



Original Article

Seven-year clinical outcomes in patients undergoing percutaneous coronary intervention with biodegradable polymer coated sirolimus-eluting stent: Results from a single-center real-world experience



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ABSTRACT

Objective: The aim of the present study was to assess seven-year clinical outcomes of biodegradable polymer coated Supralimus sirolimus-eluting stent (S-SES) [Sahajanand Medical Technologies Pvt. Ltd., Surat, India] in real-world patients with coronary artery disease.

Methods: This observational, retrospective study was carried out in all 346 consecutive enrolled patients who underwent percutaneous coronary intervention (PCI) with the S-SES, between April 2008 and December 2009, at a single center. We analyzed major adverse cardiac events (MACE) [a composite of cardiac death, myocardial infarction (MI), target lesion revascularization (TLR) and target vessel revascularization (TVR)] as primary outcomes at seven-year follow-up.

Results: Out of 346 patients, seven-year follow-up was obtained in 327 (94.5%) patients and hence results were analyzed for 327 patients. At seven-year, MACE occurred in 41 (12.5%) patients, consisting of 23 (7.0%) cardiac deaths, 14 (4.3%) TLR, and 4 (1.2%) TVR. The incidence of late stent thrombosis was observed in 3 (0.9%) patients. At follow-up of seven-year, the cumulative event-free survival was found to be 84.7% by Kaplan-Meier method.

Conclusions: The present study demonstrated satisfactory and sustained seven-year clinical outcomes as evidenced by the low rates of MACE and ST for the biodegradable polymer coated S-SES.

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1. Introduction

First-generation drug-eluting stents (DES) with durable polymers significantly reduced the risk of target lesion revascularisation (TLR) compared to bare metal stents (BMS).^{1,2} However, the delayed arterial healing associated with DES has led to an increase in the rates of late and very late stent thrombosis (ST) and rebound of restenosis, termed as late catch-up.³ Although ST and restenosis are multifactorial in cause, durable polymer coatings may play an important role in their etiology. Several histopathological studies indicated that the durable polymer coatings of DES, which were associated with hypersensitivity reactions directed against the polymer, localized vascular inflammation, apoptosis of smooth muscle cells, and

thrombogenic reactions, may play important roles in late or very late ST.^{4,5} Therefore, there is increasing interest in designing a new generation of DES with a biodegradable polymer that may overcome these potential drawbacks of durable polymer DES.

Newer generation DESs were developed featuring biodegradable polymers that release limus analogues at lower dosages.^{6,7} These refinements resulted not only in a remarkable reduction in the risk of ST compared with early generation DESs but also improved efficacy (lower risk of repeat revascularization) and safety (lower risk of death and myocardial infarction [MI]).⁸ However, the clinical evidences of such advantages in real-world practice, especially those with long-term follow-up, are limited.^{9–11} Furthermore, very few long-term clinical studies (up to 7-year) related to sirolimus-eluting stent (SES) are there and most of these are related to SES with durable polymers. In addition, there is limited long-term clinical data related to biodegradable polymer coated SES.

The Supralimus sirolimus-eluting stent (S-SES) [Sahajanand Medical Technologies Pvt. Ltd., Surat, India] uses stainless steel as

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its stent platform, which is coated with a biodegradable polymer to deliver sirolimus. The S-SES has been available for clinical use since 2005 and the clinical safety and effectiveness of the S-SES is already established in various clinical studies.^{12–16} The present study was aimed at determining the clinical outcome of the S-SES at seven-year, which is the longest available follow-up of the biodegradable polymer coated SES technology.

2. Methods

2.1. Study design and patient population

This observational, retrospective study was carried out in all 346 consecutive enrolled patients who underwent percutaneous coronary intervention (PCI) with the S-SES between April 2008 and December 2009, at the Shree B.D. Mehta Mahavir Heart Institute, Surat, India. In this study, the list of all patients who had been implanted with the S-SES during this period was procured. Therefore, even though, it was retrospective analysis, all consecutive patients were included in the study. Since, there was no plan at the time of performing the procedure to conduct seven-year follow up evaluation; there was no selection bias (cherry picking) at the time of implanting the S-SES. During this period, no other stent of any other brand of same technology (sirolimus drug with biodegradable polymer) was available. All other DESs used during this period were SES or paclitaxel-eluting stents (PES) with durable polymers. The S-SES constituted 45.7% of total DESs used during this period. The seven-year follow-up was conducted by an independent clinical research organization (Therapeutic Medical Service, Surat, India) and was supervised by an independent cardiologist from a remote institute between June 2016 and August 2016. The study was approved by the institutional ethics committee.

2.2. Description of the study stent

The S-SES has stainless steel as its stent platform having a strut thickness of 80 μm with biodegradable polymers and drug load of 1.4 $\mu\text{g}/\text{mm}^2$. About 70% of drug is released within 7 days and remaining drug is released over a period of 48 days. The coating layer comprises of the drug Sirolimus blended together with biodegradable polymeric matrix. This matrix includes blend of hydrophobic and hydrophilic biodegradable polymers – Poly L-Lactide, 50/50 Poly DL Lactide-co-Glycolide and Polyvinyl Pyrrolidone to control the drug elution from stent coating.

2.3. Interventional procedures and adjunctive medication

Coronary interventional procedures and adjuvant medications were performed according to standard guidelines. All patients received dual antiplatelet therapy (DAPT) including a loading dose of aspirin (300 mg) and clopidogrel (600 mg). The procedural anticoagulation was achieved with heparin. However, the intra-procedural administration of glycoprotein IIb/IIIa inhibitor was at the investigator's discretion. All patients were advised to maintain DAPT (aspirin; 75–300 mg daily indefinitely and clopidogrel; 75 mg daily for at least 12 months) after the procedure.

2.4. Data acquisition and follow-up

According to the standard data-management procedures in our institute, data were collected on demographics, cardiovascular history, clinical risk factors, and treatment characteristics for all patients undergoing PCI. As part of study end points, the seven-year follow-up was conducted by an independent clinical research organization and was supervised by an independent cardiologist

from a remote institute between June 2016 and August 2016. Follow-up data of all patients were obtained at visits to outpatient clinics or, if not feasible, by telephone follow-up. Those patients, who did not come for follow-up visit, were again followed after 15 days. During the follow-up contacts, information about patients' clinical condition, adverse events, hospitalizations, and changes to concomitant (cardiac and antiplatelet) medications were collected.

2.5. Outcomes and definitions

We analyzed major adverse cardiac events (MACE) [a composite of cardiac death, MI, target lesion revascularization (TLR) and target vessel revascularization (TVR)] as primary outcomes and estimated event-free survival by the Kaplan-Meier method at seven-year of follow-up. Any death due to undetermined cause was reported as cardiac death. Q-wave MI was considered, when there was development of new Q-wave of more than 0.04 s in two or more adjoining leads along with increase in cardiac markers like Troponin I or T, creatine kinase (CK) or MB isoform. Non-Q-wave MI was considered when there was more than three times elevation in CK levels along with elevation in MB isoform and Troponin markers T or I without development of new Q-waves. TLR was considered when there was stenosis in treated segment (5 mm proximal and 5 mm distal edges). TVR was considered when there was stenosis in any segment of the treated vessel and had to undergo revascularization with either PCI or coronary artery bypass grafting (CABG). We also analyzed the incidence of ST as a safety end point during follow-up period. ST was defined according to criteria of Academic Research Consortium (ARC) with its timing being classified as early (within 24 h of the index procedure), late (occurred between 30 days to 1-year of the index procedure), or very late ST (occurred beyond 1-year of the index procedure), while its degree of certainty was classified as definite (if confirmed angiographically), probable (the patient had a target vessel-related MI or died of a coronary event), or possible (any unexplained death from 30 days after intracoronary stenting).

2.6. Statistical analysis

Data are presented using descriptive statistical methods. Continuous variables were presented as mean \pm standard deviation, whereas categorical variables were expressed as percentages. All data were processed using the Statistical Package for Social Sciences, version 15 (SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline and lesion characteristics

Out of 346 patients, seven-year follow-up was obtained in 327 (94.5%) patients and hence results were analyzed for 327 patients. The mean age of patients was 56.0 ± 11.4 years, and 40.1% (131/327), 34.9% (114/327) and 31.2% (102/327) had diabetes, hypertension and hypercholesterolaemia, respectively. The baseline demographics and clinical characteristics of all the treated patients are described in Table 1. A total of 386 target lesions were treated, including 11 (2.8%) unprotected left mains, 24 (6.2%) bifurcations, and 18 (4.7%) total occlusions. Among overall population most lesions (35.8%; 138/386) were located in the left anterior descending artery and 237 (61.4%) of 386 lesions were type B2/C, according to the American College of Cardiology/American Heart Association classification scheme. A total of 386 S-SES were implanted at index procedure (1.18 stents per patient) with an average diameter and total stent length of 3.0 ± 0.4 mm and 25.04 ± 9.1 mm, respectively. No patients had an additional dissimilar DES implanted but 11 patients had an additional short

Table 1
Demographic and clinical characteristics at baseline (n = 327 patients).

Characteristics	Data
Demographic characteristics	
Age, (mean ± SD, years)	56.0 ± 11.4
Male, n (%)	269 (82.3%)
Risk factors	
Current smoking, n (%)	62 (19.0%)
Hypertension, n (%)	114 (34.9%)
Hypercholesterolemia, n (%)	102 (31.2%)
Diabetes mellitus, n (%)	131 (40.1%)
Cardiac history	
Prior MI, n (%)	20 (6.1%)
Prior CABG, n (%)	4 (1.2%)
Prior PCI, n (%)	18 (5.5%)
Clinical presentation	
Stable angina, n (%)	93 (28.4%)
Unstable angina, n (%)	54 (16.5%)
STEMI, n (%)	112 (34.3%)
NSTEMI, n (%)	68 (20.8%)
Cardiogenic shock, n (%)	8 (2.4%)

CABG: coronary artery bypass grafting; MI: myocardial infarction; NSTEMI: non ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

Table 2
Lesion and procedural characteristics.

Characteristics	Data
Number of patients, n	327
Number of lesion, n	386
Target vessel location	
Left anterior descending artery, n (%)	138 (35.8%)
Right coronary artery, n (%)	122 (31.6%)
Left circumflex artery, n (%)	113 (29.3%)
Left main artery, n (%)	11 (2.8%)
Saphenous vein graft, n (%)	2 (0.5%)
Lesion classification (ACC/AHA score)	
Type A, n (%)	62 (16.1%)
Type B1, n (%)	87 (22.5%)
Type B2, n (%)	99 (25.6%)
Type C, n (%)	138 (35.8%)
Disease severity	
Moderate to severe calcification, n (%)	26 (6.7%)
Bifurcation, n (%)	24 (6.2%)
Total occlusion, n (%)	18 (4.7%)
Total number of stent, n	386
Number of stents per patient, mm (mean ± SD)	1.18 ± 0.4
Average stent length, mm (mean ± SD)	25.04 ± 9.1
Average stent diameter, mm (mean ± SD)	3.0 ± 0.4

ACC/AHA: American College of Cardiology/American Heart Association.

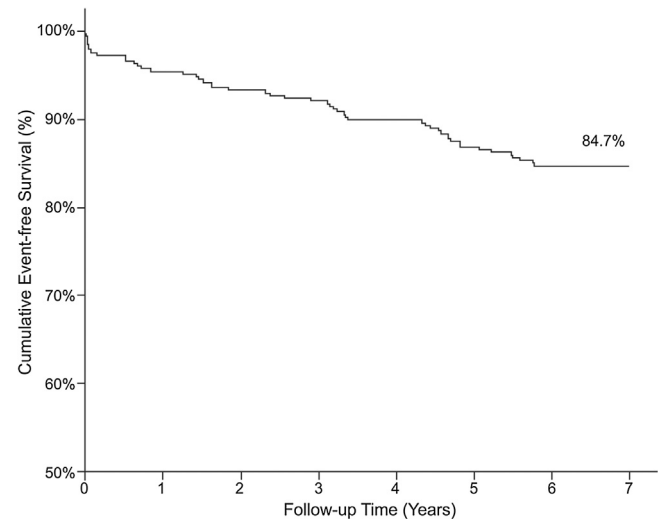
BMS (8–10 mm length) implanted to cover border dissections. The detailed lesion and procedural characteristics are described in Table 2.

3.2. Clinical outcomes

Table 3 summarizes the clinical outcomes. At 7-year, MACE occurred in 41 (12.5%) patients, consisting of 23 (7.0%) cardiac deaths (9 sudden deaths, 5 from heart failure, 8 from acute MI, 1 perioperatively for CABG), 14 (4.3%) TLR, and 4 (1.2%) TVR. The incidence of late ST was observed in 3 (0.9%) patients during 7-year follow-up with an annual thrombotic rate of 0.1% and 0.0004% ST per patient-year. Non-cardiac deaths were reported in 6 (1.8%) patients. At seven-year follow-up, the cumulative event-free survival was found to be 84.7% by Kaplan-Meier method (Fig. 1). A total of 259 (79.2%) patients were still on DAPT at seven-year with no major bleeding complication requiring readmission or blood transfusion.

Table 3
Clinical outcomes at seven-year follow-up (n = 327 patients).

Outcomes	0-1-year	>1-year	0-7-year
Death, n (%)	7 (2.1%)	22 (6.7%)	29 (8.9%)
Cardiac death, n (%)	6 (1.8%)	17 (5.2%)	23 (7.0%)
Non-cardiac death, n (%)	1 (0.3%)	5 (1.5%)	6 (1.8%)
Myocardial infarction, n (%)	6 (1.8%)	4 (1.2%)	10 (3.1%)
Target lesion revascularization, n (%)	3 (0.9%)	11 (3.4%)	14 (4.3%)
Target vessel revascularization, n (%)	2 (0.6%)	2 (0.6%)	4 (1.2%)
Stent thrombosis, n (%)	3 (0.9%)	0 (0)	3 (0.9%)
Major adverse cardiac events, n (%)	11 (3.4%)	30 (9.2%)	41 (12.5%)
All events, n (%)	15 (4.6%)	35 (10.7%)	50 (15.3%)

**Fig. 1.** Kaplan-Meier curve of cumulative event-free survival over seven-year.

4. Discussion

Several studies had demonstrated the safety and efficacy of biodegradable polymer based DES in selected patients.^{9,17–19} However, the validity of extrapolating those results to daily practice had remained uncertain because the follow-up period of most studies were not long enough to elucidate the consequences after completed degradation of a biodegradable polymer. To our knowledge, the present study is the first longest real-world experience of biodegradable polymer coated SES technology. In the present study, the S-SES has shown satisfactory and sustained seven-year clinical outcomes during daily interventional practice, which suggests the long-term clinical benefits of biodegradable polymer-based SES.

DESs were designed with the primary purpose of inhibiting restenosis after PCI. Early data from randomized trials have confirmed the efficacy of such devices in reducing restenosis and TLR compared with BMS. However, long-term (two years or longer) observations show the 'late catch-up' phenomenon of first-generation DES, namely, an increase of rates of very late restenosis or TLR.^{20–22} Furthermore, previous studies have suggested that first-generation DES could delay local vessel healing and increase the risk of potentially fatal late ST,²³ an adverse event that has been at least partly attributed to the durable polymer coatings of DES. As a result, new generation DESs with biodegradable polymer coatings have been recently developed as an alternative to reduce the risk of late ST. In this context, the S-SES was developed using biodegradable polymer-based, SES technology. The clinical safety and effectiveness of the S-SES was already established in various clinical studies.^{12–16}

Table 4
Long-term (5-year) follow-up results of randomised trials.

Trial Name	DES	Drug	Polymer Type	Patients	Follow-up Time	MACE (%)	TLR (%)	ST (%)
RAVEL Trial ²⁸	Cypher (Cordis, Johnson & Johnson)	Sirolimus	Durable Polymer	120	5-year	25.8	7.4	3.3
SIRIUS Trial ²⁹	Cypher (Cordis, Johnson & Johnson)	Sirolimus	Durable Polymer	533	5-year	20.3	9.4	3.9
TAXUS II Trial ²¹	Taxus (Boston Scientific)	Paclitaxel	Durable Polymer	131	5-year	20.4	16.6	2.7
TAXUS IV Trial ³⁰	Taxus Express ² (Boston Scientific)	Paclitaxel	Durable Polymer	651	5-year	24.0	9.1	2.2
ENDEAVOR II Study ³¹	Endeavor (Medtronic Vascular)	Zotarolimus	Durable Polymer	597	5-year	15.4	7.5	0.9
ENDEAVOR III Study ³²	Endeavor (Medtronic Vascular)	Zotarolimus	Durable Polymer	307	5-year	14	8.1	0.7
ENDEAVOR IV Study ³³	Endeavor (Medtronic Vascular)	Zotarolimus	Durable Polymer	722	5-year	17.9	7.8	4.6
SPIRIT FIRST Trial ³⁴	Xienc V (Abbott Vascular)	Everolimus	Durable Polymer	24	5-year	16.7	8.3	0
SPIRIT III Trial ³⁵	Xienc V (Abbott Vascular)	Everolimus	Durable Polymer	621	5-year	13.7	8.6	1.4

Further recently, a pooled analysis of individual patient data from the three major randomized trials comparing biodegradable polymer and durable polymer DES (ISAR TEST 3, ISAR TEST 4 and LEADERS Trials) with an extended follow-up to 4-year, showed for the first time a significant reduction in terms of definite ST in favor of biodegradable polymer DES.²⁴ These conclusions received further support by the recent release of 5-year follow-up data of the LEADERS Trial, which confirm a significant superiority of biodegradable polymer DES compared with durable polymer DES, driven primarily by the reduction in the incidence of very late ST.²⁵ In this study, the S-SES demonstrates a very low rate of ST (0.9%) at seven-year, which is lower than the CREATE study, 5-year clinical outcomes of biodegradable polymer coated sirolimus-eluting EXCEL stent, which reported 2.4% ST at 5-year follow-up.²⁶

Furthermore, El-Hayek et al. reported an important meta-analysis of 16 randomized controlled trials comprising 19,886 patients, investigating the safety and efficacy of biodegradable polymer coated DES compared with current second-generation durable polymer coated DES.²⁷ In that analysis, there were no differences in TVR, cardiac death, MI, or ST rates between biodegradable polymer coated DES and durable polymer coated DES. However, the outcomes of 11,866 patients from only 6 randomized controlled trials were studied beyond one year of follow-up (mean duration 26 months) in that meta-analysis. The results of the present study provide an insight into the long-term (seven-year) clinical outcomes for patients undergoing PCI with the biodegradable polymer coated S-SES which is the longest available follow-up of the biodegradable polymer coated SES technology.

In addition, in the present study, patient population had higher rates of hypertension (34.9%), hypercholesterolemia (31.2%), type B2/C (61.4%) lesions, and total occluded (4.7%) lesions. The combination of these factors makes the patient population for this study unusually complex. Regardless of this individuality, the present study reported a low rate of TLR (4.3%) and MACE (12.5%) at seven-year follow-up compared to available long-term (5-year) follow-up results of randomized trials with durable polymer based DES (Table 4).^{21,28–35} This numeric differences in long-term clinical outcomes between the present study and other DES studies imply there are potential benefits of biodegradable polymer based DES in reducing late catch-up.

The present study was conducted with the aim to collect real-world long-term data of the S-SES. Although limited by its single arm, non-randomized, retrospective study design, it had certain robust features: 1) there was no plan at the time of performing the

procedure to conduct 7-year follow up evaluation and total number of implanted S-SES constituted large percentage of total DESs used during this period. Thus, it was an unselected population and largely devoid of selection bias; 2) all consecutively enrolled patients who underwent PCI with the S-SES were considered for this study; 3) after seven-year, a very high percentage (94.5%) of follow-up was available; 4) the seven-year follow-up was conducted by an independent clinical research organization and was supervised by an independent cardiologist from a remote institute who was not involved in the original procedures.

5. Limitations

There are several limitations in the present study. First, this study was a single arm, non-randomized, retrospective study that did not include a control group. Second, the present study included a small number of patients. Third, the study had follow-up without any mandatory objective assessment for recurrent myocardial ischemia. However, asymptomatic MIs are typically associated with lesser clinical significance than symptomatic events, suggesting that the under-reporting of ischaemic events in the present study has a limited impact on the conclusions. Despite these limitations, this study provides an insight into the long-term (seven-year) clinical outcomes for patients undergoing PCI with the biodegradable polymer coated S-SES.

6. Conclusions

The results of the present study demonstrate satisfactory and sustained seven-year clinical outcomes for the biodegradable polymer coated S-SES in treating patients in real-world settings, with low rates of MACE and ST.

7. Impact on daily practice

Present study demonstrates acceptable seven-year clinical outcomes of the S-SES during daily interventional practice, which suggests the long-term clinical benefits of biodegradable polymer-based SES.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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