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Research Article

Clinical Outcomes of the Eucalimus Sirolimus-Eluting Coronary Stent System with a Biodegradable Polymer in All-Comers Coronary Artery Disease Patients: Results from Registry in Greece

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ABSTRACT

Background: Biodegradable polymer drug-eluting stents with biodegradable polymer coatings have shown reduced restenosis rates and low rates of stent thrombosis. The present post marketing retrospective study assessed clinical outcomes of patients who had received eucaLimus DES in real practice.

Aim: To investigate 2-year clinical outcomes of eucaLimus DES in real practice.

Methods: Data obtained from a two-center cohort of patients who had received eucaLimus stents between February 2016 to September 2018 as part of routine treatment of Coronary Artery Disease (CAD) were retrospectively investigated at follow-up of 27.8 months ± 5.2 months. The primary study endpoint was to determine the rate of Target Lesion Failure (TLF) defined as the aggregate of cardiac death, target vessel Q-wave or non Q-wave Myocardial Infarction (MI), and TLR procedure during the follow-up period after the index procedure. Secondary endpoint was MACE defined as the composite of all-cause mortality, any MI and any repeat revascularization (includes all target and non-target vessel). The Stent Thrombosis (ST) was also evaluated in this study and was classified according to the definitions of the Academic Research Consortium.

Results: A total of 196 patients with 253 lesions were enrolled. The most common comorbid conditions were hypertension (43.4%), diabetes mellitus (27.5%), hyperlipidemia (54.6%) and smoking (60.7%). Procedural success was achieved in all patients and no in-hospital MACE was reported. The incidence of composite TLF at follow-up was 4.0%. The MACE rate shows 8.6 % including non-cardiac death (2%), myocard infarction not related to target vessel (1%). Beside one sub-acute thrombosis the rate of late or very late stent thrombosis was 0%.

Conclusion: Compared to the mid-term follow-up the relatively low rates of TFL and MACE and non-late or very late stent thrombosis in this study support safety and performance of eucaLimus stents, suggesting it to be an effective alternative to other contemporary stents for the treatment of de novo lesions in native coronary arteries.e.

Keywords: Drug-eluting stent; Percutaneous coronary interventions; PLGA; Myocardial Infarction; Stent thrombosis

INTRODUCTION

Drug-Eluting Stents (DES) was developed to minimize the risk of instant restenosis by the local delivery of anti-proliferative drugs from different kind of stent coatings to control the release kinetics of the drugs. While effectively reducing restenosis rate, first-generation DES with durable polymer-based coatings did not improve mortality following Percutaneous Coronary Interventions (PCI) due to a limited biocompatibility of early DES [1].

Second-generation DES with more biocompatible durable polymer-based coatings then showed on average a more favorable clinical outcome [2-7], while contemporary third generation DES with

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more refined stent designs showed improved stent deliverability in challenging coronary anatomies [8-12].

In parallel with the refinement of durable coating DES, concerns about durable polymers as a potential trigger of vessel wall inflammation and late adverse events prompted the development of DES with biodegradable polymer based coatings [13], which, after degradation, leave only a bare metal stent in the vessel wall that does not induce an excessive or prolonged inflammatory response [13,14]. Such DES is demonstrating favorable safety and efficacy compared to first generation durable coating DES [15]. Meanwhile, novel biodegradable coating DES have been introduced, which utilize modern, flexible, thin-strut stent platforms and drugs based on Rapamycin or Rapamycin analogs that are highly efficacious in preventing restenosis [16,17]. These devices using coating concepts as either the entire stent (i.e. circumferential coating) or only the abluminal stent surface (i.e., external coating) is covered by the biodegradable coating.

PCI with DES has become the standard of care. Current randomized comparisons of approved DES therefore address so-called all-comer populations with very limited exclusion criteria, and comprise patients with all clinical syndromes [8]. The findings of such trials are particularly valuable as they reflect the performance of DES in routine clinical practice.

Therefore, we assessed in an all-comer patient population the safety and efficacy of the eucaLimus biodegradable coating DES**.**

METHODS

Study design and patient selection

Data obtained from a two center cohort of patients who had received eucaLimus stents as part of routine treatment for CAD between February 2016 to September 2018 were identified in the hospitals database and recruited to the analysis. There were no exclusion criteria except patients lost to follow-up or those who could not be contacted for assessment at follow-up.

Description of device

The eucalimus is an ultrathin cobalt-chromium platform with a strut thickness of 65 µm and a biodegradable polymer based coating. In eucalimus a biodegradable polymer Poly Lactic-co-Glycolic Acid (PLGA) is used to achieve a controlled drug release using a validated formulation of sirolimus (1.40 µg/mm2) timed to elute in 90 - 120 days in parallel with the polymer resorption. The configuration of the coating is asymmetrical and thicker on the abluminal side than on the luminal side (5 µm vs. 3 µm, respectively), which results in a higher drug dose on the abluminal side of the DES. The eucalimus is available in sizes ranging from 8 to 48 mm length and from 2.25 to 4.00 mm diameter.

Study procedure and data collection

This was an all-comer study, and the indications for the angioplasty procedure and technique of stent implantation were as per the discretion of the treating physician. All patients were advised to receive dual antiplatelet therapy with clopidogrel and aspirin. Patients who were not pretreated received a bolus dose of 300-600 mg of clopidogrel or 60 mg of prosugrel and ≥ 100 mg of **soluble** aspirin just before the procedure.

Data were sourced from clinical notes, including inpatient progress notes and outpatient notes and letters, angiogram reports, and procedural angiographic images. Case report forms were completed for all patients, and completely anonymized data were stored in a secure, off-site database. Follow-up data were collected using telephonic interactions by using structured questionnaires developed for this study to determine endpoint status.

Endpoint definitions

The primary endpoint of the study was to determine the rate of Target Lesion Failure which is defined as the aggregate of cardiac death, target vessel Q-wave or non Q-wave Myocardial Infarction (MI), and TLR procedure during the follow-up period after the index procedure. Secondary endpoint was MACE which is defined as the aggregate of all-cause mortality, any MI and any repeat revascularization (includes all target and non-target vessel). The Stent Thrombosis (ST) was classified according to the definitions of the Academic Research Consortium [16]. Procedural success was defined as successful stent placement at the desired position with <30% residual stenosis.

Statistical analysis

Categorical data were presented as counts and percentages. Continuous variables were recorded as mean ± standard deviation. All data were processed using the Statistical Package SPSS® 22.0 for Windows® (SPSS, Chicago, IL, USA).

RESULTS

Baseline demographic and clinical characteristics

In total 196 patients with 253 lesions were retrospective analyzed. Baseline demographics and clinical characteristics are summarized in Table 1. Mean age of patients was 66.7 ± 10.7 years, and the majorities were men (79.8%). The most common comorbid conditions were hyperlipidemia (54.6%), hypertension (43.4%), followed by diabetes mellitus (37.5%). 43.3 % of patients presented ST or Non ST myocardial infarction, 13.8 % unstable angina.

Lesion and procedural characteristics

Most lesions were located in LAD (54.9%), RCA (31.6%), and LCx (22.5%) (Table 2). Lesion length was 17.0 ± 9.0 mm. 23.7% of patients had a lesion length longer than 20 mm. The stenosis rate was 86.6% ± 10.7% (Table 2).

63.2% lesions were moderate- to high risk B2/C lesions as per ACC/AHA criteria and 78.3% of the lesions had a TIMI flow grade below 3. The average length and diameter of the stent was 21.2 ± 9.1 and 3.2 ± 1.4 respectively. Average number of stents per patient was 1.34 ± 0.5 and pre- and post-dilation was performed in 71.9% and 75.9% of patients respectively. Procedural success was achieved in all patients (Table 3).

Clinical outcomes during follow-up period

The incidence of composite of TFL at follow-up of 27.8 months ± 5.2 months was 4.6% with two cardiac deaths (1%), two MI

Table 1: Baseline clinical characteristic.

Characteristics	Patients (n=196)
Patient demographics	
Age	66.7 ± 10.7
Male	159 (79.8%)
BMI (kg/m^2)	27.6 ± 3.3
Family history of MI	37 (18.8%)
Diabetes Mellitus (insulin depending)	23 (11.7%)
Diabetes Mellitus (non-insulin depending)	31 (15.8%)
Current Smoker	119 (60.7%)
Hypertension	85 (43.4%)
Hyperlipidemia	107 (54.6%)
History of stroke TIA	12 (6.1 %)
Peripheral Vascular Disease	12 (6.1%)
Renal insufficiency (Creatine>1.3 mg/dl)	9 (4.6%)
Previous PCI	18 (9.2%)
Previous CABG	8 (4.1%)
Previous MI (>72 h)	16 (8.2%)
Chronic stable angina	84 (42.9%)
Unstable angina	27 (13.8%)
ST elevation myocardial infarction	42 (21.4%)
Non ST elevation myocardial infarction	43 (21.9%)
Data presented at Mean ± SD or n per patient and %	

Table 2: Lesion characteristic.

Per Patient* Per Lesion†	196 patients 253 lesions
Target vessels*	
One-vessel disease	161 (82.2%)
Two-vessel disease	32 (16.3%)
Three-vessel disease	3 (1.5%)
Target lesions*	1.29 ± 0.6
1 lesion treated	152 (77.6 %)
2 lesions treated	35 (17.9 %)
3 lesions treated	6 (3.0 %)
3 lesions treated	3 (1.5 %)
Target lesion location†	
LAD	116 (54.9 %)
LCX	57 (22.5 %)
RCA	80 (31.6 %)
Left ventricular ejection fraction*(%)	59.7 ± 7.6
Reference Vessel Diameter (RVD)†(mm)	3.09 ± 0.34
Small vessels (RVD <2.75 mm)†	16 (6.2%)
Diameter Stenosis†(%)	86.6 ± 10.7
Total Occlusions (100 %)†	28 (11.1%)
Preprocedural Timi Flow Grade†	
Timi Flow 0	28 (11.1%)
Timi Flow 1	73 (28.9%)
Timi Flow 2	97 (38.3%)
Timi Flow 3	55 (21.7%)
Lesion length† (mm)	17.9 ± 9.0
Lesion length>20 mm†	60 (23.7%)
Lesion types B2/C†	160 (63.2%)
Data presented at Mean ± SD or n per patient* or lesion† and %	

Table 3: Procedural characteristic.

Per Patient* Per Lesion†	196 patients 253 lesions
Stents per patient*	1.29 ± 0.6
Stent length†(mm)	21.2 ± 9.1
Stent diameter†(mm)	3.2 ± 1.4
Pre dilatation†	182 (71.9%)
Direct Stenting†	71 (28.1%)
Post Dilatation†	192 (75.9%)
Technical Success†	100%
Clinical Procedural success*	100%
Data presented at Mean ± SD or n per patient* or lesion† and %	

Table 4: Clinical outcome at follow-up 27.8 ± 5.2 months.

Target lesion failure	**9 (4.6 %)**
Cardiac Death	2 (1.0 %)
Myocard infarction - attributed to a target Vessel	2 (1.0 %)
Target Lesion Revascularisation (TLR) Solved by PCI	5 (2.6 %)
MACE	**13 (8.6 %)**
Cardiac death	2 (1.0 %)
Non cardiac death	4 (2.0 %)
Myocard infarction–attributed to a target vessel	2 (1.0 %)
Myocard infarction–attributed to a non-target vessel	2 (1.0 %)
Target Lesion Revascularisation (TLR) Solved by PCI	5 (2.6 %)
Target Vessel Revascularisation (TVR) Solved by PCI	1 (0.5 %)
Non Target Vessel Revascularisation (Non TVR) Solved by PCI	1 (0.5 %)
ARC Stent Thrombosis Definite/Probable	1 (0.5 %)
Sub acute stent thrombosis (definite)	1 (0.5 %)
Data presented at n and %	

attributed to the target vessel (1%) and 5 TLR´s solved by PCI (2.6%).

MACE rates during the follow-up duration are depicted in Table 4. In brief, MACEs were reported in 13 (8.6%) patients at follow-up, consisting of two cardiac deaths (1%), four non-cardiac death (2%), two (1%) Myocardial Infarctions attributed to the target vessel, two Myocardial Infarctions (1%) attributed to a non-target vessel and 5 (2.6%) TLR events. All TLR events were PCI, and the patients recovered after treatment. TVR was observed in 1 patient (0.5%), one Non-TVR (0.5%) occurred. Both were solved by PCI. As shown in Table 4, the cumulative rate of ST was 0.5% (1/196) during follow-up period. One sub-acute ST was ARC-definitely. No in-hospital MACE and no late or very late stent thrombosis were reported.

DISCUSSION

The presented retrospective study was conducted to support the safety of eucaLimus stent for treatment of coronary artery lesions

in real-world clinical practice. The mid-term follow-up results demonstrated the favorable safety and performance of the stent with low rates of TFL (4.6%), MACE (8.6%) and ST of 0.5%.

We evaluated real-world data of eucaLimus in an unselected clinical practice population with diverse clinical profiles, which included diabetes (39.53%), hypertension (49.61%), bifurcation and thrombotic lesions (11.04%), and ACC/AHA type B and C lesions (94.77%). The presentation of patients was similar to that reported in studies of other similar stents [13,14].

The eucaLimus stent is designed to have thin struts (65 μm) on a cobalt-chromium platform with a unique and innovative "s" link and an alternate "C" link, which provides high radial strength and no foreshortening, making it ideal for all lesion locations including ostial lesions.

The first-generation DES were built on bulky stent platforms, making deliverability quite challenging [15]; however, the thin struts and growth of 8% from nominal pressure to rated burst pressure of this new-generation eucaLimus DES offer good deliverability and conformability, thereby allowing complete deployment and good wall apposition. The design leads to a minimal balloon overhang, minimizing the risk of edge dissection/injury, which is a common procedural complication of PCIs. The finding that procedural success was achieved in 100% of patients in this study supports these claims.

Compared with BMS, first-generation DES with a durable polymer has reduced the rate of restenosis but are associated with higher late ST [11]. Delayed endothelial healing secondary to a hypersensitivity reaction to the durable polymer could be responsible for the observed high rate of ST with such DES [16-18]. BP-DES was developed to address this potential limitation of durable polymer DES. The drug encapsulated in polymer is completely released within 3–9 months, and the polymer also gradually degrades into carbon dioxide and water molecules. Therefore, BP-DES initially provides anti-proliferative benefits similar to durable polymer DES and later behaves like BMS once drug delivery and polymer biodegradation are complete [19].

Given the importance of ST in evaluating the overall performance of DES, we estimated the ST rate in our study. The rates of both possible and probable late ST was 0.78% in the present study, which are comparable to those of other standard BP-DES such as sirolimus-eluting Orsiro stents (0.4%), biolimus-eluting Nobori stents (1.2%), and Biolimus A9 stents (0.2%) at 1-year follow-up [14,20].

The low rate of ST observed in our study could be attributed to complete wall apposition of the EucaLimus stent and appropriate endothelial healing over the 1-year period.

Although there is no scientific difference between indigenously developed DES vs. those developed and marketed by global manufacturers, cost effectiveness remains a key factor in the decision-making process for patients and health care providers in India [21]. The most promising results of this retrospective study are 100% procedural success rate and low rates of MACE (4.87%). MACE rates in our study are comparable to previously reported incidence rates for other BP-DES: Endeavor stent (12.9%), NOBORI stent (11%), and Meta for SES (1.6%) [13,22,23]. Moreover, our results are comparable to the rate observed in the SPIRIT II trial (7.2%) [7].

STUDY LIMITATIONS

A major limitation of the present study is the observational design and retrospective analysis of data. However, observational data allow true representation of all-comer population unlike randomized trials with restricted enrollment criteria. Therefore, our results must be further substantiated in well-designed studies with longer follow-up duration.

CONCLUSION

In conclusion, the relatively low rates of TLF, MACE and ST in this cohort of patients after more than two years of follow-up support the favorable safety and performance of eucaLimus stents. Product characteristics such as advanced thin strut stent design with the use of short term polymer degradation could be responsible for these results. EucaLimus could be suggested as an effective alternative to other contemporary stents available in the market for the treatment of de novo lesions in native coronary arteries.

DISCLOSURES

Conflict of interest

None

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