INDIAN HEART JOURNAL 66 (2014) 691–695

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ihj

Sponsored Article

A prospective, multi-centric, observational registry to evaluate performance of Excel™ DES in 'Real World, All Comers' patient population

Shirish Hiremath [a], *Praveen Chandra* [b], *Devang Desai* [c], *R. Sivakumar* [d], *S. Selvamani* [d], *Anand Srinivasan* [e], *Madhu Paulose* [e], *Sajy Jose* [e], *B.C. Kalmath* [f], *Vilas.P. Magarkar* [g], *Abhijeet Pathak* [h], *Tushar Mhetre* [i,*]

[a] *Ruby Hall Clinic and Research Centre, Pune, India*
[b] *Max Hospital, New Delhi, India*
[c] *Shree B. D. Mehta Mahavir Heart Institute, Surat, India*
[d] *Meenakshi Mission Hospital, Madurai, India*
[e] *St. Gregorios Cardio-Vascular Center Parumala, Kerala, India*
[f] *Zynova Hospital, Mumbai, India*
[g] *Seth Nandlal Dhoot Hospital, Aurangabad, India*
[h] *Anand Rishiji Hospital, Ahmednagar, India*
[i] *Assistant Manager, Clinical Research Department, Biosensors Interventional Technologies (India) Pvt. Ltd, India*

ARTICLE INFO

Article history:
Received 11 November 2014
Accepted 21 November 2014
Available online 23 December 2014

Keywords:
Excel
DES
Rapamycin
MACE
DAPT

ABSTRACT

Objectives: This study aims to assess the safety and efficacy of a biodegradable polymer-coated Rapamycin-Eluting Stent (Excel) used in conjunction with six-month dual anti-platelet therapy in daily practice.

Background: The polymeric material of cardiac stents has been reported to adversely affect the safety profile of the drug-eluting stents and is also suspected to cause serious long-term complications. It has been proposed that the biodegradable polymer coatings may reduce such late-stage adverse effects.

Methods: This is a prospective, multi-center registry of 654 patients from across 9 cardiology centers in India, who were enrolled and exclusively treated with Excel stents between February 2008 and May 2010. The recommended antiplatelet regimen included clopidogrel and aspirin for 6 months period, followed by lifelong aspirin therapy.

Results: The study population included 46.94% diabetics, 24.31% smokers, 48.93% hypertensives and 14.98% hyperlipidemics. The cumulative rates of major adverse cardiac events were 0.153% at discharge and 1.38% at 12 months. The mean percentage of stenosis was 88.24 ± 9.17% No events occurred between 6 and 12 months.

Conclusions: This multi-center registry study on "real world, all comers" has, thus, showed that EXCEL™ stent which is PLA-coated biodegradable Rapamycin-Eluting Stent exhibited high efficacy and safety profile in treatment of patients undergoing PCI as evidenced by

* *Corresponding author*. Tel.: +91 09561116269 (mobile).
E-mail address: t.mhetre@biosensorsindia.com (T. Mhetre).

http://dx.doi.org/10.1016/j.ihj.2014.12.009

significantly lower rates of MACE and no case of stent thrombosis. There was no event even after DAPT was discontinued after 6 months.

1. Background

Interventional cardiology has witnessed major breakthrough with introduction of first-generation drug-eluting stents (DES) because of their efficacy in reducing in-stent restenosis and target lesion revascularization (TLR) rates compared with bare-metal stents.[1–3] But the initial enthusiasm has been tempered by concerns about their long-term safety, particularly numerically higher rates of late and very late stent thrombosis, which has been associated with catastrophic consequences.[4–7] This has lead to continuous search for newer development in order to improve performance of drug-eluting stents worldwide including use of biodegradable polymers, bioresorbable stents etc. The mechanisms of late or very late stent thrombosis after DES implantation have not yet been clarified, but the stent platform design, the toxicity of active drug and the durable polymer coatings are considered potentially relevant to this problem. Several histopathological studies have indicated that the durable polymer coatings of DES, which were associated with hypersensitivity reactions directed against the polymer, localized vascular inflammation, apoptosis of smooth muscle cells, and thrombogenic reactions, may play significant roles in late or very late stent thrombosis.[8–11] Based on this rationale, biodegradable polymer coatings have been used in some newer generation DESs, including the Excel stent. The efficacy of various biodegradable polymer-coated drug-eluting stents (DES) has been shown to have non-inferior clinical and angiographic outcomes in several randomized trials.[12–15]

Excel stent (C51H79NO13, molecular weight 914.2), one of the new generation drug-eluting stent represents a breakthrough in biodegradable coating technology. This reduces the inflammatory effects on vascular endothelial cells caused by the durable polymer coating residual on the other drug-eluting stents.

In Excel drug-eluting stent, the polymer is asymmetrically coated onto the abluminal side of the stent only ensuring that the optimal amount of drug is released into the wall of the blood vessel. This effectively inhibits intimal hyperplasia and significantly reduces the incidence of post-stenting restenosis, thus, achieving complete vascular endotheliasation. Total rapamycin dosage varies from 195 to 376 μg per stent according to the stent length. The stent platform is a laser-cut, 316LVM stainless steel, open cell design with strut thickness of 0.0044 inches.

The objective of this study was to evaluate the long-term safety and efficacy of the Excel stent along with 6-month dual antiplatelet therapy (DAPT) for the treatment of coronary artery lesions in "real-world" practice.

2. Materials and methods

The e-EXCEL registry is a post marketing surveillance multicenter, prospective study of patients who underwent successful Excel stent implantation at 9 cardiology centers in India between February 2008 and May 2010. For the purpose of this study, patients who had device or procedural failure; who received >1 stent other than the protocol stent; or had contraindications for DAPT; heart function worse than New York Heart Association functional class III; or a planned upcoming surgery were excluded. Institutional Ethics Committee approval was taken and a written informed consent was obtained from each enrolled patient before participation.

3. Definitions, follow-up and outcomes

The rate of major adverse cardiac events (MACE) was the predetermined primary outcome. MACE is defined as a composite of cardiac death, non fatal myocardial infarction (MI), and TLR at the time of discharge as well as 6,9 and 12 months after stent implantation. In-stent late lumen loss and binary restenosis at 9 months, and cumulative thrombotic event rates up to 12 months post index procedure were stated as the secondary outcomes.

Unless a non-cardiac cause could be clearly established on clinical or pathological examination, all deaths were considered to be due to a cardiac cause. Myocardial infarction (MI) was diagnosed based on – development of new pathological Q waves on the ECG in more than 2 contiguous leads; elevation of creatinine kinase myocardial band isoenzyme to three times the upper limits of normal (ULN) after the procedure during index hospitalization; and/or cardiac enzyme level more than twice the upper normal limit thereafter. Any repeat intervention inside the implanted stent or within 5 mm segment proximal/distal to the stent during the index procedure, is defined as TLR. According to Academic Research Consortium (ARC) criteria, stent thrombosis is classified as definite, probable and possible.

Off-label indications of the Excel stent included patients with acute MI or who had lesions in the left main coronary artery or ostial, bifurcated or totally occluded lesions, as well as lesions that did not meet the manufacturer's instructions for use for the RES.

4. Data collection and data management

Demographic, clinical and angiographic data and information on the follow-up variables was prospectively collected on

case-report forms and submitted to a data coordination center. Third party data management team was used to audit the consistency and accuracy of the data-including baseline, in-hospital, and follow-up outcomes. At least 15% of patients in each center were randomly selected for audit checks. In case of discrepancy between the case-report forms versus source documentation, all data from that particular center were audited. Visual estimation of lesion characteristics in relation to those in the index procedure was performed by the operator and the procedures were recorded for follow up and auditing. If a patient underwent angiographic follow up, coronary angiograms obtained at baseline, procedure completion, and follow-up were also audited and kept in the patient records as source document for data verification. Binary restenosis was defined as >50% diameter stenosis at follow up and was classified as in-stent if inside the stent or in-segment if located at the stented segment or up to 5 mm proximal or distal to the stents.

5. Statistical analysis

SAS v9.1.3 was used for carrying out all statistical analyses. Standard descriptive statistics were used for describing the baseline, lesion, and procedural characteristics and also for explaining the 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. The one year clinical outcome data includes stratified analyses according to the presence or absence of DM, ACS, acute ST-elevation myocardial infarction, left anterior descending artery, multi-vessel disease, reference vessel diameter, LVEF, small-vessel disease, and long-lesions. The MACE-free survival curve was calculated by the Kaplan–Meier method.

6. Results

This study includes a total of 654 patients who underwent PCI having symptomatic coronary artery disease (CAD), of which 86.39%patients were male and remaining 13.61% patients were female. The baseline clinical characteristics of the inclusive patients are summarized in Table 1. The study population included 46.94% diabetics, 24.31% smokers, 48.93% hypertensives and 14.98% hyperlipidemics. Among these, 35% had previous history of MI (Myocardial Infarction) and 56.12% were reported to have previous history of angina. Nearly three-fourth of the patients (70.34%) had single-vessel disease, 22.78% had double-vessel disease and 6.88% had a triple-vessel disease (Table 2). The lesion and stent characteristics of these patients are detailed in Tables 3 and 4.

EXCEL™ stents were implanted in all of these patients and no device related complications were noticed in the peri-operative period. A total of 691 EXCEL stents were implanted, with an average of 1.06 ± 0.148 stents per patient (range 1–3) (Table 4). The mean stent diameter was 3.00 ± 0.32 mm (range 2.5–3.5) and mean stent length was 20.31 ± 06.07 mm (range 14–36). The device success rate for EXCEL stents was 100% with 46.64% stent(s) implantations post-dilation. Of the remaining, 2.59% received stents with overlapping, 20.64% were having thrombotic lesion(s) prior to the procedure and 1.83% had lesion(s) at bifurcation.

Four patients were lost to follow up after discharge and 650 were analyzed for MACE at 6, 9 and 12 month period. The details of the major cardiac adverse events at discharge and at the end of 6, 9 and 12 month evaluation periods are shown in Table 5(a) and (b). At the time of discharge, there was only 01 cardiac death. A cumulative of 7 (1.08%) patients had suffered from cardiac death between discharge and 6-month follow up, while 2 (0.308%) were reported to suffer from MI. Of these 2 cases of MI, one was revealed to undergo TVR (target vessel revascularization). Thus, there were 8 cases of new MACE between the discharge and 6-month period making a cumulative of 9 (1.38%) cases of MACE at the end of 6-month period. By the end of 9-month period, all of the 641 patients that underwent evaluation were found to be MACE-free. The mean percentage of stenosis was 88.24 ± 9.17% (range 65–100).

7. Discussion

This post marketing surveillance study characterizes one of the largest prospective single arm studies in India designed to support the long-term safety and efficacy of the Excel stent for treatment of coronary artery lesions in "real-world" clinical practice. The development of stents has been a major advance in the treatment of obstructive coronary artery disease (CAD) since the introduction of balloon angioplasty.[16] Drug-eluting stents have undergone a series of revolutionary changes starting from first-generation DESs to polymer-based and now the focus has been shifted to newer biodegradable polymer DESs. This newer platform contributes a significant advancement in cardiology, which was intended to lower late ST associated with persistence of durable polymers after completion of drug-release. The analysis of 1-year data collected by the e-Cypher registry suggested a high degree of safety of RES (Rapamycin-Eluting Stents).[17] In several randomized trials, Rapamycin-Eluting Stents have been found to be highly efficacious and significantly reduce the risk of in-stent restenosis and target lesion revascularization (TLR) after percutaneous coronary intervention (PCI).[18,19] Single or multiple centers have conducted clinical registries or observational studies to find out the safety of RES mainly and, its efficacy to a lesser extent in a wider variety of indications and coronary disease presentations as well as to monitor their broad utilization pattern and performance.

Table 1 – Baseline clinical characteristics of the inclusive patients ($n = 654$).

Observed index	n%
Diabetes	307 (46.94%)
Smoking	159 (24.31%)
Hypertension	320 (48.93%)
Hyperlipidemia	98 (14.98%)
Previous H/O MI	229 (35.02%)
Previous H/O Angina	367 (56.12%)

Table 2 – Distribution of patients depending on number of vessels involved in CAD.

Number of vessels involved in CAD	*n*%
Single vessel disease	460 (70.34%)
Double vessel disease	149 (22.78%)
Triple vessel disease	45 (06.88%)

The polymer coatings used in the first-generation DES were non-biodegradable. Although RES (Rapamycin-Eluting Stents) limit restenosis, most of them use a polymer coating as a drug carrier, long-term adverse vascular pathologies and toxicities associated with a permanent polymer coating continue to be of major concern. This had stimulated the development of non-polymer drug-eluting stent (DES) or DES based on bio-absorbable polymers. Biodegradable polymer-based stents, including EXCEL stent, have been shown to be effective in inhibiting neointimal hyperplasia. The novel PLA material is gradually biodegraded within approximately 6 months and eventually becomes water and carbon dioxide after stent implantation. The PLA polymer is now used in the coronary DES by many manufacturers.[19,20]

The MEDISTRA trial [Medistra Excel Drug-ElutIng Stent TRiAl], a first in man study with a bioabsorbable polymer based Excel DES, showed that despite the inclusion of challenging "real world cases" the preliminary results were encouraging with very low MACE rate. Another multi-center registry trial of EXCEL biodegradable RES [CREATE] documented satisfactory safety and efficacy profiles, as evidenced by low rates of major adverse cardiac events and stent thrombosis up to 5years when used with 6 months of dual antiplatelet therapy in a "real-world" setting.[21] In yet another single-center experience with complex patients and lesions, the EXCEL stent implantation with 6-month dual antiplatelet treatment proved to markedly reduce the incidence of 24-month ISR and MACE.[22]

In the study of 100 patients, overall MACE rate at one-year was better than the results of other studies for the currently marketed DES.[17] The current study was conducted at 9 centers as an open-label study involving 654 patients having symptomatic CAD (coronary artery disease) and qualifying for percutaneous coronary intervention (PCI). The mean percentage of stenosis was 88.24 ± 9.17%.

Table 3 – Lesion characteristics of inclusive patients (*n* = 654): number, target and type of lesions.

a. Number of lesions in patients (*n* = 654)	*n*%
One lesion	545 (83.33%)
Two lesion	90 (13.76%)
Three lesion	19 (02.91%)
b. Target lesion locations (*n* = 782)	*n*%
LAD	542 (69.31%)
RCA	130 (16.62%)
LCX	76 (09.72%)
Others	34 (04.3 5%)
c. Type of lesions (AHA/ACC classification) (*n* = 782)	*n*%
Type-A	434 (55.50%)
Type-B1	285 (36.45%)
Type-B2 and Type-C	63 (08.05%)

Table 4 – EXCEL stent characteristics and PCI peri-operative parameters.

Total stents implanted	691
Mean no. of stent per patient	1.06
Stent diameter (Mean)	3.00 mm
Stent length (Mean)	20.31 mm
Basic peri-operative parameters	
Post-dilation	305 (46.64%)
Stent overlapping	17 (2.59%)
Bifurcation	12 (1.83%)
Thrombus lesion	135 (20.64%)
Device success rate	100%

The overall clinical success rate of the EXCEL™ stent, indicated by the percentage of MACE-free patients, was found to be 99.84% at the time of discharge and 98.76% at the end of 6 months and 9 months. The overall clinical success remains to be 98.76% at 12 month follow-up. This is even more significant where almost half of the patient population enrolled were diabetic, thereby increasing complexity and worsening the prognosis. There has been no withdrawal of any of the study patients or any death due to AE or SAEs apart from those comprising the primary efficacy endpoints in this study. These results are in line with similar studies conducted with other biodegradable polymer-based Rapamycin-eluting stents.[18,19,20,21]

8. Study limitations

Any post marketing surveillance registry has study limitation of being single arm with no control arm for direct comparison. Since patients treated with other than Excel stent during the

Table 5a – MACE (Major Adverse Cardiac Events) occurring during post-operative follow up.

Events	At discharge (*n* = 654)	6 months (*n* = 650)	9 months (*n* = 650)	12 months[a] (*n* = 650)
MACE	1 (0.153%)	[b]9 (1.38%)	[b]9 (1.38%)	[b]9 (1.38%)
Cardiac death	1 (0.153%)	7 (1.08%)	7 (1.08%)	7 (1.08%)
MI	0 (0%)	[b]2 (0.308%)	[b]2 (0.308%)	[b]2 (0.308%)
TVR	0 (0%)	1 (0.154%)	1 (0.154%)	1 (0.154%)

n = No. of evaluable patients.
MACE = Major Adverse Cardiac Events; MI = Myocardial Infarction.
TVR = Target Vessel Revascularization.
[a] 12 month visit: All 641 patients after the 9 month evaluation period are alive and have not been reported to have any CAD symptoms until the time of preparation of this report. Out of these patients, 380 patients have completed the 12 month follow up period and the remaining patients are still under follow up for the 12 month. However, all the patients who have completed their 70% follow up period are considered as treatment completers per protocol patients' treatment compliance.
[b] Out of the 2 patients that were reported with MI and had undergone angiography, the reports revealed that one patient had the complication of TVR and had undergone revisualization. However, both the events were recorded in the same patient, thus the cumulative MACE at 6-month period onwards remained 9.

Table 5b – Success rate during post-operative follow up.

No. of Patients who	At discharge	6 months	9 months	12 months
Underwent follow up	654	649	643	380[a]
MACE-free	653	641	641	641
Clinical success rate	99.84%	98%	98%	98%

MACE = Major Adverse Cardiac Events; MI = Myocardial Infarction. TVR = Target Vessel Revascularization.

[a] 12 month visit: All 641 patients after the 9 month evaluation period are alive and have not been reported to have any CAD symptoms until the time of preparation of this report. Out of these patients, 380 patients have completed the 12 month follow up period and the remaining patients are still under follow up for the 12 month. However, all the patients who have completed their 70% follow up period are considered as treatment completers per protocol patients' treatment compliance.

index procedure were excluded, therefore, no information was collected on other DES. This might lead to selection bias to some extent.

9. Conclusion

The current multicenter registry study on "real world, all comers" has thus shown that EXCEL™ stent exhibits high efficacy and safety profile in treatment of patients undergoing PCI. The 1-year incidence of MACE was significantly lower as compared to previously published data. There was no incidence of stent thrombosis. This study also underlines that 6months DAPT is safe enough for Excel™ DES.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. Babapulle MN, Joseph L, Belisle P, et al. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet*. 2004;364:583–591.
2. Moses JW, Leon MB, Popma JJ, et al, on behalf of SIRIUS Investigators. Rapamycin-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315–1323.
3. Stone GW, Ellis SG, Cox DA, et al, on behalf of TAXUS-IV Investigators. One-year clinical results with the slow-release, polymer based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation*. 2004;109:1942–1947.
4. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;364:1519–1521.
5. Liistro F, Colombo A. Late acute thrombosis after paclitaxel eluting stent implantation. *Heart*. 2001;86:262–264.
6. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al, on behalf of BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol*. 2006;48:2584–2591.
7. Ong AT, McFadden EP, Regar E, et al. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol*. 2005;45:2088–2092.
8. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol*. 2006;47:175–181.
9. Virmani R, Liistro F, Stankovic G, et al. Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. *Circulation*. 2002;106:2649–2651.
10. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a rapamycin-eluting stent: should we be cautious? *Circulation*. 2004;109:701–705.
11. Sousa JE, Costa MA, Farb A, et al. Images in cardiovascular medicine: vascular healing 4 years after the implantation of rapamycin-eluting stent in humans: a histopathological examination. *Circulation*. 2004;110:e5–6.
12. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet*. 2008:1163–1173.
13. Ahmed TA, Bergheanu SC, Stijnen T, Plevier JW, Quax PH, Jukema JW. Clinical performance of drug-eluting stents with biodegradable polymeric coating: a meta-analysis and systematic review. *EuroIntervention*. 2011 Aug;7:505–516.
14. Mehilli J, Byrne RA, Wieczorek A, et al. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J*. 2008;29:1975–1982.
15. Byrne RA, Kastrati A, Kufner S, et al. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial. *Eur Heart J*. 2009;30:2441–2449.
16. Htay Thein, Liu Ming W. Drug-eluting stent: a review and update. *Vasc Health Risk Manag*. 2005;1:263–276.
17. Urban Philip, Gershlick Anthony H, Guagliumi Giulio, et al. Safety of coronary rapamycin-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. *Circulation*. 2006;113:1434–1441.
18. Neumann Franz-Josef, Desmet Walter, Grube Eberhard, et al. Effectiveness and safety of rapamycin-eluting stents in the treatment of restenosis after coronary stent placement. *Circulation*. 2005;111:2107–2111.
19. Dani Sameer, Kukraja Neville, parikh Prakashvir, et al. Biodegradable-polymer-based, rapamycin-eluting Supralimus® stent: 6-month angiographic and 30-month clinical follow-up results from the Series I prospective study. *EuroIntervention*. 2008;4:59–63.
20. Ge Junbo. Limus-eluting stents with Poly-L-lactic acid coating. *Asia-Pacific Cardiol*. 2007;1.
21. Han Ya-Ling, Zhang Lei, Yang Li-Xia, et al, for the CREATE investigators. A new generation of biodegradable polymer-coated sirolimus eluting stents for the treatment of coronary artery disease: final 5-year clinical outcomes from the CREATE study. *EuroIntervention*. 2012;8:815–822.
22. Han Y, Jing Q, Chen X, et al. Long-term clinical, angiographic, and intravascular ultrasound outcomes of biodegradable polymer-coated Rapamycin-eluting stents. *Catheter Cardiovasc Interv*. 2008 Aug 1;72:177–183.