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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Cohort Study

Safety and performance of the EverPro™ everolimus-eluting coronary stent system with biodegradable polymer in a real-world scenario

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Author contributions: Vani P, Patel A, and Salgotra V designed the study; Trimukhe R was involved in data collection, analysis and interpretation; all authors were involved in drafting, reviewing and approved the final version of the manuscript.

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Conflict-of-interest statement: Vani P, Patel A, Salgotra V are employees of Sahajanand Laser Technology Ltd., and Dr. Trimukhe R is an employee of Atma Malik Hospital. The authors do not have any other conflicts of interest to declare.

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Abstract

BACKGROUND

The EverPro™ (Sahajanand Laser Technology Ltd., India) everolimus-eluting coronary stent system (EES) is a second-generation drug-eluting stent with a biodegradable polymer.

AIM

To determine the safety and performance of the EverPro™ EES in patients with coronary artery disease (CAD) during a 1-year clinical follow-up.

METHODS

This observational, retrospective, single-center study enrolled patients who had been implanted with the EverPro™ stent between June 1, 2018 and January 31, 2019, and had completed a 1-year follow-up period after the index procedure. The primary clinical endpoint was major adverse cardiac events (MACE) at 6 mo defined as the composite of cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR). Secondary endpoints were the incidence of TLR at 1, 6 and 12 mo follow-up, MACE at 1 and 12 mo follow-up, and stent thrombosis up to 1 year after the index procedure.

RESULTS

The study population comprised 77 patients (98 lesions). A total of 37 (48.1%) patients had comorbid hypertension. In total, 26 (33.8%) patients presented with ST segment elevation MI and 10.4% patients with non-ST segment elevation MI. Treated lesions were located mainly in the left anterior descending artery (49%)

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followed by the right coronary artery (29.6%), left circumflex (12.2%) and obtuse marginal (9.2%) arteries. The majority of patients were with single-vessel disease (79%), 22.2% of lesions had a mild to severe thrombus load, and 94.9% were American College of Cardiology/American Heart Association type B or C. *De novo* stenting was performed in 96.9% of patients and 3% were treated for in-stent restenosis. Procedural success was attained in all patients. In-hospital or follow-up MACE and stent thrombosis were not reported during the 1-year follow-up period.

CONCLUSION

These findings suggest that the EverPro™ EES is a safe and effective treatment option with no MACE or stent thrombosis reported during the 1-year study period in patients with CAD.

Key Words: Coronary artery disease; Everolimus; Major adverse cardiac event; Retrospective, EverPro™, Myocardial infarction

Core Tip: New-generation drug-eluting stents (DES) reduce the risk of stent thrombosis. However, the everolimus-eluting coronary stent system (EES) exerts higher interaction with rapamycin complex 2, higher bioavailability, shorter half-life than sirolimus, decreases vascular inflammation and promotes rapid endothelialization; therefore, outperforms paclitaxel DES in safety and efficacy. EverPro™, a second-generation EES with a biodegradable polymer and a 60 μm cobalt-chromium platform design, facilitates reduction in intra-arterial injury. This observational study enrolled 77 patients with coronary artery disease (CAD), implanted with the EverPro™ stent who completed a 1-year follow-up period after the index procedure. Our findings suggested that EverPro™ EES is safe and effective with no major adverse cardiac events/stent thrombosis during the 1 year follow-up period in patients with CAD.

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INTRODUCTION

The incidence of coronary artery disease (CAD) has been increasing, causing significant morbidity and mortality worldwide[1]. Percutaneous coronary intervention is an increasingly performed revascularization modality for the treatment of CAD. It aims to restore blood supply to myocardial tissues with poor blood supply due to coronary stenosis or vessel occlusion.

Bare-metal stents (BMS) have demonstrated superior clinical outcomes over balloon angioplasty, but neointimal hyperplasia and restenosis are the major challenges in BMS technology. Evidence suggests that revascularization rates have markedly decreased with the use of drug-eluting stents (DES) compared to BMS[2-4], but the risk of late stent thrombosis was the major limitation of the first-generation of DES. Second-generation DES were designed to reduce stent thrombosis and maintain good acute and long-term results. Advances in DES technology, such as new polymers, novel platform material and structure, alteration in coating distribution or additional coating and better antiproliferative drugs, have resulted in the development of new generations of DES.

Polymer composition and stent strut thickness are important factors affecting the clinical outcomes of DES. First-generation DES were manufactured from durable polymer and had thick struts which trigger the inflammatory process and induce stent thrombosis, while the new-generation DES employ biocompatible polymers that will be fully resorbed by hydrolysis after drug release. The strut thickness greatly differs

among the available biodegradable polymer DES and thinner struts reduce vessel wall injury, decrease inflammation and promote faster endothelialization[5]. The strut thickness of new-generation biodegradable polymer stents is half of that in the first-generation biodegradable polymer DES[6]. Therefore, new-generation DES reduce the risk of stent thrombosis compared with first-generation DES, particularly very late stent thrombosis that can occur after discontinuation of dual antiplatelet agents[4]. Coronary stent systems with metal alloys and biodegradable polymers show similar clinical outcomes compared with durable polymer DES[7-9].

Antiproliferative drugs in the second-generation DES belong to the "limus family" (sirolimus, everolimus, zotarolimus) that inhibit mammalian target of rapamycin, and everolimus is known to exert much higher interaction with rapamycin complex 2. This interaction blocks protein synthesis and arrests cell cycle progression, inhibits smooth muscle cell proliferation and reduces stent restenosis. Everolimus has higher bioavailability and a shorter half-life than sirolimus; it decreases vascular inflammation and promotes rapid endothelialization. Everolimus-eluting stents have outperformed paclitaxel DES, and outcomes are comparable with zotarolimus- and sirolimus-eluting stents in terms of safety and efficacy as shown in various clinical studies[10-12]. The EverPro™ everolimus-eluting coronary stent system (EES) is an approved coronary stent system with a biodegradable polymer. It has an ultra-thin (60 μm) cobalt-chromium platform design that facilitates a reduction in intra-arterial injury. The present post-marketing surveillance study aimed to determine the safety and performance of the EverPro™ EES in patients with CAD during the 1-year clinical follow-up.

MATERIALS AND METHODS

Study design

In this single-center, observational study, consecutive patients who were implanted with the EverPro™ stent between June 1, 2018 and January 31, 2019 at The Atma Malik Hospital, Maharashtra, India, and who completed 1-year follow-up were retrospectively selected from June 2019 to January 2020. The study protocol was approved by an independent ethics committee (Sangini Hospital Ethics Committee on June 8, 2020), and a waiver of informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki and the principles of good clinical practice, CTRI/2020/07/026564.

Patient selection

All patients aged > 18 years and implanted with EverPro™ stents to treat CAD were included. Patients treated with stents other than the EverPro™ stent during the index procedure, pregnant/lactating women, and those with grade III renal insufficiency, left ventricular ejection fraction < 30%, history of cardiac failure, structural heart disease, cardiomyopathies, or arrhythmia were excluded. A detailed description of the inclusion and exclusion criteria is provided in Figure 1.

Device description

The EverPro™ (Sahajanand Laser Technologies Ltd., India) EES is an approved DES comprising a biodegradable polymer and surgical grade cobalt-chromium L605 alloy, everolimus as the active pharmaceutical ingredient and poly-l-lactide (PLLA) and poly-dl-lactide-co-glycolide (PLGA) as the drug carrier. PLLA and PLGA in the EverPro™ EES slowly and gradually erode within six months into small molecules, and are metabolized and excreted as carbon dioxide and water. The design of the everolimus-eluting coronary stent is an 8-crown laser cut hybrid design that provides uniform vessel scaffolding and drug distribution (Figure 2).

Study procedure and data collection

The indications for the angioplasty procedure and stent implantation were at the discretion of the treating physicians per the standard treatment guidelines. Baseline patient data, including age, gender, medical history, angina status, and clinical presentation were collected retrospectively from inpatient and outpatient clinical notes, angiogram reports, and procedural angiographic images and discharge summaries. Routine laboratory data including cardiac biomarkers, blood chemistry, and 12-lead electrocardiogram were also collected. The data from the paper case report forms were translated to a central database that was used for the final analysis. The

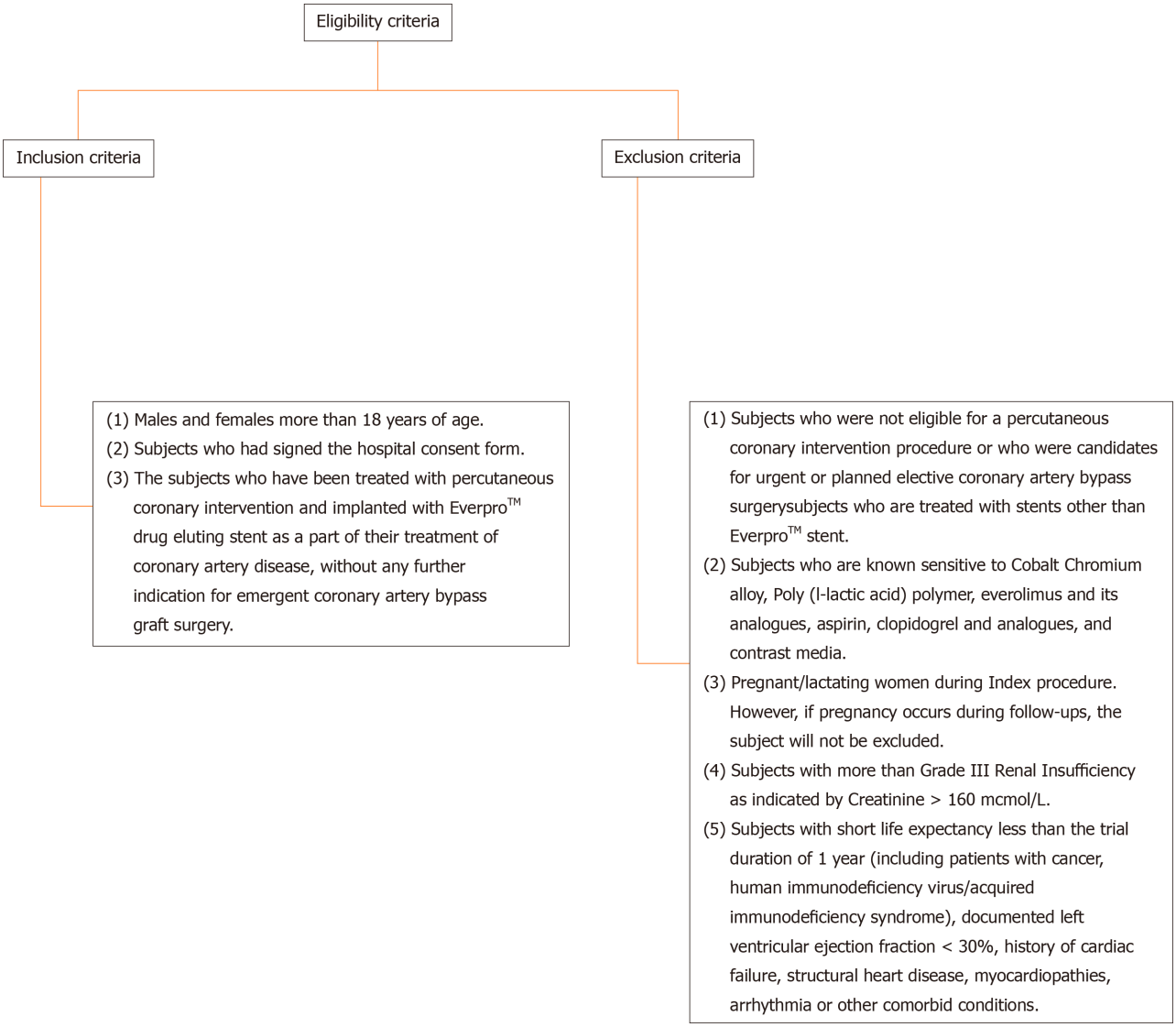

Figure 1 Eligibility criteria for the study.

follow-up data of patients attending the clinic were extracted from their medical records. A few patients were followed up by telephone and asked a list of questions from a structured questionnaire to determine the exact status of the endpoint. We excluded patients with incomplete medical notes or those who did not respond to telephonic follow-ups.

Study endpoints and definitions

The primary clinical endpoint of this study was major adverse cardiac events (MACE) at 6-mo follow-up. MACE was defined as a composite of cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR). The secondary endpoints consisted of TLR at 1, 6 and 12 mo follow-up, MACE at 1, and 12 mo follow-up, and the frequency of stent thrombosis up to 1 year after the date of stent implantation. The outcomes of stent thrombosis were further divided into definite, probable, and possible stent thrombosis, as defined by The Academic Research Consortium[13,14]. Cardiac death was considered in the case of any death owing to cardiac cause (MI, low output failure and lethal arrhythmia), unobserved death, death due to unknown reasons, and all procedure-related deaths, including those associated with concomitant treatment. MI was defined as an increase in cardiac troponin values [> 5 × 99th percentile upper reference limit (URL)] in patients with normal baseline values (≤ 99th percentile URL) or an increase in cardiac troponin values of > 20% when the baseline values were elevated and stable, or declining. Pathological Q waves were defined as per amplitude, location, and depth if they were present in at least two contiguous leads. Restenosis within the stent or in the 5-mm distal or proximal to the stent was considered to require TLR. Stenosis in any segment of the treated vessel was defined

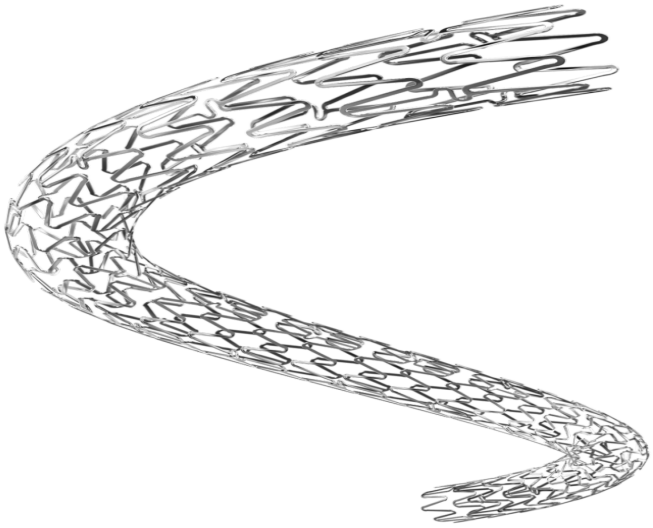

Figure 2 Design of the everolimus-eluting coronary stent.

as target vessel revascularization. The incidence of stent thrombosis was considered acute if it occurred within 24 h, sub-acute if it occurred between 1 and 30 d, and late if it took place after 30 d. Any symptoms suggestive of an acute coronary syndrome and angiographic or pathological confirmation were termed as definite stent thrombosis. Any unexplained death within 30 d or target vessel MI without angiographic confirmation of stent thrombosis was described as probable stent thrombosis. Unexplained death after 30 d was described as possible stent thrombosis.

Statistical analysis

All calculations were based on the available data and missing data were excluded from the calculations. Categorical data are presented as frequency and percentages. Continuous variables are presented as the mean ± standard deviation (SD). The data were analyzed using the Statistical Package for Social Sciences program (SPSS Inc., Chicago, IL, United States), version 23.

As no hypothesis was tested in the study, we did not perform formal sample size calculation and included patients who met the eligibility criteria during the stipulated time.

RESULTS

Baseline demographic and clinical characteristics

The total study population comprised 77 patients (98 lesions). Baseline demographic and clinical characteristics are shown in Table 1. The mean (SD) age of patients was 55 ± 11.8 years, and 77% were men. A total of 48% of patients had comorbid hypertension, 19.4% had diabetes, and 31% were smokers. The majority of patients presented with MI (44.2%) followed by stable angina in 39%. The majority of patients had single-vessel disease (79%).

Procedural and lesion characteristics

A total of 102 lesions were detected in these patients, and 98 lesions were treated by implantation of the EverPro™ stent. Treated lesions were located mainly in the left anterior descending artery (49%), followed by the right coronary artery (29.6%), left circumflex (12.2%) and obtuse marginal (9.2%) arteries. Approximately 22.2% of lesions had a mild to severe thrombus load and 94.9% lesions were American College of Cardiology/American Heart Association type B or C. *De novo* stenting was performed in 96.9% of patients and 3% were treated for in-stent restenosis. Procedure-related details are shown in Table 2. Procedural success was attained in all patients with no in-hospital MACE. All patients were prescribed antiplatelet agents at discharge (Table 2).

Table 1 Baseline demographics and clinical characteristics

Characteristics	*n* = 77
Age (mean ± SD), yr	55 ± 11.8
Men, *n* (%)	59 (76.6)
Medical history, *n* (%)	
Hypertension	37 (48.1)
Diabetes	15 (19.48)
Smoking	24 (31.2)
Consumption of alcohol	9 (11.7)
Stroke	2 (2.6)
Previous coronary intervention	4 (5.2)
Previous myocardial infarction	34 (44.2)
Cardiac status, *n* (%)	
Stable angina	30 (39)
Unstable angina	13 (16.9)
STEMI	26 (33.8)
NSTEMI	8 (10.4)
Coronary angiogram finding, *n* (%)	
Single-vessel disease	61 (79.2)
Double-vessel disease	16 (20.8)
Triple-vessel disease	0 (0.0)
Heart rate (mean ± SD), bpm	81.26 ± 12.08
Systolic blood pressure (mean ± SD), mmHg	134.91 ± 27.51
Diastolic blood pressure (mean ± SD), mmHg	83.19 ± 13.57
Serum creatinine (mean ± SD), mg/dL	1.13 ± 0.23
LVEF (mean ± SD), %	46.38 ± 8.19

LVEF: Left ventricular ejection fraction; NSTEMI: Non-stent thrombosis segment elevation myocardial infarction; SD: Standard deviation; STEMI: Stent thrombosis segment elevation myocardial infarction; bpm: Beats per minute.

Clinical outcomes during follow-up

MACE and stent thrombosis were not observed in any patient throughout the 1-year follow-up period.

DISCUSSION

This post-marketing surveillance study was performed to determine the safety and performance of EverPro™ stents for the treatment of CAD in a real-world clinical setting. The results of this study show that the EverPro™ stent was not associated with MACE or TLR. In addition, stent thrombosis was not observed during the 1-year follow-up period.

The clinical performance and safety of everolimus-eluting stents in the treatment of CAD have been well documented. The series of SPIRIT clinical trials demonstrated the superior efficacy of EES over BMS and paclitaxel-eluting stents[10]. Furthermore, a meta-analysis of the final results of SPIRIT II, III, and IV clinical trials demonstrated that EES was superior to paclitaxel-eluting stents in reducing target lesion failure (8.9% *vs* 12.5%, $P = 0.0002$), all-cause mortality (3.2% *vs* 5.1%, $P = 0.003$), MI (3.2% *vs* 5.1%, $P = 0.002$), cardiac death or MI (4.4% *vs* 6.3%, $P = 0.005$), ischemia-driven TLR (6.0% *vs* 8.2%, $P = 0.004$), stent thrombosis (0.7% *vs* 1.7%, $P = 0.003$), and MACE (9.4% *vs* 13.0%,

Table 2 Procedural and lesion characteristics

Characteristics	*n* = 77
Access site approach, *n* (%)	
Femoral	20 (26)
Radial	57 (74)
Total number of lesions	102
Total number of lesions treated with EverPro™	98
Lesions per patient	1.32
Stents per patient	1.27
Lesion location, *n* (%)	
Right carotid artery	29 (29.6)
Left anterior descending artery	48 (49)
Left circumflex artery	12 (12.2)
Obtuse marginal artery	9 (9.2)
Stenosis type, *n* (%)	
De novo	95 (96.9)
In-stent	3 (3.1)
Thrombus load, *n* (%)	
None	76 (77.6)
Mild	10 (10.2)
Moderate	5 (5.1)
Severe	7 (7.1)
ACC/AHA lesion type, *n* (%)	
A	5 (5.1)
B1	30 (30.6)
B2	38 (38.8)
C	25 (25.5)
Percent stenosis (mean ± SD)	88.39 ± 9.30
Stent length (mean ± SD), mm	18.20 ± 4.34
Stent diameter (mean ± SD), mm	2.89 ± 0.36
TIMI flow post-procedure, *n* (%)	
TIMI 3	98 (100)
Discharge medications, *n* (%)	
Aspirin	77 (100)
Clopidogrel	44 (57.1)
Ticlopidine	2 (2.6)
Prasugrel	3 (3.9)
Ticagrelor	27 (35.1)

ACC: American College of Cardiology; AHA: American Heart Association; SD: Standard deviation; TIMI: Thrombolysis in myocardial infarction.

P = 0.0002)[11]. The safety and efficacy of EES have also been demonstrated in selected high-risk patients in real-world studies. The XIENCE V United States trial evaluated 5054 participants, and 98.1% reached the 1-year follow-up. No stent thrombosis was observed in standard-risk and high-risk patients even after discontinuation of dual antiplatelet therapy after 6 mo[15]. EES have been compared with sirolimus-eluting stents, and at 5 years, MACE (14.0% *vs* 17.4%, respectively) and stent thrombosis (0.4% *vs* 2.0%, respectively) rates were found to be lower in the EES group than in the SES group[16]. Clinical studies comparing zotarolimus-eluting stents (ZES) to EES have shown that ZES are non-inferior to EES with regard to death from cardiac causes, MI, or clinically indicated TLR within 1 year. However, the rate of stent thrombosis was higher with ZES than with EES (2.3% *vs* 1.5%)[17]. In a meta-analysis, compared to paclitaxel and sirolimus, EES were also found to be more efficacious and safe in patients with concomitant diabetes, resulting in a reduction in MACE by 18%, MI by 43%, and stent thrombosis by 46%[18].

The 12-mo MACE rate following implantation of EES ranged from 0.3% to 6.2% for diverse clinical presentations in randomized trials, and real-world studies[19-24]. The 1-year incidence of MACE following treatment with another indigenous biodegradable polymer DEC ranged from 0.9% to 4.2%[25-27]. No MACE was reported during the 1-year follow-up period in our study. The EverPro™ stent has a very thin strut (60 μm) and it is built on a cobalt-chromium L605 alloy platform with SCHIFSORB polymer technology. The biodegradable polymers PLLA and PLGA degrade entirely and reduce the risk of thrombosis. The stent has an innovative "S"- and alternate "C"-linked 8-crown design that enhances flexibility and provides high radial strength. With foreshortening of < 0.2%, it is ideal for all lesion locations, including ostial lesions. Additionally, the utilization of electropolishing technology results in an ultra-smooth stent surface that reduces the risk of edge dissection and very late stent thrombosis. These properties may have contributed to the procedural success and good clinical outcomes observed in this study.

While these data on the use of the EverPro™ stent in the treatment of CAD are very promising, this study is limited by its observational design, retrospective analysis of data, small sample size, and a short follow-up period. Therefore, the results need to be substantiated in well-designed studies with a longer follow-up duration.

CONCLUSION

The findings of this study support the favorable safety and performance of the EverPro™ EES. Product characteristics, such as the conformal coating of everolimus and ultra-smooth stent surface, which provides high radial strength with minimal foreshortening, may be responsible for the results. The EverPro™ EES could be an effective alternative to other contemporary DES for the treatment of CAD.

ARTICLE HIGHLIGHTS

Research background

The increasing prevalence of coronary artery disease (CAD) has caused significantly higher rates of morbidity and mortality worldwide. Thus, percutaneous coronary intervention, a revascularization modality to treat CAD, restores blood supply to myocardial tissues. Antiproliferative drugs in second-generation drug-eluting stents (DES) inhibit mammalian target of rapamycin and affect stent restenosis. However, EverPro™, an approved second-generation everolimus-eluting coronary stent system (EES) with a biodegradable polymer facilitates a reduction in intra-arterial injury.

Research motivation

Sirolimus has a longer half-life, lower bioavailability and does not directly affect stent restenosis. However, everolimus outperforms sirolimus and can decrease vascular inflammation and promote rapid endothelialization. These findings indicate the potential of EES to replace second-generation DES and impart benefits to patients with CAD.

Research objectives

The objectives of this study were to determine the safety and performance of EverPro™ EES in a real-world scenario and to translate its use in the real world as an

effective alternative to DES for the treatment of CAD. The EverPro™ EES could offer various benefits in addition to reduced stent restenosis and rapid endothelialization.

Research methods

This single-center, observational study enrolled patients who completed a 1-year follow-up period after being implanted with the EverPro™ stent (between June 1, 2018 and January 31, 2019). As no hypothesis was tested in the study, we did not perform a formal sample size calculation and included patients who met the eligibility criteria during the stipulated time.

Research results

Of the 102 lesions detected in the included patients, 98 lesions were treated by implantation of the EverPro™ stent. *De novo* stenting was performed in 96.9% of patients and 3% were treated for in-stent restenosis. Procedural success was attained in all patients with no in-hospital major adverse cardiac events (MACE) or stent thrombosis observed throughout the follow-up period. However, the results were limited by the study's observational nature, retrospective data analysis and a shorter follow-up period.

Research conclusions

The results showed that EverPro™ EES is a safe and effective treatment alternative as no MACE or stent thrombosis was observed during the 1-year study period in patients with CAD.

Research perspectives

The data on the use of the EverPro™ stent in the treatment of CAD are very promising. However, if future studies can overcome the study limitation by conducting well-designed studies with a larger sample size and a longer follow-up duration, EverPro™ EES can be used as an alternative to contemporary DES for treating CAD.

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