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FRED-UK: Multicentre UK experience of FRED and FRED Jr flow re-direction endoluminal device for intracranial aneurysms: 6 months and 1 year clinical and anatomical results

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Abstract

Background: Flow diverting stents (FDS) are an established endovascular treatment for intracranial aneurysms but are reported to have varying rates of adequate occlusion and thromboembolic complications. This study reports clinical safety and efficacy results of the FRED and FRED Jr FDS in clinical practice in the UK at 6 months and 1 year.

Methods: The FRED-UK study is a single arm, multicentre, prospective, observational study conducted in the UK. Safety was reviewed by evaluating morbidity (modified Rankin Score $\leq$2) and mortality. Efficacy was assessed as adequate occlusion of the treated aneurysm. A clinical event committee and core laboratory independently assessed clinical and anatomical results.

Results: Seven neurointerventional centers treated 61 patients, 57 of which met the full inclusion and exclusion criteria. Of these, 75.4% were treated with FRED and 24.6% with FRED Jr. The aneurysms were located on the cavernous or supraclinoid internal carotid artery (ICA) in 75.4%, on the anterior cerebral artery (ACA) or anterior communicating artery (Acom) in 21.1%, and on the middle cerebral artery (MCA) in 3.5%. 57.9% of aneurysms were small (<10 mm), 40.4% were large (10–24 mm) and 1.8% were giant ($\geq$25 mm). All-cause morbidity and mortality were 0% at 6 and 12 months, and adequate occlusion was 86.7% at 12 months in the per protocol population.

Conclusions: The FRED and FRED Jr devices are safe and efficacious in the treatment of intracranial aneurysms

Keywords
Flow diverter, aneurysm, hemorrhagic stroke

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Introduction

Flow diverting stents (FDS) have become established in the endovascular management of intracranial aneurysms. Following the placement of a FDS across the aneurysm neck, there is alteration of the flow and shear stress within the aneurysm which promotes thrombosis.[1] The aneurysm thromboses and occludes, and the FDS is used as a scaffold for arterial wall remodelling and endothelialisation[2] with neointimal formation starting at the device/mural interface.[3] FDS are used predominantly in wide-necked aneurysms particularly in the anterior circulation but are reported to have varying rates of thromboembolic complications.[4] The Flow Re-direction Endoluminal Device (FRED, Microvention Inc.) and FRED Junior (FRED Jr, Microvention Inc.) have been evaluated in prospective studies in France and the US.[5,6] The FRED-UK study is a prospective, UK based, single arm, multicentre study to further evaluate the safety and efficacy of FRED and FRED Jr in real world clinical practice in the UK.

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FRED and FRED Jr stents

FRED and FRED Jr are dual layer, self-expanding, closed cell, nitinol braided flow diverters. In both FRED and FRED Jr, the low porosity inner layer (36 strand for FRED Jr and 48 strand for FRED) is supported by a porous 16 strand outer layer which allows for optimal positioning. The central 80% of the stent where the two layers overlap is considered the working flow diversion length. The FRED Jr was developed as a lower profile FDS to treat aneurysms whose parent vessel diameter is ≤3 mm. FRED and FRED Jr are available in lengths 13–62 mm with working length dual layer coverage of 7–59 mm and fully open implant diameters of 2.5–5.5 mm for target vessels 2–5.5 mm. Both FRED and FRED Jr have two radio-opaque helical wires woven between the two layers with four radiopaque markers at each end for maximum visibility of the stent on deployment. Deployment is performed via delivery pusher wire through the Headway 27 microcatheter (Microvention Inc.). The 2.5 and 3.0 mm FRED/FRED Jr can be delivered via a Headway 21 (Microvention Inc.). Both can be recaptured at up to 80% deployment.

Material and methods

Study design

The FRED-UK study is a single arm, multicentre, prospective, observational study conducted in 7 neurointerventional centres in the UK. Ethics committee approval was acquired (17/EM/0241) and local management committees for each site approved this observational study.

The FRED-UK study is registered in ClinicalTrials.gov under NCT03423290 and funded by Microvention.

The study was conducted according to the principles of Good Clinical Practice. Anatomical results were independently evaluated by a Corelab interventional neuroradiologist. All adverse events were independently assessed by the Clinical Event Committee (CEC), which included 2 interventional neuroradiologists.

All included patients were fully informed and signed a written informed consent prior to their enrolment.

Inclusion criteria at baseline were patients over 18 years of age, presenting with an unruptured or recanalized anterior circulation intracranial aneurysm and a Modified Rankin Score (mRS) ≤ 2. According to the study protocol, only patients who had not had an intracranial haemorrhage in the preceding 30 days were eligible for inclusion. Blister aneurysms, dissecting aneurysms, aneurysms associated with arteriovenous malformations and aneurysms where there was >50% parent vessel stenosis were excluded. Aneurysms which had previously undergone flow diversion or patients who had another FDS procedure within 3 months were also excluded.

The decision to use FRED or FRED Jr with or without adjunctive coiling was at the discretion of the individual operator following multidisciplinary team discussion to reflect real-world usage of FRED and FRED Jr. Minimum operator experience of 10 previous flow diversion procedures of which 3 were with FRED or FRED Jr was required.

Antiplatelet treatment was as per usual institutional practice, and platelet function testing was not required.

Study endpoints

The primary safety endpoint is defined as morbidity (mRS >2) or mortality at 6 months. The primary efficacy endpoint is the rate of complete aneurysm occlusion at 6 months without stenosis (>50%) of the parent vessel.

Adequate occlusion is defined as complete occlusion and/or a neck remnant which does not require treatment.

Secondary endpoints include number of FRED/FRED Jr devices needed per patient, per-operative complications, post-operative complications, morbidity and mortality at 1, 6 and 12 months, and anatomical results at 6 and 12 months.

Data collection

All data were collected by the sites in an electronic eCRF and monitored independently by a Clinical Research Associate. Clinical evaluation, including antiplatelet/anticoagulant therapy and mRS score, was performed before the procedure, at discharge, at 30 days (±7 days), at 6 months (±3 months) and at 12–24 months.

Imaging was collected during the initial hospitalisation, at 6 (±3 months) and at 12–24 months. The type of imaging collected (DSA, MRA, CT) was performed according to the routine practice in each centre.

Statistical analysis

The safety and effectiveness analyses were performed based on both the intent to treat (ITT) population and on the full analysis set (FAS) and per protocol (PP) populations.

The intent to treat (ITT) population consisted of all subjects who have undergone at least one intended FRED implant independently of inclusion and exclusion criteria. The full analysis set (FAS) population consisted of all subjects who met all the inclusion and none of the exclusion criteria and have undergone at least one intended FRED implant. The per protocol (PP) population consists of all subjects who met all inclusion and non-inclusion criteria, who were implanted with at least one FRED device and had follow-up performed according to the protocol. In this study the PP population is equal to the FAS population.

The present paper will focus on the FAS population results.

Results

Patient and aneurysm characteristics

Between November 2017 and December 2019, 61 patients who underwent insertion of a FRED or FRED Jr FDS were enrolled from 7 UK neuroscience centres and

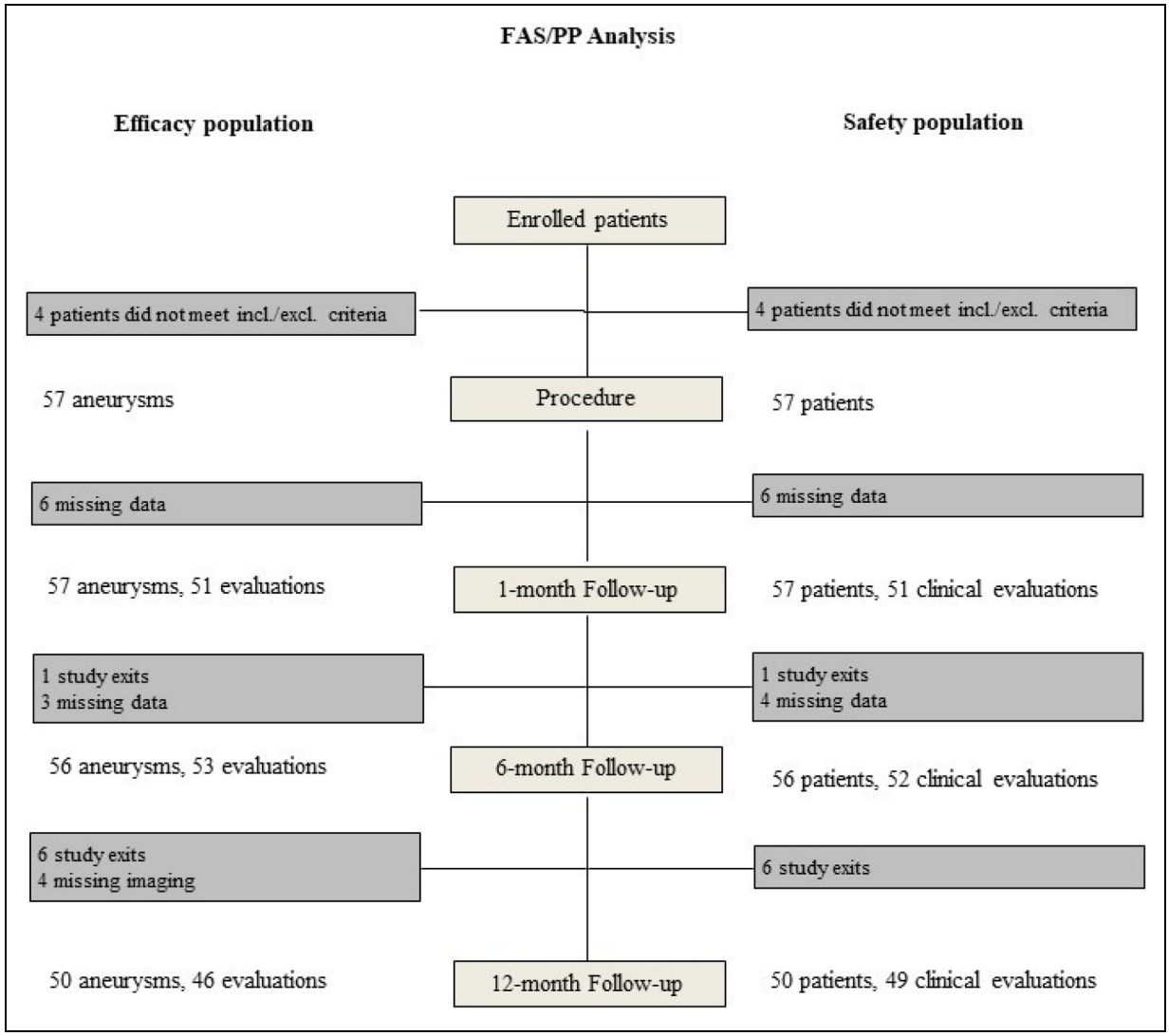

Figure 1. Flowchart of all patients included in the FAS/PP population split into the efficacy and safety populations.

formed the ITT population. Among them, 57 patients met the full inclusion and exclusion criteria and are part of the FAS population. The results presented in the paper will focus on the FAS population (Figure 1).

Ages ranged from 35 to 76 years (mean ± SD: 56.6 ± 11.1 years). Among the 57 patients, 41 were female (71.9%) and 16 were male (28.1%). The pre-operative mRS score was 0 in 36 patients (63.2%), 1 in 18 patients (31.6%), 2 in 3 patients (5.3%). No patient had an mRS score higher than 2.

Twenty-six patients (45.6%) had a history of hypertension, 18 (31.6%) a history of intracerebral haemorrhage, 14 (24.6%) of smoking, 5 (8.8%) of transient ischaemia attack (TIA), 5 (8.8%) had a family history of aneurysms, 3 (5.3%) had diabetes, 1 (1.8%) had a previous ischaemic stroke, and 1 (1.8%) had polycystic kidney disease.

Based on Corelab evaluation, the aneurysms were located on the cavernous or supraclinoid internal carotid artery (ICA) aneurysms in 43 patients (75.4%), on the anterior cerebral artery (ACA) or anterior communicating artery (Acom) in 12 (21.1%) (Figure 2), and on the middle cerebral artery (MCA) in 2 (3.5%). 14/61 (23%) were bifurcation aneurysms (Acom, ACA or MCA). The majority of aneurysms were saccular in 54 patients (94.7%) and 3 (5.3%) had a fusiform aneurysm.

Aneurysms were small (<10 mm) in 33 patients (57.9%), large (10–24 mm) in 23 (40.4%) and giant (≥25 mm) in 1 (1.8%). The majority of treated aneurysms were wide necked (defined as neck ≥4 mm) in 37 (64.9%), with a dome-to-neck ratio <2 in 39 (68.4%). Among the 57 aneurysms treated with a FRED/FRED Jr device, 19 were previously treated (33.3%) and 12 (21.1%) were previously ruptured (Figure 3).

Forty-three aneurysms were treated with a FRED (75.4%) and 14 with FRED Jr (24.6%). No aneurysm was treated with more than one FDS. Ten aneurysms (17.5%) received adjunctive coiling.

Patient follow-up

Patients were followed up by their institution as per their standard follow-up timelines. Their clinical and

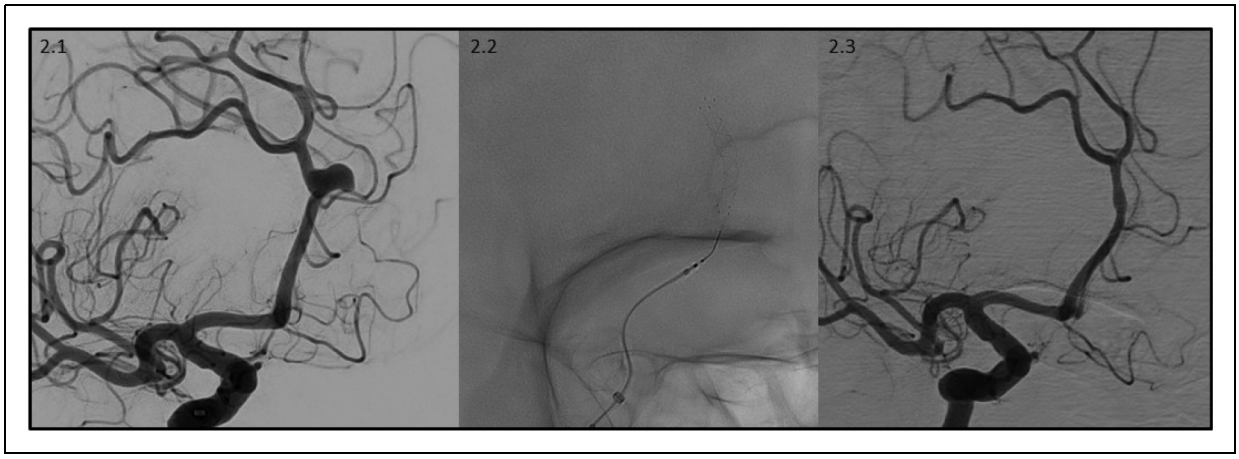

Figure 2. 7 mm unruptured incidental right pericallosal artery aneurysm (2.1) treated with a FRED Jr device deployed in the right pericallosal artery across the aneurysm neck (2.2). On angiographic follow up at 6 months there was complete occlusion of the aneurysm (2.3).

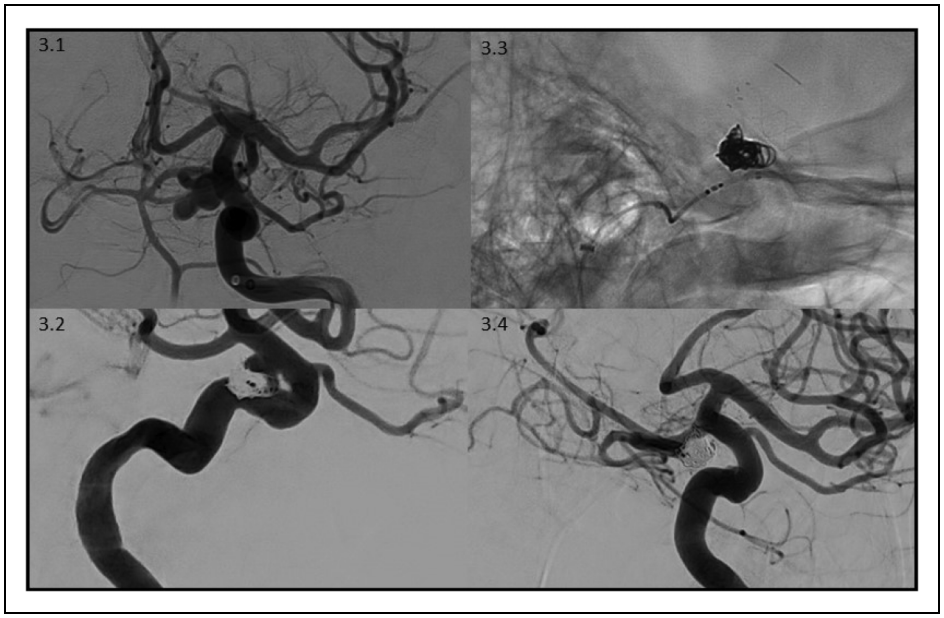

Figure 3. Acutely ruptured 10 mm paraopthalmic aneurysm (3.1) which was previously coiled showed on the 6-month follow-up angiogram that the coil ball had impacted resulting in a significant neck recurrence (3.2). Treatment was performed with the FRED device deployed to cover the aneurysm neck (3.3), and on angiographic follow-up at 1 year there was complete occlusion of the aneurysm (3.4).

radiological follow-up was not altered by participation in the trial with mean 1-month follow-up at 1.4 months, mean 6-month follow-up at 6.6 months and mean 12-month follow-up at 18.6 months.

Safety

Morbidity-mortality rates. Fifty-two patients had a clinical evaluation (mRS) at 6 months follow-up and 49 patients at 12 months follow-up.

The mRS was 0 in 38/52 (73.1%), 1 in 13/52 (25.0%) and 2 in 1/52 (1.9%) at 6 months. At 12 months, mRS was 0 in 33/49 (66.7%), 1 in 14/49 (28.6%) and 2 in 2/49 (3.5%).

The all-cause mortality in the FAS population at 6 months was 0/56 (0%) and 0/57 (0%) at 12 months. One patient (included in the ITT population but not the FAS population) died between the 6- and 12-month follow-up from an ischaemic stroke with underlying vascular dementia unrelated to the FRED device and its implantation.

The primary safety endpoint, defined as morbidity (mRS >2) and mortality at 6 months was 0/52 (0%).

Peri-procedural complications. Five peri-procedural complications occurred in 5 patients (8.8%). One (1.8%) had a technical device complication adjudicated as related to the FRED device and the procedure. The FRED could not be advanced in the microcatheter. This was removed without clinical sequalae, and another FRED device was inserted and deployed successfully. Three (5.3%) had puncture site complications including pseudoaneurysm,

haematoma and pain, all of which were adjudicated as related to the procedure, and resolved without sequelae. One (1.8%) had haematuria following catheter insertion for the procedure, adjudicated as related to the procedure and resolved without sequelae. None of the peri-procedural events were considered serious complications.

Post-procedural complications. In the post operative period, 7/57 (12.3%) in the FAS experienced non-serious complications related to the FDS. Of these, 4/7 experienced headaches, 1 had a TIA, and 2 had symptoms relating to mass effect from the thrombosing aneurysm. Four patients (7%) experienced serious complications related to the FDS and to the procedure, including 3 related to cerebral ischaemia. The remaining 1/57 serious complication patient experienced visual impairment and was subsequently lost to follow-up. All other non-serious and serious adverse complications completely resolved. Finally, one patient developed bilateral ringing in the ears which started on the day of the procedure and has not resolved but the cause could not be identified. Of the 50 FAS patients who received follow-up at 1 year or later, there were no further reported adverse events related to the device or the procedure. There were no reported intracranial haemorrhages or aneurysm ruptures.

Efficacy

Anatomical results at 6 and 12-months follow-up. At 6 months follow-up, 53 patients had imaging follow-up: 25 (47.2%) had digital subtraction angiography (DSA), 25 (47.2%) had MR angiography and 3 (5.6%) had CT angiography.

At 12 months follow-up, 46 patients had imaging follow-up: 10 (21.7%) had digital subtraction angiography (DSA), 34 (73.9%) had MR angiography and 2 (4.3%) had CT angiography.

41 patients (80.4%) had an adequate occlusion at 6 months (defined as complete occlusion or residual neck) and 39/45 (86.7%) at 12 months.

The primary efficacy endpoint, defined as complete occlusion without stenosis of the parent artery at 6 months, was achieved in 31/49 patients (63.3%) (Table 1).

Retreatment. No index aneurysms were retreated through the 12-month follow-up.

Table 1. Anatomical results at 6- and 12-month follow-up. At 6 months, the aneurysm occlusion could not be assessed for 2 patients, and the degree of parent artery permeability could not be assessed for 2 patients. At 12 months, the degree of occlusion and parent artery permeability could not be assessed for 1 patient, and the degree of parent artery permeability could not be assessed for 1 further patient.

	6-month follow-up n = 53	12-month follow-up n = 46
Occlusion degree		
Complete occlusion	32/51 (62.7%)	30/45 (66.7%)
Residual neck	9/51 (17.6%)	9/45 (20.0%)
Residual aneurysm	10/51 (19.6%)	6/45 (13.3%)
Not assessable from imaging	2	1
Parent artery permeability		
No stenosis	23/51 (45.1%)	5/44 (11.4%)
Stenosis <50%	3/51 (5.9%)	0
Stenosis >50%	0	0
Complete occlusion	0	1/44 (2.3%)
Not assessable from imaging	2	2
Primary endpoint		
Complete occlusion without stenosis of parent artery (or ≤ 50%)	31/49 (63.3%)	28/44 (63.6%)
Missing data	4	2

Antiplatelets

Antiplatelet treatment was at the discretion of the physician in line with their institutional guidelines and is detailed in Table 2. The majority of patients received a preoperative antiplatelet (63.2%) and had at least 1 antiplatelet within 12-months follow-up (96.0%). Platelet function testing was performed in 22 cases (38.6%). Of these, 5/22 (22.7%) were found to be resistant to clopidogrel. None were resistant to aspirin. Of those patients who developed peri- or post-procedural complications, the proportion who underwent platelet function testing (46.7%) was not significantly different to the proportion that did not (53.3%).

Discussion

The all-cause morbidity and mortality rate is 0% at 6 months and 12 months. This represents a further progressive improvement compared to 3% at 6 months and 5% at 12 months in the SAFE study of FRED and FRED Jr[5,7] and is in line with the 1.2% mRS 3–6 at median follow-up of 6.6 months in the EuFRED retrospective registry analysis.[8] In the US, the FRED Pivotal Trial reported 2.8% major neurological disability or death at 12 months.[6] The pooled analysis of 3 studies using Pipeline (Medtronic) reported a rate of 7.1% of combined neurological morbidity and mortality at 6 months,[9] the larger PEDESTRIAN retrospective study of the Pipeline registry reported 5.8% major morbidity and neurological mortality and 4.6% all-cause mortality[10] and in the more recent PREMIER Pipeline study the combined major morbidity and mortality rate was 2.1%.[11] The original Surpass (Stryker) study reported 5.4% combined neurological morbidity and mortality at 6 months[12] and the more recent SCENT Surpass trial reported 8.3% major ipsilateral stroke or neurological death at 12 months.[13] A retrospective analysis evaluating the Silk (Balt) prospective database reported 10.8% morbidity and mortality.[14] The Diversion study for p64 (Phenox) reported 2.42% morbidity and mortality at 6 months.[15] Whilst the patient and aneurysm populations, antiplatelet strategies and primary outcome definitions of each FDS registry or trial are

Table 2. Antiplatelet treatment before, during and following the FDS insertion procedure.

Antiplatelet medications	*Before n = 57*	*During n = 57*	*1 month n = 57*	*6 months n = 56*	*12 months n = 50*
0 antiplatelet	21 (36.8%)	2 (3.5%)	0	1 (1.8%)	2 (4.0%)
1 antiplatelet	2 (3.5%)	3 (5.9%)	3 (5.3%)	32 (57.1%)	46 (92.0%)
Aspirin	0	0	2 (3.5%)	31 (55.4%)	44 (88.0%)
Clopidogrel	0	0	1 (1.8%)	1 (1.8%)	2 (4.0%)
Prasugrel	1 (1.8%)	3 (5.3%)	0	0	0
Ticagrelor	1 (1.8%)	0	0	0	0
2 antiplatelets	34 (59.6%)	51 (89.5%)	53 (93.0%)	22 (39.3%)	2 (4.0%)
Aspirin + Clopidogrel	16 (28.1%)	23 (40.4%)	19 (33.3%)	8 (14.3%)	1 (2.0%)
Aspirin + Prasugrel	14 (24.6%)	23 (40.4%)	27 (47.4%)	9 (16.1%)	0
Aspirin + Ticagrelor	4 (7.0%)	5 (8.8%)	7 (12.3%)	5 (8.9%)	1 (2.0%)
3 antiplatelets	0	1 (1.8%)	1 (1.8%)	1 (1.8%)	0
Aspirin + Clopidogrel + Prasugrel	0	1 (1.8%)	1 (1.8%)	1 (1.8%)	0

heterogenous, FRED and FRED Jr have shown consistently good safety outcomes with low morbidity and mortality compared to other FDS. There is an overall trend to a reduction in morbidity and mortality in FDS over time. This likely relates to improving operator familiarity with FDS, evolving understanding of optimal aneurysm characteristics for FDS, operator skill in FDS deployment and development in new generation FDS.

Adequate occlusion was 80.4% at 6 months. As previously observed in FDS, the rate of adequate occlusion increased over time to 86.7% at 12 months.[16] Longer term follow-up is required to assess for progressive occlusion of these aneurysms. The primary efficacy endpoint of complete aneurysm occlusion without parent vessel stenosis was 63.3% at 6 months. The rate of complete aneurysm occlusion at 12 months was 66.7% which is slightly lower than in the Pipeline combined analysis (83.5%),[9] SAFE (73.3%)[7] and Diversion-64 (83.7%).[15] This could be due to the relatively high proportion of bifurcation aneurysms (23%). There were no instances of intracerebral haemorrhage or aneurysm retreatment at 12 months.

The antiplatelets prescribed to study participants pre-, intra-, and post-operatively were at the discretion of each operator in line with their own institutional guidelines (Table 2) and only 38.6% patients had platelet function testing making the antiplatelet treatment regimens extremely heterogenous. The majority of patients received dual antiplatelet therapy up to the 1 month follow-up. This heterogeneity is in line with previous FDS trials and reviews of institutional practices.[17] Most data on platelet function testing is in patients with acute coronary syndrome where the pathophysiology is most often related to plaque rupture than in situ thrombus formation relevant to FDS.[18] Whilst the CHANCE investigators found that adding clopidogrel to aspirin monotherapy did not improve outcomes in loss of function (LOF) CYP2C19 allele patients at low risk of recurrent ischaemic stroke in the Chinese population,[19] a substudy of the European and American populations in the POINT study[20] found no significant association of LOF CYP2C19 alleles and major ischaemic outcomes in patients treated with dual antiplatelet therapy for TIA or minor ischaemic stroke. Analysis of the pipeline registry found higher morbidity in patients who had undergone platelet function testing.[21] Different surface modifications of FDS including antithrombotic coatings are being explored with several surface modified FDS currently available, each aiming to reduce reliance on dual antiplatelet therapy.[22] Standardised antiplatelet treatment in future randomised control trials for FDS with or without surface modification is crucial. The COATING study[23] evaluating the coated or uncoated p64 MW FDS (Phenox) use in patients treated with ticagrelor or prasugrel with or without aspirin is currently recruiting. It is further hypothesised that thrombosis between the stent and the vessel wall can hinder epithelialisation of the FDS, leading to a slower or reduced rate of complete occlusion.[24] The FRED X second generation FDS (Microvention Inc.) aims to maximise direct apposition of the stent and vessel wall by combining poly (2-methoxyethyl acrylate) antithrombotic coating with improved navigability compared to FRED and FRED Jr FDS. In direct comparison, complete occlusion rates were higher with FRED X than FRED/FRED Jr.[25] However, thromboembolic complication rates were not significantly different, and this is limited to a single centre comparison.

Limitations

As FRED-UK was not randomised, safety and efficacy cannot be compared with a control population. The priority in the study design was given to patients receiving their normal clinical and angiographic follow-up to evaluate real world practice, but this meant that there is a wider range of post procedure time points used for follow-up and the antiplatelet regimens are heterogenous. The 12-month follow-up of several patients was affected by the early Sars-Cov2 pandemic in the UK.

Conclusion

The rate of adequate occlusion at 12 months was 86.7% with no aneurysm ruptures during the follow-up period. The all-cause morbidity and mortality rates were 0% at

6 and 12 months. This further demonstrates the safety and efficacy of FRED and FRED Jr flow diverting stents.

Contribution statement

ET and KL drafted the article.
JD, SL, AC, PK, CG, CJ, and KL assisted in acquiring the data.
TB, AG, and JL analysed and interpreted the data.
KL contributed to the conception and original design of the study.

Data availability

Data available on request.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: ET, AC, CG, CJ, AG and PK report no conflicts of interest.

JD has been paid by Microvention as a consultant and paid speaking fees by Medtronic, Phenox and Microvention.

JD, SL and JL have each been paid by Microvention to participate in data monitoring or clinical events committee for another Microvention study.

SL and KL have been paid consulting and proctoring fees by Microvention.

TB has been paid by Microvention to be part of a core laboratory for another interventional study investigating a Microvention product. TB has also been paid to give an educational lecture on an independent, non-industry sponsored study published in AJNR on the Pipeline Flow Diverter Stent.

JL was paid by Microvention to adjudicate clinical events for this study as part of the clinical events committee.

The study was funded by Microvention Europe who manufactures the FRED and FRED Jr stents.

Ethical approval

The FRED-UK study is registered in ClinicalTrials.gov under NCT03423290. Ethics committee approval was acquired (reference no 17/EM/0241). Patient consent obtained.

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Patient consent

Obtained.

Provenance and peer review

Not commissioned.

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