INDIAN HEART JOURNAL 64 (2012) 547–552

Available online at www.sciencedirect.com

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Original article

A first-in-man study of sirolimus-eluting, biodegradable polymer coated cobalt chromium stent in real life patients☆

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ARTICLE INFO

Article history:
Received 3 March 2012
Received in revised form
3 May 2012
Accepted 17 July 2012
Available online 27 July 2012

Keywords:
Coronary artery disease
Drug-eluting stent
Sirolimus
First-in-man

ABSTRACT

Introduction: Despite considerable benefits associated with current drug-eluting stents, continued attention to the safety, efficacy, and deliverability of available drug-eluting stent has led to the development of newer stent.

Methods: This study was a single-centre, prospective, non-randomized, first-in-man study which included clinical follow-up data was collected at 1, 8 and 12 months after the procedure. The study included 105 patients with *de novo* native coronary artery lesions including multi-vessel disease treated with Supralimus-Core® stent. Repeat angiography was performed 8 months post-stent implantation.

Results: At quantitative coronary angiography 8-month luminal late loss was 0.39 ± 0.33 mm in-stent and 0.33 ± 0.35 mm in-segment. The incidence of any major adverse cardiac event at 30 days, 8 months and 12 months was 1 (1%), 6 (6%) and 7 (7%) respectively.

Conclusion: This study demonstrates that the Supralimus-Core® SES is a safe and effective treatment for patients with obstructive coronary artery disease.

ClinicalTrials.gov ID: NCT00811616.

1. Introduction

Endoluminal metallic stents are the preferred treatment during percutaneous coronary interventions because of their proven superiority over balloon angioplasty.[1–3] In bare metal stainless steel stents restenosis still occurs in 20%–40% patients.[4–6] The principal cause of in-stent restenosis is neointimal hyperplasia resulting from proliferation and migration of smooth muscle cells and extracellular matrix production.[7] It has also been demonstrated that thin strut Cobalt-Chromium (Co-Cr) stents may lead to lower restenosis than thick strut stainless steel stent. Stent-based drug delivery has resulted in a revolutionary change in the field of percutaneous intervention, with recent clinical trials of paclitaxel-eluting stents (PES) or SES demonstrating promising results in the treatment of *de novo* coronary lesions.[8] Although the first generation of DES have drastically reduced rates of restenosis and revascularization,[9–12]

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0019-4832/$ – see front matter
http://dx.doi.org/10.1016/j.ihj.2012.07.011

concerns persist regarding their long-term safety.[13–15] The presence of a permanent non-degradable polymer may contribute to late and very late stent thrombosis in some cases as a result of delayed healing, inflammatory and hypersensitivity reaction in some cases.[16–20] To address this issue, a new generation of DES has been developed, incorporating biodegradable, biocompatible polymers as vehicles for drug delivery. The polymers retain the drug to the vessel wall over days and then degrade over months to biologically inert end products. This remains behind a BMS in a hope to avoid the potentially harmful effects of permanent polymers.[20]

Supralimus-Core® (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) uses L605 Co-Cr alloy as its stent platform which is coated with a biodegradable polymer to deliver sirolimus. The present 'First-in-Man' study was undertaken to establish safety and efficacy of using Supralimus-Core® stent in PCI of real life patients with angiographic and clinical follow-up.

MAXIMUS study (A First-In-Man Study of Sirolimus-Eluting, Biodegradable Polymer Coated Cobalt-Chromium Stent) was a prospective, non-randomized, singlecentre FIM study with Supralimus-Core_ sirolimus-eluting coronary stent system.

2. Methods

2.1. Study design and patient population

Patients included in the study were more than 18 years of age, with symptomatic ischaemic heart disease with *de novo* stenotic coronary lesion with reference vessel diameter (RVD) of ≥2.5 and ≤3.5 mm. The study included 49 (47%) patients with multi-vessel disease and 12.83 ± 7.0 mm lesion length.

The study was conducted in compliance with ICH-GCP and the Declaration of Helsinki. The study protocol was approved by the local hospital ethics committee. All the patients were enrolled in study only after informed consent was being signed. They were explained the risks and benefits of participations in study.

Patients were excluded if any of the following conditions were present: **General exclusion criteria**: (1) Women of childbearing potential; (2) impaired renal function (creatinine >2.0 mg/dl or 177 μmol/l); (3) any patient who has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3, a WBC of <3,000 cells/mm^3, or documented or suspected liver disease (including laboratory evidence of hepatitis); (4) recipient of heart transplant; (5) restenosis or significant lesion in graft; (6) Patient with a life expectancy less than 12 months; (7) known allergies to aspirin, clopidogrel bisulphate (Plavix®), ticlopidine (Ticlid®), heparin or cobalt chromium; (8) any significant medical condition which in the investigator's opinion may interfere with the patient's optimal participation in the study; (9) currently participating in an investigational drug or another device study, or subject to inclusion in another investigational drug or another device study during follow-up. **Angiographic exclusion criteria:** (1) Unprotected left main coronary artery disease with ≥50% stenosis; (2) angiographic evidence of thrombus (thrombus larger than half the diameter of the vessel and/or requiring other interventions such as angiojet, exciser, thrombolysis, etc.); (3) Ejection fraction ≤30%.

2.2. Description of the study stent

Supralimus-Core® (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) has L605 Co-Cr alloy as its stent platform having strut thickness of 60 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. The coating layer comprises of drug sirolimus blended together with biodegradable polymeric matrix. This matrix includes different biodegradable polymers – poly L-lactide, 50/50 poly-DL-lactide-co-glycolide and polyvinyl pyrrolidone to control the drug elution from stent coating. After releasing the drug within 48 days, these polymers eventually degrades naturally and are excreted from the body in the form of their metabolites. The average coating thickness of Supralimus-Core® stent is between 5 and 6 μm.

The Supralimus-Core® stent was made available in lengths of 8, 12, 16, 20, 24, 28 and 32 mm and available diameters were 2.5, 3.0 and 3.5 mm. Total 105 consecutive patients were included in the MAXIMUS study from July, 2006 to April, 2007.

2.3. Interventional procedure and adjunctive medications

All patients were on aspirin in a dose of 75–150 mg at least 24 h prior to the procedure. A loading dose of 300 mg of clopidogrel was given 24 h prior to procedure or 600 mg on the day of the procedure was given to patients before procedure. During the procedure initial dose of 70–100 IU/kg bolus of heparin was given to the patient. Additional heparin was used if necessary during procedure to achieve activated coagulation time >250 s. Administration of GP IIb/IIIa inhibitor was left to the investigator's discretion. Angiographic success was defined as ≤20% stenosis by visual estimation.

Following PCI, recommended standard dual antiplatelet regimens, every patient received daily minimum 150 mg aspirin for 1 month and 75 mg thereafter for 1 year plus minimum 75 mg clopidogrel for 1 year.

2.4. Follow-up

Patients were clinically followed-up at (1) 7 days window period at 1 month, (2) 30 days window period at 8 months and (3) 45 days window period at 12 months after the procedure. The clinical follow-up consisted of either a telephone interview or a clinic visit. Angiographic follow-up was performed at 8 months (±30 days).

2.5. Study endpoints and definitions

MACE was defined as the primary safety endpoint which was defined as the incidence of cardiac death, myocardial infarction (Q-wave and non-Q-wave), emergent cardiac surgery and clinically justified target lesion revascularization (TLR) at 30 days following index procedure. MI was defined as Q-wave MI

(development of new pathological Q waves in 2 or more leads with CK-MB levels elevated above normal) or non-Q-wave MI (elevation of CK levels to 2 times upper normal limit with CK–MB levels elevated above normal).

The primary efficacy endpoint was in-stent binary restenosis rate at 8 months which determined by off-line Quantitative Coronary Angiographic Analysis (QCA). Binary angiographic restenosis was defined as a diameter stenosis (DS) ≥50% at follow-up angiography.

Secondary efficacy end points were assessed as acute gain, post-procedure minimum lumen diameter (MLD), post-procedure percentage diameter stenosis and late loss at follow-up, clinically justified TLR, angiographic and procedural success. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up. TLR was clinically justified if diameter stenosis was ≥50% (by off-line QCA) or if the patient exhibited one of the following symptoms: (1) recurrent angina pectoris, (2) ischaemia at rest or during exercise (3) abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve).

Secondary safety endpoint was defined as device related serious adverse events (SAEs) and angiographic sub-acute and late stent thrombosis up to 12 months (standard definition of stent thrombosis using standard Academic Research Consortium (ARC) criteria used). The stent thrombosis is defined as acute if it occurred between 0 and 24 h, sub-acute between 25 h and 30 days, late between 31 days and 1 year, and very late beyond 1 year after stent implantation. With respect to probability, stent thrombosis is defined as definite, probable, or possible.

2.6. Data management and statistical analysis

Baseline and 8-month follow-up angiograms were evaluated by an independent contract research organization (Cardialysis, Westblaak 92, 3012 KM Rotterdam, The Netherlands). All analysis was based on the intention-to-treat principle. The stented segment refers to the stent and 5 mm proximal and distal to the stent edges. The following data were obtained: MLD, interpolated reference vessel diameter and percentage diameter stenosis. The baseline characteristics (patient demographics, cardiovascular disease history, other risk factors, pre-procedure target lesion characteristics and procedure characteristics) have been summarized with the mean, standard deviation, median and range for continuous variables and with frequencies and percentages for discrete variables. MACE was reviewed and adjudicated by an independent clinical events committee. QCA was analysed with the SAS software.

3. Results

3.1. Baseline patient characteristics and follow-up

The baseline demographics, procedural and lesion characteristics of the MAXIMUS study population have been summarized (Tables 1 and 2).

Table 1 – Baseline demographic characteristics.

Characteristics	Supralimus-Core® SES $n = 105$ patients
Age (mean ± SD, years)	58.8 ± 10
Male, *n* (%)	83 (79.0%)
Diabetes mellitus, *n* (%)	39 (37.1%)
Insulin requiring, *n* (%)	7 (6.7%)
Non-insulin requiring, *n* (%)	32 (30.4%)
Hypertension, *n* (%)	50 (47.6%)
Smoker, *n* (%)	32 (30.4%)
Dyslipidemia, *n* (%)	37 (35.2%)
Previous MI, *n* (%)	35 (33.3%)

SES = Sirolimus-Eluting Stent.

3.2. Angiographic and clinical outcomes

Total 105 patients (194 lesions) were implanted with 234 stents with mean stent length of 19.72 ± 9.2 mm. An average of 2.23 stents was implanted per patient and 1.2 stent implanted per lesion. All angiograms were evaluated by readers blinded to the study stent, by an independent core laboratory (Cardialysis, Westblaak 92, 3012 KM Rotterdam, The Netherlands). One-month and 12-month clinical follow-up were performed in 101 (96%) patients. Eight-month angiographic follow-up was performed in 84 (80%) patients (Table 3). The normality of the distributions of in-stent late loss was tested with Kolmogorov–Smirnov test (K–S test: $P = 0.041$) and right skewness 1.06 (Fig. 1).

No in-hospital events were reported. The incidence of any MACE at 30 days, 8 months and 12 months was 1 (1%), 6 (6%) and 7 (7%) respectively. Two patients were underwent TVR. Repeat revascularization at target lesion was done in 1 patient at 8-month follow-up. There was one incidence of sub-acute thrombosis and one incidence of late stent thrombosis (Table 4).

3.3. Deaths during follow-up

Total of 4 deaths (3 non-cardiac and 1 probable cardiac) occurred during follow-up period. This death has been documented as cardiac death as per ARC definition. The 3 non-cardiac deaths were due to brain haemorrhage, multiple organ failure, and pyrexia of unknown origin.

Table 2 – Procedural and lesion characteristics.

Characteristics	Supralimus-Core® SES, $n = 194$ lesions
Target coronary artery	
LAD, *n* (%)	76 (39.2%)
RCA, *n* (%)	62 (32.0%)
Circumflex, *n* (%)	56 (28.8%)
Lesion classification (ACC/AHA class)	
Type A, *n* (%)	6 (3.1%)
Type B1, *n* (%)	78 (40.2%)
Type B2, *n* (%)	96 (49.5%)
Type C, *n* (%)	14 (7.2%)

ACC = American College of Cardiology; AHA = American Heart Association; SES = Sirolimus-Eluting Stent.

Table 3 – Quantitative coronary angiographic analysis.

	Supralimus-Core® SES		
	Pre-procedure	Post-procedure	8-month follow-up
No. of lesions	172	194	152
Reference vessel diameter, mm			
In-stent	2.48 ± 0.5	2.63 ± 0.46	2.37 ± 0.40
In-segment	–	2.55 ± 0.49	2.33 ± 0.43
Minimal luminal diameter, mm			
In-stent	0.89 ± 0.44	2.3 ± 0.42	1.91 ± 0.43
In-segment	–	2.05 ± 0.47	1.72 ± 0.44
Late loss, mm			
In-stent	–	–	0.39 ± 0.33
In-segment	–	–	0.33 ± 0.35
Diameter stenosis, %			
In-stent	63.77 ± 16.63	12.32 ± 6.38	19.20 ± 12.86
In-segment	–	20.02 ± 8.68	25.98 ± 12.02
Binary angiographic restenosis, *n* (%)			
In-stent	–	–	5 (3.3%)
In-segment	–	–	7 (4.6%)

Values expressed as number (%) or mean (±SD).

3.4. *Revascularization during follow-up*

There were total 3 TVR/TLR up to 12 months. The decision to perform further TLR or TVR after the 8 months angiographic follow-up was left to the investigator's discretion as per protocol design.

4. Discussion

Efficacy of sirolimus-eluting stent using stainless steel platform and biostable polymer has been well documented in medical literature.[10,21–24]

The Co-Cr stent platform provides flexibility for easy delivery, conformability and scaffolding that adapts vessel to the blood. Hence using Co-Cr as stent platform is likely to improve technical and procedural success of SES as well as influence late loss and restenosis. Supralimus-Core® stent has a strut thickness of 60 μm (thin strut) which is also likely to improve long-term angiographic result as has been shown in ISAR STEREO study.[25]

The first generation SES has used permanent (non-degradable) polymers. Persistence of polymers in the coronary artery after the elution of drug may become the source of inflammation in the artery. This may partly explain the higher incidence of late and very late thrombosis. It is inherently logical that disappearance of polymer after complete drug elution would be highly desirable.[26]

ISAR-TEST 3 trial which compared outcomes of DES with biodegradable-polymer, no-polymer, and permanent-polymer SES showed best outcomes with biodegradable polymer (revascularization at 1 year: 5.9%, 12.9%, 7.9%, respectively and death or myocardial infarction at 1 year: 2.5%, 4.0%, and 3.5%, respectively for biodegradable-polymer, no-polymer, and permanent-polymer SES).[27] The present study used biodegradable polymer as vehicle for sirolimus-eluting Co-Cr stent showed excellent procedural success 100% and very low in-

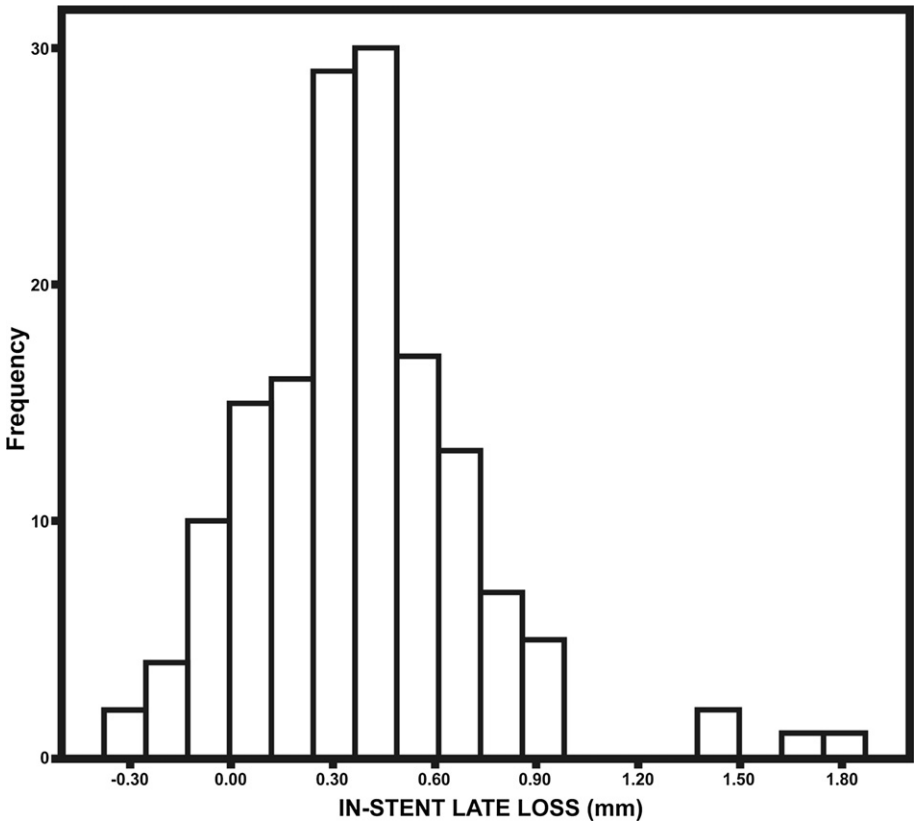

Fig. 1 – Distribution of in-stent late loss.

Table 4 – Clinical outcomes at 30 days, 8 months and 12 months follow-up.

	Supralimus-Core® SES			
	30 days	8 months	12 months	MACE
No. of patients	101	84	101	105
Deaths				
Cardiac	0	1	0	1 (1%)
Non-cardiac	0	3	0	3 (3%)
TLR	0	1	0	1 (1%)
TVR	1	0	1	2 (2%)
CABG	0	0	0	0
Stent thrombosis[a]	1	1	0	2 (2%)

Values expressed as number (%).
a Stent thrombosis according to the ARC (Academic Research Consortium) definition TVR = Target Vessel Revascularization; TLR = Target Lesion Revascularization; CABG = Coronary Artery Bypass Grafting.

hospital MACE. Long-term safety was also well demonstrated at 1 year with low MACE rate of 7% at 1 year. Long-term follow-up is ongoing.

At 8-month follow-up, 84 patients received CAG, which is comparable with other published trials.[28,29] The study demonstrated a late loss of 0.39 ± 0.33 mm in-stent and 0.33 ± 0.35 mm in-segment. This was somewhat higher than previous studies of SESs with stainless steel platform (late loss of 0.17 ± 0.45 mm in the SIRIUS trial).[30] This may have happen because of complex demographic factors (e.g. Diabetes 37%, hypertension 48%, type C lesion 6.7%, ≥28 mm lesion 20% and small vessel 3 mm ≤84%) might have contributed to slightly higher late loss. Late loss is also not higher in comparison to other Co-Cr platform drug-eluting stents.[29,31–34] However this slightly higher late loss at angiographic QCA follow-up did not result in significant increase in-binary restenosis rate. In fact the restenosis rate and TLR were lower than study demonstrating relatively lower angiographic late loss.

4.1. *Study limitations*

This study is limited by its non-randomized, single-centre with moderate sample size. The follow-up period is limited to 1 year.

5. Conclusions

In a cohort of real-world patient with significantly high percentage of unfavourable demographic and angiographic factors sirolimus-eluting Co-Cr Supralimus-Core® stent showed very low MACE rate, TLR and angiographic restenosis at 1 year. Further longer-term follow-up would be desirable to document very long safety and recommend preferred use of biodegradable polymers for SES. The present study data provides a strong foundation for a pivotal randomized trial of the Supralimus-Core® platform. Larger number of patient studies will provide greater insight into the benefit of this system in patients.

Funding

MAXIMUS study was supported by Sahajanand Medical Technologies Pvt. Ltd., Surat, India.

Conflicts of interest

Mr. Ashok Thakkar is an employee of Sahajanand Medical Technologies Private Limited. The other authors have no conflicts of interest to declare.

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