ECRONICON OPEN ACCESS

EC CARDIOLOGY
Research Article

Long Term Follow up of a Carbofilm Coated Stent in ST-Elevation Myocardial Infarction: Insight from the Real World SAVONA Registry

Matteo Ghione[1]*, Luca Bacino[1], Stefano Cordone[1], Rodrigo Estevez-Loureiro[2], Marco Botta[1], Fabio Critelli[1], Paolo Bellotti[1] and Pietro Bellone[1]

[1]S.C. Cardiologia, Ospedale San Paolo, Savona

[2]Unidad de Cardiología Intervencionista, Complejo Asistencial Universitario de León, Fundación Investigación Sanitaria de León (FISLeón), León, Spain

***Corresponding Author:** Matteo Ghione, S.C. Cardiologia, Ospedale San Paolo, Savona.

Received: May 03, 2017; **Published:** June 12, 2017

Abstract

Background: Primary percutaneous coronary intervention (PPCI) with bare metal stents (BMS) significantly improved the clinical outcomes in patients with ST elevation myocardial infarction (STEMI).

Aim of our registry was to analyze the safety and efficacy of a new generation carbofilm™ coated BMS in patients treated with PPCI.

Methods and Results: A total of 235 patients (mean age 68.2 ± 12.6; 68.9% male) treated with PPCI between January 2005 and December 2008, were enrolled in our registry. The primary endpoint was the occurrence of any major adverse cardiac events (MACE) up to 6 years, defined as composite of cardiac death, recurrent myocardial infarction, target lesion revascularization (TLR) and target vessel revascularization. Stent thrombosis (ST) was evaluated as secondary endpoint. The left anterior descending artery was the culprit vessel in 43.8% of cases. The mean stent length was 24.6 ± 11.8 mm. Device success reached 100% while no-reflow was present in 1.7% of patients. Six years follow up was completed for 88.9% of patients. Event free survival from MACE was 77,4% and 8.1% of patients had TLRs. Five ST were recorded throughout the study of which one occurred beyond three years.

Conclusion: Our study confirms the safety and efficacy of a carbofilm™ coated BMS mainly supported by the low incidence of MACE and stent thrombosis in the long term follow up.

Keywords: *Carbostent; STEMI; BMS*

Abbreviations

BMS: Bare Metal Stent; DES: Drug Eluting Stent; MACE: Major Adverse Cardiac Events; MI: Myocardial Infarction; PPCI: Primary Percutaneous Coronary Intervention; ST: Stent Thrombosis; STEMI: ST Elevation Myocardial Infarction; TLR: Target Lesion Revascularization; TVR: Target Vessel Revascularization

Introduction

Primary percutaneous coronary intervention (PPCI) significantly improves clinical outcomes in patients with ST elevation myocardial infarction (STEMI) [1,2] and implantation of bare metal stents (BMS) has been the treatment of choice for several years [3].

The initial experiences with drug eluting stents (DES) in the setting of acute myocardial infarction showed controversial results [4,5]. Compared to BMS, DES reduced the incidence of in stent restenosis and target lesion revascularization (TLR) [6]. On the contrary, the main drawback was represented by the increased incidence of late and very late stent thrombosis (ST) [7,8] and the need for a prolonged dual antiplatelet therapy [9].

In fact, the inflammatory response to durable polymer, the antiproliferative effect of the drugs and the malapposition of stent' struts to the vessel wall might delay the vessel healing after DES deployment leading to ST [10]. To overcome these disadvantages, new stent platforms and technologies has been developed and novel generations of DES seem to perform better than old generations of BMS [11]. However, the role of new generation BMS with bioactive properties has not been fully investigated yet, especially in the long term follow up.

The aim of our registry was to evaluate the safety and efficacy of the carbofilm™ coated stent (Chrono™, CID SpA, Saluggia, Italy) in an unselected population undergoing to PPCI for STEMI.

Methods

Study Population

From January 2005 to December 2008, all STEMI patients admitted for a PPCI and treated with at least one study device were eligible for the registry.

Inclusion criteria were age over 18 years and occurrence of STEMI treated with PPCI. Patients with cardiogenic shock (defined as systolic blood pressure of less than 80 mmHg or the need for intravenous vasopressors or intra-aortic-balloon pump) were also included.

Procedural details

After loading with clopidogrel (300 - 600 mg) and aspirin (300 mg per os or 500 mg intravenously), patients received heparin (maintaining an activated clotting time more than 250 seconds checked every 30 min) at the beginning of the procedure.

Patients received Glycoprotein IIb/IIIa inhibitors according to operator's evaluation.

A six or seven French guiding catheter, via radial or femoral access, was used according to the operator's preference.

Thrombus aspiration was performed when required. Post-dilation with a balloon shorter than the stent length was performed to achieve an optimal stent expansion if required. If multiple stenting was necessary, the same type of stent was used. The treatment of non-culprit lesions, during the target procedure, was discouraged unless the patient was in cardiogenic shock.

Device success was defined as the ability to reach, cross and dilate the lesion with the index stent. Procedural success was defined as residual stenosis less than 30% and a final thrombolysis in myocardial infarction (TIMI) flow 3.

During the follow up dual antiplatelet therapy was mandated for at least 12 months.

Device

Carbostent™ stent consists of a stent made of cobalt chrome (CrCo) alloy with a strut thickness of 80 μm. It has a homogeneous closed-cell design, which avoids elastic distortion and stress concentration on the vessel wall while allowing zero foreshortening during expansion. It is coated by an integral thin (< 0.5 mm) coating of turbostratic carbon (Carbofilm™) which enhance stent thromboresistance and biocompatibility. Available Chrono Carbostent™ sizes ranged from 2.5 to 4.0 mm, whereas stent lengths ranged from 8 to 31 mm.

Clinical endpoints and follow-up

The occurrence of any major adverse cardiac event (MACE) up to 6 years, defined as death from cardiac causes, recurrent myocardial infarction (MI), TLR and target vessel revascularization (TVR) were analyzed as primary endpoint.

Re-infarction was defined as the occurrence of relapsing chest pain or electrocardiographic changes associated with a Troponin I level elevation above the upper range limit.

TLR and TVR were defined as PCI or coronary surgery performed to treat a restenosis (>50%) or a re-occlusion of the infarct-related lesion or vessel.

The secondary endpoint was the evaluation of ST incidence up to 6 years of follow-up. ST was defined according to the Academic Research Consortium definition [12] as definite, probable, or possible ST. Event time was categorized as acute, sub-acute, late and very late.

All patients were followed-up by telephone call to obtain information on clinical status and occurrence of any clinical event. All other information, derived from hospital readmission, by referring physician or municipality live registries were used to complete the database.

Statistical Analysis

Continuous normally distributed variables are presented as mean ± SD, as median [interquartile range] for continuous non-normally distributed data and as percentages for categorical data.

Analysis of normality was performed with the Kolmogorov-Smirnov and Shapiro-Wilk test.

Categorical data and proportions were compared using χ^2 test or Fisher exact test as required.

Comparisons of continuous variables were analysed using Student's T test and the Mann-Whitney U test as appropriate.

Events free survival curves were generated by the Kaplan-Meier method.

The statistical analysis were performed using the specific software SPSS 20 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline and procedural characteristics

A total of 235 patients were enrolled in the registry. Clinical and procedural characteristics are shown in table 1 and table 2 respectively. Briefly, the mean age was 68.2 ± 12.6 and 68.9% were male. Among our population, 9.3% of patients had a prior myocardial infarction and 2.1% presented in cardiogenic shock.

Age (years), mean ± SD	68.2 ± 12.6
Male	162 (68.9%)
Daibetes mellitus	41 (17.4%)
Hypertension	146 (61.9%)
Dyslipidemia	93 (39.6%)
Smoker	76 (32.2%)
Familial History of cardiovascular disease	74 (31.4%)
Prior MI	22 (9.3%)
Prior PCI	11 (4.7%)
Prior CABG	1 (0.4%)
Renal impairment	17 (7.2%)
Cardiogenic shock	5 (2.1%)
Ejection Fraction (%), mean ± SD	47.9 ± 8.5
Anterior ECG	94 (40%)
Data are expressed as No. (%) unless otherwise specified	

Table 1: *Clinical Characteristics.*

Infarct related artery	
LAD	103 (43.8)
LCx	31 (13.2)
RCA	100 (42.6)
Graft	1 (0,4)
Lesions characteritics	
Bifurcation lesions	56 (23.7)
Ostial lesions	10 (4.2)
Type of lesions	
A	2 (0.8)
B1	20 (8.5)
B2	127 (53.8)
C	87 (36.9)
Thrombus aspiration	125 (53.2)
Gp IIb/IIIa administration	173 (74.5)
Direct stenting	44 (18.6)
Single stent implantation	167 (71.1)
Number of stent	1.4 ± 0.7
Stent overlapping	68 (28.9)
Stent lenght ± SD	24.6 ± 11.8
Stent diameter ± SD	3.2 ± 0.4
Number of lesion	1.1 ± 0.3
Basal TIMI flow	
0 - 1	150 (63.8)
2	42 (17.9)
3	43 (18.3)
Final TIMI flow	
0 - 1	8 (3.4)
2	9 (3.8)
3	218 (92.8)
No reflow	4 (1.7)
Data are expressed as No. (%) unless otherwise specified	

Table 2: *Procedural Characteristics.*

Left anterior descending artery was the culprit vessel in 43.8% of cases and 23.7% of lesions involved a bifurcation. According to ACC/AHA classification, 53.8% and 36.9% of lesions were B2 type or C type respectively. Device success was 100% and 53.2% required mechanical thrombus aspiration. Direct stent technique was employed in 18.6% and a single stent was implanted in 71.1% of cases. The average stented segment length was 24.6 ± 11.8 mm. Final TIMI 3 flow was achieved in 92.8% of patients whereas no reflow was present in 1.7% of patients.

Follow up

Six years follow up was completed for 88.9% of population. At one year follow up the MACE occurred in 15.9% of patients while at the end of the study the rate reached 21.5% (Table 3).

	In hospital N = 232	1 year f.u. N = 232	6 year f.u. N = 209
MACE	14 (6)	37 (15.9)	45(21.5)
Cardiac death	9 (3.8)	14 (6)	17 (8.1)
TLR	1 (0.4)	9 (3.9)	17 (8.1)
PCI	1 (0.4)	9 (3.9)	17 (8.1)
CABG	-	-	-
TVR		1 (0.9)	8 (3.8)
MI	1 (0.4)	3 (1.3)	16 (7.6)
Data are expressed as No. (%) unless otherwise specified			

Table 3: *Major Adverse Cardiovascular Events.*

Six years event free survival was 77.4% (Figure 1).

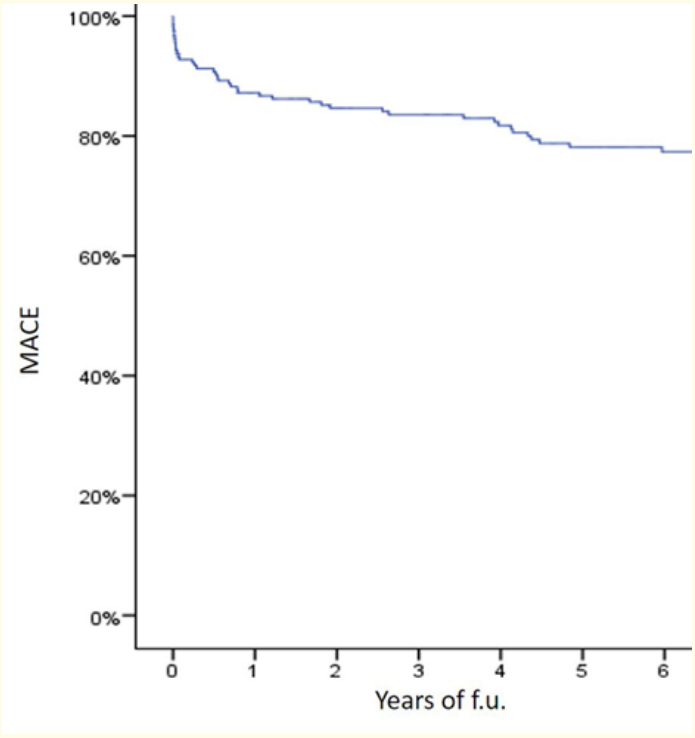

Figure 1: *Kaplan-Meier curve for MACE.*

The total rate of cardiac death was 8.1% and half of them occurred during hospital stay.

Although at one year follow up the TLR were 3.9%, the percentage doubled at the end of observation. The main reason for TLR was in stent restenosis. In fact, during the whole follow-up five ST were recorded. Among them 3 definite (1 acute and 2 sub-acute) and 1 probable ST occurred within 30 days. One definite very late ST was detected at 1294 days of follow up. Figure 2 illustrates definite and probable ST rate according to the time of their occurrence.

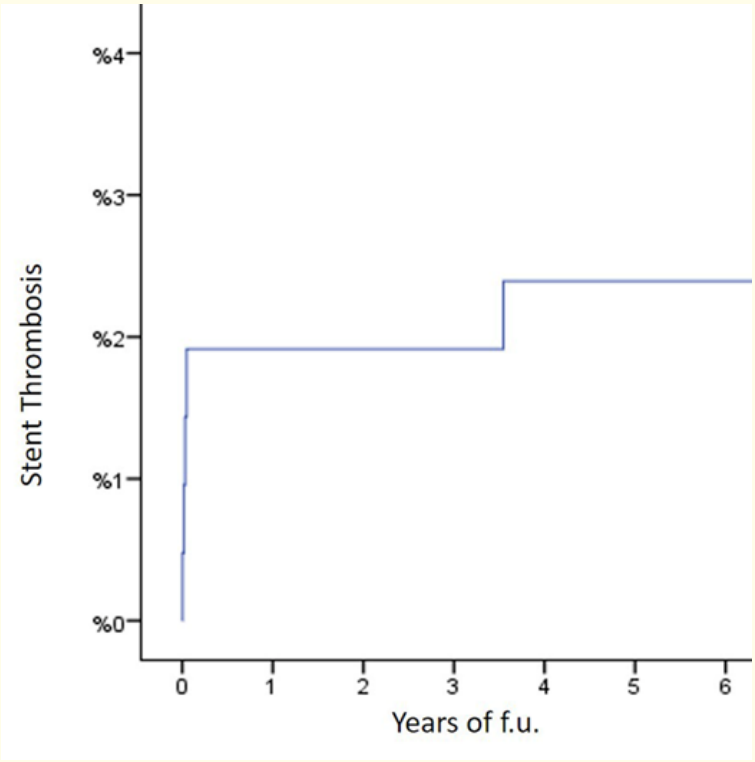

Figure 2: *Definite and probable thrombosis rate according to the time of their occurrence.*

Discussion

The SAVONA registry is a large monocentric, real world, all comers registry designed to analyze the outcomes of carbostent in patients treated with PPCI.

Limited data are available on carbostent in the setting of STEMI. In an initial two centers experience [13], this device was implanted in 112 patients and 55% of them suffered from unstable angina. At six months, clinical and angiographic follow up, the event free survival from MACE (composite of death, myocardial infarction, and target lesion revascularization) was 84 ± 4% and TLR was required in 10% of cases.

The HEART study [14] examined the performance of the carbostent in a cohort of 107 patients treated for STEMI. Among them 77% underwent PPCI while 23% to rescue PCI. In this registry the incidence of in hospital and one year MACE (composite of cardiac death, non-

fatal MI and TLR) was 9.3% and 17.7% respectively. Our data are in line with these findings. In fact, in the SAVONA registry the incidence of MACE at one year was 15.9% while in hospital MACE were 6%. Notably the rate of TLR was 0.4% in the in hospital period and 3.9% of cases had TLR at one year follow up while in the HEART study the incidence of TLR was 2.8% and 9.3% respectively in the two periods.

No data on long term follow up are available for this device in STEMI setting.

A recently published analysis on long term outcomes of BMS versus DES in a large all comers cohort showed no difference in terms of MACE between these devices. However, the need for any revascularization was higher in the BMS group (19.8 %), while the stent thrombosis were low in both groups [15].

The MISSION trial investigated five years results of BMS vs SES in patients with STEMI. The rate of TLR was 12.9% in BMS group and stent thrombosis 2.7% [16]. Similarly, in the DEDICATION trial the rate of TLR reached 16.6% at five years follow up for BMS treated patients [17].

In our cohort, the incidence of TLR was 8.1% and the main component of TLR was represented by in stent restenosis.

The other reason for a re-intervention was because of ST. ST is considered as the most dreadful complication after stent implantation. STEMI presentation is known to be one of the most powerful predictor of ST and is mainly related to the suboptimal stent apposition to the vessel wall due to the presence of thrombus [18,19]. In fact, in this acute condition, the enhanced inflammatory response and the higher platelet reactivity may lead to a higher risk of ST. In STEMI patients enrolled in randomized trial, the 1 year rate of ST, regardless if a BMS or DES was implanted, ranged between 1% to 4% [20-22]. In the long-term period BMS ST accounted for 2.7% to 3.8% [16-17,23-24].

In our registry, the rate of definite or probable stent thrombosis was less than 2% at one year follow up and 2.4% at end of the study. One of them was acute and three occurred within 30 days. Only one very late definite ST was registered in our study. These findings could be partially explained by the high use of thrombectomy and the relatively high administration of gp IIb/IIIa drugs that may have contribute to reduce the thrombotic burden at the time of stent implantation. Moreover, the particular design of the device may have decreased the event's occurrence. In fact, the biocompatible and haemocompatible characteristics of pyrolitic carbon showed in in-vitro models to attenuate platelet adhesion and activation [25] and to be a powerful enhancer of endothelial cell attachment and growth [26].

Although acute and sub-acute ST could be explained by procedural features and devices properties, the reason for a very late ST is still unknown. BMS are more prone than DES to in-stent restenosis. The main mechanism was thought to be secondary to neointimal proliferation [27] which peaks in the early phase after stent implantation. However, very late restenosis of BMS occasionally are observed beyond 4 to 5 years [28].

Habara., *et al*. showed that OCT morphological characteristics of BMS restenotic tissue in very late in stent restenosis corresponded predominantly to a heterogeneous pattern and were different from that in early in stent restenosis with a homogeneous pattern. The heterogeneous pattern was found to be similar to that of atherosclerotic plaques of coronary artery [29,30]. In an OCT sub analysis of the EXAMINATION trial, neoatherosclerotic plaques and macrophage accumulations were more frequent with BMS. Thus, the cause of very late in stent restenosis of BMS might be associated with the atherosclerotic progression of neointimal proliferation of the stent which could lead to a thrombotic event.

Limitations

This study has several limitations. First, our study is a monocentric, all comers registry in which only one device was tested. Thus, we cannot speculate on potential differences with other devices.

Second, the extensive use of gpIIb/IIIa inhibitor for all patients may have create a bias, reducing the thrombotic burden and influencing stent thrombosis in the follow up.

However, this study represents a wide all comers registry which provides a real picture of a large series of patients treated with a Carbostent in the setting of STEMI with long term follow up.

Conclusion

Our real world all comers experience shows that carbostent implantation is safe and related to high procedural success in patients treated with PPCI.

The ST rate is low and occurred mainly in the first month after implantation.

Long term results are encouraging and this device might represents an alternative for patients not eligible for DES implantation.

Conflict of Interest

We have no conflict of interest to declare.

Bibliography

1. Weaver WD., *et al*. "Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review". *Journal of the American Medical Association* 278.23 (1997): 2093-2098.

2. Zijlstra F., *et al*. "Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction". *New England Journal of Medicine* 341.19 (1999): 1413-1419.

3. Zhu MM., *et al*. "Primary stent implantation compared with primary balloon angioplasty for acute myocardial infarction: a meta-analysis of randomized clinical trials". *American Journal of Cardiology* 88.3 (2001): 297-301.

4. Steg PG., *et al*. "Mortality following placement of drug-eluting and bare-metal stents for ST-segment elevation acute myocardial infarction in the Global Registry of Acute Coronary Events". *European Heart Journal* 30.3 (2009): 321-329.

5. Kastrati A., *et al*. "Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction". *European Heart Journal* 28.22 (2007): 2706-2713.

6. Shishehbor MH., *et al*. "Comparison of drug-eluting stents versus bare-metal stents for treating ST-segment elevation myocardial infarction". *JACC: Cardiovascular Interventions* 1.3 (2008): 227-232.

7. Daemen J., *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* 369.9562 (2007): 667-678.

8. Iakovou I., *et al*. "Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents". *Journal of the American Medical Association* 293.17 (2005): 2126-2130.

9. Pfisterer M., *et al*. "Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents". *Journal of the American College of Cardiology* 48.12 (2006): 2584-2591.

10. Finn AV., *et al*. "Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialisation". *Circulation* 115.18 (2007): 2435-2441.

11. Palmerini T., *et al*. "Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis". *Lancet* 379.9824 (2012): 1393-1402.

12. Cutlip DE., *et al*. "Clinical end points in coronary stent trials: a case for standardized definitions". *Circulation* 115.17 (2007): 2344-2351.

13. Antoniucci D., *et al*. "Clinical and angiographic outcome after coronary arterial stenting with the carbostent". *American Journal of Cardiology* 85.7 (2000): 821-825.

14. Leone AM., *et al*. "The HEART study: a real-world experience using the CID Chrono Carbostent in primary and rescue PCI". *Journal of Cardiovascular Medicine* 13.12 (2012): 775-782.

15. Bønaa KH., *et al*. "Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease". *New England Journal of Medicine* 375 (2016): 1242-1252.

16. Boden H., *et al*. "Five-year clinical follow-up from the MISSION! Intervention Study: sirolimus-eluting stent versus bare metal stent implantation in patients with ST-segment elevation myocardial infarction, a randomised controlled trial". *EuroIntervention* 7.9 (2012): 1021-1029.

17. Holmvang L., *et al*. "Long-term outcome after drug-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: 5 years follow-up from the randomized DEDICATION trial (Drug Elution and Distal Protection in Acute Myocardial Infarction)". *JACC: Cardiovascular Interventions* 6.6 (2013): 548-553.

18. Sianos G., *et al*. "Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden". *Journal of the American College of Cardiology* 50.7 (2007): 573-583.

19. Gonzalo N., *et al*. "Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography". *JACC: Cardiovascular Interventions* 2.5 (2009): 445-452.

20. Laarman GJ., *et al*. "Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention". *New England Journal of Medicine* 355.11 (2006): 1105-1113.

21. Stone GW., *et al*. "Bivalirudin during primary PCI in acute myocardial infarction". *New England Journal of Medicine* 358.21 (2008): 2218-2230.

22. Valgimigli M., *et al*. "Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial". *Journal of the American Medical Association* 299.15 (2008): 1788-1799.

23. Vink MA., *et al*. "5-year follow-up after primary percutaneous coronary intervention with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-segment elevation myocardial infarction: a follow-up study of the PASSION (Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation) trial". *JACC: Cardiovascular Interventions* 4.1 (2011): 24-29.

24. Sabaté M., *et al*. "Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial". *Lancet* 387.10016 (2016): 357-366.

25. Cenni E., *et al*. "Adhesive protein expression on endothelial cells after contact in vitro with polyethylene terepthalate coated with pyrolytic carbon". *Biomaterials* 16.16 (1995): 1223-1227.

26. Sbarbati R., *et al*. "Pyrolitic carbon coating enhances Teflon and Dacron fabric compatibility with endothelial cell growth". *International Journal of Artificial Organs* 14.8 (1991): 491-498.

27. Schwartz RS., *et al*. "Pathophysiology of coronary artery restenosis". *Reviews in Cardiovascular Medicine* 3.5 (2002): S4-S9.

28. Kimura T., *et al*. "Long-term clinical and angiographic follow-up after coronary stent placement in native coronary arteries". *Circulation* 105.25 (2002): 2986-2991.

29. Habara M., *et al*. "Difference of tissue characteristics between early and very late restenosis lesions after bare-metal stent implantation: an optical coherence tomography study". *Circulation: Cardiovascular Interventions* 4.3 (2011): 232-238.

30. Gomez-Lara J., *et al*. "Five-Year Optical Coherence Tomography in Patients With ST-Segment-Elevation Myocardial Infarction Treated with Bare-Metal Versus Everolimus-Eluting Stents". *Circulation: Cardiovascular Interventions* 9.10 (2016).

Volume 3 Issue 2 June 2017