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Original Article

Twelve months clinical outcomes of ultrathin strut sirolimus-eluting stent in real-world Indian patients with coronary artery disease

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Abstarct: Purpose: Although the field of interventional cardiology has witnessed extraordinary progression, the search of an ideal coronary drug-eluting stent is still going on. Tetriflex (Sahajanand Medical Technologies Limited, Surat, India) is a latest generation biodegradable polymer-coated ultrathin (60 μm) sirolimus-eluting stent (SES) with unique Long Dual Z-link (LDZ) design. The present registry reports the 12 months clinical follow-up results of Tetriflex SES in unselected, real-world patients with coronary artery disease (CAD). Methods: This was an investigator-initiated, retrospective, multi-center, single-arm, observational registry conducted in India between March-2017 and March-2018. The registry included 1269 consecutive patients with CAD who underwent implantation of at least one Tetriflex SES. The primary outcome was considered as target lesion failure (TLF), which was a composite of cardiac death, target-vessel myocardial infarction (TV-MI) and clinically-driven target lesion revascularisation (CD-TLR) at 12 months follow-up. The safety outcome, at 12 months follow-up, was stent thrombosis. Results: Mean age of patients was 54.99±10.80 years. Among all, 36.6% patients had diabetes and 51.7% patients had multi-vessel disease. A total of 1515 lesions were treated with 1682 Tetriflex SES of which 73.2% lesions were complex B2/C type and 14.7% were totally occluded. At 12 months, the cumulative incidence of TLF was 5.75% comprising 0.8% cardiac death, 3.20% TV-MI and 1.72% CD-TLR. All the incidences of definite/probable stent thrombosis (n = 4, 0.32%) were reported within 30 days of the index procedure. Twelve-month cumulative incidence of TLF in diabetic subgroup was 7.10%. Conclusion: Twelve months clinical follow-up results of an ultrathin (60 μm), biodegradable polymer-coated Tetriflex SES, with unique LDZ-link, further clarify its safety and effectiveness in real-world, unselected Indian patients.

Keywords: Coronary artery disease, drug-eluting stents, sirolimus-eluting stents, ultrathin

Introduction

In preceding decade, the field of interventional cardiology has witnessed dramatic advancements in search of an ideal coronary drug-eluting stent (DES). Though 2nd generation DES has significantly reduced the rate of restenosis and stent thrombosis compared to first generation DES, adverse events still endure. Latest generation DES with biodegradable polymers, newer stent platforms, ultrathin struts and improved stent design not only enhances procedural safety but also reduces long-term complications such as in-stent restenosis and very late stent thrombosis. However, it is quite challenging to discover that which of these components improve outcomes for any stent [1-3]. Although DES with biodegradable polymers, as a class, offers theoretical advantages over durable polymer DES, it has not yet conferred improvement in clinical outcomes [4-6]. Stents with thinner struts, on the other hand, reduce vascular injury, flow separation, and stagnation and also accelerate endothelialization which modulate thrombogenicity and neointimal hyperplasia. These modulations physiologically reduce the rate of restenosis, stent thrombosis, and myocardial infarction (MI) as observed with ultrathin struts DES (<70 μm) compared to contemporary thin struts DES (<100 μm)

and even to 1st generation DES (>132 μm). Recently, several meta-analyses have stated reduced incidences of target lesion failure (TLF) with ultrathin DES (<70 μm) compared to contemporary thicker strut DES (70-100 μm) not only at short-term but also at long-term follow-up [4, 7-10].

Tetriflex (Sahajanand Medical Technologies Limited, Surat, India), a sirolimus-eluting coronary stent (SES), is a latest generation ultrathin (60 μm) DES developed with a unique Long Dual-Z link (LDZ) design to improve its deliverability and flexibility compared to previous generation DES designs without compromising safety and efficacy. The safety and effectiveness of Supra family SES have already been stated in varied population [9, 11-19]. Additionally, several randomized controlled trials as well as registries are ongoing all around the world to further establish its safety and efficacy in different subsets of patient population [20-22]. A multi-center registry was conducted to evaluate safety and clinical performance of Tetriflex SES in unselected, real-world Indian patients with coronary artery disease (CAD) and 6 months follow-up data of this registry were already published elsewhere [23]. Here, the present registry demonstrates clinical outcomes of the same registry on Tetriflex SES in unselected, real-world CAD patients at 12 months follow-up. In addition, this registry also describes safety and clinical performance of Tetriflex SES in diabetic patients at 12 months.

Methods

Study design and population

This was an investigator-initiated, retrospective, multi-center, single-arm, observational registry carried out at five different tertiary-care centres in India. The registry included consecutive 1269 CAD patients who underwent implantation of at least one Tetriflex SES between March-2017, and March-2018. The registry was approved by the institutional ethics committee of each center and was performed in accordance with the Declaration of Helsinki. At the time of percutaneous coronary intervention (PCI), the written informed consent was obtained either from patient or from patient's designee for the procedure and for the use of properly anonymized clinical data.

The registry included real-world patients (age ≥18 years), who presented with either ST elevation myocardial infarction, non-ST elevation myocardial infarction, unstable angina, or stable angina along with other risk factors and complex lesion characteristics. The diagnostic criterion of significant CAD includes presence of >70% stenosis in the major coronary arteries confirmed by angiographic finding.

Device description

Tetriflex SES (Tetrinium-L605) is a latest generation ultrathin (60 μm) biodegradable polymer-coated, cobalt-chromium sirolimus-eluting coronary stent designed with unique LDZ-link. The multilayer conformal coating on the surface of Tetriflex SES contains sirolimus drug and biodegradable polymeric matrix. It comprises of a combination of hydrophobic [PLLA: poly-L-lactic acid, and PLCL: poly (L-Lactide-co-ε-Caprolactone)] polymers in blend with sirolimus in centre and innermost layer, and outer drug-free hydrophilic polymer (PVP: polyvinylpyrrolidone) coating. The drug-free top layer contains antioxidants which tend to improve product shelf-life and protect coating from light, moisture, premature drug release and provide lubricity during stent implantation. The average coating thickness of Tetriflex SES is 4-6 μm. It has unique LDZ-link with 'valley-to-valley' connection between the strut rings that increases the flexibility and trackability which was confirmed by the results of bench test performed using a standard *ex-vivo* artery simulator mimicking coronary anatomy [22]. The release profile of sirolimus (80% releases in one month and remaining 20% within three months) from Tetriflex SES and scanning electron microscopic images of the sterile crimped and expanded stent are presented in previous study [23].

Study procedure, medication and follow-up

PCI procedure was performed according to routine practices of all the institutes. Peri-procedural dual antiplatelet therapy includes loading dose of aspirin (150-300 mg) and either clopidogrel (600 mg), prasugrel (60 mg) or ticagrelor (two tablets of 90 mg each). All patients received heparin or bivalirudin, whereas use of glycoprotein IIb/IIIa inhibitor was at the investigator's discretion. Post-procedural dual antiplatelet therapy was recommended for

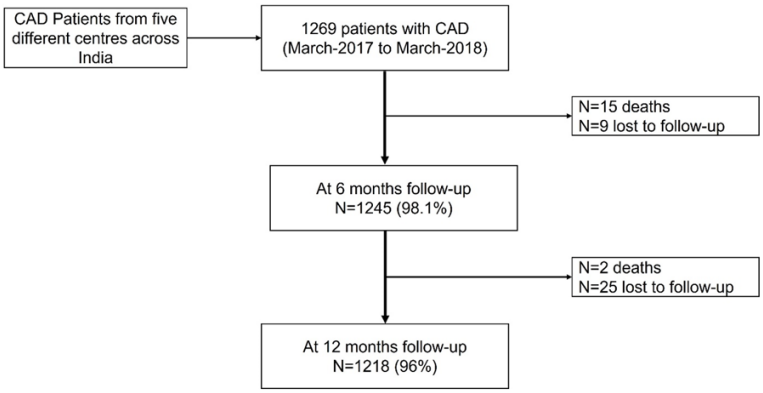

Figure 1. Study flow chart.

Table 1. Baseline characteristics for 1269 patients implanted with Tetriflex SES

Characteristics	
Number of patients, n	1269
Age (years), mean ± SD	54.99±10.8
Age Distribution	
18-30 years	12 (0.9%)
31-40 years	111 (8.7%)
41-50 years	323 (25.5%)
51-60 years	436 (34.4%)
61-70 years	296 (23.3%)
71-80 years	85 (6.7%)
>80 years	6 (0.5%)
Male, n (%)	910 (71.7%)
Cardiovascular risk	
Hypertension, n (%)	622 (49.0%)
Diabetes mellitus, n (%)	465 (36.6%)
Hypercholesterolemia, n (%)	370 (29.2%)
Smoking, n (%)	218 (17.2%)
Previous MI, n (%)	136 (10.7%)
Previous PCI, n (%)	89 (7.0%)
Previous CABG, n (%)	23 (1.8%)
Previous stroke, n (%)	26 (2.0%)
Renal insufficiency, n (%)	17 (1.3%)
Family history of CAD, n (%)	32 (2.5%)
Cardiogenic shock, n (%)	40 (3.2%)
Clinical presentation	
Stable angina, n (%)	336 (26.5%)
Unstable angina, n (%)	364 (28.7%)
ST-elevation myocardial infarction, n (%)	398 (31.4%)
Non-ST-elevation myocardial infarction, n (%)	171 (13.5%)
12 months DAPT	(N = 1269)
Aspirin	1204 (94.9%)
Thienopyridine	1160 (91.4%)

MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypasses graft, CAD: coronary artery disease.

at least up to 12 months (aspirin: 75-100 mg and clopidogrel: 75 mg daily or prasugrel: 10 mg daily or ticagrelor: 90 mg twice daily) followed by aspirin daily indefinitely.

Follow-up data at 12 months of the index procedure were collected either via clinical follow-up or telephonic contact (**Figure 1**).

Clinical endpoints and definition

The primary endpoint was the occurrence of TLF at 12 months follow-up, defined as the composite of cardiac death, target-vessel myocardial infarction (TV-MI), or clinically-driven target lesion revascularization (CD-TLR). Cardiac death was defined as any death unless unequivocally caused by a non-cardiac cause. MI was defined as per the third universal definition [24]. CD-TLR was defined as any repeat revascularization to treat the stented segment (including 5 mm proximal or 5 mm distal to stent margins) demonstrated as ≥50% diameter stenosis on quantitative coronary angiography at the target lesion. Non-target lesion target vessel revascularization (TVR) was defined as any repeat revascularization in the epicardial vessel treated during index procedure other than the target lesion. Stent thrombosis was evaluated as a secondary safety endpoint, defined as per Academic Research Consortium (ARC) definition [25].

Statistical analysis

Data were evaluated using the statistical package for social sciences (SPSS Inc., USA;

Table 2. Lesion characteristics for 1269 patients implanted with Tetriflex SES

Characteristics	
Number of lesions, n	1515
Disease vessel (n = 1269 patients)	
Single-vessel disease, n (%)	613 (48.3%)
Double-vessel disease, n (%)	536 (42.2%)
Triple-vessel disease, n (%)	120 (9.5%)
Target coronary artery (n = 1515 lesions)	
Left main, n (%)	5 (0.3%)
Left anterior descending artery, n (%)	723 (47.7%)
Left circumflex artery, n (%)	311 (20.5%)
Right coronary artery, n (%)	470 (31.0%)
Saphenous vein graft, n (%)	6 (0.4%)
Lesion details (n = 1515 lesions)	
Type A*, n (%)	206 (13.6%)
Type B1*, n (%)	200 (13.2%)
Type B2*, n (%)	226 (14.9%)
Type C*, n (%)	883 (58.3%)
Total occlusion, n (%)	222 (14.7%)

*According to American College of Cardiology (ACC)/American Heart Association (AHA) lesion morphology criteria.

Version 20) program. The continuous and categorical variables were presented as mean ± standard deviation and frequencies (percentage), respectively. The event-free survival curves at 12 months follow-up were generated using the Kaplan-Meier method.

Results

Baseline, lesion and procedural characteristics

The mean age of patients was 54.99±10.8 years with male dominance (71.7%) and male to female ratio of 2.53:1. Among all, 465 (36.6%) patients had diabetes, 622 (49%) had hypertension and 218 (17.2%) were smokers. A total of 44.9% (n = 569) patients presented with acute MI. The complete baseline and clinical characteristics of all the patients are outlined in **Table 1**.

The detailed lesion and procedural characteristics of all the patients are depicted in **Tables 2** and **3**, respectively. Of note, 656 (51.7%) patients were diagnosed with multi-vessel CAD. A total of 1682 Tetriflex SES were implanted to treat 1515 coronary lesions. Maximum lesions were in left anterior descending artery (47.7%). Overall, 73.2% lesions were classified as complex type B2/C lesions (as per the American College of Cardiology/American Heart Association) and 14.7% lesions were totally occluded. On an average, 1.23 stents were deployed in each patient and 1.11 stents per lesion. A total of 156 (9.3%) deployed stents were of ≥40 mm length. At 12 months follow-up, 1204 (94.9%) patients were taking aspirin.

Twelve months clinical outcomes

Twelve months clinical follow-up was completed in 96% patients (n = 1218). At 12 months follow-up, the cumulative incidence of TLF was 5.75% (**Table 4**; **Figure 2**). TV-MI constituted most of the primary events with cumulative incidence of 3.2% followed by CD-TLR (1.72%) and cardiac death (0.82%) at 12 months (**Table 4**). Notably, no cardiac death was reported between 6-12 months of the index procedure. The cumulative incidence of stent thrombosis (definite/probable/possible), defined by ARC definition, was 0.9% (**Table 4**). However, all the incidences of definite/probable stent thrombosis (n = 4, 0.32%) were reported within 30 days of the index procedure. Furthermore, three cases of possible stent thrombosis were observed between 30 days to 6 months follow-up and only one case of possible stent thrombosis was reported between 6-12 months follow-up.

A total of 439/465 diabetic patients completed 12 months follow-up. The cumulative incidence of the primary endpoint (TLF) in diabetic patient's subgroup was 7.1%. As shown in **Figure 3**, the incidence of TLF as well as its individual subsets (cardiac death, TV-MI and CD-TLR) were consistent in diabetic patients as well, at 12 months follow-up.

Discussion

Several technical iterations in the latest generation DES such as ultrathin stent platform with unique design characteristic without compromising its mechanical property, and biodegradable polymers/polymer-free coating. These characteristics potentially alleviate the risk of acute/chronic inflammation and vessel wall injury, accelerate re-endothelialization and strut coverage, and reduce neointimal proliferation and thrombogenicity which ultimately decrease the incidence of stent thrombosis and the need of revascularization [1, 26, 27]. The present registry represents 12 months follow-up results of latest generation ultrathin (60 μm) Tetriflex SES, which was conducted on unselect-

Table 3. Procedural characteristics for 1269 patients implanted with Tetriflex SES

Characteristics	
Stent details	
Total no. of stent, n	1682
No. of stents deployed per patient, mean ± SD	1.23±0.45
No. of stents deployed per lesion, mean ± SD	1.11±0.33
Stent length (mm), mean ± SD	25.15±8.83
Stent diameter (mm), mean ± SD	2.89±0.32
Stent size description	
Stent length	
8 mm, n (%)	8 (0.5%)
12 mm, n (%)	134 (8.0%)
16 mm, n (%)	255 (15.2%)
20 mm, n (%)	293 (17.4%)
24 mm, n (%)	287 (17.1%)
28 mm, n (%)	234 (13.9%)
32 mm, n (%)	201 (12.0%)
36 mm, n (%)	114 (6.8%)
40 mm, n (%)	74 (4.4%)
44 mm, n (%)	47 (2.8%)
48 mm, n (%)	35 (2.1%)
Stent diameter	
2.25 mm, n (%)	6 (0.4%)
2.50 mm, n (%)	386 (22.9%)
2.75 mm, n (%)	463 (27.5%)
3.00 mm, n (%)	573 (34.1%)
3.50 mm, n (%)	253 (15.0%)
4.00 mm, n (%)	1 (0.1%)

Table 4. Clinical outcomes of Tetriflex SES at 12 months follow-up

Clinical outcomes	At 12 months (n = 1218, 96%)
Death from any cause, n (%)	17 (1.39%)
Cardiac death, n (%)	10 (0.82%)
Non-cardiac death, n (%)	7 (0.57%)
Target-vessel myocardial infarction, n (%)	39 (3.20%)
Clinically-driven TLR, n (%)	21 (1.72%)
Non- target lesion TVR, n (%)	13 (1.07%)
Overall stent thrombosis†, n (%)	8 (0.65%)
Definite stent thrombosis, n (%)	2 (0.16%)
Probable stent thrombosis, n (%)	2 (0.16%)
Possible stent thrombosis, n (%)	4 (0.33%)
Target lesion failure, n (%)	70 (5.75%)

TLR: target lesion revascularization; TVR: target vessel revascularization.

ed, real-world CAD patients at multiple centres across India. The main findings of this registry at 12 months follow-up include: i) Tetriflex SES reported acceptable safety and clinical performance with 5.75% TLF rate which was primarily driven by TV-MI (3.2%); ii) Definite/probable stent thrombosis was low at 0.32%; and iii) TLF was 7.1% in diabetic subgroup which was consistent with the previous studies.

During six months follow-up of the present registry, Tetriflex SES reported 2.5% TLF, consisting of 0.8% cardiac deaths, 1.3% TV-MI, and 0.4% TLR which were coherent with previous studies [23]. Additionally, 12-month results of Tetriflex SES, as reported in this registry, were also in accordance with other similar studies of other ultrathin/thin strut DES. The TLF rate in the present registry was 5.75% compared to 5.3% in Thailand Orsiro registry on Orsio SES, 5.1% in BIOFLOW-III registry on Orsio SES, and 5.8% in all-comers registry on Synergy everolimus-eluting stent (EES) [28-30]. Moreover, a study by Azzalini L et al. [31] compared three contemporary thin-strut DES (Xience EES, Promus EES and Synergy EES) in patients undergoing complex PCI. Twelve-month follow-up results of that study revealed 8.9%, 8.9%, and 8.6% major adverse cardiac events with Xience EES, Promus EES, and Synergy EES, respectively which represent higher events compared to the present registry on ultrathin Tetriflex SES though it includes complex subset of patients. Furthermore, it was noteworthy that the overall incidence of CD-TLR (1.72%) and non-target lesion TVR (1.07%) in this registry were considerably low, indicating the robust efficacy of ultrathin Tetriflex SES in preventing restenosis. The ultrathin struts in Tetriflex SES might be one of the components associated with the low rate of restenosis as they initiate early endothelial cell coverage which is extremely essential in regulation of vascular inflammation, smooth muscle cell proliferation and prevention of neoatherosclerosis [32-34]. In addition to this, several meta-analyses have also reported reduced rates of TLF with ultrathin DES (strut thickness <70 μm) compared to contemporary thicker strut DES at short-term (1 year) and even at long-term (mean 2.5 years)

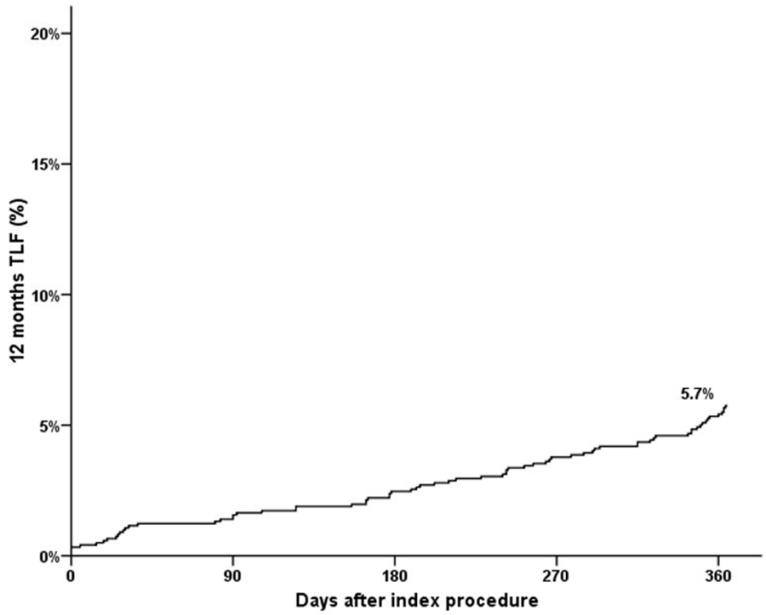

Figure 2. Cumulative rate of target lesion failure at 12 months follow-up.

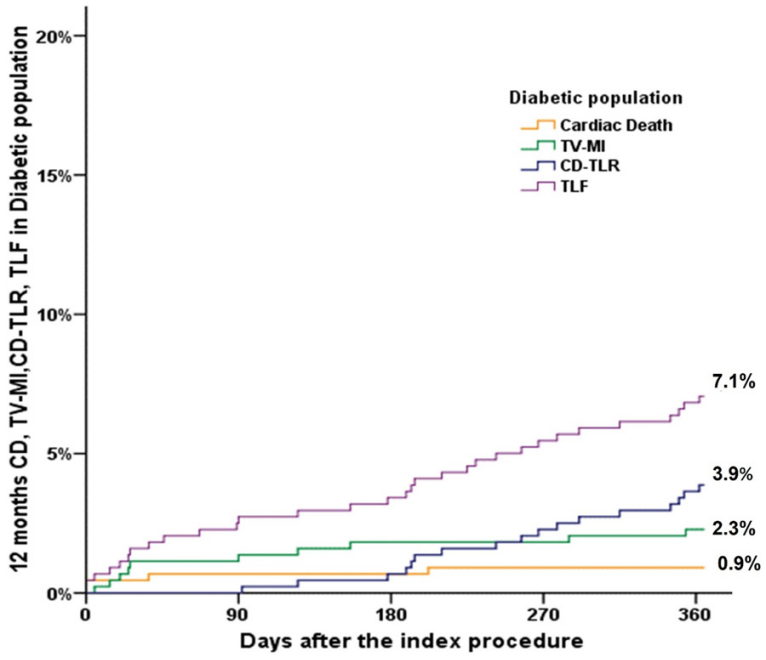

Figure 3. Cumulative rate of target lesion failure at 12 months follow-up in diabetic subset of patients.

follow-up [4, 7, 8, 10]. A recently published meta-analysis demonstrated reduce rate of device oriented composite events by 11% with ultrathin strut DES compared to thicker strut DES at a maximum follow-up of three years [9]. The primary and safety outcomes of the present registry are compared with the previous studies on different second and newer generation DES in **Table 5**.

Lack of complete strut coverage and optimal healing have been strongly associated with the incidence of late stent thrombosis. The prime determinant factor for the duration of strut coverage after stent implantation is strut thickness. Various studies have reported that thinner struts provide complete endothelial coverage with rapid healing and thus may lessen the risk of platelet aggregation and stent thrombosis. In support to these, the present registry reported only 0.32% rate of definite/probable stent thrombosis with ultrathin Tetriflex SES at 12 months follow-up. In contrast to the present registry, Thailand Orsiro registry reported 1.3%, an all-comers registry on thin strut Synergy EES reported 0.5%, SPIRIT-V registry on thin strut Xience EES reported 0.66%, and E-Five registry on thin strut Endeavor zotarolimus-eluting stent (ZES) reported 1.1% definite/probable stent thrombosis [28, 30, 35, 36]. Furthermore, recently published two optical coherence tomographic (OCT) studies, namely SiBi [18] and TAXCO [19], have examined arterial healing pattern and strut coverage of ultrathin Tetriflex SES with LDZ-link at 4-6 weeks and at six months of implantation, respectively. Tetriflex SES showed 91.26% strut coverage at mean OCT follow-up of only 35 days in SiBi study, and 98.13% strut coverage at six months OCT follow-up in TAXCO study. Notably, the present registry did not report any case of cardiac death between 6-12 months and definite/probable stent thrombosis between 1-12 mon-

Table 5. Twelve-month clinical outcomes of standard biodegradable polymer DES and durable polymer DES in various studies and of Tetriflex SES in present registry

Stents	Polymers	Platform	Strut thickness (μm)	Study Name	Events at 12 months follow-up			
					TLF/ MACE	CD-TLR	MI	ST (D/P)
Tetriflex	Biodegradable	Co-Cr	60	Present registry	5.75%	1.72%	3.2%	0.32%
Synergy [30]	Biodegradable	Pt-Cr	74-81	Prospective all-comers registry (Asian population)	5.8%	1.3%	1%	0.5%
Ultimaster [40]	Biodegradable	Co-Cr	80	CENTURY study	3.8%	1.9%	1.9%	0.95%#
Orsiro [29]	Biodegradable	Co-Cr	60-80	BIOFLOW-III registry	5.1%	3.0%	2.7%	0.2%*
Endeavor [36]	Durable	Co-Cr	91	E-Five Registry	7.5%	4.5%	1.6%	1.1%
Xience [35]	Durable	Co-Cr	81	SPIRIT-V registry	5.1%	1.8%	3.5%	0.66%

*Only definite stent thrombosis; #Acute stent thrombosis. TVR: Target vessel revascularization. DES: drug eluting stents; TLF: target lesion failure; MACE: major adverse cardiac events; CD-TLR: clinically driven target lesion revascularization; MI: myocardial infarction; ST (D/P): definite and probable stent thrombosis; Co-Cr: cobalt-chromium; Pt-Cr: platinum-chromium; EES: everolimus-eluting stent.

ths follow-up which point towards its excellent safety after implantation. The OCT results and low rate of stent thrombosis in the present registry altogether concentrate on the positive influence of ultrathin struts (60 μm) on better, uniform, and faster vessel healing of Tetriflex SES.

The present registry reported the cumulative incidence of TLF in diabetic subgroup as 7.1% at 12 months follow-up. This result was in line with the findings of T-Flex registry on ultrathin Supra family SES (6.8%), and BIOFLOW-III Italian satellite registry on ultrathin/thin Orsiro SES (6.9%). In contrary to this, E-five registry (thin strut Endeavor ZES) and NOBORI-2 registry (thick strut Nobori Biolimus A9-eluting stent) reported higher rate of TLF (9.5% and 9.86%, respectively) in diabetic patients at 12 months follow-up [13, 36-38]. Thus, ultrathin Tetriflex SES can be considered as safe and clinically effective even in high-risk diabetic patients. However, an ongoing randomized-controlled TUXEDO-2 trial (Trial Registration Number: CTRI/2019/11/022088), comparing ultrathin Supraflex Cruz SES with LDZ-link and Xience EES family on Indian patients with diabetes mellitus and multivessel disease, will further validate its effectiveness in high-risk diabetic patients [22].

The unique LDZ-link design in Tetriflex SES along with long connectors and in-phase strut offer exceptional trackability, aid flexibility, provide good structural support with better push force through the complex lesions and tortuous coronary arteries. Consequently, ultrathin struts and these unique design characteristics collectively augment stent integrity and radial strength and also resist longitudinal stent compression and foreshortening [4, 22, 39]. Thus, all these characteristics along with its broad size matrix (diameter 2.0-4.5 mm and length 8-48 mm) make Tetriflex SES, an appropriate DES to handle complex coronary lesions as well. A recently published study by SK Sinha et al. confirmed effective use of ultrathin Supra family SES with LDZ-link in complex bifurcation lesion (Medina class: 1, 1, 1 and 0, 1, 1) using specific Nano-crush technique with ease without any procedural complications [15]. Similarly, another study reported safety and effectiveness of ultra-long (≥40 mm) ultrathin Supralimus Grace SES with LDZ-link for the treatment of long coronary lesions at 12 months follow-up (TLF: 6.1%) [14]. In addition to these, various randomized controlled trials, and prospective registries on Supra family SES are ongoing and in pipeline all around the globe on broad array of complex subset of patients and lesions which will answer various unanswered questions on this unique ultrathin DES [20-22].

Tetriflex ultrathin strut (60 μm) SES with unique LDZ-link has already been proved as a most deliverable DES and as efficacious as standard of care DES. The results of this registry and all ongoing studies of Tetriflex SES on wide range of complex and heterogenous patient population all around the globe will take it more closer towards the title of an ideal DES for all sorts of patients.

Study limitations

The limitations of this registry include i) its retrospective and observational nature, ii) lack

of direct head-to-head comparison, and iii) the registry only report 12 months follow-up outcomes; however, long-term follow-up should be reported in future.

Conclusion

Twelve months results of Tetriflex SES reported favourable clinical outcomes with low incidence of TLF and stent thrombosis in real-world patients and even in high-risk diabetes patients. The results of the present registry clearly indicate extrapolation of the safety and effectiveness of ultrathin (60 μm), biodegradable polymer-coated Tetriflex SES with unique LDZ-link in real-world, unselected Indian patients.

Disclosure of conflict of interest

None.

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