









Twelve-month clinical outcomes of sirolimus-eluting stent in coronary artery disease: An experience in real-world Indian patients

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ABSTRACT

Objective: Supraflex (Sahajanand Medical Technologies Pvt. Ltd, Surat, India) is the latest generation of biodegradable polymer-coated sirolimus-eluting coronary stent designed on ultra-thin (60 µm) cobalt–chromium platform with flexible “S-link.” The present study was designed to establish the safety and clinical performance of Supraflex in real-world Indian patients with coronary artery disease.

Methods: The study included 839 consecutive patients with coronary artery disease who were implanted with Supraflex from January 2014 to August 2017 at six different tertiary care centers in India. Follow-up was performed at 30 days, 6 months, and 12 months after the index procedure. The primary end-point of the study was the incidence of major adverse cardiac events (MACE), a composite of cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR) at the 12-month follow-up. The occurrence of stent thrombosis was analyzed as safety end-point.

Results: A total of 1025 lesions were treated by implantation of 1098 Supraflex stents. At the 12-month follow-up, MACE was 4.92%, including 7 (0.86%) cardiac deaths, 16 (1.97%) MI, and 17 (2.09%) TLR. Only three incidences of stent thrombosis were found at the 12-month follow-up.

Conclusion: The study results showed excellent safety and clinical effectiveness of Supraflex in a high proportion of high-risk real-world Indian patients with coronary artery disease. (*Anatol J Cardiol* 2020; 24: 364-9)

Keywords: coronary artery disease, drug-eluting stents, percutaneous coronary intervention, sirolimus, stent thrombosis

Introduction

Cardiovascular disease is considered as the leading cause of death worldwide, accounting for approximately 31% of deaths (1, 2). The Global Burden of Disease has reported that in India, the deaths and disabilities due to coronary heart disease doubled in the last three decades considering premature occurrence of coronary heart disease as an utmost concern (2). Although the introduction of bare metal stents was considered as a remarkable advancement in interventional cardiology, the increased incidence of in-stent restenosis prompted the development of a drug-eluting stent (DES).

Gradually, DESs are technically evolving to stand as an ideal stent. The latest generation of DESs, with ultra-thin struts, bio-

degradable polymer-coating technology, and novel stent design, have minimized vessel wall injury and local inflammatory responses, which ultimately reduced adverse complications, such as late stent thrombosis and need for repeat revascularization (3-6). The DES with biodegradable polymers, thinner struts, and unique design have been frequently used in clinical practice; thus, a large number of randomized clinical trials and real-world patient registries have been conducted to assess their safety and efficacy in early and later stages after stent implantation.

Supraflex (Sahajanand Medical Technologies Pvt. Ltd, Surat, India) is the latest generation biodegradable polymer-coated sirolimus-eluting coronary stent designed with ultra-thin struts (60 µm) and flexible “S-link.” Various studies have demonstrated its safety and effectiveness in heterogeneous patients with coro-

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nary artery disease (7-9); however, further data in the real-world scenario will establish its favorability in daily clinical practice. Thus, in the present study, we sought to evaluate the safety and clinical performance of Supraflex in real-world patients with coronary artery disease at 12 months of implantation.

Methods

Patient population

This retrospective, multi-center, single-arm study included patients from six different tertiary care centers in India. The study included 839 consecutive patients aged ≥ 18 years who underwent implantation of at least one Supraflex stent per lesion for the treatment of coronary artery disease between January 2014 and August 2017. The study strictly obeyed the principles of good clinical practice and Declaration of Helsinki, and the Institutional Ethics Committee of the respective centers approved the study. At the time of the index procedure, a written informed consent for percutaneous coronary intervention (PCI) and for use of properly anonymized clinical data was obtained from each patient.

Description of the study stent

Supraflex contains the Flexinimum L605 cobalt–chromium alloy coronary stent as its stent platform. The characteristic features of the Supraflex include its ultra-thin struts (60 μm) and highly flexible “S-link,” which leads to better trackability, better crossability, and excellent pushability. A blend of sirolimus drug (1.4 $\mu\text{g}/\text{mm}^2$) and biodegradable polymers (poly L-lactide, 50/50 poly DL-lactide-co-glycolide, and polyvinyl pyrrolidone) has been coated on the surface of Supraflex, with a mean coating thickness of 4–5 μm for spontaneous release of the drug. The release profile of sirolimus has been divided into two phases: 70% of sirolimus releases within 7 days and the remaining 30% releases within 48 days. The drug release kinetics and scanning electron microscopy images of Supraflex have already been described in a previous publication (9). The polymers retain their properties for a limited period until the drug is fully released and then gradually degrade into biologically acceptable molecules (H_2O and CO_2) and removed from the body via normal excretion pathways within 9–12 months.

Interventional procedure and treatment

The coronary interventional procedure was performed in accordance with the standard guidelines and local practice. All patients were administered a loading dose of aspirin (75–300 mg) and clopidogrel (600 mg)/prasugrel (60 mg)/ticagrelor (90 mg). Heparin or bivalirudin were used to achieve anticoagulation during the procedure. However, the intra-procedural administration of glycoprotein IIb/IIIa inhibitor was left to the operator’s discretion. All patients were instructed to maintain dual antiplatelet therapy (aspirin 75–100 mg daily and clopidogrel 75 mg daily/prasugrel 10 mg daily or ticagrelor 90 mg twice daily) for at least 12 months after the procedure, and its extended use was recommended as per

operator’s preference depending on the individual case. Aspirin (75–100 mg daily) was recommended for lifetime use.

Study end-points and definitions

The primary end-point of the study was major adverse cardiac events (MACE), which is a composite of cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR) up to 12-months of Supraflex implantation. Any death due to a cardiac cause (such as MI, low-output failure, and lethal arrhythmia), unwitnessed death, and death of unknown reason, and all procedure-related deaths, involving linkage to concomitant treatment were considered as cardiac death. Non-cardiac death was considered as any death with well-established non-cardiac cause (10). MI was defined as either development of new pathological Q waves in at least two contiguous leads of the electrocardiogram with elevated cardiac troponin (cTn) values [$>5 \times 99^{\text{th}}$ percentile upper reference limit (URL) in patients with normal baseline values ($\leq 99^{\text{th}}$ percentile URL) or an increase of cTn values $>20\%$ when the baseline values are elevated and are stable or declining] (11). TLR was defined as repeat revascularization due to restenosis within the stent or in subsequent 5 mm of the distal/proximal segment. The incidence of stent thrombosis was analyzed as a safety end-point and was defined as per Academic Research Consortium criteria (10).

Data collection and follow-up

Baseline demographics, cardiac history, and angiographic data were retrospectively extracted from patients’ medical records in consecutive fashion, and follow-up was performed prospectively by clinical evaluation or telephone contact at 30 days, 6 months, and 12 months. Patients whose clinical notes were incomplete or who cannot be contacted via telephone for follow-up were excluded in the analysis.

Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS Inc; Chicago, IL, USA) program, version 20. Continuous and categorical variables were presented as mean \pm standard deviation and counts and percentages, respectively. At 12 months, cumulative MACE-free survival and sub-group analysis of clinical outcomes were mentioned using Kaplan–Meier curves.

Results

Baseline demographic characteristics

The data of 839 patients were collected from six different centers and analyzed. The baseline demographic details are shown in Table 1. The mean age of patients was 54.8 ± 10.7 years. Of 839 patients, 642 (76.51%) were male, 273 (32.53%) had diabetes mellitus, 378 (45.05%) had hypertension, and 102 (12.15%) were smokers. In addition, 285 (33.96%) patients had stable angina, 259 (30.87%) had non-ST elevated MI, 169 (20.14%) had ST-segment elevated MI, and 126 (15.01%) had unstable angina.

Table 1. Baseline demographic characteristics

Characteristics	Supraflex SES (n=839 patients)
Age (mean±SD, years)	54.8±10.7
Male, n (%)	642 (76.51%)
Diabetes mellitus, n (%)	273 (32.53%)
Hypertension, n (%)	378 (45.05%)
Family history of CAD, n (%)	41 (4.88%)
Smoker, n (%)	102 (12.15%)
Hypercholesterolemia, n (%)	369 (43.98%)
Previous stroke, n (%)	6 (0.71%)
Previous MI, n (%)	125 (14.89%)
Previous PCI, n (%)	195 (23.24%)
Coronary vessel diseases	
Single-vessel disease, n (%)	459 (54.70%)
Double-vessel diseases, n (%)	326 (38.85%)
Triple-vessel diseases, n (%)	54 (6.42%)
Anginal status	
Unstable angina, n (%)	126 (15.01%)
Stable angina, n (%)	285 (33.96%)
NSTEMI, n (%)	259 (30.87%)
STEMI, n (%)	169 (20.14%)

SES - sirolimus-eluting stent; CAD - coronary artery disease; MI - myocardial infarction; PCI - percutaneous coronary intervention; NSTEMI - non-ST-elevation myocardial infarction; STEMI - ST-elevation myocardial infarction

Procedural and lesion characteristics

The detailed characteristics of the procedure and lesions are outlined in Table 2. A total of 1025 lesions were angiographically diagnosed and treated using 1098 Supraflex stents. The left anterior descending (LAD) artery was found as the most prominent diseased vessel involving 533 (52.0%) lesions. A total of 447 (43.60%) lesions were classified as type C lesions. The mean stent length and diameter were 22.1±8.5 and 3.0±0.4 mm, respectively.

Clinical outcomes

At the 12-month follow-up, the incidence of MACE was seen in 40 (4.92%) patients comprising 7 (0.86%) cases of cardiac deaths, 16 (1.97%) cases of MI, and 17 (2.09%) cases of TLR. The rate of overall stent thrombosis was 0.37%, considering definite and probable stent thromboses in 2 (0.24%) patients and 1 (0.12%) patient, respectively. Of the three patients who experienced stent thrombosis, the first patient developed stent thrombosis immediately after stent implantation in the proximal LAD and underwent TLR with stent implantation. The second suddenly complained of chest pain again after PCI. We rechecked the right coronary artery (RCA) angiogram and found a newly developed intraluminal filling defect due to stent thrombosis of the proximal RCA, which was treated with intravenous administration of a glycoprotein IIb/IIIa receptor block-

Table 2. Procedural and lesion characteristics

Characteristics	Supraflex SES (n=1025 lesions) (n=1098 stents)
Target coronary artery	
LAD, n (%)	533 (52.0%)
RCA, n (%)	296 (28.87%)
LCX, n (%)	192 (18.73%)
LMCA, n (%)	4 (0.39%)
ACC/AHA lesion classification	
A, n (%)	258 (25.17%)
B1, n (%)	162 (15.80%)
B2, n (%)	158 (15.41%)
C, n (%)	447 (43.60%)
Total occlusion, n (%)	204 (19.90%)
Bifurcation involved, n (%)	81 (7.90%)
Small vessel (≤2.75 mm), n (%)	507 (46.17%)
Restenotic lesion, n (%)	75 (7.31%)
Number of lesions per patient (mean±SD, mm)	1.7±0.3
Total stented length per lesion (mean±SD, mm)	24.8±11.5
Overlapping stents, n (%)	70 (6.82%)
Pre-dilatation, n (%)	851 (83.02%)
Post-dilatation, n (%)	875 (85.36%)
Stents (n=1098 stents)	
Total stented length per patient (mean±SD, mm)	30.0±16.7
No. of stents per patient (mean±SD, mm)	1.3±0.6
No. of stents per lesion (mean±SD, mm)	1.1±0.3
Mean stent length (mean±SD, mm)	22.1±8.5
Mean stent diameter (mean±SD, mm)	3.0±0.4

SES - sirolimus-eluting stent; LAD - left anterior descending; RCA - right coronary artery; LCX - left circumflex artery; LMCA - left main coronary artery; ACC/AHA - American College of Cardiology/American Historical Association

er (abciximab), thrombus aspiration, and balloon angioplasty. The third patient had sudden chest pain and was admitted at another hospital and underwent PCI in the same vessel during the 12-month follow-up.

The clinical outcomes at 30 days, 6 months, and 12 months of follow-up are shown in Table 3. Cumulative MACE-free survival rate as per Kaplan–Meier method was 95.08% (Fig. 1).

The MACE in patients with diabetes, small vessel lesions (≤2.75 mm), and totally occluded lesions were 14/273 (5.13%), 18/421 (4.28%), and 3/199 (1.51%), respectively.

Discussion

The present study showed favorable results, even in a high proportion of high-risk real-world Indian patients, in terms of safety and clinical effectiveness of Supraflex at the 12-month follow-up.

Table 3. Cumulative clinical outcomes of Supraflex at the 12-month follow-up

Clinical outcomes	At 30 days 839 follow-up	At 6 months 824 follow-up	At 12 months 810 follow-up
Death from any cause, n (%)	4 (0.47%)	12 (1.45%)	17 (2.09%)
Cardiac death, n (%)	4 (0.47%)	7 (0.85%)	7 (0.86%)
Non-cardiac death, n (%)	0.00%	5 (0.60%)	10 (1.23%)
Myocardial infarction, n (%)	7 (0.83%)	14 (1.67%)	16 (1.97%)
Target lesion revascularization, n (%)	2 (0.23%)	7 (0.85%)	17 (2.09%)
Target vessel revascularization, n (%)	2 (0.23%)	11 (1.33%)	23 (2.84%)
Overall stent thrombosis, n (%)	2 (0.23%)	2 (0.24%)	3 (0.37%)
Definite stent thrombosis, n (%)	2 (0.23%)	2 (0.24%)	2 (0.24%)
Probable stent thrombosis, n (%)	0.00%	0.00%	1 (0.12%)
Possible stent thrombosis, n (%)	0.00%	0.00%	0.00%
Major adverse cardiac events, n (%)	13 (1.54%)	28 (3.40%)	40 (4.92%)

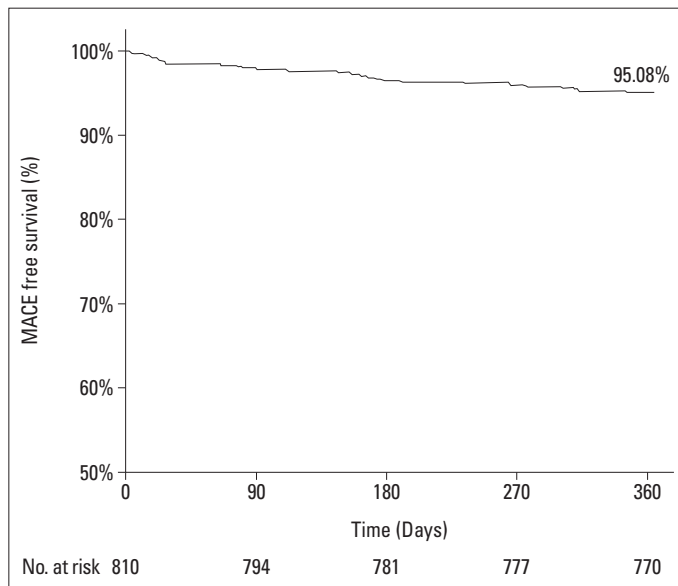


Figure 1. MACE-free survival rate at the 12-month follow-up

In search of an ideal DES, Supraflex was designed with ultra-thin (60 µm) cobalt–chromium platform and a biodegradable polymer technology to ensure the controlled release kinetics of sirolimus. Various registries and a recent randomized trial have demonstrated the favorable safety and clinical applicability of Supraflex in patients with coronary artery disease (7-9). The randomized controlled TALENT trial (8), published in 2019, compared the performance of Supraflex with the standard of care Xience (Abbott Vascular, Santa Clara, CA, USA), an everolimus-eluting coronary stent. In the TALENT trial, at 12-month follow-up, Supraflex (60 µm) was found to be non-inferior to Xience (81 µm) in terms of device-oriented composite end-points (35/720 (4.9%) vs. 37/715 (5.3%); $p < 0.0001$). Furthermore, FLEX registry (7) reported acceptable optical coherence tomography results at 6 months with 98.1% strut coverage and healing index of 4.8 (1.0–22.9), which were satisfying compared with other stents and also re-

ported favorable clinical outcomes at the 12-month follow-up. The MANIPAL-FLEX study (9) had reported in-stent late lumen loss of 0.18 ± 0.23 mm at the 9-month angiographic follow-up.

The present study adds another evidence to the clinical applicability and safety of Supraflex with favorable clinical outcomes at 12 months in real-world high-risk Indian patients. At 12 months, MACE was 4.92%, which was a composite of 0.86% cardiac death, 1.97% MI, and 2.09% TLR. Various other biodegradable polymer-coated coronary stents, such as BioMatrix (12) (Biosensors Inc., Newport Beach, CA, USA), Nobori (13-15) (Terumo Corporation, Tokyo, Japan), Orsiro (16) (Biotronik AG, Bülach, Switzerland), and Synergy (17) (Boston Scientific Corporation, Marlborough, MA) displayed comparable clinical outcomes with the present results. The rate of definite stent thrombosis in our study at 12 months was 0.24%, which was similar to various other studies. Waltenberger et al. (16) reported 0.2% definite ST at 1 year after Orsiro implantation, and Ananthakrishna et al. (17) documented 0.4% definite stent thrombosis at 1 year after Synergy implantation in a multiethnic Asian population. However, some studies have stated varied results with Supraflex. Sharifi et al. (18) reported the definite stent thrombosis rate as 1%. The MANIPAL-FLEX Registry documented 0.5% definite stent thrombosis at the 12-month clinical follow-up (9). In addition, Choudhury et al. (19) reported the definite stent thrombosis rate as 0% at 12 months after Supraflex implantation in the S-FLEX UK Registry.

The literature suggests that utilization of biodegradable polymers promote arterial healing, reduce local inflammatory reaction, and overcome potential risks for hypersensitivity reactions compared with permanent polymers (20, 21). However, recently, research has been shifted towards stent design and strut thickness because superiority of biodegradable over permanent biocompatible polymer technology has not yet been proven.

Thinner struts were proven to reduce stent-induced vessel trauma and local inflammation, decrease neo-intimal proliferation, reduce laminar flow disturbance, facilitate faster endothelialization, afford greater flexibility and deliverability, and also exhibit

good stent crossing and superior trackability in small and tortuous coronary vessels (22-25). All these lead to the reduction of in-stent restenosis, peri-procedural MI, and stent thrombosis with thinner strut DESs compared with thicker strut DESs. Various meta-analyses showed that the reduction in the rate of stent thrombosis, re-stenosis, and MI have been observed in DES with thinner struts (26, 27). Thus, low frequencies of MI (1.97%), cardiac death (0.86%), TLR (2.96%), and stent thrombosis (0.37%) in the present study are due to the ultra-thin (60 µm) struts of Supraflex.

The flexible “S-link” design of Supraflex has also contributed towards revamped clinical outcomes, wherein the rigid stents resulted into the development of thicker neo-intima compared with flexible stents, leading to more in-stent restenosis (28). In addition, studies have showed the advantages of cobalt–chromium DESs in terms of mechanical performance compared with stainless steel DESs. The L605 cobalt–chromium alloy used in Supraflex has higher density, tensile strength, and elastic nodules, which provide radial strength with thinner struts to the stent and also enhances visibility and deliverability (29). Thus, stent characteristics, such as stent strut thickness, material, design, type of drug, and type of polymer (durable/biodegradable), influence the safety and clinical performance of any device, which was similar to the favorable outcomes observed in the present study.

The present study included 32.53% patients with diabetes, 59.01% Types B2 and C lesions, 19.90% totally occluded lesions, and 46.17% small vessels (≤ 2.75 mm), which depicted high-risk patients with complex lesion characteristics. Thus, the primary end-point (MACE), at 12 months follow-up, was presented separately for patients with diabetes, small vessel (≤ 2.75 mm) disease, and totally occluded lesions (Table 4, Fig. 2). This finding indicated that not only particular stent characteristics but also patient characteristics, such as diabetes mellitus and small vessel size, might be influencing factors for adverse outcomes. However, specific clinical studies are required in the future to confirm the exact effects.

Study limitations

Although the study adds another evidence to the already established safety and efficacy of Supraflex, it has some limitations. First, it was a retrospective and single-arm study. Second,

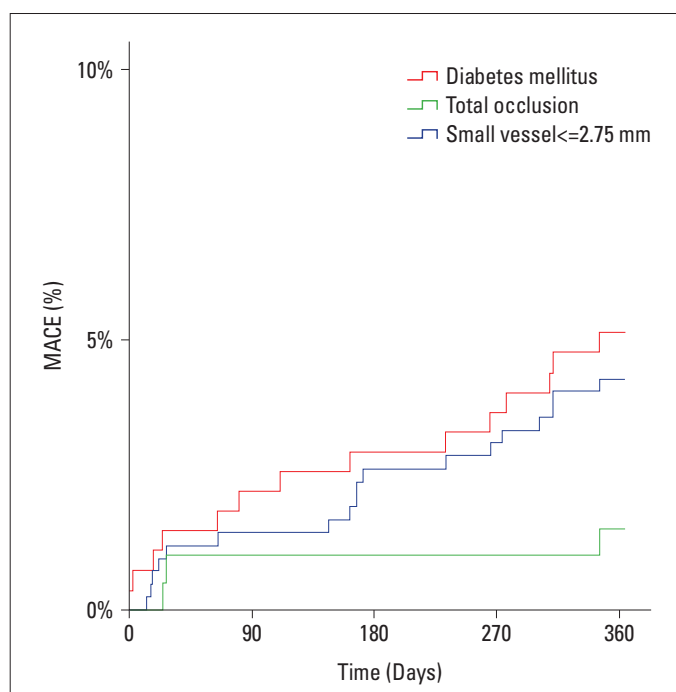


Figure 2. MACE in patients with diabetes, small-vessel lesions, and total occlusion at the 12-month follow-up

it also depicts 12-month follow-up results similar to other previous studies; thus, in the future, long-term follow-up should be planned to ascertain the long-term safety of Supraflex.

Conclusion

The study shows a favorable performance of Supraflex, a biodegradable polymer-coated ultra-thin (60 µm) coronary stent with flexible “S-link,” in a high proportion of high-risk real-world patients, with low MACE rate and stent thrombosis at the 12-month follow-up. Moreover, long-term follow-up will further establish the performance of Supraflex.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Table 4. Clinical outcomes of the patients with diabetes, chronic total occlusion, and small vessel disease

Clinical outcomes	Diabetes (n=273)	Total occlusion (n=199)	Small-vessel (n=421)
Cardiac death, n (%)	4 (1.5%)	1 (0.5%)	3 (0.7%)
Non-cardiac death, n (%)	-	-	-
Myocardial infarction, n (%)	5 (1.8%)	1 (0.5%)	7 (1.7%)
Target lesion revascularization, n (%)	5 (1.8%)	1 (0.5%)	8 (1.9%)
Target vessel revascularization, n (%)	-	-	-
Overall stent thrombosis, n (%)	-	-	-
Major adverse cardiac events, n (%)	14 (5.1%)	3 (1.5%)	18 (4.3%)

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