# Safety and Efficacy of Sirolimus-Eluting Stent in Diabetic Patients Compared with Non-Diabetic Patients Undergoing Percutaneous Coronary Intervention

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**Abstract:** *Background*: The research has been shown that the clinical outcomes of diabetic patients undergoing revascularization either coronary artery bypass grafting or percutaneous coronary intervention (PCI) are inferior to that of non-diabetic patients.

*Objectives*: We have carried out the registry to assess the clinical outcomes of the patients with diabetes mellitus (DM) compared to the patients without DM after the PCI with sirolimus-eluting stent.

*Methods*: Indolimus Diabetic registry is a single-centre; single-armed, retrospective registry that enrolled 530 patients who underwent PCI with Indolimus® stent at the Sri Venkateswara Institute of Medical Sciences, Tirupati, India during the study period. The endpoint of the registry was a major adverse cardiac event (MACE) defined as a composite of cardiac death, myocardial infarction (Q-wave and non-Q-wave not clearly attributable to a non-target vessel), target lesion revascularization (TLR) and target vessel revascularization (TVR) and that were observed at 30-days and at 6-monthsfollow-up.

*Results*: Among 530 patients, 169 patients were having DM. It is noteworthy that the patients with DM were more often women (29.6% vs. 18.0%), hypertensive (54.4% vs. 34.1%) and higher incidence of revascularization (4.2% vs. 2.5%). Double vessel disease was more prevalent in diabetic population as compared to non-diabetics (37.9% vs. 24.9%). Total 617 lesions were encountered in 530 patients (202 in diabetic patients and 415 in non-diabetic patients). There was no significant difference observed in the lesion class. There was no statistical significant difference observed for cardiac death (1.8% vs. 1.7%, $p$=1.00) and MACE (1.8% vs. 1.9%, $p$=1.00) in diabetic and non-diabetic patients at 30-days follow-up. However, at 6-month follow-up, it has been observed that the occurrence of MACE was higher but not statistically significant in diabetic patients as compared to non-diabetic patients (4.1% vs. 2.5%, $p$=0.29).

*Conclusions*: In this Indolimus Diabetic registry, MACE rate did not significantly differ between diabetic and non-diabetic population at 30-days and at 6-months follow-up. However, long term follow-up is needed to determine whether a similar safety profile is maintained.

**Keywords:** Percutaneous coronary intervention, Diabetes, Drug eluting stent.

## INTRODUCTION

Diabetes Mellitus (DM) is one of the risk factors for coronary artery diseases (CAD). People with diabetes have two- to four-fold higher risk of developing CAD than the general population and CAD accounts for an approximately 65-75% of deaths in people with diabetes [1].

It has been found that the clinical outcomes of diabetic patients, undergoing revascularization either bypass grafting or percutaneous coronary intervention (PCI), are inferior to that of non-diabetic patients [2, 3]. There is two-fold increased occurrence of long-term risk of death, myocardial infarction (MI) and repeat revascularization [4]. There are several factors identified which attribute to these inferior outcomes in diabetic patients. For example, vessel size has been reported to be smaller in diabetic compared with to that of non-diabetic patients [5]. Apart from vessel size, diabetes constitutes an independent predictor of in-stent restenosis [6]. Angiographic and ultrasonic studies also demonstrate a higher degree of late luminal loss and neointimal hyperplasia in diabetic patients which may probably explain the high occurrence of restenosis in this population [7].

Though drug-eluting stent (DES) improve clinical outcomes and survival over bare-metal stent (BMS), the rate of restenosis, repeat revascularization, MI and death rate is still higher in patients with diabetes [8]. So, we have carried out the study to determine the clinical outcomes of the implanted sirolimus-eluting stent (SES) in diabetes patients as compared to non-diabetic patients.

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E-ISSN: 2311-052X/14 

## METHODS

### Study Design and Patient Population

The Indolimus Diabetic registry is a single-centre, single-armed, retrospective registry. Our registry included 530 patients (169 with DM and 361 without DM) who successfully treated with Indolimus® SES (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) at the Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India between August 2012 and February 2013.

#### *Inclusion Criteria*

Patients who were at least 18 years of age, had stable or unstable angina or myocardial ischemia or acute/recent MI, and were undergoing PCI with Indolimus® stents were considered for the study.

#### *Exclusion Criteria*

Patients were excluded 1) if they had known allergy to aspirin, clopidogrel, ticlopidine, heparin, sirolimus, cobalt chromium and polymers; 2) patients with a target lesion located in the left main stem and malignancies were excluded.

Patients were divided into two groups according to their diabetic status. At the time of enrollment, the patients were classified as diabetics if 1) they were treated with insulin and/or oral hypoglycemic agents, 2) reported by the patients and mentioned in the previous medical record of the patients, 3) random blood sugar level >140mg/dL. The study protocol was approved by the institutional ethics committee of the hospital and written informed consent was obtained from all enrolled patients.

### Description of the Study Stent

Indolimus® stent (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) is a sirolimus-eluting coronary stent coated with biodegradable polymer. The description of the stent and the drug release profile has been described previously [9].

### Interventional Procedure and Adjunctive Medications

All the patients were administered loading doses of aspirin (300 mg) and clopidogrel (300 mg) at least 24 hours prior to PCI. The use of low-molecular weight heparin and glycoprotein IIb/IIIa inhibitors during the peri-procedure period was left to operators' discretion. All the patients (if their condition was not contraindicated) were prescribed dual antiplatelet therapy, minimum 75-150 mg aspirin daily plus minimum 75 mg clopidogrel daily, for one year. However, after 1 year aspirin 75 mg daily was recommended lifelong. Longer duration antiplatelet therapy of clopidogrel was left to the discretion of the investigator.

### Safety End Points and Follow-Up

The endpoint of the registry was a major adverse cardiac event (MACE) defined as a composite of cardiac death; MI (Q-wave and non-Q-wave not clearly attributable to a non-target vessel), target lesion revascularization (TLR) and target vessel revascularization (TVR) and that were observed during 30-days and at 6-months follow-up. The death was considered as of cardiac origin if causes were remained undetermined. If there is development of new Q wave of more than 0.04 seconds in two or more contiguous leads along with significant elevated level of MB isoform creatine kinase or troponin I or T levels, Q-wave MI was diagnosed. Non-Q-wave MI was considered when there was increase in creatine kinas level more than three times the upper limit of the normal range as well as increased troponin I or T levels without development of new-Q-waves. All reported re-interventions inside the implanted stent during the index procedure or within 5 mm proximal or distal to the stent were classified as TLR. Other repeated PCI in the same vessel were recorded as TVR. We have considered occurrence of stent thrombosis as1) Definite: confirmed angiographically; 2) Probable: if there was target vessel–related MI or cardiac-death; 3) Possible: caused by stent thrombosis or occurred within 30 days of the index procedure. Stent thrombosis was also classified as acute (within 24 hours of the index procedure); sub-acute (between one and 30 days) and late (occurred after 30 days).

Clinical follow-up after discharge was performed by out-patient clinic interview or telephone contact in all patients or their relatives. At the time of follow-up, data were collected pertaining to current clinical status, prior hospitalisation and occurrence of any of the above mentioned adverse events.

### Statistical Analysis

All data were analysed with the use of Statistical Package for the Social Sciences (SPSS) version 15 (IBM SPSS, Inc. in Chicago, Illinois). Continuous variables were presented as mean±SD and were

compared by means of the Student's t test. Categorical variables were presented as counts and percentages and compared by means of the $\chi^2$ test or Fisher's exact test. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method and compared by the log rank test. *p*-value < 0.05 was considered statistically significant.

## RESULTS

### Baseline and Lesion Characteristics

A total of 530 patients with 617 lesions were treated with SES, of whom 169 patients were diabetic. Table **1** lists the baseline characteristics of all treated patients, grouped according to the diabetic status.

Patients with DM were more often female (29.6%), hypertensive (54.4%), and had higher previous revascularization (4.2%). There was no difference between the two groups in left ventricular ejection fraction. Target lesion location and angiographic lesion characteristics at the baseline revealed no significant differences between the patients with DM and without DM (Table **2**). Double vessel disease was more common in diabetic patients (37.9% *vs*. 24.9%, *p*=0.002), where as single vessel disease was more common among the non-diabetic patients (74.5% *vs*. 60.4%).

### Clinical Outcomes

MACE during 30-days and 6-months follow-up are listed in Table **3**. A total of 9 (1.7%) cardiac death occurred during the 30-days follow-up from which 3 (1.8%) in diabetic group and 6 (1.7%) in non-diabetic group (*p*=1.00). The overall MACE rate was similar in diabetic and non diabetic group (1.8% *vs*. 1.9%, *p*=1.00) at 30-days follow-up. However, at 6-month follow-up, it has been observed that the occurrence of MACE was higher but not statistically significant in diabetic patients as compared to non-diabetic patients (4.1% *vs*. 2.5%, *p*=0.29).

Kaplan-Meier survival analysis and log-rank test revealed that six-month cumulative MACE free survival also not significantly differed between the two groups (95.9% and 97.5%, *p*=0.31) (Figure **1**).

## DISCUSSION

DM, metabolic abnormalities of hyperglycemia and insulin resistance, is a major cause of morbidity and mortality in patients with CAD [10]. There are various mechanisms which play an important role in acceleration of atherosclerosis and excessive neointimal formation after coronary intervention in patients with DM [7]. Some of these mechanisms, identified so far, are endothelial dysfunction, abnormal

**Table 1: Baseline Demographics Characteristics**

| Characteristics | Diabetic (n=169 patients) | Non-Diabetics (n=361 Patients) | *p* Value |
|---|---|---|---|
| Age (mean ± SD, yrs) | 55.5 ± 10.13 | 54.6 ± 11.09 | 0.571 |
| Male, n (%) | 119 (70.4%) | 296 (82.0%) | 0.003 |
| Hypertension, n (%) | 92 (54.4%) | 123 (34.1%) | <0.001 |
| Dyslipidemia, n (%) | 0 (0.0%) | 2 (0.6%) | 1.000 |
| Family history of CAD[1], n (%) | 1 (0.6%) | 2 (0.6%) | 1.000 |
| Smoking, n (%) | 68 (40.2%) | 205 (56.8%) | <0.001 |
| Alcoholics, n (%) | 35 (20.7%) | 95 (26.3%) | 0.162 |
| Tobacco chewing, n (%) | 5 (3.0%) | 12 (3.3%) | 0.824 |
| Renal insufficiency at the screening, n (%) | 9 (5.3%) | 16 (4.4%) | 0.651 |
| Previous MI[2], n (%) | 22 (13.0%) | 34 (9.4%) | 0.209 |
| Previous PCI[3], n (%) | 5 (3.0%) | 9 (2.5%) | 0.775 |
| Previous CABG[4], n (%) | 2 (1.2%) | 0 (0.0%) | 0.101 |
| Previous Stroke, n (%) | 7 (4.1%) | 5 (1.4%) | 0.060 |
| Ejection fraction, (mean ± SD, mm) | 48.8 ± 9.46 | 50.4 ± 10.06 | 0.102 |

[1]Coronary artery disease.
[2]Myocardial infarction.
[3]Percutaneous coronary intervention.
[4]Coronary artery bypass grafting.

**Table 2: Angiographic and Procedural Characteristics**

| Characteristics | Diabetic (Patients = 169 / Lesions = 202) | Non-Diabetics (Patients = 361 / Lesions = 415) | *p* Value |
|---|---|---|---|
| **Lesion Location** | | | |
| Right coronary artery, n (%) | 58 (28.7%) | 115 (27.7%) | 0.795 |
| Left anterior descending, n (%) | 103 (51.0%) | 231 (55.7%) | 0.274 |
| Left circumflex, n (%) | 41 (20.3%) | 69 (16.6%) | 0.264 |
| **Lesion Classification according to American College of Cardiology/ American Heart Association** | | | |
| Type A, n (%) | 20 (9.9%) | 53 (12.8%) | 0.636 |
| Type B1, n (%) | 55 (27.2%) | 98 (23.6%) | 0.300 |
| Type B2, n (%) | 85 (42.1%) | 179 (43.1%) | 0.329 |
| Type C, n (%) | 42 (20.8%) | 85(20.5%) | 0.804 |
| Total occlusion, n (%) | 43 (21.3%) | 92 (22.2%) | 0.804 |
| **No. of Diseased Vessels** | | | |
| Single vessel disease, n (%) | 102 (60.4%) | 269 (74.5%) | 0.001 |
| Double vessel disease, n (%) | 64 (37.9%) | 90 (24.9%) | 0.002 |
| Triple vessel disease, n (%) | 3 (1.7%) | 2 (0.6%) | 0.085 |
| **Procedural variables** | | | |
| Total no. of stents, n | 206 | 420 | - |
| Number of stents per patient, (mean ± SD, mm) | 1.22 ± 0.43 | 1.16 ± 0.38 | 0.139 |
| Number of stents per lesion, (mean ± SD, mm) | 1.02 ± 0.14 | 1.01 ± 0.11 | 0.451 |
| Average stent diameter, (mean ± SD, mm) | 2.8 ± 0.25 | 2.9 ± 0.30 | 0.005 |
| Average stent length, (mean ± SD, mm) | 18.3 ± 5.67 | 19.0 ± 6.15 | 0.229 |

**Table 3: Clinical Outcomes at 30-Days and at 6-Months Follow-Up**

| | Diabetic (n=169 Patients) | Non-Diabetics (n=361 Patients) | *p* Value |
|---|---|---|---|
| **30-Days Follow-up** | | | |
| Death, n (%) | 3 (1.8%) | 7 (1.9%) | 1.00 |
| Cardiac death, n (%) | 3 (1.8%) | 6 (1.7%) | 1.00 |
| Non-cardiac death, n (%) | 0 (0) | 1(0.3%) | - |
| Myocardial infarction, n (%) | 0 (0) | 1 (0.3%) | - |
| Target lesion revascularization, n (%) | 0 (0) | 0 (0) | - |
| Target vessel revascularization, n (%) | 0 (0) | 0 (0) | - |
| Stent thrombosis, n (%) | 0 (0) | 0 (0) | - |
| Major adverse cardiac events, n (%) | 3 (1.8%) | 7 (1.9%) | 1.00 |
| **6-Months Follow-up** | | | |
| Death, n (%) | 6 (3.6%) | 10 (2.8%) | 0.63 |
| Cardiac death, n (%) | 6 (3.6%) | 8 (2.2%) | 0.40 |
| Non-cardiac death, n (%) | 0 (0) | 2 (0.6%) | - |
| Myocardial infarction, n (%) | 1 (0.6%) | 1 (0.3%) | 0.54 |
| Target lesion revascularization, n (%) | 0 (0) | 0 (0) | - |
| Target vessel revascularization, n (%) | 0 (0) | 0 (0) | - |
| Stent thrombosis, n (%) | 0 (0) | 0 (0) | - |
| Major adverse cardiac events, n (%) | 7 (4.1%) | 9 (2.5%) | 0.29 |

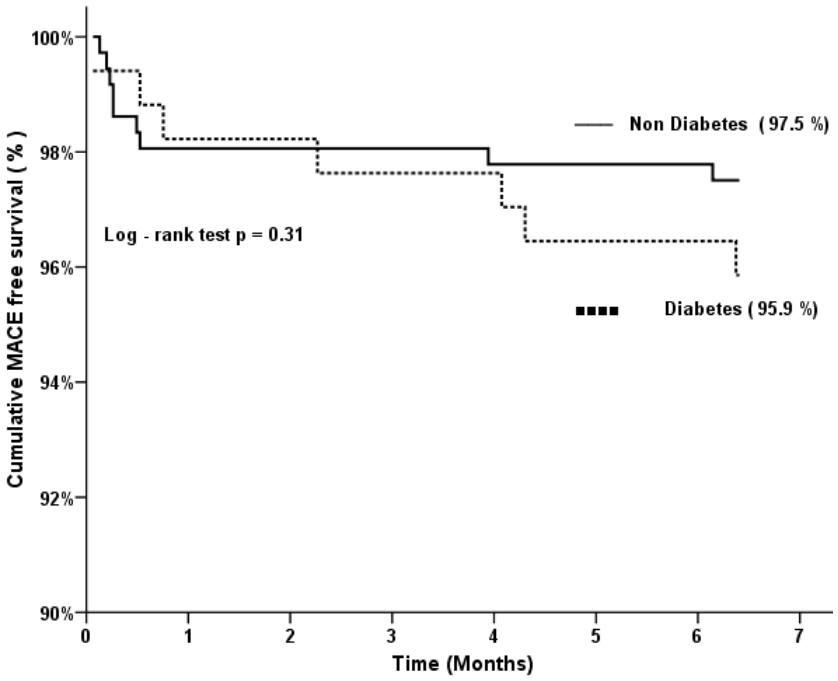


**Figure 1:** Cumulative MACE free survival rate between the two groups at 6-month follow-up.

platelet function, and coagulation abnormalities which may explain significantly greater risk of restenosis following percutaneous transluminal coronary angioplasty in diabetic patients as compared to normal population [2, 11-16].

The introduction of DES significantly improves the clinical outcomes in patients with CAD by reducing the restenosis and subsequent TVR, even in the diabetic population [17, 18]. Though use of DES has considerably reduced the risk of restenosis, this still remains a major limitation in patients with diabetes. The antiproliferative effects of DES target only the local responses to stent-induced injury through prevention of smooth muscle cell proliferation; they do not address the underlying systemic derangements that affect the entire coronary circulation [19].

Jimenez-Quevedo *et al*., which showed that SES implantation in diabetic patients with de novo coronary stenosis remains effective at 2-year follow-up [20]. Also the DES-DIABETES trial, SES was associated with reduction in restenosis and MACE up to two years of follow-up [21, 22]. In our registry, we implanted the Indolimus® biodegradable polymer coated sirolimus-eluting coronary stent in both the groups which show satisfactory outcomes in diabetic patients.

In the present registry, we compared the clinical outcomes at 30-days and at 6-months follow-up in patients with and without DM. The overall MACE rate was similar in diabetic and non diabetic group (1.8% *vs*. 1.9%, *p*=1.00) at 30-days follow-up. However, at 6-month follow-up, it has been observed that the occurrence of MACE was higher in diabetic patients as compared to non-diabetic patients (4.1% *vs*. 2.5%, *p*=0.29). In our registry, the DM group had a higher prevalence of hypertension, previous revascularization and multi-vessel disease. On the basis of these differences, higher MACE in diabetic patients could be expected compared with non-diabetic patients. However, the long term follow-up is needed to determine whether a similar safety profile is maintained.

## CONCLUSIONS

In this Indolimus Diabetic registry, the early clinical outcomes were similar in diabetic and non-diabetic patients treated with Indolimus® SES implantation. Although the cumulative MACE rate at six-month was higher but not statistically significant in diabetic patients as compared to non-diabetic patients. However, long term follow-up is needed to determine whether a similar safety profile is maintained.

## STUDY LIMITATIONS

In the present study, we acknowledge some limitation. First, the present study was a real world, but single centre, non-randomized and retrospective study. Second, the number of patients was low in both groups

in comparison to other registries, so further studies on a larger number of patients are warranted.

## DISCLOSURE

Dr. 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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Received on 26-12-2013 Accepted on 14-02-2014 Published on 21-03-2014

DOI: http://dx.doi.org/10.12970/2311-052X.2014.02.01.5