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Title

SAFETY AND EFFICACY OF THE SILK FLOW DIVERTER: INSIGHT FROM THE DIVERSION PROSPECTIVE COHORT STUDY

Authors

Florent Gariel¹, Gaultier Marnat¹, Xavier Barreau¹, Patrice Menegon¹, Romain Bourcier²,
Laurent Pierot³, Lauren Spelle⁴, Alain Bonafé⁵, Francis Turjman⁶, Benjamin Gory^{7,8}, Jérôme
Berge¹; DIVERSION investigators*.

Affiliations

¹ Department of Neuroradiology, University Hospital of Bordeaux, France.

² Department of Neuroradiology, University Hospital of Nantes, France.

³ Department of Neuroradiology, CHU Reims, France.

⁴ Department of Interventional Neuroradiology, CHU Bicêtre, Le Kremlin-Bicêtre, France.

⁵ Department of Neuroradiology, Hôpital Gui de Chauliac, Montpellier, France.

⁶ Department of Interventional Neuroradiology, Hospices Civils de Lyon, France.

⁷ Université de Lorraine, CHRU-Nancy, Department of Diagnostic and Therapeutic
Neuroradiology, F-54000 Nancy, France

⁸ Université de Lorraine, IADI, INSERM U1254, F-54000 Nancy, France

E-Mail

florent.gariel@chu-bordeaux.fr

gaultier.marnat@chu-bordeaux.fr

xavier.barreau@chu-bordeaux.fr

patrice.menegon@chu-bordeaux.fr

romain.bourcier@chu-nantes.fr

lpierot@gmail.com

laurent@spelle.fr

a-bonafe@chu-montpellier.fr

drturjman@gmail.com

benjagory@gmail.com

jerome.berge@chu-bordeaux.fr

Corresponding author

Dr Florent Gariel, MD-MSc

Neuroradiology Department

Pellegrin Hospital, Place Amélie Raba-Léon

33076 Bordeaux, France

florent.gariel@chu-bordeaux.fr

Tel: +33556794880/Fax: +3355695669

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ABSTRACT

Background and purpose: Flow diverters are considered as an essential tool in the stent-based treatment of complex intracranial aneurysms. We report here a subgroup analysis of the nationwide prospective DIVERSION study to investigate the safety and efficacy of the Silk flow diverter at 12 months follow-up.

Methods: We performed a subgroup analysis of patients included in the DIVERSION, a national prospective cohort study including all flow diverters placement between 2012 and 2014 in France, and treated with the Silk. The primary outcome was the morbi-mortality at 12 months, including death, morbidity event and aneurysm retreatment within 12 months post-treatment. All reported serious events were adjudicated by an independent Data Safety and Monitoring Board. Satisfactory occlusion was defined as 3 or 4 on Kamran's scale by an independent imaging core laboratory during follow-up.

Results: A total of 102 procedures involving 101 patients (mean age \pm standard deviation, 54.3 \pm 13.5 years) harboring 118 aneurysms (113/118 located in the anterior circulation; mean size 8.2 \pm 7.1mm) were included. During the 12-month follow-up, 34 (33.3%) procedures experienced at least one morbi-mortality event: 3 deaths, 27 morbidity events and 4 retreatments. Overall, 1/3 deaths and 10/27 morbidity events were related to the device and/or the procedure, leading to a specific survival rate and a specific free-morbidity survival rate at 12 months of 98.98% [95% confidence interval, 92.98%–99.86%] and 89.73% [95%CI, 81.71% – 94.36%], respectively. The rate of permanent-related neurological deficit was 5.9% within 12 months. One year follow-up imaging showed satisfactory occlusion in 82.2% of cases.

Conclusion: Flow diversion with the Silk device has a reasonable safety and effectiveness profile for the endovascular treatment of intracranial aneurysms.

KEYWORDS

Intracranial aneurysms, endovascular treatment, flow diversion, flow diverter, Silk.

ABBREVIATIONS

DSMB: Data Safety and Monitoring Board; FD: Flow Diverter; mRS: modified Rankin Scale

INTRODUCTION

Flow diverter (FD) stents have become an important device in the endovascular treatment of intracranial aneurysms.¹ Flow diversion redirects the blood flow away from the aneurysm thanks to the low porosity of the stent, thereby promoting growth of a new endothelial lining across the aneurysm neck. These biomechanical changes induce intra-aneurysmal thrombosis while preserving the patency of the parent artery and covered collateral arteries.² The Silk Flow Diverter is a 48 Nitinol wires braided self-expandable stent. The DIVERSION registry is a prospective multicentric study including all consecutive patients treated with FD between October 2012 and February 2014 among French participating centers.³ We performed a focused analysis on patients treated only with the Silk (Balt-Extrusion, Montmorency, France) device to investigate its safety and efficacy.

METHODS

Patient selection

Our study is an ancillary analysis of the DIVERSION study. DIVERSION was a national prospective observational cohort study including all patients, aged of 18 years or older, treated with a flow diverter in routine practice in a French neuroradiology center from October 9, 2012 to February 7, 2014.^{3,4} The study protocol and the consent form were approved by the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés; CNIL). According to French laws, written informed consent was obtained from all patients. Inclusion criteria were any intracranial aneurysm, unruptured or ruptured, treated by FD in all French interventional neuroradiology centers, with or without additional coils. In each center, the indication for treatment was decided by the neuroradiologists, considering flow diversion as the appropriate technique. In case of ruptured aneurysms, flow diverter placement was performed in the setting of failure or deemed

impossibility of coiling with or without use of balloon remodeling. During the inclusion period, 5 different FDs were available in France. The present study included all patients treated with the Silk FD (Balt, Montmorency, France) within the DIVERSION study.

Outcomes

The primary composite endpoint of this study was the morbi-mortality rate at 12 months, including death, morbidity event and aneurysm retreatment within 12 months post-treatment. Morbidity included the occurrence of the following events: intracranial hemorrhage, ischemic stroke, transient ischemic attack, non-cerebral hemorrhage, neurologic deficit due to mass effect or retreatment. Assessment of the secondary endpoints included the feasibility of Silk FD placement, procedural complications, angiographic and clinical results at discharge, at 3-6 months, and 12 months follow-up. Clinical outcome was assessed using the modified Rankin Scale (mRS). Regarding safety, adverse events were prospectively recorded and reviewed (procedure-related or not) by an independent Data Safety and Monitoring Board (DSMB) composed of a neurologist, a neurosurgeon, a methodologist and a neuroradiologist. The degree of aneurysmal occlusion was assessed by an independent core laboratory composed of two neuroradiologists using Szikora's scale for immediate occlusion,⁵ and Kamran's scale for occlusion status during follow-up.⁶ Kamran's scale of 3 or 4 was considered as satisfactory occlusion at 12 months.

Statistical Analysis

We used different statistical units for descriptive analysis of the population and outcome assessment. Descriptive analyses of baseline characteristics were performed on two statistical units: the patient population and the aneurysm population. Quantitative variables are expressed as means (standard deviation, SD) and categorical variables are expressed as

numbers (percentage). Primary and secondary outcomes were assessed on the population of procedures with Silk FD placement. Survival analyses were also conducted on procedure basis. The time between the procedure and the occurrence of a morbidity/mortality event defined the event-free survival time.

RESULTS

Baseline characteristics

Between October 2012 and February 2014, 412 procedures were included in the Diversion study, representing 398 patients with 477 aneurysms treated in 18 centers. Baseline characteristics are summarized in **Table 1**. Among them, 102 procedures met inclusion criteria of the present study. These procedures were achieved in 101 patients with 118 aneurysms by using a Silk in 11 centers. One patient was treated for 2 aneurysms using a Silk at two different times and was then included 2 times. Seventy-nine patients were women (78.2%), and the mean age at the time of the procedure was 54.3 ± 13.5 years. Most of patients presented an unruptured aneurysm ($n=83$, 81.4%), of which 55 were asymptomatic (66.3%). Among symptomatic patients, the most frequent symptom was oculomotor palsy in 16 cases (57.1%). Nineteen procedures involved previously ruptured aneurysms (18.6%). Among them, 5 procedures were performed at the acute phase within one month following the hemorrhagic event. Four of these patients presented with a WFNS score of I and one patient with of score of V. Hundred and nine aneurysms (92.3%) were located in the anterior circulation (71 on the internal carotid artery, 13 on the anterior communicating complex and 10 on the middle cerebral artery) while 5 aneurysms (5.1%) were located on the posterior circulation. Aneurysm morphology was most often saccular (105/115; 91.3%), whereas fusiform (9/115; 7.8%) and blister-like (1/115; 0.9%) aneurysms were less frequent. The mean aneurysm size was 8.2 ± 7.1 mm.

Eighty-nine patients (87.2%) received a dual antiplatelet therapy before the endovascular procedure. Dual antiplatelet therapy consisted mainly in an association of Aspirin and Clopidogrel (85/102; 83.3%). Antiplatelet therapy was given at least 48 hours before the procedure in almost 85% of cases. Ninety-seven procedures (95.1%) were performed under full anticoagulation. At discharge, a dual antiplatelet regimen was given in 91.1% of patients.

Morbi-mortality and re-treatment

During one-year follow-up, 34 (33.3%) procedures experienced at least one morbi-mortality event: 3 deaths, 27 morbidity events and 4 retreatments. This corresponded to an event-free survival rate of 80.4% [95% confidence interval, 71.0% – 87.1%] (**Figure 1**). None of these deaths were observed before discharge. Only one death was related to the procedure and/or the device according to the DSMB by secondary rupture of the aneurysm. The two other deaths were considered not related to the procedure and the device (1 post-traumatic sub-dural with parenchymal hematoma and 1 aggravated aneurysmal pathology with mass effect on brainstem due to a progression of a fusiform basilar artery aneurysm). Overall, the specific survival rate at 12 months was of 98.98% [95%CI, 92.98% – 99.86%].

Concerning morbidity events, we observed 16 ischemic strokes, 2 intracranial bleedings due to aneurysm rupture, one intracranial bleeding, one neurological deficit due to mass effect and 7 non-cerebral bleedings (3 gastrointestinal bleedings in 2 patients and 4 parietal or puncture site bleedings in 3 patients). According to the DSMB, 10 interventions with at least one morbidity event related to the procedure and/or the device, were recorded with a total of 14 events. These events led to a specific free-morbidity survival rate at 12 months of 89.73% [95%CI, 81.71% – 94.36%].

We identified 4 re-treatments during the 12-months follow-up, including one during the initial hospitalization. The free-retreatment survival rate was of 95.39% [95%CI, 88.16% – 95.25%]. At 12 months, we observed clinical functional worsening in 2/86 patients (2.3%). These patients had a worsening from a pre-procedure mRS of 0 to mRS 1 in one case and to mRS 2 in the other case at 12 months. Clinical outcomes at 12 months are summarized in **Table 2**.

Of the 28 serious adverse events reported, the DSMB was able to rule on the imputability of the device and/or the procedure for 26 of them: 3 deaths (1 related), 13 ischemic strokes (10 related), 1 hemorrhagic stroke (related) and 11 others (4 related). A total of 16/26 serious adverse events were considered to be related to the device and/or the procedure (61.5%), of which 6 resulted in a permanent neurological deficit (**Table 3**). The rate of permanent-related neurological deficit was therefore 5.9% within 12 months.

Procedural results and occlusion rate

A total of 122 Silk were deployed in 118 patients with 101 aneurysms during 102 procedures. Silk flow diverter placement failed in only one case (0.8%). This aneurysm was treated with another FD. Deployment and wall apposition of the Silk was considered as satisfactory in 107/109 aneurysms. The majority of patients were treated with a single Silk (88.2%). Multiple FDs were required in 13 patients: 9 patients with 2 Silk devices, 3 patients with 3 Silk and one patient with 7 Silk devices. Other devices were used as complementary treatment: additionnal coiling in 29 aneurysms (24.6%), ballon remodelling in 8 (6.7%) and conventional stenting in 13 (11%).

Angiographic outcomes are summarized in **Table 4**. At least one per-operative complication occurred in 12 out of 102 procedures (11.8%): 3 thrombo-embolic events, 6 incomplete deployments, one dissection and 2 complications at the puncture site. At the end

of the procedure, the core laboratory assessed 5 complete stasis (6.4%), 17 significant flow reduction (22.1%), 24 slow flow (31.2%) and 31 unchanged flow (40.3%). At the 12 months angiographic follow-up, we observed a satisfactory occlusion in 82.2% of cases: 47 aneurysms (64.4%) with a Kamran grade IV and 13 (17.8%) with a grade III. We observed intrastent stenosis of >50% of the vascular lumen in 3 (4.1%) and 4 (5.8%) patients at 3-6 months and 12 months follow-ups, respectively. Occlusion of covered branches occurred in 7 cases (9.9%) at 12 months follow-up. These occlusions involved 2 middle cerebral arteries, 2 anterior cerebral arteries, one anterior communicating artery and one posterior communicating artery.

DISCUSSION

We report here the safety and efficacy of the Silk FD in a large prospective consecutive multicentric nationwide study. Our major findings are as follow: 1) Device and/or procedure related mortality and morbidity rates are 1% and 9.8% at 12 months, respectively, 2) The rate of permanent-related neurological deficit was therefore 5.8% within 12 months, 3) Satisfactory occlusion was achieved in 82.2% of cases at 12 months.

Clinical Outcome

Our data suggest that Silk for the endovascular treatment of intracranial aneurysm is safe. We found a mortality rate of 1% and the specific survival rate at 12 months was 98.98%. As reported in the DIVERSION study,³ mortality rate was lower than that of most large published studies to date ranging from 0.8% to 3.8%.^{7,8} Additionally, we found a specific morbidity-free survival of 89.7%, and a permanent-related serious events rate of 5.8% at 12 months. Most of these events were strokes. The morbidity rate in our study is in line with

previous publications.⁹ Previous Silk studies demonstrated morbidity rates ranging from 0% to 12%.^{10,11,12} Delayed rupture occurred in 2 patients, leading to one death and one morbidity event. Meta-analysis reported that the majority of these ruptures are early, within one month of treatment.^{9,13} Interestingly, both ruptures happened within the 30 days following the procedure. This concern may discuss the interest of additional coiling in cases of FD treatment for supracavernous aneurysms. The morbidity and mortality rates in our study appear to be acceptable compared to alternative endovascular treatments for complex aneurysms, particularly to stent-assisted coiling. Stent assisted coiling literature reports permanent morbidity and mortality rates between 1.9 to 4.4% and 0.4 to 1.0%, respectively.^{14,15} For complex aneurysms requiring a Y-stenting technique, a meta-analysis has recently showed a procedure-related permanent morbidity and mortality rates of 4% and 2%, respectively.¹⁶ Concurrently, the management of wide-neck aneurysms with the WEB intrasaccular flow disruption device appeared to be relatively safe compared to stent-based approach with a cumulative morbidity of 2.85% and a mortality of 0.93%.¹⁷

In addition, the safety profile of the Silk appears to be quite reasonable regarding the natural history of unruptured intracranial aneurysms. In the ISUIA study, the five years cumulative rupture rates was of 2.5% for anterior circulation aneurysms > 7mm and more than 10% for posterior circulation aneurysms.¹⁸

Procedural and Imaging Outcomes

Failure in Silk FD deployment occurred in only one case and we observed incomplete deployments (6.8%). These results are consistent with those reported from large case series published regarding technical feasibility with a rate of successful deployment varying between 75% and 96%, with an average of 88.6%.^{19,20}

At 12-month follow-up, we observed satisfactory occlusion and complete occlusion in 82.2% and 64.4% of aneurysms, respectively. In DIVERSION study, satisfactory occlusion was obtained in 79.9% of cases at 12 months. Pumar et al reported complete occlusion and residual neck occlusion rates of 81.2% and 92.2%.²⁰ In meta-analysis, complete occlusion rates range from 76% to 89.6% between 6 and 12 months.^{9,21} We emphasize here that the assessment of occlusion was done by an independent core laboratory, unlike many retrospective series. Another explanation may be the use of different scales for assessment of the occlusion rate. Indeed, Roy Raymond scale applied in the vast majority of these studies whereas we choose the Kamran scale. In addition, some discrepancies may be explain by a different distribution in aneurysm location with less extra-dural internal carotid artery aneurysms in our study than in others series (55.3% in PFUS).²² Intra-stent stenosis >50% and occlusion of covered branches were found unexceptionally at 12 months. Our 5.8% rate of >50% intra-stent stenosis is consistent with previously published rates ranging from 0% to 7.9%.²³ As in DIVERSION study, occlusion of a covered branch occurred in 9.9%. Rangel-Castilla et al reported occlusion of side wall covered branches in 15.8% of cases at mean angiographic follow-up of 10 months.²⁴ None of these occlusions concerned the anterior choroidal artery.

Limitations

The present study suffers from several limitations. The first one is inherent to the study design: it is a subgroup descriptive analysis of a non randomized observational cohort. Then, peri-operative protocols were not standardized among participating centers (aneurysm treatment indication, antiplatelet protocol, peroperative anticoagulant and antiplatelet regimen, follow-up imaging modality etc). Unfortunately, there are some missing data especially considering angiographic outcomes at 12 months. Nevertheless, the assessment of

the angiographic outcome by an independent core laboratory is a strength of our study, as well as the allocation of any adverse event by an independent board.

CONCLUSION

The Silk device has a reasonable safety and efficacy profile for endovascular treatment of intracranial aneurysms. In our subgroup analysis of DIVERSION registry, Silk was associated with permanent-related serious event and mortality rates of 5.9% and 0.98% at 12 months, respectively, whereas satisfactory occlusion was obtained in 82.2%.

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APPENDIX

DIVERSION Investigators: Vincent Costalat,¹ Gregory Gascou,¹ Cyril Dargazanli,¹ Sébastien Soize,² Georges Metaxas,² Jacques Moret,³ Léon Ikka,³ Jildaz Caroff,³ Aymeric Rouchaud,³ Christian Mihaela,³ Nidal Benachour,³ Michel Pötin,⁴ Raphaël Blanc,⁴ Hocine Redjem,⁴ Elisa Pomero,⁵ Alessandra Biondi,⁵ Christophe Cognard,⁶ Anne Christine Januel,⁶ Jean Darcourt,⁶ Adrien Guenego,⁶ Philippe Tall,⁶ Fabrice Bonneville,⁶ Charbel Mounayer,⁷ Suzana Saleme,⁷ Nader Sourour,⁸ Frédéric Clarençon,⁸ Charlotte Barbier,⁹ Denis Herbreteau,¹⁰ Ana Paula Narata,¹⁰ Richard Bibi,¹⁰ Serge Bracard,¹¹ René Anxionnat,¹¹ Anne-Laure Derelle,¹¹ Romain Tonnelet,¹¹ Liang Liao,¹¹ Emmanuel Chabert,¹² Hervé Brunel,¹³ Frederic Ricolfi,¹⁴ Hubert Desal,¹⁵ Zsolt Kulcsar,¹⁶ Christian Taschner.¹⁷

Affiliations:

¹ Department of Neuroradiology, Hôpital Gui de Chauliac, 34295 Montpellier, France.

² Department of Neuroradiology, CHU Reims, 51092 Reims, France.

³ Department of Interventional Neuroradiology, CHU Bicêtre, 94270 Le Kremlin-Bicêtre, France.

⁴ Interventional Neuroradiology Department, Rothschild Foundation Hospital, 75019 Paris, France.

⁵ Department of Interventional Neuroradiology, Jean-Minjoz University Hospital, 25030 Besançon, France.

⁶ Neuroradiology Department, Toulouse University Hospital, 31300 Toulouse, France.

⁷ Department of Interventional Neuroradiology, CHU Limoges, 87042 Limoges, France.

⁸ Department of Neuroradiology, Pitié-Salpêtrière Hospital, 75013 Paris, France.

⁹ Department of Neuroradiology, CHU Caen, 14000 Caen, France.

¹⁰ Department of Neuroradiology, CHU Tours, 37032 Tours, France.

¹¹ Department of Diagnostic and Therapeutic Neuroradiology, 54000 Nancy, France.

¹² Department of Neuroradiology, CHU Clermont-Ferrand, 63000 Clermont-Ferrand, France.

¹³ Department of Neuroradiology, CHU Marseille, 13005 Marseille, France.

¹⁴ Department of Neuroradiology, CHU Dijon, 21079 Dijon, France.

¹⁵ Department of Neuroradiology, CHU Nantes, 44093 Nantes, France.

¹⁶ Department of Neuroradiology, University Hospital Zurich, Zurich, Switzerland.

¹⁷ Department of Neuroradiology, Medical Center-University of Freiburg, Germany.

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TABLES

Table 1. Baseline characteristics.

	Procedures n=102
Number of patients	101
Gender, women n (%)	80 (78.4)
Age, mean±SD years	54.3±13.5
Elevated blood pressure, n (%)	43 (42.2%)
Tobacco use, n (%)	28 (27.45%)
Familial history of intracranial aneurysm, n (%)	10 (9.8%)
Aneurysm multiplicity, n (%)	39 (38.2%)
Number of aneurysms	118
Prievously treated aneurysm	26 (22%)
Ruptured aneurysms	19 (18.6%)
<i>Rupture <1 month</i>	5 (4.9%)
<i>Rupture >1 month</i>	14 (13.7%)
Unruptured aneurysms	83 (81.4%)
<i>mRS <2</i>	80 (96.4%)
<i>Symptomatic aneurysms</i>	28 (33.7%)
<i>Oculomotor palsy</i>	16 (19.3%)
Aneurysm type	
<i>Saccular</i>	105 (91.3%)
<i>Fusiform</i>	9 (7.8%)
<i>Blister-like</i>	1 (0.9%)
Aneurysm location	
<i>Extra-dural internal carotid artery</i>	18 (15.2%)
<i>Intra-dural internal carotid artery</i>	72 (61.0%)
<i>Middle cerebral artery</i>	10 (8.5%)
<i>Anterior communicating complex</i>	13 (11.0%)
<i>Vertebrobasilar</i>	5 (4.2%)
Maximal diameter, mean±SD mm	8.2±7.1
Intra-aneurysmal thrombosis	16 (13.56%)

SD: standard deviation ; mRS: modified Rankin Scale

Table 2. 12 months clinical outcomes.

Mortality	3/102 (2.9%)
<i>Related to SFD and/or procedure</i>	1 (0.98%)
Morbidity	27/102 (26.5%)
<i>Related to SFD and/or procedure</i>	10 (9.8%)
<i>Stroke</i>	16 (15.7%)
<i>Neurological deficit due to mass effect</i>	1 (0.98%)
<i>Intracranial bleeding due to aneurysm rupture</i>	2 (1.96%)
<i>Intracranial bleeding</i>	1 (0.98%)
<i>Non neurologic bleeding</i>	7 (6.7%)
Re-treatment	4/102 (3.9%)
Overall survival rate	96.66% [89.95% – 98.91%]
Specific survival rate	98.98% [95% CI, 92.98% – 99.86%]
Overall free-morbidity survival rate	81.55% [72.28% – 87-98%]
Specific free-morbidity survival rate	89.73% [95%CI, 81.71% – 94.36%]
Free-retreatment survival rate	95.39% [95%CI, 88.16% – 95.25]
mRS at 12 months	
<i>Missing</i>	16/102 (15.7%)
<i>Unchanged or improved mRS</i>	84/86 (97.7%)
<i>Worsed mRS</i>	2/86 (2.3%)

SFD: Silk Flow Diverter ; mRS: modified Rankin Scale

Table 3. Serious adverse events.

	Overall	Related to SFD and/or procedure by the DSMB
Serious adverse event, n (%)	28/102 (27.4%)	16/102 (15.7%)
<i>Death, n (%)</i>	3 (2.9%)	1 (0.98%)
<i>Ischemic stroke, n (%)</i>	13 (12.7%)	10 (10.2%)
<i>Hemorrhagic stroke, n (%)</i>	1 (0.98%)	1 (0.98%)
<i>Others, n (%)</i>	11 (10.8%)	4 (3.9%)
Resolved serious adverse event with sequelae, n (%)	8 (7.8%)	7 (7.8%)
Permanent neurologic deficit, n (%)	7 (6.8%)	6 (5.9%)

DSMB: Data Safety and Monitoring Board

Table 4. Procedural and 12 months angiographic outcomes.

<i>Procedural outcomes</i>	
SFD deployment failure	1 (0.98%)
Procedural complications	12 (11.8%)
<i>Thromboembolic event</i>	3/12 (25%)
<i>Dissection</i>	1/12 (8.3%)
<i>Incomplete deployment</i>	6/12 (50%)
<i>Puncture site complication</i>	2/12 (16.7%)
Szikora occlusion scale	
<i>Missing</i>	37/118
<i>Complete stasis</i>	5/77 (6.4%)
<i>Significant flow reduction</i>	17/77 (22.1%)
<i>Slow flow</i>	24/77 (31.2%)
<i>Unchanged flow</i>	31/77 (40.3%)
<i>12 months angiographic outcomes</i>	
Kamran occlusion scale	
4	47/73 (64.4%)
3	13/73 (17.8%)
2	3/73 (4.1%)
1	3/73 (4.1%)
0	7/73 (9.6%)
Intrastent stenosis >50%	4/73 (5.8%)
Pre or post stent stenosis >50%	4/73 (5.8%)
Occlusion of covered branches	7/73 (9.9%)
Missing data	41/118

SFD: Silk Flow Diverter

FIGURE LEGENDS

Figure 1. Event-free survival.

