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One-year clinical outcomes of BioMatrix™-Biolimus A9™ eluting stent: The e-BioMatrix multicenter post marketing surveillance registry in India

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ABSTRACT

Objective: The e-BioMatrix is a post marketing multicenter registry with an objective to evaluate the 2 year clinical safety and efficacy outcomes in patients treated with BioMatrix™ - Biolimus A9™ (BA9™) drug eluting stents (DES).

Background: Drug-eluting stents still have late-stage disadvantages that might be attributable to the permanent polymer. BioMatrix a new generation DES containing anti-proliferative drug Biolimus A9™ incorporating a biodegradable abluminal coating that leaves a polymer-free stent after drug release enhancing strut coverage while preventing neointimal hyperplasia.

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Methods: This interim analysis consists of a total of 1189 patients with 1418 lesions treated with BioMatrix stent who entered this multicenter registry in India. We analyzed the incidence of major adverse cardiac events (MACE) and stent thrombosis (ST) at 1, 6, and 12 months with an extended follow-up of 2 years. Recommended antiplatelet regimen included clopidogrel and aspirin for 12 months.

Results: The mean age was 57.6 ± 10.9 years, 81.8% were males, comorbidity index was 1.20 ± 1.33, 68% presented with acute coronary syndrome, 49% had hypertension and 40.8% had diabetes mellitus. One-year clinical follow-up was completed in 987 patients at the time of interim analysis. The incidence of MACE is 0.45 for 1544 person-year follow-up. There were only 03 cases of ST (01 late ST) reported during this time.

Conclusion: This registry demonstrates excellent one-year clinical safety and efficacy of BioMatrix stents. The 1-year result shows that BioMatrix stent may be a suitable alternative as compared to contemporary DESs which are currently available in the market for simple as well complex disease.

1. Introduction

Era of Percutaneous Coronary Intervention (PCI) started with plain old balloon angioplasty (POBA) and progressed to bare metal stent (BMS) and then to drug-eluting stent (DES). In DES, polymer was used in addition to the drug, so that it could hold the drug on the stent platform and could facilitate controlled drug release. Thus, drug and polymer became hallmark of DES.

The first generation drugs utilized with DESs for prevention of restenosis were sirolimus[1–5] and paclitaxel.[6,7] Large cohort studies[8,9] have reported rates of ST between 0.7% and 1.7% in the first year and <0.6% per year depending on the type of DES implanted, and the population studied. Several recent studies have shown that limus derivatives are superior to paclitaxel delivered from a durable polymer platform.[10–12] Stent thrombosis remains the main safety concern and long-term complication associated with the use of both BMS and DES. Even though the initial clinical trials that led to the approval of DESs included low- to moderate-risk, patients with de novo lesions in native coronary arteries,[13–16] majority of patients treated in daily clinical practice fall outside the approved indications of DES.[17,18] This is especially relevant with respect to stent thrombosis (ST), as the rates are higher in real world patients than in those from pivotal trials.[19,20] Current polymer-based DESs allow for controlled release of therapeutic agents at the site of injury. The second generation DES, have shown to have lower adverse event rates and target lesion revascularization than BMSs attesting to the efficacy and safety of these devices.[21,22] Then, came the era of biodegradable polymer DES, which was intended to lower late ST associated with persistence of durable polymers after completion of drug release. The efficacy of biodegradable polymer coated DES has been proved in terms of clinical and angiographic outcomes.[17,23,24] Couple of other randomized trials have also supported these established results.[25,26]

BioMatrix™-Biolimus A9™ eluting stent is a new generation DES incorporating a biodegradable polymer containing the antiproliferative 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 is able to reversibly inhibit growth factor-stimulated cell proliferation. Current data suggests that Biolimus A9™, 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 has been established in LEADERS trial,[27] 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. BioMatrix™ stent was shown to have a higher degree of functional re-endothelialization due to improved vasomotion as compared to SES at 6–9 months post stent implantation.[28] More complete strut coverage was observed in an optical coherence tomography substudy[29] 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 emerge at acute and mainly during longer-term follow-up once the polymer had completely metabolized. The pivotal DES studies were largely done with strict inclusion criteria, which limit wider applicability of their results to real world setting. Post marketing surveillance registry studies play an important role in extrapolating the outcomes of these studies to day-to-day clinical practice.

This registry study was initiated in India with aim to gather the clinical outcomes of patients for a period of 2 years who received BioMatrix stents during PCI. The interim analysis from this multicenter post market surveillance registry includes the initial report of 1-year follow-up in terms of incidence of MACE (major adverse cardiac events) and consequences of stent thrombosis (ST).

2. Methodology

This is a prospective observational study of patients who underwent implantation of BioMatrix stents conducted at 18 interventional cardiology sites in India between December

2008 and February 2012. The primary endpoint of this registry was device oriented 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 follow-up. The secondary endpoints were stent thrombosis (ST); MACE; any cause mortality, MI, or any clinically driven TVR; death and MI and total revascularization rate at 1, 6, 12, and 24 months.

The inclusion criteria for the study were – patients eligible for PCI with lesions suitable for stent implantation with age ≥18 years, presence of ≥1 coronary artery stenoses in a native coronary artery or saphenous bypass graft or radial vein graft from 2.25 to 4.0 mm in diameter that can be covered with one or multiple stents with no limitation to the number of treated lesions, number of treated vessels or lesion length. Those patients who received additional stent other than BioMatrix were excluded. The Ethics Committee approval was sought and consent for participation was obtained from each willing and eligible patient before or after PCI who underwent implantation of Biolimus A9™ eluting stent according to standard procedure.

Implantation of BioMatrix stent 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. 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. Every vessel in which a BioMatrix stent was implanted within 90 days of the initial implant procedure was considered a target vessel. All postoperative medical management, including dual antiplatelet therapy, was prescribed according to usual local practice at the discretion of the cardiologist. The data collected by the registry include demographic information, cardiovascular history, comorbidity, lesion and procedure characteristics, antiplatelet regimen, and on events if any. Patients were followed at 1, 6, 12 and 24 months by on-site visit with study physicians or telephone communication. The adverse event assessment was done in hospital. Interventional cardiologists selected to participate as investigators in this registry were qualified and/or board certified. The study data were monitored on-site by the study monitoring group for consistency with source data and to ensure compliance with the protocol as well as Indian regulatory guidelines. This PMS is notified to DCG(I) and is registered with clinical trial registry of India with CRTI number: CTRI/2012/05/002657.

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. The biodegradable polymer is applied to the stent's abluminal surface, which is metabolized within 6–9 months. BA9™ appears to have higher degree of functional re-endotheliazation and better arterial healing.[30]

An Independent Clinical Events Committee adjudicated all MACE and other Serious Adverse Event (SAE) 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, when necessary.

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. 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. The two year clinical outcome data will include stratified analyses according to the presence or absence of DM, ACS, acute ST-elevation myocardial infarction, left anterior descending artery, multivessel disease, reference vessel diameter, LVEF, small-vessel disease, and long-lesions (Table 1).

3. Results

The e-BioMatrix study database registry interim data analysis includes 1189 patients recruited between December 2008 and February 2012 with 1418 lesions. The age group distribution is described in Table 1. Patients' baseline demographics are summarized in Table 2. Mean age was 57.6 ± 10.9 years (range 25–88), comorbidity index was 1.20 ± 1.33, angiographic LVEF (%) was 50.2 ± 11.9% (range 15–95) of which 278 (24.69%) had angiographic LVEF ≤40%. Patients included were compliant with the eligibility criteria specified in the protocol. Study comprised the entire clinical spectrum of coronary artery disease, more than half (68%) of the patients had an acute coronary syndrome (ACS), a high proportion of patients (40.8%) had diabetes, 49% had

Table 1 – Age group distribution.

Age group	%
25–35	1.7
35–45	9.3
45–55	26.6
55–65	36.3
65–75	19.8
75–85	5.3
85–95	0.9

Table 2 – Baseline characteristics.

BES ($n = 1189$)	%	BES ($n = 1189$)	
Diabetes mellitus-	40.8	Male	81.8%
Current smoker	17.0	Female	18.2%
Renal insufficiency at screening	1.3	Average age (yrs)	57.6
Hypercholesterolemia	14.9	Average LVEF	50.2
Hypertension	49.0	LVEF $\leq$ 40	24.6%
Family history of CAD	9.2	Total number of lesions treated	1418
Stroke	1.2	Lesion per patient	1.19
Congestive heart failure	3.5	Total number of stents	1520
Previous myocardial infarction	7.0	Stent per patient	1.27
Previous CABG	2.3	Long length (28 mm)	24.5%
Previous PCI(s)	4.7	Small vessel ($\leq$2.75 mm)	46%
Peripheral vascular disease	0.9	Lesion treated previously	0.8%
Acute coronary syndromes	68.3	Total occlusion	15.87%
Asymptomatic	6.9		
Silent ischemia only	9.5	Single vessel (SVD)	83.9%
Stable angina	15.3	Multi vessel (MVD)	16.1%

hypertension, 14.9% had hypercholesterolemia and 17% were current smokers. A total of 1520 Biolimus eluting stents were implanted during the index procedure. Almost one half of the patients, 46% had lesions that were $\leq$2.75 mm in diameter and one fourth, 24.5% patients had long length lesions (stent length ranged between 8 and 28 mm). Most of the lesions were located in the left anterior descending artery (51.5%). Multiple vessel intervention was performed in 16.1% of patients. On average, 1.27 stents were used to treat 1.19 lesions per patient. Total percentage of lesion segment is described in Table 3.

The interim analysis includes clinical follow-up data equivalent to 1544 person-year follow-up. Clinical/Telephonic follow-up was complete in 99.8% of the patients at day 30, in 99.4% at six months, and in 97.9% at 12 months. Table 4 shows the number of patients taking dual antiplatelet therapy (DAPT) at 1, 6, and 12 months.

Non-hierarchy approach was used for counting of MACE. The cumulative rates of major adverse cardiac clinical events and overall ST classification are presented in Tables 5 and 6. The incidence rate for MACE in 1544 person (patient) years was 0.45. There were 4 cardiac deaths, 1 case of myocardial infarction and 2 cases of TVR reported during the 1-year follow-up period. The incidence rate of overall stent thrombosis was 0.2 in 1544 person (patient) years. Of 3 patients who developed ST, one each presented with acute onset within 24 h, subacute onset within 1 month and late onset within 1 year.

Table 3 – Total percentage of lesion segments.

Lesion segment	%
LAD	51.5
LCX	23.9
RCA	23.1
Left main	1.1
Bypass graft stenting	0.2

4. Discussion

Our post marketing surveillance registry was designed to support the long-term safety and efficacy of the BioMatrix stent for treatment of coronary artery lesions in real world clinical practice. This registry characterizes one of the largest prospective single arm studies in India. A significant percentage of the patients had diabetes and more than half presented with ACS. The interim analysis findings of 1-year clinical follow-up exhibit very low rates of MACE (cardiac death, TVR and MI) and stent thrombosis.

The first generation DES, e-Cypher Registry[31] of 15,157 patients treated with SES Cypher stent (J&J, Cordis Corporation, Bridgewater NJ) reported a MACE rate (all death, MI, and TLR) of 1.36% at 30 days and 5.8% and cumulative ST rate was 0.87% at 1 year. 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.[13] Subsequently, the WISDOM registry[32] of 778 patients treated with the Express2 PES reported a 12 month MACE rate (death, MI, and TLR) of 5.2% and a protocol-defined ST rate of 0.6%. The combined ARRIVE 1 and ARRIVE 2[33] registry population of 7492 patients who underwent deployment of the TAXUS Express2 PES had a higher 1-year MACE rate (cardiac death, MI, TVR) of 9.5% and ARC-defined definite and probable ST rate of 1.8% than simple use patients in the pivotal trials. The SORT OUT II randomized

Table 4 – Patient taking DAPT.

DAPT	Visit description		
	30 days follow-up ($n = 1169$)	6-months follow-up ($n = 1126$)	12 months follow-up ($n = 987$)
Patient taking DAPT	99.3%	99.6%	99.3%

Non-hierarchy approach was used for counting of MACE.

Table 5 – Major adverse cardiac events.

*MACE (major adverse cardiac event)	Numbers	MACE	Incidence rate per 100 person-year
Cardiac death	4	7	0.45
Myocardial infarction	1		
TVR	2		

*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.

trial, which compared sirolimus and paclitaxel-eluting stent, reported no significant differences in clinical outcomes with MACE rate of 9.3% (SES) vs. 11.2% (PES) and stent thrombosis rate of 2.5% (SES) vs. 2.9% (PES).[34]

The second generation ZES and EES stents have been compared in randomized trials with the SES[35] and PES.[36] The X-SEARCH study showed subacute and late definite ST rates of 0.3% and 0%, respectively, at 6-month follow-up.[37] The COMPARE trial (EES and PES) at 1 year reported rates of subacute and late ST as 0.1% and 0.4%, respectively.[4] The reported rate of cardiac death was 1.1%, overall MI was 3.5% and cumulative rate of definite and probable ST was 0.66% in SPIRIT V Clinical Evaluation of the XIENCE V EES.[38] The results of EES post marketing registry[39] have also demonstrated low rate of ARC-defined definite and probable ST of 0.84% and composite rate of cardiac death and ARC-defined myocardial infarction of 6.5% in the overall population. Considering the results from these studies, the lower ST through 1 year seen in e-BioMatrix registry is quite supportive of an indication of long-term benefit of BA9 eluting stent.

Recently, CREATE post marketing surveillance registry of biodegradable SES has demonstrated cumulative rate of MACE to be 7.4% and the rate of stent thrombosis to be 2.4% at five years[40] which were very less compared with other registries like Sirius, Taxus-IV SR and Endeavor II.

The safety and efficacy of BioMatrix been established in large randomized controlled trial called LEADERS trial[29], 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. Clinical trial with BA9 eluting stents conducted in the recent decade has also established its high efficacy in reducing late lumen loss post PCI.[41]

The interim results from our e-BioMatrix registry contribute significantly towards the analysis of the incidence and clinical impact of MACE and ST receiving BioMatrix stents in real world setting. In our registry, patients who received BES stents, the incidence of MACE (Cardiac Death, MI, TVR) and ST at 12 months of clinical follow-up were significantly lower (0.45 and 0.2 per 100 person-year). There was only one reported case of late ST. These results are quite lower than the recent real world registry trial[42] of ZES and EES with reported of 0.9% and 1.2% and XIENCE India single arm[43] trial, which reported cumulative ST of 0.5% at 1-year follow-up. Our 1-year clinical outcome data showed clinical benefit of biodegradable polymer BioMatrix stents, which was primarily attributable to reduced risk of very late definite ST. This analysis includes 2-year follow-up of 37% of enrolled patients, in which there was not a single case of very late stent thrombosis. Thus, BioMatrix DES appears to have excellent clinical outcome applicable to real world setting. The initial findings from this registry also suggests that favorable results from earlier randomized trials of BioMatrix stent can be seen in daily clinical practice involving patients with significant comorbidities and complex disease.

Table 6 – Definite and probable stent thrombosis.

Stent thrombosis	Acute	Subacute	Late	Very late	Total	Incidence rate per 100 person-year
Definite	1	1	1	0	3	0.2
Probable	0	0	0	0	0	3
Total: 3						

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. 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-year incidence of MACE in this cohort of patients treated with BioMatrix stents was significantly lower as compared to previously published data. The incidence of stent thrombosis was also very low as compared to similar other registries. Thus, this interim 1-year follow-up results show that BioMatrix stent could be a suitable alternative even in high risk patients to contemporary DES which are currently available in the market. Highlights like advanced stent design, highly lipophilic Biolimus A9™ drug (which is 10 times more lipophilic than its analogs), biodegradable polymer (PLA) and their application on the abluminal side of the stent could be responsible for better results of BioMatrix BES. The final analysis will include results of two years.

Conflicts of interest

Tushar Mhetre and Hrishikesh Rangnekar are working for Biosensors International, India.

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