Original Article

Three-Year Outcomes of Biodegradable Polymer-Coated Ultra-Thin (60 µm) Sirolimus-Eluting Stents in Real-World Clinical Practice

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Abstract

Introduction: Although drug-eluting stents (DES) have outclassed the use of bare metal stents, the safety and efficacy of DES at long-term follow-up has still been conflicting because of increased occurrence of late or very late restenosis and stent thrombosis after DES implantation. Hence, the present study was aimed to evaluate the 3-year safety and clinical performance of biodegradable polymer-coated ultra-thin (60 µm) sirolimus-eluting stent (SES) in real-world patients with coronary artery disease (CAD). Materials and Methods: This was a physician-initiated, retrospective, single-centre, observational study that included 237 consecutive patients who had previously undergone implantation of only Supraflex SES (Sahajanand Medical Technologies Pvt Ltd, Surat, India) for the treatment of CAD. Follow-up was received after 1 year and 3 years of stent implantation. The primary endpoint was major adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction (MI) and target lesion revascularisation (TLR). Stent thrombosis was considered as a safety endpoint. Results: The mean age of patients was 64.1 ± 10.2 years, and 192 (81.0%) patients were male. The average stent length and diameter were 24.4 ± 9.0 mm and 3.1 ± 0.4 mm, respectively. The cumulative MACE rate at 3 years follow-up was 6.5% which included 4 (1.8%) cardiac deaths, 6 (2.8%) MI, and 4 (1.8%) TLR. There were 2 (0.9%) cases of stent thrombosis. Conclusion: Treatment of patients with CAD in real-world clinical practice was associated with sustained clinical safety and low rates of restenosis, stent thrombosis and MACE up to 3 years after Supraflex SES implantation.

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Key words: Coronary artery disease, Percutaneous coronary intervention

Introduction

Coronary artery disease (CAD) has been found to be a cause of around 17.9 million global deaths per year, accounting for around 75% of deaths in developing countries.[1] In the 1970s, percutaneous coronary intervention (PCI) with balloon angioplasty was used for the management of CAD. However, due to the several adverse events of plain old balloon angioplasty, bare metal stents (BMS)—which scaffold the atherosclerotic plaque in the diseased vessel—came into use in the 1980s. Although, the advent of coronary stents had reduced the incidences of restenosis, in-stent restenosis (ISR) continued to develop in 20% to 30% of lesions due to neointimal hyperplasia and proliferation of vascular smooth muscle cells.[2-5]

The limitations of BMS spurred further refinements of coronary stents and thus drug-eluting stents (DES) were developed with coated polymers and controlled release kinetics of antiproliferative or immunosuppressant agents.[2-4] The development of DES was considered as another pronounced leap in the field of interventional cardiology and various clinical trials demonstrated the superiority of DES over BMS with significant decrease in the target lesion revascularisation (TLR) and ISR rates.[6-11] However, with the incidence of late stent thrombosis, the usage of earlier generation DES with durable polymers and thick strut reduced significantly. This led to another breakthrough in the development of newer generation DES with thinner struts that were coated with biodegradable polymers and

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newer antiproliferative agents. However, the long-term safety of DES in real-world use has always remained a serious concern.[2-4,12]

Supraflex (Sahajanand Medical Technology Pvt Ltd, Surat, India), a biodegradable polymer coated sirolimus-eluting stent (SES), is a newer generation DES that has been designed with ultra-thin (60 μm) cobalt-chromium (Co-Cr) platform and flexible "S-link" design. A number of studies have demonstrated its safety and clinical performance in all-comer population up to 1 year follow-up.[13-15] However, its long-term safety and clinical performance have not been reported yet. Thus, the present study sought to evaluate the long-term (3 years) safety and clinical performance of biodegradable polymer-coated ultra-thin (60 μm) Supraflex SES in patients with CAD in real-world clinical practice.

Materials and Methods

Study Design and Patient Population

This was a physician-initiated, retrospective, single-centre, observational study conducted on real-world patients in India, from March 2013 to December 2013. The study population included 237 consecutive patients who underwent PCI with implantation of only Supraflex SES for the treatment of CAD at our centre. There were no specific inclusion or exclusion criteria. The study was approved by the Institutional Review Board and data release consent was received from all patients before the interventional procedure.

Description of Study Stent

The Supraflex SES has the Flexinnium (Sahajanand Medical Technology Pvt Ltd, Surat, India) L605 Co-Cr alloy coronary stent as its stent platform. The characteristic features of the stent include its ultra-thin strut thickness (60 μm) and the highly flexible "S-link" design, which leads to better trackability, crossability and excellent pushability. The drug—at a concentration of 1.4 μg/mm^2—together with the polymeric matrix is coated on the conformal surface of the stent. The biodegradable polymeric matrix, comprising poly L-lactide, 50/50 poly DL-lactide-co-glycolide and polyvinyl pyrrolidone, provides programmed drug release. The average coating thickness is 4 μm to 5 μm. The drug release occurs in 2 phases—about 70% of the drug is released within 7 days and the remainder is released over a period of 48 days. The drug release profile of the study stent has been mentioned in previous studies.[13,14] The polymers retain their properties for a limited period and then gradually degrade into biologically acceptable molecules that are metabolised and excreted from the body via normal metabolic pathways within 9 to 12 months. During the study period, Supraflex SES was available in the following diameters (mm): 2.0, 2.25, 2.5, 2.75, 3.0, 3.50, 4.0 and 4.5; and in the following lengths (mm): 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.

Interventional Procedure and Adjuvant Medical Therapy

The procedures were performed as per standard clinical guidelines. Before the interventional procedure, each patient received a loading dose of aspirin (150-300 mg) and clopidogrel (600 mg)/prasugrel (60 mg)/ticagrelor (2 tablets each of 90 mg). During the procedure, anticoagulation was achieved either with heparin or bivalirudin and bailout use of glycoprotein IIb/IIIa inhibitor was done as per the investigator's choice. After the procedure, dual antiplatelet therapy (aspirin 75-100 mg daily, and clopidogrel 75 mg daily/prasugrel 10 mg daily/ticagrelor 90 mg twice daily) was prescribed to patients for at least 12 months followed by only aspirin (75-100 mg) for lifetime.

Data Collection and Follow-up

Baseline demographics and interventional procedure details were obtained from hospital medical records. All the patients were followed-up at 1 year and 3 years of stent implantation either clinically or via telephonic contact.

Study Endpoints and Definitions

The primary endpoint of the study was major adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction (MI) and TLR after 3 years of index procedure. Any death due to a cardiac cause (such as MI, low output failure, lethal arrhythmia), unwitnessed death or death of unknown reason, and all procedure-related deaths, involving those linked to concomitant treatment, were stated as cardiac death. Non-cardiac death included any death where non-cardiac cause was well established. MI was defined as either development of new pathological Q-waves in at least 2 contiguous leads of the electrocardiogram with elevated cardiac troponin (cTn) values (>5 × 99th percentile upper reference limit [URL]) in patients who have normal baseline values (≤99th percentile URL), or an increase of cTn values >20% when the baseline values are elevated and are stable or declining.[16] A TLR was defined as repeat revascularisation of the lesions within the stent or in subsequent 5 mm of distal or proximal segment of the stent. A target vessel revascularisation (TVR) was considered when repeat revascularisation was performed in any segment of the treated vessel.

The incidence of stent thrombosis, defined as per Academic Research Consortium criteria, was analysed as a safety endpoint.[17]

Statistical Analysis

Continuous variables were presented as mean ± standard deviation and categorical variables as counts and percentages. The event-free survival rate was calculated according to the Kaplan-Meier curve. All data were analysed using Statistical Package for Social Sciences programme, version 15 (Chicago, IL, USA).

Results

Baseline Characteristics

A total of 237 patients were assessed in the study. The baseline demographic characteristics are delineated in Table 1. The average age was 64.1 ± 10.2 years with majority of male patients (n = 192, 81.0%). Among the total of 237 patients, 87 (36.7%) were hypertensive, 32 (13.5%) were diabetic and 27 (11.4%) were smokers. Majority of patients were presented with non-ST elevation myocardial infarction (n = 135, 57.0%).

Lesion and Procedural Characteristics

Details of lesion and procedural characteristics are depicted in Table 2. Left anterior descending artery was the main culprit diseased vessel with 117 lesions (40.8%). Majority of lesions were of type B2/C (n = 207, 72.1%), classified as per American College of Cardiology/American Heart Association (ACC/AHA) lesion classification. Among the 237 patients, 200 (84.4%) patients had 1 lesion, 24 (10.1%) patients had 2 lesions and 13 (5.5%) patients had 3 lesions which were treated with a total of 321 Supraflex stents. The average stent length and diameter were 24.4 ± 9.0 mm and 3.1 ± 0.4 mm, respectively.

Clinical Endpoint

The follow-up was obtained in 91.6% patients at 1 and 3 years of the index procedure. At 3 years, the prevalence of MACE was found to be 6.5% (n = 14) which included 4 (1.8%) cardiac deaths, 6 (2.8%) MI, and 4 (1.8%) TLR.

Table 1. Baseline Demographic Details of Patients

Characteristic	Patient (n = 237)
Demographics	
Age (mean ± SD, years)	64.1 ± 10.2
Male, n (%)	192 (81.0%)
Medical history	
Hypertension, n (%)	87 (36.7%)
Diabetes mellitus, n (%)	32 (13.5%)
Smoker, n (%)	27 (11.4%)
Family history of coronary artery disease, n (%)	76 (32.1%)
Previous myocardial infarction, n (%)	38 (16.0%)
Previous percutaneous coronary intervention, n (%)	49 (20.7%)
Previous coronary artery bypass grafting, n (%)	11 (4.6%)
Clinical presentation	
Stable angina, n (%)	15 (6.3%)
Unstable angina, n (%)	41 (17.3%)
ST elevation myocardial infarction, n (%)	46 (19.4%)
Non-ST elevation myocardial infarction, n (%)	135 (57.0%)

SD: Standard deviation

Table 2. Lesion and Procedural Characteristics

Characteristic	
No. of diseased vessels (patients, n = 237)	
Single vessel disease, n (%)	62 (26.2%)
Double vessel disease, n (%)	87 (36.7%)
Triple vessel disease, n (%)	88 (37.1%)
Total occlusion, n (%)	46 (16.0%)
Target coronary artery (lesions, n = 287)	
Left main artery, n (%)	5 (1.7%)
Left anterior descending artery, n (%)	117 (40.8%)
Right coronary artery, n (%)	85 (29.6%)
Left circumflex artery, n (%)	79 (27.5%)
Saphenous venous graft, n (%)	1 (0.3%)
ACC/AHA lesion classification (lesions, n = 287)	
A, n (%)	33 (11.5%)
B1, n (%)	47 (16.4%)
B2/C, n (%)	207 (72.1%)
Total no. of stents, n	321
No. of stents per patient, (mean ± SD, mm)	1.4 ± 0.5
No. of stents per lesion, (mean ± SD, mm)	1.1 ± 0.3
Average stent length, (mean ± SD, mm)	24.4 ± 9.0
Average stent diameter, (mean ± SD, mm)	3.1 ± 0.4
Antiplatelet drugs (patients, n = 237)	
Aspirin, n (%)	235 (99.2%)
Clopidogrel, n (%)	98 (41.4%)
Prasurgrel, n (%)	31 (13.1%)
Ticagrelor, n (%)	108 (45.6%)

ACC/AHA: American College of Cardiology/American Heart Association; SD: Standard deviation

Among all patients, TVR was observed in 5 (2.3%) patients. There were 2 (0.9%) incidences of stent thrombosis which included 1 case of acute (1 day) and the other case of late stent thrombosis (90 days). The clinical outcomes at 1 year and 3 years of index procedure are outlined in Table 3. The cumulative MACE-free survival at 3 years follow-up was found to be 93.5%, obtained by Kaplan-Meier method (Fig. 1).

Discussion

Cardiovascular disease (CVD) is the leading cause of death in India and 80% of CVD deaths are due to CAD and stroke. Currently in India, more than 850 catheterisation laboratories have been performing coronary interventions using >95% of DES.[18] The use of DES has extensively increased as it greatly reduces neointimal hyperplasia and the rate of TLR. DES have evolved from durable polymers to biodegradable polymers, from thick strut to ultra-thin strut with newer antiproliferative agents; however, there is still a

Table 3. Clinical Outcomes of Supraflex Implantation at One Year and Three Years (n = 217)

Clinical Outcome	1 Year	3 Years
Death, n (%)	4 (1.8%)	7 (3.2%)
Cardiac death, n (%)	3 (1.4%)	4 (1.8%)
Non-cardiac death, n (%)	1 (0.5%)	3 (1.4%)
Myocardial infarction, n (%)	3 (1.4%)	6 (2.8%)
Target lesion revascularisation, n (%)	2 (0.9%)	4 (1.8%)
Target vessel revascularisation, n (%)	2 (0.9%)	5 (2.3%)
Stent thrombosis,* n (%)	2 (0.9%)	2 (0.9%)
Acute/definite stent thrombosis, n (%)	1 (0.5%)	1 (0.5%)
Late/probable stent thrombosis, n (%)	1 (0.5%)	1 (0.5%)
MACE, n (%)	8 (3.7%)	14 (6.5%)

MACE: Major adverse cardiac events

*According to Academic Research Consortium (ARC) criteria.

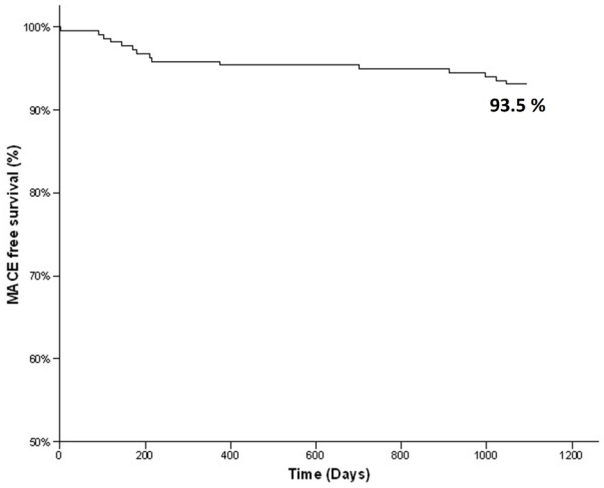

Fig. 1. Graph showing the cumulative MACE-free survival curve up to three years follow-up. MACE: Major adverse cardiac events.

lack of long-term studies which prove its clinical safety.[2-4] Thus, a retrospective, single-centred, observational study was initiated by the authors in the present study to evaluate the long-term (3 years) safety and clinical performance of biodegradable polymer-coated ultra-thin (60 μm) Supraflex SES in patients with CAD in real-world clinical practice.

The present study depicted 3.7% MACE at 1 year which was comparable with the results of various other studies.[19-21] Furthermore, the results of the current study depicted 6.5% MACE, 1.8% TLR and 0.9% stent thrombosis at 3 years follow-up. Similarly, the CENTURY study, I-LOVE-IT 2 trial and BIOFLOW-II study have also reported 3 years follow-up of biodegradable polymer coated SES with Co-Cr platform.[19,21,22] The CENTURY study reported 5.7% TLF, 2.9% TLR and 0.9% stent thrombosis.[19] The I-LOVE-IT 2 trial also demonstrated a higher rate of TLR (4.3%) and a similar rate of stent thrombosis (0.8%) when compared to the present study data.[21] The BIOFLOW-II study presented 9.0% target lesion failure (TLF) and the rate of TLR (5.6%) was found to be higher than the present study.[22]Thus, the 3 years follow-up data obtained from the present study is comparable to other third-generation SES, thus showing that Supraflex SES is safe and effective even at 3 years of the procedure.

The durable polymers used in the first 2 generations of DES have been linked to chronic local inflammatory reactions, hypersensitivity issues, lack of complete endothelisation, thrombus formation and local toxicity owing to the presence of permanent polymer after complete drug release. In order to surpass these issues, DES with biodegradable polymers as a vehicle for controlled drug release were developed, which degrade gradually into inert molecules. Thus, biodegradable polymer DES satisfies the dual problem—first, it prevents neointimal hyperplasia with controlled drug release which helps reduce the risk of restenosis and later, it completely transfigures into BMS, which offers a lower risk of restenosis and late stent thrombosis.[23-27] The 5 years follow-up of LEADER trial between biodegradable polymer biolimus-eluting stents (BES) and durable polymer SES reported that the incidences of stent thrombosis with biodegradable polymer BES became stable after 1 year, whereas in patients with durable polymer SES, it persisted beyond 1 year.[28]

Another study on Firebird SES with stainless steel platform showed higher MACE rate (7.9%) after 3 years of the index procedure.[29] The RAVEL and SIRIUS trials compared Cypher SES with conventional BMS. Conversely, compared to the present study, the RAVEL trial displayed a higher MACE rate (16.7%) with SES at 3 years follow-up. The SIRIUS trial also showed a higher MACE rate (10.3%) with SES even at 2 years follow-up.[30,31] However, the present study displayed a comparatively lower MACE rate (6.5%) at 3 years follow-up and only 2 incidences of stent thrombosis were observed. The lower clinical outcomes might be due to the presence of biodegradable polymers as well as the use of ultra-thin struts (60 μm) in the study.[32-35]

Various studies have described that a thinner strut size of the stent has numerous mechanical as well as clinical benefits such as better flexibility, lower stent profile, better trackability, low risk of side branch occlusion, decreased risk of arterial wall injury, reduced neointimal growth and hyperplasia, faster re-endothelisation, reduced peri-strut inflammation and fibrin deposition—all these ultimately play a role towards reduced rates of restenosis and late stent thrombosis with ultra-thin DES.[34-37] This has been proved by various meta-analyses and clinical studies, indicating that ultra-thin strut DES provides better safety and clinical performance compared to thick struts DES.[38-41] Apart from

these, the highly flexible "S-link" of the Supraflex SES also provides better flexibility, trackability and deliverability to the stent. More flexible stents tend to develop thinner neointimal layers which eventually lowers the rate of restenosis.[13,42,43] A recent randomised TALENT trial, which compared Supraflex SES with the Xience (everolimus-eluting stent) EES, demonstrated the non-inferiority in terms of device-oriented composite outcomes (4.9% vs 5.3%, *P* value for non-inferiority ≤0.006) of Supraflex SES compared to Xience EES at 12 months in all-comer population.[15]

The biodegradable polymer coating, ultra-thin strut size (60 μm) and unique flexible "S-link" design of the Supraflex SES all contribute towards lowered clinical events and good safety in both the present study and in previous other studies. Thus, it can be said that besides the polymer type, stent thickness and strut design equally affect the clinical applicability of DES. In order to find an ideal biodegradable polymer DES, further long-term (>3 years) safety of Supraflex SES should be reported.

The major limitation of this study is the lack of head-to-head comparison with any similar DES, which would have effectively confirmed the safety and clinical performance of Supraflex SES. Another limitation is its observational, non-randomised, single-centre and retrospective study design along with lesser number of included patients. Other limitations of the study include absence of independent event adjudication, absence of propensity-matching to adjust the cohort characteristic known to affect clinical outcomes and lack of independent quantitative coronary analysis core laboratory angiographic analyses. A final limitation of the study is the low proportion of high-risk patients (represented by 13.5% diabetic patients, 36.7% hypertensive patients and 11.4% smokers), which might have also played a role in the lower clinical events observed in the present study.

Conclusion

The results of the present study clearly demonstrated good clinical safety of Supraflex SES with lower rates of MACE, repeat revascularisation and stent thrombosis at up to 3 years of treatment of CAD in real-world patients.

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