International Journal of Clinical Medicine, 2014, 5, 216-224
Published Online March 2014 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2014.55035

Scientific Research

Seven Years Follow-Up of Biodegradable Polymer Coated Paclitaxel-Eluting Infinnium Coronary Stent in Saudi Arabia

Layth Mimish[1], Abdullateef Khoja[2], Mohammad Anwar[3], Vitek Rizniceck[3], Taher Hasan[4], Ashok Thakkar[5]

[1]King Abdulaziz University, Jeddah, KSA
[2]King Fahad Hospital, Jeddah, KSA
[3]Soliman Fakeeh Hospital, Jeddah, KSA
[4]Bugshan Hospital, Jeddah, KSA
[5]Sahajanand Medical Technologies Pvt. Ltd., Surat, India
Email: layth_mimish@hotmail.com

Received 22 December 2013; revised 21 January 2014; accepted 20 February 2014

Abstract

Aim: In the present study, we analyzed 7-year clinical outcomes of patients included in the BIO degradable Polymer coated drug-eluting stent REgistry of Sahajanand Medical Technologies Pvt. Ltd. stents in Saudi Arabia (BIOPRESS)-Infinnium® registry. Methods: This was multicentre, observational, non-randomized, post-marketing surveillance registry, which included 276 consecutive patients treated with Infinnium® paclitaxel-eluting stent between July-2004 and June-2006. All patients underwent single-vessel or multiple-vessel percutaneous coronary intervention with high atherosclerotic risk factors and the patients were followed up to 7 years. Baseline and post-procedure angiographic follow-up were pre-specified in 231 patients. Results: The registry included 276 consecutive patients (81.5% male) with a mean age of 56.0 ± 11.1 years. Among 276 patients, diabetes and hypertension were present in 142 (51.4%) and 172 (62.3%) of patients respectively. Of all patients studied, 186 (67.4%) had single-vessel disease, 75 (27.2%) had double-vessel disease, and 15 (5.4%) had triple-vessel disease. Total 476 Infinnium® stents were implanted with an average stent length of 21.8 ± 7.5 mm. The incidence of major adverse cardiac events (MACE) up to 1 year was 26 (9.4%). Clinical follow-up was completed in 235 patients at seven-year follow-up. The data of seven-year clinical outcomes were as follow: cumulative MACE rate of 18.1% with 7.6% of total mortality and 3.6% of restenosis. Conclusion: These 7-year results of BIOPRESS-Infinnium® registry clearly provide evidence for safety and long-term effectiveness of the Infinnium® paclitaxel-eluting stent with the biodegradable polymer in real-life patients.

How to cite this paper: Mimish, L., Khoja, A., Anwar, M., Rizniceck, V., Hasan, T. and Thakkar, A. (2014) Seven Years Follow-Up of Biodegradable Polymer Coated Paclitaxel-Eluting Infinnium Coronary Stent in Saudi Arabia. *International Journal of Clinical Medicine*, **5**, 216-224. http://dx.doi.org/10.4236/ijcm.2014.55035

Keywords

Coronary Artery Disease; Paclitaxel Eluting Stent; Stent Thrombosis

1. Introduction

In-stent restenosis is a significant complication associated with the use of bare-metal stents (BMS). The recognition of this important adverse event led to the development of drug-eluting stents (DES) that inhibit smooth muscle cell proliferation and extracellular matrix production. These devices have successfully reduced the restenosis rates observed with BMS [1]-[5].

However, early generation, durable polymer DES are associated with an increased risk of very late (>1 year) stent thrombosis (ST) compared with BMS [2] [4] [6] [7]. Although the difference in very late ST did not result in an increased risk of death or myocardial infarction (MI), it raised concerns about the long-term safety of DES. Experimental data, autopsy findings, and *in-vivo* intravascular ultrasound studies of patients with very late ST showed evidence of incomplete endothelialisation, delayed arterial healing, and vessel remodelling due to chronic inflammation [8]-[11]. It has been proved that durable polymer which persists after the completion of the drug release lead to very late ST by triggering for the chronic inflammatory response.

Biodegradable polymer DES aim to overcome this limitation by providing controlled drug release with subsequent degradation of the polymer material, thereby eliminating the inflammatory stimulus. The Infinnium® (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) uses 316 L stainless steel as its stent platform which is coated with a biodegradable polymer to deliver paclitaxel. Infinnium® stent system proved its effectiveness by reducing restenosis at 6 months and safety with an acceptable rate of cardiac events at 9 months [12]. The present study was aimed at determining whether the safety and efficacy of the Infinnium® stent are maintained at seven-year follow-up, which is the longest available follow-up of biodegradable polymer stent technology.

2. Materials and Methods

2.1. Overview and Study Population

This registry was multicentre, observational, single-armed, post-marketing surveillance registry, which included 276 consecutive patients treated with Infinnium® (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) paclitaxel-eluting stent between July-2004 and June-2006. The study flow chart has been shown in **Figure 1**. Eligible patients included those with clinical evidence of ischemia or a positive functional study that were undergoing percutaneous coronary intervention (PCI) with Infinnium® stent were considered for this registry. Patients were excluded if they had known allergy to aspirin, clopidogrel, ticlopidine, heparin, paclitaxel, stainless-steel and polymers. Baseline characteristics, cardiac history, risk factors, medications, and angiographic and procedural data were obtained and recorded by experienced research coordinators. The registry was conducted at 4 sites in Saudi Arabia in compliance with the Declaration of Helsinki. The protocol was approved by local ethics committees, and all participants provided voluntary, written informed consent.

2.2. Device Overview

The active ingredient in the Infinnium® stent is Paclitaxel. The paclitaxel concentration loaded on each stent was maintained to 1.4 μg/mm^2. The drug was applied to the surface of a stainless steel (slotted tube design), balloon-expandable stent (Matrix®, Sahajanand Medical Technologies Pvt. Ltd.) using biodegradable polymers (Poly L-Lactide, 50/50 Poly DL-Lactide-co-Glycolide, 75/25 Poly L-Lactide-co-Caprolactone and Polyvinyl Pyrrolidone) in multiple layers. The drug is coated in 3 different layers of combination of drug and polymers. Each layer has a different release profile. The cumulative release of drug from the polymer is at 48 days after implantation (**Figure 2**). The Infinnium® stent was made available in lengths of 11, 16, 19, 23, 29, 33, and 39 mm and available diameters were 2.5, 2.75, 3.0, 3.5 and 4.0 mm.

2.3. Study Procedure and Adjunctive Medications

Stents were implanted according to standard procedures. Per the study protocol, all patients received a 300 mg

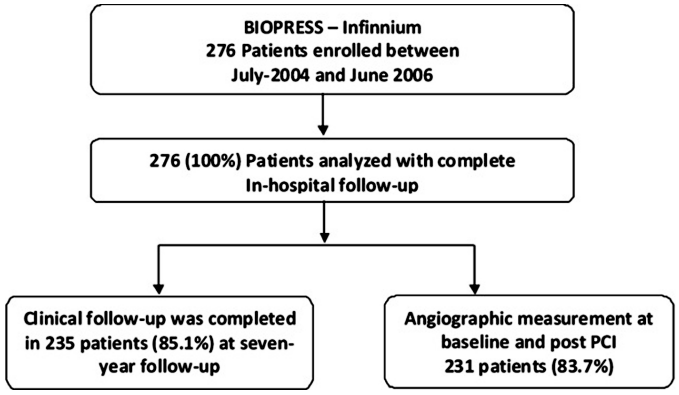

Figure 1. Study flow chart.

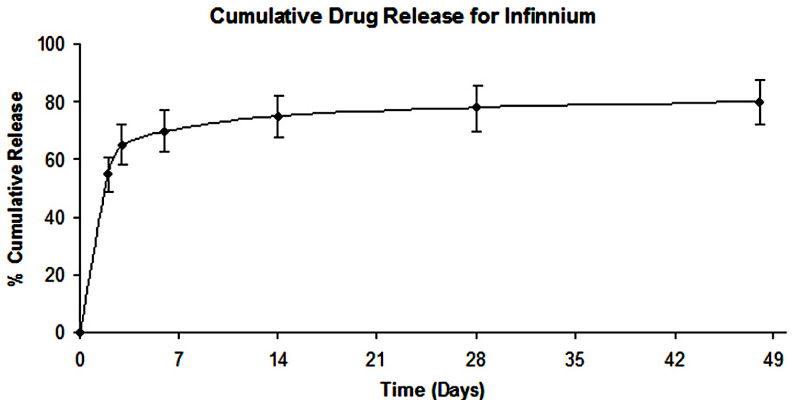

Figure 2. Cumulative *in-vitro* release profile of paclitaxel from Infinnium® paclitaxel-eluting stent.

loading dose of clopidogrel before the procedure, followed by clopidogrel 75 mg/day (or ticlopidine 250 mg twice daily) for at least 6 months. Acetylsalicylic acid ≥ 75 mg was mandated for at least 12 months after the procedure and recommended indefinitely. Use of low-molecular weight heparin and glycoprotein IIb/IIIa inhibitors during the periprocedure period was left to operators' discretion.

2.4. Outcomes and Definitions

The safety and efficacy outcomes of the BIOPRESS-Infinnium® were major adverse cardiac event (MACE), cumulative target lesion revascularization (TLR) and thrombotic event rates at seven years after the index procedure. MACE was defined as a composed of any death, any MI (Q-wave and non-Q-wave MI), any percutaneous or surgical TLR or target vessel revascularization (TVR) procedure and ST. All deaths were considered to be cardiac unless a non-cardiac origin could be clearly established by clinical and/or pathological study. The diagnosis of MI was based on either the development of new pathological Q-waves in ≥2 contiguous electrocardiogram leads and/or level elevation of creatine kinase myocardial band isoenzyme > 3 times the upper normal limit after the procedure during index hospitalisation, or cardiac enzyme level elevation > 2 times the upper normal limit thereafter. All reported re-interventions inside the stent implanted 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. As per the definition of the Academic Research Consortium [13], ST was classified as definite, probable, and possible and it was also stratified as acute (≤24 h), subacute (24 h to 30 days), late (30 days to one year), and very late (≥1 year).

2.5. Data Collection and Follow-Up

Out of 276 patients, 21 patients died during the follow-up and complete clinical follow-up was obtained from

235 patients at seven-year follow-up, so the attrition rate is 7.84%. We obtained clinical follow-up data by a combination of review of hospital records for patients who continue to be followed at institutions and by enquiry to the cardiologists within the referral area as well as by sending questionnaires to general practitioners. Attention was focused on the occurrence of the any of the aforementioned MACE of death, MI and revascularization.

2.6. Angiogram Assessment

Quantitative coronary angiograms obtained before and after the procedure and angiograms were analysed using an automated edge contour detection computer analysis system (CAAS 5.9.2, Pie Medical Imaging B.V., The Netherlands). Angiographic measurements at baseline and post stenting were possible in 231 patients (296 lesions). Baseline angiographic variables included reference vessel diameter (RVD), minimal luminal diameter (MLD), percent diameter stenosis, lesions length and complexity as defined by the American Heart Association/American College of Cardiology (AHA/ACC) classification. Type B2 and C were considered complex lesions. In-stent diameter stenosis, RVD, MLD and acute gain (post MLD - pre MLD) were noted post-procedure.

2.7. Statistical Analysis

All analyses were conducted according to the intention-to-treat principle. Binary variables are presented as percentages (counts). Continuous variables are presented as mean and standard deviation. Event-free incidence or cumulative incidence of events was calculated according to the Kaplan-Meier method. All data were analysed with the use of Statistical Package for the Social Sciences (SPSS) version 15 (IBM SPSS, Inc. in Chicago, Illinois).

3. Results

3.1. Baseline and Procedural Characteristics

A total of 276 patients were enrolled between July-2004 and June-2006. Baseline characteristics are shown in **Table 1**. The mean age was 56.0 ± 11.1 years, 225 (81.5%) were men. The co-morbidities *i.e*. diabetes mellitus, hypertension and hypercholesterolemia were present in 142 (51.4%), 172 (62.3%) and 185 (67.0%) patients respectively. Indications for PCI were unstable angina in 115 (41.7%) of the patients, stable angina in 80 (29.0%), acute MI in 47 (17.0%) and cardiogenic shock in 3 (1.1%) patients.

A total of 353 target lesions were treated, including 47 (13.3%) long lesions, 22 (6.2%) bifurcation lesions, 27 (7.6%) calcified lesions and 22 (6.2%) restenotic lesions. Detail lesion and procedural characteristics are described in **Table 2**. The target lesion was most commonly located in the left anterior descending artery 170 (48.2%), followed by the right coronary artery 100 (28.3%) and the left circumflex 78 (22.1%).

Table 1. Baseline demographics characteristics.

Characteristics	Infinnium® PES[1] n = 276 Patients
Age (mean ± SD, yrs)	56.0 ± 11.1
Male, n (%)	225 (81.5%)
Diabetes mellitus, n (%)	142 (51.4%)
Hypertension, n (%)	172 (62.3%)
Smoker, n (%)	106 (38.4%)
Hypercholesterolemia, n (%)	185 (67.0%)
Family history, n (%)	24 (8.7%)
Previous myocardial infarction, n (%)	148 (53.6%)
Previous PCI[2], n (%)	174 (63.0%)
Previous CABG[3], n (%)	12 (4.3%)
Left ventricular ejection fraction (mean ± SD)	55.4 ± 12.5
PCI Indication	
Stable angina, n (%)	80 (29.0%)
Acute myocardial infarction, n (%)	47 (17.0%)
Cardiogenic stroke, n (%)	3 (1.1%)
Unstable angina, n (%)	115 (41.7%)

[1]Paclitaxel-eluting stent; [2]Percutaneous coronary intervention; [3]Coronary artery bypass graft.

Table 2. Lesion and procedural characteristics.

Characteristics	Patients = 276/Lesions = 353
Lesion Location	
Left anterior descending, n (%)	170 (48.2%)
Right coronary artery, n (%)	100 (28.3%)
Left circumflex, n (%)	78 (22.1%)
Left main, n (%)	1 (0.3%)
Saphenous vein graft, n (%)	4 (1.1%)
ACC/AHA Lesion Classification	
A, n (%)	11 (3.1%)
B1, n (%)	71 (20.1%)
B2, n (%)	218 (61.8%)
C, n (%)	53 (15.0%)
Lesion Characteristics	
Long (≥30 mm) lesion, n (%)	47 (13.3%)
Bifurcation lesion, n (%)	22 (6.2%)
Calcified (moderate/severe), n (%)	27 (7.6%)
Restenotic lesion, n (%)	22 (6.2%)
Total occlusion, n (%)	54 (15.3%)
Direct stenting, n (%)	8 (2.3%)
No. of Diseased Vessels	
Single vessel disease, n (%)	186 (67.4%)
Double vessel disease, n (%)	75 (27.2%)
Triple Vessel Disease, n (%)	15 (5.4%)
Procedural data	
Total no. of stents, n	476
No. of stents per patient, (mean ± SD, mm)	1.72 ± 1.04
Average Stent Length, (mean ± SD, mm)	21.8 ± 7.5
Average Stent Diameter, (mean ± SD, mm)	3.0 ± 0.5

A total of 476 Infinnium® stents were implanted at index procedure (1.72 stents per patient) with an average diameter and total stent length of 3.0 ± 0.5 mm and 21.8 ± 7.5 mm, respectively. Quantitative coronary analysis was carried out on 231 patients (296 lesions) at baseline and after post stenting. All angiographic measurements are listed in **Table 3**.

3.2. Clinical Outcomes

The safety measures up to 7-years are shown in **Table 4**. There were 10 (3.6%) patients who died during the first year of follow-up period, including 7 (2.5%) cardiac deaths and 3 (1.1%) non-cardiac deaths. MACE occurred in 50 (18.1%) patients, consisting of 13 (4.7%) cardiac deaths and 10 (3.6%) TLR at 7-year follow-up.

The 7-year MACE-free survival curve of the study patients is depicted in **Figure 3**. Stent thrombotic events developed in 7 (2.5%) patients up to 7 years. There is no late stent thrombosis between one to seven years.

4. Discussion

Early generation durable polymer drug-eluting stents are associated with a steadily increasing risk of very late ST compared with bare-metal stents during long-term follow-up, [4] [6] [7] [14] a difference that is especially apparent in complex patients, such as those with acute MI, multi vessel disease, diabetes, and bifurcation lesions. [15]-[17] Intrinsic properties of durable polymers used for controlled drug release of early generation DES are likely to be related to several pathophysiological mechanisms, which in turn might result in very late ST—a chronic inflammatory response causing delayed arterial healing with impaired stent strut endothelialisation, persistent fibrin and platelet deposition, altered flow dynamics, local thrombus formation, and vessel remodeling [8]-[10] [18] [19].

Biodegradable polymer DES were designed to diminish long-term adverse events related to the persistence of

Table 3. Angiographic measurements at baseline and post-stenting.

	Patients = 231/Lesions =296
Pre-procedure	
Reference vessel diameter (mm)	2.45 ± 0.51
Minimal luminal diameter (mm)	1.06 ± 0.55
Diameter stenosis (%)	56.24 ± 21.32
Lesion length (mm)	14.11 ± 10.81
Post-procedure	
Reference vessel diameter (mm)	2.53 ± 0.46
Minimal luminal diameter (mm)	2.18 ± 0.41
Diameter stenosis (%)	13.72 ± 6.72
Acute gain (mm)	1.12 0.56

Table 4. Clinical outcomes at 7 years.

7-year outcomes (n = 276)	0 - 1 year	>1-year	0 - 7 years
Death, n (%)	10 (3.6%)	11 (4.0%)	21 (7.6%)
Cardiac death, n (%)	7 (2.5%)	6 (2.2%)	13 (4.7%)
Non-cardiac death, n (%)	3 (1.1%)	5 (1.8%)	8 (2.9%)
Target lesion revascularisation, n (%)	6 (2.2%)	4 (1.4%)	10 (3.6%)
Target vessel revascularisation, n (%)	3 (1.1%)	9 (3.3%)	12 (4.3%)
Stent thrombosis, n (%)	7 (2.5%)	0 (0%)	7 (2.5%)
Myocardial infarction, n (%)	0 (0%)	0 (0%)	0 (0%)
Major adverse cardiac events, n (%)	26 (9.4%)	24 (8.7%)	50 (18.1%)

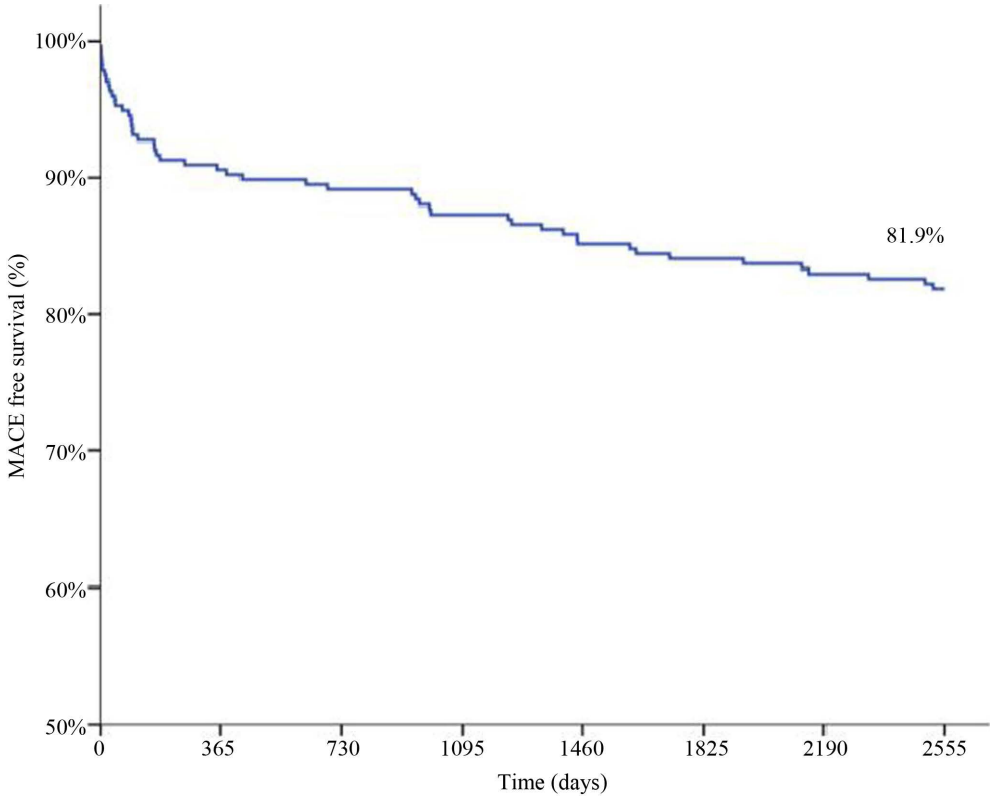

Figure 3. Kaplan-Meier MACE-free survival curve of the study patients.

durable polymers after completion of drug-release. In our study we preferred biodegradable polymer-based Infinnium® stent, which is made up of Millennium Matrix® stainless-steel stent as a platform and biodegradable

polymer coating releasing paclitaxel as an anti-proliferative agent. Safety and efficacy of Infinnium® stent was proved in several studies [12] [20]. SIMPLE II study included 103 patients with a single, de novo, focal lesion; the rate of MACE was reported as 9.7% for 9 months. Also, two registries showed that biodegradable polymer coated paclitaxel-eluting Infinnium® stent provided comparable results with Taxus™ trials at the end of 1-year follow-up [20]-[25].

Lack of strut coverage and late malapposition have been attributed to the antiproliferative effects of the drug eluted and/or to a hypersensitivity type chronic inflammation in which the stent polymer may play a crucial role [8] [9]. The Infinnium® optical coherence tomography (OCT) study showed, 0.41% uncovered and 0.18% malapposed struts in biolimus-A9 eluting stents (BES), which on the other hand were significantly higher compared to paclitaxel-eluting stent [26]. This result showed more complete strut coverage in patients treated with biodegradable polymer paclitaxel-eluting stent compared with those treated with BES at 6 months' follow-up, suggesting an important difference in arterial healing.

The BIOPRESS-Infinnium® registry demonstrated satisfactory and sustained seven-year clinical safety and efficacy profiles as evidenced by the low rates of MACE (18.1%) and ST (2.5%) in daily interventional practice in Saudi Arabia.

5. Conclusion

These 7-year results of BIOPRESS-Infinnium® registry clearly provide evidence for safety and long-term effectiveness of the Infinnium® paclitaxel-eluting coronary stent system (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) with the biodegradable polymer in real-life patients. The midterm clinical benefit of paclitaxel-eluting stent implantation is maintained over a long-term follow-up with low MACE rate and an overall incidence of stent thrombosis.

Study Limitations

A few limitations of the present registry must be addressed. First patient enrolment was not randomised. Second, this is an observational registry of daily clinical practice with both prospective and retrospective data collection during the first 7 years of stent implantation, with many stent types used in diverse clinical circumstances. Third, the number of patients is very limited in comparison to other registries.

Conflict of Interest

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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