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Original Article

Cardiology Section

Experience with Biodegradable Polymer Coated Sirolimus-Eluting Coronary Stent System in "Real-Life" Percutaneous Coronary Intervention: 24-Month Data from the Manipal-S Registry

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ABSTRACT

Introduction: Despite the undeniable clinical efficacy of drug-eluting stents with durable polymers, concerns regarding their long-term safety have been raised, especially in more complex subsets. The Manipal-S Registry was designed to evaluate the safety and effectiveness of the biodegradable polymer coated Supralimus® Sirolimus-Eluting Coronary Stent for the treatment of coronary artery disease, across a wide range of patients who are treated in real-life clinical practice.

Methods: All the consecutive 116 patients who underwent single-vessel or multiple vessel percutaneous coronary interventions with the use of Supralimus® sirolimus-eluting stents between September 2009 and December 2010, were included in this study. Patients were clinically followed-up at 1, 9, 12 and 24 months post-procedure. All clinical, procedural, and follow-up information were collected and analysed.

Results: In total 116 patients, 126 lesions were implanted with 144 stents which had an average stent length of 25.8±8.0 mm. The incidences of any major adverse cardiac and cerebral events at 1, 9, 12 and 24 months were 0, 5 (4.3%), 8 (6.9%), and 10 (8.6%) respectively.

Conclusion: These 24-month results clearly provide evidence for safety and effectiveness of the Supralimus® Sirolimus-eluting coronary stent system with the biodegradable polymer in real-life patients, even in those with acute myocardial infarctions.

Key words: Coronary artery disease, Biodegradable polymer, Sirolimus-eluting stent

INTRODUCTION

Endoluminal metallic stents are the preferred treatment during percutaneous coronary interventions (PCIs) because of their proven superiority over balloon angioplasty [1-3]. In bare metal stainless steel stents, restenosis still occurs in 20% to 40% of the patients [4-6]. The principal cause of in-stent restenosis is neointimal hyperplasia which results from proliferation and migration of smooth muscle cells and extracellular matrix production [7]. Although the first generation of drug-eluting stents (DESs) have drastically reduced rates of restenosis and revascularisation [8-11], concerns persist regarding their long-term safety [12-14]. 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 and inflammatory and hypersensitive reactions in some cases [15-19]. To address this issue, first generation (stainless steel) DESs have been developed, in which biodegradable and biocompatible polymers have been incorporated as vehicles for drug delivery. The polymers retain the drug to the vessel wall over days and they then degrade over months to biologically inert end products. This remains behind as BMS which can avoid the potentially harmful effects of permanent polymers [20].

Supralimus® (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) uses stainless steel as its stent platform, which is coated with a biodegradable polymer to deliver sirolimus. The present 'Real-Life' study was undertaken to evaluate safety and efficacy of using Supralimus® stents in PCIs which are undertaken in real life patients for short to long-term clinical follow-ups.

MANIPAL-S study (A study which was done on sirolimus-eluting, biodegradable polymer coated Supralimus® stents at Kasturba Medical College, Manipal on real life patients) was a prospective, non-randomised, single- centre study which was conducted in accordance with the International Conference on Harmonisation guidelines Good Clinical Practices, Declaration of Helsinki, and medical ethics committee requirements.

We measured the short and long-term major adverse cardiac and cerebral events (MACCE), which were defined as death, myocardial infarction (MI), stent thrombosis (ST), repeat target- and non-target vessel-revascularisation, target lesion revascularisation (TLR), coronary artery bypass surgery (CABG) and stroke.

MATERIAL AND METHODS

Study Design and Patient Population

A total of 116 consecutive patients who underwent PCIs with the use of Supralimus®SES (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) between September 2009 and December 2010 at Kasturba Medical College, Manipal, India, were included in this study. Patients who were at least 18 years of age, who had stable or unstable angina or myocardial ischaemia or acute/recent myocardial infarction, and were undergoing PCIs with the use of Supralimus® stents were considered for the study. Patients were excluded if they had known allergies to aspirin, clopidogrel, ticlopidine, heparin, sirolimus, stainless-steel and polymers.

The study protocol was approved by the institutional ethics committee. All the patients were enrolled after obtaining informed consents from them.

Description of the Study Stent

The Supralimus® SES is a stainless-steel alloy, CE approved, coronary stent. It is laser cut from 316L Stainless Steel alloy tubes in a serpentine pattern. 316L Stainless Steel alloy has a good radiopacity with an MRI-compatibility that increases its visibility during its implantation. Its design is based on that of CE approved Millennium Matrix® stent [Table/Fig-1].The design is made up of serpentine struts which provides high radial strength with minimum recoil (<5%).

Supralimus® (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) has stainless steel as its stent platform, which has a strut thickness of 80 µm with biodegradable polymers and a 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.

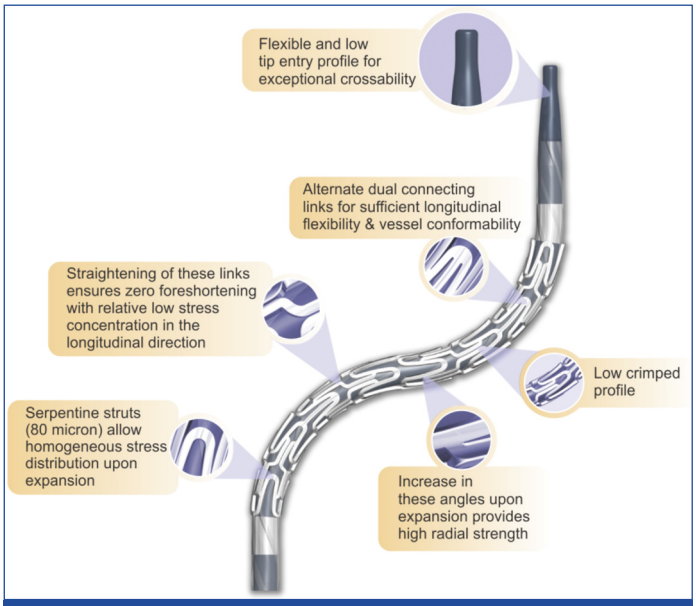
In Supralimus® , Poly L- Lactide (PLA), Poly DL-Lactide-co-Glycolide (PLGA) and Poly Vinyl Pyrrolidone (PVP) polymers are used to achieve a controlled drug release from drug eluting stent. The coating layer comprises of the drug, Sirolimus, which is blended together with biodegradable polymeric matrix. This matrix includes a blend of hydrophobic and hydrophilic biodegradable polymers- Poly L-Lactide, 50/50 Poly DL Lactide-co-Glycolide and PVP, which control the drug elution from stent coating. When it was experimented in-vitro, polymers of Supralimus® stent exhibited their presence for approximately 9 to 12 months on stent.

Scanning electron microscope (SEM) analysis indicated uniform coating on surface of the stent. Stent surface coating was found to be free from irregularities such as cracking, flaking or delamination. After stent dilation, the drug-polymer coating exhibited adherence to the greatest possible extent. This demonstrated that coating film was elastic enough to withstand the expansion mechanism, with no crack formation on the coating film, at the mechanically stressed sites of the stent. SEM analyses revealed complete adhesion of the film. After releasing the drug within 48 days, these polymers eventually degrade naturally and are excreted from the body in the forms of their metabolites. The average coating thickness of Supralimus®stent is between 5 to 6 µm.

The Supralimus® stent was made available in lengths of 11, 16, 19, 23, 29, 33 and 39mm and available diameters were 2.5, 2.75, 3.0 and 3.5.

Interventional Procedure and Adjunctive Medications

All patients were on Aspirin of a dose of 75-150mg, at least 24 hours prior to the start of the procedure. A loading dose of 300 mg of clopidogrel was given 24 hours prior to the start of procedure or a dose of 600 mg was given on the day of the procedure. During the procedure, an initial bolus of 70-100 IU/kg of heparin was given to the patient. Additional heparin was used if necessary during procedure, to achieve an activated coagulation time of > 250 seconds. Administration of GP IIb/IIIa inhibitor was left to the investigator's discretion.



[Table/Fig-1]: Design of Matrix stent platform

Following PCIs, recommended dual antiplatelet regimens were prescribed. Every patient received daily, a minimum of 150 mg of Aspirin for one year, after which aspirin 75 mg daily was recommended lifelong, plus minimum 75 mg clopidogrel for one year. Longer duration antiplatelet therapy of clopidogrel was left to the discretion of the investigator.

Follow-Up

Patients were clinically followed-up at 1) 7 days window period at 1 month 2) 30 days window period at 9 months 3) 45 days window period at 12 months and 4) 45 days window period at 24 months after the procedure. The clinical follow-up consisted of either a telephonic interview or a clinic visit.

Study Endpoints and Definitions

MACCE was defined as death which occurred due to all causes, Q- and non-Q-wave MI, ST, repeat target- and non-target-vessel-related PCI, TLR, CABG and stroke. Revascularisation of the target lesion was defined as a PCI or a CABG which was performed for restenosis of the target lesion, in association with recurrent angina, an objective evidence of myocardial ischaemia or both. Deaths were classified as cardiac or non-cardiac. Deaths which occurred due to undetermined causes were reported as caused by cardiac problems. Diagnosis of a Q-wave myocardial infarction was based on a prolonged typical chest pain and documentation of new, >0.04s Q-waves on a standard electrocardiogram, which were recorded at baseline and before discharge of the patient from the hospital. A non-Q-wave infarction was defined as a blood creatine kinase, or its MB fraction, which was >twice the upper limit of normal, with or without prolonged chest pain. An ST was defined according to Academic Research Consortium (ARC) definitions [21]. An angiographic success was defined as a final residual stenosis of the target site which was < 30%, by using the implanted stent alone. A procedural success was defined as an angiographic success without any in-hospital major adverse cardiac events. All events were adjudicated by an independent clinical events committee.

Data Management and Statistical Analysis

The stented segment refers to the stent and edges which are 5 mm proximal and distal to the stent. The baseline characteristics (patient demographics, cardiovascular disease history, other risk factors, pre-procedure target lesion characteristics and procedure characteristics) were summarised with the mean, standard deviation for continuous variables and with frequencies and percentages for discrete variables. MACCE was reviewed and adjudicated by an independent clinical events committee.

RESULTS

Baseline Patient Characteristics and Follow-Up

The baseline demographics and procedural and lesion characteristics of the MANIPAL-S study population have been summarised [Table/Fig-2 and 3].

A total of 116 patients (126 lesions) were implanted with 144 stents which had an average stent length of 25.8± 8.0 mm. An average of 1.24 stents were implanted per patient. Patients were followed up at 1, 9, 12 and 24 months post-procedure.

Characteristics	Supralimus® SES n = 116 Patients
Age (mean ± SD, yrs)	56.4 ± 11.1
Male, n (%)	85 (73.3%)
Diabetes Mellitus, n (%)	38 (32.8%)
Insulin Requiring, n (%)	4 (3.5%)
Non-Insulin Requiring, n (%)	34 (29.3%)
Hypertension, n (%)	52 (44.8%)
Smoker, n (%)	29 (25.0%)
Hypercholesterolemia, n (%)	43 (37.1%)
Primary PCI, n (%)	81 (69.8%)
Rescue PCI, n (%)	35 (30.2%)

[Table/Fig-2]: Baseline demographics characteristics
SES = Sirolimus-Eluting Stent

Characteristics	Supralimus® SES n = 144 Lesions
Target Coronary Artery	
LAD, n (%)	64 (50.8%)
RCA, n (%)	43 (34.1%)
LCX, n (%)	17 (13.5%)
Left main, n (%)	2 (1.6%)
Target Vessels	
Single Vessel Disease, n (%)	101 (80.2%)
Double Vessel Disease, n (%)	19 (15.1%)
Triple Vessel Disease, n (%)	6 (4.8%)
ACC/AHA Lesion Classification	
A, n (%)	7 (4.9%)
B1, n (%)	27 (18.7%)
B2, n (%)	49 (34.0%)
C, n (%)	61 (42.4%)
Mean Stent Length, (mean ± SD, mm)	25.8 ± 8.0
Mean Stent Diameter, (mean ± SD, mm)	2.8 ± 0.3

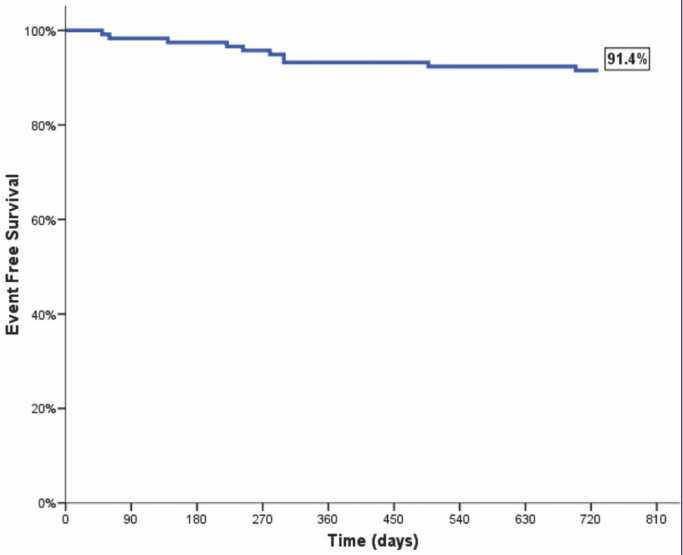
[Table/Fig-3]: Procedural and Lesion Characteristics
SES = Sirolimus-Eluting Stent, ACC/AHA = The American College of Cardiology/ the American Historical Association

	Supralimus® SES (N =116)				
	30 days	9 months	12 months	24 months	Cumulative Events
No. of patients	103	99	97	94	116
Deaths					
Cardiac	0	1 (0.9%)	1 (0.9%)	2 (1.7%)	2 (1.7%)
Non Cardiac	0	1 (0.9%)	2 (1.7%)	3 (2.6%)	3 (2.6%)
MI	0	0	0	0	0
TLR	0	2 (1.7%)	2 (1.7%)	2 (1.7%)	2 (1.7%)
TVR	0	0	0	0	0
Non-TVR	0	0	2 (0.9%)	2 (0.9%)	2 (0.9%)
Stent Thrombosis[a]					
Possible	0	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
Total					**10 (8.6%)**

[Table/Fig-4]: Cumulative Clinical Outcomes at 1, 9, 12 and 24 months Follow-up
Values expressed as number (%);TVR = Target Vessel Revascularisation;
TLR = Target Lesion Revascularisation; [a]Stent thrombosis according to the ARC (Academic Research Consortium) definition

Clinical Outcomes

No in-hospital events were reported. The incidence of any MACCE at 1, 9, 12 and 24 months was 0, 5 (4.3%), 8 (6.9%), and 10 (8.6%) respectively [Table/Fig-4]. The two years event free survival was 91.4% [Table/Fig-5].



[Table/Fig-5]: Two year MACCE free survival curve (90.5%, n =116)

Deaths during follow-up

A total of 5 deaths were documented during the follow-up period. These deaths have been documented as per ARC definition. Two patients died because of urosepsis. One patient died of a stroke, 2 months after the index procedure. One patient died after 699 days of index procedure, who had no history of cardiac symptoms. It may have probably been a sudden cardiac death (arrhythmia or very late stent thrombosis). One patient died 10 months after index procedure. He underwent CABG for new lesions on non-target vessels. However, he died 7days after undergoing CABG.

Revascularisation during Follow-Up

There were a total of two target lesion revascularisations; one patient underwent POBA (plain old balloon angioplasty), while the second patient was treated with balloon dilatation and re-implantation of a Supralimus® stent. Both the patients have been doing well over the past 15 months. The decision to perform further TLR or TVR during the follow-up was left to the investigator's discretion as per protocol design.

There were a total of two non-target vessel revascularisations (non-TVR); one patient was diagnosed with a *de novo* lesion in another vessel and was treated with stent implantation, while the second patient underwent CABG. One patient had late ST, 140 days after index procedure; he was treated with redilatation, but unfortunately he died later due to urosepsis.

DISCUSSION

Efficacy of a sirolimus-eluting stent with the use of a stainless steel platform and a biostable polymer has been well documented in medical literature [22-26]. The stents' clinical effectiveness and safety was initially demonstrated in the 100-patient SERIES I (Study on the Supralimus® Sirolimus-Eluting Stent in the Treatment of Patients With Real World Coronary Artery Lesions) First-in-Man study, which reported a rate of in-stent angiographic restenosis of 0.0% and a late loss of 0.09 ± 0.37 mm at 6-months of follow-up. At 30 months, the rate of target vessel revascularisation (TVR) was 4%, with no reported definite ST [27]. Similar clinical effectiveness and safety have been reported at 6-months of follow-up in the larger e-SERIES multicenter registry, which included over 1,100 patients [28].

The Supralimus® stent was compared to the Infinnium® paclitaxel-eluting stent (Sahajanand Medical Technologies), which also has a biodegradable polymer, and a BMS in the randomised, multicenter PAINT (Percutaneous Intervention With Biodegradable-Polymer

Based Paclitaxel-Eluting, Sirolimus-Eluting, or Bare Stents for the Treatment of *De Novo* Coronary Lesions) study which was done on 274 low-risk patients. Results demonstrated that as compared to BMS controls, the 2 DES stents had a significantly lower late loss and significantly lower rates of TVR and MACE at 9 months, 12-months and three years of follow-up. In addition, the Supralimus® SES stent was shown to have a significantly lower late loss as compared to the Infinnium® PES; however, this did not translate into any difference in clinical outcomes [29-30].

First generation stents use durable thick polymers to carry and control the release of their anti-proliferative agents. The permanent presence of these polymers has been correlated to inflammatory responses, hypersensitivity issues, lack of a complete endothelization, thrombus formation, and local toxicity in preclinical trials as well as clinical studies [31-34]. Furthermore, durable polymers which were used in first-generation DES were associated with mechanical complications (e.g., polymer delamination and "webbed" polymer surface which led to stent expansion issues) [35] and the non-uniform coating had resulted in an erratic drug distribution. In order to address these limitations, bioresorbable polymers have been developed, which have the potential for a controlled drug release, combined with a biodegradation process, which ultimately leaves only the bare-stent platform behind. Several newer generation DES platforms utilize biodegradable as opposed to durable polymers and they have been reviewed here. ISAR-TEST 3 trial which compared outcomes of DES with those of biodegradable-polymer, no-polymer, and permanent-polymer SES showed best outcomes with biodegradable polymer (Revascularisation 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).

The drug coating in multiple layers with the use of biodegradable polymer layers for the Supralimus® stent, is designed to deliver the drug in a biphasic manner: an initial burst dose, followed by a controlled release of the drug, which are most likely to reduce late adverse clinical events as compared to stents with non-biodegradable polymers.

The present study used a biodegradable polymer as a vehicle for sirolimus-eluting Supralimus® stent and it showed excellent procedural success (100%) and no in-hospital MACCE. A long-term safety was also well demonstrated at 2 years of follow up, with a low MACCE rate of 8.6%. Long term follow-up is on-going.

CONCLUSIONS

These 24-month results clearly provide evidence on safety and effectiveness of the Supralimus® Sirolimus-eluting coronary stent system with the biodegradable polymer in real-life patients, even in those with acute myocardial infarctions.The stents were easily deployed despite the complexity of the lesions which were treated, which represent real world day-to-day cases, rather than selected ideal lesions.

STUDY LIMITATIONS

This study was limited by its non-randomised, single-centre design and moderate sample size.

REFERENCES

[1] Al Suwaidi J, Berger PB, Holmes DR, Jr. Coronary artery stents. *JAMA* 2000;284(14):1828-36.

[2] Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med*. 2003;138(10):777-86.

[3] Nordmann AJ, Hengstler P, Leimenstoll BM, Harr T, Young J, Bucher HC. Clinical outcomes of stents versus balloon angioplasty in non-acute coronary artery disease. A meta-analysis of randomised controlled trials. *Eur Heart J*. 2004;25(1):69-80.

[4] Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schomig A. Vessel size and long-term outcome after coronary stent placement. *Circulation*. 1998;98(18):1875-80.

[5] Mercado N, Boersma E, Wijns W, Gersh BJ, Morillo CA, de Valk V, van Es GA, Grobbee DE, Serruys PW. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. *J Am Coll Cardiol*. 2001;38(3):645-52.

[6] Scheen AJ, Warzee F, Legrand VM. Drug-eluting stents: meta-analysis in diabetic patients. *Eur Heart J*. 2004;25(23):2167-8; author reply 2168-9.

[7] Nikol S, Huehns TY, Hofling B. Molecular biology and post-angioplasty restenosis. *Atherosclerosis*. 1996;123(1-2):17-31.

[8] Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, et al . Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356(10):1030-09.

[9] Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomised comparison of a sirolimus-eluting stent with a standard stent for coronary revascularisation. *N Engl J Med*. 2002;346(23):1773-80.

[10] Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet*. 2007;370(9591):937-48.

[11] Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, et al . Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007;356(10):998-1008.

[12] Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, et al . Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet*. 2007;369(9562):667-78.

[13] Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N *Engl J Med*. 2007;356(10):1009-19.

[14] Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomised clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356(10):1020-9.

[15] Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48(1):193-202.

[16] Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol*. 2006;47(1):175-81.

[17] Van Beusekom HM, Saia F, Zindler JD, Lemos PA, Swager-Ten Hoor SL, van Leeuwen MA, et al. Drug-eluting stents show delayed healing: paclitaxel more pronounced than sirolimus. *Eur Heart J*. 2007;28(8):974-9.

[18] Van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation*. 1996;94(7):1690-07.

[19] Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109(6):701-5.

[20] Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007 May 1;115(17):2344-51.

[21] Kereiakes DJ, Cox DA, Hermiller JB, Midei MG, Bachinsky WB, Nukta ED,et al. Usefulness of a cobalt chromium coronary stent alloy. *Am J Cardiol*. 2003;92(4):463-06.

[22] Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomised comparison of a sirolimus-eluting stent with a standard stent for coronary revascularisation. *N Engl J Med*. 2002;346(23):1773-80.

[23] Schofer J, Schlu¨ter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (ESIRIUS). *Lancet*. 2003;362:1093–09.

[24] Lee CH, Lim J, Low A, Zhang XL, Kyaing TT, Chan MY, et al. Sirolimus-eluting, bioabsorbable polymer-coated constant stent (Cura) in acute ST-elevation myocardial infarction: a clinical and angiographic study (CURAMI Registry). *J Invasive Cardiol*. 2007;19:182-5.

[25] Ge J, Qian J, Wang X, Wang Q, Yan W, Yan Y, et al. Effectiveness and safety of the sirolimus-eluting stents coated with bioabsorbable polymer coating in human coronary arteries. *Catheter Cardiovasc Interv*. 2007;69(2):198-202.

[26] Dani S, Kukreja N, Parikh P, Joshi H, Prajapati J, Jain S, et al. Biodegradable-polymer-based, sirolimus-eluting Supralimus® stent: 6-month angiographic and 30-month clinical follow-up results from the series I prospective study. *EuroIntervention*. 2008;4(1):59-63.

[27] Han Y, Jing Q, Xu B, Yang L, Liu H, Shang X, et al. Safety and efficacy of biodegradable polymer-coated sirolimus-eluting stents in "real-world" practice: 18-month clinical and 9-month angiographic outcomes. *JACC Cardiovasc Interv*. 2009;2(4):303-9.

[28] Lemos PA, Moulin B, Perin MA, Oliveira LA, Arruda JA, Lima VC, et al. Randomized evaluation of two drug-eluting stents with identical metallic platform and biodegradable polymer but different agents (paclitaxel or sirolimus) compared against bare stents: 1-year results of the PAINT trial. *Catheter Cardiovasc Interv*. 2009;74(5):665-73.

[29] Lemos PA, Moulin B, Perin MA, Oliveira LA, Arruda JA, Lima VC, et al. Late clinical outcomes after implantation of drug-eluting stents coated with biodegradable polymers: 3-year follow-up of the PAINT randomised trial. *Euro Intervention*. 8(1):117-09.

[30] Pendyala LK, Li J, Shinke T, Geva S, Yin X, Chen JP, et al. Endothelium-dependent vasomotor dysfunction in pig coronary arteries with Paclitaxel-eluting stents is

associated with inflammation and oxidative stress. *JACC Cardiovasc Interv*. 2009;2(3):253-62.
[31] Luscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation.* 2007;115(8):1051-8.
[32] Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol.* 2007;27(7):1500-10.
[33] Silva GV, Fernandes MR, Madonna R, Clubb F, Oliveira E, Jimenez-Quevedo et al. Comparative healing response after sirolimus- and paclitaxel-eluting stent implantation in a pig model of restenosis. *Catheter Cardiovasc Interv*. 2009;73(6):801-8.
[34] Hossainy S, Prabhu S. A mathematical model for predicting drug release from a biodurable drug-eluting stent coating. *J Biomed Mater Res A.* 2008;87(2):487-93.
[35] Mehilli J, Byrne RA, Wieczorek A, Iijima R, Schulz S, Bruskina O, et al . Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J.* 2008;29(16):1975-82.

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