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TWO YEARS CLINICAL OUTCOMES OF PATIENTS TREATED WITH EUCALIMUS SIROLIMUS-ELUTING STENTS A REAL WORLD EXPERIENCE

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SUMMARY

To evaluate the 2-years clinical outcomes of consecutive patients in a real-world population who received the eucalimus drug eluting stent.

This was a single-centre, retrospective registry analysis that reviewed the clinical data from all patients who were implanted with EucaLimus Sirolimus-Eluting Stents (SES) between November 2016 and May 2018. Clinical follow-up was performed at 25.6 ± 5.7 months post-implantation. The primary endpoint was Target Lesion Failure (TLF) as a composite of cardiac death, target vessel Q-wave or non-Q-wave Myocardial Infarction, Coronary Artery Bypass Graft (CABG) and clinically driven Target Lesion Revascularization (TLR). Secondary endpoint was Major Adverse Cardiovascular Events (MACE) as a composite of all-cause mortality, any Myocardial Infarction, and any repeat revascularization (includes all target and non-target vessel). In addition, Stent thrombosis (ST) was analysed at respective follow-up period.

A total of 171 patients (mean age; 70.0 ± 11.9 years) received a eucalimus stent. Among those 127 (80.9%) patients had hypertension and 37 (25.0%) patients had diabetes mellitus. A total of 229 lesions were treated with the eucalimus SES (1.47 stents per patient). 36.3% of patients treated with lesion length ≥ 20 mm, 58.5 % presented Type B2/C lesions.

At 25.6 ± 5.7 months follow-up, Target Lesion Failure (TLF) was observed in 2 (0.9%) patients. No cardiac death or myocardial infarct attributed to the target vessel was reported in any patient. Target lesion revascularization (TLR) occurred in 2 patients solved by PCI. Mayor adverse event rate (MACE) was observed in 8 patients (3.9%). No cardiac death, no myocardial infarction at all, 3 cases of non-cardiac death, two cases of TLR solved by PCI, two cases of TVR and one case of non-TVR occurred. No Stent thrombosis (ST) was reported at respective follow-up period.

In our study the EucaLimus stent showed a favourable 2-years clinical performance in a real-world population.

Key words

Drug-eluting stent; biodegradable polymer; PLGA; Sirolimus-Eluting Stent; coronary artery disease.

Impact statement

EucaLimus Sirolimus Eluting Stent has demonstrated a very favourable outcome in terms of safety and efficacy in a Real-World Population of patients with coronary artery disease, treated with percutaneous coronary angioplasty.

INTRODUCTION

Drug eluting stents (DES) have become a cornerstone in the treatment of coronary artery disease (CAD) by effectively reducing restenosis and target vessel revascularization (TVR) (1-3). Despite that, first-generation DES sometimes caused an increase in adverse events, such as inflammation, vascular hypersensitivi-

ty reactions, neo-atherosclerosis, late and very late stent thrombosis (ST) (4-6). In the development of the newest generation drug eluting stents, several strategies have been adopted to overcome the above-mentioned issues: more bio-compatible metal alloys, more effective anti-restenosis drugs and more bio-compatible polymer carriers (3, 7, 8). Even if modern non-biodegradable polymer-coated drug eluting stents have shown to be safe in a long period of follow-up, there are still some concerns regarding the long-term negative effects exerted by a permanent polymer (9). Accordingly, one strategy to reduce the clinical long-term adverse events, such as restenosis or stent thrombosis, is to use biodegradable polymers, with the purpose of deliver the drug to the vessel and then dissolve. Polymers like poly (lactic acid) (PLA), poly (glycolic acid) and their copolymer, poly (lactic-co-glycolic acid) (PLGA), are the most adopted, as they can be completely metabolized by the human body (10, 11). Moreover, biodegradable polymers can improve safety and performance of DES by a slow release of the anti-restenotic agent and, subsequently, a gradual degradation of the coating (12, 13). In a real-world patient population, biodegradable polymers have demonstrated excellent safety and performance in CAD patients, as quoted by several studies (14, 15).

EucaLimus (Eucatech AG, Germany - CE approved) is a new-generation sirolimus-eluting coronary stent (SES), with a bio-resorbable polymer, developed to improve the outcomes of patients undergoing percutaneous coronary intervention. The aim of this study was to evaluate the 2-years clinical outcomes of consecutive patients in a real-world population who received the EucaLimus sirolimus eluting stent

MATERIALS AND METHODS

Study design and population

This was a single-centre retrospective data analysis. All patients treated with EucaLimus stents in the Division of Cardiology, Sacco University Hospital, Milan, between November 2016 and May 2018 were retrieved from the Hospital Database and included in the analysis. There were no exclusion criteria except patients lost to follow-up or those who could not be contacted for assessment at 2 years follow-up after stent implantation. Baseline demographics, procedural details and follow-up data were recorded. All treatment and clinical decision-making processes were subject to the attending cardiologists.

Study device

The EucaLimus SES is an ultrathin cobalt-chromium platform with a strut thickness of 65 μm and a biodegradable polymer-based coating. In the EucaLimus SES, poly (lactic-co-glycolic acid) (PLGA) polymer is used to achieve a controlled drug release using a validated formulation of sirolimus (1.40 μg/mm^2), timed to elute in 90-120 days from a biodegradable polymer base which degrades simultaneously. The eucalimus SES is available in sizes ranging from 8 to 48 mm length and from 2.25 to 4.00 mm diameter.

Interventional procedure and adjunctive medications

All patients received a loading dose of 325 mg of aspirin and 600 mg of clopidogrel or 60 mg of prasugrel or 180 mg of ticagrelor. The procedure was performed according to the standard treatment guideline of the centre. All the patients received dual antiplatelet therapy (DAPT) after the procedure (aspirin 75-300 mg/day indefinitely and clopidogrel 75 mg/day or prasugrel 10 mg/day or ticagrelor 90 mg twice daily for at least 12 months).

Study endpoints

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 proce-

dure during the follow-up period after the index procedure. The secondary endpoint was the occurrence of MACE (Major Adverse Cardiovascular Events), which is 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 (16).

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

From November 2016 to May 2018 a total of 171 patients were implanted with eucaLimus stents and entered the analysis. A total of 229 stents were implanted.

The study included a high-risk population, as shown in **table I**: a total of 86 patients (65.3%) presented with acute coronary syndrome (unstable angina ST and Non-ST elevated MI). 127 patients (80.9%) were hypertensive. 37 patients (26%) were diabetic.

With regards to lesion characteristic, 134 patients (58.5%) presented Type B2/C lesions, 83 lesions (36.3%) longer than 20 mm were treated. Lesion length was 22.00 ± 12.27 mm (**table II**).

The procedural characteristics are shown in **table III**. Average stent length was 24.58 ± 9.22 mm. Per patient 1.47 stents were implanted.

Table I. Baseline clinical characteristics.

Characteristics	Patients (n = 171)
Age	70.0 ± 11.9 years
Male	138 (80.7 %)
BMI (kg/m2)	27.2 ± 5.1
Family history of MI	35 (20.7 %)
Diabetes Mellitus (insulin depending)	9 (6.1 %)
Diabetes Mellitus (non-insulin depending)	28 (18.9%)
Current Smoker	35 (21.7 %)
Hypertension	127 (80.9 %)
Hyperlipidemia	71 (42.0 %)
History of stroke TIA	6 (3.6 %)
Peripheral Vascular Disease	6 (3.6 %)
Previous PCI	45 (26.3 %)
Previous CABG	29 (16.9%)
Previous MI (> 72 h)	25 (14.6%)
Chronic stable angina	59 (34.5 %)
Silent Ischemia	26 (15.2 %)
Unstable angina	26 (30.2 %)
ST elevation myocardial infarction	38 (22.2 %)
Non-ST elevation myocardial infarction	22 (12.9 %)

Data presented at Mean ± SD or n per patient and %
BMI: Body Mass Index; MI: Myocardial Infarction; TIA: Transient Ischemic Attack; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft.

Table II. Lesion characteristic.

Per Patient + Per Lesion *	171 patients 229 lesions
Target vessels +	
One-vessel disease	134 (78.4 %)
Two-vessel disease	30 (17.5 %)
Three-vessel disease	7 (4.1 %)
Target lesions +	
1 lesion treated	124 (72.5 %)
2 lesion treated	36 (21.1 %)
3 lesion treated	11 (6.4 %)
Target lesion location *	
LAD	88 (38,4 %)
LCX	46 (20.1 %)
RCA	92 (40.2 %)
LM	3 (1.3 %)
Left ventricular ejection fraction +	56.6 ± 9.8
Reference Vessel Diameter (RVD) *	3.38 ±0.51 mm
Small vessels (RVD < 2.75 mm) *	25 (11.1 %)
Diameter Stenosis *	83.01 ±13.31 %
Total Occlusions (100 %) *	27 (11.8 %)
Lesion length *	22.00 ±12.27 mm
Lesion length > 20 mm *	83 (36.3 %)
Lesion types B2 / C *	134 (58.5 %)

Data presented at Mean ± SD or n per patient + or lesion * and %
LAD: Left Anterior Descending Artery; LCX: Left Circumflex artery; RCA: Right Coronary Artery; LM: Left Main.

The primary endpoint TLF after more than 2 years occurred in only 2 patients (0.9%). No cardiac death or myocardial infarction attributed to the target vessel was observed. Two target lesion revascularisations were performed by PCI.
Mace at that follow-up point was 3.9 % based on 3 non cardiac death (1.7%), 2 TLR (0.9%)

Table III. Procedural characteristic.

Per Patient + Per Lesion *	171 patients 229 lesions
Stents per patient +	1.47
Stent length *	24.58 ± 9.22 mm
Stent diameter *	3.18 ± 0.48 mm
Pre Dilatation +	115 (50.2 %)
Direct Stenting +	108 (47.2 %)
Post Dilatation +	153 (66.8 %)

Data presented at Mean ± SD or n per patient + or lesion * and %

solved by PCI, 2 TVR (0.9%) solved by PCI and 1 (0.4%) non target TVR solved by PCI.
There was no in-stent thrombosis at all (**table IV**).

DISCUSSION

In our retrospective study of 171 patients and 229 coronary lesions treated with eucaLimus SES, we observed a very low rate of target late failure and no stent thrombosis during a mean follow-up period of 25.6 ± 5.7 months.
Demographic data showed that 80.9% of the patients had hypertension and 65.3% of the patients presented with acute coronary syndrome, allowing us to evaluate the eucaLimus SES in a "real-world", high-risk, patient population.
Real-World Evidence is of paramount importance in Interventional Cardiology to assess new devices in the post-marketing phase. Indeed, even if randomized trials are considered the best method to assess a new device or a new technique, sometimes they don't necessary reflect the real clinical practice (17-18). The ISCHEMIA Trial, for example, is a randomized trial which compared invasive coronary angiography and revascularization (on top of optimal medical treatment) versus optimal medical treatment alone in 5179 patients with stable angina and evidence of inducible ischemia (19). The authors found that, over a median follow-up of 3.2 years, there was no significant difference between the two groups in terms of incidence of the primary endpoint (a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest). The study excluded patients with clinically significant left main coronary artery disease, low ejection fraction, class III or IV heart failure, or those who were very symptomatic despite the use of medical therapy at maximum acceptable doses. Since this type of patients represent a significant proportion among patients with ischemic heart disease,

Table IV. Clinical outcome at follow-up 25.6 ± 5.7 months.

Target Lesion Failure	**2**	**(0.9 %)**
Cardiac Death	0	(0 %)
MI - Attributed to the target Vessel	0	(0 %)
Target Lesion Revascularisation (TLR) Solved by PCI	2	(0.9 %)
MACE	**8**	**(3.9 %)**
Cardiac Death	0	(0 %)
Non-Cardiac Death [1 – 3]	3	(1.7 %)
Myocard infarction (all)	0	(0 %)
Target Lesion Revascularisation (TLR) Solved by PCI	2	(0.9 %)
Target Vessel Revascularisation (TVR) Solved by PCI	2	(0.9 %)
Non Target Vessel Revascularisation (Non TVR) Solved by PCI	1	(0.4 %)
Thrombosis All (Definite / Probably)	**0**	**(0 %)**
[1] Sepsis (Pneumonia) - 2 months post-PCI [2] Pancreatic malignancy - 6 months post-PCI [3] Bladder Cancer - 3 months post-PCI		

MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention.

the trial results cannot be easily translated into daily-based clinical practice.

Comprehensive studies report that the presence of a durable polymer with lack of biocompatibility in first-generation DES was associated with inflammation and vascular hypersensitivity reaction delay in re-endothelization, and most importantly, with late and very late stent thrombosis and death (4, 20). Thus, biodegradable polymers are being considered and investigated in many clinical studies to deliver drugs. Several clinical studies were conducted to analyse the safety and performance of biodegradable polymers.

The NEXT trial reported that one-year clinical outcome after implantation of both biolimus-eluting stent and everolimus-eluting stent was phenomenal, with a low rate of TLR and stent thrombosis (21). Along with NEXT trial, the NOBORI 2 study also concluded good and sustained performance of biodegradable polymers in high-risk patients with significant comorbidities and/or complex lesions (22). Moreover, the safety and performance of biodegradable polymers with limus family of DES were firmly demonstrated in a real-world patient population (15, 21).

We recognise that it's not formally and statistically possible to compare results of different studies (and different type of stents), however our findings represent a strong suggestion that EucaLimus has a favourable safety and efficacy performance in a real-world population, adding a small, but important, contribution to the evidence in favour of bioresorbable polymer coated, new-generation, drug eluting stents.

Study limitations

Our study has some limitations. 1) Retrospective and observational design; 2) This was a non-randomised, single-arm study without comparison groups. Therefore, long-term (> 5 years) follow-up is essential to assess the factual event rates.

CONCLUSIONS

In conclusion, the lower episodes of TLF and MACE in uncontrolled and real-world patient population at long term follow-up clearly represent the prolonged safety and performance of the eucaLimus SES. Therefore, eucaLimus stent could be an acceptable substitute to contemporary DES which are presently available in the market.

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ETHICS

Fundings

The study was not funded. The EucaLimus Stent is a CE Mark Approved device, available in Europe. It is provided by the Italian SSN (National Health System).

Conflict of interests

The authors have declared no conflict of interests.

Availability of data and material

The data underlying this article cannot be shared publicly due to privacy of research partecipants. The data can be shared just before a reasonable request to the corresponding author.

Authors' contribution

All the authors:

1. Gave substantial contributions to the conception or design of the work and to the acquisition, analysis or interpretation of data for the work;
2. drafted the work or revising it critically for important intellectual content;
3. provided approval for publication of the content;

4. agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical approval

The study was a retrospective analysis of data. Patient's data have been anonymised and protected. The study was conducted in accordance with the ethical standards established in the ***Declaration of Helsinki of 1946***. The study protocol has been submitted to the local ethical committee and its approval is currently pending.

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