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Safety and Clinical Performance of Biodegradable Polymer-Coated Ultra-Thin Everolimus-Eluting Stents in "Real-World" Patients: A Multicenter Registry (PERFORM-EVER)

ORIGINAL INVESTIGATION

ABSTRACT

Background: Tetrilimus (Sahajanand Medical Technologies Limited, Surat, India) is a biodegradable polymer-coated everolimus-eluting stent with cobalt–chromium stent platform and ultra-thin (60 μm) strut thickness. We aimed to report 1-year safety and clinical performance of Tetrilimus everolimus-eluting stent in patients with coronary artery disease in "real-world" clinical practice.

Methods: The PERFORMance of biodegradable polymer-coated ultra-thin EVERolimus-eluting stents was an observational, multicenter, single-arm, and investigator-initiated retrospective registry. All "real-world" patients who had received Tetrilimus everolimus-eluting stent between July-2015 and October-2016 at four study centers were analyzed. The data were collected retrospectively either by extraction from existing databases in consecutive fashion where index and follow-up data existed or the follow-up was obtained by telephonic contact. Primary endpoint was 1-year incidence of target lesion failure, which was defined as a composite endpoint of cardiac death, myocardial infarction, and target lesion revascularization by percutaneous or surgical methods. The Academic Research Consortium-defined stent thrombosis was assessed as additional safety endpoint.

Results: During the study period, 815 Tetrilimus everolimus-eluting stents (1.4 ± 0.5 stent/patient) were implanted to treat 735 coronary lesions (1.1 ± 0.3 stent/lesion) in 594 patients (mean age: 55.6 ± 12.1 years). The cumulative incidence of target lesion failure at 1-year follow-up was 3.7%, which included 9 (1.5%) cardiac deaths, 8 (1.4%) myocardial infarctions, and 5 (0.8%) target lesion revascularizations. There were 5 (0.8%) cases of probable stent thrombosis and 4 (0.7%) cases of possible stent thrombosis at 1-year follow-up.

Conclusion: Low incidences of target lesion failure and stent thrombosis at 1-year follow-up indicates that biodegradable polymer-coated ultra-thin Tetrilimus everolimus-eluting stents may have encouraging safety and efficacy in unselected real-world patients with coronary artery disease, including those with high-risk characteristics and complex lesions.

Keywords: Biodegradable polymer, everolimus-eluting stent, percutaneous coronary intervention, stent thrombosis, target lesion failure, ultra-thin strut

INTRODUCTION

Drug-eluting stents (DES) remain the mainstay in the management of patients with coronary artery disease (CAD).[1] Although they effectively countered the restenosis rates after percutaneous coronary intervention (PCI),[2] concerns still remain about their long-term safety due to late and very late stent thrombosis.[3,4] Polymer coating, stent platform design, and toxicity of active drug are considered potentially relevant factors for the incidents of stent thrombosis after DES implantation. With significant innovations over time, each of these three DES components has been improved to overcome the limitations of prior-generation DES in order to develop a stent with maximal safety and efficacy profiles and improved performance.[1]

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The initial-generation DES (i.e., paclitaxel- and sirolimus-eluting stents) had an identical stent structure to their bare metal stents counterparts, with polymer and eluting drug applied to the surface. Subsequently evolved DES incorporated newer medications (everolimus and zotarolimus), more biocompatible polymers, a cobalt or platinum chromium platform, with thinner struts.[5] While the zotarolimus-eluting stent exhibited an excellent safety profile, its ability to prevent restenosis was similar to that of the paclitaxel-eluting stent and was less effective than the sirolimus-eluting stent.[6] On the other hand, the clinical performance of everolimus is most widely established among all antiproliferative drugs used in DES.[5,7-14] Reports indicate that everolimus-eluting stents (EESs) outperform paclitaxel-eluting stents,[15] and its safety and efficacy profile is similar to that of sirolimus-eluting stent[16,17] and zotarolimus-eluting stents.[18] Further, EESs have demonstrated excellent long-term results in a wide range of patients and lesions including those with diabetes,[17] chronic total occlusion,[19] bifurcation lesion,[20] small vessel lesion,[21] and in-stent restenosis.[22] While everolimus is identified as the safe and highly effective antiproliferative drug, new stent engineering is aimed at improving its means of delivery and, potentially, its safety profile.[6]

Polymeric coatings in DES offer a controlled release of eluting medication, cause gradual degradation of the coating, and monitor the timing of drug delivery.[6] The earlier generation DES comprised durable/permanent polymeric coatings, which were considered to affect the long-term clinical outcomes negatively as the presence of polymer, even after the drug has been eluted, stimulates local inflammatory reaction and delays healing of affected arteries. Subsequently, biodegradable polymers have been developed, which not only provide the efficacy of DES after stenting in the initial period, when the risk of restenosis and stent thrombosis is high, but also offer long-term safety benefits of a bare-metal stent once the polymer has biodegraded.[23,24]

It has also been noted that strut thickness of the stent platforms significantly influence the clinical outcomes as conventional stents with thick strut platforms were found to have worse vessel response.[25] Progressively, thinner strut stents have been developed to enhance the biocompatibility of these stents. Clinical studies have also demonstrated that reduced strut thickness results in lower restenosis rates after stent placement.[25,26] Moreover, thinner struts are also associated with improved stent deliverability, increased flexibility, and clinical performance.[27,28]

Based on these considerations, it can be postulated that the choice of DES should most likely incorporate newer and improved stent components and technology to further enhance safety, efficacy, and clinical performance.[27] Tetrilimus EES is a new-generation coronary stent from Sahajanand Medical Technologies Limited, Surat, India, with ultra-thin strut design (60 µm), cobalt–chromium stent platform, biodegradable polymer coating, and everolimus as an active drug. The preliminary clinical outcomes with Tetrilimus stents have been presented elsewhere.[29-32] This report presents the 1-year clinical safety and efficacy outcomes for Tetrilimus EESs in patients with CAD in real-world clinical practice.

HIGHLIGHTS

- Drug-eluting stents are the mainstay of treatment in patients with coronary artery disease.
- The performance of the drug-eluting stent greatly depends upon the type of drug coating, polymer coating, and strut thickness.
- The study evaluated ultra-thin strut biodegradable polymer-coated everolimus-eluting stent in all-comers population.

METHODS

Study Design and Patient Population

The safety and clinical PERFORMance of biodegradable polymer coated ultrathin EVERolimus-eluting stents in "real-world" patients (PERFORM-EVER) was an observational, multi-center, single-arm, and investigator-initiated retrospective registry. All consecutive patients with CAD who had received at least one Tetrilimus EES between July-2015 and October-2016 at our study centers were analyzed. The registry was aimed at studying "all-comers" and "real-world" population; hence, no major clinical or angiographic exclusion criteria were defined.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee and the study conformed to the principles of good clinical practice[33] and the Declaration of Helsinki.[34] All patients provided informed consent for the procedure, subsequent data collection, and analysis for the research purposes, which is the practice of associated hospitals, irrespective of any study to be conducted in future.

Description of Study Stent

Tetrilimus is the new-generation DES from Sahajanand Medical Technologies Limited, Surat, India. It is a biodegradable polymer-coated everolimus-eluting coronary stent comprising L605 cobalt–chromium alloy stent platform with ultra-thin (60 µm) strut thickness. As antiproliferative agent, it contains everolimus (1.0 µg/mm^2) blended together with biodegradable drug-carrier polymeric matrix, which is coated multi-layer on conformal surface of the stent with an average coating thickness of 3-4 µm. The polymeric matrix comprises a combination of hydrophilic and hydrophobic polymers, containing poly-L-lactide, poly-L-lactide-co-caprolactone, and polyvinyl pyrrolidone, which gives elastomeric property to the coating in line with the metal expansion mechanism and controls the release of drug from stent coating. Here, the unique coating matrix offers excellent coating adhesion with stent surface. The multi-layer coating technology offers precise control over drug release to accommodate arterial drug requirement post-stent implantation. Further, the unique blend of biodegradable polymers in each layer aids in achieving controlled drug release and offers

unmatched coating integrity. In addition, drug-free top layer composed of hydrophilic polymers with antioxidants tends to improve product's shelf life and protects coating layers during implantation. The blend of semi-crystalline polymer provides biphasic drug release with reduced initial burst and sustained drug release up to 3-4 months. The drug release profile of Tetrilimus stent (Figure 1) suggests that nearly 80% of everolimus drug is released within 1 month, while remaining drug is programed to get released at a slow rate for about 3 months.[29] Gradually, the biodegradable polymers undergo hydrolysis to degrade into biologically acceptable molecules that are excreted from the body in the form of metabolites. A sample scanning electron microscopy images of sterile-crimped stents and expanded stents show a smooth and uniform coating surface, without any coating anomalies and defects such as webbing, bridging, and strut-to-strut contact, even after expansion of the stent (Figure 2). During the study period, Tetrilimus EES was made available in lengths of 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 mm and diameters of 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, and 4.50 mm.

Coronary Intervention Procedure and Adjunctive Medications

Coronary interventional procedures and adjuvant medications were performed according to the standard guidelines. All patients received dual antiplatelet therapy (DAPT) including a loading dose of aspirin (300 mg) and clopidogrel (600 mg) or prasugrel (60 mg) or ticagrelor (90 mg). The procedural anticoagulation was achieved either with heparin or bivalirudin. 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 or prasugrel 10 mg daily or ticagrelor 90 mg twice daily for at least 12 months) after the procedure.

Data Collection and Patient Follow-up

Demographic data including age, gender, cardiovascular risk factors, medical history, and clinical presentation were collected from hospital records. Details of affected lesions and implanted stents were obtained from angiography and angioplasty reports. Adverse events were monitored during hospital stay. In addition, follow-ups were conducted

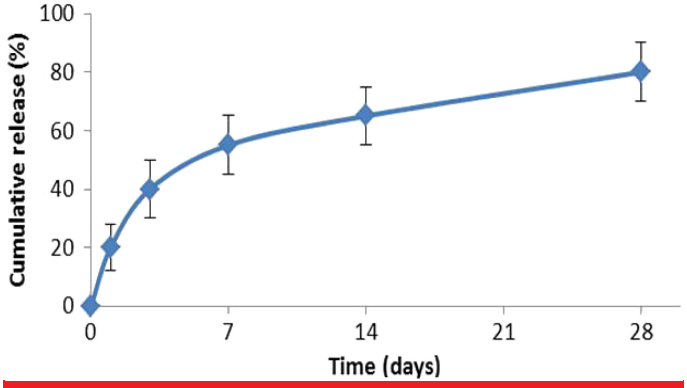

Figure 1. *In-vitro* drug release profile of Tetrilimus everolimus-eluting stent.

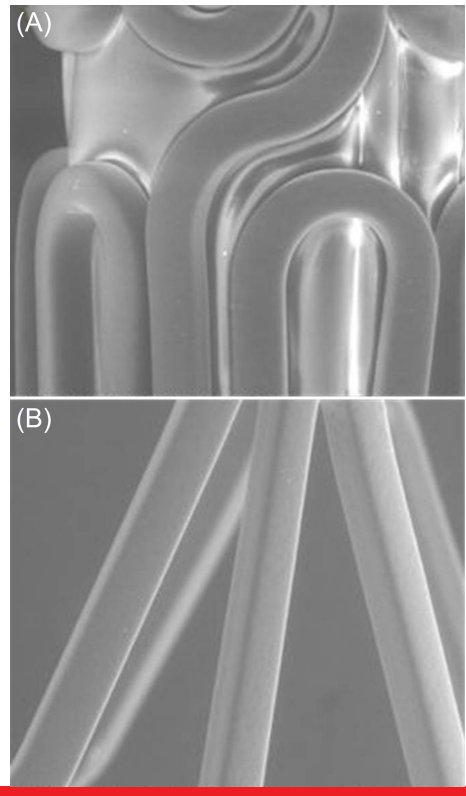

Figure 2. SEM images of (A) crimped and (B) expanded Tetrilimus stent.

at 30-day, 6-month, and 1-year of stent implantation. The follow-up data were collected retrospectively either by extraction from existing databases in consecutive fashion where index and follow-up data existed or was obtained by telephonic contact.

Study Endpoints

Procedural success rate was estimated as performance endpoint. Primary efficacy endpoint was 1-year incidence of target lesion failure (TLF), which was defined as a composite endpoint of cardiac death, myocardial infarction, and target lesion revascularization (TLR) by percutaneous or surgical methods. Secondary endpoints included incidence of all separate components of the primary endpoint and target vessel revascularization as well as non-cardiac death at 30-day, 6-month, and 1-year follow-up. At each follow-up, events of Academic Research Consortium (ARC)–defined stent thrombosis were also estimated as additional safety endpoint.[35]

Study Definitions

Procedural success was defined as a successful delivery and deployment of the coronary stent(s) at the intended target lesion and successful withdrawal of the stent delivery system with the achievement of final diameter stenosis of <30% in the intervene vessel without the occurrence of clinical complications such as death, reinfarction, repeat revascularization, access site complication, blood-transfusion due to bleeding, or cerebrovascular accident during the

hospital stay. Death from any cause was examined during the follow-up period, and all deaths were considered cardiac unless the unequivocal non-cardiac cause was established. Myocardial infarction was defined either as the development of new pathological Q-waves in at least two contiguous leads of electrocardiogram with or without elevated cardiac enzymes (Q-wave MI) or elevation of creatine kinase (CK-MB) >3 times the upper limit of normal and without pathological Q-waves (non-Q wave MI) in electrocardiogram. Target lesion revascularization was described as any revascularization procedure in the target lesion with stenosis >50% in association with clinical or functional ischemia (positive functional study, electrocardiographic changes, or ischemic symptoms), or stenosis >70% in the absence of clinical or functional ischemia. Similarly, target vessel revascularization was defined as any repeat revascularization procedure in the target vessel during the follow-up period. Stent thrombosis was defined using the ARC definitions. The stent thrombosis was counted as "definite" when it was detected angiographically; "probable" if the patient had a target vessel-related MI or died of a coronary event within the first 30 days; and "possible" if any unexplained death occurred from 30 days after the index procedure until the final follow-up.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency and percentages. The TLF event curve was obtained using the Kaplan-Meier method. All data were analyzed with the Statistical Package for Social Sciences (SPSS; Chicago, Ill, USA) program, version 15.

Table 1. Baseline Characteristics for Patients Implanted with Tetrilimus Stents

Demographic Details	594 Patients
Age (years), mean ± SD	55.6 ± 12.1
Male, n (%)	453 (76.3%)
Diabetes mellitus, n (%)	138 (23.2%)
Hypertension, n (%)	192 (32.3%)
Smoking, n (%)	141 (23.7%)
Tobacco chewing, n (%)	106 (17.8%)
Alcoholism, n (%)	205 (34.5%)
Family history of coronary artery disease, n (%)	53 (8.9%)
Previous MI, n (%)	37 (6.2%)
Previous CABG, n (%)	7 (1.2%)
Previous PCI, n (%)	39 (6.6%)
Previous stroke, n (%)	2 (0.3%)
Clinical presentation	
Stable angina	246 (41.4%)
Acute coronary syndrome	348 (58.6%)
Unstable angina	109 (18.4%)
Non-ST elevation myocardial infarction	148 (24.9%)
ST elevation myocardial infarction	91 (15.3%)

RESULTS

Baseline Characteristics

During the study period, a total of 594 patients were implanted with at least one Tetrilimus stent. The baseline characteristics of this study population are outlined in Table 1. The mean of the patients was 55.6 ± 12.1 years. Among them, 453 (76.3%) were male, 192 (32.3%) were hypertensive, 138 (23.2%) were diabetic, 205 (34.5%) were alcoholics, 141 (23.7%) were smokers, 106 (17.8%) were tobacco chewers, and 46 (7.7%) had previous revascularization. More than half, that is, 348 (58.6%), patients presented with acute coronary syndrome.

Lesion and Stent Characteristics

A total of 815 Tetrilimus EESs (1.4 ± 0.5 stent/patient) were implanted to treat 735 coronary lesions (1.1 ± 0.3 stent/lesion) in the study population. Overall lesion and stent characteristics are outlined in Table 2. About 225 (37.8%) patients displayed multi-vessel coronary disease. The majority of culprit lesions were found in the left anterior descending artery (51.8%) followed by the right coronary artery (29.1%) and left circumflex artery (18.9%). Of treated lesions, 577 (78.5%) were complex (i.e., Type B2/C) and 103 (14.0%) had total occlusion. The average length and diameter of implanted Tetrilimus EESs were 27.6 ± 9.7 mm and 3.0 ± 0.3 mm, respectively. The inclusion of high-risk patients with complex lesions reflected the "all-comers" "real-world" study population.

Clinical Outcomes

Table 3 provides an overview of clinical outcomes at up to 1-year follow-up. Procedural success was reported in 99.2% of cases. Events of TLF were reported in 5 (0.8%) patients at 30-day follow-up, owing to in-hospital cardiac death in all cases. At 6-month follow-up, cardiac death, myocardial infarction, and TLR were reported in 7 (1.2%), 4 (0.7%), and 2 (0.3%) patients, respectively, leading to the cumulative TLF events in 13 (2.2%) patients. Subsequently, the primary endpoint of cumulative TLF at 1-year follow-up was noted in 22 (3.7%) patients, which included 9 (1.5%) cardiac deaths, 8 (1.4%) myocardial infarctions, and 5 (0.8%) TLR. The Kaplan-Meier curve for cumulative TLF events during 1-year follow-up is illustrated in Figure 3. Figure 4 demonstrates the Kaplan–Meier event curve for cumulative TLF events during 1-year follow-up for patients with ACS and SCAD. Additionally, there were 2 (0.3%) cases of non-cardiac death and 7 (1.2%) cases of target vessel revascularization at 1-year follow-up. Moreover, the additional safety endpoint of ARC-defined stent thrombosis at 1-year follow-up was reported in 9 (1.5%) patients, comprising 5 (0.8%) cases of probable stent thrombosis and 4 (0.7%) cases of possible stent thrombosis.

DISCUSSION

The present study reports the findings of 1-year outcomes with Tetrilimus EESs in 594 "real-world" patients from the PERFORM-EVER registry. The recruitment of consecutive patients along with minimal exclusion criteria facilitated a representation of "all-comers" population in a "real-world"

Table 2. Lesion and Stent Characteristics for Patients Implanted with Tetrilimus Stents

Characteristics	594 Patients/735 lesions
Disease vessel (594 patients)	
Single-vessel disease, n (%)	369 (62.1%)
Double-vessel disease, n (%)	204 (34.3%)
Triple-vessel disease, n (%)	21 (3.5%)
Target coronary artery (735 lesions)	
Left main, n (%)	1 (0.1%)
Left anterior descending artery, n (%)	381 (51.8%)
Right coronary artery, n (%)	214 (29.1%)
Left circumflex artery, n (%)	139 (18.9%)
Lesion details (735 lesions)	
Type A*, n (%)	42 (5.7%)
Type B1*, n (%)	116 (15.8%)
Type B2*, n (%)	113 (15.4%)
Type C*, n (%)	464 (63.1%)
Total occlusion, n (%)	103 (14.0%)
Stent details (815 stents)	
No. of stents deployed per patient, mean ± SD	1.4 ± 0.5
No. of stents deployed per lesion, mean ± SD	1.1 ± 0.3
Stent length (mm), mean ± SD	27.6 ± 9.7
Stent diameter (mm), mean ± SD	3.0 ± 0.3

The data is according to the American College of Cardiology (ACC)/ American Heart Association (AHA) criteria.

scenario. This is reflected in the demographic and angiographic characteristics of study population, representing an inclusion of high-risk population. We are of the opinion that results of such registry would provide valuable insights regarding the device performance and clinical outcomes in routine clinical practice.

In our study, the incidents of TLF at 1-year follow-up were noted in 3.7% patients, while stent thrombosis was noted in 1.5% patients. These data confirms the good clinical safety and performance of the Tetrilimus EESs in CAD patients from routine clinical practice, including in those with higher risk or complex lesions. Here, it should be noted that prospective, randomized controlled trials, or first-in-man studies usually enroll a low-risk study population (clinically stable or straightforward lesions), and thus results of such studies cannot be extrapolated to "real-world" patients with higher risk or with complex coronary anatomy.

Table 4 outlines the comparison of the clinical data of Tetrilimus EES from the present PERFORM-EVER registry with the clinical data of other EESs.[5,11-13,30,36-39] The results of an earlier report published on Tetrilimus by Abhyankar et al[30] is also in line with the present study (MACE 4.2%), however, the number of patients in that study are lower than the present study. The comparative review suggests that the 1-year clinical outcomes of Tetrilimus EESs in PERFORM-EVER Registry (TLR: 0.8%; TLF: 3.7%) are comparable to 1-year clinical outcomes of Xience EES in THRIVE[36] (TLR: 1.0%; TLF: 3.9%), but on the other hand DESSOLVE III trial[37] reports higher rates of TLR and TLF (TLR: 4.1%; TLF: 9.4%) and SPIRIT-V trial has slightly higher event rates (TLR: 1.8%; TLF: 6.8%) than the present study.[11] In addition, the clinical outcomes with Tetrilimus EESs were also numerically comparable with that of durable polymer-coated Promus Element EESs (Boston Scientific, USA) from PLATINUM (TLR: 1.9%; TLF: 3.5%)[5] and PLATINUM PLUS (TLR: 1.6%; MACE: 4.7%)[12] studies. Interestingly, the incidents of adverse clinical outcomes with Tetrilimus EESs were marginally lower than that observed with another biodegradable polymer-coated Synergy EESs (Boston Scientific, USA) in the EVOLVE II (TLR: 2.6%; TLF: 6.4%)[13] study. An all-comers registry[39] in Asian population receiving Synergy stent also reported numerically higher MACE rates (7.2%) at 1-year follow-up while SYNERGY ACS[38] study showed similar MACE rates (3.0%). Further, the 1-year incidents of stent thrombosis with Tetrilimus EESs in PERFORM-EVER registry was 1.5%, which was in range of 0.0–1.7% rates of stent thrombosis rate observed with other EESs at 1-year follow up in various clinical trials.[5,11-13,30,36-39]

We believe that the encouraging safety and efficacy outcomes of Tetrilimus EESs in the present study should be principally attributed to ultra-thin strut thickness, biodegradable nature of polymeric matrix, and elution kinetics of the antiproliferative drug everolimus. The utility of biodegradable polymers in the Tetrilimus EESs is considered to

Table 3. Clinical Outcomes for 594 Patients Implanted with Tetrilimus Stents

Clinical Outcomes	At 30-Day Follow-Up	At 6-Month Follow-Up	At 12-Month Follow-Up
Death from any cause, n (%)	5 (0.8%)	9 (1.5%)	11 (1.8%)
Cardiac death, n (%)	5 (0.8%)	7 (1.2%)	9 (1.5%)
Non-cardiac death, n (%)	0 (0%)	2 (0.3%)	2 (0.3%)
Myocardial infarction, n (%)	0 (0%)	4 (0.7%)	8 (1.4%)
Target lesion revascularization, n (%)	0 (0%)	2 (0.3%)	5 (0.8%)
Target vessel revascularization, n (%)	0 (0%)	2 (0.3%)	7 (1.2%)
Overall stent thrombosis*, n (%)	5 (0.8%)	7 (1.2%)	9 (1.5%)
Definite stent thrombosis, n (%)	0 (0%)	0 (0%)	0 (0%)
Probable stent thrombosis, n (%)	5 (0.8%)	5 (0.8%)	5 (0.8%)
Possible stent thrombosis, n (%)	0 (0%)	2 (0.3%)	4 (0.7%)
Target lesion failure, n (%)	**5 (0.8%)**	**13 (2.2%)**	**22 (3.7%)**

*The data is according to the Academic Research Consortium (ARC) criteria.

Table 4. Tetrilimus vs. other Everolimus-Eluting Stents: Comparison of Technical Features and Demographic Data and Clinical Outcomes

Brand Name	**Tetrilimus**			**Xience**			**Promus Element**		**Synergy**		
Manufacturer	SMT			Abbott Vascular			Boston Scientific		Boston Scientific		
Stent Material	Co–Cr			Co–Cr			Pt–Cr		Pt–Cr		
Drug	Everolimus			Everolimus			Everolimus		Everolimus		
Dosage	1.0 μg/mm^2			1.0 μg/mm^2			1.0 μg/mm^2		1.0 μg/mm^2		
Strut Thickness	60 μm			81 μm			81 μm		74 μm		
Polymers	Biodegradable			Durable			Durable		Biodegradable		
Study /Registry	**PERFORM-EVER**	**Abhyankar et al (30)**	**Bolinera et al (32)**	**THRIVE (36)**	**DESSOLVE III (37)**	**SPIRIT-V (11)**	**PLATINUM (5)**	**PLATINUM PLUS (12)**	**EVOLVE II (13)**	**SYNERGY ACS (38)**	**Ananthakrishna et al (39)**
Demographic Data	n=594	n=213	n=558	n=400	n=695	n=2663	n=768	n=1952	n=846	n=1008	n=807
Age (mean ± SD, years)	55.6±12.1	55.1±11.5	57.0±10.2	63.3±10.6	66·3±10·7	63.0±11.0	64.1±10.3	65.7±10.5	63.5±10.4	65.4±14.8	60.4±10.9
Male gender (%)	76.3%	66.7%	70.4%	70.3%	74.0%	78.0%	71.6%	77.7%	70.6%	76.2%	83.8%
Diabetes mellitus (%)	23.2%	39.9%	38.5%	35.0%	27.1%	30.0%	22.0%	29.1%	31.1%	24.5%	38.2%
Current smoker (%)	23.7%	22.5%	18.1%	16.3%	26.4%	NA	21.0%	22.0%	21.8%	36.0%	35.8%
Hypertension (%)	32.3%	48.4%	48.9%	69.3%	75.4%	64.0%	70.9%	68.0%	77.3%	64.7%	65.2%
Follow-up at 12 months	n=594	n=213	n=558	n=377	n=695	n=2600	n=768	n=1862	n=846	n=1008	n=765
Death (%)	1.8%	0.9%	0.9%	2.1%	2.6%	1.7%	1.3%	1.5%	1.1%	3.3%	6.0%
Cardiac death (%)	1.5%	0.5%	0.7%	0.7%	1.6%	1.1%	0.9%	1.0%	0.5%	1.3%	4.2%
Non-cardiac death (%)	0.3%	0.5%	0.2%	1.4%	1.0%	0.6%	0.4%	0.5%	0.6%	NA	NA
Myocardial infarction (%)	1.4%	1.4%	1.4%	2.1%	2.2%	3.5%	1.1%	0.8%	5.4%	1.6%	1.7%
TLR (%)	0.8%	2.3%	0.4%	1.0%	4.1%	1.8%	1.9%	1.6%	2.6%	1.0%	1.3%
TVR/CABG (%)	1.2%	0.5%	–	1.6%	5.9%	2.8%	2.7%	3.2%	3.8%	1.3%	2.2%
Stent thrombosis (%)	1.5%	0.9%	0.7%	1.0%	1.6%	NA	0.4%	0.8%	0.7%	0.9%	0.5%
MACE/TLF (%)	3.7%	4.2%	2.5%	3.9%*	9.4%	6.8%	3.5%	4.7%*	6.4%	3.0%	7.2%

*MACE indent rates; CABG, Coronary artery bypass grafting; Co–Cr, Cobalt–chromium alloy; MACE, major adverse cardiac event; Pt–Cr, Platinum–chromium alloy; TLF, Target Lesion Failure; TLR, Target Lesion Revascularization, TVR, Target Vessel Revascularization.

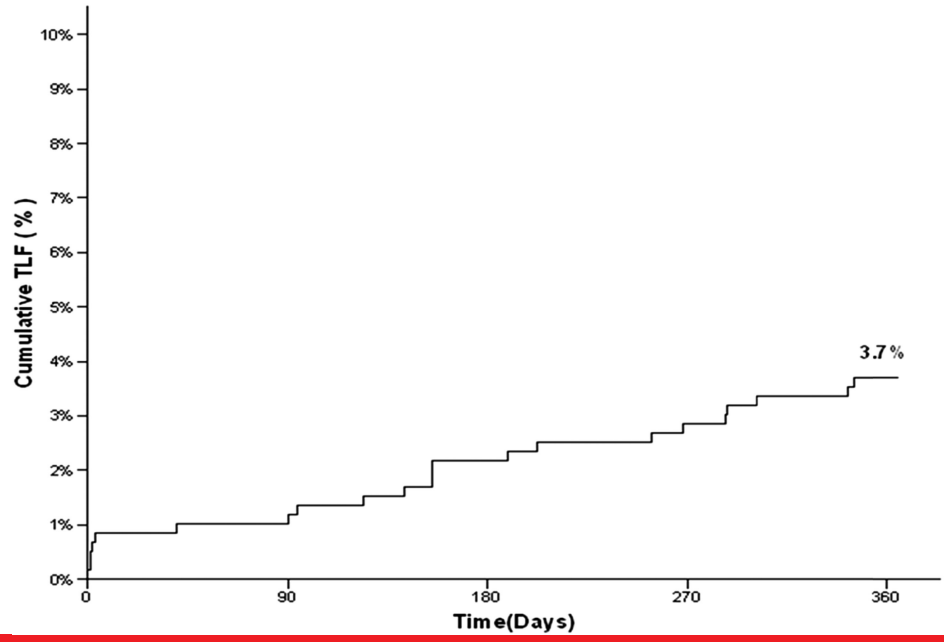

Figure 3. Kaplan-Meier event curve for cumulative target lesion failure during 1-year follow-up for patients implanted with Tetrilimus stents (n = 594).

reduce the risk of local inflammatory reaction and irritation in the target coronary vessel. In addition to this, Tetrilimus stent also offers advantages of cobalt–chromium stent platform with uniform ultra-thin struts and highly flexible design, which may enhance the deliverability of the stent, particularly in complex and challenging lesions, leading to reduced procedural complications. Further, the effect of stent strut thickness has been well established. As depicted in Figure 5, thick protruding stent struts disrupt laminar flow and induce flow disturbances, and thereby causing high endothelial shear stress microgradients, which may induce platelet aggregation and formation of microthrombi with potential embolization, leading to stent thrombosis. On the other hand, stents with thin struts have less thrombogenic risk as they may cause less flow disturbance, inflammation, vessel injury, neointimal proliferation, and thrombus formation.[40] The positive role of ultra-thin strut thickness in achieving excellent efficacy and safety outcomes was also indicated in BIOFLOW V study on Orsiro sirolimus-eluting stent with 60-µm strut thickness against Xience V EESs with 81-µm strut thickness.[41] Previously published study of Tetrilimus EESs also confirmed the safety and performance of the device in the long lesion subset.[32] The use of ultra-thin struts in the Tetrilimus EES platform showed early healing, as proven by optical coherence tomography.[31] Conversely, the clinical benefits observed with Tetrilimus EESs in PERFORM-EVER registry is because of one specific design feature or multiple factors remains questionable. However, the emerging evidences in recent years suggest the need for future comparative studies evaluating the impact of stent strut thickness on clinical outcomes.

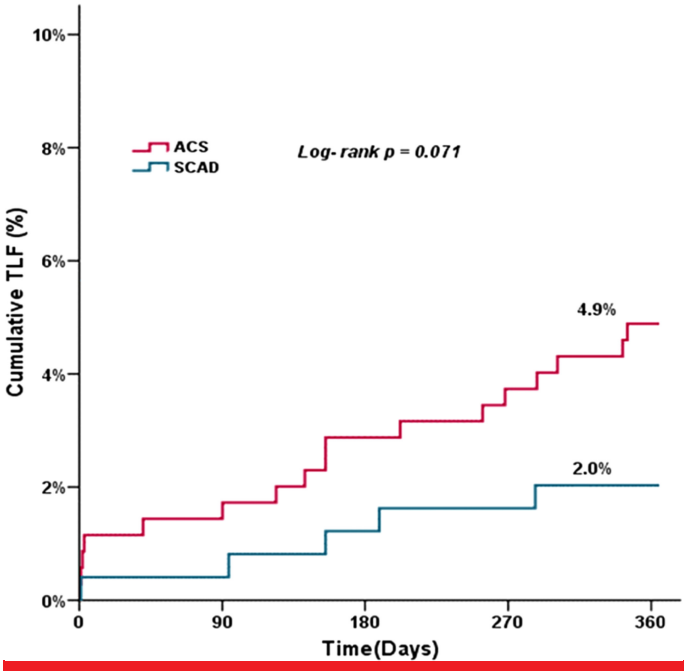

Figure 4. Kaplan-Meier event curve for cumulative target lesion failure during 1-year follow-up for patients with acute coronary syndrome (ACS) and stable coronary artery disease (SCAD).

Overall, the results with Tetrilimus EESs in the PERFORM-EVER registry are consistent with those observed in previous studies on biodegradable polymer-coated as well as durable polymer EESs. Further follow-up is intended to assess the long-term safety and efficacy outcomes with Tetrilimus EESs.

Study Limitations

The major limitation of our registry is its retrospective, single-arm, observational study design. Another limitation of this study is the lack of head-to-head comparison with other

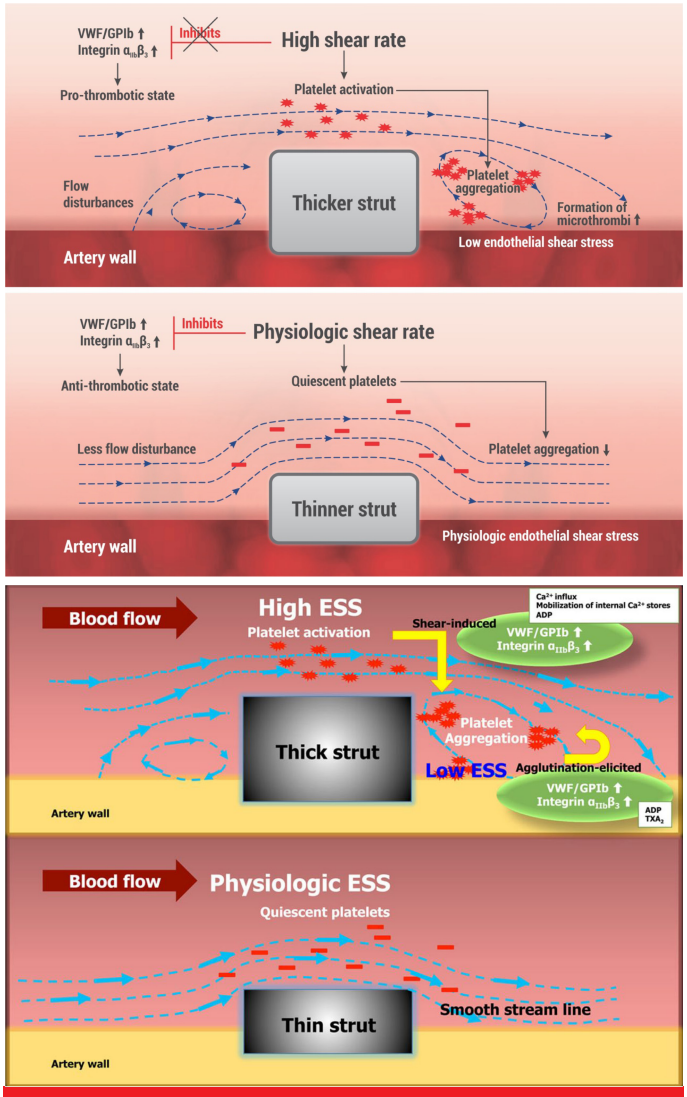

Figure 5. Impact of stent strut thickness on thrombotic status.

stents, which could have provided better insights into the outcomes. Moreover, a larger pool of study patients might have been more valuable. However, we believe that the present study provides useful insights into the promising safety and efficacy of Tetrilimus everolimus-eluting coronary stents in real-world patients. For more reliable long-term data, evaluation of outcomes at up to 3-year follow-up is eagerly anticipated.

CONCLUSION

The study findings indicate low incidence for primary study endpoint of TLF and for additional safety endpoint of stent thrombosis at 12-month follow-up, which indicates that Tetrilimus EESs have encouraging safety and efficacy in unselected real-world patients with CAD, including those with high-risk characteristics and complex lesions. The favorable outcomes with Tetrilimus EESs can be principally attributed to ultra-thin strut thickness, biodegradable nature of the polymeric matrix, and elution kinetics of the antiproliferative drug everolimus. Future studies, however, are needed with comparative analysis and a long-term follow-up.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee Sunshine Hospital (IEC 224).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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