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Safety and Effectiveness of FlexyRap® Cobalt-Chromium Rapamycin-Eluting Stents with Biodegradable Polymer in Coronary Artery Disease: Results from a 2-year, Multicenter Postmarketing Study in India

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Abstract

Background: Data supporting effectiveness and safety of indigenously developed Drug-Eluting Stents (DES) for treatment of Indian patients with *de novo* Coronary Artery Disease (CAD) remain scarce. In this Postmarketing Surveillance (PMS) study, we evaluated effectiveness and safety of an indigenously developed DES, FlexyRap®, for treatment of Indian patients with obstructive native artery.

Methods: We enrolled 100 patients with obstructive native artery who underwent Percutaneous Coronary Intervention (PCI) using DES technology called FlexyRap®. The primary efficacy endpoint was Target Vessel Revascularization (TVR) at 1-year follow-up. The primary safety outcome was incidence of a Major Adverse Cardiac Event (MACE), defined as a composite of cardiac death, myocardial infarction, target lesion revascularization, and TVR at 12 months. Secondary efficacy endpoints included procedural and device success. Additional safety endpoints were incidences of any device-related Serious Adverse Events (SAEs) and stent thrombosis.

Results: In this study, of the 100 patients treated with FlexyRap®, data was available for 96 patients at the end of the 24-month surveillance period. Device and procedural success was observed in 100% of patients. At 12 months after implantation of FlexyRap®, 6.25% of patients developed MACE; the incidence of MACE remained at 6.25% at completion of the 24-month PMS period. The primary endpoint of TLR developed in 5% of patients. The MACE-free survival rate was 93.78%. No SAE leading to death was reported throughout the 24-month surveillance period. No patient experienced AEs that led to major bleeding, permanent disability, or death.

Conclusion: FlexyRap® was safe and effective in Indian patients with CAD. Results of the study are encouraging and support clinical benefits of the indigenously developed FlexyRap® DES for treating Indian patients with CAD in a real-world scenario.

Abbreviations: BMS: Bare-Metal Stents; DES: Drug-Eluting Stents; BD-DES: Biodegradable Drug-Eluting Stents; PCI: Percutaneous Coronary Intervention; DP-DES: Durable Polymer Drug-Eluting Stents; TVR: Target Vessel Revascularization; CAD: Coronary Artery Disease; PMS: Postmarketing Survey; MI: Myocardial Infarction; LVEF: Left Ventricular Ejection Fraction; QCA: Quantitative Coronary Angiography; MACE: Major Adverse Cardiac Event; TLR: Target Lesion Revascularization; SAE: Serious Adverse Event; TIMI: Thrombolysis In Myocardial Infarction; CABG: Coronary Artery Bypass Grafting

Keywords: Coronary artery disease; Drug-eluting stents; Percutaneous coronary intervention; Rapamycin; Myocardial infarction; Thrombosis; Myocardial revascularization

Introduction

Implantation of stents is an effective treatment for revascularization of narrowed and obstructed coronary arteries [1]. Although Bare-Metal Stents (BMS) have shown remarkable improvements compared with balloon angioplasty, the long-term success of BMS is hindered owing to the risk of restenosis and requirement of a re-intervention [2,3]. To overcome these limitations, Drug-Eluting Stent (DES) technology was developed. DES is a localized drug delivery system designed to release drugs such as rapamycin (sirolimus) or its analogues into narrowed coronary arteries to minimize the risk of restenosis. DES has demonstrated to reduce neointimal hyperplasia after vascular injury and, hence, expected to be more effective than BMS in averting angiographic restenosis [4].

The technology used in DES has significantly evolved over the past two decades. Biodegradable (second-/third-generation) Polymer Drug-Eluting Stents (BP-DES) have demonstrated improved prognosis of Percutaneous Coronary Interventions (PCIs) compared with Durable Polymer Drug-Eluting Stents (DP-DES) [5]. BP-DES have demonstrated reduction in the inflammatory response of arterial wall, which facilitates re-endothelialization, thus minimizing the risk of

thrombus formation and late restenosis [5,6]. The architecture of the stent and the type of metal used in stent construction play crucial roles in determining accuracy of drug loading, drug delivery, and prevention of in-stent intimal hyperplasia [7]. In addition, lower strut thickness of stents is associated with reduced occurrences of Stent Thrombosis (ST), late ST, and the need for Target Vessel Revascularization (TVR) [7,8]. Considering these, a novel biodegradable rapamycin-eluting coronary stent (hereinafter referred to as FlexyRap®) was developed by utilizing a patented radial star, semi-opened, hybrid designed FlexyStar® platform with a low strut thickness of 60 µm combined with a flexible link endowed with L605 cobalt-chromium metal. These characteristics ensure optimal drug delivery, radial strength, vessel conformability, radio-opacity, and biocompatibility. Data supporting efficacy and safety of indigenously developed DES in Indian patients with de novo Coronary Artery Disease (CAD) remain scarce. In this Postmarketing Surveillance (PMS) study, we evaluated real-world safety and efficacy of a rapamycin-eluting biodegradable polymer-based FlexyRap® coronary stent system in Indian patients with obstructive native coronary arteries over a period of 2 years (REFLECTION study).

Methods

Study design and study population

This was a prospective, multicenter PMS study conducted in 100 patients with obstructive native arteries. The study included patients eligible for PCI with lesions suitable for stent implantation, aged ≥ 18 years, who presented with stable or unstable angina pectoris or evidence of Silent Ischemia (SI) or positive functional test. Patients with acute/recent (<72 hour) Myocardial Infarction (MI) who had undergone PCI within 1 month before participation, those with a life expectancy of <1 year, those allergic to metals, aspirin, clopidogrel, bisulfate, heparin, and rapamycin, and those with lesions located in the left main coronary artery, bifurcation lesions, in-stent restenosis, lesions with >70% angulations, presence of thrombus in target vessel, chronic total occlusion and a significant thrombus in a target vessel, severe calcified lesions, two lesions in one vessel that cannot be treated with a single stent, documented Left Ventricular Ejection Fraction (LVEF) <30%, and acute/chronic renal dysfunction (creatinine >2.0 mg/dL or >150 µmol/L) were excluded. This study was conducted in accordance with the Declaration of Helsinki. Institutional review boards and independent ethics committees of all participating study centers approved this study. Written informed consent was obtained from each patient before enrolment in this study.

Study device

The FlexyRap® stent consists of a thin strut, balloon-expandable, cobalt-chromium L605 stent platform that delivers rapamycin from a polylactide-based biodegradable polymer. The coating thickness of the drug polymer was optimized to 4-6 µm in a multilayered formulation for sustained drug release for up to 1 month. The formulation has an optimized drug dose of 1.0 µg/mm^2 (32-213 µg, varying with the length of the stent). FlexyRap® is available in various lengths (7, 10, 13, 15, 17, 20, 24, 28, 33, 38, 42, and 45 mm) and diameters (2.50, 2.75, 3.00, and 3.50 mm).

Study procedure

Procedural anticoagulation was achieved using unfractionated heparin (at least 5000 IU or 70-100 IU/kg to maintain an activated clotting time of >250 s during the procedure). Aspirin (≥100 mg) and clopidogrel (300-600 mg) or prasugrel (60 mg) were administered before or during the procedure at investigator's discretion. Patients continued to take aspirin (100 mg QD) indefinitely. Clopidogrel (75 mg QD) or prasugrel (60 mg) was administered for at least 6 months after stent implantation in all patients and for at least 12 months in those who did not have a high risk of bleeding. In addition, glycoprotein IIB/IIIA inhibitors were administered in certain patients at investigator's discretion. Biomarkers and ECGs were recorded at different time points to assure the safety and well-being of patients. Quantitative Coronary Angiography (QCA) and echocardiography were scheduled before discharge. Clinical or telephonic follow-up was scheduled at day 30 and at months 6, 9, 12, and 24.

Study endpoints

The primary efficacy endpoint was TVR at the 1-year follow-up. Secondary efficacy endpoints included device and procedural success. The primary safety endpoint was incidence of any Major Adverse Cardiac Event (MACE) at 12 months, defined as a composite of cardiac death, MI, Target Lesion Revascularization (TLR), and TVR. Secondary safety endpoints were incidence of MACE and device-related Serious Adverse Events (SAEs) up to 2 years of follow-up and incidence of acute, subacute, and late angiographic ST.

Statistical analysis

Descriptive statistics was used for data analysis. Data were provided as mean ± Standard Deviation (SD) or median (minimum, maximum) to summarize continuous variables. Categorical variables were reported as numbers and percentages. Statistical analysis was performed using statistical analysis software (SPSS, version 21 or higher; SPSS Inc., Chicago, IL, USA).

Results

Baseline demographic characteristics

Overall, 100 patients were enrolled in this study, of whom, 99 patients continued the study until day 30, and 96 patients continued until 24 months, i.e., till the end of the study. Baseline and clinical characteristics are summarized in Table 1. Eighty-eight percent of patients were men. The mean ± SD age of the enrolled patients was 55.61 ± 8.39 years. Overall, 19% of patients were diagnosed with two lesions based on their angiographic characteristics at baseline. The most frequently used stent diameter was 3.5 mm (43%) and sent length used was 10-25 mm (55%). As per guidelines for PTCA, 98.4% of study stents were implanted after predilation of the target lesion, and 51.6% of patients received the stents postdilation.

Significant comorbidities such as diabetes, hypertension, and hyperlipidemia were reported in 27%, 31%, and 36% of patients, respectively. One patient had a familial history of CAD. Nineteen percent of patients were smokers. Prior history or current conditions such as angina pectoris, MI, and SI were reported in 28%, 45%, and 44% of patients, respectively. Table 2 summarizes baseline lesion morphology along with the target lesion location.

Procedural characteristics

In total, 129 FlexyRap® rapamycin-eluting coronary stents for 119 lesions were implanted at an average of 1.29 stent per patient. The average ± SD stent length and diameter were 26.42 ± 9.13 and 3.16 ± 0.39 mm, respectively. According to the American College of Cardiology/American Heart Association classification of lesions, 52.9% (n=63), 10.1% (n=12), and 4.2% (n=5) of B1, B2, and C types of lesions, respectively, were reported in this study. TIMI flow grade 0, 1, 2, and 3 were observed in 11.8% (n=14), 19.3% (n=23), 59.7% (n=71), and 9.2% (n=11) of lesions, respectively, with a mean ± SD length of 26.42 ± 9.13 mm. An existing thrombus was observed in 5.9% of lesions, and the average ± SD percentage of stenosis was 87.11 ± 9.39% (Table 2). Procedural success was observed in 100% of patients.

Clinical outcomes

Clinical outcomes of this study are described in Table 3. No MACEs were observed until day 30. The primary endpoint of TLR developed in 5% of patients at 12 months. The incidence of MACE at 6, 9, and 12 months of interim analysis was 1.04% (n=1), 2.08% (n=2), and 6.25% (n=6), respectively, in patients assessed during the 24-month surveillance period (Table 3). Cumulative MACE was 6.25% at 24 months. A majority (5%) of the reported MACEs were clinically driven by TLR. One patient suffered from MI, while another underwent Coronary Artery Bypass Grafting (CABG). All patients recovered after treatment. The MACE-free survival rate was 93.78% based on the Kaplan–Meier curve (Figure 1). In addition, 3% of patients displayed late ST. No SAEs leading to death were reported throughout the 24-month surveillance period. There were no reports of AEs such as major bleeding, permanent disability, or death (Table 4). Overall, FlexyRap® rapamycin-eluting stent was found to be safe and effective in minimizing the risk of MACE in this 2-year real-world PMS study.

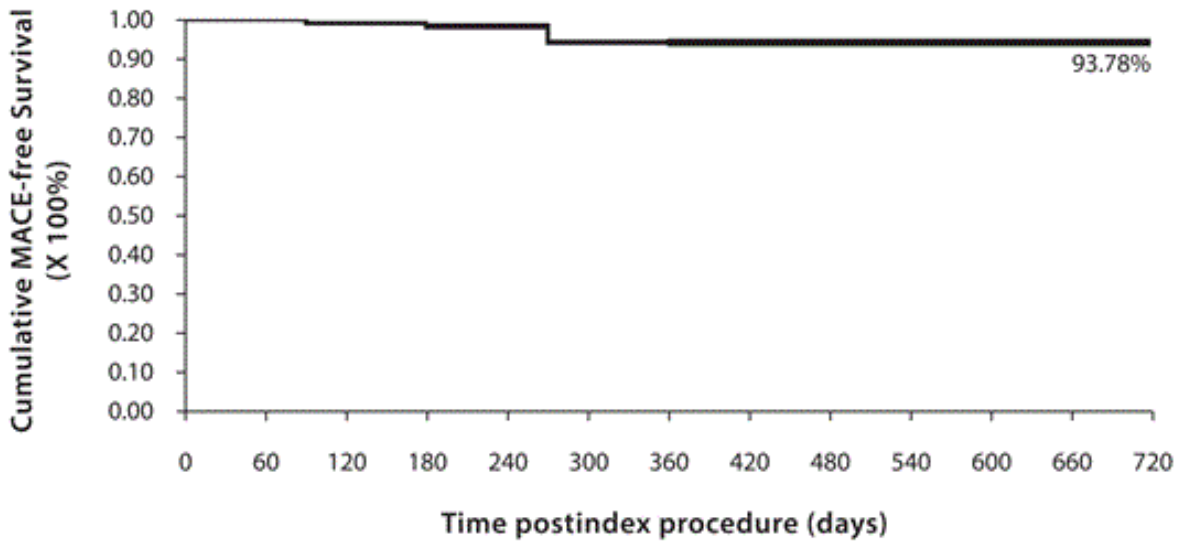

Figure 1: Kaplan-Meier cumulative MACE-free survival rate at 2-year clinical follow-up.

Characteristics	Population (N=100)
Age, years	55.61±8.39
Men	88 (88)
History of Smoking	19 (19)
Blood Pressure, mmHg	
Systolic	126.53±16.36
Diastolic	80.72±8.42
Heart Rate, bpm	78.26±14.73
Medical History	

Diabetes mellitus	27 (27)
Hypertension	31 (31)
Hyperlipidemia	36 (36)
Familial CAD history	1 (1)
Previous MI	
Q wave	24 (53.3)
Non-Q wave	7 (15.6)
Unknown	14 (31.1)
Angina Pectoris	
Stable	6 (21.4)
Unstable	11 (39.3)
Unknown	11 (39.3)
Silent Ischemia	44 (44)
Data presented as mean ± SD or n (%)	

Table 1: Demographic and baseline clinical characteristics.

Characteristics	**N=100 patients and 119 lesions**
Target vessel location	
LAD	54 (45.4)
LCx	27 (22.7)
RCA	35 (29.4)
Ramus	1 (0.84)
Other	2 (1.68)
Target lesion location	
Proximal	22 (18.5)
Mid	75 (63.0)
Distal	19 (15.9)
Other	1 (0.84)
Unknown	2 (1.68)
Average reference vessel diameter, mm	3.16 ± 0.39
Lesion length	
10-20 mm	53 (44.5)
>20 mm	66 (55.5)
Patients with one lesion	81 (81)
Patients with two lesions	19 (19)
Mean lesion length, mm	26.42 ± 9.13

Stenosis, %	87.11 ± 9.39
Thrombotic lesions	7 (5.9)
ACC/AHA lesion type	
A	37 (31.1)
B1	63 (52.9)
B2	12 (10.1)
C	05 (4.2)
Unknown	2 (1.68)
TIMI flow grade at baseline	
0	14 (11.8)
1	23 (19.3)
2	71 (59.7)
3	11 (9.2)
Unknown	2 (1.68)
Average stent length (mm)	26.42 ± 9.13
Average stent diameter	3.16 ± 0.39
Average stent per patient (n)	1.29 ± 0.53
Diameters of stent used	
2.5 mm	23 (18)
2.75 mm	15 (11)
3 mm	36 (28)
3.5 mm	55 (43)
Length of stent used	
10-25 mm	71(55)
25-40 mm	39 (30)
>40 mm	19 (15)
Predilation	119 (100)
Postdilation	66 (51.6)

Data presented as mean ± SD or n (%)

ACC: American College of Cardiology; AHA: American Heart Association; LAD: Left Anterior Descending; LCx: Left Circumflex; RCA: Right Coronary Artery; TIMI: Thrombolysis In Myocardial Infarction

Table 2: Lesion and procedural characteristics.

Description	1 month (N=99)	6 months (N=96)	9 months (N=96)	1 year (N=96)	2 years (N=96)
MACE	0	1 (1.04)	2 (2.08)	6 (6.25)	6 (6.25)
Death (Cardiac/noncardiac)	0	0	0	0	0
Myocardial Infarction					

Q wave	0	0	0	1 (1.04)	1 (1.04)
Non-Q wave	0	0	0	0	0
Clinically Driven TLR	0	1 (1.04)	2 (2.08)	4 (4.17)	4 (4.17)*
Repeat PTCA	0	1 (1.04)	2 (2.08)	4 (4.17)	4 (4.17)
On target lesion	0	1 (1.04)	2 (2.08)	4 (4.17)	4 (4.17)
On nontarget lesion	0	0	0	0	0
CABG	0	0	0	1 (1.04)	1 (1.04)
Major Bleeding	0	0	0	0	0
Stent Thrombosis, ARC Definition	0	0	0	3 (3)	3 (3)

Data are described as n (%); *all patients recovered

ARC: Academic Research Consortium; CABG: Coronary Artery Bypass Grafting; MACE: Major Adverse Cardiovascular Event; PTCA: Percutaneous Transluminal Coronary Angioplasty

Table 3: Clinical outcomes.

AE Type	**N=100**
Number of patients with ≥1 AE	7 (7)
Prolonged hospitalization	4 (4)
AEs related to procedure	
Yes	0
No	7 (7)
Medical management	2 (2)
Percutaneous procedure	4 (4)
Repeat angiogram	0
Cardiac surgery	1 (1)
Other surgery	0
Death	0
Permanent disability	0

Data are described as n (%) unless mentioned otherwise

AE: Adverse Event; MACE: Major Adverse Cardiac Event; TLR: Target Vessel Revascularization.

Table 4: Incidence of AEs (safety analysis set).

Discussion

The REFLECTION study demonstrated real-world effectiveness of FlexyRap® coronary stents for treatment of patients with CAD. Two-year follow-up results established favorable safety and performance of the stent with low rates of MACE (6.25%) and ST (3%).

Demographic and angiographic characteristics of the enrolled study population of Indian patients with CAD demonstrated a "real-world" clinical scenario. Incidences of comorbidities such as diabetes (27%), hypertension (31%), and hyperlipidemia (36%) were significantly lower than those reported previously [9,10]. Moreover, in our study, patients with SI were also considered for PCI as previous reports have suggested the use of PCI for such patients in order to improve their survival [11,12]. Reportedly, PCI was shown to be superior than anti-ischemic drug therapy in patients with SI in a randomized, unblinded controlled trial named SWISS II [12].

The drug rapamycin, a macrolide and cytostatic in nature, arrests cells in the G1 phase of the cell cycle, thus attenuating cellular fibrosis [13,14]. Rapamycin prevents vascular damage and facilitates rapid re-endothelialization within 30 days, thereby minimizing the risk of thrombus formation and late restenosis [13-15]. In addition, it is known to play a protective role against ischemia/reperfusion injury [16,17], making it a drug of choice in DES for treatment of patients with CAD. The FlexyRap® rapamycin-eluting stent evaluated in this

study is an effective device for delivering rapamycin through a unique biodegradable polymer system and a FlexyStar® platform. A key advantage of using FlexyRap® is its ability to avoid cracking, webbing, lumping, or sticking to the balloon surface, making it a potential candidate for coronary-based applications. In this study, procedural success was observed in all patients, which could be attributed to these product characteristics. Moreover, both pre- and post-dilation stenting were used in the present study. No significant difference was observed in the occurrence of MACE and MI during or after completion of the procedure.

Although there remains no scientific distinction between indigenously developed DES versus those developed and marketed by global manufacturers, cost effectiveness remains a key factor in the decision-making process for Indian patients and health care providers [18]. Results of a preclinical study in rabbits were in line with those of the REFLECTION PMS study and supported the benefits of indigenously developed FlexyRap® stents [14]. Moreover, the primary endpoint of 6.25% of MACE at 12 months and 2 years is concordant with results of other indigenous DES such as Supraflex DES (SMTPL, Gujarat, India; 5.3%) in the Manipal Flex registry and Firebird-2 stent in the focus registry (MicroPort®, Shanghai, China; 5.93%) [19,20]. Furthermore, the incidence of MACE in the present study was similar to that reported with MiStent® (6.7%) (MICELL TECHNOLOGIES, INC., Durham, North Carolina U.S.) in DISSOLVE I and DISSOLVE II studies, Endeavor® Stent (13.3%) (Medtronic, Dublin, Ireland), and other BP-DES, wherein the incidence of MACE ranged from 5 to 7.25% [21-25].

At the end of the 24-month analysis period, 7% (n=7) of patients reported AEs. None of the AEs were found to be causally related to the procedure or the device, and no patient experienced SAEs such as permanent disability or death. The radial star segment design and low strut thickness provide excellent radial strength, thus ensuring delivery of the device through the blood vessel. In addition, the reduced incidence of AEs could be attributed to the noninflammatory nature of a biodegradable polymer with excellent drug release kinetics. The rate of AEs observed in the REFLECTION study was comparable to rates reported in other relevant studies, which ranged 4–15% [19,21]. Most importantly, no deaths were recorded in this PMS registry during the 24-month evaluation period after implantation of FlexyRap®. Taken together, the unique radial star stent design, the patented laser technology to achieve optimal finish of the surface, an automated inspection system, and use of a biodegradable polymer for sustained release of rapamycin assured promising clinical outcomes associated with the REFLECTION study.

A major limitation of the present study is its observational nature. Moreover, the number of patients included in the REFLECTION study is low to draw any conclusive clinical inferences; however, the results are encouraging and support the need to extend this investigation in larger patient samples.

Conclusion

In summary, this PMS study provided preliminary evidences regarding feasibility, safety, and efficacy of the FlexyRap® rapamycin-eluting stent for treatment of de novo CAD. Results of this study are encouraging and support clinical benefits of the indigenously developed FlexyRap® DES for treatment of Indian patients with CAD in a real-world scenario. However, further investigation in a larger randomized trial is warranted to affirm the study findings.

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Conflict of Interest

Mr. Prashant, Dr. Malte, and Ms. Preeti are employees of Sahajanand Laser Technology Ltd. (SLTL), India. All other authors have nothing to disclose.

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