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ORIGINAL ARTICLE

Retrospective Study

Real-world five-year outcomes of FlexyRap® cobalt-chromium rapamycin-eluting stents with biodegradable polymer in patients with *de-novo* coronary artery disease

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Abstract

BACKGROUND

The use of biodegradable polymer drug-eluting stents (BP-DES) has been proven to minimize restenosis and stent thrombosis. The current post-marketing monitoring was observed at the 5-year clinical outcomes of individuals who had been treated with FlexyRap® DES in the real world.

AIM

To assess the safety and effectiveness of FlexyRap® DES at the 5-year follow-up in real-world settings.

METHODS

Findings from a retrospective, multi-center, observational, post-market clinical follow-up study of patients treated with FlexyRap® DES for *de novo* coronary artery disease (CAD) were reported. During the 12-mo follow-up, the primary endpoint was target lesion failure, which was defined as the composite of

cardiovascular death, target vessel myocardial infarction (TV-MI), and clinically driven target lesion revascularization.

RESULTS

The data of 500 patients received with FlexyRap® DES was obtained at the completion of the surveillance timeline of 5-year. After the implantation of FlexyRap® DES, the device success rate was 100%. Adverse events that led to major bleeding, permanent disability, or death were not experienced in the patients. The major adverse cardiac event rate at 12-mo, 3-year, and 5-year follow-up was 1 (0.2%), 0 (0%), and 1 (0.2%) respectively with 0 (0%) cardiovascular death, 2 (0.4%) TV-MI, and 0 (0%) TLR compositely. Furthermore, late stent thrombosis was found in 2 (0.4%) patients at the follow-up of 12-mo, very late stent thrombosis was observed in 2 patients (0.4%) at 3-year follow-up.

CONCLUSION

FlexyRap® DES was proved to be safe and efficacious in real-world patients with *de novo* CAD, indicating a lowered rate of cardiac events and stent thrombosis at 5-year follow-up.

Key Words: Coronary artery disease; Drug-eluting stents; Percutaneous coronary intervention; Rapamycin; Sirolimus

Core Tip: Biodegradable polymer drug-eluting stents (BP-DES) have been proven to minimize restenosis and stent thrombosis. Our study evaluates the safety and effectiveness of FlexyRap® DES at the 5-year clinical response in real-world settings. The study proved the feasibility, safety, and efficacy of the FlexyRap® rapamycin-eluting stent for the treatment of *de novo* coronary artery disease, indicating low rates of events and stent thrombosis at 5-year follow-up.

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INTRODUCTION

Percutaneous coronary intervention (PCI) is a frequently conducted cardiac procedure aimed at enhancing the quality of life and reducing symptoms for individuals suffering from coronary artery disease (CAD)[1]. CAD is the leading cause of mortality across the globe[2]. Drug eluting stents, commonly referred to as DES, are considered as the primary method of percutaneous coronary revascularization for patients experiencing acute coronary syndromes and stable ischemic heart disease[3]. Recent advancements in the design of newer generation DES have centered on enhancing tissue biocompatibility and facilitating arterial healing. This has been achieved by incorporating innovative stent platform materials with thinner struts, utilizing biocompatible or biodegradable polymers with improved coatings, and implementing novel antiproliferative agents by lowering the content of drug and precisely controlling the rate of elution[4]. The advent of DES has decreased the rates of restenosis and become the preferred method of choice for most of the patients undergoing the procedure of PCI [1]. These stents have become widely used across a range of anatomic and clinical aspects due to their reduced rates of restenosis and the requirement for the repetition of the revascularization procedure[2]. The utilization of a polymer that is biodegradable has the possibility of lowering the chronic inflammatory response of the wall of blood vessels, facilitating the process of re-endothelialization and reducing the likelihood of blood clots and late restenosis[5]. Biodegradable polymers are being considered and analyzed to acquire and carry drugs. Polymers like poly lactic acid, polyglycolic acid, and their copolymer, poly lactic-co-glycolic acid, are most prevalent as they sight characteristics to get completely degraded and metabolized in the body[6]. It would have improved safety and performance of DES as they deliver controlled release of anti-restenosis agent and gradual degradation of coating[7].

FlexyRap® is one such novel biodegradable rapamycin-eluting coronary stent that has been developed by using a unique patented design of radial star, semi-opened, hybrid FlexyStar® platform, with a lower 60 μm thickness of strut and flexible link made of L605 cobalt-chromium metal. This design ensures the optimal delivery of the drug, radio-opacity, radial strength, biocompatibility, and vessel

conformability. The evidence supporting the effectiveness and safety of indigenously produced drug-eluting stents in patients with newly diagnosed coronary artery disease is limited[8]. This study aimed to assess post-market clinical follow-up of real-world safety and efficacy of the rapamycin-eluting FlexyRap® coronary stent system, made of biodegradable polymer, in patients with obstructive native coronary arteries over a 5-year period.

MATERIALS AND METHODS

The FlexyRap® DES study was conducted at 5 centers with the total of 500 patients included in this study. The study was a retrospective, single-arm, multi-center, observational, post-market clinical follow-up conducted in 500 patients who were eligible for PCI and coronary artery bypass grafting (CABG). The patients in whom the target lesion located within a native coronary vessel and the target lesion diameter stenosis ≥ 50% were included in the study. Out of a total of 613 patients assessed for eligibility, 113 patients were excluded due to screen failure, and 500 patients were ultimately included in the study after meeting the predefined inclusion criteria as shown in Figure 1. The study was conducted in accordance with the declaration of Helsinki and IS0 14155:2020 GCP standards, ICH-GCP, MEDDEV 2.7.1 Appendix 1, MDR 2017/745 and applicable local regulatory requirements. The study was performed with the approval of an independent ethics committee. The PCI procedures were performed according to current standard guidelines. Clinical and angiographic data from all the patients who were treated with FlexyRap® DES were observed in this study. The clinical follow-up was performed at the time point of 12-mo, 3-year and 5-year after the discharge.

Device description

FlexyRap® cobalt chromium rapamycin-eluting coronary stent system consisting of a drug/polymer coated balloon expandable stent premounted on rapid exchange percutaneous transluminal coronary angioplasty (PTCA) balloon catheter. The stent is made from L605 cobalt chromium alloy (Co-Cr) which consists of cobalt, chromium, tungsten, iron and nickel with its strut thickness 60 μm. The stent is laser cut from the seamless tubing in hybrid design pattern and electro polished for ultra-smooth stent surface. The coating is comprised of biodegradable polymer matrix that contains an active pharmaceutical ingredient rapamycin (sirolimus). A conformal coating of a polymer carrier with approximately 1.0 μg/mm^2 of rapamycin of total stent surface area with minimal nominal drug content of 32 μg on the smallest stent (7 mm) to maximum nominal drug content of 213 μg on the largest stent (45 mm). Stent of 48 mm in length approved by the Central Drug Standard Control Organization was also implanted in the desired population. The stent delivery balloon catheter system is a semi-compliant polyamide balloon, which is nominally 0.5 mm longer than the stent. The two opaque platinum-iridium markers are nominally placed beyond the stent at each end which defines the stent location in length. Two proximal delivery system shaft markers (90 cm and 100 cm proximal to distal tip) indicate the relative position of delivery system to the end of appropriate guiding catheter. FlexyRap® DES is available in various lengths (7, 10, 13, 15, 17, 20, 24, 28, 33, 38, 42, 45 and 48 mm) and diameters (2.25, 2.5, 2.75, 3.0, 3.5, 4.0 and 4.5 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 > 250s during the procedure). Aspirin (≥ 100 mg) and clopidogrel (300-600 mg) or prasugrel (60 mg) were administered before or during the procedure at the 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-mo after stent implantation in all patients and for at least 12-mo in those who did not have a high risk of bleeding. In addition, glycoprotein IIB/IIIA inhibitors were administered in certain patients at the investigator's discretion. Biomarkers and electrocardiograms were recorded at different time points to assure the safety and well-being of patients.

Definitions and study endpoints

Target lesion failure (TLF) is defined as a composite of cardiovascular death, target- vessel myocardial infarction (TV-MI), and clinically driven target lesion revascularization (CD-TLR)[9]. In the following study the primary endpoint was the TLF where the follow-up was taken at the interval of 12-mo and the secondary endpoints were cardiovascular death, TV-MI, clinically driven TLR, stent thrombosis (ST), target vessel failure, target vessel revascularization where the follow-up was taken at 12-mo, 3-year, and 5-year. The composite of cardiac death, target lesion-revascularization and myocardial infarction is defined as major adverse cardiac event (MACE). ST was also evaluated in this study which was classified according to the definitions of the academic research consortium[10]. Device success was defined as the successful delivery and deployment of the study stent at the intended target lesion, as well as the successful withdrawal of the delivery system, with final in-stent residual diameter stenosis of < 30% of all treated lesions, as determined by visual inspection or quantitative coronary angiography. Procedural success was defined as the delivery and deployment of the study stent at the intended target

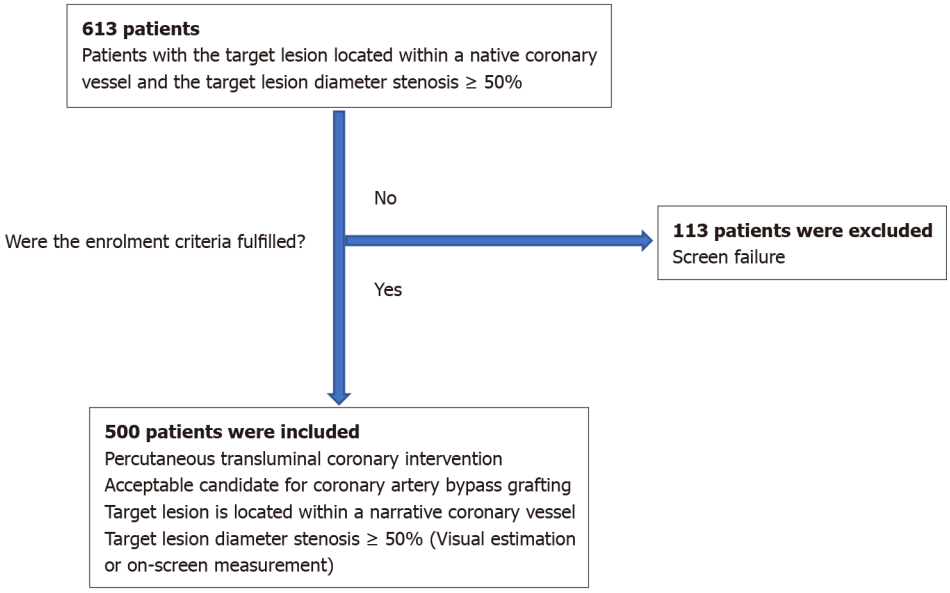

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Figure 1 Patient selection criteria flowchart.

lesion, as well as the withdrawal of the delivery system, with a residual diameter stenosis of less than 30% as determined by visual inspection or quantitative coronary angiography, and no in-hospital major adverse cardiac event (death, MI, or repeat coronary revascularization of the target lesion)[11,12].

Sample size and statistical analysis

A sample size of 500 subjects was calculated based on the primary endpoint of the study. Categorical variables were summarized by frequency distribution for each categorical component (relative frequencies and percentage). All the analysis were done by using statistical package for the social sciences (SPSS) v.20. Results were reported as mean ± standard deviation for continuous variables and as number (%) for nominal variables. For changes in pre–post differences, Wilcoxon-test was used for ordinal variables and paired t-test for continuous variables. Other variables frequency was compared using the chi-square test or fisher's exact test. Result was significant at $P < 0.05$. For time-to-event variables, survival curves were represented using Kaplan Meier estimates.

RESULTS

Baseline demographics characteristics

Baseline demographics and clinical characteristics are summarized in Table 1. The data for 500 patients were collected retrospectively at 12-mo, 3-year, and 5-year. The average age of the study patients was 59.30 ± 11.27 years, with the majority being male (70.2%). The most frequently occurring comorbidities were hypertension (43.4%), smoking (40.6%), diabetes mellitus (14%), alcoholic (9.6%), and dyslipidemia (3.4%). History of myocardial infarction was found in 54.8% followed by CAD (4.8%), PCI (4.2%) and stroke (1.8%). Out of 500 patients, 299 (59.8%) were having stable angina and 201 (40.2%) patients with unstable angina.

Clinical outcomes

Lesion details are mentioned in the Table 2. Total 729 lesions were identified and 730 stents were deployed to treat the lesion. The average stent length and diameter was 26.03 ± 10.86 mm and 3.06 ± 0.41 mm. The device success rate were observed to be 100%.

The cardiac event rate associated with the use of FlexyRap® DES at the follow-up of 12-mo, 3-year, and 5-year is presented in Table 3. Total 2 (0.4%) patients experienced MACE during 5-year. The MACE rate at 12-mo, 3-year, and 5-year follow-up was 1 (0.2%), 0 (0%), and 1 (0.2%) respectively with 0 (0%) cardiovascular death, 2 (0.4%) TV-MI and 0 (0%) TLR compositely. Furthermore, late stent thrombosis was found in 2 (0.4%) patients at 12-mo follow-up, very late stent thrombosis was observed in 2 patients (0.4%) at 3-year follow-up. The Kaplan-Meier method was used to conduct a time-to-event analysis, which showed a 98.8% result (Figure 2).

Table 1 Demographic baseline and clinical characteristics

Characteristics	FlexyRap® cobalt chromium rapamycin eluting coronary stent system; Number of patients, (*n* = 500)
Patient demographics	
Age, yr (mean ± SD)	59.30 ± 11.27
Male, *n* (%)	351 (70.2)
Female, *n* (%)	149 (29.8)
Heart rate (mean ± SD)	86.36 ± 11.34
Systolic blood pressure (mean ± SD)	133.57 ± 20.88
Diastolic blood pressure (mean ± SD)	83.36 ± 9.70
Haemoglobin (g/dL) (mean ± SD)	12.64 ± 2.45
Platelet count (mean ± SD)	205.85 ± 52.19
Baseline medical history, *n* (%)	
Hypertension	217 (43.4)
Smoking current	203 (40.6)
Diabetes mellitus	70 (14)
Alcohol current	48 (9.6)
Dyslipidemia	17 (3.4)
Previous MI	274 (54.8)
History of CAD	24 (4.8)
Previous PCI	21 (4.2)
Previous Stroke	9 (1.8)
Baseline cardiac history, *n* (%)	
Stable angina	299 (59.8)
Unstable angina	201 (40.2)
Angina class, *n* (%)	
Class I	12 (2.4)
Class II	30 (6)
Class IIA	1 (0.2)
Class IIB	12 (2.4)
Class IIC	6 (1.2)
Class III	198 (39.6)
Class IIIA	15 (3)
Class IIIB	51 (10.2)
Class IIIC	37 (7.4)
Class IV	138 (27.6)
Disease vessel, *n* (%)	
Single vessel	314 (62.8)
Double vessel	150 (30)
Triple vessel	27 (5.4)
Quadra vessel	9 (1.8)
LVEF (mean ± SD)	52.88 ± 15.46
Serum creatinine (mean ± SD)	1.47 ± 0.47

CABG: Coronary artery bypass graft; CAD: Coronary artery disease; LVEF: Left ventricular ejection fracture; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

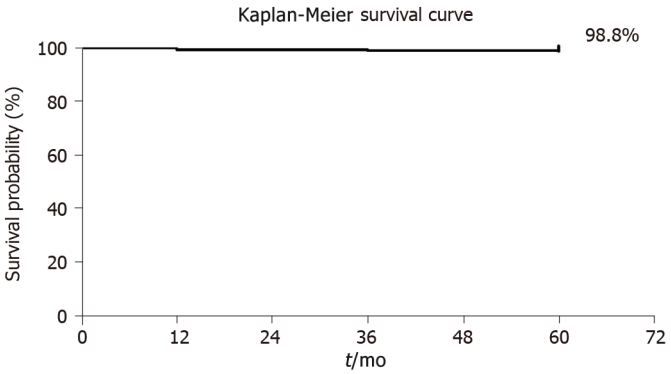

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Figure 2 Time-to-event curve at up to 5-year follow-up by Kaplan-Meier method.

DISCUSSION

In the proposed retrospective study, the FlexyRap® DES has showed exceptional positive results in the patients with *de novo* obstructive native CAD including high procedural success and clinical performance. The patient population had hypertension (43.4%), smoking (40.6%), diabetes mellitus (14%), previous myocardial infarction (54.8%), alcoholism (9.6%), and dyslipidemia (3.4%).

As per the observed study, FlexyRap® cobalt-chromium rapamycin-eluting coronary stent system consisting of drug/polymer coated balloon expandable stent is premounted on rapid exchange PTCA balloon catheter. The polymers are biodegradable, biocompatible, and bioresorbable. Degradation of these materials has been thoroughly studied and has been shown to be safely resorbed by the body after implantation. Rapamycin belongs to a class of therapeutic agents known as macrocyclic lactone or macrolide. It's a cytostatic drug and an immunosuppressant. Rapamycin inhibits T cell activation and growth in response to antigenic stimuli and cytokines such as IL-3, IL-4, and IL-15 are inhibited through a unique mechanism that differs from other immunosuppressive agents. It has been noted that a variety of elements, including the design of the stent, thickness of its struts, antiproliferative agent used, release dynamics of the drug, the duration of drug release, and the type of polymer, can have an impact on the safety and effectiveness of coronary stent system[13]. The first-generation stent were constructed with bulky stent frameworks, making their delivery quite difficult[14]. However, the newest generation boasts thin struts and has demonstrated an 8% increase in its nominal pressure to rated burst pressure. These latest-generation FlexyRap® DES offer improved ease of delivery and vessel conformability, resulting in full deployment and proper placement against the vessel wall. Its design minimizes balloon overhang, reducing the likelihood of edge dissection or injury - a typical procedural issue in PCI. The results of the study, where procedural success was accomplished in all patients, support these claims. Compared to bare metal stent, the first-generation DES featuring a long-lasting polymer have been successful in lowering the rate of re-narrowing, but they have a higher incidence of late ST[15].

Also, the FlexyRap® has the advantage of not cracking, webbing, clumping, or adhering to the balloon surface, making it a promising option for coronary applications. The finding of 100% procedural success in this study can be attributed to these favorable product features.

Iglesias *et al*[16], compared the safety and effectiveness of ultrathin strut biodegradable polymer sirolimus-eluting stents (BP-SES) with thin strut durable polymer everolimus-eluting stents in patients experiencing acute ST-segment elevation myocardial infarction (STEMI). The results showed that 25 (4%) out of 649 patients who received (BP-SES) biodegradable polymer sirolimus-eluting stents and 36 (6%) out of 651 patients who received durable polymer everolimus-eluting stents (DP-EES) experienced TLF. Shetty *et al*[17], conducted a study illustrating the late-term clinical outcomes among patients treated with ultrathin strut BP-SES and thin-strut DP-EES where significant differences in target vessel MI and target lesion revascularization was observed. Out of 884 patients with BP-SES, target lesion failure was observed in 8.2% of patients, and 13.6% of patients shown up with TLF for DP-EES out of 450 patients[17]. Dani *et al*[8], assessed the comparative performance of a BP-SES compared with a DP-EES in the treatment of calcified or narrow vessel blockages. A total of 1553 patients were implanted with BP-SES and 784 patients with DP-EES with the validation of 12-mo follow-up. TLF and TV-MI were significantly lower in BP-SES than in DP-EES in non-small vessel lesions. In the patients with TLF, calcified lesions and cardiac death were numerically higher in DP-EES than in BP-SES. Similarly, the outcomes of the proposed study are comparable with the other studies where TLR was not observed in

Table 2 Procedural characteristics

Procedural characteristics (*n* = 500)	
Lesion details	
Total number of lesions treated with FlexyRap® (*n*)	730
Total number of stents deployed (*n*)	730
Total stent per lesion (*n* = 500 patients) (Total no. stent deployed (730)/Total lesion locations (729)	1.001
Total lesion per vessel (*n* = 500 patients); Total lesion locations (729)/(Sum of total No of diseased vessel (731)	0.997
Lesion locations (729) *n* (%)	
D1	6 (0.82)
Distal LAD	17 (2.33)
Distal LCx	4 (0.54)
Distal RCA	16 (2.19)
LAD	279 (38.27)
LCx	98 (13.44)
LM	1 (0.13)
MID LAD	19 (2.6)
MID LCx	9 (1.23)
MID RCA	15 (2.05)
O Mid	7 (0.96)
OM	4 (0.54)
OM1	8 (1.09)
OM2	6 (0.82)
OM3	1 (0.13)
OMI	1 (0.13)
Osteoproximal LAD	2 (0.27)
Osteoproximal RCA	4 (0.54)
PDA	7 (0.96)
PLV	3 (0.41)
Proximal LAD	23 (3.15)
Proximal RCA	15 (2.05)
Proximal LCx	7 (0.96)
PTCA	8 (1.09)
Ramus intermedius	8 (1.09)
RCA	156 (21.40)
RCX	2 (0.27)
PLB	2 (0.27)
POM	1 (0.13)
Stent length (mean ± SD)	26.03 ± 10.86
Stent diameter (mean ± SD)	3.06 ± 0.41
Type of stenosis, *n* (%)	
de novo	500 (100)

Thrombus load (n = 731), n (%)	
None	519 (71)
Mild	90 (12.31)
Moderate	59 (8.07)
Severe	63 (8.62)
Lesion type [ACC/AHA classification] (n = 731), n (%)	
Type A	20 (2.73)
Type B1	193 (26.40)
Type B2	302 (41.31)
Type C	216 (29.55)
Stent balloon inflation pressure (atm) (mean ± SD) (n = 500)	12.52 ± 1.75
TIMI FLOW n (%)	
II	9 (1.8)
III	491 (98.2)
% of occlusion (mean ± SD) (n = 500)	88.60 ± 8.79
All values are presented in n (%) or mean ± SD	

ACC/AHA: American college of cardiology/American heart association; LAD: Left anterior descending artery; LCx-: Left circumflex; LM: Left main; OM: Obtuse marginal artery; PDA: Patent ductus arteriosus; PLV: Posterior left ventricular artery; PTCA: Percutaneous transluminal coronary angioplasty; PLB: Posterolateral branch; POM: Medial preoptic nucleus; RCAL Right coronary arterial ligation; RCX: Right Circumflex artery; SD: Standard deviation; TIMI: Thrombolysis in myocardial infarction.

Table 3 Cardiac event rate, *n* (%)

Clinical event	12-mo (n = 500)	3-yr (n = 500)	5-yr (n = 500)
TLF	0 (0)	0 (0)	0 (0)
Cardiovascular Death	0 (0)	0 (0)	0 (0)
TV-MI	1 (0.2)	0 (0)	1 (0.2)
Clinically-driven TLR	0 (0)	0 (0)	0 (0)
Late ST	2 (0.4)	0 (0)	0 (0)
TVF	0 (0)	0 (0)	0 (0)
TVR	0 (0)	0 (0)	0 (0)
Very late ST	0 (0)	2 (0.4)	0 (0)
Total MACE	1 (0.2)	0 (0)	1 (0.2)

MACE: Major adverse cardiac event; TLF: Target lesion failure; TV-MI: Target vessel myocardial infarction; TLR: Target lesion revascularization; ST: Stent thrombosis; TVF: Target vessel failure; TVR: Target vessel revascularization.

the patients and the TV-MI in 0.4% of the patients at the cumulative follow-up of 5-year demonstrating the successful clinical outcomes of the study device.

At the end of the 5-year analysis period, cumulative cardiac events presented with 0.4% of MACE where 0 (0%) cardiovascular death, 2 (0.4%) TV-MI, and 0 (0%) TLR was observed compositely, with 0.4% of late ST and 0.4% of very late ST. The unique configuration of the radial star segments and the minimal thickness of the struts ensure exceptional radial stability, facilitating the smooth navigational progress of the device through the circulatory system. Additionally, the decline in the occurrence of cardiac incidents is likely due to the biodegradable polymer's non-inflammatory properties and optimal drug release kinetics[17]. A decreased thickness of stent struts has been linked to a lower frequency of ST[8]. The main benefit of the study was that it was a 5-year follow-up thus the results were sustained in well- designed with longer follow-up duration. The positive outcomes seen in this study could be attributed to the unique design features of the product, such as the advanced stent design utilizing a

biodegradable polymer that offers strong radial strength, reduced overhang from the balloon, low recoil, and consistent support. The device and procedural success rate were 100% for the patients implanted with FlexyRap® DES. The survival probability of 98.8% was observed.

One significant drawback of this study was its observational design and examination of retrospective data. However, this approach provides a more accurate representation of a diverse patient population, unlike randomized trials with strict criteria for enrollment.

CONCLUSION

In conclusion, the present PMCF study offers evidence regarding the safety, and effectiveness of the FlexyRap® rapamycin-eluting stent for treatment of *de novo* CAD. In the present study, FlexyRap® DES was found to have clinical benefits in treating patients with CAD in a real-world setting.

ARTICLE HIGHLIGHTS

Research background

Drug-eluting stents manufactured with biodegradable polymers (BP-DES) effectively reduce restenosis and the risk of stent thrombosis.

Research motivation

The motivation of the present study is focused on the safety and effectiveness from the stent eluting rapamycin for treating the *de novo* coronary artery disease (CAD).

Research objectives

Our study evaluates the safety and effectiveness of FlexyRap® DES at the 5-year clinical response in real-world settings. The outcome of the study proved to be viable, safe, and efficacious results of the FlexyRap®, rapamycin-eluting stent for treating *de novo* CAD, indicating low rates of events and ST at 5-year follow-up.

Research methods

Findings from a retrospective, multi-center, observational, post-market clinical follow-up study of individuals treated with FlexyRap® DES for *de novo* CAD. During the 12-mo follow-up, the primary endpoint was to determine the rate of target lesion failure (TLF). TLF was established as the culmination of three events: Death caused by cardiovascular issues, a myocardial infarction in the target vessel, and the requirement for revascularization of the target lesion due to clinical findings.

Research results

The major adverse cardiac event rate at 12-mo, 3-year, and 5-year follow-up was 1 (0.2%), 0 (0%) and 1 (0.2%) respectively with 0 (0%) cardiovascular death, 2 (0.4%) TV-MI and 0 (0%) TLR compositely. Furthermore, late stent thrombosis was found in 2 (0.4%) patients at the follow-up of 12-mo, very late stent thrombosis was observed in 2 patients (0.4%) at 3-year follow-up.

Research conclusions

In conclusion, this PMCF study investigated the preliminary indications of the feasibility, safety, and effectiveness of using the FlexyRap® rapamycin-eluting stent for treating *de novo* lesion in CAD. In the present study, FlexyRap® DES was found to have clinical benefits in treating patients with CAD in a real-world setting.

Research perspectives

To improve the inner luminal diameter and decrease the likelihood of repeat blockages in the treatment of *de novo* lesions in the native coronary arteries.

FOOTNOTES

Author contributions: Vani P concept and study design, Neuss M, Garg N, Chawla R, Tandon V, Garg D, Parshottam N performed the research; All authors have reviewed and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the OM Institutional Ethics Committee.

Informed consent statement: As per ICH guidelines - E6 (R2/4.8), there is a need to obtain informed consent from subjects in the case of prospective/RCT/Observational clinical studies/investigations. However, in the case of Retrospective post-market clinical follow-up studies, where data collection is done from the hospital records, the permission for the patient (Anonymous) data collection shall be taken from the E/IRB/Head of the Institution from the medical records and not mandatorily requires Informed consent from the patient.

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