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Prospective evaluation of an ultrathin strut biodegradable polymer-coated sirolimus-eluting stent: 12 months' results from the S-FLEX UK registry

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ABSTRACT

Objective To prospectively evaluate safety and efficacy of the ultrathin strut biodegradable polymer-coated Supraflex sirolimus-eluting stent (S-SES) in 'real world' patient population requiring percutaneous coronary intervention (PCI).

Methods National, prospective, multicentre, single-arm, all-comers, observational registry of 469 patients treated with S-SES from July 2015 and November 2016 in 11 centres in UK. Primary endpoint was target lesion failure (TLF) at 12 months (cardiac death, target vessel myocardial infarction (MI) or clinically driven target lesion revascularisation (TLR)). Secondary endpoints included safety and performance outcomes at 12 months—overall stent thrombosis (ST), all-cause mortality, any MI, target vessel failure (TVF) and major adverse cardiac events (MACE—composite of cardiac death, MI, emergent or repeat revascularisation).

Results At 12 months, the primary endpoint occurred in 11 (2.4%) of 466 patients, consisting of 4 (0.9%) cardiac deaths, 3 (0.6%) target vessel MI and 7 (1.5%) TLR. Secondary endpoints findings included all-cause mortality in 6 (1.3%), TVF of 14 (3%), no definite ST, 1 (0.2%) probable ST and 3 (0.6%) possible ST. Overall MACE was observed in 18 (3.9%).

Conclusions The S-FLEX UK registry showed that the S-SES is safe with a low incidence of TLF in routine clinical practise in patients with coronary artery disease being treated by PCI.

Strengths and limitations of this study

- The S-FLEX UK registry provides reassuring evidence that the ultrathin strut biodegradable polymer-coated sirolimus-eluting Supraflex stent can be safely and effectively used in routine clinical practice in UK patients with coronary artery disease being treated by percutaneous coronary intervention (PCI).
- The findings add to the emerging evidence that ultrathin strut biodegradable polymer stents can be used safely for PCI in routine clinical practice with the potential of further reducing target lesion failure.
- This is a non-randomised observational study of relatively small patient population with the inherent limitations of such studies. Nevertheless, the findings are consistent with other studies using the same product.
- The follow-up period was 12 months, and a longer period of follow-up would allow for more accurate assessment of very late stent thrombosis.

INTRODUCTION

Drug-eluting stents (DES) reduce neointimal proliferation and restenosis compared with bare-metal stents.[1 2] However, the persistence of adverse events with both first-generation and contemporary permanent polymer-based DES presents an opportunity for iterative improvement.[3–5] These include development of new metal alloys with thin struts, improved stent design and development of bioresorbable polymers.[6–10]

The potential link between durable polymer and late adverse events prompted development of biodegradable polymers to reduce inflammatory response, facilitating re-endothelialisation and minimising risk of thrombus formation and late restenosis.[11 12] Furthermore, first-generation DES with thick-strut design, are associated with more thrombotic events in ex vivo and experimental models.[13 14] Newer DES technologies, with progressively thinner stent struts and biodegradable polymers promise additional benefit in terms of earlier re-endothelialisation and reduced restenosis.[15 16]

In this multicentre UK registry, the objective was to assess safety and outcomes at 12 months of the CE-approved Supraflex (Sahajanand Medical Technologies (SMT) Pvt Ltd, Surat, India), a biodegradable polymer-coated SES, ultrathin (60 µm) cobalt-chromium (Co-Cr) stent for the treatment of coronary artery disease (CAD) treated in routine clinical practice.

METHODS

Study design and patient population

The S-FLEX UK registry was a prospective, observational, multicentre, postmarketing registry designed to evaluate the safety and efficacy of the Supraflex sirolimus-eluting stent (S-SES) in a 'real-world' patient population. The study enrolled 469 patients from July 2015 until November 2016 in 11 centres in UK. All patients over the age of 18, undergoing percutaneous coronary intervention (PCI) with at least one study stent, according to guidelines for revascularisation, irrespective of indication, disease location or complexity, were eligible for enrolment. In keeping with its real-world design, exclusion criteria were minimal and included patients with a high-probability of non-adherence to the follow-up requirements (due to social, psychological or medical reasons); females of childbearing age; those with planned surgery within 6 months of PCI unless dual antiplatelet therapy (DAPT) could be maintained throughout the peri-surgical period; those participating in another study that has not completed the primary endpoint or that clinically interfered with the current registry requirements and those with a known intolerance to aspirin, any P2Y12 drug, heparin, bivalirudin, cobalt, chromium, sirolimus or any other analogue or derivative, or contrast media. The registry, design and procedures complied with the principles of good clinical practice and the Declaration of Helsinki and were approved by the local ethics committee of each participating institution.

Patient and public involvement: All patients provided informed consent for the procedure and subsequent data collection and analysis for the research purposes. Patient and public were not involved in the designing of the registry, recruitment or conducting the registry.

Device description

The S-SES is a balloon-expandable stent using a medical grade cobalt-chromium alloy with ultra-thin struts of 60 µm and crowns which are linked together by flexible 'S' links to provide flexibility and improved deliverability. The coating layer, applied on the conformal surface of the stent with a mean thickness of 4–5 µm, comprises sirolimus, at a concentration of 1.4 µg/mm^2, blended together with biodegradable polymeric matrix (poly L-lactide, 50/50 poly DL-lactide-co-glycolide and polyvinyl pyrrolidone). The polymer facilitates programmed release such that 70% of the drug is released within 7 days and the remaining released over 48 days. The polymers retain their properties for a limited period and then gradually degrade into biologically inert molecules and excreted via normal metabolic pathways over 9–12 months. In addition, the device has a top protective layer that protects from light and moisture preventing premature drug release (figure 1). The device is available in diameters of 2.0, 2.25, 2.5, 2.75, 3.0, 3.50, 4.0 and 4.5 mm and in lengths increasing in 4 mm intervals from 8 to 48 mm. Across the range, the strut thickness is 60 µm.

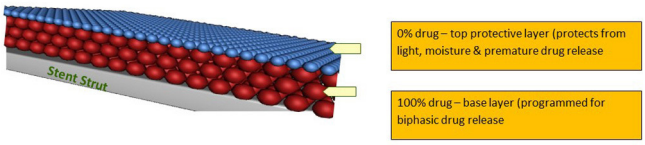

Figure 1 Bio-degradable polymer matrix of Supraflex sirolimus-eluting stent. Drug dose: 1.4 µg/mm^2 · Unique biodegradable polymer matrix: poly L-lactide, 50/50 poly DL-lactide-co-glycolide and polyvinyl pyrrolidone· Total coating thickness of 4–5 µm.

Study procedure

Standard interventional techniques were used to treat the lesion, with predilatation and postdilatation, procedural anticoagulation, use of glycoprotein IIb/IIIa inhibitors and duration of DAPT left to the operator's discretion.

Data collection and follow-up

Patient demographic data, lesion characteristics, procedure details and antithrombotic regimens were collected from each centre as per the prespecified case report form.

Follow-up was obtained at 12 months (±30 days) after the index procedure by hospital visit (14%) or telephonic follow-up. During follow-up consultations, information about patients' clinical condition, adverse events, hospitalisations and changes to concomitant (cardiac and antiplatelet) drugs were collected. Details of the above were further corroborated with review of the patients' electronic records and/or contacting the general practitioner.

Angiographic data were recorded for patients readmitted with ischaemia. For patients readmitted for ischaemia who underwent angiographic re-examination within 1 year, image analysis was performed to determine whether disease progression had occurred at the previously stented segment, including peri-stent areas 2 mm adjacent to the stent, or was limited to arterial segments remote from the stented region. If repeat angiography was performed <30 days after successful stent placement during the index procedure and demonstrated a significant stenosis or subacute stent thrombosis (ST) in the target vessel, the subject was considered an acute failure. If angiography took place ≥30 days after the index procedure and demonstrated restenosis of the target vessel and/or target lesion in association with objective evidence of recurrent ischaemia, the angiogram was analysed according to the secondary endpoints.

All events were investigator reported at site with no independent clinical events committee; however, site monitoring was performed to ensure continued protocol compliance and accurate data reporting by Psephos Biomedica (Sussex Innovation Centre, University of Sussex, Brighton BN1 9SB, UK).

Study endpoints

The primary endpoint of the study was target lesion failure (TLF) at 12 months: a composite of cardiac death, target vessel myocardial infarction (MI) or clinically driven target lesion revascularisation (TLR) by percutaneous

or surgical methods. Secondary endpoints assessed at 12 months included: overall ST; any death; any MI; any repeat revascularisation; target vessel failure (TVF) (a composite of cardiac death, target vessel MI or clinically driven TVR) and major adverse cardiac events (MACE—a composite of cardiac death, any MI, emergent or repeat revascularisation).

Statistical analysis

The sample size of subjects was selected to be similar to the patient numbers enrolled in the S-CORE registry.[17] Data are presented using descriptive statistical methods. Continuous variables are presented as mean±SD, whereas categorical variables are expressed as percentages. All data were processed using the SPSS V.15

RESULTS

Baseline, lesion and patient characteristics

The S-FLEX registry enrolled 469 patients from 11 centres in UK between the prespecified recruitment periods of July 2015 to November 2016. Three patients withdrew consent and 12 were lost to follow-up leaving 454 (97.4%) patients for 12 months' clinical follow-up.

Baseline patient, lesion and procedural characteristics are shown in tables 1 and 2. Consistent with the all-comers design and reflective of a high-risk population active smoking, presence of diabetes, medical history of MI and revascularisation was noted in a quarter while over half had hypertension and hyperlipidaemia. Not all participating centres had a primary angioplasty service thereby explaining the lower number of patients with ST-elevation myocardial infarction that were recruited. However, in line with contemporary UK practice, the main indication for revascularisation was acute coronary syndrome (59.7%).[18] The mean number of lesions per patient was 1.23±0.5, with >10% of these lesions bifurcations or chronic total occlusions. The mean number of stents deployed per patient was 1.48±1.0, with average length of coronary artery stented was 32.99±24.70 mm. Overall device implantation success on the lesion was 98.6%.

Clinical outcomes

Patient outcomes at 30 day, 6 months and 12 months are shown in table 3. The rate of the primary endpoint of TLF was 2 (0.4%) and 8 (1.7%) at 30 days and 6 months, respectively. At 12 months, the components of TLF, cardiac death was observed in 4 (0.9%), target vessel MI in 3 (0.6%) and TLR in 7 (1.5%). Cumulative TLF-free survival, at 12 months' follow-up, determined by the Kaplan-Meier method, was 97.4% as shown in figure 2.

Secondary endpoints findings included all-cause mortality in 6 (1.3%) and TVF in 14 (3%). According to ARC definition, overall ST was observed in 4 (0.8%) including no definite ST, 1 (0.2%) probable ST and 3 (0.6%) possible ST. Overall MACE were observed in 18 (3.9%) patients.

Table 1 Baseline characteristics of the study population

n (%) unless stated	
Patient characteristics	**n=466**
Age, mean±SD (years)	64.8±10.4
Male	350 (75.1%)
Body mass index (kg/m^2)	28.9±6.1
Diabetes mellitus	113 (24.2%)
Insulin requiring	30 (6.2%)
Non-insulin requiring	83 (18.0%)
Hypertension	237 (50.9%)
Hypercholesterolemia	251 (53.9%)
Family history of CAD	226 (48.5%)
Current smoker	120 (25.8%)
Renal insufficiency	10 (2.1%)
Peripheral vascular disease	17 (3.6%)
Congestive heart failure	12 (2.6%)
Previous transient ischaemic attack	12 (2.6%)
Previous stroke	17 (3.6%)
Previous myocardial infarction	127 (27.3%)
Previous PCI	108 (23.2%)
Previous CABG	18 (3.9%)
Acute coronary syndromes	278 (59.7%)
Unstable angina	187 (40.2%)
Silent ischaemia	10 (2.1%)
NSTEMI	58 (12.5%)
STEMI	23 (4.9%)
Stable angina	188 (40.3%)
Lesion characteristics	**n=573 lesions**
Number of lesions per patient (mean±SD)*	1.23 (±0.5)
Target vessel	
Left main stem	7 (1.2%)
Left anterior descending	249 (43.5%)
Left circumflex	119 (20.8%)
Right coronary artery	197 (34.4%)
Saphenous vein graft	1 (0.2%)
Re-stenotic lesion	16 (2.8%)
Bifurcation	61 (10.6%)
Total occlusion	75 (13.1%)

CABG, coronary artery bypass grafting; CAD, coronary artery disease; NSTEMI, non ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

DISCUSSION

This UK multicentre real-world registry of the thin strut, cobalt-chromium, biodegradable polymer S-SES demonstrated safety with a low incidence of TLF and ST at 12 months.

Table 2 Procedural characteristics	
Mean±SD unless stated	
Procedural characteristics	n=691 stents
No. of stents per patient	1.48±1.0
No. of stents per lesion	1.21±0.5
Mean stent length	22.48±7.6
Mean stent diameter	3.01±0.4
Predilatation, n (%)	471 (82.2)
Postdilatation, n (%)	394 (68.8)
Total stent length per patient	32.99±24.70
Device success (%)	98.6

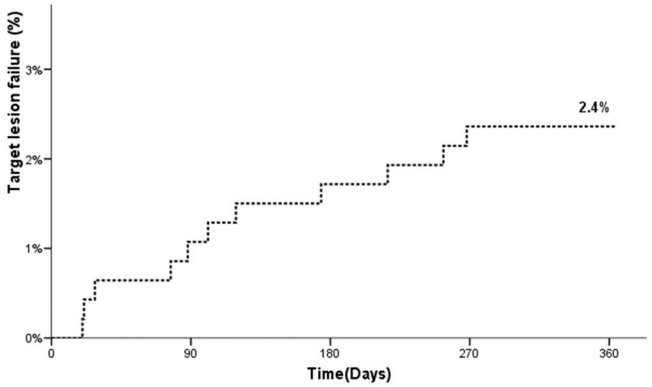

Figure 2 Kaplan-Meier curve of target lesion failure.

Concerns related to impaired healing and persistent inflammation associated with first-generation durable polymer DES, led to the development of improved polymers, metallic platform technologies and thinner struts.[3–10 14] The change in stent platform from stainless steel (132–140 µm) to chromium alloys (81–91 µm), reduced both procedural and late target vessel MI by about 40%–80%.[19–22] The BIOFLOW V study compared the ultrathin strut (60 µm) bioresorbable polymer sirolimus-eluting Orsiro stent with the thin strut (81 µm) durable polymer everolimus-eluting Xience stent and reported an approximate further 40% reduction in target vessel MI in favour of Orsiro[10] The Orsiro stent polymer degrades over a 2 year span and thus the observed outcome differences at 1 year between the Orsiro and Xience stents are possibly largely driven by the difference in strut thickness rather polymer durability. Pooled analysis of large multicentre randomised trials reported lower risk of TVR

Table 3 Hierarchical and non-hierarchical subject counts of adverse events through 12 months (intent-to-treat population)			
n (%)	**30 days**	**6 months**	**12 months**
Hierarchical events			
TLF	2 (0.4)	8 (1.7)	11 (2.4)
Cardiac death	1 (0.2)	3 (0.6)	4 (0.9)
Target-vessel MI	1 (0.2)	3 (0.6)	3 (0.6)
Target-lesion revascularisation	0 (0)	5 (1.1)	7 (1.5)
Target vessel failure	2 (0.4)	11 (2.4)	14 (3.0)
Major adverse cardiovascular events	4 (0.9)	14 (3.0)	18 (3.9)
Non-hierarchical events			
Death	1 (0.2)	1 (0.2)	6 (1.3)
Cardiac death	1 (0.2)	3 (0.6)	4 (0.9)
Non-cardiac death	0 (0.0)	1 (0.2)	2 (0.4)
Myocardial infarction			
Target vessel	1 (0.2)	3 (0.6)	3 (0.6)
Non-target vessel	2 (0.4)	3 (0.6)	4 (0.9)
Revascularisation			
Target lesion revascularisation	1 (0.2)	5 (1.1)	7 (1.5)
Target vessel revascularisation	1 (0.2)	10 (2.2)	14 (3.0)
Non target vessel revascularisation	2 (0.4)	4 (0.8)	6 (1.2)
Stent thrombosis	1 (0.2)	3 (0.6)	4 (0.9)
Definite ST	0 (0.0)	0 (0.0)	0 (0.0)
Probable ST	1 (0.2)	1 (0.2)	1 (0.2)
Possible ST	0 (0.0)	2 (0.4)	3 (0.6)

MACE, major adverse cardiac events (composite of cardiac death, any MI, emergent or repeat revascularisation); MI, myocardial Infarction; ST, stent thrombosis; TLF, target lesion failure (composite of cardiac death, target vessel MI or clinically driven TLR); TVF, target vessel failure (composite of cardiac death, target vessel MI and TVR); TVR, target vessel revascularisation.

and very late ST associated with biodegradable polymers compared with durable polymer-coated DES.[23] However, it remains debatable whether this reduction of adverse events is a class effect of biodegradable polymers and may well be influenced by additional factors including stent strut thickness, polymer composition, distribution and load.[24 25]

Studies assessing the Supralimus-Core (previous version of the S-SES with the same strut thickness, polymer and drug concentration) reported reassuring vessel healing properties by optical coherence tomography at 4 months,[26] along with satisfactory 1-year TLR of 1.1% along with MACE of 3.4% in real-world patients.[17]

The S-SES is an improved version of the Supralimus-Core SES with replacement of the rigid interlink/joint of the Supralimus-Core SES with a highly flexible 'S-link', which increases flexibility and deliverability. Preliminary evaluation of clinical and angiographic outcomes of the Supraflex stent in the MANIPAL-FLEX Study reported a TLR of 2.1%.[27] Angiographic in-stent late lumen loss, a dependable predictor of the long-term clinical efficacy of DES,[28] was observed to be 0.18±0.23 mm with the Supraflex stent at 9 months in keeping with currently used effective DES systems.[29–31]

The subsequent retrospective, multicentre FLEX registry that included 995 unselected patients treated with the S-SES across nine centres in India reported a 12-month MACE of 3.7%.[32] This included TLR of 0.7%, definitive ST of 0.3% and overall ST of 1.1% at 12 months. Late ST remains a major concern even in contemporary DES and has been shown to be dependent on lack of strut coverage.[33] In the FLEX registry OCT subgroup analysis, the authors reported 98.1% strut coverage at 6 months with the S-SES, that compared favourably with the 91.5% and 94.1% strut coverage reported with Promus Element and Xience DES.[34] The authors also reported S-SES to have an excellent healing index of 4.8 (1.0–22.9) comparing favourably with BioMatrix (35.2±25.0), Cypher (43.3±36.2), Resolute (18.7±20.4) and the Xience (10.8±15.3) DES systems.[35 36]

In this registry, 12-month TLF of 2.4% and TLR of 1.5% is in keeping with the previous findings of the S-SES in the MANIPAL-FLEX and FLEX registries. These findings are encouraging when compared with the 12-month TLR and TLF of contemporary DES systems (figure 3).[10 22 37–40] The promising clinical outcomes with the S-SES might be attributed to the combination of its ultrathin struts, biodegradable polymer and unique platform design. Extensive strut coverage within 4–6 months and low 'healing index' provide possible explanations for low ST and TLR rates.[41] The relative safety and efficacy of the S-SES seen in this registry was confirmed by the TALENT (*T*hin strut sirolimus-eluting stent in *All* comers' population vs *E*vorolimus-eluting ste*nt*) study.

Study limitations

This was a non-randomised observational study of relatively small patient population with the inherent limitations of such studies. Nevertheless, the findings were consistent with other studies using the same product and complications at 12 months were qualitatively similar to contemporary DES. The end points were not adjudicated by a core laboratory, but all events reported were verified by external, qualified clinical trial monitors. No ECG was performed as part of the 12-month FU and majority of the follow-up was via telephonic questionnaire raising the possibility of under-reporting of endpoints. However, the study endpoints were 'clinically driven' and every effort was made to capture clinical events by reviewing the patients' electronic health records in addition to the in person/telephonic follow-up.

CONCLUSIONS

The S-FLEX UK registry provides evidence that the S-SES can be used safely and effectively in routine clinical practice in UK patients with CAD being treated by PCI.

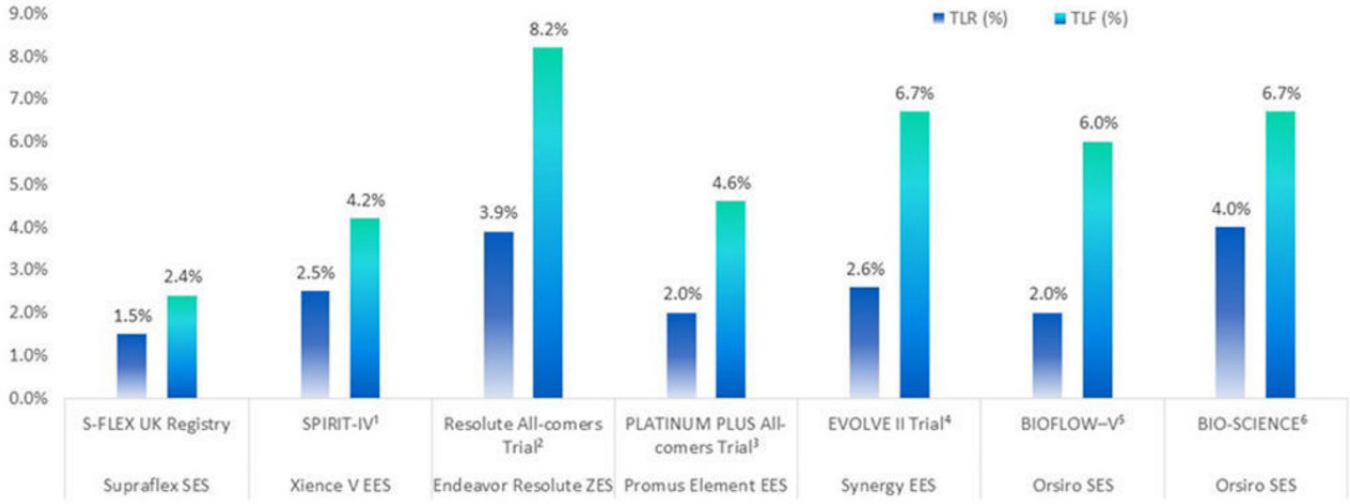

Figure 3 12-Month target lesion revascularisation and target lesion failure of contemporary stents.[1–6] See references.[10 22 37–40]

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