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RESEARCH ARTICLE

Three years performance of Biodegradable Polymer Sirolimus Eluting Stent in all comer patients undergoing Percutaneous Coronary Intervention.

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ABSTRACT

Introduction: Contemporary evidence suggest the comparable performance of biodegradable polymer sirolimus eluting stents (BPSES) with that of second generation durable polymer drug eluting stents. This study was done to evaluate the performance of BPSES in all comer patients undergoing percutaneous intervention (PCI) in real world setting over a period of three years.

Materials & Methods: This was a prospective observational study, wherein all comer consecutive patients undergoing PCI with BPSES (Yukon Choice Elite stent by Translumina Therapeutics, India) were enrolled and followed up for 3 years. The study's primary endpoint was the Device Oriented Composite Endpoint (DOCE), which included cardiac death, target vessel myocardial infarction (MI), and clinically driven target lesion revascularization (TLR); the co-primary endpoint was the Patient-Oriented Composite Endpoint (POCE), which included all-cause mortality, any MI , and any repeat revascularization and the secondary endpoint was definite or probable stent thrombosis (DST & PST).

Results: 301 patients with 502 lesions were treated with 485 BP-SES. Mean age of the study cohort was 61.6± 9.3 yrs and males were 79.1%. 18.6% patients were diabetic, 29.6% had ejection fraction less than 40% and 73.1% patients presented with acute coronary syndrome (ACS). Majority of the patient had triple vessel disease (TVD) (51.8%), multivessel PCI was done in 15.6% and complex PCI in 26.2% patients. A mean of 1.6 ±0.8 stents per patient with mean diameter 3.0 ± 0.3 mm and mean length of 27.2 ± 0.8 mm were placed. DOCE & POCE occurred in 7.9% (cardiac death-4.8%, TLR-2.6% & target vessel MI-0.4%) and 12.8% (All deaths-9.7%, any MI- 0.4% and any revascularisation-2.6%) patients respectively at three years follow-up. DST & PST rate was 0.9% and 0.4% respectively in the study cohort. All the cases of stent thrombosis occurred within 30 days. Kaplan Meier analysis revealed that diabetes mellitus, low ejection fraction (EF), acute coronary syndrome (ACS), long stents and complex intervention had no impact on occurrence of DOCE & POCE while using BP-SES in all-comer patient population.

Conclusion: Present study showed favourable long term safety and efficacy profile of BP-SES for all-comer patients undergoing PCI.

Keywords: Biodegradable Polymer Drug Eluting Stent, Durable Polymer Drug Eluting Stent, Biodegradable Polymer Sirolimus Eluting Stent, Durable Polymer Sirolimus Eluting Stent, Bare metal stent, Percutaneous Coronary Intervention, Stent thrombosis, Yukon choice PC Elite.

1. Introduction

Era of percutaneous coronary intervention (PCI) started with the first successful balloon angioplasty performed by Andreas Gruentzig in 1977. However, the unpredictable nature of vessel response to a balloon dilatation sometimes resulted in severe dissections causing acute vessel compromise or chronic constrictive remodelling resulting in high re-stenosis rates of over 40% at 6 months[1]. This limitation was overcome partially with a bare-metal coronary stent (BMS) to scaffold the luminal surface for sealing dissections, resisting recoil and favourably effecting vascular remodelling, thereby building upon the results of balloon angioplasty. However, even with optimal stent implantation, in-stent restenosis (ISR) still occurred in approximately 20% to 40% of patients within 6 to 12 months[2]. Drug eluting stents (DES) were thus designed with an anti-re-stenotic drug coated over BMS, which would deliver the drug locally on the arterial wall and helped in a 50% to 75% reduction in rates of restenosis[2,3,4]. First generation DES had sirolimus or paclitaxel as anti-proliferative drug coated over stainless steel stent platform with the help of a durable polymer. Studies have shown that these first-generation DES lead to significant reduction in ISR and repeat revascularization as compared to BMS, but at the cost of delayed stent endothelialization resulting in late or very late stent thrombosis. This late complication was chiefly attributed to the inflammatory response of the vessel wall against the polymer substance[5,6,7]. To overcome these issues, second generation DES came into light with cobalt–chromium platforms, thinner stent struts (50–90 μm), newer anti-proliferative drugs (everolimus and zotarolimus, biolimus and novolimus) and with biocompatible polymers (fluorinated co-polymer, phosphorylcholine or Biolinx polymer). These newer DES reduced the late safety issues that became apparent with first-generation DES[8]. Randomized control trials (RCTs), observational studies, and meta-analyses thereafter suggested that second-generation DES have a better safety and efficacy profile than first-generation DES[9,10,11].

Biodegradable polymer-based DES (BP-DES) were thereafter developed to further negate the risk of very late adverse events attributable to durable polymers. Through drug elution and complete absorption of the polymer, BP-DES aimed to couple DES efficacy with the late safety profile of BMS. Although theoretically advantageous, the BP-DES has shown benefit in very late stent thrombosis only when compared to the first generation DES[12,13]. However against the second generation DES which employ biocompatible and thromboresistant polymers, various metanalysis and trials have shown no additional benefit even in the risk of very late stent thrombosis[12,14,15,16].

BP-DES may improve arterial healing by removing the chronic source of inflammation, the durable polymer. This study was done to evaluate the long-term safety and efficacy profile of a biodegradable polymer sirolimus eluting stent (BP-SES) in all comer patients undergoing PCI.

2. Methodology

2.1 STUDY DESIGN AND POPULATION

This was an investigator initiated, prospective, single arm observational study. All consecutive patients undergoing PCI with BP-SES were

enrolled between January 2018 and January 2019 in department of cardiology, Base Hospital Delhi Cantt, New Delhi, India. To replicate real world scenario, all patients undergoing both urgent and elective (including complex) PCI were included in the study cohort. Patients were excluded if they had a contraindication to antiplatelet therapy, pregnant women and known hypersensitivity to sirolimus. The study complied with the provisions of the Declaration of Helsinki and was approved by the institutional ethics committee of our institution. All patients provided written informed consent at enrolment.

2.2 STUDY DEVICE

BP-SES used in the study was Yukon choice PC Elite from Tanslumina therapeutics manufactured in India[17]. This stent has stainless steel platform (strut thickness of 87 micron) with microporous abluminal surface for delivery of sirolimus at target site and poly-lactic acid as biodegradable polymer. Sirolimus drug concentration is 2.6 microgram/mm^2. Drug is released only towards abluminal surface to prevent smooth muscle proliferation. The stainless steel platform has micro-porous surface created by sandblasting – a special characteristic used to enhance drug delivery for longer duration. The micro-pores on its surface act like reservoirs for delivering the drug to the target site. There is no drug or polymer on the luminal side of stent surface thereby promoting endothelialization. Sirolimus is released in 4-6 weeks' time and polymer is completely degraded by 90 days and it essentially becomes a bare metal stent thereafter. Sirolimus is temperature sensitive drug and gets degraded at a temperature more than 30^0 into open-chain isomer, resulting in less than 10% of its immunosuppressive activity. The Yukon Choice PC Elite is an improved version of Yukon Choice PC stent, which is specially adapted for conditions of extreme temperatures particularly seen in the tropical regions. It comes in dual packing with outer thermal insulated polystyrene box and inner aluminium cover. The thermal insulated pack is further monitored by an electronic monitoring device TagAlert manufactured by SENSITECH USA that has built in alarms to ensure the stent remains within the desired temperature for optimal Sirolimus potency.

2.3 PROCEDURAL AND DISCHARGE MEDICATIONS

All patients were loaded with Aspirin and a P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel) as clinically indicated. During the procedure, all patients received unfractionated heparin, whereas the use of glycoprotein IIb/IIIa antagonists was left at the discretion of the operators. All patients were discharged on Aspirin 150 mg daily indefinitely and clopidogrel 75 mg daily/ Ticagrelor 90 mg twice daily/ prasugrel 10 mg once daily, for at least 1-year duration. Dual antiplatelet therapy was continued for more duration as per operator's discretion.

2.4 FOLLOW-UP AND END POINTS

Clinical follow-up was mandatory at 1 month, 3 months and thereafter 6 monthly upto 3 years after index procedure. In-person follow-up as office visits were strongly recommended, however telephone interviews were permitted if the patient did not turn up. The primary endpoint of the study was device oriented composite endpoints (DOCE) defined as a composite of cardiac death, myocardial

infarction (MI, not clearly attributable to the non-target vessel), and clinically driven target lesion revascularization. The co-primary endpoint was patient-oriented composite endpoints (POCE) defined as a composite of all-cause mortality, any MI (including non-target vessel territory), any repeat revascularization (including all target and non-target vessels). The key secondary endpoint was the incidence of definite or probable stent thrombosis as per Academic Research Consortium (ARC) criteria. Sub-group analysis was done to assess the impact of diabetes mellitus, low ejection fraction, stent length, presentation and complex intervention on both DOCE and POCE.

2.5 DEFINITIONS

Cardiac death was defined as any death due to approximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and sudden death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment. Non-cardiac death was defined as any death not covered by the above definition, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma. Acute coronary syndrome was defined according to the fourth universal definition of myocardial infarction[18]. Target lesion revascularization was defined as any clinically driven repeat percutaneous intervention or surgical bypass of the target lesion. Stent thrombosis (ST) was defined as per the ARC definition as definite or probable[19]. Timing of stent thrombosis was defined as acute (< 24 h), subacute (24 h to 30 days), late (> 30 days to 1 year), and very late (> 1 year). Device success was defined as successful delivery and deployment of the device and attainment of <30% diameter stenosis using only the study device[20]. Procedural success was defined as freedom from death, MI, CABG during hospitalization for index procedure.

2.6 STATISTICAL ANALYSIS

A univariate followed by multivariate analysis was done. For categorical variable, univariate comparison was done using the chi-square / fisher test exact test as applicable. The continuous variable was compared using the independent sample 't' test. Univariate "time to event" analysis was performed using the Kaplan-Meier survival curves and comparison were made using the "log rank" test, time to event analysis of continuous variables was done using the "cox – regression". Multivariate analysis was done using the cox – regression analysis. The factors found to significant on univariate analysis were used as independent predictors in regression analysis. All P-values <0.05 were taken as significant. Analysis was conducted using IBM SPSS STATISTICS (version 22.0).

3. Results

A total of 301 patients were prospectively enrolled in the study and underwent PCI with biodegradable polymer coated Sirolimus-eluting stent. Baseline and procedural characteristics are as shown in Table 1 & 2 respectively. The mean age of the study group was 61.6±9.3 years. 79.1% patients were males and 18.6% patients were diabetic. Mean left ventricular ejection fraction (LVEF) of the study cohort was 47.9±10.6% with 29.6% patients intervened were having an EF <40%. Acute coronary syndrome was the most common presentation (73.1% patients) of the study cohort.

Table 1: Baseline characteristics of study cohort.

Table 1: Baseline patient characteristics (n= 301) of the study cohort			
Age (years)			61.6 ±9.3
Age <50 years			24 (8.0%)
Male			238 (79.1%)
LV Ejection Fraction (%)			47.9 ±10.6
Low LVEF (<40%)			89 (29.6%)
Diabetes mellitus			56 (18.6%)
Hypertension			55 (18.3%)
Chronic Kidney Disease			2 (0.7%)
Hypothyroidism			2 (0.7%)
Dyslipidemia			66 (22%)
Family History of CAD			35 (11.6%)
Smoker			145 (48.2%)
Obesity			52 (17.3%)
Prior CABG			4 (1.3%)
Clinical presentation	CCS		81 (26.9%)
	ACS 220 (73.1%)	STEMI	166 (55.1%)
		NSTEMI	29 (9.6%)
		USA	25 (8.3%)

LVEF- left ventricle ejection fraction, CABG- coronary artery bypass grafting, CCS- chronic coronary syndrome, ACS- acute coronary Syndrome, STEMI- ST elevation myocardial infarction, NSTEMI- non-ST segment elevation myocardial infarction, USA-unstable angina

Table 2: Procedural characteristics of study cohort.

Table 2: Procedural characteristics of the study cohort		
Vessel involvement	Single Vessel Disease	60 (19.9%)
	Double Vessel Disease	85 (28.2%)
	Triple Vessel Disease	156 (51.8%)
Dominance	Right	262 (87%)
	Left	26 (8.6%)
	Co-dominant	13 (4.3%)
Route	Radial	238 (79.1%)
	Femoral	41 (13.6%)
	Ulnar	22 (7.3%)
Lesion complexity	Single vessel	254 (84.4%)
	Multi vessel	47 (15.6%)

Lesion complexity (ACC/AHA)	Type A	19 (6%)
	Type B1	72 (24%)
	Type B2	81 (27%)
	Type C	129 (43%)
Target vessel	Left Main	7 (2.0%)
	Left Anterior Descending	135 (38.7%)
	Right Coronary Artery	148 (42.4%)
	Left Circumflex	49 (14.0%)
	Diagonal 1	5 (1.4%)
	Ramus	4 (1.1%)
	RSVG	1 (0.3%)
Complex interventions 79 (26.2%)	Bifurcation PCI	16 (5.3%)
	Primary PCI	32 (10.6%)
	PCI under ROTA	3 (1.0%)
	Chronic Total Occlusion	25 (8.3%)
	LM Intervention	7 (2.3%)
Device Features	length stent <30 mm	193 (64.1%)
	length stent ≥30 mm	108 (35.9%)
	Number of stents implanted	485
	Mean number of stents	1.6 ±0.8
	Mean stent length (mm)	27.2±0.8
	Mean stent diameter (mm)	3.0 ±0.3
Procedural Features	Imaging guided PCI	23 (7.6%)
	Balloon pre-dilatation	276 (91.7%)
	Direct stenting	25 (8.3%)
	Balloon post dilatation	144 (47.8%)
	Fluoro time (min)	13.5±10.3
	Contrast volume (ml)	109.2±53.4
	Air Kerma (mG)	658.2±701.1

RSVG- reversed saphenous venous graft, PCI- percutaneous coronary intervention, ROTA- rotational atherectomy, LM- left main

Majority of the patients had a triple vessel disease (TVD) (51.8%), but most of them were revascularized for a single target vessel (84.4%). Right coronary artery (42.2%) followed by left anterior descending artery (40%) were commonly intervened. Complex interventions were performed in 26.2% patients that included bifurcation PCI (5.3%), chronic total occlusive (CTO) PCI (8.3%), rota-ablation (1%), primary PCI (10.6%) and left main (LM) intervention (2.3%). Total lesions treated were 502 and total stents deployed were 485 with a mean of 1.6±0.8 stents per patient. The mean diameter and mean length of the stents were 3.0±0.3 mm and 27.2±0.8 mm respectively.

Clinical follow-up was completed in 286 (95.0%) patients at 1 month, 281 (93.4%) at 3 months, 277 (92.0%) at 6 months, 268 (89.0%) at 1 year, 239 (79.4%) at 2 years and in 227

(75.4%) patients at 3 years respectively. All patients had in person visits at 4 weeks and at 3 months. Thereafter, only 80% patients had in person visits on subsequent follow-ups till 3 years and remaining 20% were followed up telephonically. All patients had complete adherence to the antiplatelet drugs prescribed to them. Out of 227 patients who completed the 3-year follow-up, DOCE occurred in 18 (7.9%) patients and POCE occurred in 29 (12.8%) patients. Definite and probable stent thrombosis was seen in 2 (0.9%) and 1 (0.4%) patients respectively. All cases had acute and sub-acute ST and there was no late or very late ST. All cause deaths included cardiac and non-cardiac deaths. Among non-cardiac deaths, the reasons included death due to sepsis and septic shock, renal failure, carcinoma related and ARDS. Individual outcomes at the end of 1 month, 3 months, 6 months, 1 year, 2 year and 3 years are summarized in Table 3. The device success rate was 99.3% and procedure success rate was 98.3%.

Table 3: Clinical outcome of study cohort at different time frames over a period of 3 years.

Table 3: Clinical outcomes						
	30 Days	3 Months	6 Months	12 Months	24 Months	36 Months
DOCE	6 (2.1%)	7 (2.5%)	8 (2.9%)	10 (3.7%)	16 (6.7%)	18 (7.9%)
CARDIAC DEATH	5 (1.7%)	6 (2.1%)	6 (2.2%)	8 (2.9%)	11 (4.6%)	11 (4.8%)
MI → CARDIAC DEATH	1 (0.3%)	1 (0.4%)	1 (0.4%)	3 (1.1%)	5 (2.1%)	5 (2.2%)
Target Vessel MI	1 (0.3%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
TLR	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	4 (1.7%)	6 (2.6%)
POCE	9 (3.1%)	11 (3.9%)	12 (4.3%)	16 (5.9%)	25 (10.5%)	29 (12.8%)
ALL CAUSE DEATH	8 (2.8%)	10 (3.6%)	10 (3.6%)	14 (5.2%)	20 (8.4%)	22 (9.7%)
CARDIAC DEATH	5 (1.7%)	6 (2.1%)	6 (2.2%)	8 (2.9%)	11 (4.6%)	11 (4.8%)
NON - CARDIAC DEATH	3 (1.0%)	4 (1.4%)	4 (1.4%)	6 (2.2%)	9 (3.8%)	11 (4.8%)
MI → CARDIAC DEATH	1 (0.3%)	1 (0.4%)	1 (0.4%)	3 (1.1%)	5 (2.1%)	5 (2.2%)
ANY MI	1 (0.3%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
ANY TLR	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.4%)	4 (1.7%)	6 (2.6%)
DEFINITE STENT THROMBOSIS	2 (0.7%)	2 (0.7%)	2 (0.7%)	2 (0.8%)	2 (0.8%)	2 (0.9%)
PROBABLE STENT THROMBOSIS	1 (0.3%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
	286	281	277	268	239	227

On multivariate analysis (Table 4) older age (P=0.001, HR=1.10, 95% CI 1.04-1.16) & LM intervention (P=0.030, HR= 5.12, 95% CI, 1.17-22.43) were found to be significant predictors of DOCE. The "time to event" Kaplan Meier curve analysis showed that diabetic status, ejection fraction, stent length (≥ 30mm) and type of presentation (ACS or CCS) had no impact on occurrence of DOCE and POCE while using study device (Figure 1

and 2). This BP-SES performed equally good in patients undergoing complex coronary interventions when compared with patient who underwent non-complex intervention by study definition (Figure 3).

Table 4: Univariate and multivariate analysis for predictors of Device and Patient Oriented Composite Endpoints (DOCE and POCE).

VARIABLE (Univariate analysis)		DOCE	NO DOCE	P VALUE	POCE	NO POCE	P VALUE
GENDER	MALE	14	224	1.000	22	216	0.578
	FEMALE	4	59		7	56	
AGE LESS THAN 50	<50	1	23	1.000	2	22	1.000
	>50	17	260		27	250	
BIFURCATION	YES	0	16	0.611	1	15	1.000
	NO	18	267		28	257	
PRIMARY	YES	2	30	1.000	2	30	0.751
	NO	16	253		27	242	
ROTA	YES	0	3	1.000	2	1	0.024
	NO	18	280		27	271	
CTO	YES	0	25	0.377	1	24	0.489
	NO	18	258		28	248	
LM	YES	2	5	0.008	2	5	0.131
	NO	16	278		27	267	
COMPLEX	YES	76	208	1.000	8	71	0.769
	NO	13	4		21	201	
OCT	YES	1	21	1.000	3	19	0.706
	NO	17	262		26	253	
DM	YES	4	52	0.748	8	48	0.199
	NO	14	231		21	224	
HTN	YES	1	12	0.538	2	11	0.619
	NO	17	271		27	261	
HYPOTHYROIDISM	YES	0	2	1.000	0	2	1.000
	NO	18	281		29	270	
CKD	YES	0	2	1.000	0	2	1.000
	NO	18	281		29	270	
CABG	YES	0	4	1.000	0	4	1.000
	NO	18	281		29	268	
CAD	SVD	1	59	0.207	4	56	0.382
	DVD	4	81		6	79	
	TVD	13	143		19	137	
PRESENTATION	YES	4	77	0.791	21	299	0.835
	NO	14	206		8	73	
TYPE OF ACS	STEMI	11	155	0.954	16	150	0.968
	NSTEMI	2	27		3	26	
	USA	1	24		2	23	

	NO	4	77		8	73	
EF LESS THAN 40	YES	8	81	0.104	12	77	0.106
	NO	10	202		17	195	
DOMINANCE	RT	13	249	0.060	25	237	0.289
	LT	5	21		4	22	
	CD	0	13		0	13	
MULTIVESSEL	YES	2	45	0.752	2	45	0.276
	NO	16	238		27	227	
ROUTE	RADIAL	14	224	0.759	22	216	0.790
	FEMORAL	2	39		5	36	
	ULNAR	2	20		2	20	
PRE-DILATATION	YES	17	259	1.000	28	248	0.489
	NO	1	24		1	24	
DIRECT STENT BALLOON	YES	1	24	1.000	1	24	0.489
	NO	17	259		28	248	
POST DILATATION	YES	6	138	0.286	12	132	0.579
	NO	12	145		17	140	
COMPLICATION	NO	18	279	0.886	29	268	0.812
	DST	0	2		0	2	
	UES	0	2		0	2	
VARIABLE		DOCE	NO DOCE	T TEST - P VALUE	POCE	NO POCE	T TEST - P VALUE
AGE		68.6 (±11.2)	61.2 (±9.0)	**0.001**	66.2 (±10.9)	61.1(±9.0)	**0.006**
LVEF		45 (±11.0)	48.2 (±10.5)	0.231	45 (±10.7)	48.3 (±10.5)	0.117
STENT NUMBER		1.8(±1.0)	1.6 (±0.8)	0.430	1.7 (±0.9)	1.6 (±0.8)	0.488
STENT LENGTH		27.9 (±8.1)	27.2 (±7.2)	0.668	29.3 (±7.4)	27 (±7.2)	0.132
STENT DIAMETER		3.1 (±0.2)	3.0 (±0.3)	0.777	3. 0(±0.2)	3.0 (±0.3)	0.794
FLUORO TIME		14.8(±8.8)	13.4 (±10.4)	0.533	14.5 (±10.4)	13.4 (±10.3)	0.611
AIR KERMA		606.1 (±412.8)	661.3 (±715.0)	0.753	707.3 (±559.2)	653.2 (±714.7)	0.638
CONTRAST		112.4(±64.8)	108.9 (±52.7)	0.801	107.5 (±57.5)	109.3 (±53.0)	0.872
VARIABLE (Multivariate analysis)		B COEFFECIENT	P VALUE	HR (95% CI)	B COEFFECIANT	P VALUE	HR (95% CI)
AGE		0.091	0.001	1.10 (1.04 - 1.16)	0.059	0.006	1.06 (1.02 - 1.11)
LM		1.630	0.030	5.12 (1.17 - 22.43)	-	-	-
ROTA		-	-	-	2.103	0.004	8.19 (1.93 - 34.80)

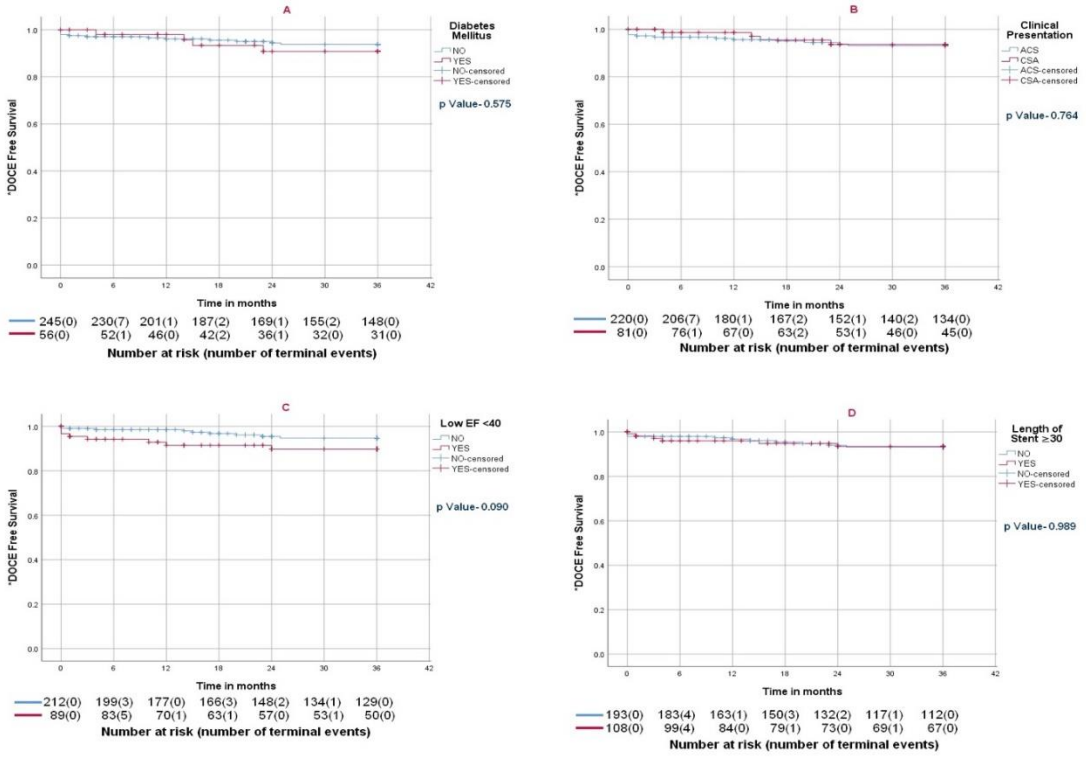

Figure 1: Kaplan Meier curve survival analysis comparing device oriented composite endpoint (DOCE) free survival between (A) diabetic versus non-diabetic patients, (B) patients presenting with acute coronary syndrome versus chronic coronary syndrome, (C) patient with low versus >40% ejection fraction, and (D) patient implanted with > 30mm long versus < 30mm long stent.

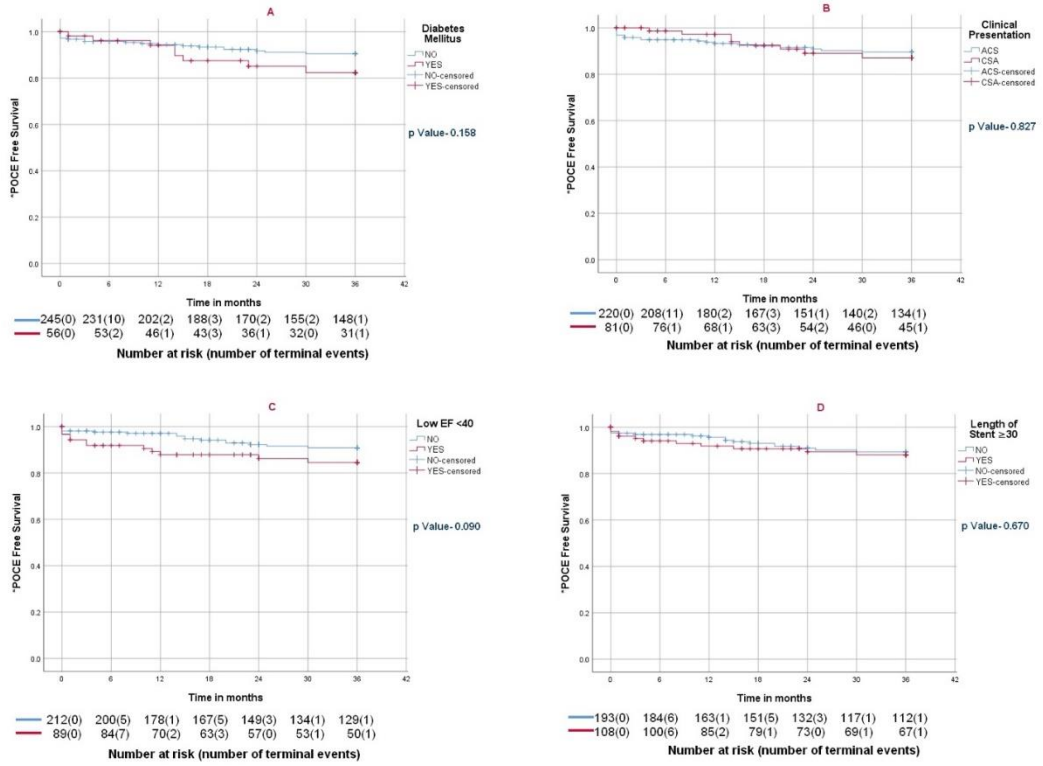

Figure 2: Kaplan Meier curve survival analysis comparing patient oriented composite endpoint (POCE) free survival between (A) diabetic versus non-diabetic patients, (B) patients presenting with acute coronary syndrome versus chronic coronary syndrome, (C) patient with low versus >40% ejection fraction, and (D) patient implanted with ≥ 30mm long versus < 30mm long stent.

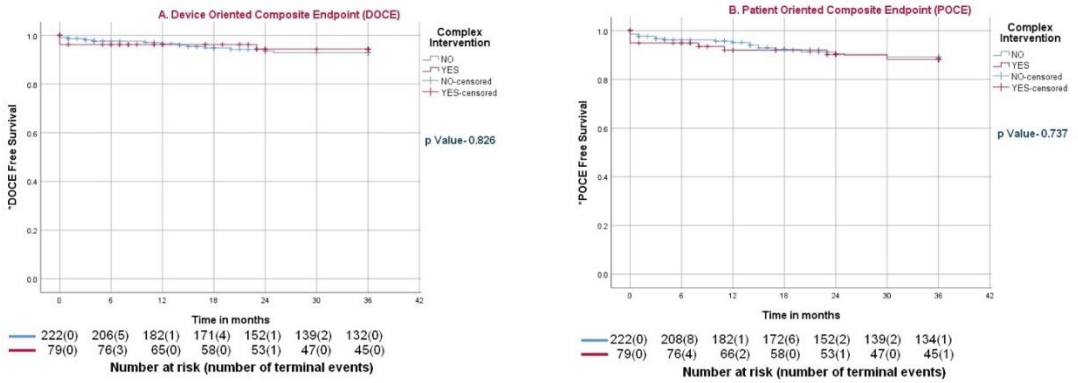

Figure 3: Kaplan Meier curve survival analysis comparing (A) device oriented composite endpoint (DOCE) free survival between patients undergoing complex versus non-complex intervention and (B) patient oriented composite endpoint (POCE) free survival between patients undergoing complex versus non-complex intervention.

4. Discussion

To the best of our knowledge, present study represents the first prospective observational analysis evaluating the performance of Yukon choice PC ELITE (YCET), a BP-SES in all-comer patients over a period of 3 years. The safety and efficacy of a coronary artery stent platform is dependent on its components, namely its platform, its design, the anti-proliferative drug used, the presence and type of polymer vehicle. BP-DES have been developed with the aim of reducing the adverse long-term sequelae related to the persistence of durable polymers in the arterial wall beyond the period necessary to control drug release. Several clinical trials have confirmed the safety and efficacy of BP-DES when compared with durable polymer DES (DP-DES)[15,21,22]. While it has been proven superior to the early generation DP-DES, when compared to the second generation DP-DES, which utilize more biocompatible polymers, major trials have shown no additional benefit even in the risk of very late stent thrombosis[12,14,15,16].

The YCET stent uses the same platform, design, antiproliferative drug and biodegradable polymer as is used in Yukon choice PC (another BP-SES, by Translumina therapeutics).Yukon choice PC stent has been found to be superior to 'cypher stent' (DP-SES, gold standard among early generation DES) in a pooled analysis of 3 large trials[12], during long-term follow-up of 4 years, which was driven mainly by the significant reduction of risk of TLR and reduced very late stent thrombosis. In the individual ISAR TEST 4 trial, the Yukon choice PC stent was having comparable clinical outcomes to the second generation DP-EES (Xience by Abbot laboratories, Abbot Park, IL, USA) in the short as well as long term follow-up of upto 10 years in the series of ISAR TEST trials[23]. Yukon Choice PC Elite stent system is expected to carry forward similar efficacy and safety as that of its predecessor. The only difference between the two stent platforms being the temperature control system present with the elite stent which would be useful as sirolimus is temperature sensitive drug. Table 5 summarizes and compares the outcome of various trials evaluating the performance of BP-SES in coronary intervention including the present study.

Table 5: Summarizes and compares the outcome of various trials evaluating the performance of biodegradable polymer sirolimus eluting stent (BP-SES) in coronary intervention including the present study.

Table 5: Trials for performance of BP-SES in coronary intervention including the present study

Trial	Journal, Year	Follow-up	Stent/ Strut	N	Attrition	DOCE	POCE	Target vessel MI	Cardiac Death	TLR	Stent thrombosis	Remarks
ISAR-TEST 3(14)	EHJ, 2008	1 yr	Yukon choice PC, 79 µm	202	-	-	-	3 (1.5%)	4 (2%)	12 (5.9%)	2 (1%)	BP-SES stents have a 1-year safety profile similar to that of the PP-DES stent
ISAR-TEST 4(15)	EHJ, 2009	30 d		1299	-	57 (4.4%)	-	45 (3.5%)	12 (0.9%)	7 (0.5%)	-	BP-SES is non-inferior to PP- DES in terms of clinical efficacy over 1 year
ISAR-TEST 4(15)	EHJ, 2009	1 yr		1299	3.1%	176 (13.8%)	-	53 (4.1%)	35 (2.8%)	109 (8.8%)	13 (1%)	
ISAR-TEST 4(22)	JACC, 2011	3 yr		1299	8%	252 (20.1%)	-	59 (4.6%)	58 (4.7%)	168 (13.9 %)	15 (1.2%)	BP-SES and PP-DES are associated with similar clinical outcomes at 3 years
ISAR-TEST 4(21)	Euroint erventi on, 2016	5 yr		1299	8.8%	258 (20.5%)	-	59 (4.6%)	64 (5.2%)	170 (13.9 %)	15 (1.2%)	BP-SES and PP-XIENCE stents showed comparable clinical outcomes at five years
ISAR-TEST 4(23)	Circulat ion, 2019	10 yr		1299	17.6%	575 (47.7%)	-	88 (7.7%)	213 (19.9%)	225 (20.3 %)	20 (1.8%)	BP-SES and PP-EES showed comparable clinical outcomes out to 10 years
ISAR TEST 4 Impact of diabetes(33)	JAHA, 2021	10 yr		560 With DM	17.6%	MACE 286 (56.5%)	-	38 (8.4%)	112 (27.7%)	109 (23.9 %)	11 (2.3%) with DM and 1.9% without DM	Clinical outcome of patients with diabetes after PCI with different new-generation DES is considerably worse than that of patients without diabetes mellitus, with event rates constantly increasing out to 10 years
Xhepa et al(30)	IHJ, 2014	1 yr	Yukon Choice Flex, 79 µm	778	-	-	-	15 (1.9%)	19 (2.4%)	163 (11.3 %)	2 (0.3%)	BP-SES YCF stent in an all-comers population of patients with complex coronary artery disease is associated with a favourable safety and efficacy profile up to one year follow up
ELITE INDIA(17)	IHJ, 2019	1 yr	Yukon Choice PC Elite, 87 µm	636	0.6%	18 (2.7%)	26 (4.2%)	3 (0.5%)	9 (1.4%)	8 (1.2%)	4 (0.6%)	In patients with STEMI undergoing primary PCI, the use of BP-SES has excellent results at one year

CENTURY II(25)	EHJ, 2014	9 m	Ultimaster, 80 µm	362	0.7%	15 (4.14%)	27 (7.5%)	5 (1.4%)	3 (0.83%)	6 (1.7%)	1 (0.28 %)	BP-SES showed safety and efficacy profiles similar to DE-EES (Xience) at 9-month follow-up
ULISSE registry(26)	International Jr of cardiology, 2018	1 yr	Ultimaster, 80 µm	1660	15.6%	70 (5%)	-	19 (1.4%)	25 (1.8%)	45 (3.2%)	16 (1.2%)	BP-SES real-world performance was comparable with that observed in clinical trials, with low rate of primary endpoint and TLR
BIOSCIENCE (28)	Lancet, 2014	1 yr	Orsiro, 60 µm - 80 µm	1063	3%	69 (6.7%)	123 (11.8 %)	30 (2.9%)	20 (1.9%)	35 (3.4%)	29 (2.8%)	Ultrathin strut BP-SES were non-inferior to thin-strut DP-EES for the combined safety and efficacy outcome at 1 yr
BIOFLOW II(34)	Circulation, 2015	1 yr	Orsiro, 60 µm	298	4%	19 (6.5%)	56 (19.2 %)	8 (2.7%)	2 (0.7%)	10 (3.5%)	0	BP-O-SES was noninferior for the primary end point in-stent LLL via OCT at 9 months compared with DP-X-EES
BIOFLOW V(35)	Lancet, 2017	1 yr	Orsiro, 60 µm	884	5.7%	52 (6%)	-	39 (5%)	1 (<1%)	17 (2%)	4 (<!%)	It endorsed the safety and effectiveness of the ultrathin strut, BP-SES in a complex PCI
BIOSTEMI(29)	Lancet, 2019	1 yr	Orsiro, 60 µm - 80 µm	649	5.4%	25 (4%)	49 (8%)	5 (1%)	18 (3%)	9 (1%)	10 (2%)	In acute STEMI undergoing primary PCI, ultrathin strut BP-SES were **superior** to thin strut DP-EES with respect to the target lesion failure at 1 year
BIORESORT(36)	JAMA cardiology, 2019	3 yr	Orsiro, 60 µm	525	4.3%	36 (7%)	-	17 (3.3%)	12 (2.4%)	11 (2.1%)	3 (0.6%)	In small coronary vessels, fewer TLRs if they were treated with ultrathin-strut SES vs previous-generation thin-strut ZES
INDEX STUDY	-	1 yr	Yukon Choice PC Elite, 87 µm	268	11%	10 (3.7%)	16 (5.9%)	1 (0.4%)	8 (2.9%)	1 (0.4%)	3 (1.3%)	BP-SES has favourable safety and efficacy profile at 1 year follow-up
INDEX STUDY	-	3 yr	Yukon Choice PC Elite, 87 µm	227	24.6%	18 (7.9%)	29 (12.7 %)	1(0.4%)	11 (4.8%)	6 (2.6%)	3 (1.3%)	BP-SES has favourable safety and efficacy profile at 3 years follow-up. There was no case of late or very late stent thrombosis till 3 years follow-up.

DOCE- device oriented composite endpoint, POCE- patient oriented composite endpoint, MI- myocardial infarction, TLR- target lesion revascularization.

In the present study, YCET had comparable device and procedural success rates. The study population comprised of a cohort of patients with a high prevalence of diabetes mellitus (18.6%), multivessel disease (51.8%), acute coronary syndromes (73.1%) and complex interventions (26%). Our study had lower rates of DOCE (3.7% & 7.9%) when compared to the BP-SES arm of ISAR-TEST 4 trial at its 1 year and 3 follow-up which had DOCE of 13.8% and 20.4% respectively. This might reflect the lower number of complex interventions (CTO PCI- 8.3%, bifurcations-5.3%) in the present study as compared to ISAR-TEST 4 trial (CTO PCI- 5% and bifurcations -25%), which could have resulted in lower TLRs (2.6% vs 13.9%). On sub group analysis, YCET performed equally good in patients with diabetes mellitus, low LVEF, patients presenting with ACS, placement of long stent (≥ 30mm) and complex intervention in comparison to patient without diabetes, patient with normal EF, patient presenting with chronic coronary syndrome (CCS), patient with < 30 mm stent length and patient undergoing non-complex intervention respectively. Recently concluded HOST-REDUCE-POLYTECH-ACS trial[24] included multiple BP-DES and showed them to be non-inferior to second generation DP-DES with regard to POCE at 1 year. However, DOCE occurred less frequently in the DP-DES group mostly driven by a reduction in target lesion revascularization, although they also included earlier generation thicker strut BP-DES such as the 'Biomatrix' and 'Nobori' which could have influenced the outcome.[24] The overall DOCE in this trial was 3.9% at 1 yr follow-up which was very similar to our study.[24] The 1 yr DOCE & POCE was also comparable to ELITE INDIA study[17] which included only primary PCI patients and had a DOCE & POCE of 2.7% & 4.2% respectively.

When compared to other stent systems, CENTURY II trial[25] established non-inferiority of BPSES (Ultimaster by Terumo corporation, Tokyo, Japan) compared with the second generation DP-EES (Xience by Abbot laboratories, Abbot Park, IL, USA). It reported a POCE of 7.5% at 9-month follow-up and a DOCE of 4.1%, which is comparable to our study results. ULISSE registry[26] demonstrated the Ultimaster BP-SES real-world performance at 1 year follow-up, with a low rate of DOCE (5%) and TLR (3.2%). Other studies have compared the thin strut BP-SES (Orsiro by Biotronik AG, Bülach, Switzerland) with Everolimus or Zotarolimus-eluting DP-DES (Xience/Resolute Integrity stent by Abbot laboratories, Abbot Park, IL, USA/ Medtronic Inc., Minneapolis, MN, USA), which again showed non-inferiority of the BP-SES platform[27,28]. Only one previous study (BIOSTEMI trial)[29] compared BP-DES and DP-DES in ACS patients, where BP-SES (Ultra-thin strut Orsiro stent) was statistically superior to the DP-DES (Xience stent) in terms of DOCE. The main driver being TLR which occurred much more frequently in the DP-DES group within the first three months and thereafter was mostly similar between the two stent types.

Despite not having the power to test this low-frequency event, the 3-year cumulative rate of definite and probable stent thrombosis (0.9% & 0.4%) observed in our study was at par with that reported in the ISAR TEST 4 trial (0.7% & 0.5%). Xhepa et al[30] utilizing the YCF stent system had a rate of definite stent thrombosis at 0.3% during a 1 yr follow-up. Majority of our

cohort were ACS patients (73.1%) and could have contributed to the slightly higher rates of stent thrombosis and we could not rule out the possibility of clopidogrel resistance as all stent thrombosis cases were on clopidogrel. Notably, in our study all of the definite and probable stent thrombosis cases were acute or sub-acute and there were none thereafter till 3-year follow-up, which re-enforces the late safety profile of YCET due to biodegradable polymer. Previous studies using optical coherence tomography have suggested the complete strut coverage within the first month after BP-SES implantation (Ultimaster by Terumo corporation, Tokyo, Japan).[31] Neointimal coverage in BP-DES (Ultimaster) was found to be significantly superior to that in DP-EES (Synergy by Boston Scientific, Natick, MA, USA)[32] thus reducing the chances of stent thrombosis in the early high risk period post stent implantation.

Contemporary evidence and present study suggest that biodegradable polymer sirolimus eluting stent system is a reasonable option for all comer patient undergoing percutaneous coronary intervention with excellent short and long term safety profile, which is comparable to commonly used second generation DP-DES .

5. Conclusion

This prospective observational study shows that Yukon Choice PC ELITE, which is a biodegradable polymer sirolimus eluting stent system has a favourable 3 years safety and efficacy profile in all comer patients undergoing percutaneous coronary intervention in real world setting. Its outcome profile is comparable to the other BP-SES and commonly used second generation DP-DES.

6. Limitations

Firstly, it was an observational study and not a head to head trial which could have better compared the safety and efficacy profile in comparison to an established stent system. Secondly the attrition rates during follow-up were high probably due to the patients being dependents of veterans and not localized to a particular geographical region for astute follow-up and due to the COVID pandemic disruption. Thirdly, absence of routine angiographic follow up and a scarce use of intravascular imaging for PCI optimization.

Conflict of Interest Statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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