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Clinical outcomes with Biolimus (A9)™ eluting stent, 'BioMatrix' in diabetic patients – interim results from multicenter post market surveillance registry in India

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ABSTRACT

Objective: The objective of this registry is to establish safety and efficacy of BioMatrix, BioMatrix™-Biolimus A9™ eluting stent in diabetic population in India.

Background: Diabetes mellitus is a major predisposing factor for coronary artery disease. Prognosis for diabetic population patients presenting with coronary artery disease who undergo coronary revascularization is inferior to non diabetics and remains an independent risk factor of restenosis, need for revascularization, and overall mortality. Stent thrombosis is a potential complication of first generation, permanent polymer drug-eluting stents. Biodegradable polymer is a good relief in this era and its utility in diabetic patients will be a major advantage for them.

Methods: 334 patients with diabetes mellitus and requiring angioplasty, implanted with BioMatrix stent were followed at 1, 6, 12 and 24 months who entered in a multicenter registry in India. We analyzed the incidence of major adverse cardiac events (MACE) and stent thrombosis (ST) at 1, 6, 12 and 24 months.

Results: The mean age was 58.71 ± 9.2 years, 81% were males, comorbidity index was 1.6 ± 1.02, and 59.1% presented with acute coronary syndrome. The incidence of adverse event rates was: MACE 1.27%. There were no incidences of myocardial infarction (MI) and target vessel revascularization (TVR). Definite stent thrombosis occurred only in 2 patients.

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Conclusion: In this registry of diabetic population treated with BioMatrixTM-Biolimus A9TM eluting stent (BioMatrix), the reported incidence of MACE and ST were much lower than previously published results. The 1- and 2-year follow-up result supports favorable clinical outcomes of using BioMatrix stents as a suitable alternative to contemporary DES available during PCI in diabetic patients.

1. Introduction

Diabetics are prone to coronary artery disease (CAD) along with other conditions. Patients with CAD and diabetes mellitus (DM) undergoing percutaneous coronary intervention (PCI) are at significantly increased risk for short and long term adverse clinical outcomes.[1,2] The underlying mechanism is due to the more diffuse and accelerated form of atherosclerosis and endothelial dysfunction which lead to diffused coronary lesions, small vessel disease, multi-vessel involvement, larger plaque burden as well as higher incidence of left main and ostial lesions.[3] Diabetic patients respond less favorably to revascularization and have higher restenosis rates. Nevertheless, stent thrombosis (ST) still remains the main safety concern and long term complication associated with the use of both bare metal stents (BMS) and drug eluting stents (DES). The use of effective DES has definitely reduced the restenosis rates and the need for repeat intervention as compared with BMS, which has brought great hope of providing diabetic patients better and longer-lasting interventional solutions.[4–8] Thus, DES has greatly improved clinical outcomes in diabetic patients. Still, smaller vessels (decreased lumen) in diabetic patients remain an important predictor of restenosis even in the era of DES.[9,10] There may be an increased atherothrombotic risk in DM patients due to hyperglycemia, and an improved glycemic control has been shown to improve blood thrombogenicity.[11]

Current polymer-based, DES allow for controlled release of therapeutic agents at the site of injury. Most effective drugs utilized with DES for prevention of restenosis up to this point in time have been sirolimus[12–16] and paclitaxel.[17–19] Large cohort studies[8,20] have reported rates of ST between 0.7% and 1.7% in the first year and <0.6% in subsequent years depending on the type of DES implanted, and the population studied.

BioMatrix™-Biolimus A9™ eluting stent (BA9™) (BioMatrix) is a new generation DES incorporating a biodegradable polymer containing the anti-proliferative drug Biolimus A9™ that is only coated on the abluminal side. The proprietary is a semi-synthetic sirolimus analog and shares a similar adverse event profile when used at equivalent dose levels. It is highly lipophilic, (10 times more than its analogs) rapidly absorbed in tissues, and able to reversibly inhibit growth factor-stimulated cell proliferation. With the facts, very highly lipophilic BA9™ and which is coated only on the abluminal surface of the stent assures targeted action of the drug. Moreover, systemic exposure of the drug and the polymer is avoided by this technology. Current data shows that BA9™ on a molecular level forms a complex with the cytoplasmic proteins that inhibit the cell cycle between the G0 and G1 phase. The result is an interruption of the cascade governing cell metabolism, growth, and proliferation. The safety and efficacy of BioMatrix stents has been established in several large randomized controlled trials including LEADERS trial,[21] which showed BA9™ with biodegradable polymer had 80% relative risk reduction of very late stent thrombosis (1–4 years) when compared to first generation durable polymer DES.

This registry was initiated with aim to gather the clinical outcomes of diabetic patients receiving the BioMatrix stents. We captured 1- and 2-year incidence rates of MACE and ST from this multicenter post market surveillance registry.

2. Methodology

This is a prospective observational study of diabetic patients who underwent implantation of BA9™ eluting stent, 'BioMatrix' conducted at seven interventional cardiology sites in India between April 2009 and December 2011. This prospective study was conducted with prior notification to DCGI and with EC approval of individual centers. Study was registered with clinical trial registry of India with CTRI number: CTRI/2011/10/002088. Primary endpoint of this registry was major adverse cardiac events (MACE) defined as composite of cardiac death, myocardial infarction (MI), or target vessel revascularization (TVR) within the study population at 12 months of follow-up. Secondary outcomes were stent thrombosis (ST) at 1, 6 and 12 months and 2 years; Patient oriented composite endpoint defined as any cause mortality, MI, or any clinically driven TVR at 1, 6 and 12 months and 2 years, and total revascularization rate at these time points. However, in this interim analysis, primary endpoint is looked at along with ST.

The inclusion criteria for the study were diabetic patients (Type I or Type II diabetes with documented treatment with insulin or oral hypoglycemics or undocumented or newly diagnosed diabetics with either blood sugar fasting value >115 mg/dl, post meal 140 mg/dl or glycosylated hemoglobin >7.3%), eligible for PCI with lesions suitable for stent implantation with age ≥18 years, presence of ≥1 coronary artery stenoses in a native coronary artery, saphenous bypass graft or radial vein graft from 2.25–4.0 mm in diameter that can be covered with one or multiple stents. Patients excluded were: patients needing additional stent not of the BA9™ eluting stent type; receiving in addition to the Biolimus eluting stent and/or other coronary vascular interventions like balloon angioplasty; receiving the BioMatrix™ stent during index and/or staged procedure and if admitted for treatment of diabetic ketoacidosis ≥2 times in the past 6 months. EC approved consents for participation were obtained from each willing and eligible patient before or after PCI who underwent

implantation of BioMatrix stent/s according to standard procedures.

The baseline data were collected from enrolled patients. Implantation of BioMatrix™-Biolimus A9™ eluting stent, BioMatrix in each target lesion during the index procedure was mandatory. The appropriate length and diameter of the stents to be implanted ensuring complete coverage of the lesion were chosen by visual estimate. The stent length ranged between 8 and 28 mm (20.88 ± 5.9), with long length lesion in 30.99% patients, and the nominal stent diameter ranged between 2.2 and 4.0 mm (2.88 ± 0.4), with ≤2.75 mm in 50.74% patients. Multiple stents were implanted in 66 (19.76%) patients. At least 2 mm overlap was achieved if more than one stent was implanted. Treatment of multiple target vessels (within the same procedure) and staged procedures which occur within 90 days of the initial implant procedure were allowed. All postoperative medical management, including dual antiplatelet therapy, was prescribed according to usual local practice at the discretion of the cardiologist. Data collected by the registry include demographic information, cardiovascular history, comorbidity, lesion and procedure characteristics, and antiplatelet regimens. Patients were followed at 30 days, 6, 12, 24 months by on-site visit with the study physicians or by telephone communication. Interventional cardiologists selected to participate as investigators in this registry were qualified and/or board certified. All the patients were followed for up to 2 years after stent implantation. The study data were verified on-site by the study monitoring group for consistency with source data and to ensure compliance with the protocol as well as with Indian regulatory guidelines.

The drug-eluting coronary stent system (BioMatrix™ DES) is comprised of two key components: the stent (which includes Biolimus A9™ incorporated into a polymer coating), and the delivery catheter. A balloon expandable 316L stainless steel stent with polymer coating containing Biolimus A9™ is pre-mounted onto a high pressure, semi-compliant rapid exchange balloon delivery system available in six and nine cell models. The delivery catheter has two radiopaque markers, which fluoroscopically mark the ends of the stent to facilitate proper stent placement. The nominal dosage of Biolimus A9™ for the BioMatrix™ stent ranges from 133 to 451 μg depending on stent length. The biodegradable polymer is polylactic acid (PLA), which has been widely used in a variety of medical applications, including orthopedic and dental devices and implants. BioMatrix™ is Biosensors' DES having abluminal coated biodegradable polymer. Its abluminal coating (coating only to outer surface) is absorbed after 6–9 months and turns the DES into a BMS. It combines the proven safety of a DES with an abluminal biodegradable polymer, the proven efficacy of BA9™ and an advanced stent design. As this DES virtually becomes a BMS after 6–9 months, long term safety to the patients is ensured. As there is no polymer present, no drug present after 6–9 months, incidence of ST falls considerably.

An independent clinical events committee adjudicated all MACEs and other serious adverse events developing in the patient population. The committee arbitrated all MACE, other SAE and ST by a systematic review of the data collection forms and by review of the source documents, electrocardiograms, and angiograms in case of suspected stent thrombosis and MACE.

As this is an interim analysis and follow-up is in progress, we have different quantum of follow-up done for patients. Calculations in the paper are based on person-year calculations. Definition of Person-Year: A measurement combining the number of persons and their time contribution in a study. All statistical analyses were performed with SPSS (Version 16.0). Standard descriptive statistics were used for baseline, lesion, and procedural characteristics and for clinical results for all patients. Continuous variables were presented as mean ± SD and range, and categorical variables were presented as numbers and percentages. Descriptive data of the patient population and serious adverse events were compiled as per protocol specified time intervals.

3. Results

336 patients were enrolled but 334 were followed up. The data of these 334 patients were collected between April 2009 and December 2011 and the results are mentioned below. The interim analysis includes data of 393.2 person-year follow-up. As this is an interim analysis and follow-up is still on, person-year calculation is considered. The mean age was 58.71 ± 9.2 years (range 36–83), comorbidity index was 1.6 ± 1.02, angiographic LVEF(%) was 52.09 ± 11.36% (range 20–81) of which 60 (20.0%) had angiographic LVEF ≤40%. The patients included were compliant with the eligibility criteria specified in the protocol. Subject age group distribution is described in Table 1.

Patients' baseline characteristics were as per listed in Table 2. Around, 19% (65) patients were insulin dependent (IDDM), and 81% (271) patients were non-insulin dependent. Two third of the patients (65.3%) had hypertension, 22.8% had family history of CAD, 16.6% had hypercholesterolemia and 22.3% had suffered previously with MI, 59.1% presented with acute coronary syndrome. A total of 471 BioMatrix DES (1.41 stents/patient) were implanted during the index procedure, to treat a total of 454 lesions with a minimum of 1 and maximum of 6 lesions in 334 patients. The total lesion segment percentage is described in Table 3. Table 4 shows the number of patients who were taking dual antiplatelet therapy (DAPT) at 1,6 and 12 months.

Non-hierarchy approach was used for counting of MACE. The cumulative rate of MACE is presented in Table 5 and overall stent thrombosis classification (as per ARC definitions) is presented in Table 6. The incidence rate per 100 person-year was 1.27 for all MACE. There were 3 cases of Re-PCI, but all happened in non-targeted vessel. Two year follow-up of 111 patients (33%) was completed till this interim report. There

Table 1 – Age group distribution.

Age group	%
30–40	0.6%
40–50	14.5%
50–60	37.4%
60–70	33.8%
70–80	12.5%
≥80	1.2%

Table 2 – Baseline characteristics.

Baseline characteristics	%	Baseline characteristics	%
Diabetes mellitus	100	Male	81%
IDDM	19	Female	19%
Current smoker	9.8	Average age (yrs.)	58.71
Renal insufficiency at screening	0.9	Average LVEF	52.09
Hypertension	65.3	Total number of lesions treated	454
Hypercholesterolemia	16.6		
LVEF<40%	20.13		
Family history of CAD	22.8	Lesion per patient	1.36
Stroke	1.2	Total number of stents	471
Congestive heart failure	1.5	Stent per patient	1.41
Previous myocardial infarction	22.3	Long length (>28 mm)	30.99
Previous CABG	5.6	Small vessel (≤2.75 mm)	50.74
Previous PCI(s)	8.3	Lesion treated previously	1.27
Acute coronary syndromes	59.1	Total occlusion	8.38%
Asymptomatic	15.0	Device success	100%
Silent ischemia only	4.2	Single vessel (SVD)	74.9%
Stable angina	21.7	Multi-vessel (MVD)	25.1%

were no cases of myocardial infarction and TVR reported in the 2-year follow-up of these 111 patients. The overall incidence of ST, including probable and possible ST was 0.8 per 100 person-year. Definite stent thrombosis occurred in 2 patients only.

4. Discussion

The interim analysis findings from our e-BioMatrix registry show that BioMatrix™-Biolimus A9™ eluting stent with biodegradable polymer can improve clinical outcomes in diabetic population for up to 2 years. Thus, it contributes significantly towards determining incidence and relative clinical impact of MACE and ST in a large post-marketing surveillance registry, which is one of the largest studies dedicated to diabetic population in India. Diabetic patients are known to be at high-risk for developing cardiovascular disease, increased restenosis, accelerated atherosclerosis and more diffuse diseases. There is always a debate in the medical fraternity regarding use of DES in DM patients.[2]

So far, two randomized trials exclusively with diabetic patients have been published, that we know, with an angiographic primary endpoint at 9 months. The first diabetes trial

Table 3 – Total percentage of lesion segments.

Lesion segment	%
RCA	27.04
LAD	42.79
LCX	27.27
Left main	0.66
Venous graft bypass	1.77

Table 4 – Patient taking DAPT.

DAPT	Visit description		
	30 days follow-up	6 months follow-up	12 months follow-up
Patient taking DAPT	99.4%	99.7%	98.8%

compared SES and BMS in 80 diabetic patients with SES showing TLR of 7.3% and MACE of 11.3% at 9 months.[22] The second is the ISAR-Diabetes registry[23] study showing intermediate-term follow-up on diabetes patients, the TVR after SES implantation was 6.4% and there were no clinical differences between SES and PES in the clinical endpoints at the end of follow-up.

A lot of clinical studies included only subgroups of diabetic mellitus patients and were not solely dedicated to these patients.[24] Usually data accumulated over the years are derived from subgroup, post-hoc analysis of diabetics included in various clinical trials or from single and multicenter registries. Randomized controlled trials do not represent the complex diabetic population seen in daily practice due to vessel and patient selection criteria. Moreover, meta-analysis, with more statistical power, does not allow for a systematic evaluation of important biological confounders (diabetes control, lipid concentrations, blood pressure, or inflammatory markers) that may affect outcomes.

The subgroup studies include the SIRIUS trial[25] with 131 diabetic patients with SES, and the TAXUS IV trial[5] with 155 diabetic patients with PES. The clinical benefits of DES as compared to BMS at 12 months were lower rates of TLR (6.9% and 7.4%), TVR (9.9% and 11.3%), target vessel failure (TVF) (12.2% and 15%), and MACE (9.2% and 15.6%) respectively. In single center prospective Cypher (RESEARCH) and Taxus (T-Search) registries involving 293 diabetic patients (SES, 145 and PES, 148), mortality was similar in ITDM (11.6%) and in NITDM (6.2%), and the MACE rate was only significantly higher in ITDM by univariate analysis (27.4% vs. 14.6%). Clinical endpoints of different DES were shown to be comparable among SES, PES and ZES in the SCARR[26] registry in the subgroup of diabetic patients. Furthermore, consistently lower rates of ST

Table 5 – Major adverse cardiac events.

MACE (major adverse cardiac event)	Numbers	Total MACE	Incidence rate per 100 person-year
Cardiac death	5	5	1.27
Myocardial infarction	0		
TVR	0		

* Major adverse cardiac events (MACE) within the study population, defined as composite of cardiac death, myocardial infarction (Q-wave and non Q-wave), or justified target vessel revascularization at 12 months.
Non-hierarchy approach was used for counting of MACE.

Table 6 – Stent thrombosis.

Stent thrombosis	Acute	Subacute	Late	Very late	Total	Incidence rate per 100 person-year
Definite	1	1	0	0	2	0.8
Probable	0	1	0	0	1	
Total					3	

have been observed with SES than with paclitaxel-eluting stents in diabetics, particularly over long follow-ups. In the Bern–Rotterdam registry, the rate of definite ST was 3.6% at 4 years with paclitaxel-eluting stents vs. 2.7% with SES.[27] To date, the BARI trial[25] has been used as a reference for treatment of the diabetic population with cardiovascular disease, which suggested that CABG patients had improved survival compared to angioplasty. At one year, CARDia trial[28] showed no apparent difference between these two treatment options in terms of death or composite of death, non-fatal myocardial infarction and non-fatal stroke which suggested that PCI is a safe alternative to CABG in selected patients with diabetes and multi-vessel coronary artery disease. In this regard, our registry shows a lower definite and probable ST of 0.8 in 393 person-year followup, which is an indication of benefit of BA9 eluting stent in high-risk diabetic population.

Supporting this, the LEADERS trial[29] has demonstrated results favoring to BES over SES where 26% were patients with diabetes mellitus. There was 80% relative risk reduction in ST as compared to permanent polymer DES, in the long run (post one year, at least up to four years). Couple of other randomized trials have also supported the established results.[30,31] More complete strut coverage was observed in an optical coherence tomography substudy[32] of the LEADERS trial patients allocated to BESs at 9 months when compared with SESs suggesting complete endothelialization, which may have impact on clinical outcome and, in particular, on the risk of late stent thrombosis. The potential clinical advantage of BES is expected to fully emerge during longer-term follow-up once the polymer is completely metabolized.

Most of the earlier trials have reported significantly higher rates of MACE as compared to our study results. In German Cypher Stent Registry,[33] reported MACE rate in the DM group was significantly higher than in the non-DM group (16.4% vs. 13.0%) at 6 months but lower than expected from historical data with the use of BMS, which was really encouraging. MACE rate in both group (IDDM and NIDDM) were comparable (16.3% vs. 16.4%) at 1-year in the SPIRIT V Diabetic Study,[34] which was a randomized trial in a high-risk group of diabetic patients, implantation of EES compared with PES. These reported rates are much higher than the results we observe in this diabetic registry thus so far.

A recently published pooled analyses[35] of various DES or BMS in diabetic patients from 42 randomized trials demonstrated that new generation stents are efficacious and safe. Long term results are unknown, making speculative any assumptions on the potential benefit of DES on mortality and rate of MI in diabetic patients.

We have reported 1-and 2-year follow-up data from our registry of diabetic patients who received BioMatrix stents. The incidence of MACE (cardiac death, MI, TVR) and stent thrombosis (definite and probable) were significantly lower (1.27 and 0.8, respectively) than previously published data from trials following diabetic cohort. It also reveals a good overall reported compliance with the administration of antiplatelet therapy after PCI. Thus, in patients with diabetes mellitus, 1 and 2-year outcomes (of 111 patients) from the present interim analysis show substantial benefit after treatment with BioMatrix stents as compared to other devices. BA9™ eluting stents appears to have comparable and favorable clinical outcome in the high-risk diabetic population.

5. Study limitations

Since patients treated with other than Biolimus stents during the index procedure was an exclusion criterion, no information was collected on other DES, which might have contributed to some degree of selection bias. However, this was the very intention of the study, to know safety and efficacy of BioMatrix™-Biolimus A9™ eluting stent in diabetic patients in India. Secondly, the study design was single-arm with no control arm for direct comparison. However, these limitations are part of any post-marketing surveillance registry.

6. Conclusion

In conclusion, the 1-and 2-year incidence of MACE in this diabetic population treated with BioMatrix stents is significantly lower as compared to previously published data. The incidence of ST is lower than similar recent registries. These results could be due to unique combination of Biolimus A9 drug (which is 10 times more lipophilic than its analogs), biodegradable polymer PLA and technology of abluminal coating. These support favorable clinical outcomes of using BioMatrix stents as a suitable alternative to contemporary DES during PCI in diabetic patients. Highlights like advanced stent design, highly lipophilic Biolimus A9 drug, biodegradable polymer (PLA) and their application on the abluminal side of the stent could be responsible for such encouraging results of BioMatrix BES. This registry is especially important for Indian set-up, where increasing prevalence of diabetes is a concern.

Conflicts of interest

Bhushan Khemnar and Hrishikesh Rangnekar are working for Biosensors.

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