Comparison of Two Biodegradable Polymer Coated, Drug-Eluting Coronary Stents Paclitaxel vs. Sirolimus, with 6-Years Clinical Follow-Up: BIOPRESS (BIOdegradable Polymer REgistry Smt Stents) Infinnium vs. Supralimus

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Abstract: *Background*: The safety and efficacy of drug-eluting stents has been shown in randomized trials, but some controversy exists regarding which stent, sirolimus-eluting or paclitaxel-eluting is more effective in unselected real-world patients. Therefore, we investigated, long term safety and efficacy of paclitaxel-eluting stents (PES) compared to sirolimus-eluting stents (SES) when used without restriction in unselected real-world patients.

Methods: We created a prospective, open label, non-randomized, multicenter registry and analyzed data on a consecutive series of all patients who presented to our institution with symptomatic coronary artery disease between July-2004 and June-2006 and who were treated with the Infinnium® PES or the Supralimus® SES. All enrolled patients were divided into two groups based on stent type. By outpatient clinic visit and telephone interview, we obtained up to 6-years clinical outcomes including death, myocardial infarction (MI), stent thrombosis (ST), target lesion revascularization (TLR), target vessel revascularization (TVR), and major adverse cardiac events (MACE, the composite of cardiac death, TLR, TVR and ST).

Results: In total, 571 patients were treated with either the Infinnium® PES (n=276) or the Supralimus® SES (n=295). Baseline clinical and angiographic characteristics were almost similar in the two groups. The six-year clinical follow-up was completed in 529 patients (92.6%). Total 1.4% in-hospital major adverse cardiac event (MACE) were recorded (1.8% Infinnium® PES vs. 1.0% Supralimus® SES) with 99% procedural success. At 6-years, all-cause death was significantly lower in Supralimus® SES group than in Infinnium® PES group (3.1% vs. 6.9%, *p*=0.03). The incidence of cardiac death (4.3% vs. 2.7%, *p*=0.29), TLR (3.6% vs. 3.7%, *p*=0.95, TVR (4.0% vs. 2.4%, *p*=0.27) and ST (2.5 vs. 1.0, *p*=0.17) was more frequent in the Infinnium® PES group compare to Supralimus® SES group, but it did not reach statistical significance.

Conclusion: The long-term follow-up of 6-years, demonstrated the safety and efficacy of both Infinnium® PES and Supralimus® SES biodegradable polymer coated drug-eluting stents (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) in real-world practice. Also superiority of Supralimus® SES proved on long term follow-up with complex lesions.

Keywords: Biodegradable polymer, paclitaxel-eluting stent, sirolimus-eluting stent, percutaneous coronary intervention.

INTRODUCTION

The drug-eluting stent (DES) has been proved to largely resolve the problem of restenosis, the major limitation of balloon angioplasty and bare-metal stenting [1, 2]. A recent meta-analysis of 38 randomized trials has further demonstrated that DES was associated with lower risk of target vessel revascularization (TVR) compared to bare-metal stent (BMS) [3]. Approved DESs have addressed one of the key limitations of bare metal stents by using site-specific therapy to reduce neointimal proliferation and subsequent in-stent restenosis [4]. Both sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have been demonstrated to reduce rate of angiographic and clinical restenosis after percutaneous coronary intervention (PCI) [5-7].

Some recent studies have also cautioned that either SES or PES could increase thrombotic complications compared to BMS, especially late stent thrombosis [8-9], due to decreased endothelial function [10], delayed vascular healing [11], and/or hypersensitivity reactions to the polymer coating of the DES and the drug itself

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[12, 13]. Furthermore, in meta-analyses of studies comparing the two stent types, authors have confirmed a clinical advantage for those who receive the SES [14-17]. However, the long-term safety of drug-eluting stents has been questioned [17-19]. Despite the results of meta-analyses of randomized studies that refute these concerns [20], the possible association of the stents with late stent thrombosis remains a limitation of this new technology.

Limited data exist to compare outcomes beyond 1-year between SES and PES platforms and in larger unselected patient cohorts with complex lesion subsets of Saudi patients. The primary purpose of this registry was to determine if clinically meaningful differences exist in MACE-free survival by comparing 6-year clinical outcomes in unselected, "real world" patients undergoing intervention with Supralimus® SES and Infinnium® PES (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) in Saudi Arabia.

MATERIALS AND METHODS

Overview and Study Population

BIOPRESS–Infinnium vs. Supralimus was a prospective, open label, non-randomized, multicenter registry. Consecutive coronary interventions with DES, which were performed from July 2004 to June-2006 at four clinical centers in Saudi Arabia, were entered into the registry. The registry population consisted of 571 consecutive series of all patients who had undergone coronary stent implantation for coronary artery disease; 276 of the patients received the Infinnium® PES (Sahajanand Medical Technologies Pvt. Ltd., Surat, India), and the other 295 patients received the Supralimus® SES (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) (Figure **1**).

Inclusion Criteria

Patients were eligible for enrollment if there was symptomatic coronary artery disease or positive functional testing that were undergoing PCI with Infinnium® PES or Supralimus® SES stent were considered for this registry.

Exclusion Criteria

Because there were no exclusion criteria, the intent was to enroll every patient undergoing PCI.

All centers obtained institutional review board (IRB) approval to prospectively consent and enroll patients. The study complied with the Declaration of Helsinki regarding investigation in humans and all patients provided written informed consent.

Overview of Devices

Infinnium® PES

The active ingredient in the Infinnium® stent is paclitaxel. The paclitaxel concentration loaded on each stent was maintained to 1.4 μg/mm^2. The drug was applied to the surface of a stainless steel (slotted tube design), balloon-expandable stent (Matrix®, Sahajanand Medical Technologies Pvt. Ltd.) using biodegradable polymers (Poly L-Lactide, 50/50 Poly DL-Lactide-co-Glycolide, 75/25 Poly LLactide-co-Caprolactone and Polyvinyl Pyrrolidone) in multiple layers. The drug is coated in 3 different layers of combination of drug and polymer. Each layer has a different release profile. The cumulative release of drug from the polymer is at 48 days after implantation (Figure **2**). The Infinnium® stent was made available in lengths of 11, 16, 19, 23, 29, 33, and 39 mm and

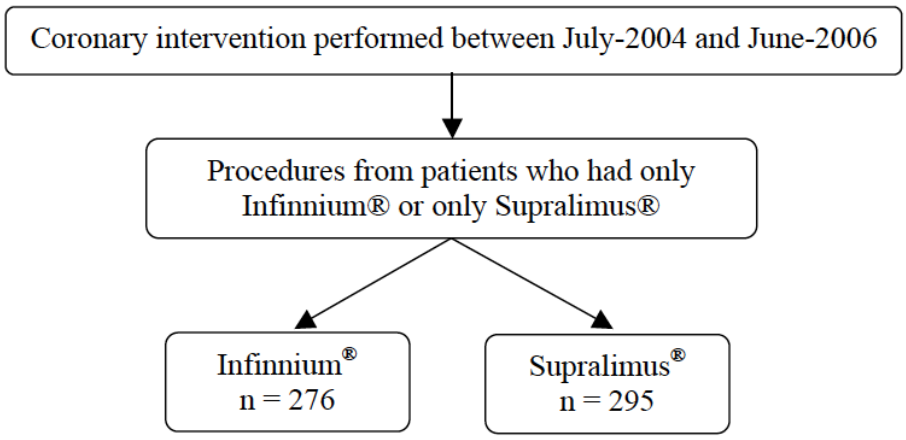

Figure 1: Flow chart of study population.

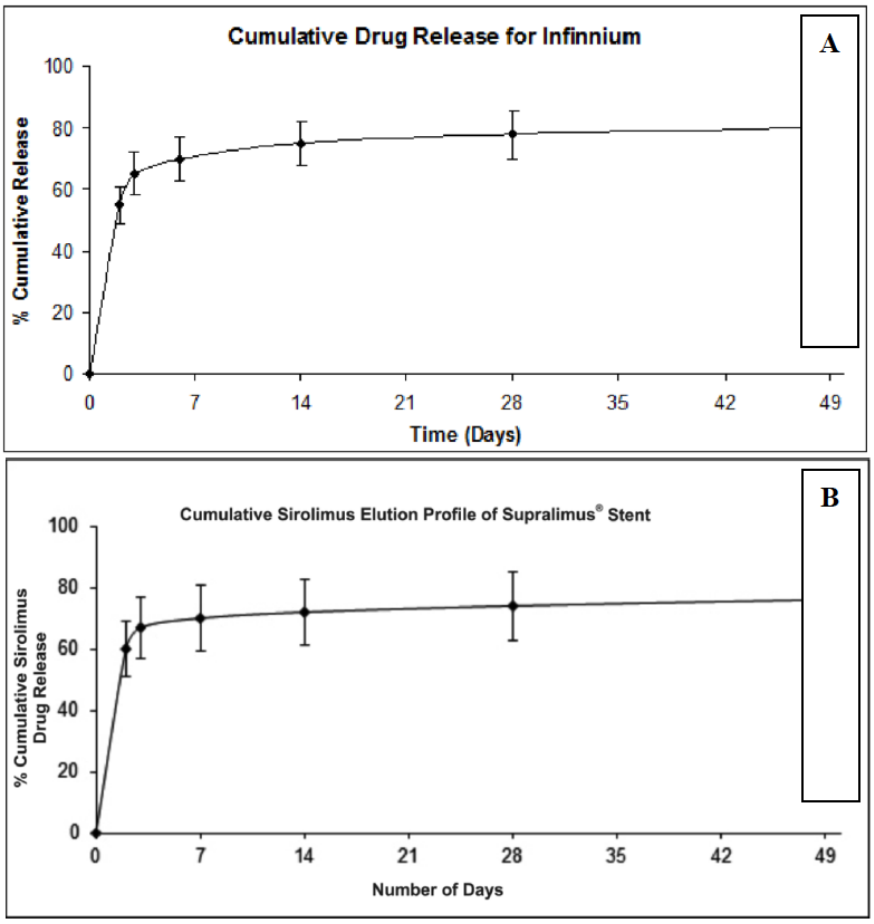

Figure 2: Cumulative in-vitro release profile of (**A**) paclitaxel from Infinnium® PES; (**B**) sirolimus from Supralimus® SES.

available diameters were 2.5, 2.75, 3.0, 3.5 and 4.0 mm.

Supralimus® SES

Supralimus® (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) has stainless steel as its stent platform having a strut thickness of 80 µm with biodegradable polymers and drug load of 1.4 µg / mm^2. About 70% of drug is released within 7 days and remaining drug is released over a period of 48 days (Figure **2**). The coating layer comprises of the drug Sirolimus blended together with biodegradable polymeric matrix. This matrix includes blend of hydrophobic and hydrophilic biodegradable polymers - Poly L-Lactide, 50/50 Poly DL Lactide-co-Glycolide and Polyvinyl Pyrrolidone to control the drug elution from stent coating. The Supralimus®stent was made available in lengths of 11, 16, 19, 23, 29, 33 and 39 mm and available diameters were 2.5, 2.75, 3.0 and 3.5.

Coronary Intervention and Procedural Treatment

Coronary stenting was performed using conventional techniques, and stents were chosen at cardiologist' discretion. Infinnium® PES and Supralimus® SES were used in 276 and 295 patients, respectively. During the intervention, all patients received 100–140 IU/kg of unfractionated heparin. Patients also received 75 mg/day of clopidogrel (at least 6 month), and 81 mg/day of aspirin for the remainder of their lives. Glycoprotein IIb/IIIa inhibitor was also administered according to cardiologist' preferences.

Outcomes and Definitions

The primary outcome was the occurrence of major adverse cardiac events (MACE), defined as a composite of: 1) cardiac death, 2) target lesion revascularization (TLR), 3) target vessel revascularization (TVR) and 4) stent thrombosis (ST). Deaths were classified as cardiac or non-cardiac. Deaths from undetermined causes were reported as cardiac. MI was defined as the elevation of creatine kinase (CK) > 2 times above the upper limit of normal with any associated elevation in the CK myocardial band or the development of new pathologic Q waves in 2 contiguous electrocardiographic leads [21]. TLR was

defined as a repeat intervention (surgical or percutaneous) to treat a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. TVR was defined as a re-intervention driven by any lesion located in the same epicardial vessel. ST was classified as acute when it occurred within 24 hours of the index procedure, sub-acute when it occurred between one and 30 days, and late when it occurred beyond 30 days. ST was considered 'definite' when confirmed angiographically and 'probable' when the patient had a target vessel–related MI or died of a coronary event, possibly caused by stent thrombosis, within 30 days of the index procedure [21].

Data Collection and Clinical Follow-Up

Baseline clinical and angiographic data were collected for all patients; including age, sex, traditional coronary risk factors, prior myocardial infarction, and clinical presentation. Adverse events, angina status, and cardiovascular medication intake were assessed in hospital, at 1, 6, and 9 months, and on an annual basis up to 6-years. All repeat interventions and re-hospitalizations were prospectively collected during follow-up. Referring physicians and institutions were contacted for additional information if required.

Statistical Analysis

All data were analysed with the use of Statistical Package for the Social Sciences (SPSS) version 15 (IBM SPSS, Inc. in Chicago, Illinois). Continuous variables were presented as mean±SD and were compared by means of the Student's t test. Categorical variables were presented as counts and percentages and compared by means of the χ^2 test or Fisher's exact test. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method and compared by the log rank test. A P value < 0.05 was considered statistically significant.

RESULTS

Study Population

Between July-2004 and June-2006, 571 consecutive patients underwent successful Infinnium® PES or Supralimus® SES implantation were prospectively enrolled in the present registry. Of these, 276 patients (353 lesions) received Infinnium® PES stents, 295 patients (358 lesions) received Supralimus® SES stents.

Baseline and Procedural Characteristics

Baseline clinical, angiographic, and lesion characteristics are shown in Tables **1** and **2**. Of 571

Table 1: Baseline Demographics Characteristics

Characteristics	Infinnium® PES n = 276 patients	Supralimus® SES n = 295 patients	*p* value
Age (mean ± SD, yrs)	56.0 ± 11.1	55.0 ± 10.8	0.27
Male, n (%)	225 (81.5%)	246 (83.4%)	0.56
Diabetes mellitus, n (%)	142 (52.0%)	153 (51.9%)	0.92
Hypertension, n (%)	172 (62.3%)	173 (58.6%)	0.37
Smoker, n (%)	106 (38.4%)	159 (53.9%)	< 0.001
Hypercholesterolemia, n (%)	185 (67.0%)	189 (64.1%)	0.46
Family history, n (%)	24 (8.7%)	27 (9.2%)	0.85
Previous myocardial infarction, n (%)	148 (53.6%)	182 (61.7%)	0.05
Previous PCI, n (%)	174 (63.0%)	131 (44.4%)	<0.001
Previous CABG, n (%)	12 (4.3%)	12 (4.1%)	0.87
Left ventricular ejection fraction (mean ± SD)	55.4 ± 12.5	52.4 ± 11.5	0.003
PCI Indications			
Unstable angina, n (%)	115 (41.7%)	106 (35.9%)	0.16
Stable angina, n (%)	80 (29.0%)	67 (22.7%)	0.09
Acute myocardial infarction, n (%)	47 (17.0 %)	44 (14.9%)	0.49
Cardiogenic stroke, n (%)	3 (1.1%)	1 (0.3%)	0.28

PES: paclitaxel-eluting stent, PCI: percutaneous coronary intervention, CABG: Coronary arteries bypass graft.

Table 2: Lesion and Procedural Characteristics

Characteristics	Infinnium® PES Patients = 276 / Lesions = 353	Supralimus® SES Patients = 295 Lesions = 358	*p* value
Lesion Location			
Left anterior descending, n (%)	170 (48.2%)	177 (49.4%)	0.73
Right coronary artery, n (%)	100 (28.3%)	103 (28.8%)	0.90
Left circumflex, n (%)	78 (22.1%)	72 (20.1%)	0.52
Left main, n (%)	1 (0.3%)	3 (0.8%)	0.62
Saphenous vein graft, n (%)	4 (1.1%)	3 (0.8%)	0.72
ACC/AHA Lesion Classification			
A, n (%)	11 (3.1%)	15 (4.2%)	0.45
B1, n (%)	71 (20.1%)	88 (24.6%)	0.15
B2, n (%)	218 (61.8%)	206 (57.5%)	0.25
C, n (%)	53 (15.0%)	49 (13.7%)	0.61
Lesion characteristics			
Long (≥30 mm) lesion, n (%)	47 (13.3%)	48 (13.4%)	0.97
Bifurcation lesion, n (%)	22 (6.2%)	45 (12.6%)	0.004
Calcified (moderate/severe), n (%)	27 (7.6%)	40 (11.2%)	0.11
Restenotic lesion, n (%)	22 (6.2%)	22 (6.1%)	0.96
Total occlusion, n (%)	54 (15.3%)	53 (14.8%)	0.85
Direct stenting, n (%)	8 (2.3%)	27 (7.5%)	<0.001
No. of Diseased Vessels			
Single vessel disease, n (%)	186 (67.4%)	203 (68.8%)	0.72
Double vessel disease, n (%)	75 (27.2%)	75 (25.4%)	0.64
Triple Vessel Disease, n (%)	15 (5.4%)	17 (5.8%)	0.87
Procedural data			
Total no. of stents, n	476	495	
No. of stents per patient, (mean ± SD, mm)	1.72 ± 1.04	1.68 ± 1.11	
Average Stent Length, (mean ± SD, mm)	21.8 ± 7.5	21.8 ± 7.4	
Average Stent Diameter, (mean ± SD, mm)	3.0 ± 0.5	3.1 ± 0.5	

patients, 471 (82.5%) were male with a mean age of 55.48±10.94 year. The baseline clinical or demographic characteristics indicated no statistically significant differences between patients who received the Infinnium® PES vs. those who received the Supralimus® SES, except smoking history. A total of 221 (38.7%) patients had unstable angina, 147 (25.7%) had stable angina and 91 (15.9%) had acute myocardial infarction. With respect to target vessels, the frequency of type B2, C, and complex lesions (long lesions, calcified lesions, restenotic lesion) was similar between the two groups. A total of 971 DES were implanted in 571 patients (Infinnium® PES=476 vs. Supralimus® SES=495). The mean stent diameter was 3.0±0.5 mm among those who received the Infinnium® PES and 3.1±0.5 mm among those who received the Supralimus® SES. The mean stent length was 21.8±7.5 mm in the Infinnium® PES group and 21.8±7.4 mm in the Supralimus® SES group (Table **2**).

In-Hospital and Long-Term Clinical Outcomes

Complete clinical follow-up at 6-years was accomplished for 529 (92.6%) patients. Total 1.4% in-hospital major adverse cardiac event (MACE) were recorded (1.8% Infinnium® PES vs. 1.0% Supralimus® SES) with 99% procedural success (*p*=0.49). The safety measures up to 6-years are shown in Table **3**. At 1-year, 10 (3.6%) patients died in the Infinnium® PES group and 4 (1.4%) patients died in the Supralimus® SES group (*p*=0.08). Also, stent thrombosis was higher

in Infinnium® PES group compare to Supralimus® SES group (p=0.08) at 1-year. At 6-years, all-cause death was significantly lower in Supralimus® SES group than in Infinnium® PES group (3.1% vs. 6.9%, p=0.03). MACE occurred in 40 (14.5%) patients in the SES group and 29 (9.8%) patients in the PES group (p=0.09) at six-year follow-up. The prevalence of cardiac death, TLR, TVR and ST was lower in the Supralimus® SES group compared to the Infinnium® PES group, but did not achieve statistical significance (p=0.29, 0.95, 0.27 and 0.17 respectively) at 6-years follow-up (Table **3**).

The cumulative event rates estimated by the Kaplan-Meier method and the log-rank test showed no significant difference between the two groups for time to event for cardiac death, TLR, TVR and MACE (Figure **3**).

DISCUSSION

It has been demonstrated that use of drug-eluting stent (DES) is associated with equivalent safety outcomes and more than a slightly better efficacy outcomes, as compared to BMS [3, 22-24]. Furthermore, some studies have demonstrated a potential benefit of sirolimus-eluting stent (SES) over paclitaxel-eluting stent (PES) [13, 17, 25].

Therapeutic differences between the two first-generation DES (PES and SES) have been addressed in numerous randomized trials. Angiographic studies have consistently shown superior reduction of neointimal hyperplasia afforded by SES. In contrast, individual clinical trials comparing SES and PES have reported mixed results, although the synthesis of the available evidence as summarized in several meta-

Table 3: Clinical Outcomes at 6-Years

	Events	Infinnium® PES (n=276)	Supralimus® SES (n=295)	*p*-value
0-1 year	Death, n (%)	10 (3.6%)	4 (1.4%)	0.08
	Cardiac Death, n (%)	7 (2.5%)	4 (1.4%)	0.31
	Non-Cardiac Death, n (%)	3 (1.1%)	0 (0%)	0.07
	Myocardial infarction, n (%)	0 (0%)	0 (0%)	-
	Target lesion revascularisation, n (%)	6 (2.2%)	6 (2.0%)	0.91
	Target vessel revascularisation, n (%)	3 (1.1%)	4 (1.4%)	0.77
	Stent thrombosis, n (%)	7 (2.5%)	2 (0.7%)	0.08
	MACE, n (%)	23 (8.3%)	16 (5.4%)	0.17
>1-year	Death, n (%)	9 (3.3%)	5 (1.7%)	0.23
	Cardiac Death, n (%)	5 (1.8%)	4 (1.4%)	0.66
	Non-Cardiac Death, n (%)	4 (1.4%)	1 (0.3%)	0.16
	Myocardial infarction, n (%)	0 (0%)	0 (0%)	-
	Target lesion revascularisation, n (%)	4 (1.4%)	5 (1.7%)	0.81
	Target vessel revascularisation, n (%)	8 (2.9%)	3 (1.0%)	0.10
	Stent thrombosis, n (%)	0 (0%)	1 (0.3%)	0.33
	MACE, n (%)	17 (6.2%)	13 (4.4%)	0.35
0-6 years	Death, n (%)	19 (6.9%)	9 (3.1%)	0.03
	Cardiac Death, n (%)	12 (4.3%)	8 (2.7%)	0.29
	Non-Cardiac Death, n (%)	7 (2.5%)	1 (0.3%)	0.03
	Myocardial infarction, n (%)	0 (0%)	0 (0%)	
	Target lesion revascularisation, n (%)	10 (3.6%)	11 (3.7%)	0.95
	Target vessel revascularisation, n (%)	11 (4.0%)	7 (2.4%)	0.27
	Stent thrombosis, n (%)	7 (2.5%)	3 (1.0%)	0.17
	MACE, n (%)	40 (14.5%)	29 (9.8%)	0.09

MACE: Major Adverse Cardiac Events.

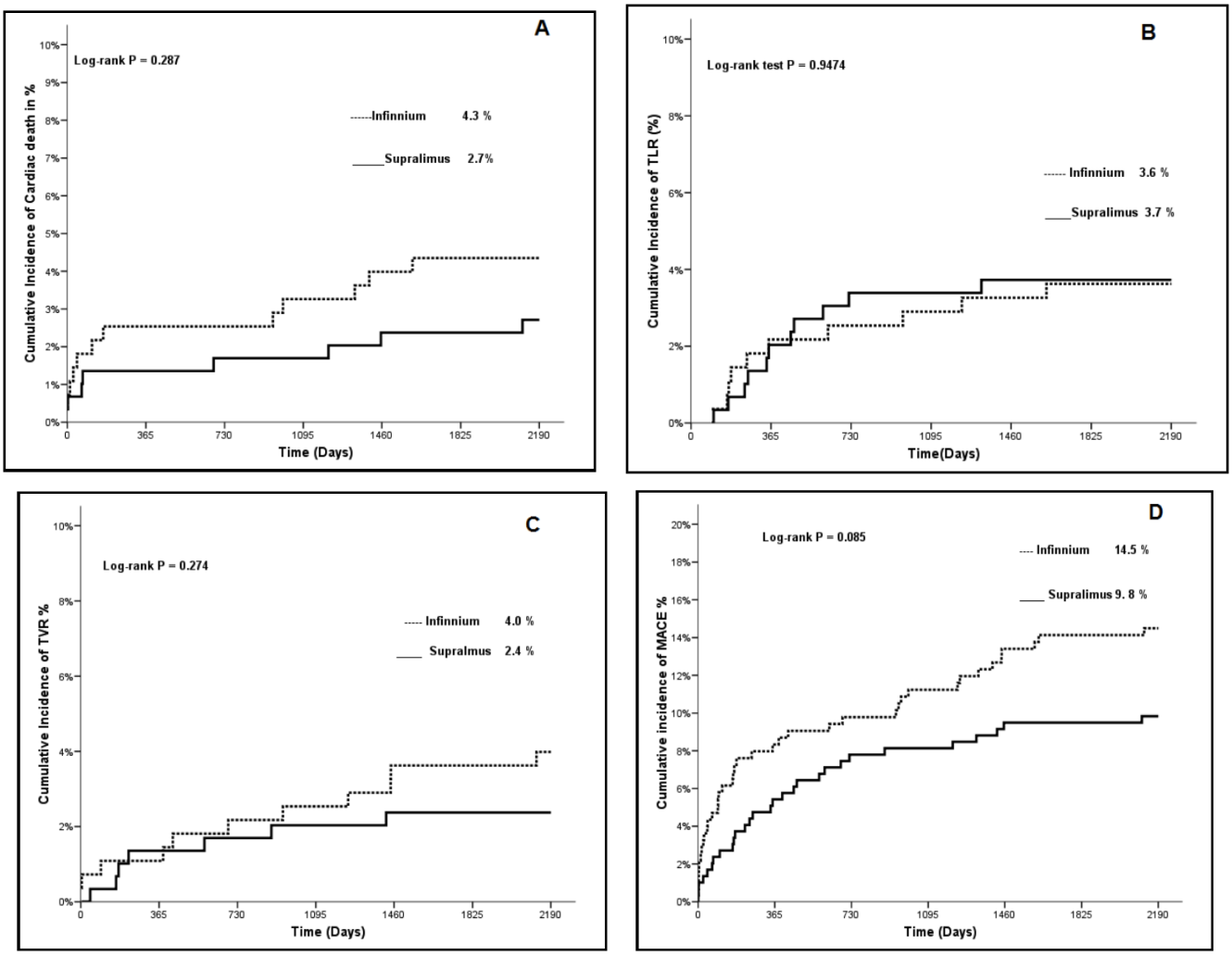

Figure 3: Kaplan-Meier estimates of (**A**) cardiac death; (**B**) target lesion revascularization (TLR); (**C**) target vessel revascularization (TVR) and (**D**) major adverse cardiac events (MACE).

analyses suggests a lower risk of TLR with SES [3]. The superior suppression of neointimal hyperplasia and lower risk of restenosis associated with SES have been attributed to differences in the mode of action of the therapeutic agent [26], and have been confirmed more recently with other limus analogues [27]. However, previous studies comparing SES with PES reported angiographic outcomes at 6 to 8-months, and the longest available clinical follow-up is limited to 2-years [28]. The present registry provides additional information by extending the follow-up to 6-years in the unrestricted use of SES and PES.

Biodegradable polymer drug-eluting stents were designed to diminish long-term adverse events related to the persistence of durable polymers after completion of drug-release. In our study we preferred biodegradable polymer-based Infinnium® PES and Supralimus® SES, which are made up of Millennium Matrix® stainless-steel stent as a platform and biodegradable polymer coating. Infinnium® PES and Supralimus® SES tested in the PAINT trial were effective in reducing late lumen loss in comparison to bare metal stents, resulting in a significant decrease in the rate of re-intervention and major adverse cardiac events during the first year. In the PAINT trial, the head-to-head comparison between two novels DES, which differed by the drug but were identical, otherwise, suggested that the agent sirolimus is more effective in reducing angiographic neointimal proliferation than paclitaxel [29].

There are limited data regarding comparison of relative differences in long-term safety and efficacy between the SES and PES in Saudi population. In our study, no differences existed in baseline clinical and angiographic characteristics between those who received the Infinnium® PES and those who received the Supralimus® SES. The Supralimus® SES was associated with better clinical outcomes compared with

the Infinnium® PES; rates of MACE were 9.8% vs. 14.5% (p=0.09) at 6-years follow-up in real-word Saudi population. Also rate of stent thrombosis is lower in SES group compare to PES group (1.0 vs. 2.5, p=0.17) at six years.

CONCLUSIONS

The long-term follow-up of 6-years, demonstrated the safety and efficacy of both Infinnium® PES and Supralimus® SES biodegradable polymer coated drug-eluting stents (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) in real-world practice. Also, the efficacy of the Supralimus® SES was maintained up to 6-years in a very challenging real world population.

STUDY LIMITATIONS

There are several limitations to this study. First limitation is that each group was treated in different time periods. This might lead to some bias in terms of patient selection and affect procedural characteristics, as treatment strategy has evolved over time. However, it should be noted that this registry enrolled consecutive patients treated in daily practice: we enrolled all comers and had no exclusion criteria. Second, there was no significant difference in either clinical or angiographic baseline data. And third, the number of patients is very limited in comparison to other registries.

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