Flow diverter stents for endovascular treatment of aneurysms: a comparative study of efficacy and safety between FREDX and FRED

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ABSTRACT

Background The FRED X flow diverter (FREDX), as the second generation in the FRED series, aims to improve the treatment of cerebral aneurysms. This study compares the efficacy and safety of FREDX with its predecessor, FRED.

Methods This prospective registry included patients treated with FRED and FREDX devices. Efficacy was assessed using digital subtraction angiography with 3D volumetric reconstruction at immediate and 1 year follow-ups. Safety was evaluated by recording complications, analyzed through univariate contrasts, generalized mixed models, and Bayesian network analyses.

Results We treated 287 patients with 385 aneurysms, with 77.9% receiving FRED and 22.1% FREDX. The median age was 55 years (IQR 47–65) and 78.4% were women. The FREDX group showed a higher prevalence of saccular-like aneurysms (70.6% vs 52.7%, P=0.012) and a higher rate of complete occlusion compared with FRED interventions (79.4% vs 59.3%, P=0.022). After adjusting for confounders, these differences represented a 3.04-fold increased likelihood (95% CI 1.44 to 6.41, P=0.003) of achieving complete occlusion at 1 year with FREDX interventions. Regarding safety, two (3.5%) complications (both non-symptomatic) were observed in the FREDX group and 23 (10.4%) in the FRED group (P=0.166). Bayesian network analysis suggested a trend towards fewer complications for FREDX, with a median reduction of 5.5% in the posterior distribution of the prevalence of complications compared with FRED interventions.

Conclusions The FREDX device shows improved complete occlusion rates at 1 year compared with the FRED device while maintaining a favourable safety profile, indicating its potential advantage in the treatment of cerebral aneurysms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Flow diversion devices (FDs), including the FREDX, are effective and safe endovascular treatments for cerebral aneurysms. However, comparative analyses between different generations of FDs are still limited.

WHAT THIS STUDY ADDS

This study provides an in-depth comparison between the FRED and FREDX devices and shows that the FREDX device has superior efficacy in 1-year follow-up evaluations while maintaining a comparable safety profile to that of the FRED device.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

These findings highlight the need to update device selection policies, reflecting improved outcomes and encouraging further innovation in FD technology.

INTRODUCTION

Cerebral aneurysms represent a significant threat to life if ruptured and require timely and effective treatment. Flow diverter stents (FDs) have emerged as a promising option for treating complex and wide-necked aneurysms.1–3 Despite the demonstrated efficacy, these devices are associated with complications, the main one being a risk of ischemic events due to stent thrombogenicity.4 Recent advancements in FD technology have included surface modifications to mitigate ischemic risks, alongside other enhancements to facilitate the device deployment.5–8 The Flow-Redirection Endoluminal Device (FRED) series (MicroVention, Aliso Viejo, California, USA) encompasses the first-generation FRED and FRED Jr. These FDs feature a dual-layer structure: an outer stent with a high-porosity outer stent for stability and a low-porosity inner mesh for flow redirection. The flared ends of the outer layer extend about 3 mm beyond the inner flow-diverter layer on both sides, enhancing the flow-diverting effect in a targeted manner.9–11 The FRED X (FREDX), as the latest evolution in this series, is designed with reduced delivery and retraction forces according to the manufacturer’s website.12 This feature facilitates easier navigation through tortuous anatomicies. Additionally, the FREDX uses a poly (2-methoxyethyl acrylate) copolymer (X-Technology) to form a protective hydration layer, reducing thrombogenicity while preserving cellular adhesion.13–14 Despite these advances, clinical data on the safety and efficacy of FREDX remain limited and no direct comparison studies between FRED and FREDX have been...
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conducted to date. Therefore, our study aims to compare the clinical outcomes of FRED and FREDX in the treatment of cerebral aneurysms, assessing their efficacy and safety while controlling for possible confounders within the first year after treatment.

METHODS

Design

A prospective observational registry was designed to include all consecutive aneurysms electively treated with FRED (including FRED Jr) and FREDX between January 2016 and June 2023. The study was conducted by the same therapeutic neuroangiography department operating at two Barcelona hospitals: Hospital Universitari General de Catalunya and Hospital del Mar. Patient data were collected using a predefined electronic questionnaire, which included variables such as age; sex; previous subarachnoid hemorrhage; number of aneurysms; aneurysm location; aneurysm morphology (saccular, fusiform, dissecting, blister, dysplasia, or pre-treated); rupture/unruptured; additional coiling and aneurysm size based on the largest diameter (small: <5 mm; medium: 5–10 mm; large: >10 mm). Patients underwent digital subtraction angiography with 3D volumetric reconstruction (3D-DSA) evaluations before treatment, immediately after treatment, and subsequently at 3–6 and 12 months after treatment, based on the physician’s assessment. Clinical follow-up assessments were scheduled at the physician’s discretion and conducted every 3–6 months. These assessments were carried out through a coordinated multidisciplinary approach, involving close collaboration between interventional neuroradiologists and neurology teams, all adhering to standard medical protocols. Technical complications and mortality were identified and recorded by neurologists not involved in performing the procedures. Technical complications and efficacy were determined by consensus between at least two interventional neuroradiologists from the same team directly involved in the treatment.

Patient selection

Each stent placement procedure was either performed or directly supervised by one of two senior interventional neuroradiologists on the team. The decision for treatment was made jointly by the senior interventional neuroradiologists following morphologic and morphometric aneurysm criteria in cases in which other endovascular treatments were inadvisable due to wide neck saccular aneurysms (fundus-to-neck ratio <2 or neck diameter >4 mm), fusiform, dissecting, blister-like, or giant (>25 mm maximum diameter) aneurysms or pretreated with coiling/surgery/stenting. Exclusion criteria included unfavourable branch configuration (an acute angle in relation to the parent vessel or a very small diameter of the parent artery (<1.0 mm) and evidence of active infection.

Description of technique

Patients were initiated on dual antiplatelet therapy (DAPT) comprising aspirin (300 mg once daily) and clopidogrel (75 mg once daily), starting 5 days before the intervention. The efficacy of the antiplatelet therapy was assessed using the VerifyNow system (Accumetrics, San Diego, California, USA). After the procedure, patients continued DAPT for 6 months, consisting of aspirin (300 mg once daily) and clopidogrel (75 mg once daily). Subsequently, the aspirin dosage was adjusted to 100 mg once daily while the clopidogrel dosage remained at 75 mg once daily up to the 1-year follow-up. After this period, single antiplatelet therapy, typically aspirin at a dose of 100 mg once daily, was recommended for an additional 12 months. The duration of antiplatelet therapy could be extended beyond this, based on the medical team’s judgment, in certain clinical scenarios such as stenosis, arterial occlusion, or ischemic events. At the beginning of the procedure, all patients received IV heparin (50 IU/kg), followed by an additional bolus of 1000 IU during the intervention to maintain a clotting time >250–300 s. Throughout the intervention the patients were under general anesthesia. The anatomy of the parent artery was delineated and the diameters proximal and distal to the aneurysm were measured using 3D-DSA on a biplane angiographic system (Philips AlluraClarity, The Netherlands). Selecting the appropriate FD size was crucial to ensuring safe and complete occlusion of the aneurysm; this was determined through 3D-DSA reconstruction, including both volume rendering and shaded surface display. The FD diameter was selected based on the maximum diameter of the parent artery segment where the device would be deployed, occasionally oversized by 25–30%. The working length for flow diversion was designed to cover the aneurysm neck or the length of the fusiform or dissecting aneurysm, with a margin of 2.5–3 mm on both the proximal and distal ends. The FD was delivered using a coaxial system (6 Fr Envoy and Headway 21/27; MicroVention) over a 0.016 inch Terumo microguidewire. The pusher facilitated stent retraction and repositioning, providing no more than 80% of its length had been unsheathed/deployed, in cases where the device was not correctly positioned across the aneurysm neck. Once the delivery microcatheter was fully withdrawn over the delivery microwire, the coupling wire was released, enabling deployment of the stent.

Efficacy

Aneurysm occlusion was assessed by 3D-DSA examinations. The grade of aneurysm occlusion was measured using the O’Kelly-Marotta grading scale (OKM), which has shown good intra- and inter-observer agreement in previous studies. This scale assigns a letter for each grade of occlusion (A, total; B, subtotal; C, entry remnant; or D, complete occlusion) based on the degree of filling and stasis of flow within the aneurysm. OKM scores were recorded both immediately after treatment and closest to the 1-year post-treatment mark to determine efficacy.

Safety

All patients underwent neurological evaluations conducted by vascular-trained neurologists before and immediately after the intervention, followed by assessments every 12 hours throughout their stay in the stroke unit until hospital discharge. In cases where patients exhibited neurological symptoms, they underwent cranial CT and MRI scans to identify the underlying causes. Complications were recorded at the time of stent deployment (procedure-related) or during subsequent follow-up (non-procedure-related), including hemorrhagic strokes, thrombosis (any clot formations, including those resolved with urokinase without resulting in symptoms), ischemic strokes, arterial dissections, stent migrations or misplacements, and stenosis or vessel occlusions. Complications were classified as symptomatic or non-symptomatic and transient or permanent if symptoms resolved or persisted, respectively.

Statistical analysis

Patient and aneurysm characteristics were reported using frequencies (percentages), means (SD), or medians (interquartile ranges (IQR)) based on the type and distribution of each variable. The characteristics of aneurysms were compared considering
the type of stent (FRED vs FREDX) and occlusion status at follow-up (OKM A–C vs OKM D) with bivariate analyses using $\chi^2$ tests, t tests, and Mann–Whitney U tests as appropriate, with an $\alpha$ level set at 0.05.

To compare the probability of complete aneurysm occlusion (OKM A–C vs OKM D) at the follow-up visit between aneurysms treated with FRED or FREDX stents, generalized mixed models were employed,16 17 acknowledging the fact that one patient might have multiple aneurysms treated with various stents. These models were adjusted for main confounding variables, as described in the online supplemental methods.

Despite the limited number of complications in the sample, we compared the prevalence of complications (both symptomatic and non-symptomatic) between patients treated only with FRED and those treated with FREDX. In addition, to achieve a better understanding of the benefits of the FREDX stent in terms of efficacy and safety, we also conducted a Bayesian network analysis.18 19 The complete statistical methods are available in the online supplemental material. This report adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. All statistical analyses were conducted within the R statistical software (R version 4.3.12023, The R Foundation for Statistical Computing).

**RESULTS**

A total of 385 aneurysms were treated in 287 patients. The main characteristics of the participants enrolled in the study are shown in table 1. The median age of the sample was 55 years (IQR 47–65) and most patients were women (78.4%). A total of 74 (25.8%) individuals had more than one aneurysm (table 1). Patients treated only with FRED or FREDX stents (n=280) did not differ in terms of clinical characteristics and vascular risk factors (online supplemental table 1).

Regarding aneurysms, 300 (77.9%) and 85 (22.1%) were treated with FRED and FREDX devices, respectively. We employed FRED stents from January 2016 to January 2021 and introduced FREDX in July 2021 (see online supplemental figure 1). Notably, during the transition period we used 40 FRED and 20 FREDX devices. The characteristics of the aneurysms are summarized in table 2, indicating that most aneurysms were saccular-like (56.6%) in morphology and located in the carotid circulation territory (50.4%).

Regarding characteristics, as shown in table 2, aneurysms treated with FREDX only differed in terms of morphology compared with FRED placements, such that there was a higher prevalence of saccular-like aneurysms (70.6% vs 52.7%, $\chi^2$ (4, n=385)=12.02, P=0.012) in FREDX placements. On the other hand, FRED and FREDX interventions did not differ in terms of size, circulation territory, or immediate OKM (see table 2 and figure 1A). We observed no differences in the prevalence of additional coiling between aneurysms treated with FRED and FREDX stents (2.3% vs 0%, $\chi^2$ (1, n=385), P=1.0).

**Efficacy**

Among the full cohort we were able to conduct the follow-up 3D-DSA in 276 patients (96.2%) for whom 368 aneurysms were treated. This subset of participants was used to check the differences in the rate of complete occlusion (OKM grade D) at the follow-up between aneurysms treated with FRED and FREDX. Among these aneurysms, 232 (63.0%) showed complete occlusion at the follow-up. The figure increased to 305 (82.8%) when considering near-complete and complete occlusion (OKM grades C–D). Additionally, complete occlusion was associated at the aneurysm level with the morphology, size, circulation territory and baseline OKM (see online supplemental table 2). Aneurysms treated with FREDX stents showed a higher rate of occlusion than those treated with FRED stents in the bivariate analyses (79.4% vs 59.3%, $\chi^2$ (7, n=368)=16.45, P=0.022), as shown in figure 1A and table 2. As practitioners gained experience within the study period, we tested whether there was an effect of time on OKM and, as shown in online supplemental figure 1A,B, we observed no linear effect of time on either baseline or follow-up grade of occlusion.

Generalized mixed models showed that aneurysms treated with the FREDX stent had a 3.04-fold (95% confidence interval 1.44 to 6.41, P=0.003) increased probability of complete occlusion compared with aneurysms treated with the FRED stent, independently of baseline OKM and aneurysm morphology (see online supplemental figure 2 and table 3). Additionally, we re-ran these analyses in the subset of participants for whom we had data about aneurysm size (N_{sub} = 208, N_{small} = 273) and adjusted by this variable instead of aneurysm morphology, observing the same results and confirming the benefit of FREDX stents in terms of efficacy independently of aneurysm size (see online supplemental table 4; OR 2.93 (95% CI 1.30 to 6.56), P=0.009).

**Safety**

The mortality rate was 0.35%, representing a single case among the 287 patients in the sample. As shown in table 2, we detected 27 (7.01%) complications out of 385 aneurysms, with 16 of them (59.3%) being procedure-related and 11 (40.7%) non-related (figure 1B). Additionally, 10 (3.12%) stent placements had symptomatic events in the cohort. Online supplemental table 5 shows detailed data about the type of each event. We observed no significant associations between clinical variables and the presence of complications at the aneurysm level (online supplemental table 2; all P values >0.05) but, interestingly, patients with complications had a higher prevalence of diabetes than patients with no complications (12.0% vs 2.8%, P=0.05; see online supplemental table 6). Although aneurysms treated with the FREDX device had a lower number of complications...
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Table 2  Main characteristics of aneurysms treated in the cohort

<table>
<thead>
<tr>
<th>Type of stent</th>
<th>Whole sample (n=385)</th>
<th>FRED (n=300)</th>
<th>FREDX (n=85)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruptured aneurysm</td>
<td>79 (20.5%)</td>
<td>64 (21.3%)</td>
<td>15 (17.6%)</td>
<td>0.555</td>
</tr>
<tr>
<td>Type of aneurysm</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blister/dysplasia</td>
<td>25 (6.49%)</td>
<td>19 (6.33%)</td>
<td>6 (7.06%)</td>
<td></td>
</tr>
<tr>
<td>Dissecting</td>
<td>16 (4.16%)</td>
<td>12 (4.00%)</td>
<td>4 (4.71%)</td>
<td></td>
</tr>
<tr>
<td>Fusiform</td>
<td>29 (7.53%)</td>
<td>27 (9.00%)</td>
<td>2 (2.35%)</td>
<td></td>
</tr>
<tr>
<td>Pretreated</td>
<td>97 (25.2%)</td>
<td>84 (28.0%)</td>
<td>13 (15.3%)</td>
<td></td>
</tr>
<tr>
<td>Saccular</td>
<td>218 (56.6%)</td>
<td>158 (52.7%)</td>
<td>60 (70.6%)</td>
<td></td>
</tr>
<tr>
<td>Size*</td>
<td>0.793</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>23 (7.99%)</td>
<td>16 (7.41%)</td>
<td>7 (9.72%)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>50 (17.4%)</td>
<td>37 (13.7%)</td>
<td>13 (18.1%)</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>215 (74.7%)</td>
<td>163 (59.9%)</td>
<td>52 (72.2%)</td>
<td></td>
</tr>
<tr>
<td>Territory</td>
<td>0.758</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid artery</td>
<td>194 (50.4%)</td>
<td>150 (50.0%)</td>
<td>44 (51.8%)</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>24 (6.23%)</td>
<td>19 (6.33%)</td>
<td>5 (5.88%)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>54 (14.0%)</td>
<td>41 (13.7%)</td>
<td>13 (15.3%)</td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>7 (1.82%)</td>
<td>4 (1.33%)</td>
<td>3 (3.53%)</td>
<td></td>
</tr>
<tr>
<td>Choroidal artery</td>
<td>34 (8.83%)</td>
<td>28 (9.33%)</td>
<td>6 (7.06%)</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>72 (18.7%)</td>
<td>58 (19.3%)</td>
<td>14 (16.5%)</td>
<td></td>
</tr>
<tr>
<td>Immediate OKM</td>
<td>0.263</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>2 (0.52%)</td>
<td>2 (0.67%)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>99 (25.7%)</td>
<td>89 (29.7%)</td>
<td>10 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>56 (14.5%)</td>
<td>53 (17.7%)</td>
<td>3 (3.53%)</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>21 (5.45%)</td>
<td>20 (6.67%)</td>
<td>1 (1.18%)</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>112 (29.1%)</td>
<td>90 (31.3%)</td>
<td>22 (26.9%)</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td>47 (12.2%)</td>
<td>36 (12.0%)</td>
<td>11 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>6 (1.56%)</td>
<td>6 (2.00%)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>21 (5.45%)</td>
<td>19 (6.33%)</td>
<td>2 (2.35%)</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>10 (2.60%)</td>
<td>9 (3.00%)</td>
<td>1 (1.18%)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>11 (2.86%)</td>
<td>7 (2.33%)</td>
<td>4 (4.71%)</td>
<td></td>
</tr>
<tr>
<td>Follow-up OKM†</td>
<td>0.022</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>2 (0.54%)</td>
<td>2 (0.67%)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>4 (1.09%)</td>
<td>4 (1.33%)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>14 (3.80%)</td>
<td>13 (4.33%)</td>
<td>1 (1.47%)</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td>43 (11.7%)</td>
<td>40 (13.3%)</td>
<td>3 (3.53%)</td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>31 (8.42%)</td>
<td>23 (7.67%)</td>
<td>8 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>31 (8.42%)</td>
<td>29 (9.67%)</td>
<td>2 (2.94%)</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>11 (2.99%)</td>
<td>11 (3.67%)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>232 (60.3%)</td>
<td>178 (59.3%)</td>
<td>54 (79.4%)</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>27 (7.01%)</td>
<td>25 (8.33%)</td>
<td>2 (2.35%)</td>
<td></td>
</tr>
<tr>
<td>Type of complications</td>
<td>0.096</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No events</td>
<td>358 (93.0%)</td>
<td>275 (91.7%)</td>
<td>83 (97.6%)</td>
<td></td>
</tr>
<tr>
<td>Non-symptomatic</td>
<td>17 (4.42%)</td>
<td>15 (5.00%)</td>
<td>2 (2.35%)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>10 (2.60%)</td>
<td>10 (3.33%)</td>
<td>0 (0.00%)</td>
<td></td>
</tr>
</tbody>
</table>

Data represent frequencies and percentages of main characteristics of aneurysms by stent type, compared using χ² tests.

*Size not applicable for 97 pretreated aneurysms.
†No 1-year follow-up data in 17 cases.


Bayesian network analyses

To achieve additional insight into the effect of the FRED device on aneurysm occlusion and the incidence of complications, we conducted a Bayesian network analysis. We first learnt the structure of the graph (see online supplemental material). We obtained the network represented in figure 2A, showing that the type of the stent influenced both the presence of complications and the OKM grade at the follow-up. OKM grade at the follow-up was also influenced by the type of the aneurysm and baseline OKM, while the presence of diabetes increased the risk of complications. We subsequently ran 100 000 conditional probability queries by conditioning the node corresponding to the stent type to be FRED or FREDX, thereby obtaining a posterior distribution of the proportion of complete occlusions at the follow-up and complications for each stent type (figure 2B). Regarding OKM at the follow-up, in 99.2% of simulations we observed a higher proportion of completely occluded aneurysms in the group of FREDX placements. Specifically, the median proportion of aneurysms with OKM grade D was 75.5% (95% CI 60.8% to 87.2%) for FRED queries and 59.4% (95% CI 53.8% to 64.9%) for FREDX queries. Similarly, we observed a lower number of complications for FREDX in 97.4% of simulations, such that simulated FRED placements showed on average a 5.5% (95% CI −9.00×10⁻⁶ to 10.1%) increased prevalence of complications, suggesting a trend towards reduced complications.

DISCUSSION

The FREDX represents a novel option for the endovascular treatment of complex and wide-necked aneurysms. Our study presents the first real-world comparative analysis of the efficacy and safety of FREDX versus FRED in the treatment of these aneurysms. The key findings highlight potential advantages of FREDX in improving the follow-up occlusion rates after adjusting for covariables such as aneurysm size, location, and type of aneurysm. We also observed that patients with aneurysms treated with FREDX stents had a lower incidence of complications, although the difference was not statistically significant.

Our results are consistent with the existing literature which shows similar efficacy and safety profiles for the FRED device. Previous studies on the FRED stent have reported first-year occlusion rates ranging between 64.3% and 95.3%, with morbidity rates from 0.5% to 8.9% and mortality rates from 0.7% to 8.9%. Regarding FREDX, existing data are limited to a report by Vollherbst et al which identified a 66% occlusion rate and a 4.3% thrombotic complication rate. Our study shows a slightly higher 79.4% occlusion rate, with a potentially favourable safety profile and no major complications.

Our study did not show any benefit of FREDX over FRED in terms of initial hemodynamic changes within aneurysms, as evidenced by the initial OKM scores. Nonetheless, during the follow-up period within the first year we observed a higher percentage of complete occlusion. We also checked the potential training effect of interventional neuroradiologists, accounting for (figure 1B), these differences were not statistically significant (2.4% vs 8.3%, χ² (1, n=385)=2.77, P=0.096). Besides, no FREDX placement showed symptomatic complications (table 2 and figure 1B; P=0.120). We then aggregated our data at the patient level and filtered those subjects who were only treated with FRED or FREDX stents (table 1, n=280), observing no significant differences between the two groups in terms of safety (see online supplemental table 6; 3.5% vs 10.4%, χ² (1, n=385)=1.92, P=0.166).
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for the accumulated experience from years of FRED placements before transitioning to FREDX. The multivariate analysis confirmed a higher efficacy of FREDX adjusted for possible confounders, and although we did not find a statistical influence of the training effect, we cannot rule out that this effect exists. Regarding safety, only two non-symptomatic complications were noted with FREDX—stent misplacement and intimal hyperplasia-induced stenosis—without significant differences compared with FRED. This led us to use Bayesian network analysis for a more nuanced analysis of both efficacy and safety, understanding the relationship between variables. This statistical approach, involving massive simulations with 100,000 queries for each type of stent, confirmed the superior efficacy of FREDX and suggested a trend towards reduced complications, although the confidence intervals marginally crossed zero for safety outcomes. Although it is not the focus of our study, statistical analyses and Bayesian network analysis have shown an increased risk of complications in diabetic patients, a factor already linked to the risk of complications in an extensive meta-analysis.24

In relation to other FDs, it is important to note that several manufacturers have also introduced improvements over the past decade to enhance their efficacy and safety. This led to devices such as the Pipeline Flex Embolization Device with Shield Technology (sPED; Medtronic), the Derivo Embolization Device (Acandis), and the p64 and p48 MW hydrophilic polymer coating Flow Modulation Device (Phenox), among others. Subsequently, laboratory studies reported superior thromboresistant properties between FDs with surface modifications and their predecessors.25–27 However, despite this laboratory evidence, real-world data comparing different generations of FDs remain scarce and, in general, no differences have been found in efficiency and safety.28–32 A meta-analysis of 911 patients and 1060 aneurysms reported occlusion rates of 80.5% at 6 months and 85.6% at 12 months, which were found to be comparable to those achieved with first-generation devices, thus indicating no significant differences in efficacy.4 Another meta-analysis involving 17 studies and 1238 patients found similar safety and efficacy between Phenox HPC and non-coated Phenox FDs, with occlusion rates of 80% and 71.3%, respectively (P=0.24).33 Beyond this meta-analysis, additional scientific evidence primarily stems from studies on the Pipeline embolization device (PED), one of the earliest to undergo modifications from its original generation. There were reported improvements in efficacy and safety between the first-generation (PED) and second-generation (PEDFLEX) devices.29,31 In relation to the third-generation device, which involves surface modifications (sPED), one study reported a quicker time to complete occlusion with sPED compared with PED,32 a finding consistent with our results. However, another

Figure 1  Efficacy and safety of FRED and FREDX stents. (A) Comparison of the distribution of baseline and follow-up O’Kelly–Marotta (OKM) scale for FRED and FREDX placements. (B) Incidence of any complications by group (first plot), as well as differentiating by symptomatic (second plot) and by the time at which the complication occurred (third plot).

Figure 2  Bayesian network analyses. (A) Bayesian network structure. Solid and dashed lines represent stronger and weaker links, respectively. (B) Posterior distribution of the proportion of complete occlusions or the presence of complications obtained from 100,000 conditional probability queries for each type of stent. OKM, O’Kelly–Marotta.
study found no substantial differences in safety, noting no variations in perioperative ischemic lesions between the two devices.\textsuperscript{30} Occlusion of an aneurysm after FD implantation requires several complex procedures such as re-endothelialization, correct wall apposition, and intra-aneurysmal thrombosis.\textsuperscript{34} We hypothesize that the enhanced occlusion rates observed in FREDX stents compared with FRED can be attributed to a combination of factors.\textsuperscript{2,3,4,7} The poly (2-methoxyethyl acrylate) coating diminishes thrombogenicity and platelet activation by disrupting interactions with proteins such as fibrinogen and factor XII, while concurrently supporting appropriate adhesion of endothelial and smooth muscle cells.\textsuperscript{7,9,14} Additionally, FREDX is engineered with decreased delivery and retraction forces, enabling smoother navigation through tortuous anastomoses.\textsuperscript{12} This characteristic, leading to fewer thrombotic deposits on FREDX,\textsuperscript{2} may facilitate direct stent contact with the vessel wall, which is crucial for providing a scaffold for contiguous endothelial cell growth from the parent vessel.

Limitations

Regarding the study design, our research was conducted across two hospitals by a single interventional team. While this design enhances internal consistency, it necessitates caution when generalizing the findings to different settings or populations. Clinical complications were identified by neurologists who were not involved in the procedures, although the assessment of technical complications and efficacy, carried out by the interventional neuroradiologists involved in the treatments, could still introduce a potential observer bias. The introduction of the FREDX into clinical practice coincided with its market release. Consequently, despite statistical adjustments, the accumulating experience with FRED over time could pose a potential risk of bias. Finally, the limited number of complications recorded in the FREDX group, coupled with the potential for performance bias, could restrict the conclusiveness of our findings.

CONCLUSIONS

Our study addresses a gap in the literature by providing the first real-world comparison between the FRED and FREDX FDs in the treatment of cerebral aneurysms, highlighting the potential advantages of FREDX in achieving higher rates of medium-term occlusion outcomes while maintaining a favourable safety profile. Nevertheless, it underscores the need for larger studies to validate these results and establish robust confidence intervals in diverse settings.

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Contributors

All authors made substantial contributions to the conception and design of the work, or the acquisition of data, analysis or interpretation of data; and drafting or revising it critically for important intellectual content; and final approval of the submitted version; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AO acts as the guarantor of this work, assuming full responsibility for the overall content and the decision to publish.

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Competing interests

None declared.

Patient consent for publication

Consent obtained directly from patient(s)

Ethics approval

This study involves human participants and was approved by Comité para la integridad de la investigación y las buenas prácticas científicas del Hospital del Mar (ID 2008/03081). Participants gave informed consent to participate in the study before taking part. The registry satisfies all requirements decreed by the Spain’s law on the protection of personal data.

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Supplemental material

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