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X-Factor: Antithrombotic Coating Reduces Procedural Thromboembolic Events in Flow Redirection Endoluminal Device (FRED) Aneurysm Embolization

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■ BACKGROUND: **The Flow Redirection Endoluminal Device (FRED) is a dual-layer flow diverting stent with a dense inner mesh and outer braided support providing superior deployment control. Covalently bonded Poly(2-methoxyethyl acrylate) X coating was introduced to decrease metal-induced thrombogenicity in the newer FRED X variant. The objective of the current study is to evaluate procedural thromboembolic events associated with both variants.**

■ METHODS: **A single-center retrospective analysis was undertaken comparing angiographically detected intraprocedural thromboembolic events, postprocedural magnetic resonance diffusion weighted imaging lesions (MR-DWI+), as well as a composite combined endpoint. Periprocedural (<24 hours) clinical events, demographics, aneurysm characteristics and platelet aggregation (using P2Y12 reactivity unit, PRU) were analyzed.**

■ RESULTS: **Treatment was performed with 19 FRED procedures in 18 patients with 19 aneurysms, and with 37 FRED X procedures in 35 patients harboring 40 aneurysms. Both groups achieved therapeutic preprocedural platelet inhibition by PRU testing. Intraprocedural thromboembolic events including intraluminal filling defects and side-branch slowing or loss occurred in 7/19 (36.8%) FRED and 0/37 FRED X procedures ($P = 0.0002$), with all being successfully recanalized using intra-arterial platelet inhibitors, without symptomatic ischemic or hemorrhagic events. The composite endpoint was reached in 11/19 (57.9%) FRED and 5/37 (13.5%) FRED X cases ($P = 0.001$), with multivariable analysis identifying device type ($P = 0.015$) among age, gender, and PRU.**

■ CONCLUSIONS: **The surface modification of the FRED X device may be associated with improved thrombogenic risk profile in our cohort, with elimination of intraprocedural thrombus formation and reduction of composite thromboembolic events.**

INTRODUCTION

Flow diversion (FD) has assumed a central role in the endovascular treatment of aneurysms, with multiple devices now having demonstrated acceptable safety and efficacy profiles.[1-6] As thromboembolic events cause a large fraction of the complications related to FD, surface modifications have been introduced to reduce thrombogenicity.[7-11] The Flow Redirection Endoluminal Device (FRED; Terumo Neuro, Aliso Viejo, CA, USA), a braided flow diverting stent which introduced a dual-layer design, was originally released without any surface modifications with good safety results.[6] The stent design was subsequently updated with a new covalently-bonded Poly(2-methoxyethyl acrylate, PMEA) surface modification, which was

Key words
- Aneurysm
- Device
- Flow diverter
- Intervention

Abbreviations and Acronyms
ACT: Activated clotting time
DAPT: Dual antiplatelet therapy
FD: Flow diversion
FRED: Flow Redirection Endoluminal Device
ICA: Internal carotid artery
MR-DWI: Magnetic resonance diffusion weighted imaging
MRI: Magnetic resonance imaging
MRI/A: Magnetic resonance imaging and angiography
PED-Shield: Pipeline Flex Embolization Device with Shield Technology
PMEA: Poly(2-methoxyethyl acrylate) surface coating (commercially known as "X" coating)
PRU: P2Y12 reactivity unit

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shown in-vitro to be associated with reduced thrombogenicity.[8] The surface-treated variant, known as FRED X, has been reported to show a trend in the clinical literature towards lower complication rates compared to its predecessor, although results have been mixed.[1,6,12,13]

Currently, there is a relative dearth of data directly comparing the clinical thromboembolic characteristics of FRED and FRED X while reporting possible confounding variables such as antiplatelet regimens with platelet function testing and intraprocedural anticoagulation status. Data on immediate postprocedural magnetic resonance diffusion-weighted (MR-DWI+) ischemic lesions, another objective marker of procedural thromboembolic risk, have also not been evaluated when comparing the devices. The present study attempted to address these areas by analyzing the putative clinical antithrombotic effect of FRED X.

METHODS

Patients and Study Design

This is an institutional review board-approved retrospective analysis of a single-center cohort of consecutive patients treated with the FRED and FRED X FDs longitudinally in the same clinical and equipment setting. Patients were treated between October 2013 and August 2025; FRED was used earlier, while FRED X use began in May 2022. No aneurysm size, location, or rupture status exclusions were applied; aneurysm location for internal carotid artery (ICA) lesions was defined according to the 7-segment classification scheme.[14] Adverse events were considered during the immediate procedural and postprocedural ($\leq$24 hours) period, and were reported as neurologic (intracranial hemorrhage, symptomatic ischemic stroke, cranial neuropathies) or non-neurologic. A composite thromboembolic outcome variable that includes any patient experiencing either intraprocedural thromboembolic events or postprocedural MR-DWI + lesions in the stented parent vessel territory was used as an endpoint. This was undertaken to capture overall thromboembolic tendencies between the two devices while minimizing the confounding effect of intra-arterial administration of platelet deaggregant agents during intraprocedural thromboembolic events. With the FRED's novel dual-layer design, we adopted a cautious approach when introducing it at our center by including watchful observation after stent deployment with multiple control angiograms performed over a minimum period of 20 minutes to evaluate for thrombus formation; this was performed in all patients across the FRED and FRED X groups up to the most recent cases.[15,16] Intraprocedural thromboembolic events are defined as angiographically-visible evidence of thrombus formation seen during the index FRED embolization procedure, including nonocclusive thrombus formation on the stent surface, stent/parent vessel occlusion or subocclusion, as well as jailed branch vessel occlusion or threatened occlusion (the latter characterized by delayed filling of the branch vessel beyond the early arterial phase). Postprocedural magnetic resonance imaging (MRI) was analyzed for presence of MR-DWI + lesions as well as whether the lesions conformed to the device's vascular territory; these events were not included in the number of ischemic stroke adverse events unless the patient demonstrated corresponding neurologic deficit. The apparent diffusion coefficient sequence was used to confirm true restriction versus T2 shine-through effect.

Procedures

For elective cases, dual antiplatelet therapy (DAPT) with aspirin 81 mg daily and either clopidogrel 75 mg daily or prasugrel 10 mg daily was initiated ~7 days before treatment, and same-day platelet function testing was performed using VerifyNow (Accumetrics, San Diego, CA) P2Y12 reactivity units (PRUs) to ensure therapeutic effect prior to intervention. Ruptured cases were either pretreated with DAPT or given intraprocedural antiplatelet agents prior to stent deployment, depending on clinical stability.

Embolization was performed using a transfemoral triaxial system consisting of a 6-french shuttle sheath (Cook Medical Inc., Bloomington, IN, USA), a 5-french Sofia EX intermediate catheter with either Headway 27 for ICA lesions or Headway 21 for smaller parent vessel lesions (all Terumo Neuro, Aliso Viejo, CA, USA). Intravenous heparin was administered for a goal activated clotting time (ACT) of $\geq$220 seconds with intraprocedural monitoring every 15–30 minutes; mean ACTs postheparinization were similar between FRED and FRED X groups (219.6 $\pm$ 34.1 vs. 221.1 $\pm$ 22, respectively, $P = 0.92$). Selection of FRED size and length was based on proximal and distal target vessel diameter and length measurements performed using multiplanar reconstruction of rotational angiography and cone beam CT angiography volumetric datasets. The goal of every procedure was to achieve aneurysm coverage with a single device; the decision to use any additional concentric FRED device was based solely on the adequacy of aneurysm neck coverage by the first stent's flow diverting element.

Follow-Up

Patients were observed in an intensive care unit overnight postprocedure. Routine practice at our institution includes 3-T magnetic resonance imaging and angiography (MRI/A) on postprocedure day 1 using 3.0T Achieva dStream or MR7700 MRI systems (both Philips Healthcare, Best, The Netherlands). Postprocedural MRI/A was successfully performed after 17/19 (89.5%) FRED and 35/36 (97.2%) FRED X procedures ($P = 0.26$).

Statistical Analysis

Standard mean, median, and standard deviations were calculated for patient demographic information. Statistical analysis was completed using JMP 18.2.2 statistical software package (SAS Institute, Cary, NC, USA) with statistical significance assumed for $P < 0.05$.

RESULTS

Eighteen patients with 19 aneurysms were treated with FRED, and 35 patients with 40 aneurysms were treated with FRED X; **Table 1** summarizes the relevant demographic variables between the two groups. There were 8 (42.1%) non-ICA aneurysms treated with

Table 1. Baseline Patient Demographics, Procedural Descriptors, and Outcome Analysis

Variable	FRED Patients, n = 18	FRED X Patients, n = 35	*P* Value
Age (years), mean ± SD (range)	64.1 ± 16.6 (32–86)	59.9 ± 14.1 (26–80)	0.37
Female gender, n (%)	15 (83.3)	26 (74.3)	0.73
Past medical history, n (%)			
Hypertension	12 (66.7)	19 (54.3)	0.56
Diabetes mellitus	0 (0)	7 (20.0)	0.08
Coronary artery disease	0 (0)	3 (8.6)	0.54
Prior ischemic stroke	4 (22.2)	5 (14.3)	0.47
Former smoking	7 (38.9)	7 (20)	0.19
Active smoking	4 (22.2)	8 (22.9)	1.0
Aneurysms	**n = 19**	**n = 40**	
Aneurysm locations, n (%)			0.12
C1	2 (10.5)	6 (15)	
C2	1 (5.3)	1 (2.5)	
C4	2 (10.5)	1 (2.5)	
C5	2 (10.5)	2 (5)	
C6	1 (5.3)	11 (27.5)	
C7	3 (15.8)	10 (25)	
MCA	2 (10.5)	0 (0)	
ACOM	1 (5.3)	4 (10)	
Pericallosal	2 (10.5)	2 (5)	
Vertebral	3 (15.8)	2 (5)	
PCA	0 (0)	1 (2.5)	
Non-ICA parent vessel, n (%)	8 (42.1)	9 (24.3)	0.22
Aneurysm morphologies, n (%)			0.31
Saccular	6 (31.6)	22 (55)	
Repeat treatment	3 (15.8)	3 (7.5)	
Lobulated	4 (21.1)	6 (15)	
Dissecting/pseudoaneurysm	3 (15.8)	7 (17.5)	
Fusiform	3 (15.8)	2 (5)	
Greatest dimension of treated aneurysms (mm), mean ± SD (range)	8.7 ± 5 (2.4–18)	7.8 ± 7.8 (0.9–31.3)	0.49
Ruptured at time of treatment, n (%)	2 (10.5)	1 (2.7)	0.26
Ruptured and recovered prior to flow diversion, n (%)	2 (10.5)	2 (5.4)	0.6
Previous endovascular coiling of target aneurysm, n (%)	1 (5.3)	2 (5.4)	1.0
Previous clipping of target aneurysm, n (%)	2 (10.5)	0 (0)	0.11
Procedures	**n = 19**	**n = 37**	
Right sided approach for treatment, n (%)	13 (68.4)	20 (54.1)	0.39
Number of aneurysms treated during stenting procedure, n (%)			
1	19 (100)	34 (91.9)	
2	0 (0)	3 (8.1)	0.54

ACOM, anterior communicating artery; ACT, activated clotting time; CI, confidence interval; FRED, Flow Redirection Endoluminal Device; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; MR-DWI, magnetic resonance diffusion-weighted; PCA, posterior cerebral artery; PRU, P2Y12 reactivity unit; SD, standard deviation.
*Indicates statistical significance.

Continues

Table 1. Continued

Variable	FRED Patients, n = 18	FRED X Patients, n = 35	*P* Value
Number of FRED stents deployed, n (%)			
1	18 (94.7)	37 (100)	
2	1 (5.3)	0 (0)	0.35
Total procedural time, minutes (mean ± SD, range)	71.2 ± 29, 36–152	56 ± 14, 32–97	0.04*
Total procedural time excluding intraprocedural thrombosis, minutes (mean ± SD, range)	62.8 ± 29.8 (36–152)	56 ± 14.4 (37–97)	0.46
Adjunct coiling performed, n (%)	3 (15.8)	2 (5.4)	0.32
Preprocedural PRU, mean ± SD (range)	57 ± 42, 4–130	22.8 ± 24.2, 1–76	0.01*
Stent diameter, median (range)	4 (2.5–5.5)	4.5 (2.5–5.5)	-
Initial poor stent-wall apposition, n (%)	1 (5.3)	0 (0)	0.35
Balloon angioplasty performed for incomplete apposition, n (%)	0 (0)	0 (0)	-
Placement of Neuroform Atlas stent to improve proximal apposition, n (%)	1 (5.3)	0 (0)	0.35
Procedural and Postprocedural Outcomes			***P* Value**
Composite outcome (intraprocedural thromboembolic event or MR-DWI + lesions), n (%)	11 (57.9)	5 (13.5)	0.001*
Any intraprocedural thrombosis event, n (%)	7 (36.8)	0 (0)	0.0002*
Detail of intraprocedural thrombosis events			
Nonocclusive thrombus within stent	3 (15.8)	0 (0)	
Jailed branch vessel thrombosis with filling delay	3 (15.8)	0 (0)	
Subocclusive thrombosis of parent vessel	1 (5.3)	0 (0)	
Neurologic complications within 24 hours, n (%)			0.34
Symptomatic ischemic event	0 (0)	0 (0)	
Intraparenchymal hemorrhage	0 (0)	0 (0)	
Cranial neuropathy	1 (5.3)	0 (0)	
Non-neurologic complications within 24 hours, n (%)			1.0
Access-related hematoma	1 (5.3)	2 (5.4)	

Multivariable Analysis of Composite Thromboembolic Outcome

Variable	Odds Ratio	95% CI	*P* Value
Age	0.99	0.93–1.04	0.63
Male gender	0.25	0.01–2.23	0.29
Preprocedural PRU	0.98	0.94–1.00	0.1
Coated FRED	0.08	0.01–0.54	0.015*

ACOM, anterior communicating artery; ACT, activated clotting time; CI, confidence interval; FRED, Flow Redirection Endoluminal Device; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; MR-DWI, magnetic resonance diffusion-weighted; PCA, posterior cerebral artery; PRU, P2Y12 reactivity unit; SD, standard deviation.
*Indicates statistical significance.

FRED and 9 (24.3%) were treated with FRED X (P = 0.22). Most aneurysms were saccular or lobulated without significant difference between groups (P = 0.31). One (5.3%) aneurysm was previously coiled and 2 (10.5%) were previously clipped in the FRED group, while 2 (5.4%) were previously coiled in the FRED X group. Two procedures (10.5%) occurred for ruptured aneurysms in the FRED group, and 1 (2.7%) occurred in the FRED X group (P = 0.26).

Procedures

FRED was implanted in 19 procedures and FRED X in 37 procedures. All FRED procedures treated 1 aneurysm, while 3 (8.1%)

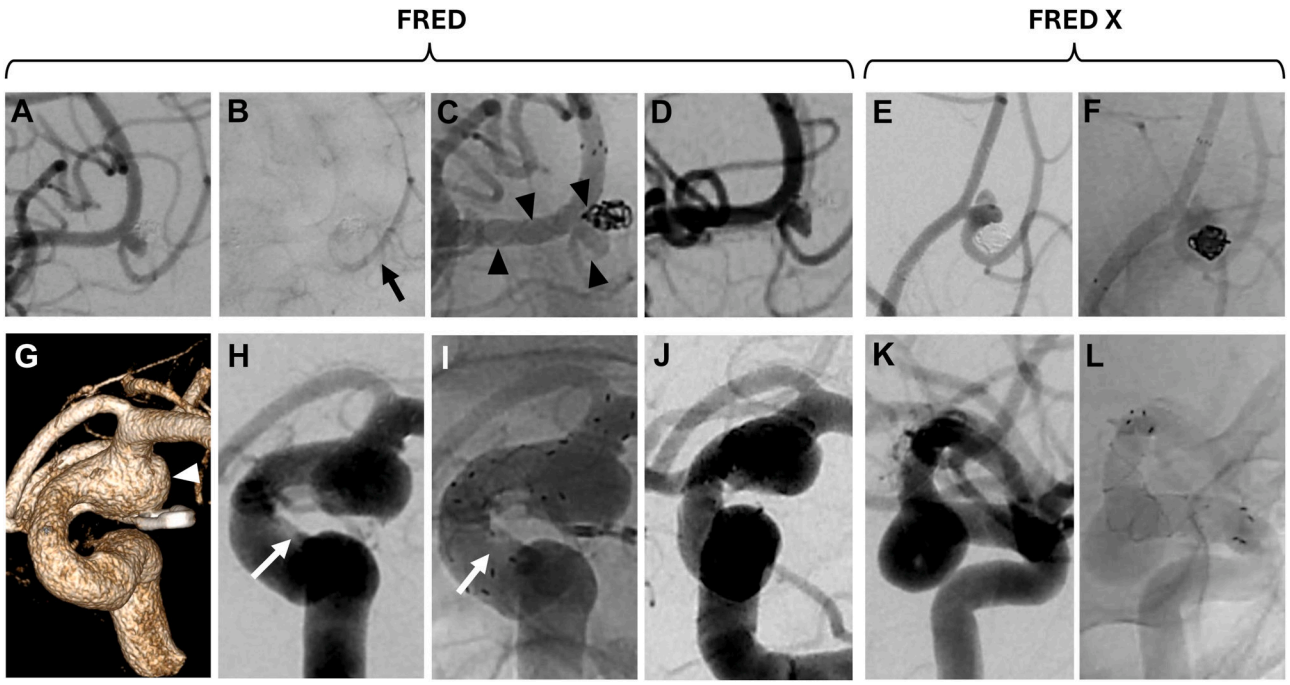


Figure 1. Illustration of cases of FRED-associated thrombosis, with comparable FRED X cases. Pericallosal cases – (**A**): Bilobed right pericallosal aneurysm questioned to have ruptured given presentation with sudden headache and subarachnoid hemorrhage (workup revealed a more proximal ACOM aneurysm which was the more likely source and was coiled earlier); this was treated with coiling of the superior dome followed by FRED placement, seen here immediately postdeployment. The patient was given 1 mg of intravenous eptifibatide before coiling, as well as a load of 0.79 mg of intravenous cangrelor followed by a continuous rate of 2 μg/kg/min 2 minutes prior to stent deployment. (**B**): Eleven minutes after deployment, the jailed callosomarginal branch (arrow) was delayed into the capillary phase. (**C**): In native view, thrombus (black arrowheads) is seen forming along the proximal stent walls, adjacent to the coil mass, and along the wall of the aneurysm. (**D**): This resolved with a total of 2.8 mg intra-arterial cangrelor plus an increased peripheral rate of 4 μg/kg/min. (**E**, **F**): Previously coiled left pericallosal aneurysm with regrowth of a superior lobulated dome, treated with a single FRED X device after an unsuccessful coiling attempt, seen after 15 minutes of observation with no thrombus formation or branch slowing. Preprocedural PRU was 19 on aspirin 81 mg and prasugrel 10 mg daily. ICA cases – (**G**): Previously clipped C7 aneurysm (white arrowhead) associated with a dominant left PCOM demonstrating significant neck recurrence, which was treated with FRED. This patient's preprocedural PRU was 69 on aspirin 81 mg daily and prasugrel 10 mg daily. A distal concentric FRED placement was required to achieve complete neck coverage. (**H**, **I**): Seventeen minutes after the second stent was deployed, an angiographic run revealed formation of a thrombus on the proximal tines of the more proximal concentric stent (white arrows). (**J**): This resolved with 3 mg of intra-arterial eptifibatide. (**K**, **L**): A different patient with a large PCOM aneurysm was treated with a single FRED X stent. Seen here 11 minutes after deployment, there remained no evidence of thrombosis. FRED, Flow Redirection Endoluminal Device; ACOM, anterior communicating artery; ICA, internal carotid artery; PCOM, posterior communicating artery; PRU, P2Y12 reactivity unit.

of the FRED X cases treated two aneurysms in the same procedure. Adjunctive coiling was performed in 3 (15.8%) FRED and 2 (5.4%) FRED X procedures ($P = 0.32$). The median stent diameter was 4 mm in the FRED group and 4.5 mm in the FRED X group. Balloon angioplasty was not used in any case and 1 (5.3%) FRED stent required deployment of a proximal Neuroform Atlas stent to achieve full apposition. Mean PRU was 57 ± 42 (range 4–130) in the FRED group and 22.8 ± 24.2 (range 1–76) in the FRED X group, ($P = 0.01$); despite the difference between device types, both averages and all ranges achieved therapeutic levels in both groups.

Thromboembolic Events

Seven of 19 (36.8%) FRED cases and no FRED X cases were affected by intraprocedural thromboembolic events during the poststenting observation period at a median time of 11 minutes, with all but two cases occurring >5 minutes from stent deployment. In the FRED group, 3 (15.8%) had delayed filling of a side branch vessel due to early thrombus formation (2 callosomarginal arteries and one anterior spinal artery); 3 (15.8%) experienced nonocclusive thrombi formation within the stent; and 1 (5.3%) patient had thrombosis within the stent with near-occlusion of the middle cerebral artery. Each of these complications was successfully treated with administration of intra-arterial antiplatelet medication with flow restoration and thrombus disaggregation. Figure 1 shows FRED cases with intraprocedural thromboembolic events (panels A-D, G-J) compared to similar FRED X cases without such events (panels E-F, K-L). Mean total procedural time was 71.2 minutes in the FRED group and 56 minutes in the FRED X group ($P = 0.04$). The longer procedural time with FRED was driven by intraprocedural thromboembolic events; excluding cases with these events from analysis revealed

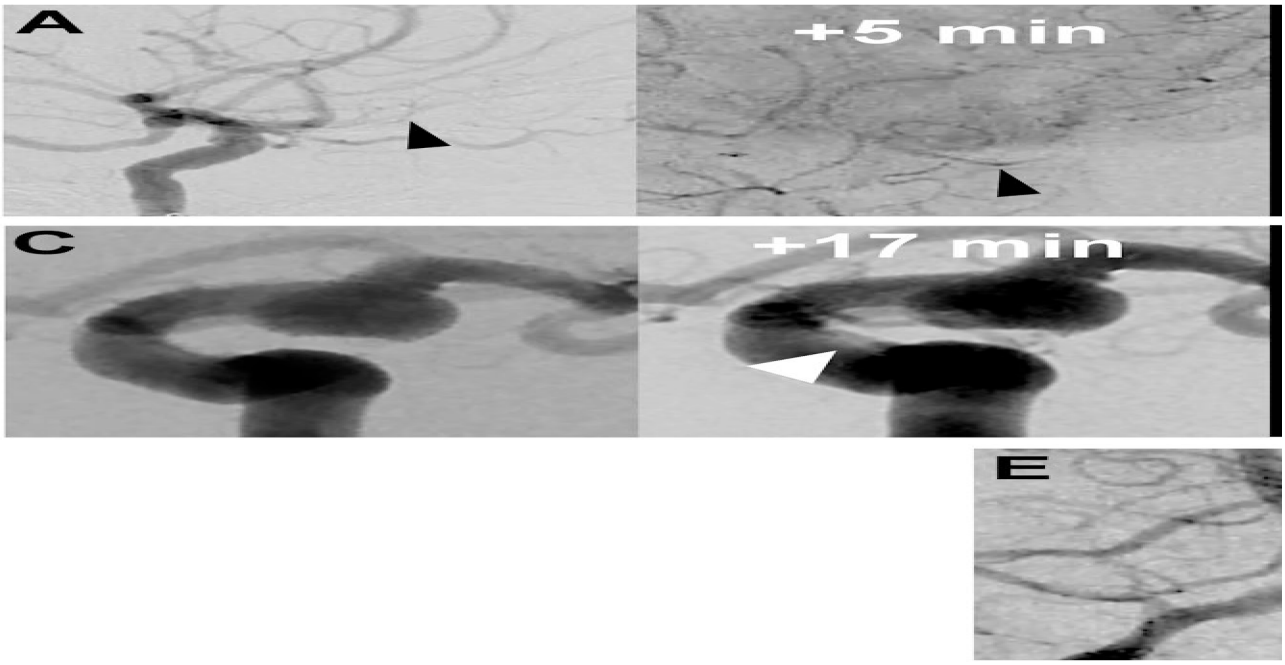


Figure 2. Cases of FRED intraprocedural thrombosis with corresponding postprocedural imaging. All cases were treated to thrombus resolution with intra-arterial antiplatelet agents. In each case, the left panel is predeployment, the middle panel shows the thrombosis event at the indicated time postdeployment, and the right panel indicates the postprocedural day 1 imaging. (**A**): C6 aneurysm; ophthalmic artery (arrowheads) before and after FRED with near-complete occlusion causing significant delay into capillary phase 5 minutes postdeployment, with external carotid angiogram confirming no collateral retinal blush (not shown); one MR-DWI + lesion (white arrow) seen on MRI in the device territory. Preprocedure PRU 5. (**B**): C5 aneurysm, before and after FRED with thrombus formation (arrowhead) along inner curve immediately post-deployment; no MR-DWI + lesions. Preprocedure PRU 130. (**C**): Previously clipped C7 aneurysm, before and after FRED with proximal thrombus formation (arrowhead) at 17 minutes postdeployment; no MR-DWI + lesions. Preprocedure PRU 69. (**D**): Bilobed pericallosal aneurysm before and after coiling and FRED, with callosomarginal branch (arrowhead) delayed into capillary phase at 11 minutes postdeployment; no MR-DWI + lesions. Given predeployment eptifibatide and cangrelor as described in Figure 1. (**E**): Ruptured fusiform right V4 aneurysm before and after FRED, with the anterior spinal artery (black arrowheads), which lost flow secondary to thrombus formation (white arrowhead) between the stent and the anterior spinal origin 9 minutes after deployment leading to delayed anterior spinal filling; few small punctate MR-DWI + lesions (white arrow) seen on MRI in the device territory. The patient had been given a load of 1.4 mg of intravenous cangrelor and started on a continuous rate of 2 μg/kg/min 17 minutes prior to stent deployment. FRED, Flow Redirection Endoluminal Device; MRI-DWI, magnetic resonance diffusion weighted imaging; PRU, P2Y12 reactivity unit.

no significant difference in time between the two groups (FRED, 62.8 minutes and FRED X, 56 minutes, $P = 0.46$). On post-procedural MRI, 6/17 (35.3%) FRED and 5/36 (13.9%) FRED X cases demonstrated ipsilateral MR-DWI + lesions ($P = 0.14$). Only 2/6 (33.3%) patients with intraprocedural thromboembolic events had any MR-DWI + lesions, and the seventh case underwent head CT with no evidence of infarct. Figure 2 illustrates example intraprocedural thrombosis cases in the FRED group with corresponding MRIs.

The composite thromboembolic event endpoint of intraprocedural thrombosis or postprocedural MR-DWI + lesions occurred in 11/19 (57.9%) of FRED and 5/37 (13.5%) FRED X procedures ($P = 0.001$), and there were significantly greater intraprocedural thromboembolic events in the FRED group ($P = 0.0002$; Figure 3, panels A and B). Mean preoperative PRU was similar in cases with (48.4, range 5–130) and without (30.6, range 1–115) intraprocedural thromboembolic events ($P = 0.49$). Similar PRU results were also noted for the composite thromboembolic event endpoint, with a mean of 30.5 (range, 1–115) in the group without any events and 39.1 (range, 2–130) in those with an endpoint event ($P = 0.53$). Multivariable logistic regression was performed for the composite endpoint, with use of FRED X remaining a significant negative predictor of composite thromboembolic outcome (odds ratio 0.08, $P = 0.015$) when controlling for age, gender and preprocedural PRU.

Clinical Outcomes

No patients experienced new symptoms from intraprocedural thromboembolic events or MR-DWI + lesions in either the FRED or the FRED X groups. One patient in the FRED group developed postprocedural oculomotor and abducens deficits after adjuvant coiling and FRED treatment of a large C4 aneurysm; no thromboembolic events or MR-DWI + lesions were noted in this patient. There were also no hemorrhages associated with

intra-arterial platelet inhibitors or DAPT seen in the 24 hours after embolization.

DISCUSSION

Although FD has become a first-line treatment modality for many intracranial aneurysms, thromboembolic complications have remained a key procedural risk despite use of DAPT. Surface modifications have emerged as a mitigation strategy, with multiple manufacturers implementing such modifications in an effort to reduce complication rates.[1,7-11,17] In-vitro and animal analyses have demonstrated support for the antithrombotic effects of these surface treatments.[8-11,17,18] In studies utilizing human blood in a loop model, deployed FRED X and Pipeline Flex Embolization Device with Shield Technology (PED-Shield; Medtronic Neurovascular, Irvine, CA, USA) outperformed the uncoated FRED with lower rates of accumulated blood cell deposits on scanning electron microscopy, higher platelet levels in the blood (indicating lower aggregation), as well as lower thrombin-antithrombin complex and β-thromboglobulin levels after circulation (indicating lower levels of blood activation).[8,11,17]

Although the preclinical data on surface modification have demonstrated the intended effect, the real-world reduction in thromboembolic complications for surface-modified FD have been conflicted across the literature. For the PED-Shield, studies have demonstrated both statistically significant and nonsignificant reductions in clinical and MR-DWI + events.[19-22] Studies directly comparing thromboembolism in FRED and FRED X have shown encouraging trends, although not all differences were significant.[2,12,13] Analysis of 137 FRED and 156 FRED X procedures found fewer symptomatic ischemic events in the FRED X group (5.1% vs. 0.6%, $P = 0.03$), but the trend became nonsignificant with improved matching (6.1% vs. 0.9%, $P = 0.07$).[13] Another study comparing the two stents revealed a trend towards fewer all-cause complications in FRED X (8.3% vs. 2.4%, $P = 0.1$) with supporting Bayesian analysis; however, complication rates specific to ischemia were not compared between the two groups.[12] Finally, another cohort analysis comparing multiple FDs found no significant difference in the postprocedural stroke rate for FRED, FRED X, PED, or PED-Shield ($P = 0.57$).[2] Intraprocedural thrombosis rates also varied between series. Of the three studies comparing FRED to FRED X directly, only one specifically reported on intraprocedural thrombosis events. Goertz et al. described apposition thrombi forming in 6/137 (4.4%) FRED and 4/156 (2.6%) FRED X stents, with one occluded ophthalmic artery in the FRED group; all thrombi resolved with intravenous tirofiban.[13] Separate series dedicated to FRED have found intraprocedural thrombosis rates of 1.1%–9.3%, while FRED X has rates ranging from 0.6% to 2.5%.[23-26] Another study investigating the utility of a standardized observation period for intraprocedural thrombosis across several FDs (including FRED and FRED X) found a rate of 8/86 (9.3%) for FRED and 3/28 (10.7%) for FRED X.[15] Only one study investigated MR-DWI + lesions in the FRED stent and found these in 9/50 cases (18%).[27]

Our study has demonstrated that the uncoated FRED stent appears to be predisposed to thromboembolic events compared to the FRED X in our cohort, with 57.9% of patients in the FRED group reaching the thromboembolic composite endpoint. There was a particularly high risk of intraprocedural, angiographically visible thrombus formation thanks to the practice of delayed observation following stent deployment. The 36.8% rate of these events in our cohort is higher compared to the existing literature and occurred despite our practice of aggressive DAPT with therapeutic PRU levels confirmed in both cohorts (and similar PRU levels seen in cases with and without thrombus formation), as well as consistent intraprocedural ACT management. Given the high rate of intraprocedural thrombus formation, we used a composite endpoint in this study in order to more accurately compare the two devices' thromboembolic profiles. This was undertaken because treatment of macroscopic intraprocedural

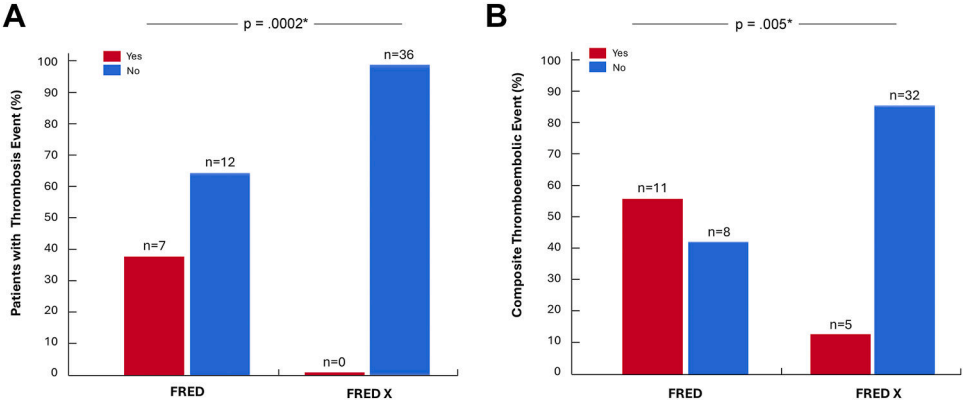


Figure 3. Bar graph comparisons of intraprocedural thromboembolic events (**A**) and composite endpoint outcomes (intraprocedural thromboembolic event or MR-DWI + lesions) (**B**) between FRED and FRED X.

FRED, Flow Redirection Endoluminal Device; MRI-DWI, magnetic resonance diffusion weighted imaging.

thrombus formation with intra-arterial platelet inhibitors may also mitigate the microemboli that otherwise manifest as post-procedural punctate MR-DWI lesions, which could confound the effect of the X-coating. This is suggested by our finding that only 2/7 FRED patients (28.6%) with intraprocedural thromboembolic events demonstrated any evidence of ischemia on postprocedural imaging (see **Figure 2**) even though if left untreated, all would have resulted in stroke. It is possible that less vigilant surveillance for intraprocedural thrombosis, without the requisite treatment with intra-arterial platelet deaggregant agents, would increase risk for MR-DWI + or symptomatic ischemic events with the uncoated device. Despite the high rate of thromboembolic events in the FRED group, it is notable that no patients experienced new ischemic symptoms (likely due in part to the practice of delayed observation with treatment of any thrombi), nor antiplatelet-associated hemorrhages.[15,16]

The thrombogenic profile of the uncoated FRED stent may be multifactorial.[17,18,28-30] It has been considered that the arrangement of the radiopaque elements of the FRED could lead to difficulty in distinguishing wall apposition; this may lead to situations where the radiopaque elements appear apposed while a portion of the more lucent nitinol mesh is not, which can result in increased thrombosis risk.[28] There have also been problems with opening and foreshortening in tortuous anatomy, leading some authors to recommend caution with its use in arterial segments with acute angles.[28,29] It has been theorized that the dual-layer design itself of the FRED stent may heighten thromboembolic risk. There is a very small (approximately 100 μm) space between the two layers of FRED. This increases the metal surface area exposed to the bloodstream, introduces a compartment in which hemodynamic platelet shearing between the struts is more likely to lead to platelet activation, and provides a possible nidus for buildup of other coagulation cascade factors like fibrin.[17,18,30] This effect was suggested by results of a flow-loop model analysis comparing PED devices with FRED, the latter of which was found on scanning electron microscopy to be coated with thrombus, including in the space between the two braid layers; this mechanism could also explain the increased fibrin accumulation seen on FRED in animal models.[17,18] This problem was not encountered in another flow-loop study that included the FRED X stent with its PMEA coating, which significantly reduced the device's thrombogenicity in-vitro.[8] Taken together with the results of the current study, the X-coating would appear to confer compelling protection against early thromboembolism compared to the original FRED when used in conjunction with appropriate DAPT, although larger numbers with extended follow-up would help to elucidate this effect.

This study is limited by its retrospective design and smaller sample size over a long study period, which could influence operator learning, incremental manufacturer changes to the device, and different institutional experience and periprocedural protocols over time, any of which could affect outcomes. However, it is strengthened by limited patient heterogeneity with similar baseline demographics between the two cohorts; the high availability of immediate postprocedural MRI/A; as well as its detailed analysis and control of confounders which are important for evaluating FD-related thromboembolic events (such as procedural ACTs and date of procedure/preprocedural PRUs). Furthermore, procedures were performed with a single center, operator, and clinical care setting, with consistent postprocedural MRI surveillance which contribute to decreased variability in procedural technique, while standardizing follow-up and DAPT regimens.

CONCLUSION

The original FRED stent may be prone to thromboembolic complications, particularly early intraprocedural thrombus formation with resulting attenuation or occlusion of side branches and parent vessels. The new generation of device incorporates the same dual-layer design but adds a PMEA surface modification to reduce the thromboembolic profile of the stent. This X-coating could be associated with a reduction in ischemic risk, with significantly fewer intraprocedural thrombosis and composite thromboembolic events observed after its implementation in our cohort. With surface modification, this stent's novel dual-layer design may be transformed from a high-thrombosis-risk factor into a useful tool with an enhanced safety profile, although a direct causal relationship in clinical practice requires further research to establish.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

M. Harrison Snyder: Writing — review & editing, Writing — original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alper Dincer:** Writing — review & editing, Writing — original draft, Methodology. **Anthony J. Yu:** Writing — review & editing, Writing — original draft, Methodology. **Shane M. Burke:** Writing — review & editing, Data curation. **Taylor Ferraro:** Writing — review & editing, Data curation. **Adel.M. Malek:** Writing — review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

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