vessel, a parent artery of <2.0 mm, or severe stenosis of the target vessel).

### **Primary End Point**

The primary outcome was complete aneurysm occlusion as assessed by DSA at 6 and 12 months. Complete occlusion was defined as complete obliteration of the aneurysm sac, including the neck.

### **Secondary End Point**

As a secondary outcome, we evaluated the safety of the FRED and FRED Jr (MicroVention) regarding stroke and death rates. Procedure-related complications were also reported, regardless of clinical impact, as well as stent underexpansion, thromboembolic events, and artery dissection or perforation.

### **Endovascular Procedure**

All procedures were performed with the patient under general anesthesia. After puncture of the common femoral artery, a 5000-IU bolus of heparin was administered. A standard triaxial apparatus was used in all cases to navigate through the stent. A delivery microcatheter (Headway 0.027 or 0.021; MicroVention) and microguidewire (Traxcess 0.014; MicroVention) were used to advance the device to the aneurysm neck under roadmap guidance.

For antiplatelet therapy, patients were given either aspirin (100 mg) + prasugrel (10 mg) or aspirin (100 mg) + clopidogrel (75 mg). The patients were started on medications at least 5 days before the elective procedure. Antiplatelet aggregation tests were not performed in any of the patients due to their unavailability at the participating centers. Patients with ruptured aneurysms were given a bolus of 500 mg of aspirin + 600 mg of clopidogrel or 60 mg of prasugrel 5 hours before embolization. Dual-antiplatelet therapy was continued for 6 months until the first follow-up angiogram. Clopidogrel or prasugrel was then discontinued if there was no evidence of in-stent stenosis or hyperplasia. Aspirin was not discontinued unless hemorrhagic complications occurred.

### **Data Collection**

All data were collected prospectively using a predefined data base query for demographic information, such as neurologic status (assessed by the mRS) and aneurysm characteristics (location, topography, rupture or unruptured status, morphology, diameter, neck size, dome-to-neck ratio, and previous treatment). Perioperative data included treated aneurysms, flow-diverter size, balloon angioplasty, technical complications, and thromboembolic

complications. Postoperative follow-up included neurologic and systemic complications, stent migration, occlusion rate, and neurologic status.

Patients were evaluated clinically, including the mRS score, before treatment, at hospital discharge, and at 30 days, 6 months, and 12 months. Vascular imaging was performed at 6 and 12 months, and data were collected from cerebral angiograms. Noninvasive imaging was not acceptable for follow-up purposes.

### **Data Analysis**

Statistical analysis was performed using SPSS, Version 26 for Windows (IBM). Categorical variables were expressed as absolute and relative frequencies, and numeric variables were expressed as mean (SD). Potential predictors of nonocclusion at 6 and 12 months were tested by univariate binary logistic regression analysis. The probability (*P*) values were estimated using the likelihood ratio test. A *P* value < .05 was considered statistically significant.

## **RESULTS**

Between June 2016 and August 2018, one hundred consecutive patients with 131 intracranial aneurysms were treated at the 3 participating centers for a total of 107 procedures. During enrollment, no flow diverters other than the FRED were used to treat intracranial aneurysms in the participating centers.

### **Patient and Aneurysm Characteristics**

Of the 100 patients, 89 were women. The mean patient age was 52.2 (SD, 12.3) years. Ninety-five patients had incidental aneurysms; 1 patient presented with subarachnoid hemorrhage; 1, with transient ischemic attack; and 3, with mass effect symptoms. Twenty-four patients had multiple aneurysms. Two aneurysms had been previously treated with an operation, and 2 had been treated with other flow diverters, all of which failed to achieve complete closure. All other patients were previously untreated. The preoperative mRS score was 0 in 100% of patients.

Of the 131 intracranial aneurysms, 124 were located in the ICA; 3, in the vertebrobasilar system; and 4, beyond the circle of Willis (3 in the anterior communicating artery and 1 in the middle cerebral artery). The most common location was the C6 segment of the ICA (88 aneurysms). Except for 1 dissecting aneurysm, all other aneurysms were saccular. One hundred eighteen aneurysms were small (< 10 mm) and 13 were large (range, 10–25 mm); there were no giant aneurysms in this series. A large neck, defined as  $\geq 4$  mm and/or a dome-to-neck ratio of <2, was observed in 93% of cases (Table 1).

### **Treatment**

Treatment was successful in all cases. All procedures were performed using only 1 FRED for each patient. In several patients, a single FRED was used to treat multiple aneurysms: 2, were used in 18 patients; 3, in 5 patients; and 4, in 1 patient. Twelve aneurysms were treated with stent and coil placement. Balloon angioplasty was attempted in 5 cases, but it failed in 2 because the balloon could not be navigated through the entire length of the stent.

**Table 1: Aneurysm characteristics (n = 131)<sup>a</sup>**

Variable	Frequency
Location	
Trunk	125 (95.4%)
Bifurcation	6 (4.6%)
Branch arising from the sac	49 (37.4%)
Topography	
Cavernous ICA	13 (9.9%)
Ophthalmic ICA	89 (67.9%)
Communicating ICA	20 (15.2%)
Carotid bifurcation	2 (1.4%)
AcomA	3 (2.2%)
MCA	1 (0.7%)
Basilar artery	1 (0.7%)
Vertebral artery	2 (1.4%)
Size	
Small	118 (90.1%)
Large	13 (9.9%)
Large neck	
No	9 (6.9%)
Yes	122 (93.1%)
Rupture etiology	1 (0.7%)
Saccular	130 (99.3%)
Dissecting	1 (0.7%)
Prior treatment	4 (3%)

**Note:**—AcomA indicates anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery.

<sup>a</sup> Values expressed as absolute and relative frequency.

**Table 2: Treatment (n = 131)<sup>a</sup>**

Variable	Frequency
Use of coils	12 (9.2%)
Angioplasty	5 (4.6%)
Antiplatelet (aspirin +)	
Clopidogrel	11 (8.4%)
Prasugrel	89 (67.9%)
Complications	5 (4.6%)
Occlusion at 6 mo <sup>b</sup>	116 (91.3%)
Occlusion at 12 mo <sup>c</sup>	117 (95.9%)

<sup>a</sup> Values expressed as absolute and relative frequencies.

<sup>b</sup> n = 127.

<sup>c</sup> n = 122.

### Primary End Point

Follow-up angiography was performed at 6 months in 116 aneurysms and at 12 months in 117 aneurysms. Complete occlusion rates were 91% and 95%, respectively. There were no cases of recanalization after complete occlusion. The rate of residual aneurysm filling did not change from 6 to 12 months. There was 1 case of asymptomatic carotid stenosis at 6 months. Table 2 shows treatment-related characteristics.

At 6-month follow-up, the likelihood of nonocclusion increased by 161% for every 10-year increase in patient age. Male sex, bifurcation aneurysm, branch involvement, large size, and use of clopidogrel (rather than prasugrel) were associated with higher odds of nonocclusion at 6 months, but these associations were not statistically significant. Branch involvement was positively associated with lower odds of occlusion at 12 months; however, due to the small sample size, the logistic model could not accurately estimate the magnitude of the association (Table 3).

### Secondary End Point

Of the 100 patients, 96 had an uneventful postoperative course. One patient who presented with retroperitoneal hemorrhage due to a femoral artery pseudoaneurysm was successfully treated with a covered stent but died of myocardial infarction during hospitalization. In 1 case acute carotid occlusion during stent deployment was successfully treated with tirofiban and balloon angioplasty, but despite complete arterial reperfusion, the patient had a stroke, with an mRS score of 3 at discharge (left hemiparesis). One case of traumatic carotid cavernous fistula occurred when we attempted to cross the aneurysm at the cavernous segment of the internal carotid artery. We decided to deploy the stent as planned and monitor the patient. Because the patient developed chemosis, proptosis, and ophthalmoplegia at early follow-up, a second procedure was performed using a venous approach. The fistula was completely closed, and the patient was asymptomatic. In 1 case, the stent did not open completely, and balloon angioplasty was not feasible. The stent was not fully attached to the vessel wall, and the patient had a minor stroke and developed right-arm paresthesia.

Periprocedural complications occurred in 5 cases. In 1 patient, a misplaced stent was removed and reinserted correctly. Two stents did not open completely at the end of the procedure. One carotid artery occluded and one ruptured, both causing a carotid cavernous fistula.

Asymptomatic parent artery thrombosis was observed in 1 patient at 6-month follow-up. The subsequent course was uneventful, and the patient was compliant with dual-antiplatelet therapy of aspirin and prasugrel. No retreatment was performed.

Most cases in this sample were small aneurysms located at the carotid artery (n = 112). The analysis of this subgroup showed 35% of the cases with branches coming out of the aneurysm, 92% with a wide neck, use of coils in 5% of the cases, angioplasty in 3% of the procedures, and occlusion rates at 6 and 12 months of 89%. Age was associated with a higher probability of nonocclusion in 6 months (OR = 2.74 for each 10-year increase in age), and male patients were more likely to not be occluded at 12 months (OR = 8.9 compared with women). Still, there was no statistically significant association among bifurcation site, secondary branch involvement, use of coils, wide neck, adjuvant angioplasty, and antiaggregation scheme in relation to the aneurysm occlusion rate at 6 and 12 months.

### DISCUSSION

Flow-diverter stents are a large step forward in the endovascular approach to intracranial aneurysms, shifting the focus from occluding the aneurysm dome to repairing the parent vessel wall. Incomplete coiling and reperfusion are still major limitations that prevent long-term stability of aneurysm occlusion. Recanalization or neck remnants or both may occur despite technologic refinements (such as coated platinum coils) and procedural modifications (such as the balloon-remodeling technique and stent-assisted coil embolization). The recurrence rate can reach up to 28.6%, especially in large and giant aneurysms.<sup>16</sup> Studies have demonstrated the safety and efficacy of flow diverters in the treatment of large and giant sidewall saccular aneurysms of the ICA, with low morbidity and mortality rates and occlusion rates of 80%–90% at

**Table 3: Univariate predictors of nonocclusion at 6 months (n = 127) and 12 months (n = 122)**

	6 Months		12 Months	
	OR (95% CI)	P	OR (95% CI)	P
Male sex	2.36 (0.5–12.5)	.345	7.13 (1.1–47.8)	.065
Age <sup>a</sup>	2.61 (1.2–5.7)	.004	1.47 (0.6–53.4)	.340
Bifurcation	6.22 (1.0–538.7)	.078	7.06 (0.6–578.4)	.172
Branch vessel aneurysm	3.20 (0.9–511.6)	.069	–	.002
Coil	–	.130	–	.304
Large aneurysm	2.12 (0.4–511.1)	.402	–	.304
Large neck	–	.139	–	.437
Postangioplasty restenosis	–	.389	–	.558
Clopidogrel <sup>b</sup>	2.01 (0.6–57.0)	.282	0.52 (0.1–5 4.8)	.542

**Note:**—Data express odds ratio (95% confidence interval). P, probability value; –, analysis not performed due to insufficient number of events.

<sup>a</sup> For every 10 years.

<sup>b</sup> Versus prasugrel.

12 months. On the basis of these good results, the indications for flow diverters have been expanded to include aneurysms of different shapes, locations, and sizes.<sup>7,8,17</sup>

New flow diverters made available in recent years have advantages over first-generation devices. Their smaller size is compatible with smaller delivery systems, such as a 0.021-inch microcatheter in the FRED Jr and a 0.017-inch microcatheter in the Silk Vista Baby (Balt Extrusion). The Pipeline Flex Embolization Device with Shield Technology (Medtronic), for example, underwent a surface modification to reduce thromboembolic complications. FRED and FRED Jr are dual-layer flow-diverter devices that have a stentlike outer layer and a flow diverter inside the stent. This design enhances navigation and facilitates deployment. Retrospective case series have demonstrated the safety and efficacy of FRED and FRED Jr, though there are few prospective reports in the literature.

The present series demonstrates the safety and efficacy of FRED and FRED Jr, with success, morbidity, and mortality rates similar to those of previous studies.<sup>12–14</sup> There was only 1 death in our series (0.9%), and the morbidity rate was 1.8% (1 patient with left hemiparesis and another with right-arm paresthesia). All cases were successfully treated. Technical complications occurred in 4.6%, and complete occlusion, in 95% of patients at 12 months. Thromboembolic complications were observed in 2 cases. In the first case, a patient previously treated with a Silk device had an acute carotid occlusion during FRED deployment. Although we do not have a definite explanation for this event, certain factors might be important in this case: The patient may have been clopidogrel-resistant; the patient already had a flow diverter in the target vessel, which may have hindered visualization, placement, and opening of the FRED stent; and the stent failed to open completely. In the second case, the FRED stent was not fully attached to the ICA. Balloon angioplasty was attempted but was not feasible, and the patient had a minor stroke.

The SAFE study reported rates of 2.9% for morbidity, 1.9% for mortality, and 6.8% for thromboembolic complications, with a 1-year complete occlusion rate of 73%.<sup>13</sup> The Italian FRED study, which achieved the highest occlusion rate (97% at 1 year), reported a slightly higher rate of complications: 4.3% for mortality and 7.3% for morbidity.<sup>18</sup> Guimaraens et al,<sup>19</sup> in a prospective study

of 185 intracranial aneurysms treated with the FRED, reported a major complication rate of 6.5%, though only 0.5% were clinically relevant. The complete occlusion rate at 12 months was 84%. In the present series, we found slightly higher complete occlusion rates: 91% at 6 months and 95% at 12 months. Of the 11 aneurysms that were not completely occluded at 6 months, 5 were occluded at 12 months. Of the remaining cases, a branch originated in 4 (66.6%). Although branch involvement was positively associated with lower odds of occlusion at 12 months, the logistic model could not accurately estimate the magnitude of the association because of

the small sample size. This was also demonstrated by Trivelato et al,<sup>20</sup> who found that the presence of a branch arising from the sac predicted persistent filling of the aneurysm at 6- and 12-month follow-up. Another factor associated with nonocclusion at 6 months in the present study was that for every 10-year increase in patient age, the likelihood of nonocclusion increased by 161%.

A problematic issue associated with the FRED is the difficulty of crossing the stent with a balloon for angioplasty, which we reported in our initial experience with this stent.<sup>14</sup> Because the FRED has a stent inside a stent, the inner mesh may hinder (and in some cases even preclude) the navigation of the balloon through the entire length of the stent. In the present series, balloon angioplasty was attempted in 5 cases, but it failed in 2, resulting in a clinical deficit in 1 of them. Surprisingly, this problem has not been reported in previously published series, and it is important for physicians to be aware of this. The device should preferably be resheathed to ensure that it will open completely before redeployment because it may not be possible to cross it with a balloon afterward to perform angioplasty. This issue may be an important risk factor for technical failure and clinical complications.

Our results are similar to those of studies using other flow diverters. The International Retrospective Study of the Pipeline Embolization Device reported a morbidity and mortality rate of 8.4% after treatment, highest in the posterior circulation group.<sup>21</sup> Pumar et al,<sup>4</sup> using Silk devices, reported morbidity and mortality rates of 9.6% and 3.2%, respectively, with complete occlusion in 78% at 12 months. The Brazilian Registry of Aneurysms Assigned to Intervention with the Derivo Embolization Device (BRAIDED) study achieved a 1-year complete occlusion rate of 89%, and there were no serious adverse events during follow-up in 94.5% of patients.<sup>20</sup> Trivelato et al,<sup>22</sup> in a series of 182 aneurysms treated with the Pipeline Flex Embolization Device with Shield Technology, reported a periprocedural complication rate of 7.3% and complete occlusion rates of 79.7% at 6 months and 85.3% at 12 months.

## CONCLUSIONS

As reported previously, the FRED has proved to be a safe and effective tool for the treatment of intracranial aneurysms, with high occlusion rates at 6 and 12 months. The design of the stent

makes it more difficult to perform balloon angioplasty compared with similar devices, and this feature may lead to clinical complications. A branch arising from the aneurysm sac was found to be a predictor of nonocclusion at 12 months, though larger series are needed to estimate the magnitude of the association.

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