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Clinical outcomes of ultrathin strut biodegradable polymer-coated everolimus-eluting stent in patients with coronary artery disease

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Original Article

Abstract

BACKGROUND: Evermine 50™ (Meril Life Sciences Pvt. Ltd., India) everolimus-eluting stent system (EES) is a novel ultrathin strut (50 µm) cobalt-chromium coronary drug-eluting stent (DES) platform with biodegradable polymer coating. The Evermine 50 EES-KLES study aimed to evaluate the Evermine 50 EES in terms of 24-month clinical safety and performance in patients with coronary artery disease (CAD).

METHODS: This retrospective study consisted of 171 patients (258 lesions) implanted with Evermine 50 EES for managing CAD. We analyzed the major adverse cardiac events (MACE) incidence, defined as a composite of cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization (ID-TLR) at 6-, 12-, and 24-month follow-up.

RESULTS: A total of 171 patients were included with a mean age of 57.85 ± 10.05 years, of which, 139 (81.29%) were men, 69 (40.35%) were hypertensive, and 70 (40.94%) were diabetic. The incidence of MACE was 1 (0.58%), 3 (1.81%), and 4 (2.42%) at 6-, 12-, and 24-month follow-up, respectively. There were three cases (1.82%) of cardiac death and one case (0.61%) of ID-TLR up to 24 months. None of the patients was presented with definite or probable stent thrombosis (ST).

CONCLUSION: This study demonstrated that implantation of ultrathin strut Evermine 50 EES resulted in a low rate of incidence of MACE, indicating a favourable clinical safety and performance profile of Evermine 50 EES in patients with CAD [Clinical Trials Registry-India (CTRI) Number: CTRI/2017/09/009939)].

Keywords: Coronary Artery Disease; Drug-Eluting Stent; Everolimus; Percutaneous Coronary Intervention

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Introduction

The clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) are notably improved after the introduction of second-generation drug-eluting stents (DES). This improvement could be attributed to a reduced risk of restenosis, myocardial infarction (MI), and stent thrombosis (ST) by second-generation DES. As a result, quality of life was better in patients with coronary artery disease (CAD) implanted with second-generation DES as compared to bare-metal stents (BMS) and first-generation DES. However, the persistent presence of durable polymers in the case of first-generation DES provokes chronic inflammatory responses that may lead to delayed endothelization of the stent and positive vessel remodeling, as a consequence of which, the risk of very late ST (VLST) increased. In addition, rate of ST was elevated in thicker stent strut which disrupts the laminar flow and induces flow turbulence, and thereby, activates platelets due to high shear stress.[1,2] With this, the research focus shifted to develop an ultrathin strut biodegradable polymer DES, which provides similar controlled release of a drug but with subsequent degradation of the polymers. Presently, everolimus-eluting stents (EES), of all the available DES, are the most frequently used. The DESSOLVE III and EXCELLENT trials established the non-inferiority of EES to sirolimus-eluting stents (SES) and superiority to paclitaxel-eluting stents in the meta-analysis of SPIRIT trial series.[3-5]

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The Evermine 50™ (Meril Life Sciences Pvt. Ltd., India) is an ultrathin strut (50 μm) with biodegradable polymer-based EES system. The Evermine 50 EES-KLES study aimed to evaluate the 24-month clinical safety and performance of the Evermine 50 EES in all-comer patients with CAD.

Materials and Methods

The Evermine 50 EES-KLES was a retrospective, single-arm, all-comers, and single-center study conducted at the KLE Academy of Higher Education and Research (KLE University), Belagavi, India, between April 2016 and December 2016. We included all-comer patients aged > 18 years with CAD. Patients with a history of allergic reaction or hypersensitivity to everolimus, heparin, polymer lactide, cobalt-chromium metal alloy, and glycolide anti-platelet drugs (clopidogrel, prasugrel, etc.), and/or those who refused or were not willing to sign informed consent form were excluded from the study.

The study complied with the Declaration of Helsinki and was approved by the institution's local ethics committee. All included patients provided written informed consent. The trial is registered at Clinical Trials Registry-India (CTRI/2017/09/009939).

The Evermine 50 EES, an ultrathin strut (50 μm) that uses a cobalt-chromium platform, has a unique hybrid design of open and closed cells coated with biocompatible and bioabsorbable polymers, poly-L-lactic acid (PLLA), and poly-lactic-co-glycolic acid (PLGA), which elutes 1.25 μg everolimus per square millimeter of the stent surface area. The available lengths of Evermine 50 EES are 8, 13, 16, 19, 24, 29, 32, 37, 40, 44, and 48 mm, and diameters of the same are 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, and 4.50 mm.

Procedures and post-intervention medications: The PCI procedure was performed according to the current standard guidelines.[6] Before catheterization, all patients were administered with aspirin (75-100 mg) and a loading dose of clopidogrel (300 mg). To maintain intra-procedural activated clotting time of > 250 seconds, intravenous heparin (70-100 units/kg) was administered. Dual antiplatelet therapy of clopidogrel (75 mg/day) or prasugrel (10 mg/day) and aspirin (75-150 mg/day) was administered to all patients after the procedure for 1 year. Beyond one year, following the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, patients were switched to mono antiplatelet therapy.[7]

The clinical outcome, major adverse cardiac events (MACE), was defined as a composite of cardiac death, MI, and ischemia-driven target lesion revascularization (ID-TLR) at 6-, 12-, and 24-month follow-up. MI was defined as the presence of ischemic symptoms, elevation in cardiac enzymes, and/or new electrocardiography changes compatible with MI. ID-TLR was defined as repeated PCI or coronary artery bypass grafting of the target vessel associated with ≥ 50% diameter reduction together with documented ischemia. The definition of the Academic Research Consortium was used to classify ST.[8] Procedural success was defined as technical success with no MACE noted within 24 hours of the index procedure.

Baseline characteristics and follow-up: The baseline characteristics assessed included age, sex, medical history, co-morbidities like diabetes mellitus (DM), hypertension (HTN), chronic obstructive pulmonary disease, history of angina, previous MI, coronary heart disease, and indication for percutaneous transluminal coronary angioplasty (stable angina, unstable angina). The left ventricular function was assessed by two-dimensional (2D) echocardiography. Lesion and procedure characteristics included the target vessel locations, CAD (single/double/triple vessel disease), lesion location, and stent length and diameter. The clinical follow-up was performed at 6, 12, and 24 months.

Based on previously-published studies,[9] the sample size was estimated to be 171 patients, assuming MACE proportion about 4%. The sample size of 171 patients provided the following two sided 95% confidence interval with 0.035 half width (Wilson), 5% alpha and a power of 85%. Categorical variables were represented as frequency and percentages. Continuous variables with normal distribution were represented as mean ± standard deviation (SD). Statistical analyses were performed using the SPSS software (version 20, IBM Corporation, Armonk, NY, USA). Event-free survival rates were constructed using the Kaplan-Meier method.

Results

Baseline demographic characteristics: Between April 2016 and December 2016, 171 patients (139 men, mean age: 57.85 ± 10.05 years) were treated for CAD with Evermine 50 EES. Among these patients, 70 (40.94%) had DM and 69 (40.35%) had HTN. Majority of patients presented with ST-elevation MI (STEMI) (n = 75, 43.86%), followed by unstable angina (n = 42, 24.56%). Baseline demographic

characteristics of the included patients are listed in table 1.

Table 1. Baseline demographic characteristics

Characteristics	Patients (n = 171)
Patient demographics	
Age (year) (mean ± SD)	57.85 ± 10.05
Gender (male) [n (%)]	139 (81.29)
Baseline medical history [n (%)]	
DM	70 (40.94)
HTN	69 (40.35)
COPD	2 (1.17)
Family history of CAD	31 (18.13)
History of angina	15 (8.77)
Previous MI	27 (15.79)
Cardiac status before index procedure [n (%)]	
Stable angina	6 (3.51)
Unstable angina	42 (24.56)
STEMI	75 (43.86)
NSTEMI	20 (11.70)
Asymptomatic	28 (16.37)
LVEF (%) (mean ± SD)	49.19 ± 8.32

DM: Diabetes mellitus; HTN: Hypertension; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; MI: Myocardial infarction; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; LVEF: Left ventricular ejection fraction; SD: Standard deviation

Lesion characteristics: A total of 246 studied stents were implanted during the index procedure. Procedural success was obtained in all patients. More than half of the total patients (n = 100, 58.48%) presented single vessel disease while nearly one-third of patients (n = 55, 32.16%) presented double vessel disease and rest of the patients (n = 16, 9.36%) had triple vessel disease. The lesion characteristics at baseline are summarized in table 2.

Clinical outcomes: Clinical follow-up was completed in 165 (96.49%) patients at the 24-month follow-up. MACE was reported in 4 (2.42%) patients including 1 (0.61%) ID-TLR and 3 (1.82%) cardiac deaths at the 24-month follow-up. None of the patients experienced probable or definite ST. The detailed clinical events are illustrated in table 3.

Table 2. Lesion and procedural characteristics

Characteristics	Patients (n = 171)
Target vessel locations [n (%)]	
LAD	121 (49.19)
RCA	67 (27.24)
LCX	55 (22.36)
Left main	3 (1.22)
Lesion characteristics [n (%)]	
Single vessel disease	100 (58.48)
Double vessel disease	55 (32.16)
Triple vessel disease	16 (9.36)
Post-procedure TIMI III flow	258 (100)
Total number of lesions	258
Total number of study stents implanted	246
Stent per patient	1.43
Occlusion (%) (mean ± SD)	88.39 ± 9.30
Average stent length (mm) (mean ± SD)	23.04 ± 7.01
Average stent diameter (mm) (mean ± SD)	3.14 ± 0.37

LAD: Left anterior descending artery; RCA: Right coronary artery; LCX: Left circumflex artery; TIMI: Thrombolysis in myocardial infarction; SD: Standard deviation

The cumulative MACE-free survival, determined by the Kaplan–Meier method, was 97.66% (Figure 1).

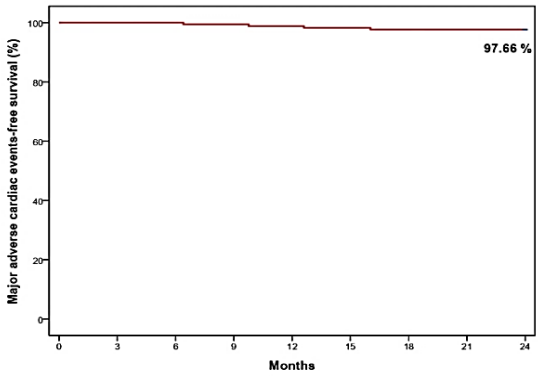

Figure 1. Kaplan-Meier event-free survival rate at 24-month follow-up

Table 3. Cumulative clinical events at 6-, 12-, and 24-month follow-up

Events	6 months (n = 171) [n (%)]	12 months (n = 166) [n (%)]	24 months (n = 165) [n (%)]
All-cause death	4 (2.34)	5 (3.01)	8 (4.85)
Cardiac death	1 (0.58)	2 (1.20)	3 (1.82)
Non-cardiac death	3 (1.75)	3 (1.81)	5 (3.03)
MI	0 (0)	0 (0)	0 (0)
ID-TLR	0 (0)	1 (0.60)	1 (0.61)
ID-TVR	0 (0)	0 (0)	0 (0)
Definite or probable ST	0 (0)	0 (0)	0 (0)
MACE	1 (0.58)	3 (1.81)	4 (2.42)

MI: Myocardial infraction; ID-TLR: Ischemia-driven target lesion revascularization; ID-TVR: Ischemia-driven target vessel revascularization; ST: Stent thrombosis; MACE: Major adverse cardiac events

Discussion

The clinical outcomes of the present study provided confirmation that Evermine 50 EES was safe and effective in all patients with CAD. The possible occurrence of CAD in all-comer patients was due to a high prevalence of DM (40.94%) and HTN (40.35%). Almost one half of patients had double and triple vessel disease. Despite all challenges, procedural success was reported in 100% of cases. Currently, the implantation of DES is the primary treatment choice for coronary artery stenosis.

However, ST has become an important safety issue. Several mechanisms of late ST and VLST have been proposed, including delayed endothelialization, chronic inflammation of arteries, hypersensitivity reactions, and incomplete stent apposition with vessel remodelling. These limitations of BMS and durable polymer DES can be resolved by employing ultrathin strut biodegradable polymer stents.[10-12] Recently, there was an additional confirmation by meta-analysis that newer generation of ultrathin strut DES was related with a 16% reduction in MACE and lower rate of ST as compared to thicker strut DES.[13] Despite the "all-comers" trial design of the present study, the absence of ST and only four patients with MACE at 24-month follow-up showed favourable clinical outcomes of Evermine 50 EES.

The unique design of Evermine 50 EES allows improved arterial healing, reduced blood flow perturbance, faster endothelialisation, and reduced in-stent restenosis.[14,15] In the BIOSCIENCE randomized trial, ultrathin strut biodegradable polymer SES were non-inferior to the reference of thin-strut durable polymer EES in terms of the safety and efficacy of outcomes by the end of 12 months.[16] A previously-reported study demonstrated that the implantations of coronary stents with thinner struts were associated with a reduced risk for angiographic and clinical restenosis when compared to the stent with thick struts.[17] The inflexible stents have resulted in the progression of thicker neointima when compared to flexible stents.[18] Hence, newer ultrathin biodegradable polymer DES was developed to improve the clinical outcomes in a complex type of lesions.

The low incidence of MACE was due to lower severity of disease in approximately 60% of patients at 24-month follow-up (Table 4). ID-TLR and cardiac death were 0.61%, and 1.82%, respectively, and none of the patients experienced any ST at 24-month follow-up. No death was reported due to ST, sudden death, progressive heart failure, and MI.

These 24-month clinical outcomes data demonstrated that apparent clinical benefit was primarily attributable to a reduced risk of MACE rate and ST consequences. However, this conclusion requires further studies with long-term follow-up evidence.

Table 4. Illustrative comparison between the current study population and historic cohorts from previous trials with other drug-eluting stents

Variables	Evermine 50	MiStent[19]	BioMatrix[20]	Nobori[21]	Synergy[22]	Orsiro[22]	Orsiro[23]
Clinical trial	Evermine 50 EES-KLES	DESSOLVE II	COMFORTABLE AMI Trial	NEXT	BIO-RESORT	BIO-RESORT	BIONYX
Number of patients	165	120	575	1617	1172	1169	1245
Strut thickness (µm)	50	64	120	112	74-81	60 or 80	
Polymer type	Biodegradable	Biodegradable	Biodegradable	Biodegradable	Biodegradable	Biodegradable	
Drug	Evermine	Sirolimus	Biolimus	Biolimus	Everolimus	Sirolimus	
Clinical follow-up	24-month	24-month	24-month	24-month	24-month	24-month	
Clinical outcomes [n (%)]							
Cardiac death	3 (1.82)	2 (1.7)	17 (3.0)	37 (2.3)	17 (1.5)	15 (1.3)	20 (1.6)
MI	0 (0.0)	3 (2.5)	7 (1.3)*	59 (3.7)	34 (2.9)	36 (3.1)	39 (3.2)
ID-TLR	1 (0.61)	2 (1.7)#	17 (3.1)	68 (4.4)#	27 (2.4)#	25 (2.2)#	41 (3.4)
ST	0 (0.0)	1 (0.0)	18 (3.2)	27 (1.7)	11 (1.0)	7 (0.6)	13 (1.1)
MACE	4 (2.42)	8 (6.7)	33 (5.8)	--	76 (6.5)	68 (5.8)	107 (8.6)

Clinically driven TLR, *Target-vessel reinfarction

MI: Myocardial infarction; ID-TLR: Ischemia-driven target lesion revascularization; ST: Stent thrombosis; MACE: Major adverse cardiac events

A few limitations of the study need to be acknowledged. First, this was a retrospective, single-center, single-arm study that included a small patient population without a control group for direct comparison. Second, this study provided the safety and efficacy of outcomes of the study stent at short-term follow-up. Third, we did not evaluate the factors associated with MACE in our patients. Hence, further large, prospective, randomized, and multicenter studies are needed to validate the safety and efficacy of Evermine 50 EES.

Conclusion

At the 24-month follow-up, the results depict, the favorable safety and performance of the ultrathin strut biodegradable polymer Evermine 50 EES. However, further evidence in the form of long-term follow-up data or prospective randomized controlled trials is required to compare Evermine 50 EES to the equivalent standard DES.

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Conflict of Interests

Authors have no conflict of interests.

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